L.A. Care
HEALTH PLAN

Cardiovascular Toolkit

2012

Dear Doctor:

L.A. Care Health Plan is pleased to provide you with this copy of the Cardiovascular Care Quality Improvement Toolkit. As you know, heart disease is the leading cause of death for both men and women in the United States. Studies have shown that controlling blood pressure and cholesterol levels can reduce the risk of developing heart disease and its associated complications. This toolkit offers clinical guidelines and patient education materials to assist you in the care of your patients.

L.A. Care Health Plan is taking an active role in addressing this personal and public health challenge. This Toolkit is an example of our efforts to assist you with the evaluation and management of these conditions. Appropriate screening and effective control of cholesterol levels, blood pressure, and use of B-blockers post myocardial infarction reduces the prevalence of preventable complications associated with cardiovascular disease.

We hope you find the enclosed guidelines and patient education materials useful. We urge you to utilize the information and resources we have provided and to join us in the effort to improve cardiovascular disease and treatment practices and to promote awareness of the disease among your patients.

Thank you for joining us in this effort and keep up the good work. Please contact Maria A. Casias, RN at (213) 694-1250 ext. 4312 or email mcasias@lacare.org if you have questions, would like to provide feedback, or would like further information.

Sincerely,

Sarita A. Mohanty, MD, MPH
Medical Director

Cardiovascular Provider Toolkit

Contents		Material Sources
A. Provider Guidelines		
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Circulation
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2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Writing Committee Members, Philip Greenland, Joseph S. Alpert, George A. Beller, Emelia J. Benjamin, Matthew J. Budoff, Zahi A. Fayad, Elyse Foster, Mark. A. Hlatky, John McB. Hodgson, Frederick G. Kushner, Michael S. Lauer, Leslee J. Shaw, Sidney C. Smith, Jr, Allen J. Taylor, William S. Weintraub and Nanette K. Wenger

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2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance

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This document was approved by the American College of Cardiology Foundation Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee and all cosponsoring organizations in September 2010.

The American Heart Association requests that this document be cited as follows: Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JMcB, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:e584–e636.

This article has been copublished in the *Journal of the American College of Cardiology* and the *Journal of Cardiovascular Computed Tomography*.

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.cardiosource.org) and the American Heart Association (my.americanheart.org). A copy of the document is also available at http://www.americanheart.org/presenter.jhtml?identifier=3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0112). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

Expert peer review of AHA Scientific Statements is conducted at the AHA National Center. For more on AHA statements and guidelines development, visit http://www.americanheart.org/presenter.jhtml?identifier=3023366.

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Preamble

It is essential that the medical profession play a central role in critically evaluating the evidence related to drugs, devices, and procedures for the detection, management, or prevention of disease. Properly applied, rigorous, expert analysis of the available data documenting absolute and relative benefits and risks of these therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favorably affect the cost of care by focusing resources on the most effective strategies. One important use of such data is the production of clinical practice guidelines that, in turn, can provide a foundation for a variety of other applications, such as performance measures, appropriate use criteria, clinical decision support tools, and quality improvement tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force) is charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, and the Task Force directs and oversees this effort. Writing committees are charged with assessing the evidence as an independent group of authors to develop, update, or revise recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines in partnership with representatives from other medical practitioner and specialty groups. Writing committees are specifically charged to perform a formal literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and clinical outcomes constitute the primary basis for recommendations in these guidelines.

In analyzing the data and developing recommendations and supporting text, the writing committee used evidence-based methodologies developed by the Task Force that are described elsewhere.[1] The committee reviewed and ranked evidence supporting current recommendations, with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, prospective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, where there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues where sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations and no references are cited. The schema for Classification of Recommendations (COR) and Level of Evidence (LOE) is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size as well as the certainty of the treatment effect. A new addition to the ACCF/AHA

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be done; is not useful/beneficial/effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be done
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence: A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

methodology is a separation of the Class III recommendations to delineate whether the recommendation is determined to be of "no benefit" or associated with "harm" to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for COR I and IIa, LOE A or B only, have been added.

The Task Force on Practice Guidelines makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose ALL relevant relationships and those existing 24 months before initiation of the writing effort. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the members voting. Members who were recused from voting are noted on the title page of this document and in Appendix 1. Members must recuse themselves from voting on any recommendation to which their relationship with industry and other entities (RWI) applies. Any writing committee member who develops a new RWI during his or her tenure is required to notify guideline staff in

writing. These statements are reviewed by the Task Force on Practice Guidelines and all members during each conference call and meeting of the writing committee and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual.[1] Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. In addition, to ensure complete transparency, writing committee members' *comprehensive disclosure information*—including RWI not pertinent to this document—is available online as a supplement to this document. Disclosure information for the ACCF/AHA Task Force on Practice Guidelines is available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of the writing committee was supported exclusively by the ACCF and AHA without commercial support. Writing group members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are not currently available in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough and systematic review of the available current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most situations. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are circumstances in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to better inform patient care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles.

The guidelines will be reviewed annually by the Task Force and considered current until they are updated, revised, or withdrawn from distribution. The executive summary and recommendations are published in the *Journal of the American College of Cardiology*, *Circulation*, and the *Journal of Cardiovascular Computed Tomography*.

Alice K. Jacobs, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this document are, whenever possible, evidence based. An extensive evidence review was conducted for the period beginning March 2008 through April 2010. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included, but were not limited to, *African Americans, Asian Americans, albuminuria, asymptomatic, asymptomatic screening and brachial artery reactivity, atherosclerosis imaging, atrial fibrillation, brachial artery testing for atherosclerosis, calibration, cardiac tomography, compliance, carotid intima-media thickness (IMT), coronary calcium, coronary computed tomography angiography (CCTA), C-reactive protein (CRP), detection of subclinical atherosclerosis, discrimination, endothelial function, family history, flow-mediated dilation, genetics, genetic screening, guidelines, Hispanic Americans, hemoglobin A, glycosylated, meta-analysis, Mexican Americans, myocardial perfusion imaging (MPI), noninvasive testing, noninvasive testing and type 2 diabetes, outcomes, patient compliance, peripheral arterial tonometry (PAT), peripheral tonometry and atherosclerosis, lipoprotein-associated phospholipase A2, primary prevention of coronary artery disease (CAD), proteinuria, cardiovascular risk, risk scoring, receiver operating characteristics (ROC) curve, screening for brachial artery reactivity, stress echocardiography, subclinical atherosclerosis, subclinical and Framingham, subclinical and Multi-Ethnic Study of Atherosclerosis (MESA), and type 2 diabetes.* Additionally, the writing committee reviewed documents related to the subject matter previously published by the ACCF and AHA, American Diabetes Association (ADA), European Society of Cardiology, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) 7. References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published in the article, data from the clinical trial will be used to calculate the absolute risk difference and number needed to treat or harm; data related to the relative treatment effects will also be provided, such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio (IRR), along with confidence interval (CI) when available.

The focus of this guideline is the initial assessment of the apparently healthy adult for risk of developing cardiovascular events associated with atherosclerotic vascular disease. The goal of this early assessment of cardiovascular risk in an asymptomatic individual is to provide the foundation for targeted preventive efforts based on that individual's predicted risk. It is based on the long-standing concept of targeting the intensity of drug treatment interventions to the severity of the patient's risk.[2] This clinical approach serves as

a complement to the population approach to prevention of cardiovascular disease (CVD), in which population-wide strategies are used regardless of an individual's risk.

This guideline pertains to initial assessment of cardiovascular risk in the asymptomatic adult. Although there is no clear age cut point for defining the onset of risk for CVD, elevated risk factor levels and subclinical abnormalities can be detected in adolescents as well as young adults. To maximize the benefits of prevention-oriented interventions, especially those involving lifestyle changes, the writing committee advises that these guidelines be applied in asymptomatic persons beginning at age 20. The writing committee recognizes that the decision about a starting point is an arbitrary one.

This document specifically excludes from consideration patients with a diagnosis of CVD or a coronary event, for example, angina or anginal equivalent, myocardial infarction (MI), or revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery. It also excludes testing for patients with known peripheral artery disease (PAD) and cerebral vascular disease. This guideline is not intended to replace other sources of information on cardiovascular risk assessment in specific disease groups or higher-risk groups such as those with known hypertension or diabetes who are receiving treatment.

1.2. Organization of the Writing Committee

The committee was composed of physicians and others expert in the field of cardiology. The committee included representatives from the American Society of Echocardiography (ASE), American Society of Nuclear Cardiology (ASNC), Society of Atherosclerosis Imaging and Prevention (SAIP), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), and Society for Cardiovascular Magnetic Resonance (SCMR).

1.3. Document Review and Approval

This document was reviewed by 2 outside reviewers nominated by the ACCF and 2 outside reviewers nominated by the AHA, as well as 2 reviewers each from ASE, ASNC, SAIP, SCAI, SCCT, and SCMR, and 23 individual content reviewers (including members from the Appropriate Use Criteria Task Force, ACCF Cardiac Catheterization Committee, ACCF Imaging Council, and ACCF Prevention of Cardiovascular Disease Committee). All reviewer RWI information was collected and distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and AHA and endorsed by ASE, ASNC, SAIP, SCCT, and SCMR.

1.4. Magnitude of the Problem of Cardiovascular Risk in Asymptomatic Adults

Atherosclerotic CVD is the leading cause of death for both men and women in the United States.[3] Risk factors for the development of atherosclerotic disease are widespread in the U.S. population. In 2003, approximately 37% of American adults reported having ≥2 risk factors for CVD. Ninety percent of patients with coronary heart disease (CHD) have at least 1 atherosclerotic risk factor.[4] Approximately half of all coronary deaths are not preceded by cardiac symptoms or diagnoses.[5] One aim of this guideline is to provide an evidence-based approach to risk assessment in an effort to lower this high burden of coronary deaths in asymptomatic adults.

CVD was mentioned on the death certificates of 56% of decedents in 2005. It was listed as the underlying cause of death in 35.3% (864,480) of all deaths (2,448,017) in 2005 or 1 of every 2.8 deaths in the U.S.[6] In every year since 1900 (except 1918), CVD accounted for more deaths than any other major cause of death in the United States.[6] It is estimated that if all forms of major CVD were eliminated, life expectancy would rise by almost 7 years.[6] Analyses suggest that the decrease in U.S. deaths due to CHD from 1980 to 2000 was partly attributable (approximately 47%) to evidence-based medical therapies, and about 44% of the reduction has been attributed to changes in risk factors in the population.[7] The estimated direct and indirect cost of CVD for 2009 is $475.3 billion.[6]

CHD has a long asymptomatic latent period, which provides an opportunity for early preventive interventions. Atherosclerosis begins in childhood and progresses into adulthood due to multiple coronary risk factors such as unfavorable levels of blood lipids, blood pressure, body weight and body fat, smoking, diabetes, and genetic predisposition.[8–10] The lifetime risk of CHD and its various manifestations has been calculated for the Framingham Heart Study population at different ages. In nearly 8000 persons initially free of clinical evidence of CHD, the lifetime risk of developing clinically manifest CHD (angina pectoris, MI, coronary insufficiency, or death from CHD) at age 40 was 48.6% for men and 31.7% for women.[11] At age 70, the lifetime risk of developing CHD was 34.9% for men and 24.2% for women. The lifetime risk for all CVD combined is nearly 2 of every 3 Americans.[12] Thus, the problem is immense, but the preventive opportunity is also great.

1.5. Assessing the Prognostic Value of Risk Factors and Risk Markers

Many risk factors have been proposed as predictors of CHD.[13,14] New risk factors or markers are frequently identified and evaluated as potential additions to standard risk assessment strategies. The AHA has published a scientific statement on appropriate methods for evaluating the predictive value of new risk factors or risk markers.[15] The scientific statement endorsed previously published guidelines for proper reporting of observational studies in epidemiology[16] but also went beyond those guidelines to specifically address criteria for evaluation of established and new risk markers. The current writing committee endorses this scientific statement and incorporated these principles into the assessments for this guideline. The general concepts and requirements for new risk marker validation and evaluation are briefly reviewed to provide a basis for the assessments in this document.

For any new risk marker to be considered useful for risk prediction, it must, at the very least, have an independent statistical association with risk after accounting for established readily available and inexpensive risk markers. This independent statistical association should be based on studies

that include large numbers of outcome events. Traditionally, reports of novel risk markers have only gone this far, reporting adjusted HRs with CIs and *P* values.[17] Although this level of basic statistical association is often regarded by researchers as meaningful in prediction of a particular outcome of interest, the AHA scientific statement called for considerably more rigorous assessments that include analysis of the calibration, discrimination, and reclassification of the predictive model. Many of the tests reviewed in this guideline fail to provide these more comprehensive measures of test evaluation, and for this reason, many tests that are statistically associated with clinical outcomes cannot be judged to be useful beyond a standard risk assessment profile. In the absence of this evidence of "additive predictive information," the writing committee generally concluded that a new risk marker was not ready for routine use in risk assessment.

Calibration and discrimination are 2 separate concepts that do not necessarily track with each other. Calibration refers to the ability to correctly predict the proportion of subjects within any given group who will experience disease events. Among patients predicted to be at higher risk, there will be a higher number of events, whereas among patients identified as being at lower risk, there will be fewer events. For example, if a diagnostic test or a multivariable model splits patients into 3 groups with predicted risks of 5%, 10%, and 15% within each group, calibration would be considered good if in a separate group of cohorts with similar predicted risks, the actual rates of events were close to 5%, 10%, and 15%. Calibration is best presented by displaying observed versus expected event rates across quantiles of predicted risk for models that do and do not include the new risk marker.

Discrimination is a different concept that refers to the probability of a diagnostic test or a risk prediction instrument to distinguish between patients who are at higher compared with lower risk. For example, a clinician sees 2 random patients, 1 of whom is ultimately destined to experience a clinical event. A diagnostic test or risk model discriminates well if it usually correctly predicts which of the 2 subjects is at higher risk for an event. Mathematically this is described by calculating a C index or C statistic, parameters that are analogous to the area under the ROC curve. These statistics define the probability that a randomly selected person from the "affected group" will have a higher test score than a randomly selected person from the "nonaffected group." A test with no discrimination would have a C statistic of 0.50 and a perfect test would have a C statistic of 1.0. Throughout this document, C statistic information is cited where available.

As an example of a risk marker that improves discrimination, MESA investigators found that the addition of coronary artery calcium (CAC) scores to standard risk factors improved the area under the ROC curve from 0.77 to 0.82 ($P<0.001$).[18] In contrast, a score based on 9 genes that code for cholesterol levels added no predictive value over established risk factors and family history.[19] Similarly, a study comparing the predictive capacity of conventional and newer biomarkers for prediction of cardiovascular events derived a C statistic of 0.760 for coronary events for the conventional risk factor model. Adding a number of newer biomarkers changed the C statistic by only 0.009 ($P=0.08$).[20] Small changes such as these in the C statistic suggest limited or rather modest improvement in risk discrimination with additional risk markers.

Some investigators have called for evaluating the number of subjects reclassified into other risk categories based on models that include the new risk marker.[21] For example, in a model of cardiovascular risk in a large cohort of healthy women, the addition of CRP resulted in reclassification of a large proportion of subjects who were thought to be at intermediate risk based on standard risk markers alone.[22] One problem with this approach is that not all reclassification is necessarily clinically useful. If a patient is deemed to be at intermediate risk and is then reclassified as being at high or low risk, the clinician might find that information helpful. It may not be known, however, whether or not these reclassifications are correct for individual subjects. Pencina and colleagues introduced 2 new approaches, namely "net reclassification improvement" and "integrated with classification improvement," which provide quantitative estimates of correct reclassifications.[23] Correct reclassifications are associated with higher predicted risks for cases and lower predicted risks for noncases.

1.6. Usefulness in Motivating Patients or Guiding Therapy

In 1996 the American College of Cardiology Bethesda Conference reviewed the concept of risk stratification, an approach that is now standard for identifying the appropriate degree of therapeutic or preventive interventions.[2] Patients deemed to be at low risk for clinical events are unlikely to gain substantial benefits from pharmaceutical interventions and therefore might best be managed with lifestyle modifications. Conversely, patients deemed to be at high risk for events are more likely to benefit from pharmacologic interventions and therefore are appropriate candidates for intensive risk factor modification efforts. Among patients at intermediate risk, further testing may be indicated to refine risks and assess the need for treatment. Although this model is attractive and has been shown to be appropriate in certain situations, there is no definitive evidence that it directly leads to improved patient outcomes. Further research is clearly needed, and it is appropriate to point out that the risk stratification paradigm has not been subjected to rigorous evaluation by randomized trials. Indeed, the impact of various risk assessment modalities on patient outcomes is rarely studied and not well documented in the few studies that have been conducted.[24]

1.7. Economic Evaluation of Novel Risk Markers

The progressively rising costs of medical care have increased interest in documenting the economic effects of new tests and therapies. The most basic goal is to estimate the economic consequences of a decision to order a new test. The ultimate goal is to determine whether performing the test provides sufficient value to justify its use.

A complete economic evaluation of the test has to account for all the subsequent costs induced by ordering the test, not

just the cost of the test itself. The results of the test should change subsequent clinical management, which might include ordering follow-up tests, starting or stopping drug therapy, or using a device or procedure. The costs of these subsequent clinical management choices must be included in an "intention-to-test" analysis of the economic consequences of the initial decision to use the test. Ideally, the analysis should be extended to account for clinical events that are either averted or caused as a result of the strategy based on performing the test.

An example of the economic consequences of testing will illustrate the importance of these principles. Suppose a patient with diabetes who has no cardiac symptoms undergoes a computed tomography (CT) coronary angiogram, which reveals obstructive CAD but also leads to contrast-induced nephropathy. Further suppose this patient has a follow-up invasive coronary angiogram, undergoes insertion of a coronary stent, and is treated for renal insufficiency. The costs of all these "downstream events" should be included in any economic assessment of the use of CCTA because they all resulted from the initial decision to perform the test. Note that the total costs of a "test strategy" may greatly exceed the cost of the initial test itself.

The cost of any medical intervention has to be placed in the context of the clinical benefits that the intervention provides. In the example of the patient with diabetes, perhaps the aggressive use of coronary revascularization actually extended life expectancy. Cost-effectiveness analysis provides a formal framework with which to compare the clinical effectiveness of an intervention (measured in patient-centered outcomes such as length of life or quality of life) with the cost of that intervention. Cost-effectiveness analysis has been most commonly applied to the evaluation of new medical therapies that directly improve clinical outcomes (eg, use of bypass surgery to treat CAD). Diagnostic tests do not improve clinical outcomes directly, however, and do so only indirectly by changing clinical management decisions, which in turn may improve clinical outcomes. Thus, determining the cost-effectiveness of a diagnostic test depends on how effectively the information is used and can be evaluated only in the context of available treatments and how effective those treatments are. A test that provides accurate risk information about an untreatable disease is unlikely to be cost-effective simply because clinical outcomes cannot be improved by its use.

In general, testing strategies such as those assessed in this document have not included evaluations of the cost and cost-effectiveness of the tests. Therefore, although this general guidance is offered to the reader as a caveat, the writing committee was generally unable to find evidence to support the cost-effectiveness of any of the tests and testing approaches discussed here. Where exceptions were identified, cost-related information is included. In addition, for the uncommon examples for which clinical outcomes of testing strategies were assessed, the writing committee included that evidence in the assessment of the value of the risk assessment test.

2. Approaches to Risk Stratification

2.1. General Approach to Risk Stratification

2.1.1. Recommendation for Global Risk Scoring

Class I

1. Global risk scores (such as the Framingham Risk Score [FRS]) that use multiple traditional cardiovascular risk factors should be obtained for risk assessment in all asymptomatic adults without a clinical history of CHD. These scores are useful for combining individual risk factor measurements into a single quantitative estimate of risk that can be used to target preventive interventions.[25] (*Level of Evidence: B*)

2.1.1.1. General Description

Prospective epidemological studies have established, primarily in studies of people ≥40 years of age, that readily measured and often modifiable risk factors are associated with the development of clinical CHD in asymptomatic individuals. There are robust prognostic data for each of the "classic risk factors," namely, cigarette smoking, cholesterol levels, blood pressure levels, and diabetes. Data obtained from the Framingham Heart Study and other population-based cohorts have demonstrated that age, sex, cigarette smoking, level of low-density lipoprotein (LDL) cholesterol or total cholesterol, diabetes, and levels of blood pressure can be combined in predictive models to estimate risk of fatal and nonfatal CHD events.[26] Beginning in the 1990s, a number of global risk prediction instruments were introduced, based on multivariable models that incorporated risk factor data and clinical events.[25–28] These instruments go beyond simple demographics by taking into account modifiable risk markers that are also appropriate evidence-based targets for preventive interventions. Table 2 summarizes a sample of published global risk score instruments.

Global risk assessment instruments, such as the FRS, are considered valuable in medical practice because clinicians and patients may not otherwise accurately assess risk. In some survey studies, clinicians presented with scenarios were found to overestimate the likelihood of a future major clinical cardiovascular event.[29] Other studies have suggested that physicians may also underestimate risk.[30–32] Failure to use global quantitative risk instruments may result in physicians inappropriately informing patients that they are at high risk and inappropriately promoting therapeutic interventions of modest or questionable benefit or, alternatively, inadequately emphasizing risk when risk is actually present.

Global risk scores, although designed to estimate risk across a continuous range from 0% to 100%, have most commonly been advocated as a method by which patients can be categorized in broad terms as "low risk," "intermediate risk," and "high risk." In general, patients are deemed to be high risk if they are found to have a global risk estimate for hard CHD events of at least 20% over 10 years. The threshold for dividing low risk from intermediate risk is not uniform, with some proposing a lower cutoff value of 6% risk over 10 years, whereas others use a value of 10% over 10 years.[27,33,34] This document, unless otherwise noted, uses a lower cutoff

Table 2. Comparison of a Sample of Global Coronary and Cardiovascular Risk Scores

	Framingham	SCORE	PROCAM (Men)	Reynolds (Women)	Reynolds (Men)
Sample size	5345	205 178	5389	24 558	10 724
Age (y)	30 to 74; M: 49	19 to 80; M: 46	35 to 65; M: 47	>45; M: 52	>50; M: 63
Mean follow-up (y)	12	13	10	10.2	10.8
Risk factors considered	Age, sex, total cholesterol, HDL cholesterol, smoking, systolic blood pressure, antihypertensive medications	Age, sex, total-HDL cholesterol ratio, smoking, systolic blood pressure	Age, LDL cholesterol, HDL cholesterol, smoking, systolic blood pressure, family history, diabetes, triglycerides	Age, HbA1C (with diabetes), smoking, systolic blood pressure, total cholesterol, HDL cholesterol, hsCRP, parental history of MI at <60 y of age	Age, systolic blood pressure, total cholesterol, HDL cholesterol, smoking, hsCRP, parental history of MI at <60 y of age
Endpoints	CHD (MI and CHD death)	Fatal CHD	Fatal/nonfatal MI or sudden cardiac death (CHD and CVD combined)	MI, ischemic stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)	MI, stroke, coronary revascularization, cardiovascular death (CHD and CVD combined)
URLs for risk calculators	http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof	http://www.heartscore.org/Pages/welcome.aspx	http://www.chd-taskforce.com/coronary_risk_assessment.html	http://www.reynoldsriskscore.org/	http://www.reynoldsriskscore.org/

CHD indicates coronary heart disease; CVD, cardiovascular disease; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; M, mean; MI, myocardial infarction; PROCAM, Münster Heart Study; and SCORE, Systematic Coronary Risk Evaluation.

value of at least 10% and a higher cutoff of <20% to designate intermediate risk.

The evidence with regard to global risk scores is most appropriate for individuals ≥40 years of age. It is important to note that there are limited data from Framingham and other long-term observational studies on 10-year risk in young adults; consequently, it is difficult to estimate 10-year risk in young adults. This is due to the fact that 10-year risk in young adults is very rarely impressively elevated, even in the face of significant risk factors, and thus there are a limited number of coronary events for calculating risk. As noted earlier in this document, the long-term or lifetime risk may be substantially raised by the presence of risk factors in young adults. Although the earliest age at which these risk scores should be used has not been rigorously established, the application of a particular risk score or test should not detract from adherence to a healthy lifestyle and identification of modifiable risk factors beginning in childhood. Therefore, to direct attention to the lifetime significance of coronary risk factors in younger adults, the writing committee considered measurement of a global risk score possibly worthwhile even in persons as young as age 20.

2.1.2. Association With Increased Risk and Incremental Risk of Additional Risk Factors

A number of global risk instruments have been developed.[35] In the United States the best known is the FRS, several variants of which have been published.[25–28,34] Some include diabetes as a risk factor.[25] The version published with the National Cholesterol Education Program Adult Treatment Panel (ATP III) report did not include diabetes,[27] which was considered to be a CHD risk equivalent. Some versions of the FRS have focused on CHD death and nonfatal MI as endpoints, whereas a more recent version focused on more comprehensive total cardiovascular events.[27,28,36] A European "SCORE" (Systematic Coronary Risk Evaluation) was developed based on a regression model derived from observations of >200,000 adults.[37] This model differs from the Framingham model in a variety of factors, including incorporation of age into a time scale and consideration of geographic variability within European countries as the calibration metric.[35]

Many of the multivariable coronary risk assessment functions have been evaluated for predictive capability.[38] In a large number of different cohort studies, multivariable risk equations typically yielded ROC areas approximately equal to 0.80, indicating relatively high levels of predictive discrimination. Data from the NHANES (National Health and Nutrition Examination Surveys) prospective cohort study were used to study how well a Framingham-type risk model could predict first-time fatal and nonfatal CVD events.[39] Risk factors included in the model to assess risk of CVD were age, systolic blood pressure, smoking status, total cholesterol, reported diabetes status, and current treatment for hypertension. In women the risk model was useful for predicting events, with a C statistic of 0.829. In men the results were similar (C statistic, 0.78). Results such as these are typical for a Framingham-like risk assessment model in most populations, but there has been concern that global risk scores developed in one population may not be applicable to other populations.[24] The FRS has been validated in several external populations, but in some cases it has required a "prevalence correction" to recalibrate the scores to reflect lower population prevalence of disease.[25] Although global risk scores have often been found to have C statistics indicating that the score

is useful for discrimination, the focus on 10-year risk estimates in clinical medicine makes many risk scores less useful for clinical decision making in most younger male patients and most women.[40–42]

Some large-scale investigations have suggested that nearly 90% of the population-attributable risk for CAD can be ascribed to traditional biological and psychosocial risk factors.[43] However, none of the current risk models, based only on traditional risk factors such as the FRS, are able to discriminate risk to an extent that would eliminate material uncertainty of risk for individual patients being seen by individual clinicians. Even in a global risk model such as the FRS, which predicts risk with an area under the ROC curve of as high as 80% in some studies,[38] there is considerable overlap in risk scores between people who are ultimately found to be affected versus those found to be unaffected. Hence, a number of investigators argue for ongoing discovery and investigation of newer risk factors and predictive risk markers to improve the ability of clinicians to discriminate risk among their individual patients.[20,44,45]

In summary, a FRS, or a similar type of multivariable predictive score based on traditional cardiovascular risk factors, is highly predictive of cardiovascular events. Given the familiarity of health professionals and the general public with the traditional risk factors and the proven efficacy of interventions for modifiable factors in these models, the writing committee agreed with many previous clinical practice guidelines that a "Framingham-like" risk score should be the basic risk assessment strategy to use for all asymptomatic adult patients.[46–53] Additional risk markers should be assessed for their ability to improve on risk assessment beyond prediction from the multivariable global risk score. The writing committee felt that it is reasonable to advocate global risk score measures coincident with guideline-supported measurements of blood pressure or cholesterol beginning at age 20 and then every 5 years thereafter.[27] The writing committee also acknowledged that some investigators advocate a shift in the risk assessment focus to 'lifetime risk" of CHD, but to date, evidence is sparse on how best to incorporate estimates of lifetime risk into clinical management.[11] Another approach to the long-term risk estimation problem in younger adults was recently presented by the Framingham Study investigators as the "30-Year Risk of Cardiovascular Disease".[54]

2.2. Family History and Genomics

2.2.1. Recommendation for Family History

Class I

1. Family history of atherothrombotic CVD should be obtained for cardiovascular risk assessment in all asymptomatic adults.[22,55] (*Level of Evidence: B*)

2.2.1.1. Association With Increased Cardiovascular Risk and Incremental Risk

A family history of premature (early-onset) atherothrombotic CVD, defined most often as occurring in a first-degree male relative <55 years of age or in a first-degree female relative <65 years of age, has long been considered a risk factor for CVD. Even a positive parental history that is not premature increases the risk of CVD in offspring.[56] The importance of family history is not surprising because the risk factors for CVD, including hypertension, dyslipidemia, diabetes, obesity, and smoking behavior, are in part heritable.[19,57–62] In addition, lifestyle habits such as diet, exercise, and smoking are in part learned behaviors influenced by family patterns. However, studies examining parents, siblings, twins, and second-degree relatives have demonstrated that the 1.5- to 2.0-fold RR of family history persists even after adjusting for coexistent risk factors.[56,63–66] The risk associated with a positive family history for CVD is observed in individuals of White European, African American, Hispanic, and Japanese descent.[67–69] The strength of the risk for an individual increases with younger age of onset, increasing numbers of relatives affected, and the relative's genealogical proximity.[56,63,66,70] Although the prevalence of a positive family history ranges from 14% to 35% in the general population, almost 75% of those with premature CHD have a positive family history, underscoring opportunities for prevention.[71,72]

The reliability of self-reported family history is imperfect.[71,73] To address recall bias, investigators from the Framingham Study used validated parental data and reported that although the negative predictive value for reports of premature MI and CHD death was superb (>90%), the positive predictive value for validated events was only fair (28% to 66%).[73] Similarly, the Health Family Tree Study found that the positive predictive value of a positive family history of CHD was 67%, but the negative predictive value was excellent at 96%.[70,71] The sensitivity of self-reported family history is ≥70%.[71,73] In addition, there has been increasing attention to improving the collection of family history through standardized questionnaires and online resources.[74]

Family history modestly improves risk stratification. In the Framingham Heart Study, the inclusion of a positive family history improved ability to predict CVD (the multivariable model C statistic [ROC] increased from 0.82 to 0.83). Family history appeared to aid in reclassifying individuals and was most useful in persons at intermediate risk (third and fourth multivariable predicted risk quintile) of CVD.[63,64]

2.2.1.2. Usefulness in Motivating Patients or Guiding Therapy

The ability of family history of CVD to motivate patients is not definitively established. Some studies have reported that persons with a positive family history of CHD were more motivated to modify their risk factors.[75] In the CARDIA (Coronary Artery Risk Development in Young Adults) study, however, young adults did not self-initiate or modify their CVD risk factors after a change in family history of heart attack or stroke.[76] Intensive interventions targeting those with a positive family history of CHD can improve risk factors; however, the sustainability of such interventions and their influence on CHD events has been more difficult to prove. For instance, a randomized study of black patients with a family history of premature CHD demonstrated that intensive community-based multiple risk factor intervention resulted in significant reductions in global CHD risk (improvements in cholesterol and blood pressure) compared with an enhanced primary care group.[77] However, the sustainability of such

efforts was disappointing; 5 years after completion, the previously observed improved risk factor profile of the intensive community-based group was no longer apparent and there was no significant difference in events.[78]

2.2.2. Genotypes: Common Genetic Variants for Coronary Heart Disease

2.2.2.1. Recommendation for Genomic Testing

Class III: No Benefit

1. **Genotype testing for CHD risk assessment in asymptomatic adults is not recommended.[79,80] (*Level of Evidence: B*)**

2.2.2.2. Association With Increased Cardiovascular Risk and Incremental Risk

CHD is typically due to the complex interplay between environmental factors and multiple common genetic variants (minor allele frequency >5%) with small or very modest effects (OR typically 1.2 to 1.5, and rarely >2.0).[81] The first widely replicated genetic variant for CHD was discovered by a genomewide association study on chromosome 9p21.3.[82–84] The 1.3- to 2.0-fold increased risk for MI observed with single nucleotide polymorphisms (SNPs) from the 9p21.3 genomic region has been observed in persons of various ethnicities, including European, Asian, and Hispanic descent, but thus far it has not been replicated in African Americans, which may relate to patterns of haplotype diversity in the genomic region.[82–87] The mechanisms underlying the 9p21.3 association with CHD remain unclear, although the variants are adjacent to CDKN2A, ARF, and CDKN2B, which are genes thought to regulate senescence and apoptosis.[88] Variants tested in the 9p21.3 region (rs10757274, GG versus AA) were associated with a HR for incident CHD of 1.6 for incident CHD in men participating in the NPHS II (Northwick Park Heart Study II).[89] The addition of the genotype to a model based on traditional CVD risk factors did not significantly improve risk discrimination (area under the ROC, 0.62 [95% CI 0.58 to 0.66] to 0.64 [95% CI 0.60 to 0.68]; $P=0.14$). However, the genotype resulted in better model fit (likelihood ratio, $P=0.01$) and shifted 13.5% of the men into a more accurate risk category.[89]

In the Women's Genome Health Study (n=22,129), an SNP at chromosome 9p21.3 was associated with an increased hazard for incident CVD; however, the SNP did not enhance model discrimination (C index, 0.807 to 0.809) or net reclassification when added to the Reynolds risk score, which includes family history.[79] In another study, investigators reported that a genome score including 9 SNPs associated with serum lipid levels was associated with an increased risk of CVD events, but the score did not improve model discrimination (ROC, 0.80 for the model with and without the score). Furthermore, investigators reported that having a parent or sibling with a history of MI conferred a 50% increased risk of incident cardiovascular events (HR 1.52; 95% CI 1.17 to 1.97; $P=0.002$) in a model including the genotype score.[90] Family history may integrate the complexity of interacting genomic and environmental factors shared by family members. Many other SNPs have been reported as risk markers for future CHD events. Given the very small OR and the small incremental risk information of the individual polymorphisms, the writing committee judged that genomic tests for CHD risk currently offer no proven benefit in risk assessment when added to a global basic risk score such as the FRS.

2.2.2.3. Usefulness in Motivating Patients or Guiding Therapy

Studies assessing whether genotype testing enhances motivation and success with adherence to recommended lifestyle and medical therapies demonstrate mixed results.[80,91] Smokers given scenarios of genotype testing information report more motivation to quit but lower levels of perceived control and similar success with smoking cessation at 1 year.[92,93] In another study, persons who agreed to receive genotype data (GSTM1 SNP) were more likely to abstain from cigarette smoking at 12-month follow-up than those who declined the test, regardless of whether they tested positive or negative for the risk SNP.[94]

No data are available as to whether the results of genotype testing alter management or improve outcomes for prevention of CHD.[92,95] Despite the uncertainty about the clinical implications of most genotypic markers for CHD, there is widespread direct-to-consumer marketing of these tests.[95] A concern is that advertisements and genetic information provided by for-profit genomic testing services may overstate claims and confuse or frighten consumers. In addition, regulation of the companies and provision for genetic counseling is sporadic.[95] Thus, the writing committee was aware of no benefit of genotype testing, and given the limited benefit in terms of risk assessment, the writing committee concluded that these types of tests should not be done at this time.

2.3. Lipoprotein and Apolipoprotein Assessments

2.3.1. Recommendation for Lipoprotein and Apolipoprotein Assessments

Class III: No Benefit

1. **Measurement of lipid parameters, including lipoproteins, apolipoproteins, particle size, and density, beyond a standard fasting lipid profile is not recommended for cardiovascular risk assessment in asymptomatic adults.[96] (*Level of Evidence: C*)**

2.3.2. Assessment of Lipoprotein Concentrations, Other Lipoprotein Parameters, and Modified Lipids

Beyond the standard fasting lipid profile (total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, and triglycerides), additional measurements of lipid parameters or modified lipids have been proposed to extend the risk factor–cardiovascular prediction relationship. Each LDL particle contains 1 molecule of apolipoprotein B (often referred to as ApoB); thus, the concentration of ApoB directly reflects LDL particle numbers. The relationship between apolipoprotein A (often referred to as ApoA) and HDL is less direct. Several techniques directly measure lipid particle numbers or their size distribution. All lipid particles (eg, LDL or HDL) are present in the circulation in a range of sizes. Oxidative

modification of lipid particles occurs and appears to influence their atherogenic potential.

Non-HDL cholesterol, meaning cholesterol transported in LDL and very-low-density lipoprotein, reflects the total concentration of atherogenic particles, is closely related to particle number, and is simply calculated as the difference between total cholesterol and HDL-cholesterol blood concentrations. Particle size is similarly closely related to HDL and triglyceride concentrations. High concentrations of triglycerides lead to triglyceride enrichment of LDL or HDL. Subsequent particle modification by hepatic lipase leads to reduction of particle size and increased density, properties associated with heightened atherogenic potential. Treatment guidelines for the consideration of pharmacotherapy and the therapeutic targets for non-HDL cholesterol are 30 mg/dL higher than the thresholds for LDL cholesterol.[27]

2.3.3. Risk Prediction Relationships Beyond Standard Risk Factors

Many so-called "advanced lipid measures" of the type discussed above, particularly apolipoprotein concentrations and particle number, have been shown by some, but not all, studies to be associated with cardiovascular outcomes comparable to standard lipid concentrations.[43,97] For example, the EPIC-Norfolk (European Prospective Investigation into Cancer and Nutrition) study among apparently healthy individuals showed a 34% increased odds for future CHD associated with the highest quartile of LDL particle number after controlling for the FRS.[97] However, this was similar to non-HDL cholesterol (38% increased odds); thus, no relative benefit of particle number determinations was found. A recent systematic review observed that no study has reported the incremental predictive value of LDL subfractions beyond that of traditional cardiovascular risk factors, nor evaluated their independent test performance (for example, sensitivity and specificity).[96] Although the distribution of advanced lipid measures is different in men and women (and is also related to menopausal status), the outcome relationships are present for both men and women in similar magnitude.[98,99]

Two studies have specifically evaluated the predictive performance of ApoB or nuclear magnetic resonance LDL-particle concentration for risk reclassification of asymptomatic individuals compared with standard lipids. In the Framingham Heart Study, little additional risk information was obtained from ApoB or ApoB/A-1 ratio compared with the total/HDL-cholesterol ratio.[100] Thus, evidence that these more "advanced" lipid measures improve predictive capacity beyond standard lipid measurements is lacking.[101]

The role of lipoprotein(a) [Lp(a)] in risk assessment has received attention as a potential additional risk marker. In the Emerging Risk Factors Collaboration, circulating concentration of Lp(a), a large glycoprotein attached to an LDL-like particle, was assessed for its relationship with risk of major vascular and nonvascular outcomes. Long-term prospective studies that recorded Lp(a) concentration and subsequent major vascular morbidity and/or cause-specific mortality published between January 1970 and March 2009 were identified through electronic and other means.[102] Information was available from 126 634 participants in 36 prospective studies and spanned 1.3 million person-years of follow-up. Lp(a) concentration was weakly correlated with several conventional vascular risk factors and highly consistent within individuals over several years. In the 24 cohort studies, the risk ratio for CHD was 1.13 per standard deviation for higher Lp(a) (95% CI 1.09 to 1.18) after adjustment for age, sex, lipid levels, and other conventional risk factors. The corresponding adjusted risk ratios were 1.10 (95% CI 1.02 to 1.18) for ischemic stroke, 1.01 (95% CI 0.98 to 1.05) for the aggregate of nonvascular deaths, 1.00 (95% CI 0.97 to 1.04) for cancer deaths, and 1.00 (95% CI 0.95 to 1.06) for nonvascular deaths other than cancer. This study demonstrated that there are continuous, independent, but modest associations of Lp(a) concentration with risk of CHD and stroke. As with previous individual reports, associations were only modest in degree, and detailed information on incremental risk prediction beyond traditional risk factors is still lacking. There have also been, and continue to be, concerns about measurement and standardization of measurement of Lp(a) in clinical settings.[103] The writing committee therefore concluded that measurement of Lp(a) did not merit consideration for cardiovascular risk assessment in the asymptomatic individual.

2.3.4. Usefulness in Motivating Patients or Guiding Therapy

Additional lipid measures, beyond the standard lipid profile, vary in their interassay agreement, laboratory standardization, and established reference ranges and are generally limited by the absence of clear thresholds for initiation of treatment, therapeutic targets, or unique treatments beyond those already recommended by lipid treatment guidelines directed by the standard lipid profile.[104]

2.3.5. Evidence for Improved Net Health Outcomes

There is no evidence that the assessment of additional lipid parameters leads to improved net health outcomes, and thus the cost-effectiveness of these measures cannot be assessed.

2.4. Other Circulating Blood Markers and Associated Conditions

2.4.1. Recommendation for Measurement of Natriuretic Peptides

Class III: No Benefit

1. Measurement of natriuretic peptides is not recommended for CHD risk assessment in asymptomatic adults.[105] (*Level of Evidence: B*)

2.4.1.1. General Description

Atrial natriuretic peptide, B-type natriuretic peptide, and their precursors (N-terminal-proatrial natriuretic peptide) are emerging markers of prevalent CVD. Natriuretic peptides are released from the myocardium in response to increased wall stress and have been shown to be helpful in the diagnosis of heart failure among symptomatic patients, as well as having prognostic value in patients with established heart failure. Levels of natriuretic peptides have also been demonstrated to be markers of prognosis in patients with either acute coronary syndromes or stable CAD.

Table 3. Cardiovascular Disease Risk Assessment for B-Type Natriuretic Peptide

Study Name	Population	N	Age	Follow-Up (y)	Event	Main Findings
Framingham, MA[108]	Ambulatory adults, 3.4% with prior MI	3,352	59	5.2	Major CVD (CHD death, MI, stroke, heart failure, coronary insufficiency)	CHD death: HR 1.27/SD of NT-proANP, HR 1.41/SD of BNP; major event: HR 1.28/SD of NT-proANP, 1.30/SD of BNP
Copenhagen, Denmark[109]	Random sample of general population without CVD	626	67.9	5.0	Death; major CVD (CHD death, MI, stroke, heart failure, unstable angina, TIA)	Death: HR 1.43/SD of NT-proBNP; CV event: HR 1.92/SD (all multivariable adjusted)
Glostrup, Denmark[107]	General population without CVD	1,994	30 to 60	9.4	CV events (CVD death, MI, stroke)	CV events: HR 1.58/SD NT-proBNP; evidence of interaction with age
Rancho Bernardo, CA[110]	General population without CVD	805	77	6.8	Death; CV death	Death: HR 1.74/SD of NT-proBNP; CV events: HR 1.85/SD of NT-proBNP (multivariable adjusted)
Glasgow, Scotland[111]	Random sample of general population, some with prevalent CHD	1,252	50.4	4.0	All-cause mortality	Death: HR 2.2 for BNP ≥17.9 pg/mL (multivariable adjusted for age, sex, prior CHD)
Kuopio, Finland[112]	Kuopio Ischemic Heart Disease Risk Factor Study, longitudinal population-based sample of men	905	55.8 (46 to 65)	10	Death, CV death, CHD death	Multivariable-adjusted HR/SD change: proANP proBNP 1.35 1.26 1.48 1.41 1.52 1.44
Olmsted County, MN[106]	General population without congestive heart failure or renal failure	2,042	62 ± 10	5.6	All-cause mortality	Mortality somewhat assay dependent (Shionogi, Biosite, NT-proBNP), adjusted mortality ranged from HR 1.63 to 1.39, somewhat attenuated if adjusted for echocardiographic measurements
Malmo, Sweden[20]	General population without CVD	5,067	58	12.8	CV events (CV death, MI, stroke)	Multivariable-adjusted HR/SD change for BNP 1.22, C index improvement, 0.004 (P=0.12)
Uppsala, Sweden[113]	General population without CVD	661	71	10	CV death	Multivariable-adjusted HR/SD change for NT-proBNP 1.58, C index improvement, 0.034 (P=0.20)

BNP indicates B-type natriuretic peptide; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NT, N-terminal; proANP, atrial natriuretic peptide; proBNP, B-type natriuretic peptide; SD, standard deviation; and TIA, transient ischemic attack.

Recent studies have examined whether natriuretic peptides also predict the development of CVD in the asymptomatic, healthy adult population. The evidence from several prospective cohort investigations (Table 3) suggests that higher levels of natriuretic peptides predict the development of incident CVD, including heart failure, stroke, and atrial fibrillation.

There is some evidence that natriuretic peptides are stronger predictors of the development of heart failure than of incident coronary events,[106–108] and other studies suggest that their prognostic value is attenuated after adjustment for echocardiographic measures such as left ventricular mass and left ventricular diameter. The mechanism for these associations is as yet undetermined, and it is possible that natriuretic peptides are markers of left ventricular hypertrophy (LVH) or subclinical myocardial damage from hypertension, ischemia, or both.

Most prospective cohort studies (Table 3) report that natriuretic peptides predict prognosis and do so independent of other cardiac risk markers. Although these cohort studies suggest that natriuretic peptide levels convey prognostic

information, the value of that information has not yet been rigorously evaluated by use of the C index or measures of risk reclassification.[105] Consequently, the value of natriuretic peptide measurement in the assessment of cardiovascular risk among asymptomatic adults free of CAD or heart failure is not definitively known. Because of the absence of such data, the writing committee does not recommend measurement of natriuretic peptides for risk assessment in the asymptomatic adult.

2.4.1.2. Usefulness in Motivating Patients or Guiding Therapy

There have been no studies evaluating whether natriuretic peptides have value in motivating healthy patients, guiding treatment, or improving outcomes (there is some evidence on these points in populations of patients with heart failure but not in asymptomatic adults).

2.4.2. Recommendations for Measurement of C-Reactive Protein

Class IIa

1. **In men 50 years of age or older or women 60 years of age or older with LDL cholesterol less than 130 mg/dL; not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, diabetes, chronic kidney disease, severe inflammatory conditions, or contraindications to statins, measurement of CRP can be useful in the selection of patients for statin therapy.[114] (*Level of Evidence: B*)**

Class IIb

1. **In asymptomatic intermediate-risk men 50 years of age or younger or women 60 years of age or younger, measurement of CRP may be reasonable for cardiovascular risk assessment.[22,115] (*Level of Evidence: B*)**

Class III: No Benefit

1. **In asymptomatic high-risk adults, measurement of CRP is not recommended for cardiovascular risk assessment.[116] (*Level of Evidence: B*)**
2. **In low-risk men younger than 50 years of age or women 60 years of age or younger, measurement of CRP is not recommended for cardiovascular risk assessment.[22,115] (*Level of Evidence: B*)**

2.4.2.1. Association With Increased Cardiovascular Risk and Incremental Risk Prediction

Inflammation is considered to be central to the pathogenesis of atherosclerosis, and numerous inflammatory biomarkers have been evaluated as risk factors or risk markers for CVD. The most intensively studied inflammatory biomarker associated with CVD risk is high-sensitivity CRP (hsCRP). CRP is associated with an adjusted increased risk for development of other CVD risk factors, including incident diabetes, incident weight gain, and new-onset hypertension.[117–119] Interventions that improve CVD risk factors, such as exercise, weight loss, smoking cessation, statins, and antihypertensive treatments, are associated with lowering of CRP.[120–124] CRP concentrations are fairly constant and repeatable over time.[125,126] In the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study participants randomly assigned to placebo, intraclass correlation was 0.54 (95% CI 0.53 to 0.55), which was similar to blood pressure and LDL cholesterol.[127] Prior guidelines have recommended measuring CRP twice, particularly in persons with intercurrent illness if elevated when first measured.[128]

A meta-analysis of >20 observational studies (both prospective and case-control) demonstrated that CRP levels are associated with incident CHD, with an adjusted odds ratio (comparing persons in the top versus bottom third) of 1.45 (95% CI 1.25 to 1.68).[129] CRP levels have been associated with incident CHD in both men and women and persons of European, Japanese, and American Indian descents.[22,130–132] CRP is also associated with other forms of CVD, including incident stroke, PAD, heart failure, atrial fibrillation, sudden death, and all-cause mortality.[133–137] Despite consistent evidence that CRP levels above the population median value are associated with increased risk of CHD, it has not been determined whether CRP is causally related to CHD.[138–142]

CRP modestly improved risk prediction of CVD endpoints in some studies beyond that accounted for by standard CVD risk factor testing.[143] However, after accounting for standard CVD risk factors in many studies, model discrimination (area under the ROC) had no or minimal improvement.[144,145] As noted earlier in this guideline, statisticians recently proposed that measures of reclassification should be used to evaluate new biomarkers in addition to metrics of test discrimination, calibration, and other standard approaches to evaluate new markers. Data from the Physicians' Health Study and Framingham Heart Study have shown that CRP measurements improve reclassification of an individual's risk beyond standard risk prediction models.[115,145] However, a meta-analysis including data from the NPHS II and the Edinburgh Artery Study concluded that the ability of CRP to reclassify risk correctly was modest and inconsistent.[144] As with most new biomarker tests, whether knowledge of CRP levels improves patients' motivation to adhere to CHD lifestyle or pharmacological treatments is unknown.

Recent clinical trial data provided evidence that measurement of CRP in highly preselected patients may have important clinical implications. The JUPITER trial was a randomized, double-blind, placebo-controlled trial of the use of rosuvastatin (20 mg/d) versus placebo in the primary prevention of CVD events in men and women (n=17,802) without diabetes with LDL cholesterol <130 mg/dL and CRP ≥2 mg/L.[146,147] After a median follow-up of 1.9 years, rosuvastatin was associated with a significant reduction in the primary endpoint of cardiovascular events. The HR for rosuvastatin versus placebo was 0.56 (95% CI 0.46 to 0.69; $P<0.00001$), and the event rate was 0.77 versus 1.36 per 100 person-years of follow-up.[147] The reduction in endpoints was consistent across prespecified subgroups, including men and women, older and younger persons, whites and non-whites, and persons at higher and lower risk as measured by the FRS.[147] Within JUPITER, 17 men and 31 women would need to be treated for 5 years to prevent the endpoint of MI, stroke,

revascularization, or death.[148] For persons at low risk (FRS ≤10), 37 persons would need to be treated for 5 years to prevent the same previous endpoints.[148]

The JUPITER trial leaves a number of questions unanswered about use of CRP levels in cardiovascular risk assessment. Specifically, JUPITER was not a trial of CRP,[149] because persons with unknown or low CRP concentrations were not studied. Cost-effectiveness of CRP testing in an asymptomatic population, beyond the specific patient population of JUPITER, has not yet been studied.

2.4.3. Metabolic: Hemoglobin A1C

2.4.3.1. Recommendation for Measurement of Hemoglobin A1C

Class IIb

1. **Measurement of hemoglobin A1C (HbA1C) may be reasonable for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes.[150–155] (*Level of Evidence: B*)**

2.4.3.2. General Description

HbA1C is a blood test useful for providing an estimate of average glycemic control over several months. The test has been shown to be predictive of new-onset diabetes.[156] A systematic review and a recent international expert committee have suggested that HbA1C might be effective to screen for the presence of diabetes.[157,158] The ADA has endorsed the use of HbA1C to diagnose diabetes (HbA1C ≥6.5%) and to identify persons at increased risk for diabetes (HbA1C, 5.7% to 6.4%).[158]

2.4.3.3. Association With Cardiovascular Risk in Persons Without Diabetes

In 1 study, in individuals without established diabetes, for every 1 percentage point higher HbA1C concentration, there was an adjusted 40% higher risk of CHD ($P=0.002$).[150] HbA1C was associated with an increased risk of incident stroke in the Japanese.[159] Whether or not HbA1C improves CVD risk discrimination and reclassification is less certain. Some studies have reported that HbA1C does not improve prediction[156] or reclassification.[160] However, other studies have observed that in persons without diabetes, higher levels of HbA1C are associated with an increased risk of CVD.[161] In a 2010 report using data from the ARIC (Atherosclerosis Risk in Communities) study, it was demonstrated that in persons without diabetes, prediction models including HbA1C levels were associated with improved risk prediction, discrimination, and reclassification compared with prediction models that included standard risk factors and fasting glucose.[155] This study is the strongest evidence available concerning the potential value of HbA1C for CVD risk assessment in asymptomatic persons without diabetes. As with most other novel markers of CVD risk, it is unknown whether HbA1C is useful for motivating individuals to adhere to preventive interventions in the absence of diagnosed diabetes.

2.4.4. Urinary Albumin Excretion

2.4.4.1. Recommendations for Testing for Microalbuminuria

Class IIa

1. **In asymptomatic adults with hypertension or diabetes, urinalysis to detect microalbuminuria is reasonable for cardiovascular risk assessment.[162–164] (*Level of Evidence: B*)**

Class IIb

1. **In asymptomatic adults at intermediate risk without hypertension or diabetes, urinalysis to detect microalbuminuria might be reasonable for cardiovascular risk assessment.[165] (*Level of Evidence: B*)**

2.4.4.2. General Description

Urinalysis for microalbuminuria is widely available, inexpensive, and associated with cardiovascular events.[166] The ADA recommends annual urinalysis for detection of microalbuminuria in persons with diabetes mellitus.[167] A recent meta-analysis showed that increased risk of CVD associated with microalbuminuria was present in persons both with and without diabetes.[166] However, standardization of the measurement of urine albumin across laboratories is suboptimal.[168,169] It is logistically difficult for most patients to perform 24-hour urine collection, but studies have demonstrated that the first morning ("spot urine") urinary albumin–to-creatinine ratio has a similar ability to predict CVD events.[170] On the basis of the urinary albumin–to-creatinine ratio on a morning spot urine sample, microalbuminuria is defined as 30 to 300 mg/g and macroalbuminuria is defined as >300 mg/g.[171] Blacks and Mexican Americans have a higher prevalence of albuminuria than their Caucasian counterparts, regardless of diabetes status.[172] Longitudinal data from the NHANES, between 1988–1994 and 1999–2004, found that the prevalence of microalbuminuria had increased from about 7.1% to 8.2% ($P=0.01$).[173]

Excretion of urinary albumin in the microalbuminuria range is considered a candidate for CVD risk biomarker for several reasons. Standard CVD risk factors are associated with microalbuminuria.[174,175] Microalbuminuria is associated with incident hypertension, progression to a higher blood pressure category, and incident diabetes.[176,177] Microalbuminuria and diabetes each appear to influence the other's progression.[178] Furthermore, microalbuminuria has been associated with other novel risk factors for CVD, such as impaired endothelial function and inflammatory markers such as CRP.[179–181] Microalbuminuria is considered to be an indicator of vascular dysfunction and early CVD.[182]

2.4.4.3. Association With Cardiovascular Risk

A meta-analysis of 26 cohort studies with 169,949 participants reported that after accounting for standard CVD risk factors, there was a dose–response relationship between albuminuria and risk of CHD.[166] Compared with individuals without albuminuria, macroalbuminuria was associated with a doubling of risk (RR 2.17; 95% CI 1.87 to 2.52), and microalbuminuria was associated with a nearly 50% greater risk (RR 1.47; 95% CI 1.30 to 1.66) of CHD.[166] The increased risk of CVD was present

across many different subgroups, including persons with and without hypertension, with and without diabetes, and with and without decreased estimated glomerular filtration rate.[165,166,183] The prognostic importance of microalbuminuria also has been observed in older and younger individuals and ethnic minorities, including American Indians, South Asians, and African Carribbeans.[166,184–186]

In studies examining the incremental yield of adding urinary albumin excretion in the microalbuminuria range to standard CVD risk factors for CVD risk prediction, the Framingham Heart Study and the Cardiovascular Health Study observed only minor improvements in the C statistic.[175,187] However, the Cardiovascular Health Study observed that the urinary albumin–to-creatinine ratio did assist with risk reclassification. Persons at intermediate risk (predicted 5-year Framingham risk of 5% to 10%) with a urinary albumin–to-creatinine ratio ≥30 mg/g had a substantially higher 5-year risk of CHD than those with a ratio of <30 mg/g (20.1% versus 6.3%, respectively).[175]

2.4.4.4. Usefulness in Motivating Patients or Guiding Therapy

The writing committee is unaware of data that suggest that knowledge of albuminuria improves patient motivation or adherence to preventive therapies.

2.4.5. Lipoprotein-Associated Phospholipase A2

2.4.5.1. Recommendation for Lipoprotein-Associated Phospholipase A2

Class IIb

1. Lipoprotein-associated phospholipase A2 (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults.[188–191] (*Level of Evidence: B*)

2.4.5.2. General Description

Lp-PLA2, or platelet-activating factor acetylhydrolase, is a proatherogenic enzyme produced by macrophages and lymphocytes.[192] Lp-PLA2 hydrolyzes oxidized phospholipids in LDL, leading to the generation of lysophosphatidylcholine, oxidized nonesterified fatty acids, as well as other active phospholipids and inflammatory mediators.[192] Reported clinical correlates of increasing Lp-PLA2 mass and activity include advanced age, male sex, smoking, and LDL; Lp-PLA2 activity also was inversely associated with HDL.[193] There have been unexplained ethnic differences in Lp-PLA2 concentrations; adjusting for standard CVD risk factors, Lp-PLA2 activity was higher in white and Hispanic participants than in black participants.[194]

2.4.5.3. Association With Cardiovascular Risk

In a meta-analysis of 14 studies, Lp-PLA2 was associated with an adjusted OR for CVD of 1.60 (95% CI 1.36 to 1.89).[190] Although there was moderate heterogeneity across studies in the meta-analysis, there was no significant difference between Lp-PLA2 mass and activity for risk prediction.[190] A number of studies have reported that the increased CVD risk of Lp-PLA2 remains after adjusting for CRP, in addition to standard CVD risk factors.[188,189,191] Several studies have examined whether Lp-PLA2 improves risk discrimination over and above models accounting for standard risk factors. Both the ARIC study and Rancho Bernardo study investigators observed that Lp-PLA2 was associated with a statistically significant increment in the area under the curve (AUC) ($P<0.05$), although the increments were small (for the ARIC study, 0.774, increased to 0.780 with the addition of Lp-PLA2; for the Rancho Bernardo study, change in ROC was 0.595 to 0.617).[189,195] In a modest-sized study (n=765), Lp-PLA2 was associated with a nonsignificant 9.5% net reclassification.[196] These reports indicate that Lp-PLA2 has modest incremental risk prediction information, meaning its use in intermediate-risk patients might be reasonable. There is little information about the predictive capability of Lp-PLA2 in ethnic minorities, because the vast majority of studies reported to date have been conducted in whites of European ancestry.[190]

2.4.5.4. Usefulness in Motivating Patients or Guiding Therapy

Presently there is no information about whether Lp-PLA2 concentrations are clinically effective for motivating patients, guiding treatment, or improving outcomes. Randomized studies have demonstrated that lipid-lowering therapies reduce Lp-PLA2, although there may be some variability by medication type.[197,198] Drugs under development that specifically inhibit Lp-PLA2 activity have been shown to lower Lp-PLA2 activity and inflammatory markers.[199]

2.5. Cardiac and Vascular Tests for Risk Assessment in Asymptomatic Adults

2.5.1. Resting Electrocardiogram

2.5.1.1. Recommendations for Resting Electrocardiogram

Class IIa

1. A resting electrocardiogram (ECG) is reasonable for cardiovascular risk assessment in asymptomatic adults with hypertension or diabetes.[200,201] (*Level of Evidence: C*)

Class IIb

1. A resting ECG may be considered for cardiovascular risk assessment in asymptomatic adults without hypertension or diabetes.[202-204] (*Level of Evidence: C*)

2.5.1.2. General Description

Epidemiological studies have shown that abnormalities on a resting 12-lead ECG are predictive of subsequent mortality and cardiovascular events among asymptomatic adults.[200,202,205,206] Specific electrocardiographic findings that have been linked to cardiovascular risk in population-based cohorts and asymptomatic patients with hypertension include LVH (especially when accompanied by repolarization changes), QRS prolongation, ST-segment depression, T-wave inversion, and pathological Q waves.[202,207–211] Several studies suggest that subtle electrocardiographic abnormalities detect-

Table 4. Sample of Longitudinal Studies Reporting the Independent Predictive Value of Resting ECG Measures in Asymptomatic Populations

Primary Measurement(s)	First Author (Year, Country)	Type of Events	Follow-Up (y)	Population Characteristics (No.)	Mean Age (y) at Entry	Main Findings: Adjusted HR
Novacode major and minor abnormalities	Denes (2007, US)[216]	Composite of cardiovascular events	3	Women in the Women's Health Initiative trial (14,749)	64	For minor abnormalities, HR 1.6; for major abnormalities HR 3.0; C index increased by 0.05 compared with FRS
Pooling project, major and minor abnormalities*	DeBacquer (1998, Belgium)[205]	CHD and CVD mortality, all-cause mortality	10	Population-based sample (5,208 men, 4,746 women)	49 (men), 48 (women)	Major ECG abnormalities predicted all-cause mortality (HR 1.8), CVD mortality (HR 3.3), and CHD mortality (HR 2.3). Minor ECG abnormalities were not predictive.
LVH with ST-depression and negative T wave	Larsen (2002, Denmark)[210]	MI, incident CHD, CVD mortality	21	Population-based sample (5,243 men, 6,391 women)	53	Predictive of MI (HR 1.9), incident CHD (HR 2.2), and cardiovascular mortality (HR 1.9)
Unrecognized MI	Sigurdsson (1995, Iceland)[211]	Death from CHD, stroke, and all causes	10+	Icelandic Heart Association Preventive Clinic, all men (9,141)	52-58	Predictive of CHD death (HR 4.6) and all-cause death (HR 2.7)
Minor ST-T abnormalities	Daviglus (1999, US)[207]	All-cause, CHD, and CVD mortality	29	Men employed at an electric company (1,673)	48	Predictive of death due to CHD (HR 1.7), CVD (HR 1.4), and all causes (HR 1.3)
Digital ECG measures	Gorodeski (2009, US)[212]	All-cause mortality	11	Ambulatory patients without known CVD (18,964)	51	Combined ECG measures predictive of all-cause death (HR 1.4, comparing 75th to 25th percentiles; C index increased by 0.04 compared with standard predictors; relative IDI increased by 3%)

*Major abnormalities include ST-segment depression, T-wave inversion, complete or second-degree atrioventricular block, complete left or right bundle-branch block, frequent premature beats, and atrial fibrillation or flutter. Minor abnormalities include nonpathological Q wave, a left- or right-axis deviation, QRS high voltage, borderline ST-segment depression, T-wave flattening, and QRS low voltage.

CHD indicates coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; FRS, Framingham risk score; HR, hazard ratio; IDI, integrated discrimination improvement; LVH, left ventricular hypertrophy; MI, myocardial infarction; and US, United States.

able only by computer analysis may also be associated with increased risk.[212–214]

The 12-lead resting ECG may provide information about other CVD, particularly cardiac arrhythmias, by documenting extra systoles, atrial fibrillation, ventricular preexcitation, or prolonged QT interval. Many cardiomyopathies display nonspecific electrocardiographic changes. There has been interest in electrocardiographic abnormalities that may be predictive of sudden cardiac death in young, seemingly healthy athletes.[215] The usefulness of screening with ECGs for these disorders is beyond the scope of the current document.

2.5.1.3. Association With Increased Risk and Incremental Risk

Table 4 presents a sample of longitudinal studies that report independent predictive value of different resting electrocardiographic measures in asymptomatic populations. A number of classification schemes have been described that may be useful for risk stratification. An example is the Novacode criteria, which divide electrocardiographic abnormalities into major and minor types.[216] Major abnormalities include atrial fibrillation or atrial flutter, high-grade atrioventricular (AV) block, AV dissociation, complete bundle-branch block, pathological T waves, isolated ischemic abnormalities, LVH with accompanying repolarization abnormalities, and arrhythmias such as supraventricular tachycardia and ventricular tachycardia. Minor abnormalities include first- and second-degree AV block, borderline prolongation of the QRS interval, prolonged repolarization, isolated minor Q-wave and ST-T abnormalities, LVH by voltage only, left atrial enlargement, frequent atrial or ventricular premature beats, or fascicular blocks. Electrocardiographic findings have also been combined with echocardiography to improve risk stratification in patients with hypertension.[201]

Abnormal Q waves on the ECG may indicate clinically unrecognized or "silent" MI. In the Framingham Study, as many as one quarter of nonfatal MIs were found only through

ECG changes.[217] In a number of population studies, Q waves on the ECG indicate a higher cardiovascular risk.[202,211]

Electrocardiographic LVH and associated repolarization abnormalities have been predictive of subsequent cardiovascular risk in numerous prospective epidemiological studies, including the Framingham Study. LVH on a resting ECG may indicate more severe or poorly controlled hypertension, which in turn increases cardiovascular risk.[218] In 1 large randomized trial that specifically focused on patients with electrocardiographic LVH, regression of left ventricular mass as assessed by ECGs was a predictor of a lower risk of major cardiovascular events.[219]

Few studies have evaluated the ability of the resting ECG to improve discrimination and reclassify risk compared with standard risk assessment. In 14 749 asymptomatic, postmenopausal women enrolled in the Women's Health Initiative, the resting ECG increased the C statistic over the FRS from 0.69 to 0.74 for prediction of CHD events.[216] In 18 964 Cleveland Clinic patients without known CVD, the resting ECG similarly increased the C statistic by 0.04 and modestly improved reclassification (relative integrated discrimination improvement, 3%, $P<0.001$).[212]

2.5.1.4. Usefulness in Motivating Patients, Guiding Therapy, and Improving Outcomes

There have been no randomized trials demonstrating that findings on a resting ECG can be used to motivate better lifestyle behaviors in the asymptomatic adult. One large randomized trial offered suggestive evidence that electrocardiographic assessment of left ventricular mass may be useful for guiding antihypertensive therapy, because regression of electrocardiographic LVH was associated with reduced risk for sudden death,[220] atrial fibrillation,[219] heart failure,[221] major CVD events,[200] and diabetes.[222] However, no randomized trial has directly addressed this question.[223] One policy-based intervention study found that an ECG-based screening program for competitive athletes may have reduced the population risk of sudden cardiac death among young adults.[224]

2.5.2. Resting Echocardiography for Left Ventricular Structure and Function and Left Ventricular Hypertrophy: Transthoracic Echocardiography

2.5.2.1. Recommendations for Transthoracic Echocardiography

Class IIb

1. Echocardiography to detect LVH may be considered for cardiovascular risk assessment in asymptomatic adults with hypertension.[225,226] (*Level of Evidence: B*)

Class III: No Benefit

1. Echocardiography is not recommended for cardiovascular risk assessment of CHD in asymptomatic adults without hypertension. (*Level of Evidence: C*)

2.5.2.2. Left Ventricular Function

Transthoracic echocardiography is a diagnostic modality widely used in cardiology practice. There are no echocardiographic findings with high sensitivity and specificity for the diagnosis of CHD in the absence of ischemia or infarction. Segmental wall motion abnormalities are the most common echocardiographic manifestation of CHD but are only present if there is active or recent (stunning) ischemia or there has been prior infarction. Moreover, segmental wall motion abnormalities do not uniformly represent ischemic territories caused by occlusive CAD, because they may also be present in patients with nonischemic cardiomyopathies. Additional manifestations of CHD include ischemic mitral regurgitation, global reduction in left ventricular systolic function, Doppler findings characteristic of diastolic dysfunction, and right ventricular dysfunction. However, none of these findings has sufficient sensitivity or specificity to be useful for screening or risk assessment in the asymptomatic patient at possible risk for CHD. Given the lack of evidence of risk assessment benefit in the general population, it was the consensus of the writing committee that echocardiography should not be performed for risk assessment in the asymptomatic adult without hypertension.

2.5.2.3. Left Ventricular Hypertrophy

LVH develops in response to varying stimuli and may be physiological in the setting of athletic training and pregnancy or pathological in response to pressure or volume overload, myocardial injury, or underlying genetic mutations. The pathophysiological mechanism for higher cardiovascular mortality in the setting of LVH is not completely understood, although studies have demonstrated decreased flow reserve and greater susceptibility to injury associated with ischemia and infarction.[227] The methodology for LVH measurement by echocardiography and the cut points for definition of LVH vary widely among studies. There is also wide variability as to whether LVH is indexed to body surface area, height, or weight.[227,228] A recent meta-analysis of 34 studies showed that 19 different criteria were used, leading to differences in the prevalence of LVH.[229] The writing committee recommends the use of the methodology and cut points defined by the ASE.[230] Separate cut points should be applied to men and women. Further studies may suggest that the definition of pathological LVH should be specific to race as well as sex. A recent study showed that athletic hypertrophy in African/Afro-Caribbeans (blacks) was greater than in whites.[231]

LVH has been shown to be predictive of cardiovascular (including stroke) and all-cause mortality, independent of blood pressure, and across all racial groups that have been studied. In the predominantly white population of the Framingham Study, for every 50 g/m^2 higher left ventricular mass index, there was a RR of death of 1.73 (95% CI 1.19 to 2.52) independent of blood pressure level.[232] In the African-American population enrolled in the ARIC study, LVH conferred an increased risk for CVD events (nonfatal MI, cardiac death, coronary revascularization, and stroke) even after adjusting for other risk factors with a HR of 1.88 in men and 1.92 in women.[228] Among American Indians enrolled in the Strong Heart Study (64% female, mean age equal to 58), the prevalence of LVH on echocardiography was 9.5% and conferred a 7-fold increase in cardiovascular mortality and a 4-fold increase in all-cause mortality.[201] In

this study, echocardiographic evidence of LVH had additive discriminatory power over ECG evidence of LVH. Data from a Hispanic population[226] are similarly suggestive of the association of LVH and cardiovascular mortality. The association of LVH and mortality in many of these studies cannot be attributed only to the risk of developing atherosclerotic CHD, because patients with hypertrophic cardiomyopathy who die suddenly may be misclassified. Recent estimates suggest a 1 in 500 prevalence of hypertrophic cardiomyopathy in the population, which may contribute to the association between LVH and cardiovascular (including stroke) and all-cause mortality.

LVH is considered evidence of target organ damage in hypertension according to JNC 7.[233] The epidemiological association between pathological hypertrophy and CVD has also been studied in hypertensive populations.[201,226] For example, in the MAVI (Massa Ventricolare sinistra nell'Ipertensione) study of patients with uncomplicated essential hypertension, there was a 40% higher risk of cardiovascular events for each 39 g/m^2 greater left ventricular mass index.[225] Left ventricular architecture is also an important variable related to risk, with most studies suggesting that the presence of concentric rather than eccentric hypertrophy in the hypertensive population carries the highest risk.

2.5.2.4. Usefulness in Motivating Patients or Guiding Therapy

Although the finding of increased left ventricular mass on echocardiography could be envisioned to guide selection or intensity of therapy in hypertensive patients, JNC 7 recommendations do not risk stratify patients on the basis of target organ damage.[233] Given the adverse prognosis associated with LVH in hypertension, further studies examined the comparative efficacy of specific antihypertensive agents in regressing LVH as well as survival benefits associated with LVH regression, but there was a lack of consistency among the trials. In a meta-analysis of 39 trials of antihypertensive therapy, angiotensin-converting enzyme inhibitors were the most effective agents, leading to a 13.3% reduction in left ventricular mass compared with 9.3% for calcium channel blockers, 6.8% for diuretics, and 5.5% for beta blockers.[234] In a comparison of enalapril and long-acting nifedipine in patients with essential hypertension, the PRESERVE (Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement) trial, a prospective randomized enalapril study evaluating regression of ventricular enlargement, systolic and diastolic pressures as well as left ventricular mass were reduced to a similar degree with both agents.[235] The LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) trial echocardiographic substudy demonstrated superior left ventricular mass reduction (21.7 g/m^2) in patients treated with losartan compared with patients treated with atenolol (17.7 g/m^2).[218] Diuretics demonstrated superiority in treating LVH regression over alternative agents in both the TOMHS (Treatment of Mild Hypertension Study) and Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents, using chlorthalidone and hydrochlorthiazide, respectively.[236,237]

LVH regression does not adversely affect cardiac function and may be associated with improvements in diastolic function. Most importantly, patients who demonstrate LVH regression on antihypertensive therapy have a lower rate of cardiovascular events than those who do not, independent of the extent of blood pressure control.[238,239]

Despite these observations, there have been no trials that target antihypertensive therapy to regress echocardiographically detected LVH, and thus the results continue to generate hypotheses.

No studies have examined whether a patient's knowledge of echocardiographic results demonstrating LVH will improve adherence to lifestyle modifications or pharmacologic treatment of hypertension.

2.5.3. Carotid Intima-Media Thickness on Ultrasound

2.5.3.1. Recommendation for Measurement of Carotid Intima-Media Thickness

Class IIa

1. Measurement of carotid artery IMT is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk.[240,241] Published recommendations on required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results.[241] (*Level of Evidence: B*)

2.5.3.2. General Description

Carotid IMT testing is a noninvasive, nonionizing radiation test using ultrasound imaging of the carotid artery wall to define the combined thickness of the intimal and medial arterial wall components. It is most commonly measured in the far wall of the common carotid artery; however, it can also be measured in the near wall and other carotid segments (bulb, internal). With well-trained operators, the test has been shown to be highly accurate with excellent intertest and interobserver reproducibility primarily in research settings and less commonly in practitioner-based settings.[242] The available data on risk associated with carotid IMT are drawn almost exclusively from research settings using highly standardized protocols. The use of common carotid IMT as a standard site of measurement has been proposed due to its inherent greater reproducibility and ability to refine the cardiovascular risk prediction. Published recommendations on the required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results.[241,243] There is a need for provider competency and lab accreditation standards to ensure quality imaging. An elevated level of carotid IMT is commonly cited as a level that surpasses the population-based 75th percentile value, but this must be identified specific to a particular carotid arterial segment (eg, common or internal carotid artery) and ultrasound methodology for which tables are available.[241]

2.5.3.3. Independent Relationship Beyond Standard Risk Factors

Carotid IMT has been independently associated with future risk for ischemic coronary events and stroke in middle-aged

and older individuals.[244] The risk of incident CHD events increases in a continuous fashion as carotid IMT increases (RR increases approximately 15% per 0.10-mm increase in carotid IMT); thus, measurement of carotid IMT has been shown in research studies to be a marker of risk for atherosclerotic CVD. Furthermore, the finding of atherosclerotic plaque, operationally defined as a focal increase in thickness >50% of the surrounding IMT, increases the predicted CAD risk at any level of carotid IMT.[245] These values were determined after adjustment for traditional CVD risk factors.

The relationship between carotid IMT and incident CHD events was initially noted in the Kuopio Ischemic Heart Disease Risk Factor study, in which risk of future MI in Finnish men increased by 11% for every 0.1-mm increment in carotid IMT.[246] For carotid IMT values >1 mm, there was a 2-fold greater risk of acute MI over 3 years. The ARIC study showed that for every 0.19-mm increment in carotid IMT, risk of death or MI increased by 36% in middle-aged patients (45 to 65 years of age).[247] CHD risk was almost 2-fold greater in men with mean carotid IMT >1 mm and even greater in women (RR 5.0). Not all studies, however, have shown differences between men and women in the predictive value of carotid IMT. For example, the Rotterdam study found that the risk of CHD events and carotid IMT was similar among men and women.[248]

The association between carotid IMT and incidence of MI and stroke has been noted in older populations and other high-risk populations. In the Cardiovascular Health Study, the RR for MI, adjusted for age, gender, and standard cardiovascular risk factors, was 3.15 (95% CI 2.19 to 4.52) when an average IMT was used for the common carotid and internal carotid arteries and when comparing the highest quintile versus the lowest quintile. These differences held true for patients with and without known CVD.[249] Among middle-aged adults with diabetes mellitus in the ARIC study, an IMT ≥1 mm was associated with an increase in the ROC AUC from 0.711 to 0.724 among women and 0.680 to 0.698 in men[250] when this elevated IMT was included in traditional risk factor predictive models. Similarly, in the Cardiovascular Health Study, the incidence of CAD was shown to increase from 2.5% to 5.5% per year among patients with diabetes with subclinical vascular disease.[251]

Carotid IMT measurement can lead to improved cardiovascular risk prediction and reclassification. In the ARIC study, 13 145 individuals were followed for approximately 15 years for incident hard coronary events and revascularization. Carotid IMT measurements, which included both IMT and carotid plaque, were incremental to traditional risk factors for prediction of incident cardiovascular events. In particular, among intermediate-risk patients (10% to 20%, 10-year estimated risk group), the addition of carotid IMT and plaque information led to clinical net reclassification improvement of approximately 9.9%.[240]

Comparisons of carotid IMT with coronary calcium scoring as methods to modify cardiovascular risk assessment have been made in both middle-aged (MESA) and older individuals (Cardiovascular Health Study). Each study showed that carotid IMT was an independent predictor of cardiovascular outcomes. Coronary calcium was a relatively stronger predictor for coronary outcomes, whereas carotid IMT was a stronger predictor of stroke in MESA.[252] In contrast, significant and similar magnitude relationships to cardiovascular outcomes (HRs for fourth quartile versus first quartile for each test, approximately 2.1) were observed in the Cardiovascular Health Study for both tests.[253] Given the discrepancy between these available studies, the data are insufficient to conclude whether these tests are clinically equivalent or not. Thus, at this time, test selection in clinical practice is better guided by local and patient factors such as expertise, cost, and patient preference.

Epidemiological studies demonstrate that IMT typically progresses at an average rate of ≤0.03 mm per year, and the rate of progression appears to be related to risk of cardiovascular event.[254] Progression can be slowed by cholesterol-lowering drugs (statins and niacin) and other risk factor modifications (eg, control of blood pressure). However, serial scanning of carotid IMT is challenging in individual patients across brief time horizons due to variability in measurement in relation to the rate of disease progression and is therefore not recommended in clinical settings.

Images of subclinical atherosclerosis are hypothesized to alter patient behavior, but the evidence is insufficient.[255]

2.5.3.4. Usefulness in Motivating Patients or Guiding Therapy

The finding of increased carotid IMT should clinically guide selection or intensity of therapy. However, evidence is lacking regarding whether measurement of carotid IMT alters outcome (Table 5). Clinical tools integrating carotid IMT within global risk scoring systems are not available.

2.5.3.5. Evidence for Improved Net Health Outcomes

The incremental value of carotid IMT and cost-effectiveness beyond that available from standard risk assessments to improve overall patient outcomes is not established.

2.5.4. Brachial/Peripheral Flow-Mediated Dilation

2.5.4.1. Recommendation for Brachial/Peripheral Flow-Mediated Dilation

Class III: No Benefit

1. Peripheral arterial flow-mediated dilation (FMD) studies are not recommended for cardiovascular risk assessment in asymptomatic adults.[256,257] (*Level of Evidence: B*)

2.5.4.2. General Description

Peripheral arterial FMD is a noninvasive measure of endothelial function. Augmented flow is produced by a sustained period (typically 4 to 5 min) of forearm compression accompanied by vascular occlusion followed by release. In the setting of healthy endothelium, increased flow stimulates release of nitric oxide, inducing local brachial artery vasodilation. The degree of dilation can be measured using high-resolution ultrasound. The technique requires a highly skilled sonographer, highly standardized measurement conditions (including time of day, temperature, drug administration), and suitable ultrasound machine. Many examiners also use specialized computer software to semiautomatically quantitate

Table 5. Summary of Prospective Studies Evaluating Carotid IMT and Incident Coronary Events in Patients Without Known CHD

	Patient Details						
Study, Participants	Carotid IMT Measurement	Clinical Events	Follow-Up (y)	Age (y)	Sex	Carotid IMT Increment (mm)	OR (95% CI)
KIHD, 905[112]	CCA/carotid bifurcation*	Fatal/nonfatal MI	1 mo to 3 y	42 to 60	Men	0.1	1.11 (1.06 to 1.16)
ARIC, 12 841[247]	CCA/ICA/carotid bifurcation†	Fatal/nonfatal MI	2 to 7	45 to 64	Men Women	0.19 0.19	1.36 (1.23 to 1.51) 1.69 (1.50 to 1.90)
CHS, 4476[249]	CCA/ICA‡	MI/stroke	6.2	>65	Men and women	0.20	1.46 (1.33 to 1.60)§‖
Rotterdam Study, 7983[248]	CCA¶	MI/stroke	2.7	>55	Men Women	0.163 0.163	1.56 (1.12 to 2.18)# 1.44 (1.00 to 2.08)#
MESA, 6698[252]	CCA	Cardiovascular events	3.9	45 to 64	Men and women	0.19	1.30 (1.10 to 1.40)

*Mean carotid IMT.
†Mean far wall, internal carotids, and bifurcation.
‡Mean of CCA and ICA.
§OR is risk for MI and coronary death only; OR for MI and stroke was 1.47 (95% CI 1.37 to 1.67).
‖CCA, carotid IMT.
¶Mean CCA.
#OR is for risk of MI only.
ARIC indicates Atherosclerosis Risk in Communities study; CCA, common carotid artery; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CI, confidence interval; ICA, internal carotid artery; IMT, intima-media thickness; KIHD, Kuopio Ischemic Heart Disease study; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and OR, odds ratio.

the brachial artery diameter. Considerable variability exists for values of FMD determined by different investigators, even in similar patient populations, suggesting technical challenges with the measurement.[258] Important technical factors influencing FMD are duration of forearm occlusion and the location of the occluding cuff, but many other factors are also important, as mentioned above. In research settings, brachial artery FMD has been shown to correlate with invasive measures of coronary artery FMD after adenosine triphosphate infusion, suggesting that peripheral FMD may be a suitable substitute for invasive coronary endothelial function testing.[257] FMD also correlates with other noninvasive measures of cardiovascular risk, including CRP, carotid IMT, and measures of arterial stiffness.

PAT is a second method of assessing postocclusion vasodilation. This method uses bilateral finger cuffs that sense pulse wave volume. After a 5-minute flow occlusion in 1 arm, the resulting augmentation of pulse volume in the occlusion arm is compared with the control arm, yielding a PAT ratio. The PAT ratio provides information similar to FMD.[256,259]

2.5.4.3. Association With Increased Risk and Incremental Prediction

Many studies have documented a relationship between FMD, PAT, and traditional CVD risk factors. FMD and PAT ratios are lower (abnormal) in subjects with greater numbers of risk factors or higher levels of FRS. Diabetes and smoking have the most powerful associations with abnormal FMD. A meta-regression analysis of 211 publications reported on 399 populations where both FMD and traditional risk factors were available.[260] By design, many of these populations had existing CVD. The relationship between FMD and risk factors was most clear in the category with the lowest baseline risk. In this group, for each percentage point higher FRS, FMD was lower by 1.42%. In populations with an intermediate or high FRS, FMD was not related to the score. This finding fits with the hypothesis that FMD is an early marker of vascular dysfunction. Once multiple risk factors are present, FMD may become so impaired that additional risk factors do not further impair it.

PAT ratio was measured in the Framingham Third Generation Cohort (n=1957).[261] In a stepwise multivariable regression model, PAT ratio was inversely related to male sex, body mass index, total/HDL-cholesterol ratio, diabetes, smoking, and lipid-lowering treatment. In this study, hypertension was not related to PAT.

It is unclear whether these measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors. The relationship between FMD and incident cardiovascular events was reported in a population-based cohort of older adults.[262] In the Cardiovascular Health Study, 2792 (2791 with complete data) adults aged 72 to 98 years underwent FMD measures.[262] During 5-year follow-up, 24.1% of these subjects had events. At study entry, 76% of this population (n=2125) was free of known CVD. In the subset without known CVD at entry, the predictive value of FMD (after adjustment for age, gender, diabetes, blood pressure, cholesterol, and HMG-CoA [3-hydroxy-3-methylglutaryl-coenzyme A] reductase inhibitor use) was directionally similar to the whole population but failed to achieve statistical significance ($P=0.08$). The addition of brachial FMD to the predictive model containing the classical cardiovascular risk factors increased the AUC by a net change of only 0.001, and the *P* value for the increase was not significant (area under receiver operating statistic 0.841 versus 0.842). NOMAS (Northern Manhattan Study), a

smaller multiethnic, prospective cohort study of 842 subjects free of CVD examined the relationship of FMD to 36-month cardiovascular events.[263] Although FMD was associated with the occurrence of future events (HR 1.12 for every 1% decrease in FMD), the association was no longer statistically significant when traditional cardiovascular risk factors were included in a multivariable analysis. In contrast, a study of 2264 asymptomatic postmenopausal women found that FMD was independently related to cardiovascular events (RR 1.12; 95% CI 1.04 to 2.00; $P<0.001$) when included in a model with traditional risk factors.[264] No measures of reclassification were reported in this study.

2.5.4.4. Usefulness in Motivating Patients or Guiding Therapy

There is no evidence that arterial FMD studies are useful for motivating asymptomatic persons to adhere to preventive therapies.

In a study of 400 hypertensive postmenopausal women followed up for an average of 67 months,[265] endothelial function was measured as FMD of the brachial artery at baseline and at 6 months after initiation of blood pressure control. After 6 months of treatment, FMD had not changed (≤10% relative to baseline) in 150 (37.5%) of the 400 women, whereas it had significantly improved (>10% relative to baseline) in the remaining 250 women (62.5%). During follow-up, failure to have an improved FMD at 6 months was an independent predictor of nonfatal cardiovascular events requiring hospitalization. This study demonstrates that a significant improvement in endothelial function may be obtained after 6 months of antihypertensive therapy and also appears to identify patients who may have a more favorable prognosis.

Due to the limited data available, the writing committee concluded that it was premature to recommend serial FMD measurements to monitor treatment effects. In addition, due to the technical challenges of standardizing measurement of FMD and the relatively modest evidence of incremental change in risk assessment, measurement for risk assessment was not regarded as appropriate for risk assessment in the asymptomatic adult.

2.5.4.5. Changes in Patient Outcomes

To date, there are no published trials evaluating the impact of specific therapy on clinical outcome in patients identified as having abnormal peripheral endothelial function.

2.5.5. Pulse Wave Velocity and Other Arterial Abnormalities: Measures of Arterial Stiffness

2.5.5.1. Recommendation for Specific Measures of Arterial Stiffness

Class III: No Benefit

1. **Measures of arterial stiffness outside of research settings are not recommended for cardiovascular risk assessment in asymptomatic adults. (*Level of Evidence: C*)**

2.5.5.2. Description of Specific Measures of Arterial Stiffness

Arterial stiffness is a consequence of arteriosclerosis, the process of arterial wall thickening, and loss of elasticity that occurs with onset of vascular disease and advancing age. Besides pulse pressure (the numeric difference between the systolic and diastolic blood pressures), multiple other specific measures of arterial stiffness have been described.[98,266,267] The most commonly studied measures of arterial stiffness are aortic pulse wave velocity (PWV) and pulse wave analyses such as the aortic augmentation index.[266]

Because blood is a noncompressible fluid, transmission of the arterial pressure wave occurs along the arterial wall and is influenced by the biomechanical properties of the arterial wall. When the arteries are stiffened, the pulse wave is propagated at an increased velocity, and increased PWV is therefore correlated with stiffness of the arteries. Factors associated with PWV include advancing age as well as the long-term effects of cardiovascular risk factors on the structure and function of the arterial wall. PWV is generally measured using applanation tonometry but can also be measured by Doppler ultrasound or magnetic resonance imaging (MRI). MRI is more costly and therefore is typically not used for testing in asymptomatic persons.

Pulse wave analysis is based on the concept that the pressure wave is partially reflected back toward the aorta at various points of discontinuity in arterial elasticity. Applanation tonometry is considered a relatively simple and reproducible method of collecting data for pulse wave analysis in research settings. The most commonly reported measure in pulse wave analysis is expressed as a fraction of the central pulse pressure, called the aortic augmentation index. The augmentation index is said to be most useful in patients under the age of 60 years.[266] Both pulse wave analysis and PWV are typically determined by commercial devices that perform the analyses based on proprietary analytic algorithms.[267]

Although predictive information (see below and Table 6) suggests a potential clinical role for measures of arterial stiffness, there are a number of technical problems that the writing committee believed would restrict the applicability of measures of arterial stiffness predominantly to research settings at this time.[266,267] For measures of arterial stiffness to be incorporated into clinical practice, measurement protocols must be well standardized, quality control procedures established, and risk-defining thresholds identified.[266] Reproducibility is a problem, as is operator dependence, both of which limit the generalizability of findings derived from research studies. Additional technical concerns include the need to standardize room temperature, time of day of testing, keeping the patient at rest for at least 10 minutes before measurements are recorded, and careful attention to timing of drug and caffeine intake.[267] The writing committee felt that the technical concerns make arterial stiffness tests less suitable for addition to the clinical practice of risk assessment in asymptomatic adults due to problems with measurement and data collection.

2.5.5.3. Evidence on the Association With Increased Cardiovascular Risk and Incremental Risk

From the standpoint of predictive studies within general "healthy" populations, measures that have been studied are the PWV, ambulatory arterial stiffness index, and carotid pulse pressure (versus brachial pulse pressure). Predictive

Table 6. Longitudinal Studies Reporting the Independent Predictive Value of Arterial Stiffness in Asymptomatic Populations

Primary Measurement Type	First Author (Year, Country)	Type of Events	Follow-Up (y)	Population Characteristics (No.)	Mean Age (y) at Entry	Main Findings: Adjusted HR
Aortic PWV	Meaume (2001, France)[268]	CV mortality	2.5	Elderly men and women (age >70 y) (141)	87	1.19 (95% CI 1.03 to 1.37) for total CVD mortality (top decile)
ΔD (strain) as primary measure	Stork (2004, the Netherlands)[269]	CV and all-cause mortality	4.0	Elderly men[367]	78	No stiffness measure associated with outcomes
Aortic PWV	Sutton-Tyrrell (2005, US)[270]	CV mortality and events	4.6	Elderly, both sexes [2,488] in Health ABC study	55	~RR 1.15 to 1.30; P=0.019 for Q4:Q1 for CHD; ~RR 2.6; P=0.004 for stroke Q4:Q1
Aortic PWV	Shokawa (2005, Japan)[271]	CVD mortality	10	General population, both sexes (492)	63.7	Top 40%: ~4.2 (95% CI 1.39 to 12.96; P=0.01)
Ambulatory arterial stiffness index	Dolan (2006, Ireland)[272]	CVD mortality	5.3	General population, both sexes, ages 16 to 96 y [11,291]	54.6	1.16 (95% CI 1.05 to 1.27) in fully adjusted model for total CVD death
Aortic PWV	Willum-Hansen (2006, Denmark)[273]	Fatal and nonfatal CVD and CHD	9.4	General population (1678), both sexes, ages 40 to 70 y	51	~HR 1.15 (95% CI 1.01 to 1.30) per 1 SD increase for all endpoints
Ambulatory arterial stiffness index	Hansen (2006, Denmark)[274]	Fatal and nonfatal CVD and stroke	9.4	General population (1678), both sexes, ages 40 to 70 y	51	~HR 1.6 (95% CI 1.14 to 2.28; P=0.007) for stroke, but NS for CHD and CVD
Carotid-femoral PWV index	Mattace-Raso (2006, the Netherlands)[275]	CVD, CHD, stroke, all-cause	4.1	Healthy elderly, both sexes (2835); Rotterdam study	71.7	~1.9 to 2.0 for T3:1 for CVD, CHD, stroke
CPP versus BPP	Roman (2007, US)[276]	CVD, fatal and nonfatal	4.8	Healthy American Indians, both sexes,[2,403] Strong Heart Study	63	Aortic PP, ~1.12 per 10 mm Hg, P=0.008
CD, CPP, BPP	Leone (2008, France)[277]	CHD, fatal and nonfatal	4	Community elderly (age >65 y),[3,337] Three-City study	73.2	CD, ~2.0 (95% CI 1.27 to 3.17) for T3:T1; CPP, ~2.1 (95% CI 1.24 to 3.70) for T3:T1; BPP, ~2.1 (95% CI 1.38 to 3.40) for T3:T1
CPP and BPP	Pini (2008, Italy)[278]	Total CV events (fatal and nonfatal)	8	Community elderly (age >65 y)[173]	73	BPP, NS; CPP HR 1.23 (95% CI 1.11 to 1.38; P<0.001) per 10 mm Hg

BPP indicates brachial pulse pressure; CD, carotid distension; CHD, coronary heart disease; CI, confidence interval; CPP, carotid pulse pressure; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; NS, nonsignificant; PP, pulse pressure; PWV, pulse wave velocity; Q, quartile; RR, relative risk; SD, standard deviation; T, tertile; and US, United States.

results in general populations are summarized for 11 longitudinal studies in Table 6. Although a few of these studies have reported no predictive capability of these measures of arterial stiffness, most studies indicated predictive capability that is additive to standard risk factors, including (in some cases) systolic and diastolic blood pressures as well as ankle-brachial index (ABI). In some studies, but not all, HRs have been higher for stroke risk than for CAD risk. No studies have directly compared these measures of CVD risk with other measures of "subclinical" CVD such as arterial IMT or CAC score. HRs have generally been in the very modest predictive range of 1.1 to 1.3 for various measures of arterial stiffness and CHD outcomes. Information on changes in the C statistic or other measures of incremental risk stratification has generally not been reported.

2.5.5.4. Usefulness in Motivating Patients or Guiding Therapy

No information has been reported on any of these topics in well-conducted studies of populations of healthy adults.

2.5.6. Recommendation for Measurement of Ankle-Brachial Index

Class IIa

1. Measurement of ABI is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk.[279] (*Level of Evidence: B*)

2.5.6.1. General Description

The ABI is an office-based test to check for the presence of PAD. It is performed by Doppler measurement of blood pressure in all 4 extremities at the brachial, posterior tibial,

and dorsalis pedis arteries. The highest lower-extremity blood pressure is divided by the highest of the upper-extremity blood pressures, with a value of <0.9 indicating the presence of PAD, which is defined as >50% stenosis. When defined in this way, the ABI has both a high sensitivity and specificity for anatomic stenosis. In addition to signifying PAD, an abnormally low ABI has also been shown to be a predictor of cardiovascular events. Intermediate values (0.9 to 1.1) also have a graded association with CVD risk. A high ABI (>1.3), which indicates calcified, noncompressible arteries, is also a marker of arterial disease. The prevalence of PAD as indicated by an abnormal ABI increases with age and is associated with traditional risk factors for CVD.[280,281]

2.5.6.2. Association With Increased Risk

Many epidemiological studies have demonstrated that an abnormal ABI in otherwise asymptomatic individuals is associated with cardiovascular events.[279,282–293] A recent collaborative study combined data from 16 studies[279] and included a total of 24 955 men and 23 399 women without a history of CHD. Importantly the study included data from a wide representation of the population, including blacks, American Indians, persons of Asian descent, and Hispanics as well as whites.[288,293–295] The mean age in the studies ranged from 47 to 78 years, and the FRS-predicted rate of CHD ranged from 11% to 32% in men and from 7% to 15% in women. There were 9924 deaths (25% due to CHD or stroke) over 480 325 patient-years of follow-up. For an ABI of <0.9 compared with an ABI of 1.11 to 1.4, the HR for cardiovascular mortality and major events was 3.33 for men and 2.71 for women.[279] When adjusted for the FRS, the HRs were only moderately lower (2.34 in men and 2.35 in women), demonstrating the additive predictive value of the ABI beyond the FRS.[279] An ABI of >1.4 was also associated with higher risk within most of the FRS categories. However, the greatest incremental benefit of ABI for predicting risk in men was in those with a high FRS (>20%), in whom a normal ABI reduced risk to intermediate.[279] In women the greatest benefit was in those with a low FRS (<10%), in whom an abnormally low or high ABI would reclassify them as high risk, and in those with an intermediate FRS, who would be reclassified as high risk with a low ABI. Reclassification occurred in 19% of men and 36% of women. Thus, an abnormally low or abnormally high ABI is associated with increased cardiovascular risk in both men and women, and the risk prediction extends beyond that of the FRS alone.

2.5.6.3. Usefulness in Motivating Patients or Guiding Therapy

There are no randomized clinical trials that demonstrate measurement of ABI is effective in motivating asymptomatic patients to comply with measures to reduce cardiovascular risk. There is also no indication that serial measurement of the ABI can be used to monitor treatment or guide treatment approaches.

2.5.7. Recommendation for Exercise Electrocardiography

Class IIb

1. An exercise ECG may be considered for cardiovascular risk assessment in intermediate-risk asymptomatic adults (including sedentary adults considering starting a vigorous exercise program), particularly when attention is paid to non-ECG markers such as exercise capacity.[296–298] (*Level of Evidence: B*)

Patients who are capable of exercising on a bicycle or treadmill with a normal resting 12-lead ECG are connected to a modified-torso 12-lead ECG and asked to exercise at increasing levels of stress until exhaustion or other milestones are met, such as a target heart rate or worrisome clinical findings (eg, severe chest discomfort). Treadmill testing is more commonly performed in the United States; a variety of protocols are used during which both speed and grade are gradually increased in stages. Ideal exercise times are about 8 to 12 minutes. Although the best known measurement is change in ST-segment deviation during and after exercise, other important prognostic measures are exercise capacity, chronotropic response, heart rate recovery, and exercise-induced arrhythmias.[299]

2.5.7.1. Association With Increased Risk and Incremental Risk

Several specific findings on exercise testing are associated with subsequent mortality and cardiovascular events (Table 7).[299] An AHA scientific statement has described in detail exercise test risk predictors in asymptomatic adults.[299] Although many clinicians typically think of the exercise test as primarily a measure of ST-segment changes that may reflect ischemia, evidence has demonstrated that the ST segment is a weak marker for prevalent and incident CAD.[300,301] In contrast, non-ECG measures have emerged as stronger predictors of risk. Probably the most powerful risk marker obtained during routine exercise testing is exercise capacity; numerous investigators have consistently found that depressed exercise capacity is associated with increased cardiovascular risk.[296,298,299,302–305] In a very large primary care population, adding exercise variables to clinical variables increased the C index from 0.75 to 0.83 for prediction of all-cause mortality.[306] Among healthy executives, adding exercise variables to clinical variables increased the C index from 0.73 to 0.76.[307]

Markers reflective of autonomic nervous system function can predict major cardiovascular events, total mortality, and sudden cardiac death.[297,308–313] Failure of the heart rate to rise appropriately during exercise has been termed chronotropic incompetence and has been linked to adverse outcome whether or not beta blockers are being taken.[299,314,315] The fall in heart rate immediately after exercise, also known as heart rate recovery, is thought to reflect parasympathetic tone.[316] Decreased heart rate recovery has been associated with death or cardiac events in a number of populations, including those that are entirely or primarily asymptomatic.[307,309,310,313,317–319] Frequent ventricular ectopy during recovery, similarly thought to reflect abnormalities of parasympathetic nervous system function, are also independently associated with long-term risk of mortality.[309] The adjusted HR is 1.5 (95% CI 1.1 to 1.9; $P=0.003$).[309]

To synthesize the clinical importance of these measures, a number of exercise test scoring schemes have been developed and validated. Probably the best-known is the Duke Treadmill

Table 7. Sample of Longitudinal Studies Reporting the Independent Predictive Value of Exercise Electrocardiography Measures in Asymptomatic Populations

Primary Measurement(s)	First Author (Year, Country)	Type of Events	Follow-Up (y)	Population Characteristics (No.)	Mean Age (y) at Entry	Main Findings: Adjusted HR
Exercise capacity	Gulati (2003, US)[296]	All-cause death	8.4	Women with mean FRS of 6 (5721)	52	Compared with >8 METs, HR 1.9 (95% CI 1.3 to 2.9) for 5 to 8 METs and 3.1 (95% CI 2.0 to 4.7) for <5 METs
Exercise capacity	Wei (1999, US)[298]	CVD death and all-cause death	10	Men in preventive medicine clinic[25,714]	44	For CVD death, HR 3.1 (95% CI 2.5 to 3.8); for all-cause death, HR 2.2 (95% CI 1.4 to 3.8); all in normal weight; similar in overweight and obese men
Exercise capacity and heart rate recovery	Adabag (2008, US)[297]	Sudden death, CHD death, nonfatal CHD, all-cause death	7	Men in MRFIT Study (12 555)	46	For all-cause death, HR 0.85 (95% CI 0.7 to 0.9) for >8 min of Bruce protocol compared with <6 min HR 0.90 (95% CI 0.82 to 0.99) for heart rate recovery >65 bpm 3 min after exercise compared with <50 bpm
Chronotropic response and heart rate recovery	Jouven (2005, France)[310]	Sudden death	23	Men in Paris civil service (5713)	47	For chronotropic response <89 bpm; HR 6.18 (95% CI 2.30 to 16.11; $P<0.001$); for heart rate recovery <25 bpm; HR 2.2 (95% CI 1.02 to 4.74; $P<0.04$)
Exercise capacity, heart rate recovery, and ST-segment changes	Mora (2003, US)[318]	CVD death and all-cause death	20	Women in LRC prevalence study (2994)	46	For CVD death, exercise capacity below median HR 2.0 (95% CI 1.29 to 3.25); heart rate recovery below median HR 2.9 (95% CI 1.85 to 4.39); ST-segment depression >1 mm, HR 1.0 (95% CI 0.59 to 1.80); similar for all-cause death
Exercise capacity, heart rate recovery, and ST-segment changes	Aktas (2004, US)[307]	All-cause death	8	Men in preventive medicine clinic (3554)	57	For impaired exercise capacity, HR 3.0 (95% CI 1.98 to 4.39; $P<0.001$); for abnormal HR recovery <12 bpm 1 min postexercise; HR 1.6 (95% CI 1.04 to 2.41; $P=0.03$); not significant for ST-segment depression
Exercise capacity	Kodama (2009, International)[305]	All-cause death and CHD/CVD events	1.1 to 26	Healthy men and women in meta-analysis (102 980)	37 to 57	For all-cause mortality, 1-MET increase; HR 0.87 (95% CI 0.84 to 0.90); for CHD/CVD

bpm indicates beats per minute; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; FRS, Framingham Risk Score; HR, hazard ratio; LRC, Lipid Research Clinics; MET, metabolic equivalent; MRFIT, Multiple Risk Factor Intervention Trial; and US, United States.

Score (DTS), which incorporates exercise capacity, ST-segment changes, and exercise-induced angina.[313,320,321] The formula for the DTS is

$$\text{exercise time} - (4 \times \text{angina index}) - (5 \times \text{maximal ST-segment depression}).$$

The DTS has been validated in a number of populations as predictive of risk. Of note however, the only element of the DTS that has been consistently associated with increased risk has been exercise capacity.[301,313] In both younger and older adults, ST-segment changes and exercise-induced angina have not consistently appeared as risk predictors.[301,313]

The DTS has been criticized for its failure to take into account demographics and simple risk factors. A nomogram based on simple demographics, easily obtained risk factors, and standard exercise test findings was found to better discriminate risk than the DTS (C index, 0.83 versus 0.73; $P<0.001$); the nomogram was also successfully validated in an external cohort.[306]

2.5.7.2. Usefulness in Motivating Patients or Guiding Therapy

No randomized trials have specifically addressed the role of exercise testing in these 3 areas. There is also no direct information on the role of the exercise test to monitor treatment effects in asymptomatic adults.

2.5.8. Recommendation for Stress Echocardiography

Class III: No Benefit

1. **Stress echocardiography is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults. (Exercise or pharmacologic stress echocardiography is primarily used for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known coronary artery disease or the assessment of patients with known or suspected valvular heart disease.) (*Level of Evidence: C*)**

2.5.8.1. General Description

Stress echocardiography can be performed with dynamic forms of exercise, including treadmill and bicycle, as well as with pharmacologic stress, most often using dobutamine. The manifestations of ischemia on echocardiography include segmental and global left ventricular dysfunction. The use of echocardiography during treadmill testing is indicated for those patients with an abnormal resting ECG, including findings of left bundle-branch block, electronically paced rhythm, and LVH, as well as for patients taking digoxin. The diagnostic performance of the test is highly dependent on the availability of skilled acquisition and interpretation of the images and should be performed according to best practices.[322] MPI with echocardiographic contrast agents has not been widely used, and there are no currently approved agents available in the United States, so this technique is not addressed here.

The current guideline focuses on the use of tests and procedures that may be employed for assessment of cardiovascular risk in the asymptomatic adult. In several sections of this document the writing committee has also assessed the evidence for applying conventional diagnostic testing with or without imaging. It is important to realize the vast difference in concepts between use of a diagnostic test, usually in the symptomatic patient, to define a patient's likelihood of obstructive CAD compared with stratification of risk in an asymptomatic patient to serve as a basis for cardiovascular preventive strategies. Stress echocardiography is a test predominantly used in symptomatic patients to assist in the diagnosis of obstructive CAD. There is very little information in the literature on the use of stress echocardiography in asymptomatic individuals for the purposes of cardiovascular risk assessment. Accordingly, the Class III (LOE: C) recommendation for stress echocardiography reflects a lack of population evidence of this test for risk assessment purposes. This contraindication to testing must be placed within the concept of accepted indications for testing asymptomatic patients for diagnosis of CAD, such as for asymptomatic individuals undergoing preoperative risk assessment,[323] patients with new-onset atrial fibrillation, or a clinical work-up after episodes of ventricular tachycardia or syncope. In contrast, the current guideline focuses on risk assessment in the asymptomatic adult, which must not be confused with evaluation of the patient without chest pain with ischemic equivalents such as dyspnea, where in some cases, stress testing may be considered appropriate. The focus of these latter evaluations is to assess a patient's ischemic burden and the ensuing likelihood of obstructive CAD. There are clinical practice guidelines and appropriate use criteria that focus on the quality of evidence for assessment of asymptomatic patients or those with ischemic equivalents and clinical indications for the use of stress echocardiography. The current guideline is not applicable in this setting of diagnosis of CAD.

2.5.8.2. Association With Increased Risk

In a cohort of 1832 asymptomatic adults with no history of CHD (mean age, 51 years; 51% male), the predictive value of exercise echocardiography was examined at a mean of almost 5 years of follow-up.[324] The incidence of significant ST-segment depression was 12%, and the incidence of inducible wall motion abnormalities was 8%. The presence of inducible wall motion abnormalities was not an independent predictor of cardiac events in the entire population or those with $\geq$2 risk factors.[324] There are additional clinical studies in patients with type 2 diabetes mellitus. One small series compared screening with combined exercise electrocardiography and dobutamine stress echocardiography to a no-screening strategy in 141 patients with type 2 diabetes. The series found that the screening strategy was associated with reduced cardiac events when those with inducible wall motion abnormalities (21%) underwent revascularization.[325]

No information is currently available to assess the role of exercise echocardiography in addition to conventional risk factors for risk assessment in asymptomatic adults. Because of the lack of information on the role of risk assessment in the asymptomatic adult, the writing committee thought that there was no basis to recommend stress echocardiography for routine risk assessment in this type of patient.

2.5.8.3. Usefulness in Motivating Patients or Guiding Therapy

There have been no randomized trials on exercise echocardiography to suggest that it can be used to motivate lifestyle behavior changes in asymptomatic adults. One small pilot trial in patients with type 2 diabetes is cited above.[325] No other trials have investigated the use of echocardiography to guide therapy in asymptomatic adults. Thus, there is no clear indication that an exercise echocardiogram can be used to motivate asymptomatic adults or guide their therapy.

2.5.9. Myocardial Perfusion Imaging

2.5.9.1. Recommendations for Myocardial Perfusion Imaging

Class IIb

1. **Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CHD or when previous risk assessment testing suggests high risk of CHD, such as a CAC score of 400 or greater. (*Level of Evidence: C*)**

Class III: No Benefit

1. **Stress MPI is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic**

adults. (Exercise or pharmacologic stress MPI is primarily used and studied for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known CAD.).[326] (*Level of Evidence: C*)

2.5.9.2. Description of Myocardial Perfusion Imaging

Exercise or pharmacologic stress MPI using single-photon emission computed tomography (SPECT) or positron emission tomography (PET) is predominantly considered appropriate for the clinical evaluation of symptoms suggestive of myocardial ischemia or for determination of prognosis in patients with suspected or previously known CAD. As noted in the stress echocardiography section, it is important to recognize the distinction between the use of a diagnostic test to define the likelihood of obstructive CAD in a symptomatic patient and the possible role of a diagnostic test in risk assessment of an asymptomatic individual, for whom the results of testing would be used in decision making about strategies for prevention of CVD. This guideline is not intended to address the evaluation of patients presenting with possible cardiovascular symptoms or signs such as dyspnea, syncope, or arrhythmia, nor does this guideline address the preoperative assessment of a high-risk patient. These patient evaluations are the topics of other guidelines, and the reader is referred to other guidelines when confronted with such symptomatic patients.

Stress myocardial perfusion SPECT and PET involve exposure to ionizing radiation. The effective radiation dose for SPECT and PET considerably exceeds that of a CAC score (median effective dose: 2.3 millisievert [mSv]), and therefore the use of these modalities should be limited to patients in whom clinical benefit exceeds the risk of radiation exposure, for example, higher-risk or older patients. Use of these procedures must be performed with the guiding principle of applying effective doses that are "as low as reasonably achievable" (ie, ALARA). The estimated effective dose for stress myocardial perfusion SPECT is ~14.6 mSv, whereas that of Rb82 PET is ~5 mSv.[327] For all patients, dose-reduction strategies should be used whenever possible (eg, stress-only imaging), and these approaches may reduce SPECT doses to as low as 5 to 8 mSv.[328] The clinician is strongly urged to consider radiation exposure when deciding whether the benefit of testing an asymptomatic patient outweighs the potential risks.

2.5.9.3. Evidence of Association With Increased Cardiovascular Risk in Asymptomatic Adults

There are few studies on the role of stress MPI for risk assessment in asymptomatic persons. The writing committee did not identify any studies in population-based (relatively unselected) asymptomatic individuals. Reported studies of stress perfusion imaging in asymptomatic persons have involved selected higher-risk patients who were referred for cardiac risk evaluation. In 1 large series of patients referred to a stress perfusion imaging laboratory (n=3664 asymptomatic patients), those with >7.5% myocardial ischemia had an annual event rate of 3.2%, which was consistent with high risk. High-risk findings were noted in <10% of asymptomatic patients who were referred. Limitations of the study include the absence of clear indications for referral and absence of prior global risk assessment as a basis for advanced risk assessment.[329] A second study, from the Mayo Clinic, selected 260 asymptomatic patients from a nuclear cardiology database (67±8 years, 72% male) without known CAD who were at moderate risk for CHD by FRS.[330] SPECT MPI images were categorized using the summed stress score. Mean follow-up was nearly 10 years. Abnormal SPECT MPI scans were present in 142 patients (55%). By summed stress score categories, SPECT scans were low risk in 67% of patients, intermediate risk in 20%, and high risk in 13%. Survival was 60% for patients with high-risk scans (95% CI 45% to 80%), 79% with intermediate-risk scans (95% CI 69% to 91%), and 83% with low-risk scans (95% CI 77% to 88%) (P=0.03), including 84% (95% CI 77% to 91%) with normal scans. In asymptomatic intermediate- to higher-risk patients, these available data suggest a possible role for stress perfusion imaging in advanced risk assessment of selected asymptomatic patients.

Risk stratification using MPI has also been studied in asymptomatic patients with diabetes.[331–337] In 1 multicenter study of 370 asymptomatic persons with diabetes recruited from departments of diabetology,[335] abnormality was defined as a fixed or reversible perfusion defect or a positive stress ECG. These abnormalities (compared with patients with normal study results) were associated with a 2.9-fold (1.3 to 6.4) higher risk for cardiovascular events in patients >60 years of age but not for those <60 years of age. In the DIAD (Detection of Ischemia in Asymptomatic Diabetics) trial, asymptomatic, relatively low-risk patients with diabetes were randomized to screening for "silent" myocardial ischemia using adenosine stress MPI as an initial screening test versus "usual care".[337] The DIAD study found evidence of effective risk stratification, with annual cardiovascular event rates of 0.4% for those with normal- or low-risk scans compared with 2.4% for those with a moderate to large perfusion defect (P=0.001).[337] However, the overall result of the DIAD study was no significant difference in clinical outcomes in the screened group versus the usual care group (see further on this point below).

Stress perfusion imaging tests have been studied in a limited way when used as a secondary test following an initial evaluation with exercise ECG, carotid IMT, or CAC.[333,338–343] A summary of the literature from the ASNC synthesized published reports in patients who had these first-level indications of higher risk. Results suggested that as many as 1 in 3 of higher-risk patients with a CAC score of ≥400 had demonstrable ischemia. The prevalence of ischemia can be quite high in patients with diabetes, especially those with a family history of CHD.[340,344] In a series of 510 asymptomatic patients with type 2 diabetes recruited from 4 London diabetes clinics, the incidence of myocardial ischemia was 0%, 18.4%, 22.9%, 48.3%, and 71.4% for those with CAC scores of 0 to 10, 11 to 100, 101 to 400, 401 to 1000, and >1000, respectively (P<0.0001).

Three studies have reported the prognosis for patients referred to either initial CAC screening or combined CAC scanning with stress MPI.[333,341,343] In 1 series that included a mixed sample of asymptomatic patients and patients with

chest pain, high-risk CAC scores did not confer an elevated cardiovascular event risk. In another series of 621 patients who underwent hybrid PET-CT imaging with CAC scoring, one third of whom were asymptomatic, cardiovascular event-free survival was worse for patients with ischemia on PET plus a CAC score ≥1000 ($P<0.001$). In another study using a patient registry, data on asymptomatic patients with type 2 diabetes were reported.[333] The inclusion criteria for the latter prospective registry included patients with diabetes who were ≥50 years of age with either prior carotid IMT ≥1.1 mm, urinary albumin rate ≥30 mg/g creatinine, or 2 of the following: abdominal obesity, HDL cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or hypertension ≥130/85 mm Hg. One-year event-free survival ranged from 96% to 76% for those with a summed stress score ranging from <4 to ≥14 ($P<0.0001$). These results suggest that stress perfusion imaging may have a role in the advanced testing of asymptomatic patients who have been evaluated with other modalities and found to be at high risk of silent ischemia. Such patients might include patients with a high-risk CAC score of ≥400 or higher-risk patients with diabetes, including those with a strong family history of CHD.

2.5.9.4. Usefulness in Motivating Patients or Guiding Therapy

There are limited data to demonstrate that stress-induced evidence of silent ischemia in asymptomatic patients will have an impact on patient management. These data are limited to the use of follow-up testing in the DIAD trial. Patients enrolled in the DIAD trial who were randomized to screening with stress MPI had a higher rate of follow-up coronary angiography and revascularization. These data are consistent with single-center studies that have shown that demonstration of high-risk myocardial perfusion scans in asymptomatic patients with diabetes leads to diagnostic cardiac catheterization to identify high-risk anatomy (eg, 3-vessel CAD or left main CAD) with a view toward revascularization.[345,346] One nonrandomized observational study showed that asymptomatic patients with diabetes with high-risk stress MPI scans had a better outcome with revascularization than medical therapy.[347]

2.5.9.5. Changes in Patient Outcomes

There is evidence from 1 randomized trial on the utility of stress MPI to screen for CVD in persons with diabetes.[337] The DIAD trial randomized 1123 patients to no screening compared with screening with adenosine stress MPI. The trial results revealed that stress MPI performed as an initial screening test had no impact on 5-year outcomes compared with nonscreening or usual care of asymptomatic patients with diabetes.[337] The relative hazard was 0.88 (95% CI 0.44 to 1.88) for those who were screened with stress myocardial perfusion SPECT compared with those who were not screened ($P=0.73$). Notable limitations to this trial are its small, underpowered sample size, the high crossover rate (n=170/562 nonscreening arm undergoing nonprotocol stress testing), and the high incomplete follow-up rate (n=81/1123) exceeding the 49 observed cardiovascular events. Importantly, the enrolled patients were low risk with an annual cardiovascular event rate of 0.6% and included patients with a normal resting 12-lead ECG.

2.5.10. Computed Tomography for Coronary Calcium

2.5.10.1. Recommendations for Calcium Scoring Methods (see Section 2.6.1)

Class IIa

1. **Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk).[18,348] (*Level of Evidence: B*)**

Class IIb

1. **Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk).[348–350] (*Level of Evidence: B*)**

Class III: No Benefit

1. **Persons at low risk (<6% 10-year risk) should not undergo CAC measurement for cardiovascular risk assessment.[18,348,351] (*Level of Evidence: B*)**

2.5.10.2. Calcium Scoring Methods

Cardiac CT, using either multidetector row CT or electron beam tomography, enables the acquisition of thin slices of the heart and coronary arteries gated to diastole to minimize coronary motion. Both are sensitive noninvasive techniques that can detect and quantify coronary calcium, a marker of atherosclerosis.[352,353] The test is typically performed in a prospectively ECG-triggered scanning mode with 2.5- to 3.0-mm thick axial images obtained through the heart. The quantity of calcium within the coronary arteries is typically scored as the area affected on the scan, multiplied by a weighting factor depending on the Hounsfield unit density of the calcium deposits.[352] The radiation dose in a prospectively triggered acquisition is low, with a typical effective dose of <1.5 mSv.[354] Due to the radiation exposure and general low prevalence of calcification in men <40 years of age and women <50 years of age, patient selection is an important consideration. CT scanning should generally not be done in men <40 years old and women <50 years old due to the very low prevalence of detectable calcium in these age groups.

The widespread use of CCTA has also raised concerns about radiation dose for patients. The National Council on Radiation Protection Report No. 160 stated that radiation exposure to the U.S. population due to medical sources increased >7 times between 1986 and 2006.[355] CT calcium scoring produces the same amount of radiation as 1 to 2 mammograms performed on each breast.[356] The radiation dose in a prospectively triggered acquisition is low, with a typical effective dose of 0.9 to 1.1 mSv,[354,357] but doses can be higher if retrospective imaging is used.[358] All current recommendations suggest prospective triggering be used for CAC scoring. CT personnel must be constantly aware of the risks of radiation and strive to apply the lowest dose to the patient consistent with the clinical study. Because of radiation exposure and the general low prevalence of calcification in

men <40 years of age and women <50 years of age, CT scanning should generally not be done in these younger-age patients.

2.5.10.3. Data on Independent Relationship to Cardiovascular Events

The majority of published studies have reported that the total amount of coronary calcium (usually expressed as the Agatston score) provides information about future CAD events over and above the information provided by standard risk factors. Intermediate-risk patients with an elevated CAC score (intermediate FRS and CAC >300) had a 2.8% annual rate of cardiac death or MI (roughly equivalent to a 10-year rate of 28%) that would be considered high risk.[352] Pooled data from 6 studies of 27,622 asymptomatic patients were summarized in an ACCF/AHA clinical expert consensus document that examined predictors of the 395 CHD deaths or MIs.[359] The 11,815 subjects who had CAC scores of 0 had a low rate of events over the subsequent 3 to 5 years (0.4%, based on 49 events). Compared with a CAC score of 0, a CAC score between 100 and 400 indicated a RR of 4.3 (95% CI 3.5 to 5.2; $P<0.0001$), a score of 400 to 1000 indicated a RR of 7.2 (95% CI 5.2 to 9.9; $P<0.0001$), and a score >1000 indicated a RR of 10.8 (95% CI 4.2 to 27.7; $P<0.0001$). The corresponding pooled rates of 3- to 5-year CHD death or MI rates were 4.6% (for scores from 400 to 1000) and 7.1% (for scores >1000), resulting in a RR ratio of 7.2 (95% CI 5.2 to 9.9; $P<0.001$) and 10.8 (95% CI 4.2 to 27.7; $P<0.0001$).

Since the ACCF/AHA expert consensus document was published, other prospective confirmatory studies have been published.[18,348,351,353,354] These studies have demonstrated that the relationships between CAC outcomes are similar in men and women and different ethnic groups.[353,354] Each of these studies demonstrated that the AUC to predict coronary artery events is significantly higher with CAC than either Framingham or PROCAM (Münster Heart Study) risk stratification alone. In MESA, the C statistic with traditional risk factors was 0.79 for major coronary events in the risk factor prediction model and 0.83 in the risk factor plus CAC model ($P=0.006$).[18]

2.5.10.4. Usefulness in Motivating Patients

To understand the clinical utility of CAC testing as a risk assessment tool, it is imperative to demonstrate that it alters clinical management (such as the use of preventive medications). In an observational survey study, Kalia et al. showed that self-reported lipid-lowering medication provision increased from 44% over 3 years to >90% in those with baseline calcium scores in the top 75th percentile for age and sex ($P<0.001$).[360] This finding was independent of underlying cardiovascular risk factors, age, and sex. Other cardiovascular risk behaviors were reported to be beneficially affected, specifically showing that higher baseline CAC was strongly associated with initiation of aspirin therapy, dietary changes, and increased exercise.[361]

A randomized controlled study suggested that although a calcium scan did not in itself improve net population healthy behaviors, the post-test recurring interactions with a healthcare provider can be useful to reinforce lifestyle and treatment recommendations that could ensue from calcium testing.[362]

2.5.10.5. Use as a Repeat Measure to Monitor Effects of Therapy in Asymptomatic Persons

Coronary calcium progresses at typically 10% to 20% of the baseline value per year, and among persons >45 years of age, approximately 7% per year of those without calcium develop detectable coronary calcium. The value of repeat calcium scanning is governed by the interscan interval, rate of coronary calcium progression, variability in repeated measurements, and independent association to shifts in prognosis and management based on the observed calcium progression rate. Although preliminary data suggest that a calcium scan progression rate of >15% per year is associated with a 17-fold increased risk for incident CHD events,[363] there are no data demonstrating that serial CAC testing leads to improved outcomes or changes in therapeutic decision making.[354]

2.5.10.6. Usefulness of Coronary Calcium Scoring in Guiding Therapy

Calcium scores >100 to 300 are associated with a high rate of incident CHD events over the ensuing 3 to 5 years, so that persons with calcium scores in this range are a suitable target group for stringent lifestyle recommendations, selection of evidence-based therapeutic agents to reduce cardiovascular risk, and focus on adherence to medical recommendations. In the Prospective Army Coronary Calcium study, among 1640 participants followed up for 6 years, use of statin and aspirin was independently 3.5- and 3-fold greater in those with any coronary calcium over 6 years, suggesting management changes can occur following calcium screening in community-based cohorts.[364] Multiple logistic regression analysis, controlling for National Cholesterol Education Program (NCEP) risk variables, showed that CAC was independently associated with a significantly higher likelihood of use of statin, aspirin, or both (OR 6.97; 95% CI 4.81 to 10.10; $P<0.001$).[364] The OR for aspirin and statin use based on NCEP risk factors alone was dramatically lower (OR 1.52; 95% CI 1.27 to 1.82; $P<0.001$). Recent data from MESA suggest similar effects of CAC visualization on lipid-lowering and aspirin therapy.[365]

2.5.10.7. Evidence for Improved Net Health Outcomes

Evidence is not available to show that risk assessment using CAC scoring improves clinical outcomes by reducing mortality or morbidity from CAD.

2.5.10.8. Special Considerations

2.5.10.8.1. Coronary Calcium Scoring in Women. A vast majority of women <75 years of age are classified by FRS to be low risk. In 1 study of 2447 consecutive asymptomatic women without diabetes (55±10 years), 90% were classified as low risk by FRS (≤9%), 10% as intermediate risk (10% to 20%), and none had a high-risk FRS >20%.[366] CAC was observed in 33%, whereas moderate (CAC ≥100), a marker of high risk, was seen in 10% of women. Overall, 20% of women had CAC ≥75th percentile for age and gender, another marker for future CHD events. However, when FRS

was used, the majority (84%) of these women with significant subclinical atherosclerosis ≥75th percentile were classified as low risk, whereas only 16% were considered intermediate risk. Thus, FRS frequently classifies women as being low risk, even in the presence of significant CAC. Based on this 1 substudy from MESA, it is possible that CAC scoring may provide incremental value to FRS in identifying which asymptomatic women may benefit from targeted preventive measures.[349] A recent report noted net reclassification improvement with CAC in relation to risk factors for all-cause mortality in women <60 years of age.[367] In terms of the overall predictive capacity of high calcium scores, several studies have demonstrated that CAC-associated outcomes are similar in men and women.[368,369]

For a discussion of the utility of CAC testing in persons with diabetes, see Section 2.6.1.

2.5.10.8.2. Comparison of Coronary Artery Calcium Scoring with Other Risk Assessment Modalities. Several studies have compared multiple techniques for cardiovascular risk stratification.[350,369–371] Four studies comparing the predictive abilities of hsCRP with CAC have demonstrated that CAC remains an independent predictor of cardiovascular events in multivariable models, whereas CRP no longer retains a significant association with incident CHD.[350,369–371] This has recently been confirmed in MESA as well.[18,351] The CAC score was also shown to be a better predictor of subsequent CVD events than carotid IMT. Multivariable analysis revealed HRs for CHD of 1.7 (95% CI 1.1 to 2.7; $P=0.07$) for carotid IMT and 8.2 (95% CI 4.5 to 15.1; $P<0.001$) for CAC score (quartile 4 versus quartiles 1 and 2).[252]

2.5.11. Coronary Computed Tomography Angiography

2.5.11.1. Recommendation for Coronary Computed Tomography Angiography

Class III: No Benefit

1. Coronary computed tomography angiography is not recommended for cardiovascular risk assessment in asymptomatic adults.[372] (*Level of Evidence: C*)

2.5.11.2. General Description

CCTA has been widely available since around 2004, when 64-detector scanners were produced by multiple vendors. Two basic scanning protocols may be used; both require ECG monitoring and gating. Helical (or spiral) scanning uses continuous image acquisition while the patient moves slowly through the scanner plane. Axial scanning incorporates a scanning period, followed by a patient movement period, followed by another scanning period (step-and-shoot). Compared with invasive coronary angiography using a cine system, both the temporal and spatial resolution of CCTA are far less (spatial: 200 microns versus 400; temporal: 10 ms versus approximately 80 to 190 ms, depending on the type of scanner). CCTA provides the best quality images when the heart rate is regular and slow (<60 bpm if possible).

CCTA has been compared with invasive coronary angiography for detection of atherosclerosis (typically defined as a 50% diameter stenosis).[373] Sensitivities and specificities from >40 studies are consistently in the range of 85% to 95%, and the most important test feature is the high negative predictive value (>98%).[373] In addition, CCTA can image mild plaque (<50%) in the vessel wall. Plaques may be roughly characterized according to their density (Hounsfield units) as calcified or noncalcified. CCTA requires a CT scanner with at least 64 detector rows and specialized software (approximate cost, $1 million). Concern has been raised that CCTA uses ionizing radiation. CCTA studies using unmodulated, helical scanning deliver 12 to 24 mSv of radiation per examination.[373] Methods to reduce the radiation dose, including ECG dose modulation or prospective ECG-triggered axial scanning, have resulted in doses of less than 3 mSv in selected patients (estimated radiation dose associated with CCTA).[374]

2.5.11.3. Association With Increased Risk and Incremental Prediction in Asymptomatic Persons

Very limited information is available on the role of CCTA for risk assessment in asymptomatic persons. In a study from Korea, 1000 middle-aged patients underwent CCTA as a component of a general health evaluation.[372] Patients were either self-referred to this examination or referred by a physician. Patients with chest discomfort or known CAD were excluded from the analysis. Clinical follow-up was obtained at 17±2 months in >97% of patients. Coronary calcium was detected in 18% of patients, and 22% had identifiable atherosclerotic plaque. Significant (>50%) stenoses were found in 5% of patients. CCTA results were compared with the NCEP ATP III risk classification. The majority of patients were classified as low risk (55.7%) by NCEP criteria. Only 10.2% were classified as high risk. The prevalence of significant coronary stenoses in the low-, moderate- and high-risk groups was 2%, 7%, and 16%, respectively. During follow-up, 15 patients had "cardiac events," although 14 of these were revascularization procedures prompted by the CCTA results. There were no deaths or MIs. Additional diagnostic testing was performed in 14% of patients identified as having coronary atherosclerosis, representing 3.1% of the entire screened population. On the basis of the small number of nonprocedural events in this study, the authors could not compare CCTA results with the NCEP risk assessment data for risk prediction purposes. No other studies have been reported to date on the potential utility of CCTA results for risk assessment in asymptomatic adults with coronary events as the outcome.

2.5.11.4. Changes in Patient Outcomes

There are no published trials evaluating the impact of specific therapy on clinical outcome in patients identified as having noncalcified atheroma by CCTA.

2.5.12. Magnetic Resonance Imaging of Plaque

2.5.12.1. Recommendation for Magnetic Resonance Imaging of Plaque

Class III: No Benefit

1. MRI for detection of vascular plaque is not recommended for cardiovascular risk assessment in asymptomatic adults. (*Level of Evidence: C*)

2.5.12.2. General Description

MRI is a noninvasive method of plaque measurement that does not involve ionizing radiation. Studies of the aorta and the femoral and carotid arteries have demonstrated the capability of MRI for detection and quantification of atherosclerosis and suggested its potential for risk assessment and evaluation of the response to treatment in asymptomatic patients. MRI seems to offer the greatest role for plaque characterization as distinct from lesion quantification. Examination of plaque under different contrast weighting (black blood: T1, T2, proton density-weightings, and magnetization prepared rapid gradient echocardiography or bright blood: time of flight) allows characterization of individual plaque components,[375,376] including lipid-rich necrotic core,[377] fibrous cap status,[378] hemorrhage,[379,380] and calcification.[377,381,382] Although most magnetic resonance plaque imaging studies do not require exogenous contrast administration, gadolinium-based contrast agents can further improve delineation of individual plaque components such as the fibrous cap and lipid-rich necrotic core.[383,384]

Several studies have demonstrated that MRI findings are correlated with atherosclerosis risk factors. Aortic MRI scanning in 318 patients participating in the Framingham Heart Study found that after age adjustment, plaque prevalence and burden correlated with FRS for both women and men.[385] In another Framingham Heart Study, subclinical aortic atherosclerosis was seen in nearly half of subjects and increased with advancing age. Hypertension was associated with increased aortic plaque burden. In the MESA study, aortic wall thickness measured with MRI increased with age, but males and blacks had the greatest wall thickness.[386] In another MESA study, it was found that thickened carotid walls and plasma total cholesterol, but not other established CHD risk factors, were strongly associated with lipid core presence by MRI.[387]

A few small prospective studies have been done to investigate characteristics of carotid artery plaque on MRI that are associated with disease progression and future cardiovascular events. One study examined patients with symptomatic and asymptomatic carotid disease to determine whether fibrous cap thinning or rupture as identified on MRI were associated with a history of recent transient ischemic attack or stroke. When compared with patients with a thick fibrous cap, patients with a ruptured cap were 23 times more likely to have had a recent transient ischemic attack or stroke.[388] In a separate study of symptomatic carotid disease, patients with lipid cores in carotid plaque by MRI had ipsilateral cerebral infarctions more often than those without lipid cores (68% versus 31%; $P=0.03$).[389] Another study performed carotid MRI on 53 patients within 7 days of a second cerebrovascular accident. Patients with "vulnerable" carotid lesions, as defined by eccentric shape and heterogeneous signal on MRI, had an 8 times greater risk of a third cerebrovascular accident compared with those without vulnerable lesions (24% versus 3%; $P=0.023$).[390]

Prospective studies demonstrated that hemorrhage within carotid atherosclerotic plaques was associated with an accelerated increase in subsequent plaque volume over a period of 18 months.[391] An increased risk of ipsilateral cerebrovascular events has also been reported over a mean follow-up period of 38.2 months in asymptomatic patients who had 50% to 79% carotid stenosis and the presence of a thin or ruptured fibrous cap, intraplaque hemorrhage, or a larger lipid-rich necrotic core.[392] These studies support the hypothesis that the presence of intraplaque hemorrhage is a potent atherogenic stimulus.

At this time there are no published prospective population data to evaluate the role of MRI findings in risk assessment of asymptomatic adults. A number of large-scale studies are ongoing. It is recommended that additional large-scale multicenter trials be conducted to evaluate the possibility of using MRI in the detection of atherosclerosis in asymptomatic patients.

Rapid technological progress is transforming the imaging of atherosclerotic CVD at the molecular level using nanoparticles.[393] In addition, a new generation of hybrid technology is now becoming available; this technology combines multiple imaging modalities, including PET in a single platform (eg, PET/CT and MR/PET), using 1 machine for >1 type of imaging to measure atherosclerotic plaque metabolic activity with anatomical special resolution and contrast.[394–396] There is no information available yet on the role of these newer tests for risk assessment in the asymptomatic adult.

2.6. Special Circumstances and Other Considerations

2.6.1. Diabetes Mellitus

2.6.1.1. Recommendations for Patients With Diabetes

Class IIa

1. **In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment.[344,397–399] (*Level of Evidence: B*)**

Class IIb

1. **Measurement of HbA1C may be considered for cardiovascular risk assessment in asymptomatic adults with diabetes.[400] (*Level of Evidence: B*)**
2. **Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of 400 or greater. (*Level of Evidence: C*)**

2.6.1.2. General Description and Background

CVD is the major cause of morbidity, mortality, and healthcare costs for patients with diabetes.[401] Compared with the general population, patients with diabetes have a 4 times greater incidence of CHD[402] and a 2- to 4-fold higher risk of a cardiovascular event.[307] The risk of MI in patients with diabetes without prior documented CHD is similar to the risk of reinfarction in patients without diabetes with known CHD.[403] Women with type 2 diabetes are particularly prone to developing cardiovascular complications (the age-adjusted risk ratio of developing clinical CHD among people with diabetes was 2.4 in men and 5.1 in women compared with patients without diabetes).[403]

The prevalence of significant coronary atherosclerosis in a truly representative population of patients with type 2 diabetes has not been ascertained. One estimate is that 20% of patients with diabetes have coronary atherosclerosis.[404] However, in an asymptomatic and uncomplicated cohort of patients with type 2 diabetes, 46.3% had evidence of coronary artery calcification reflective of coronary atherosclerosis.[344] The prevalence of CAD on multislice CT was 80% in a group of 70 asymptomatic patients with type 2 diabetes.[399] The majority of these patients had diffuse involvement of all 3 coronary arteries. In another study by this group, 60% of asymptomatic patients with diabetes had evidence of coronary calcification, of which 18% had calcium scores of >400.[405] Seventy percent had coronary luminal narrowing of 1 or more coronary arteries on multislice CT coronary angiography, patients with diabetes showed more plaques on multislice CT than patients without diabetes (7.1±3.2 versus 4.9±3.2; $P=0.01$) with more calcified plaques (52% versus 24%).[406] On invasive grayscale intravascular ultrasound, patients with diabetes in this study had a larger plaque burden (48.7%±10.7% versus 40.0%±12.1%; $P=0.03$). Asymptomatic patients with diabetes have more coronary calcification than patients without diabetes even when controlling for other variables,[407–409] and for every increase in CAC on CT scanning, mortality for patients with diabetes is higher than in patients without diabetes.[407] However, patients with diabetes with no coronary calcium have a survival rate similar to that of subjects without diabetes and with no identifiable coronary calcium.[407] The overall rate of death or MI was 0%, 2.6%, 13.3%, and 17.9% ($P<0.0001$) in patients with diabetes with a CAC score of ≤100, 100 to 400, 401 to 1000 and >1000, respectively.[344] ROC curve analysis showed by AUC that the CAC (AUC: 0.92; 95% CI 0.87 to 0.96) was superior to the UKPDS (United Kingdom Prospective Diabetes Study Risk Score) (AUC, 0.74; 95% CI 0.65 to 0.83) and FRS (AUC, 0.60; 95% CI 0.48 to 0.73; $P<0.0001$) for predicting cardiac events, with a risk ratio of 10.1 (95% CI 1.68 to 61.12) for patients with a score of 100 to 400 and 58.1 (95% CI 12.28 to >100) for scores >1000.[344]

The CAC score has been found to be predictive beyond conventional risk factors in several studies in patients with diabetes. In the PREDICT (Patients with Renal Impairment and Diabetes Undergoing Computed Tomography) study, 589 patients with type 2 diabetes underwent CAC measurement.[398] At a median of 4 years' follow-up, in a predictive model that included CAC score and traditional risk factors, the CAC score was a highly significant independent predictor of CHD events or stroke. The model found that a doubling in calcium score was associated with a 32% increase in risk of events (29% after adjustment). Only the homeostasis model assessment of insulin resistance predicted primary endpoints independent of the CAC score. In another study, after adjusting for CHD risk factors, the CAC score was significantly associated with occurrence of coronary events in patients without diabetes but not in patients with diabetes.[410] Another study performed CAC measurement in 716 asymptomatic patients with diabetes and no history of CHD .[397] During 8 years of follow-up, 40 patients had MI and 36 additional patients experienced cardiac death. The CAC score was significantly higher in those with events compared with those without events, 5.6% per year for patients with scores of >400 versus 0.7% per year for those with lower scores.[397] The area under the ROC curve with CAC in the model was significantly higher (0.77) for prediction of MI than the FRS (0.63).

2.6.1.3. Electrocardiographic Stress Testing for Silent Myocardial Ischemia (See Section 2.5.7)

The value of exercise ECG testing to detect silent ischemia and assess prognosis has been evaluated in a few small studies of asymptomatic patients with diabetes.[411–416] ECG stress testing has an approximate 50% sensitivity and 80% specificity.[401] The positive predictive value for detecting CAD using coronary angiography as the gold standard ranges between 60% and 94% and was higher in men than women.[401,416] Recommendations for exercise stress testing for risk assessment do not appear to be different in patients with diabetes and patients without diabetes.

2.6.1.4. Noninvasive Stress Imaging for Detection of Ischemia and Risk Stratification (See Section 2.5.9)

The prevalence of asymptomatic ischemia as determined by noninvasive imaging in patients with diabetes ranges from 16% to 59%[345,346,417–419] and depends on the pretest clinical risk of CAD in the population. The DIAD study[337] was composed of a group of patients with type 2 diabetes who were at lower risk than those undergoing stress imaging in other studies, with only 6% of the 522 patients manifesting large defects on adenosine MPI. All had a normal resting ECG, whereas in a separate Mayo Clinic cohort, 43% had abnormal Q waves on the ECG and 28% had peripheral vascular disease.[346] Approximately 50% of the Mayo Clinic study patients were referred for preoperative testing for risk assessment. In another report from the same group, 58.6% of asymptomatic patients with diabetes had an abnormal scan, and 19.7% had a high-risk scan.[345] In another retrospective study, 39% of asymptomatic patients with diabetes had an abnormal stress scan.[419] Of those presenting with dyspnea, 51% had an abnormal perfusion study. The annual hard event rate at follow-up (7.7%) was highest in those presenting with dyspnea compared with 3.2% in those presenting with angina. Using contrast dipyridamole echocardiography, approximately 60% of asymptomatic patients with diabetes who were ≤60 years of age had abnormal myocardial perfusion with vasodilator stress.

Asymptomatic patients with diabetes who have high CAC scores have a high prevalence of inducible ischemia on stress imaging.[339] In a prospective study, 48% of patients with diabetes with a CAC score of >400 had silent ischemia on SPECT imaging, and in those with a score of >1000, 71.4% had inducible ischemia.[344] The majority of the defects were moderate to severe. Patients with diabetes with inducible ischemia have a higher annual death or nonfatal infarction rate compared with patients without diabetes with similar perfusion abnormalities on stress imaging (10% versus 6%).[420] Also, the greater the degree of ischemia, the worse the outcome during follow-up in both asymptomatic and symptomatic patients with diabetes.[344,421] The risk ratio for cardiac events was 12.27 (95% CI 3.44 to 43.71; $P<0.001$) for

patients with >5% ischemic burden on stress SPECT.[344] These observations should be tempered by the recent report that 16% of patients with no coronary calcium had inducible ischemia by rest-stress rubidium-82 PET imaging.[343] The prevalence of diabetes was 28% in that study. These data, in aggregate, suggest that coronary calcium measurement in patients with diabetes may justify different approaches to risk assessment compared with patients without diabetes. The writing committee therefore judged it reasonable to perform coronary calcium measurement for cardiovascular risk assessment in asymptomatic patients with diabetes who were >40 years of age.

2.6.1.5. Usefulness in Motivating Patients

To date there is no evidence that performing coronary calcium imaging by CT scanning is effective in motivating patients to better adhere to lifestyle changes, medical therapy of diabetes, or primary prevention measures to reduce the risk of developing coronary atherosclerosis or future ischemic events.

2.6.1.6. Evidence of Value for Risk Assessment for Coronary Atherosclerosis or Ischemia or Both to Guide Therapy or Change Patient Outcomes

Because of the high risks associated with diabetes, diabetes has been designated as a CHD risk equivalent by the NCEP.[27] One study randomized 141 patients with type 2 diabetes without known CAD to receive exercise ECG/dipyridamole stress echocardiographic imaging or a control arm.[325] If a test result was abnormal, coronary angiography was performed with subsequent revascularization as indicated by anatomic findings. At a mean follow-up of 53.5 months, 1 major event (MI) and 3 minor events (angina) occurred in the testing arm, and 11 major and 4 minor events occurred in the control arm. Numbers in the study were too small to be considered definitive. In the DIAD study, 561 low-risk asymptomatic patients were randomized to screening with adenosine SPECT perfusion imaging; 562 patients were randomized to no testing.[337] All patients had a normal resting ECG and no prior history of CAD. Over a mean follow-up of 4.8 years, the cumulative event rate was 2.9% (0.6% per year), and there was no difference in event rates between the 2 groups. In the tested group, those with moderate or large defects had a higher cardiac event rate than those with a normal scan or small defects.[337]

2.6.1.7. Diabetes and Hemoglobin A1C

HbA1C is used to integrate average glycemic control over several months and predict new-onset diabetes.[156] A systematic review has suggested that HbA1C might be effective to screen for the presence of diabetes.[157] Some experts have noted that screening with HbA1C might be advantageous because it can be performed in nonfasting individuals.[422] The ADA now endorses the use of HbA1C to diagnose diabetes and assess for future risk of diabetes in higher-risk patients.[158,423]

2.6.1.8. Association With Cardiovascular Risk

Higher HbA1C concentrations have been associated with elevated risk of CVD in asymptomatic persons with diabetes.[154] In a meta-analysis by Selvin et al, adjusted RR estimates for glycosylated hemoglobin (total glycosylated hemoglobin, hemoglobin A1, or HbA1C levels) and CVD events (CHD and stroke) were pooled by using random-effects models.[154] Three studies involved persons with type 1 diabetes (n=1688), and 10 studies involved persons with type 2 diabetes (n=7435). The pooled RR for CVD was 1.18; this represented a 1% higher glycosylated hemoglobin level (95% CI 1.10 to 1.26) in persons with type 2 diabetes. The results in persons with type 1 diabetes were similar but had a wider CI (pooled RR 1.15 [95% CI 0.92 to 1.43]). Important concerns about the published studies included residual confounding, the possibility of publication bias, the small number of studies, and the heterogeneity of study results. The authors concluded that, pending confirmation from large, ongoing clinical trials, this analysis suggests that chronic hyperglycemia is associated with an increased risk for CVD in persons with diabetes.

2.6.1.9. Usefulness in Motivating Patients, Guiding Therapy, and Improving Outcomes

It is unknown whether knowledge of HbA1C is associated with better cardiovascular clinical outcomes in asymptomatic patients with diabetes. In persons with established diabetes, knowledge of HbA1C concentration was associated with better understanding of diabetes care and glucose control.[424] However, such knowledge was unaccompanied by objective evidence of better clinical outcomes.[424] It is unknown whether HbA1C is useful for motivating persons without diabetes.

Although the beneficial effects of glycemic control for microvascular complications have been demonstrated by numerous studies, the benefits for macrovascular complications, particularly CVD, remain controversial.[425–427] Prevention trials have demonstrated that persons with impaired glucose tolerance have less progression to overt diabetes with lifestyle and pharmacologic interventions but without accompanying reductions in CVD complications.[428] A meta-analysis of randomized controlled trials of persons with diabetes reported that improved glycemic control was associated with an improved IRR for macrovascular complications—mainly CVD—for both type 1 (IRR 0.38, 95% CI 0.26 to 0.56) and type 2 (IRR 0.81, 95% CI 0.73 to 0.91) diabetes.[429] However, the meta-analysis did not demonstrate a reduction in cardiac events in persons with type 2 diabetes (IRR 0.91, 95% CI 0.80 to 1.03).[429]

Recent large, randomized, controlled studies have also failed to demonstrate that intensive blood glucose control and a lower HbA1C level is accompanied by a reduction in macrovascular events.[430–432]

2.6.2. Special Considerations: Women

The rationale for providing a separate section for risk assessment considerations in women was based on reports of underrepresentation of females within the published literature and clinicians who considered women at lower risk when their profiles were comparable to those of men. Moreover, the focus on special considerations in testing women has been put forward as a result of frequent reporting of underutilization of diagnostic and preventive services and undertreatment in women with known disease.[433]

2.6.2.1. Recommendations for Special Considerations in Women

Class I

1. **A global risk score should be obtained in all asymptomatic women.[22,434] (*Level of Evidence: B*)**
2. **Family history of CVD should be obtained for cardiovascular risk assessment in all asymptomatic women.[22,55] (*Level of Evidence: B*)**

2.6.2.2. Detection of Women at High Risk Using Traditional Risk Factors and Scores

Nearly 80% of women >18 years of age have 1 or more traditional CHD risk factors.[435] Diabetes and hypertriglyceridemia are associated with increases in CHD mortality in women more so than in men.[436,437] In women, traditional and novel risk factors are prevalent and frequently cluster (ie, metabolic syndrome).[438–440] CHD risk accelerates greatly for women with multiple risk factors, and CHD risk notably increases after menopause.

Global risk scores, such as the FRS, classify the majority of women (>90%) as low risk, with few assigned to high-risk status before the age of 70 years.[434,441] Several reports have examined the prevalence of subclinical atherosclerosis in female FRS subsets.[349,366] In a recent study of 2447 women without diabetes, 84% with significant coronary artery calcification (≥75th percentile) were classified with a low FRS.[366] The lack of sensitivity of FRS estimates in women was presented in several reports, suggesting lower utility of FRS in female patients.[366,441] The Reynolds risk score in women improved risk reclassification when compared with the FRS by including hsCRP, HbA1C (if the patient has diabetes), and family history of premature CHD.[22] This finding has not been uniformly confirmed in other studies that included women.

2.6.2.3. Comparable Evidence Base for Risk Stratification of Women and Men

Within the past decade, high-quality, gender-specific evidence in CHD risk stratification of women has emerged for novel risk markers (eg, hsCRP) and cardiovascular imaging modalities (eg, carotid IMT, CAC). This evidence reveals effective and, importantly, similar risk stratification for women and men as based on relatively large female cohorts or a sizeable representation of females. Detailed discussions and recommendations for each of the tests are provided in Sections 2.4.2 for hsCRP, 2.5.1 for resting ECG, 2.5.3 for carotid IMT, 2.5.6 for ABI, 2.5.7 for exercise ECG, and 2.5.10 for CAC. In the case of hsCRP, carotid IMT, ABI, CAC, resting ECG, and exercise ECG, the recommendations for men apply similarly to women. Limited female-specific evidence is also available for FMD, thus warranting a Class III, LOE B recommendation similar to that for men.

2.6.3. Ethnicity and Race

A variety of disparities exist in different ethnic groups with respect to cardiovascular risk factors, incidence, and outcomes.[442] In 2002, age-adjusted death rates for diseases of the heart were 30% higher among African Americans than among whites of both sexes. Disparities were also common with respect to the presence of atherosclerotic risk factors, with Hispanics and black women demonstrating the highest rates of obesity. Blacks also had the highest rates for hypertension, whereas hypercholesterolemia was highest among white and Mexican-American males and white women. Lower educational level and socioeconomic status conferred a greater risk of dying from heart disease in all ethnic groups.[443]

Minimal information is available at this time with regard to differing risk assessment strategies in ethnic groups other than whites. The writing committee did not find evidence to suggest that ethnic groups other than whites should undergo selective risk assessment approaches based on ethnicity.

2.6.4. Older Adults

Although increasing age is a risk factor for CVD, with progression of age, the prevalence of traditional risk factors also rises. Conceptually, risk intervention could be anticipated to have greater benefit at an elderly age, due to the increased absolute risk for coronary events; however, age comparisons for risk interventions have not been rigorously tested. Furthermore, the term "elderly" is used to describe a range of age subgroups from 65 to 74, 75 to 84, and ≥85 years in different studies. Elderly patients in the community also vary substantially from those in clinical trials, with greater comorbidity, renal dysfunction, traditional risk factors, etc, and with very limited data available for the oldest of the old.

In the Cardiovascular Health Study, subclinical markers (increased carotid IMT, decreased ABI, ECG, history of MI, echocardiographic left ventricular dysfunction, coronary calcium) predicted CVD events more than traditional risk scores. The DTS does not predict cardiac survival beyond age 75, with a 7-year cardiac survival for those classified as low, intermediate, and high risk being 86%, 85%, and 69%, respectively.[444] Elderly patients have a more adverse prognosis than younger patients with the same Duke risk score. Based on information drawn largely from the Cardiovascular Health Study, application of traditional risk factors for risk assessment in the elderly, as well as selected other tests, can be considered an evidence-based approach.

2.6.5. Chronic Kidney Disease

Chronic kidney disease, the permanent loss of kidney function, is considered a coronary risk equivalent in various observational studies. However, data are insufficient to define differences in outcomes in populations with different degrees of renal insufficiency versus normal renal function. Data for lipid lowering with statins in the TNT (Treating to New Targets) study, a population with documented CAD, suggest serial improvement in renal function and clinical outcome, but extrapolation to an asymptomatic healthy population is inappropriate.[445] Lipid lowering restricted to the elderly in the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study failed to show benefit. Similarly, lipid lowering in a dialysis population failed to show benefit.[446] In TNT, patients with diabetes with mild to moderate chronic kidney disease demonstrated marked reduction in cardiovascular events with intensive lipid lowering in contrast to previous observations in patients with diabetes with end-stage renal disease. It is important to note that TNT was not a study of

asymptomatic adults (the focus of this guideline) but rather was focused on a CAD population.

3. Future Research Needs

3.1. Timing and Frequency of Follow-Up for General Risk Assessment

There is little information available in the research literature to suggest the optimal timing to initiate risk assessment in adults. There is also limited information to inform decisions about frequency of risk assessment in persons who are determined to be at low or intermediate risk on initial risk assessment. High-risk persons are likely to initiate treatment strategies, and repeat risk assessment is likely to be a standard component of patient follow-up. More research on the optimal timing to begin risk assessment and repeat risk assessment in the asymptomatic patient is warranted.

3.2. Other Test Strategies for Which Additional Research Is Needed

3.2.1. Magnetic Resonance Imaging

Although MRI is an established cardiovascular imaging modality, its use in risk assessment studies to date is very limited. Research questions to be answered should focus on 1) which MRI parameters are the best for predicting major macro- and microvascular disease in the asymptomatic patient, 2) whether such parameters add to existing risk scores, and 3) what is the cost-effectiveness of such imaging according to risk strata.

3.2.2. Genetic Testing and Genomics

At present the plethora of genetic tests available for assessing cardiovascular risk has not reached the point of being able to add to the general risk assessment approach using global risk scoring with traditional risk factors and addition of careful family history. Additional research on the role of genetic testing, with specific attention to the value for incremental risk prediction in asymptomatic people, is needed.

3.2.3. Geographic and Environmental or Neighborhood Risks

Much research indicates that socioeconomic factors play a role in cardiovascular risk. It remains unclear how this information should best be measured and incorporated into individual risk assessment or whether this area of research applies primarily at the population and policy levels. Attention to this area of research for individual risk assessment was deemed to be warranted by the writing committee.

3.2.4. Role of Risk Assessment Strategies in Modifying Patient Outcomes

Although the concept of individual risk assessment as a means of properly targeting intensity of risk treatments is now engrained in the practice of medicine and cardiology, data to support the clinical benefits of alternative testing strategies are very limited. For example, would risk assessments that use images of abnormal vessels be able to motivate patients and achieve better patient outcomes than testing strategies that use only historical information or blood tests? Studies that evaluate the specific testing strategy against a specific patient-centered outcome are needed. In addition, comparative effectiveness of various test strategies is needed to determine costs, benefits, and comparative benefits of competing testing approaches.

3.3. Clinical Implications of Risk Assessment: Concluding Comments

The assessment of risk for development of clinical manifestations of atherosclerotic CVD is designed to aid the clinician in informed decision making about lifestyle and pharmacologic interventions to reduce such risk. Patients are broadly categorized into low-, intermediate-, and high-risk subsets, and level of intensity and type of treatments are based on these differing assessments of risk.

The initial step in risk assessment in individual patients involves the ascertainment of a global risk score (Framingham, Reynolds, etc) and the elucidation of a family history of atherosclerotic CVD. These Class I recommendations, which are simple and inexpensive, determine subsequent strategies to be undertaken. Persons at low risk do not require further testing for risk assessment, as more intensive interventions are considered unwarranted, and those already documented to be at high risk (established CHD or coronary risk equivalents) are already candidates for intensive preventive interventions, so that added testing will not provide incremental benefit.

For the intermediate-risk patient, this guideline should help the clinician select appropriate test modalities that can further define risk status. Tests classified as Class IIa are those shown to provide benefit that exceeds risk. Selection among these will vary with local availability and expertise, decisions regarding cost, and potential risks such as radiation exposure, etc. Tests classified as Class IIb have less robust evidence for benefit but may prove helpful in selected patients. Tests classified as Class III are not recommended for use in that there is no, or rather limited, evidence of their benefit in incrementally adding to the assessment of risk; therefore, these tests fail to contribute to changes in the clinical approach to therapy. In addition, a number of Class III tests discussed in this guideline require additional efforts to standardize the measurement or make the test more commonly available on a routine clinical basis. Furthermore, some of the Class III tests also pose potential harm (radiation exposure or psychological distress in the absence of a defined treatment strategy) and are therefore to be avoided for cardiovascular risk assessment purposes in the asymptomatic adult. Until additional research is accomplished to justify the addition of Class III tests, the writing committee recommends against their use for cardiovascular risk assessment.

Appendix 1. Author Relationships With Industry and Other Entities: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

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(*Continued*)

Appendix 1. Continued

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Appendix 1. Continued

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This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Significant relationship.

†Recused from voting on Section 2.4.5, Lipoprotein-Associated Phospholipase A2.

‡Recused from voting on Section 2.5.11, Contrast Computed Tomography Angiography.

§Recused from voting on Section 2.6.1, Diabetes Mellitus.

‖Recused from voting on Section 2.5.10, Computed Tomography for Coronary Calcium.

¶Recused from voting on Section 2.3, Lipoprotein and Apolipoprotein Assessments.

#Recused from voting on Section 2.4.2, Recommendations for Measurement of C-Reactive Protein.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; BCBS, Blue Cross Blue Shield; BSP, Biological Signal Processing; CDC, Centers for Disease Control and Prevention; CME, continuing medical education; DSMB, Data Safety Monitoring Board; FAME, Fractional flow reserve (FFR) vs. Angiography in Multivessel Evaluation; FDA, Food and Drug Administration; LCIC, Leadership Council for Improving Cardiovascular Care; MESA, Multi-Ethnic Study of Atherosclerosis; NHLBI, National Heart, Lung, and Blood Institute; NIA, National Institute on Aging; NIH, National Institutes of Health; SAIP, Society of Atherosclerosis Imaging and Prevention; and SCCT, Society of Cardiovascular Computed Tomography.

Appendix 2. Reviewer Relationships With Industry and Other Entities: 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Paul Poirier	Official Reviewer—AHA	None	None	None	• CDA* • CIHR* • FRSQ*	None	None
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Daniel Edmundowicz	Organizational Reviewer—Society for Cardiovascular Angiography and Interventions	None	None	None	None	None	None
Steven J. Lavine	Organizational Reviewer—American Society of Echocardiography	None	None	None	None	None	None
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Appendix 2. Continued

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Vera Bittner	Content Reviewer—ACCF Prevention of Cardiovascular Disease Committee	None	None	None	• CV Therapeutics* • GlaxoSmithKline* • NHLBI* • NIH/Abbott* • Roche	None	None
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Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Appendix 2. Continued

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Christopher J. White	Content Reviewer—ACCF Interventional Council	• Baxter* • Boston Scientific*	None	None	None	None	None
Kim A. Williams	Content Reviewer—ACCF Imaging Council	• Astellas* • GE Healthcare* • King Pharmaceuticals*	• Astellas* • GE Healthcare*	None	• GE Healthcare* • Molecular Insight Pharmaceuticals*	• Molecular Insight Pharmaceuticals*	None

This table represents the relevant relationships with industry and other entities that were disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

*Significant relationship.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; ASNC, American Society of Nuclear Cardiology; CDA, Canadian Diabetes Association; CIHR, Canadian Institutes of Health; FDA, Food and Drug Administration; FRSQ, Fonds de la recherche en santé du Québec; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; JAMA, Journal of the American Medical Association; and TIMI, Thrombolysis In Myocardial Infarction.

Appendix 3. Abbreviations List

ABI = ankle-brachial index
ApoB = apolipoprotein B
AUC = area under the curve
AV = atrioventricular
CAC = coronary artery calcium
CAD = coronary artery disease
CCTA = coronary computed tomography angiography
CHD = coronary heart disease
CRP = C-reactive protein
CT = computed tomography
CVD = cardiovascular disease
DTS = Duke treadmill score
ECG = electrocardiogram
FMD = flow-mediated dilation
FRS = Framingham risk score
HbA1C = hemoglobin A1C
HDL = high-density lipoprotein
hsCRP = high-sensitivity C-reactive protein
IMT = intima-media thickness
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
Lp-PLA2 = lipoprotein-associated phospholipase A2
LVH = left ventricular hypertrophy
MI = myocardial infarction
MPI = myocardial perfusion imaging
MRI = magnetic resonance imaging
PAD = peripheral artery disease
PAT = peripheral arterial tonometry
PET = positron emission tomography
PWV = pulse wave velocity
ROC = receiver operating characteristics
SNP = single nucleotide polymorphism
SPECT = single-photon emission computed tomography

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Value of Primordial and Primary Prevention for Cardiovascular Disease : A Policy Statement From the American Heart Association

William S. Weintraub, Stephen R. Daniels, Lora E. Burke, Barry A. Franklin, David C. Goff, Jr, Laura L. Hayman, Donald Lloyd-Jones, Dilip K. Pandey, Eduardo J. Sanchez, Andrea Parsons Schram and Laurie P. Whitsel

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AHA Policy Statement

Value of Primordial and Primary Prevention for Cardiovascular Disease

A Policy Statement From the American Heart Association

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Abstract—The process of atherosclerosis may begin in youth and continue for decades, leading to both nonfatal and fatal cardiovascular events, including myocardial infarction, stroke, and sudden death. With primordial and primary prevention, cardiovascular disease is largely preventable. Clinical trial evidence has shown convincingly that pharmacological treatment of risk factors can prevent events. The data are less definitive but also highly suggestive that appropriate public policy and lifestyle interventions aimed at eliminating tobacco use, limiting salt consumption, encouraging physical exercise, and improving diet can prevent events. There has been concern about whether efforts aimed at primordial and primary prevention provide value (ie, whether such interventions are worth what we pay for them). Although questions about the value of therapeutics for acute disease may be addressed by cost-effectiveness analysis, the long time frames involved in evaluating preventive interventions make cost-effectiveness analysis difficult and necessarily flawed. Nonetheless, cost-effectiveness analyses reviewed in this policy statement largely suggest that public policy, community efforts, and pharmacological intervention are all likely to be cost-effective and often cost saving compared with common benchmarks. The high direct medical care and indirect costs of cardiovascular disease—approaching $450 billion a year in 2010 and projected to rise to over $1 trillion a year by 2030—make this a critical medical and societal issue. Prevention of cardiovascular disease will also provide great value in developing a healthier, more productive society. **(*Circulation*. 2011;124:967-990.)**

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ prevention

Cardiovascular disease (CVD), including heart disease and stroke, is the leading cause of death and disability in women and men in the United States.[1] The preclinical substrates for clinical CVD (eg, fatty streaks and atherosclerosis) begin early in life and are influenced over time by potentially modifiable risk factors, behaviors, and environmental exposures. Favorable risk factor levels in middle age are associated with a lower lifetime risk for CVD mortality, increased survival, and improved quality of life.[2] Population-based and clinical studies highlight the importance of primordial prevention, defined

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herein as prevention of the development of risk factors in the first place,[3] and primary prevention, defined as interventions designed to modify adverse levels of risk factors once present with the goal of preventing an initial CVD event.[4,5] Recently, the passage of the Patient Protection and Affordable Care Act (PPACA) (public law 111–148) has focused the attention of policy makers, providers, and consumers on the value and cost savings/cost-effectiveness of life-course primordial and primary prevention strategies.[6]

Although it is clear and accepted from clinical trial data that prevention is efficacious (ie, that prevention works within the scope of the trial), it is less well accepted that preventive community interventions are effective and provide value (ie, that prevention will work in the community and is worth what we will pay for it). This statement summarizes the rationale and available evidence that support a life-course approach to primordial and primary prevention, as well as the cost-effectiveness (ie, value) of, multilevel policy implications for, and fertile areas for future research of preventive intervention. A primer on cost-effectiveness is provided as an Appendix. Common terms used in cost-effectiveness analysis are defined in Table 1. Table 2 provides a summary of the various cost-savings/cost-effectiveness data for various primordial or primary prevention initiatives reviewed in this statement.

Table 1. Glossary of Terms in an Economic Analysis

Term	Definition
Cost-effectiveness analysis	A formal approach to assessing value in which the effectiveness and costs of a medical service are compared with a previous standard
Direct costs	Costs directly related to medical care provided such as the cost of a diagnostic test or a medication
Indirect costs	Costs that are incurred as a result of illness but not actually part of the medical service; lost income from missing time at work is a common example
Average costs	All costs related to a medical service, including both fixed and marginal costs
Fixed costs	Costs that will be spent regardless of the number of services, including the cost of developing the facility
Marginal cost	The cost of the next service of a particular type such as the next stress test, including the cost of equipment or pharmaceuticals that are used only once; the cost of a coronary stent would be a marginal cost
Utility	Overall evaluation of health status, generally with 1 meaning optimal health and functioning and 0 being death
QALYs	QALYs are calculated by multiplying survival by utility; if a patient is expected to live for 10 y at 0.8 utility, this would be 8 QALYs; QALYs are often used as a measure of effectiveness when calculating an ICER
ICER	An ICER is the most common measure of cost-effectiveness; cost-effectiveness always compares one service with another such as a new treatment for hypertension compared with the previous standard; the ICER is calculated by first determining the incremental cost-effectiveness of the new therapy compared with the standard; the ICER is then the incremental cost divided by the incremental effectiveness
Willingness-to-pay threshold	The amount of money that an individual or group of individuals will pay for a medical service; an ICER below the threshold would be considered cost-effective, whereas an ICER above the threshold is not cost-effective
Discounting	Both future cost and survival are generally discounted, which means that people value cost over a 1-y period or 1 y of survival at the present time more than costs or 1 y of survival in the future; thus, with a discount rate of 3%, next year's costs or survival is 3% less important than this year's costs or survival

QALY indicates quality-adjusted life-years; ICER, incremental cost and incremental effectiveness ratio.

Rationale for Life-Course Approach to Primordial and Primary Prevention

The life course is generally divided into 5 stages: fetal development and the maternal environment, infancy and childhood, adolescence, adulthood, and older age.[29] Although these stages are distinctly identified, they merge into one another, and influences during each life stage can have subsequent impact throughout the course of life. Disturbing trends for chronic disease and conditions like obesity and diabetes mellitus are emerging in which the incidence rates not only are increasing but also are affecting people at an earlier age.[29] These trends highlight the important need for primordial and primary prevention across the lifespan. Prevention efforts targeted at one point during the life course may have a lasting impact later in life or even from one generation to the next. For example, smoking cessation programs targeted at pregnant mothers can influence not only maternal health but also fetal health and infant and childhood well-being, including the incidence of ear infections, asthma, sudden infant death syndrome, and respiratory infections.

No multidecade, population-based, longitudinal studies have been conducted linking absolute levels of risk factors in childhood to incident clinical CVD events in adult life. Moreover, no randomized clinical trials have demonstrated that reduction of risk factor levels in childhood prevents cardiovascular events in adult life. Such studies are difficult to undertake in light of the large sample sizes, multidecade follow-up, and costs of long-term interventions and monitoring that would be required. Large cohort studies are possible; in particular, the National Children's Study is just getting underway (in 2011). It will examine the effects of the environment, defined broadly, and genetics on the growth, development, and health of children across the United States.[30] The study will follow the cohort from before birth to 21 years of age and will contribute to an understanding of the role that various factors have on health and disease.

Several lines of evidence support the need for and value of primordial and primary prevention beginning early in life. This evidence base includes pathology studies of child and adolescent decedents that demonstrate that the extent of atherosclerotic vascular change is associated with the number and intensity of premortem modifiable risk factors and behaviors.[31–33] Further evidence comes from noninvasive imaging studies demonstrating that adverse levels of major risk factors for CVD measured in childhood and adolescence are associated with a prognostically significant early indicator of subclinical atherosclerosis, increased carotid intima-media

Table 2. Summary of Cost Savings or Value for Key Primordial and Primary Prevention Strategies in the United States

Intervention	Primordial or Primary Prevention	Cost Savings/Value	Source
Comprehensive prevention programs			
Community-based programs to increase physical activity, to improve nutrition, and to prevent smoking and other tobacco use	Primordial	A return on investment of $5.60 for every $1 spent within 5 y	7
Comprehensive worksite wellness programs	Primordial and primary	Within first 12 to 18 mo, medical costs fall by approximately $3.27 for every $1 spent on worksite wellness; absenteeism costs fall by about $2.73 for every $1 spent	8
Comprehensive school-based initiatives to promote healthy eating and physical activity	Primordial	Cost-effectiveness is $900–$4305 per QALY saved	9, 10
Physical activity			
Building bike and pedestrian trails	Primordial and primary	Nearly $3 in medical cost savings is seen for every $1 invested in building these trails	11
Physical activity interventions such as pedometer and walking programs	Primordial and primary	ICERs ranging from $14 000–$69 000 per QALY gained relative to no intervention, especially in high-risk groups	12–14
Diet/nutrition			
Reducing sodium in the food supply	Primordial and primary	It is estimated that reducing population sodium intake to 1500 mg/d would result in $26.2 billion in healthcare savings annually	15
Obesity prevention			
Obesity management program	Primary	1-y interventions have shown reduction in risk categories such as poor eating and poor physical activity habits and in weight for a return on investment of $1.17 for every $1 spent	16
Tobacco control and prevention			
Excise taxes	Primary	A 40% tax-induced cigarette price increase would reduce smoking prevalence to 15.2% by 2025 with large gains in cumulative life-years (7 million) and QALYs (13 million) for a total cost savings of $682 billion	17
Comprehensive smoke-free air laws in public buildings	Primordial	Eliminating exposure to second-hand smoke would save an estimated $10 billion annually in direct and indirect healthcare costs	18
Tobacco cessation programs	Primary	ICERs for treatment programs range from a few hundred to a few thousand dollars per QALY saved	19
Comprehensive coverage for tobacco cessation programs in Medicaid programs	Primary	Comprehensive coverage led to reduced hospitalizations for heart attacks and a net savings of $10.5 million or a $3.07 return on investment for every $1 spent; states offering comprehensive smoking cessation therapy to their employees or in their tobacco control and prevention programs save $1.10–$1.40 in healthcare expenditures and productivity for every $1 spent	20, 21
Tobacco cessation programs for pregnant women	Primary for mother; primordial for fetus	These programs produce a cost-to-benefit ratio as high as 3:1 (ie, for every $1 invested in cessation/relapse programs, $3 are saved in downstream health-related costs)	22
Diabetes prevention			
Diabetes screening	Primordial	Targeted screening for T2DM based on age and risk was found to be far more cost-effective (ICERs ranging from $46 800–$70 500 per QALY gained) compared with universal screening (ICERs from $70 100–$982 000 per QALY gained); targeted screening for undiagnosed T2DM in blacks between 45 and 54 y of age was found to be the most cost-effective with an ICER of $19 600 per QALY gained relative to no screening	23, 24
Lifestyle changes in diabetes prevention	Primary	Lifestyle changes reduced the incidence of diabetes mellitus by 58%, whereas metformin therapy reduced risk by 31%; in patients with impaired glucose tolerance, primary prevention in the form of intensive lifestyle modification has median ICERs of $1500 per QALY gained	23, 25
Cholesterol screening and prevention			
Widespread use of statins	Primary	Full adherence to ATP III primary prevention guidelines would prevent 20 000 myocardial infarctions and 10 000 CVD deaths at a total cost $3.6 billion or $42 000 per QALY if low-intensity statins cost $2.11 per pill (which is substantially higher than the cost of currently available, effective generic statins); at a $50 000 willingness-to-pay threshold, statins are cost-effective up to $2.21 per pill	26
Blood pressure			
Hypertension medication therapy	Primary	Approximate $37 100 cost per life-year saved	27
Polypill administration	Primary	Polypill medication treatment in men was less expensive and more effective, with an average cost of $70 000 compared with $93 000 for no treatment, and resulted in 13.62 QALYs compared with 12.96 QALYs without treatment	28

QALY indicates quality-adjusted life-years; ICER, incremental cost and incremental effectiveness ratio; T2DM, type 2 diabetes mellitus; ATP III, Adult Treatment Panel III; and CVD, cardiovascular disease.

thickness, in adulthood.[34–37] Results from a population-based prospective cohort study, the Young Finns Study, are particularly noteworthy because risk factor exposures (including low-density lipoprotein cholesterol [LDL-C], body mass index, cigarette smoking, and systolic blood pressure) in 12- to 18-year-old adolescents predicted increased carotid intima-media thickness in adulthood independently of the risk factors for CVD present in adulthood.[32] More recently, in a cross-sectional comparative study of lean and obese children and youth with type 2 diabetes mellitus (T2DM), those with T2DM had significantly greater carotid intima-media thickness and stiffer carotid arteries than their leaner counterparts.[38] The presence of either T2DM or obesity contributed independently to adverse changes in carotid structure and function.[38] Moreover, a combined data analysis from 4 cohorts comprising 4380 patients showed that risk factors from 9 years of age were predictive of carotid intima-media thickness in adulthood.[39]

Additional evidence supporting the need for primordial and primary prevention beginning early in life comes from population-based epidemiological studies indicating that major risk factors for and adverse health behaviors associated with CVD in adulthood, including cigarette smoking, dyslipidemia (high levels of LDL-C and low levels of cardioprotective high-density lipoprotein cholesterol), elevated blood pressure, physical inactivity, and obesity, are prevalent in childhood and adolescence[1,40–42] and are potentially modifiable.[43,44] The US Surgeon General's office reported that "overweight adolescents have a 70% chance of becoming overweight or obese adults. This increases to 80% if one or more parent is overweight or obese. Overweight or obese adults are at risk for a number of health problems including CVD, T2DM, high blood pressure, and some forms of cancer."[45] Tracking of risk factors from childhood to young adulthood and intraindividual clustering of risk factors and adverse health behaviors have been well documented in clinical and population-based studies in the United States and globally.[46–48] Finally, the efficacy and safety of modifying major CVD risk factors in early life with therapeutic lifestyle change and, although data on safety are more limited, the efficacy of pharmacological interventions have also been demonstrated.[49–53] More data in large populations are needed to establish the safety of pharmacological therapy begun in the young and continued long term.

Collectively, these data have led to the development of primordial and primary prevention of CVD guidelines in children and youth[4,54–56] and throughout the life course.[57,58] With emphasis on the development of healthy lifestyle behaviors as the cornerstone of both primordial and primary prevention, the ultimate goal is to promote optimal cardiovascular health beginning in childhood and adolescence and continuing throughout the life course to reduce the risk and burden of CVD and its sequelae.

Prevention Framework in the United States

The framework for health in the United States is the Healthy People framework. Healthy People 2020 is the current iteration.[59] The US Preventive Health Services Task Force and the Task Force on Community Preventive Services, sponsored by the Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention, respectively, have attempted to evaluate the evidence for the effectiveness of preventive services.[60]

Healthy People 2020 lays out a set of objectives for optimizing the health of America. The most relevant categories of Healthy People 2020 objectives include diabetes mellitus, heart disease and stroke, nutrition and weight status, physical activity and fitness, and tobacco use.[59] However, it is clear that there are substantial deficiencies and disparities in the delivery of preventive services.[61] The PPACA tried to address some of these deficiencies in clinical and community-based prevention in several programs created by the new law.[6,62]

The PPACA mandates that clinical preventive services graded A or B by the US Preventive Health Services Task Force will be offered to people with insurance at no out-of-pocket cost. Among the CVD-related A or B services are aspirin counseling, blood pressure screening, cholesterol screening, healthy diet counseling, obesity screening and counseling, and tobacco cessation counseling.[60] The National Commission on Prevention Priorities, before the PPACA, ranked 25 US Preventive Health Services Task Force A and B–graded services according to health impact and cost-effectiveness.[63] The CVD services favorably ranked when cost-effectiveness was included as a criterion were aspirin counseling, blood pressure screening, cholesterol screening, and tobacco use counseling.

The PPACA also strengthens the Community Guide, which addresses health improvement and disease prevention at the community level by conducting systematic reviews to determine effective program and policy interventions and grading the interventions.[64,65] Nutrition, obesity, physical activity, and tobacco are among the Community Guide topics.

The Economic Burden of Cardiovascular Disease and Potential to Reduce Cost

The direct and indirect costs of CVD in the United States have been projected by the American Heart Association to increase from $272.5 and $171.7 billion in 2010 to $818.1 and $275.8 billion in 2030, respectively.[66] Most of the cost of CVD is related to short- and long-term care, not prevention.[67] In addition, these cost estimates do not include all costs related to obesity, diabetes mellitus, and tobacco use. Despite the fall in overall mortality, the prevalence of disease is expected to increase, largely as a result of the aging of the population. This troubling scenario is not inevitable; most CVD is preventable or at least can be delayed until old age with less chronic morbidity, with the potential for fewer events, less disability, and even lower costs.

Challenges in Determining the Cost-Effectiveness of Primordial and Primary Prevention

Cardiovascular disease remains a serious medical problem that can be associated with death and disability on one hand and considerable resource use on the other. Clinical efficacy remains the primary driver for the use of any service. Once efficacy is established and despite its many limitations, cost-effectiveness analysis has an important role in assessing value. Properly applied, cost-effectiveness analysis not only offers a ratio and its distribution but also renders explicit the assumptions underlying the analysis (ie, costs of therapy,

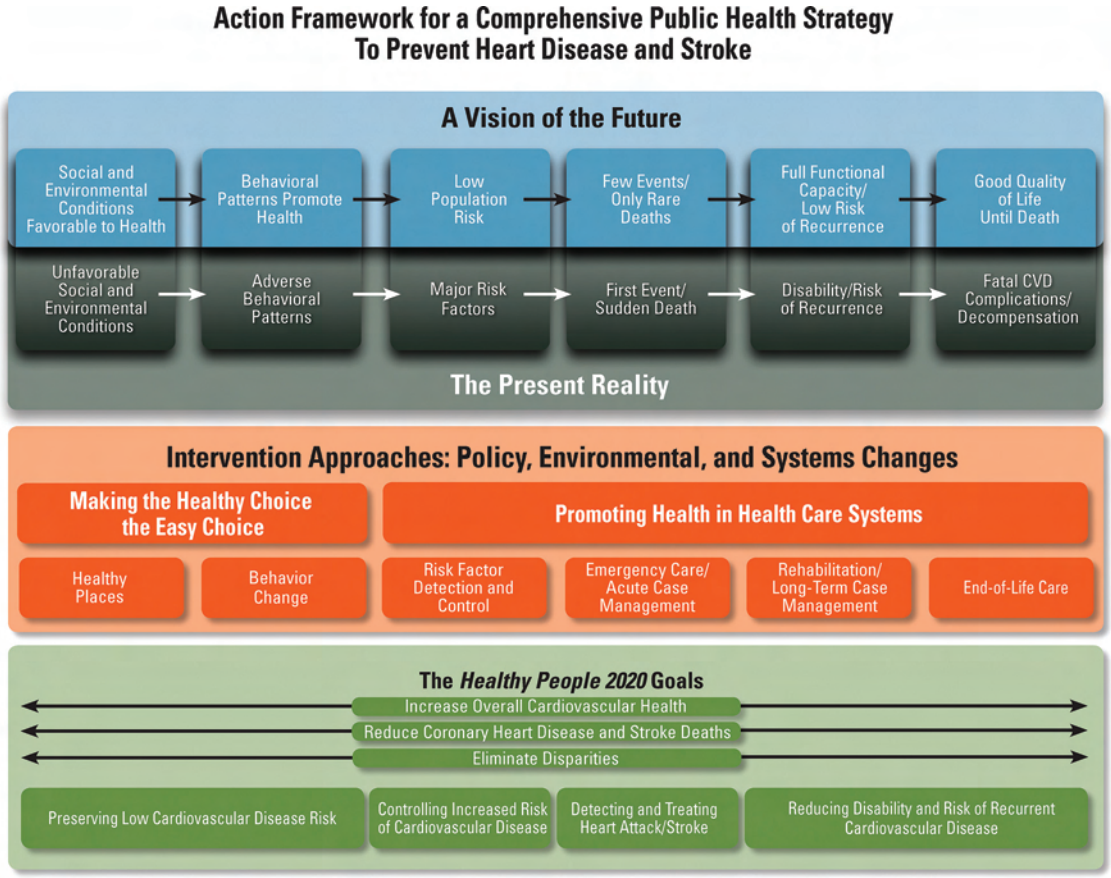

Figure 1. A framework for a comprehensive health strategy to prevent cardiovascular diseases (CVD), including policy, environmental, and systems changes to achieve Healthy People 2020 goals. Reprinted from Labarthe et al[69] with permission of the publisher. Copyright © 2005, Elsevier.

disease outcomes, and complications), thus helping patients and society evaluate the choices they make. However, in the evaluation of the value of primordial and primary prevention, formal cost-effectiveness analysis may not be realistic and may fail to evaluate value properly.

Assessing the value of prevention in apparently healthy patients is generally more difficult than evaluating therapy for established disease because the time horizon to the clinical manifestation of disease is generally long—many decades in the young. Thus, it is difficult, perhaps impossible, to assess long-term effectiveness in terms of survival or quality-adjusted life-years (QALYs) or associated costs because of increasing uncertainty about outcome the further one tries to look into the future. Furthermore, discounting (see the economics primer in the Appendix and the glossary in Table 1) works to the disadvantage of prevention because costs may accrue in the present and the benefit may become apparent only in the distant future. Thus, the costs will not be discounted but the benefit will be. Cost-effectiveness in prevention is also at a disadvantage because of the rule of rescue; for example, we will spend what it takes to save the child who falls down a well, but we will not finance the routine building of fences around wells. The rule of rescue is a fundamental, human emotional response to people in distress to which we all can respond. The decision not to build fences would be based on avoiding the costs at present to build fences around many wells to prevent 1 child from falling down a specific well perhaps years in the future, discounting the costs of rescue. Both uncertainty about value and the rule of rescue may, in part, explain why society spends most of its healthcare resources on therapy for established, often advanced, disease and comparatively little on primordial and primary prevention.

There are technical and practical limitations to studies of the cost-effectiveness of prevention. Given the difficulties of conducting long-term clinical trials, many cost-effectiveness analyses about prevention are based on mathematical models or simulations. Such models are dependent on assumptions about both overall construction and input variables and thus must be assessed with some skepticism. Because of the difficulties involved in establishing the value of prevention with formal cost-effectiveness analyses, less quantitative approaches are often appropriate and must suffice.

There are also theoretical problems with cost-effectiveness analyses of prevention. Typically, cost-effectiveness analysis considers direct medical benefit to an individual patient and both direct medical care costs and indirect costs such as lost time at work. However, it is difficult to establish the overall benefit and reduced costs that society accrues by having a healthier population and more productive workforce. The benefit is one of both preventing early death and compressing morbidity until the end of life.[68] Thus, the focus on individual benefits in the distant future and direct medical care costs incurred immediately underestimates the economic and other value to society

Table 3. American Heart Association 2010 to 2013 Strategic Policy Recommendations That Address Primordial and Primary Prevention Efforts in the United States

Federal level
Overall policy
Preserve the prevention and public health fund in the Patient Protection and Affordable Care Act
Increase funding for Centers for Disease Control and Prevention state-based heart disease and stroke prevention programs
Nutrition and dietary guidance
Develop and finalize robust nutrition standards for school meals and foods sold in schools outside the meal program; ensure schools adopt robust wellness policies that are implemented, disseminated, and evaluated
Improve food labeling to minimize consumer confusion and to increase knowledge and awareness especially about calories, sodium, saturated fat, *trans* fat, and added sugar
Effectively implement restaurant menu labeling
Address food marketing and advertising to children
Physical activity
Fit Kids Act: hold schools accountable for providing students with high-quality physical education and facilitate the integration of physical activity throughout the school day
Require that the Physical Activity Guidelines for Americans be regularly updated every 5 y in coordination with the Dietary Guidelines for Americans
Support funding for the Safe Routes to School program in the Surface Transportation Reauthorization Act, helping children walk and bike to school safely
Help implement the US National Physical Activity Plan
Tobacco
Implement Food and Drug Administration tobacco regulation in a strong and timely manner in the Family Smoking Prevention and Tobacco Control Act
Support efforts to increase access to tobacco cessation services
State level
Overall policy
Provide adequate prevention, diagnosis, treatment of overweight and obesity in the healthcare environment
Provide robust surveillance and monitoring
Implement comprehensive worksite wellness programs
Implement and monitor strong local wellness policies in all schools
Provide adequate funding and implementation of coordinated school health programs
Develop comprehensive obesity prevention strategies in early childhood and daycare programs
Provide adequate funding for state heart disease and stroke prevention programs
Nutrition
Work to eliminate food desserts and to improve access and affordability of healthy foods (community gardens, farmers' market expansion, incentives, Healthy Food Financing Initiative)
Strengthen nutrition standards in schools for meals and competitive foods and in all government nutrition assistance or feeding programs
Implement menu labeling in restaurants
Continue to monitor and pass legislation/regulation for the removal of industrially produced *trans* fats from the food supply and to ensure the use of healthy replacement oils
Implement robust procurement standards for foods purchased by employers or government feeding programs
Physical activity
Address the built environment and support efforts to design workplaces, communities, and schools around active living; integrate physical activity opportunities throughout the day
Fund and develop walking/biking trails that connect key aspects of the community
Increase Safe Routes to School
Implement zoning/building ordinances that encourage walking/using stairs
Advocate for implementation of Complete Streets policies that allow biking and walking and are pedestrian friendly with appropriate cross-walks, sidewalks, traffic lights, and slower speed limits in walking/biking areas
Implement shared use of school facilities within the community and support the construction of school fitness facilities
Increase sports, recreational opportunities, parks, and green spaces in the community
Increase the quantity and improve the quality of physical education in schools
Support 60 min/d of supervised, moderate-to-vigorous physical activity integrated throughout the school day
Tobacco
Pass and implement comprehensive clean indoor air laws
Increase excise taxes on tobacco products
Increase/sustain funding for state tobacco control/prevention programs
Implement clinical guidance and monitor health claims around smokeless tobacco products
Advocate for comprehensive smoking cessation benefits in Medicaid, Medicare, and other healthcare plans
Eliminate tobacco sales in pharmacies and other health-related institutions

and to individuals of prevention, which offers the prospect of a healthier, more productive society at all times.

Evidence Base for the Value of Cardiovascular Disease Prevention: Societal Change

The Cost-Effectiveness/Value of Prevention: The Impact of Environment and Policy Change

The conceptual basis for implementing primordial and primary prevention is an environmental model that maintains that an individual's behavior is influenced by his or her surrounding physical, social, and cultural environments (Figure 1).[69] In other words, policy change makes the greatest impact when it optimizes the environments where people live (ie, workplaces, schools, homes, and communities), making healthier behaviors and healthier choices the norm by default or by design and putting individual behavior in the context of multiple-level influences. This environmental model represents a shift away from prioritizing individual behavior change that focuses on individual-level or intrapersonal influences. For example, passing comprehensive clean indoor air laws,[70] raising tobacco excise taxes,[71] or reducing sodium from the food supply[19] can have a profound impact on a large segment of the population and may contribute to marked improvements

in cardiovascular health. State-level policies have been shown to reduce junk food in vending machines and school stores.[72] These population-based strategies are a critical complement to preventive services and treatment programs in which practitioners and patients are working together to foster important individual behavior and lifestyle changes.[73] In fact, research continues to demonstrate that environment and policy change is one of the most impactful ways to improve public health, providing the counterargument to those policy makers who argue that government has no role, that health is largely an individual's responsibility.[74–77] Many policy strategies to affect environmental change are relatively new, and evidence continues to emerge on their cost-effectiveness and economic value. This article summarizes many of them and underscores the important role that policy change has in affecting public health. Table 3 summarizes the American Heart Association's 2010 to 2013 specific strategic policy priorities that address primordial and primary prevention. These priorities certainly do not encompass all of the policy strategies that are underway in prevention efforts, but they are the priorities of one major nonprofit organization working in collaboration with coalitions and partners in public health.

Communities

Community leaders are beginning to understand the preventive value of environment and policy changes that facilitate a healthy diet, increased physical activity, and elimination of tobacco use. Three recent landmark reports have highlighted policy strategies at the community level to address cardiovascular health, sensitizing community leaders, policy makers, and organizations to a range of policy options such as access to and affordability of healthy foods; opportunities for active living through the built environment and parks, recreational spaces, and walking/biking trails; increased consumer knowledge with approaches like menu labeling in restaurants; and strengthened nutrition standards and physical education/physical activity opportunities in schools for children.[78–80] Cities across the United States are debating the best ways to convert vacant lots or brown fields in the context of economic development. Community gardens, small parks, and open green spaces are excellent options for these areas that positively impact surrounding residential properties, increase rates of home ownership, and spur economic redevelopment.[81] Other studies have shown the direct cost-benefit of building bike/pedestrian trails by reducing healthcare costs associated with physical inactivity. A study based on a simulation model found that for every $1 invested in building these trails, nearly $3 in medical cost savings may be achieved.[11] Linking different parts of the community with trails and walkways spurs community integration, more efficient land use, lower traffic congestion, and better quality of life.

Other initiatives like the Healthy Food Financing Initiative address the importance of making healthy, affordable foods available in low-income urban, rural, and minority communities. The Healthy Food Financing Initiative provides critical loan and grant financing for food retailers to renovate existing stores or to develop new stores to provide healthy foods.[82] Concurrently, the Healthy Food Financing Initiative reduces health disparities, creates jobs, and stimulates local economic development. One example is the Pennsylvania Fresh Food Financing Initiative, a public-private partnership created in 2004 that led to 83 new or renovated supermarkets and fresh-food outlets, providing 400 000 residents with access to healthy food while creating or maintaining 5000 jobs. Essentially, $190 million was leveraged as a result of $30 million in state seed money. A recent report by Trust for America's Health showed that an investment of $10 per person per year in proven community-based prevention programs could save the country more than $16 billion annually within 5 years.[7] This report is based on a model developed by researchers at the Urban Institute that assessed medical cost savings only, not additional gains from worker productivity, reduced absenteeism, or quality-of-life measures. The researchers made low-end assumptions for the drops in disease rates and high-end assumptions on costs of programs based on a comprehensive review of the literature.

New York City and several other major cities have been on the forefront of public health policy change with initiatives such as smoking bans in public buildings and workplaces, *trans* fat bans in restaurants, restaurant menu labeling, the Green Kart initiative, and healthy corner store initiatives. Most recently, the New York City Department of Health has led the National Sodium Reduction Initiative, a partnership of ≈64 cities, states, and national health organizations, in establishing target levels for sodium reduction by food categories and soliciting pledges from food companies to meet these targets. The many benefits of lowering sodium intake underscore the need for a comprehensive, coordinated public health strategy to lower the amount of salt in the food supply to 1500 mg/d by 2020. It is estimated that if the US population moved to an average intake of 1500 mg/d sodium, there would be a 25.6% overall decrease in high blood pressure and $26.2 billion in healthcare savings.[15] Such a national effort would result in fewer coronary heart disease events, strokes, heart attacks, and deaths.[83]

Worksites

The worksite is an important environment for policy implementation and program intervention. More than 130 million Americans are employed across the United States annually, and workplace wellness programs have been shown to prevent the major shared risk factors for CVD and stroke.[84] Comprehensive worksite wellness programs are aimed at improving employees' cardiovascular and general health and should include the following: tobacco cessation and prevention; regular physical activity; stress management/reduction; early detection/screening; nutrition education and promotion; weight management; disease management; CVD education, including cardiopulmonary resuscitation and automated external defibrillator training; and changes in the work environment to encourage healthy behaviors and to promote occupational safety and health.[84] An estimated 25% to 30% of companies' medical costs per year are spent on employees with obesity, hypertension, dyslipidemia, and diabetes mellitus and those who use tobacco products.[85] A recent meta-analysis showed that medical costs fell by ≈$3.27 and absenteeism costs fell by $2.73 for every dollar spent on worksite wellness programs.[8] These savings are most often realized within the first 12 to 18 months.[85] Average reduc-

tions in sick leave absenteeism, healthcare costs, and workers' compensation and disability management claims were 28%, 26%, and 30%, respectively.[86,87] Productivity outcomes are harder to measure in today's postmanufacturing economy, and many employers do not have the resources or expertise to conduct such assessment.[88,89] Most productivity estimates are based on questionnaires that often yield varied estimates of on-the-job productivity gains or losses even when administered in the same setting.[90,91] Overall, however, considerable data now suggest that health-related productivity losses from employees with health risk factors or chronic disease cost US employers $225.8 billion a year or $1685 per employee per year, of which 71% is due to reduced performance at work.[92] Currently, the low level of intervention provided in the US workforce for many at-risk employees offers the opportunity to recuperate substantial productivity gains by initiating evidence-based health promotion programs, activities, and policy change in the worksite environment.[84,93]

Healthcare Systems

Healthcare systems are increasingly a target of policy intervention concerning healthy food and beverage offerings, worksite health promotion, and tobacco-free environments because they are often leading employers and role models within the community. Many hospital systems have established tobacco-free environments and are providing healthier foods and beverages in their cafeterias, food service, and vending machines[94]; improving their procurement strategies; and/or making their worksite wellness programming and health promotion efforts more robust.

Schools

More than 55 million children spend the majority of their day in schools across the United States. Accordingly, it is vitally important to offer healthy educational environments by providing opportunities for daily physical activity and/or physical education and healthy foods and beverages to create a foundation for learning the fundamentals of healthy living. School-based interventions can be effective in preventing the development of obesity in children, even in low-socioeconomic-level neighborhoods, although results are often modest and short term.[95,96] Most research focuses on other types of outcomes such as academic performance, nutrition education, physical education, physical fitness, behavior in the classroom, and knowledge gain. For example, numerous studies have documented that children who are more physically fit perform better academically, have higher attendance, display fewer behavioral problems in the classroom, and improve the overall quality of the school environment.[97–101] Schools can provide the knowledge base children need to practice healthy behaviors for a lifetime and the policy and environment changes that reinforce this prevention-related education. Providing healthier meals can also be cost-effective and may lead to better food choices at home and outside of school.[102–104] Comprehensive school interventions to promote healthy eating and physical activity can be cost-effective, ranging from $900 to $4305 per QALY saved.[9,10]

Further research is needed to determine the long-term effectiveness of policy and environment change in schools on nutrition, physical activity, obesogenic behaviors, and health outcomes, especially in at-risk populations, and the associated impact on community and home, as well as the short- and long-term cost savings associated with these interventions.[105,106]

Addressing Disparities

Lower socioeconomic and educational status are established risk factors for CVD.[107] Additionally, the obesity epidemic and risk factors for CVD such as smoking, physical inactivity, hypertension, and diabetes mellitus are disproportionately prevalent in certain populations, especially non-Hispanic blacks, American Indians, Hispanics/Latinos, and Pacific Islanders, compared with non-Hispanic whites.[1] Children also make up a vulnerable population, and their health statistics are worsening. To attenuate these disparities, policy work will have to prioritize opportunities to address social inequities, issues specific to vulnerable populations (ethnic and racial minorities, those with low income or less education, children, blue collar workers), and the importance of removing barriers and obstacles for risk reduction and behavior change. Often, the most disadvantaged members of the population have the greatest need for preventive screenings, health promotion, or programming and have the least access to or are the most reluctant to participate in these opportunities.[108] The fundamental causes of vulnerability are rooted in issues of daily life, most often beyond the scope of traditional public health. Thus, it will be important for the public health community to consider engaging with nontraditional partners to promote increased prevention strategies and to reduce health disparities in communities.[109] Additional research is needed to determine how best to reach and engage underserved populations and to optimize policy interventions for people of all races, ages, ethnicities, and education and income levels.

Ongoing research and evaluation of preventive interventions and policy change in community settings will provide additional data on cost-effectiveness and value. The Sydney Diabetes Prevention Program, for example, is a community-based translational study with >1500 participants who are at high risk of developing diabetes mellitus. The study will ascertain the reach, feasibility, effectiveness, and cost-effectiveness of delivering a lifestyle modification program in a community setting through primary health care.[110] Too often, the difficulty in assessing the cost-effectiveness of these types of public health interventions is the lack of specific effectiveness data and insufficient sample sizes, inadequate follow-up, or different basic principles of analysis used by health promoters and economists.[111] To bridge the evidence gap and to provide a framework for informed decision making, it will be important to promote effective policy evaluation, optimal research design in real-world settings, and common outcome measures to assess the true value and economic impact of change and to incorporate individuals' broader perspective of well-being.

Evidence Base for the Value of Cardiovascular Disease Prevention: Behavior Change

As models suggest, the willingness for individuals to change their lifestyle behaviors is affected by a number of factors such as the different stages of readiness, perceived threat or

susceptibility of developing a health condition, concerns about the seriousness of the preventable condition, perceived benefits of changing behavior, and cues to action that might come from social networks and their surrounding environment.[112] This section outlines the cost-effectiveness of primordial and primary prevention concerning environment and policy change that affects behavior in the areas of tobacco use, physical activity, diet, and obesity.

Tobacco Use

Smoking costs the US economy more than $301 billion per year, including workplace productivity losses of $67.5 billion, premature death at $117 billion, and direct medical expenditures of $116 billion.[20] These costs to people's lives and their quality of living underscore the importance of primordial prevention such as state tobacco control and prevention programs and smoke-free air laws and primary prevention efforts such as adequate coverage for cessation therapy and tobacco excise taxes.

Tobacco Control and Prevention Programs

In 1998, the 4 largest US tobacco companies and the attorneys general of 46 states signed the Tobacco Master Settlement Agreement, settling the states' Medicaid lawsuits against the tobacco industry for recovery of their tobacco-related healthcare costs. Under the agreement, states received upfront payments of $12.74 billion with the promise of an additional $206 billion over the next 25 years. Ideally, states would use this money to fully fund tobacco control programs that follow Centers for Disease Control and Prevention "best practices." Unfortunately, as a result of the negative fiscal environment and competing priorities, only 1 state, North Dakota, currently funds its tobacco prevention programs at Centers for Disease Control and Prevention–recommended levels. Revenue from the settlement continues to flow toward other parts of state budgets despite the fact that state tobacco control program expenditures have been shown to be independently associated with overall reductions in smoking prevalence.[113] States are sacrificing long-term health benefits and healthcare cost reductions for short-term budget fixes. If all states had funded their tobacco control programs at the minimum or optimal levels recommended by the Centers for Disease Control and Prevention, there could have been millions of fewer smokers a decade later.[113]

Smoke-Free Environments

Passing comprehensive smoke-free air laws in public places and work environments is a cornerstone of the public health strategy in tobacco control efforts. Although these efforts have been extremely effective in protecting a large segment of the US population from the deleterious effects of secondhand smoke, >88 million nonsmokers >3 years of age are still exposed, especially children in the home.[114] The Institute of Medicine, backed by studies from around the world, published a report showing reduced incidence of acute myocardial infarction after implementation of clean indoor air laws in workplaces and communities.[115] Lightwood et al[116] developed a simulation to estimate the CVD event incidence and costs as a function of risk factor prevalence, including passive smoking. At 1999 to 2004 levels, passive smoking caused 21 800 to 75 100 CVD deaths and 38 100 to 128 900 myocardial infarctions annually, with a yearly treatment cost of $1.8 to $6.0 billion. The Institute of Medicine estimates direct and indirect healthcare costs associated with disease incidence caused by secondhand smoke exposure at $10 billion annually.[18]

There are other economic arguments for clean indoor air laws. The hospitality and tobacco industries often promote the idea that business will suffer after these laws are passed. However, increasing evidence from municipalities, states, and countries shows no significant impact on sales data, and in many instances, business actually increases after a short-term initial decline.[117] Additional benefits for businesses are lower cleaning costs, lower worker absenteeism, and increased productivity.[118]

Several federal government initiatives[114] are currently underway to address comprehensive smoke-free air policies and tobacco control, including funds from the American Recovery and Reinvestment Act that have been distributed to communities, territories, and states to address tobacco control. In 2009, the US Department of Housing and Urban Development issued notices encouraging public housing authorities to implement no-smoking policies. Moreover, the US Environmental Protection Agency conducts a national campaign that educates and encourages parents to make their homes smoke free to protect their children's health.

Tobacco Excise Taxes

Tobacco excise taxes are another pillar of the tobacco control movement. The federal government has imposed excise taxes, most recently with the expansion of the Children's Health Insurance Program. A cigarette tax increase of 61.66 cents per pack went into effect on April 1, 2009. There were also increases in the federal tax rates on other tobacco products such as smokeless products, "small cigars," roll-your-own tobacco, and regular cigars. At the same time, states have imposed tobacco excise taxes with a current nationwide average of $1.45 per pack (as of July 2010). As a leader in public health initiatives, the state of New York (June 2010) raised its cigarette tax by $1.60 to give it the highest cigarette tax in the nation at $4.35 per pack.

A robust literature has examined the impact of cigarette tax increases on smoking prevalence, especially in youth. Most studies have found that higher taxes reduce consumption, especially via cessation rates in young smokers.[71,119] Modeling techniques have estimated that a 40% tax-induced cigarette price increase would reduce smoking prevalence to 15.2% in 2025 with large gains in cumulative life-years (7 million) and QALYs (13 million) for a total cost savings of $682 billion.[17] Industry documents show, however, that the tobacco companies understand the impact of tax increases on consumption and have developed pricing strategies, including the development of lower-cost generics and price-related marketing efforts such as multipack discounts and couponing to reverse these effects.[120] The tobacco control movement has to continue to adapt to strategies to maintain the health impact and value of tobacco use prevention strategies.

Physical Activity

The benefits of regular exercise and cardiorespiratory and general physical fitness are numerous and contribute signif-

icantly to health impact and cost savings, including lower risk for CVD and diabetes mellitus, improved musculoskeletal health, better weight management, reduced risk for hypertension, less dyslipidemia, preserved cognitive function, reduced symptoms of depression, and improved overall quality of life.[121–125] The majority of children, adolescents, and adults do not achieve the recommended levels of physical activity each day, spending a majority of their time in sedentary activities.[126,127] The proportion of adults who meet the physical activity guidelines varies by education level: 46% of people with a college degree or higher are regularly active compared with only 21.4% of adults with less than a high school diploma.[128] When assessed with actual accelerometer data from the National Health and Nutrition Examination Survey rather than self-reported physical activity, the data are much more sobering: Only 3.8% of adults engage in moderate to vigorous physical activity at least 5 days a week.[129] Globally, ≈1.9 million deaths per year are attributed to physical inactivity.[127] There is a strong, positive relationship between physical inactivity and QALYs lost in the obese population.[130]

The Task Force on Community Preventive Services recommends physical activity interventions under 4 major strategies: community-wide campaigns, individually adapted healthy behavior change, community social-support interventions, and the creation of or enhanced access to physical activity information and opportunities.[12] Studies that have examined the cost-effectiveness of community-based physical activity interventions show some reduction of chronic disease incidence and incremental cost and incremental effectiveness ratios (ICERs) ranging from $14 000 to $69 000 per QALY gained relative to no intervention, especially in high-risk groups.[12–14] These interventions can also be successfully implemented in a cost-effective way in primary care settings to reduce CVD risk and to improve quality of life.[131] Pedometer programs and mass media–based community campaigns have been found to be the most cost-effective, whereas general practitioner referral to an exercise physiologist was the least cost-effective because of travel costs and the associated time spent on consultation and screening.[127] A behavior-based intervention in which participants were taught to integrate daily moderately vigorous physical activity into their lives was found to be more cost-effective than a structured exercise program for improving physical activity and cardiovascular health.[132] A report from the National Institute for Clinical Excellence in the United Kingdom found that when the costs of health care avoided are included, exercise programs are dominant(ie, offer better outcome at a lower cost).[133]

Despite accumulating evidence on the cost-effectiveness of exercise promotion and intervention in various settings, there is significant heterogeneity in study quality, intervention strategies used, and measured health and behavior outcomes. Further research and cost-effectiveness analyses are needed to determine sustainability, long-term outcomes, impact on various population subgroups, wide-ranging appeal, and perceived value that people place on the time they spend exercising.[134,135]

Diet and Obesity

The centerpiece of a healthy lifestyle is a diet and physical activity pattern that follows the evidence-based recommendations put forward by several agencies, including the US Department of Agriculture, the American Diabetes Association, and the American Heart Association. A growing body of evidence supports the benefits of following the established dietary guidelines. Compared with those who did not follow the guidelines, those who reported adherence to the dietary guideline had a lower prevalence of the metabolic syndrome,[136] and among women, there was a lower prevalence of insulin resistance,[137] a lower odds of carotid atherosclerosis,[138] and slower progression of atherosclerosis.[139] Moreover, adherence to the dietary guidelines was associated with reduced CVD mortality, significantly smaller waist circumference, and lower levels of serum insulin and C-reactive protein concentration.[140] Numerous clinical trials have demonstrated the benefits of reduced sodium intake[141–143] and the benefits of healthy eating patterns such as the Mediterranean-style diet.[144–147] However, despite the cumulative evidence supporting the benefits of a healthy diet on blood pressure, lipids, insulin sensitivity, and body weight, the majority of the population does not meet several of the public health targets set forward in the dietary guidelines. It has been estimated that >50% of global deaths can be attributed to diet.[148] Clearly, the cost of these unnecessary deaths and the comorbidity preceding the deaths is astronomical.

Today, one of the most significant and prevalent conditions associated with nonadherence to the dietary guidelines is obesity. Overall, the economic impact of obesity in the United States is substantial.[149] In 2011, ≈66% of adults in the United States are overweight, including 33% who are obese.[150] Among children, the prevalence of obesity in recent years has increased 2- to 3-fold.[151] Research examining the costs of obesity has focused on 3 areas of impact: direct medical costs, productivity costs, and human capital costs.

Direct Medical Costs

Obesity is associated with myriad comorbid conditions; for example, hypertension, diabetes mellitus, CVD, arthritis, and sleep disorders.[152–154] As the medical conditions associated with obesity increase, so do the associated medical costs—from diagnosis to treatment of these disorders. The methods used and the populations studied in examining the cost of overweight and obesity vary widely; however, there is widespread agreement that the medical costs are substantial.[155] One example of costs attributed to overweight and obesity comes from a study of a managed-care population between 35 and 64 years of age that was followed up for 9 years. On average, obese patients accumulated annual costs that were 36% higher than the healthy-weight group, which included 105% higher costs for prescriptions and 39% higher primary care costs. When the overweight group was compared with the healthy-weight group, prescription costs were 37% higher and primary care costs were 13% higher.[156] Others have used regression analysis of nationally representative surveys such as the 1998 and 2006 Medical Expenditure Panel surveys and the National Health Expenditure accounts data to derive cost estimates of obesity of $147 billion in 2008.[157] A recently published article reported that almost 17% of US medical costs can be attributed to the treatment of obesity and suggested that the obesity problem in the United States may

be having close to twice the impact on medical spending as previously estimated.[158] Estimates of medical costs for childhood obesity in the United States are ≈$14.3 billion.[159]

Productivity

Costs of lost productivity are substantial and have been studied extensively. Distinct subcategories of productivity exist, for example, absenteeism, or reduced productivity because the person is absent from work for obesity-related health reasons, and presenteeism, or decreased productivity while the person is at work. Other sequelae include premature mortality, impaired quality of life, increased rates of disability benefit payments, and increased medical care costs. It is difficult to compare the magnitude of absenteeism across studies because of the different methodologies used; however, a study reported that compared with a normal-weight employee, an overweight/obese employee lost an additional 3.73 days of work per year, with 36% of illness-related absences resulting from body habitus.[160] Nationwide, annual estimates of this loss in productivity range from $3.38 billion to $6.38 billion.[161] One investigator examined disability and reported that for men, being obese increased the probability of receiving disability income by 6.92%; for women, the increased probability was 5.64%. Premature mortality or reduced QALYs is another form of lost productivity associated with obesity. One study reported that the largest effect of obesity on morbidity was among white men; a 20-year-old white man with a body mass index >45 kg/m^2 could be expected to have a 22% reduction in remaining life-years, the equivalent of 13 years of life lost.[162] Obese people have reported lower quality of well-being, which at the national level translates into 2.93 million QALYs lost in the United States.[163]

Human Capital

Human capital is defined as the both the quantity and quality of education an individual is able to attain. The accumulation of human capital is inversely related to overweight/obesity. There is an association between body mass index and days of school missed[100] and the number of school years completed[164]; moreover, there is a consistent negative relationship between weight and grade point average among female students.[165] Among nonwhites, the relationship exists for both male and female students. These findings emphasize the impact of childhood obesity on not only educational attainment but also other related aspects of life.

The research examining the economic impact of obesity varies widely in the data sources and methodologies used. The data thus far confirm that there is a substantial cost to obesity in direct medical costs and productivity; however, further research is needed in the area of accumulation of human capital and in policy development that addresses these significant costs.[149]

Considering the negative economic impact of obesity, it would seem logical that interventions to reduce obesity would be beneficial in terms of lowering an organization's medical costs and improving worker productivity. Return-on-investment models have been used to forecast program savings in several large organizations; the most costly employees for employers were those with certain modifiable risk factors. Applying a predictive return-on-investment model, another group of investigators tested whether an obesity management program would result in reduced health risks at 119 employer sites.[16] The program included four 30-minute telephone-based coaching sessions each month for a year, plus access to educational materials, exercise planning support, nutrition education, stress management, and Web-based health tracking. Of the 1542 participants enrolled, 890 (57.7%) completed the program. At 1 year, there was a statistically significant reduction in 7 of the 10 risk categories monitored, with sizable reductions in body weight and poor eating and poor physical activity habits. On the basis of the return-on-investment analysis, compared with no changes occurring, there was a reduction in total employer expenses by $311 755. Additionally, 59% of the total projected expense reductions were attributed to a 4.3% reduction in healthcare expenditures and 41% were attributed to enhanced productivity.[16] Other investigators have reported findings consistent with these results, supporting the association between health risk reductions, absenteeism, and presenteeism.[86,157,158]

Researchers in Switzerland developed a Markov model to evaluate the lifetime effect of a 3-year lifestyle intervention and compared it with standard care among overweight and obese adults.[166] Lifestyle intervention increased both survival and quality of life and dominated standard care in borderline obese and obese men and women. In the overweight group with an average body mass index of 27 kg/m^2, costs were higher with lifestyle intervention but were offset by the reduced risk of developing obesity-related complications and comorbidities.

Another group in Europe examined published studies to determine how cost-effective dietary changes were compared with other measures targeting CVD risk reduction.[167] Although the comprehensive studies available were limited in number and quality, findings suggested that health-promoting strategies that targeted healthy eating were more cost-effective than strategies that included pharmacotherapy for lipid reduction or nurse screening and adjunctive lifestyle counseling.

Between 2005 and 2007, the Partnership for Prevention evaluated the relevant evidence to support the ranking of the health impact and cost-effectiveness of 25 clinical preventive services that had been recommended by the US Preventive Health Services Task Force and the Advisory Committee on Immunization Practices. This ranking, based on the clinically preventable burden, measures the health impact on the affected population and the cost-effectiveness of each service; each of these received a score between 1 and 5. A score of 5 for clinically preventable burden was given to the services that produced the most health benefits; a 5 was also given to the service deemed most cost-effective. Included in this list of services was obesity screening with high-intensity lifestyle counseling for obese patients, which had clinically preventable burden and cost-effectiveness scores of 3 and 2, respectively. Diet counseling, which included intensive behavioral counseling for patients with hyperlipidemia and other risk factors for CVD and diet-related chronic diseases, received clinically preventable burden and cost-effectiveness scores of 1, suggesting that these services, at least in their present format, did not appear warranted.[168] These rankings are considerably lower than those for such activities as tobacco counseling or screening for hypertension or hyperlipidemia.

Changing Diet

Although the evidence suggests that dietary counseling for CVD and diet-related disorders has limited impact on health, a diet that is high in fruits and vegetables can reduce the risk of several major causes of death and contribute to weight management.[137–139] Objectives of Healthy People 2010 included related targets such as having 75% of the population >2 years of age consume ≥2 fruit servings daily and 50% consume ≥3 vegetable servings daily. According to the latest update on progress in meeting these objectives, which was based on Behavioral Risk Factor Surveillance System data, ≈32.5% of adults consumed ≥2 servings of fruit per day and 26.3% consumed ≥3 servings of vegetables per day.[169] These results demonstrate not only that the population is far short of meeting these objectives but also that there has been a slight but significant decline in fruit consumption since 2000. Collectively, these findings emphasize the serious need for interventions at multiple levels (eg, point of purchase, schools, worksites, and community settings) that will improve access to affordable fruits and vegetables. Recently, an intensive lifestyle intervention that focuses on diet and physical activity has been shown to be successful in achieving weight loss in severely obese adults.[170] Moreover, a commercial weight loss program with free prepared meals and incentivized weight loss can effect weight loss and prevent weight regain.[171] These findings may extend the potential reach of this treatment approach to weight loss.[172,173]

Evidence Base for the Value of Cardiovascular Disease Prevention: Therapeutic Areas

Several diseases and chronic health states are associated with CVD risk: diabetes mellitus, hyperlipidemia, hypertension, and tobacco use. This section focuses on the cost-effectiveness of primary prevention in the clinical environment or community setting that is therapeutic in nature to initiate behavior change or to prevent the onset of chronic disease.

Tobacco Cessation Therapy

In general, tobacco cessation treatment remains highly cost-effective, even though a single application of any treatment for tobacco dependence may be successful in only a minority of smokers long term.[174] There is a strong relationship between the length of behavior counseling sessions, provider-to-person contact, and successful treatment outcomes.[19] Available forms of nicotine replacement therapy (gum, transdermal patch, nasal spray, inhaler, and lozenges) increase quit rates by 50% to 100% over placebo; however, fewer than 1 in 5 smokers who are trying to quit take advantage of these products. The reasons for lower use are the inadequacies of dosing strength, formulations of existing medications, perceptions about the high cost of the drugs, and smokers' concerns about the safety and efficacy of nicotine medications. The ICERs for treatment programs range from a few hundred to a few thousand dollars per QALY saved.[19]

In July 2006, the Massachusetts healthcare reform law mandated tobacco cessation coverage for the Massachusetts Medicaid population. On implementation of the benefit, MassHealth subscribers were allowed two 90-day courses per year of Food and Drug Administration–approved medications for smoking cessation, including over-the-counter medications like nicotine replacement therapy, and up to 16 individual or group counseling sessions. A total of 70 140 unique MassHealth subscribers used the newly available benefit between July 1, 2006, and December 31, 2008 (ie, ≈37% of all Medicaid smokers). Before July 2006, there had been no significant change in smoking prevalence among the MassHealth population because smoking rates remained relatively high in this state. However, after implementation, in just over 2 years, 26% of MassHealth smokers quit smoking, and there was a decline in the use of other costly healthcare services (38% decrease in hospitalizations for heart attacks, 17% drop in emergency room and clinic visits for asthma, and a 17% drop in claims for adverse maternal birth complications, including preterm labor).[175] Additional research showed that comprehensive coverage led to reduced hospitalizations for heart attacks and a net savings of $10.5 million or a $3.07 return on investment for every dollar spent.[21,175] A study by the American Lung Association showed that economic benefits to states offering comprehensive smoking cessation therapy to their employees in their public health or tobacco control programs can save $1.10 to $1.40 in healthcare expenditures and productivity for every dollar spent.[176]

The health benefit of cessation and relapse therapy during pregnancy is even more apparent, minimizing low birth weight, placental abruption, sudden infant death syndrome, and other illnesses and life-threatening conditions for mother and child.[177] Moreover, a systematic review of the literature revealed a cost-to-benefit ratio as high as 3:1 (ie, for every $1 invested in cessation/relapse programs, $3 were saved in downstream health-related costs).[22]

The PPACA requires state Medicaid programs to cover comprehensive tobacco cessation treatments, with no copayments, for pregnant women as of October 1, 2010. States have a tremendous opportunity to save even more lives by applying tobacco cessation treatments to all smokers in Medicaid. Nationwide, 36.6% of people in Medicaid smoke compared with 22.6% of the general population.[178] Ideally, comprehensive tobacco cessation services should be offered in all public and private healthcare plans.

Diabetes Mellitus

People with diabetes mellitus have CVD mortality rates that are 2 to 4 times higher than those for people without diabetes mellitus. Moreover, the estimated cost of diabetes mellitus in the United States in 2007 was $174 billion, with 28% of expenditures attributed to cardiovascular complications of diabetes mellitus.[179] Current projections suggest that 1 of 3 people born in 2000 will develop diabetes mellitus over his or her lifespan.[23] A critical aspect of CVD and stroke prevention is screening for diabetes mellitus, along with early interventions, including behavioral modification, drug therapy, or both.

Diabetes Mellitus Screening

The American Diabetes Association (2010) recommends universal screening for T2DM in adults at 45 years of age that is repeated at least every 3 years.[180] Asymptomatic adults who are overweight or obese and who have 1 or more risk

factors (physical inactivity, cigarette smoking, family history in first-degree relative, history of CVD or hypertension, high-density lipoprotein <35 mg/dL, triglycerides >250 mg/dL, impaired glucose tolerance, impaired fasting glucose, or hemoglobin A_{1c} ≥5.7%; women with polycystic ovary syndrome or who delivered a baby >9 lb; blacks; and Latinos, Native Americans, Asian Americans, or Pacific Islanders) should be considered for screening regardless of age.[180] A recent systematic review of cost-effectiveness interventions to prevent and control both diabetes mellitus and the resulting complications found that targeted screening for T2DM based on age and risk was found to be far more cost-effective (ICERs ranging from $46 800 to $70 500 per QALY gained) compared with universal screening (ICERs from $70 100 to $982 000 per QALY gained).[24] Targeted screening for undiagnosed T2DM in blacks between 45 and 54 years of age was the most cost-effective, with an ICER of $19 600 per QALY gained relative to no screening. For people with T2DM, statin therapy for the prevention of CVD was supported by strong evidence of cost-effectiveness.

Other studies examined the cost-effectiveness of more targeted screening, whether by age or risk factors. A recent study using a mathematical model based on a representative sample of the US population found that screening for T2DM at 30 and 45 years of age, repeated every 3 to 5 years, is cost-effective, with ICERs of ≈$10 500 or less per QALY gained.[181] There was a significant reduction in the incidence of myocardial infarction (5 to 7 events prevented per 1000 people screened) compared with no screening. Similar findings were shown for screening those with a diagnosis of hypertension, either annually or every 5 years, with a reduction in the incidence of myocardial infarction (3 events per 1000 people screened), although there was little or no effect on the incidence of stroke. The authors suggested that their results differed from other cost-effectiveness analyses because their model included the most recent treatment recommendations for more aggressive use of glucose-lowering drugs for T2DM.

Diabetes Mellitus Prevention and Treatment

The Finnish Diabetes Prevention Study demonstrated that lifestyle modification could delay or prevent the development of T2DM, and this approach has subsequently been implemented throughout Finland.[182,183] The US Diabetes Prevention Program (2002) demonstrated that lifestyle modification and treatment with metformin could delay or prevent the development of T2DM.[184] Of interest, the lifestyle changes reduced the incidence of diabetes mellitus by 58%, whereas metformin therapy reduced the risk by 31%.[25] In patients with impaired glucose tolerance, a systematic review of the literature revealed that primary prevention, in the form of intensive lifestyle modification, is unequivocally cost-effective compared with standard lifestyle recommendations or no intervention, with a median ICER of $1500 per QALY gained.[24] The intensity of intervention required to improve glycemic control remains unclear. One study postulated that in adults with T2DM, an additional 23.6 contact hours in diabetes mellitus self-management education would be required to produce a hemoglobin A_{1c} decrease of 1% (95% confidence interval, 13.3 to 105.4).[185] Other cost-effectiveness analyses outside the United States have also found both drug and lifestyle interventions to be cost-effective, although it is difficult to extrapolate those results to the United States because healthcare and reimbursement systems vary significantly.[184,186]

Mathematical models evaluating the cost-effectiveness of community-based diabetes mellitus prevention programs using lifestyle interventions show conflicting results. A community-based modified Diabetes Prevention Program intervention designed to reduce risk factors for T2DM decreased metabolic syndrome risk by 16.2% at 12 months compared with 12.1% for usual care at an increased cost of $3420 per QALY gained.[187] However, a 10-year community intervention study in Sweden of lifestyle changes to prevent diabetes mellitus offered equivocal results that were not as favorable as the Diabetes Prevention Program model.[188] In diabetes mellitus prevention programs from a societal perspective, model estimates may vary, depending on the intervention approach and lifetime projections.[189,190] One study showed that cost per QALY of lifestyle intervention was much less than with metformin, whereas another study found that Diabetes Prevention Program treatment with metformin or delaying lifestyle intervention until after diagnosis was more cost-effective than earlier Diabetes Prevention Program lifestyle intervention.[189,190]

Because of the improvement in risk factor control, patients who have been newly diagnosed with diabetes mellitus since 2005 have a better prognosis than their counterparts who were diagnosed 11 years earlier.[191] Once a patient is diagnosed with T2DM, there is strong evidence that it is cost-saving to implement multicomponent interventions (standard antidiabetic care, education, angiotensin-converting enzyme inhibitors, and screening for microvascular complications) compared with standard antidiabetic care.[24] Intensive glycemic control resulted in a median ICER of $12 400 per QALY gained. More intensive control of glycosylated hemoglobin (to a goal of <6%) was not shown to further reduce CVD events and was associated with increased mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[192] However, a meta-analysis of ACCORD, Action in Diabetes and Vascular Disease (ADVANCE), United Kingdom Prospective Diabetes Study (UKPDS), and VA Diabetes Trial (VADT) data showed a benefit of tight glycemic control on macrovascular outcomes and no increase in mortality.[193] Bariatric surgery, an emerging treatment strategy for diabetic patients who are severely obese, has also been found to be relatively cost-effective, with ICERs ranging from $7000 to $13 000, depending on the type of procedure (banding verses bypass) and length of time since diabetes mellitus diagnosis.[194]

The ability to compare results of current studies is limited by marked differences in methodologies and intervention descriptions, including the lack of sufficient detail describing lifestyle interventions. Overall, more economic evaluations of diabetes mellitus intervention are needed to evaluate the cost-effectiveness for both prevention and treatment.

Lipid Screening and Primary Prevention

Elevated LDL-C is a major risk factor for CVD.[195] Multiple major clinical trials and national clinical guidelines support

screening for adverse levels of cholesterol and offer recommendations for treatment, including both lifestyle and pharmacological therapy.[60] Several meta-analyses have addressed the effectiveness of statin therapy for primary prevention. Ray et al[196] found a trend toward reduced all-cause mortality. A 2011 Cochrane review found reduced risk of all-cause mortality (relative risk, 0.83; 95% confidence interval, 0.73 to 0.95) and nonfatal events with statin therapy.[197] Although there is general agreement about the value of statins to reduce elevated LDL-C in high-risk individuals, research varies as to what constitutes a "normal" range of LDL-C, when to initiate statin therapy, and the best therapeutic range for primary and secondary reduction of cardiovascular events.[198–200]

Manuel et al[201] noted that the effectiveness and efficiency of algorithms for statin treatment based on 6 different national or international guidelines on statin treatment to prevent deaths from CVD varied widely. When applied to a Canadian population, Australian and British guidelines were most effective, potentially preventing the most deaths over 5 years (>15 000 deaths). The New Zealand guideline was most efficient, potentially preventing almost as many deaths (14 700) while recommending treatment to the fewest number of people (12.9% versus 17.3% with Australian and British guidelines). If "optional" recommendations are included, US guidelines recommend treating about twice as many people as New Zealand guidelines (24.5% of the population), with almost no additional decrease in mortality. Similarly, studies conducted outside the United States found that targeted screening based on risk is less costly and can identify up to 84% of high-risk individuals compared with mass screening.[202]

The public health impact of widespread use of statins was evaluated with a Markov model analysis for the US population from 35 to 85 years of age.[26] Full adherence to Adult Treatment Panel III primary prevention guidelines would require starting statins in 9.7 million and increasing the dose in 1.4 million Americans. This strategy would prevent 20 000 myocardial infarctions and 10 000 CVD deaths at a total cost $3.6 billion or $42 000 per QALY if low-intensity statins cost $2.11 per pill (which is substantially higher than the cost of currently available, effective generic statins). At a $50 000 willingness-to-pay threshold, statins are cost-effective up to $2.21 per pill.

Multiple studies using mathematical models have evaluated the cost-effectiveness of statins for primary prevention of CVD within specific populations. One study reported that statin therapy is likely to be cost-effective in the prevention of CVD among Koreans ≥45 years of age, with an estimated ICER of $12 612 per QALY gained (based on 1200 Korean won per US $1), although it may be difficult to translate the findings to the United States because of differences within healthcare systems.[203] In the US population, statin therapy has been found to be cost-effective in individuals with T2DM who have LDL-C levels between 100 and 129 mg/dL, where cost and effectiveness vary among type of statin used.[204]

Blood Pressure Screening and Treatment

Hypertension is a major risk factor for coronary artery disease, stroke, heart failure, and renal failure.[205,206] As with lipids, multiple major clinical trials and national clinical guidelines support screening and treatment for hypertension, including both lifestyle and pharmacological therapy. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study (2002) reported that thiazide-type diuretics (chlorthalidone) are at least as effective in preventing CVD as a calcium channel blocker (amlodipine) or an angiotensin-converting enzyme inhibitor (lisinopril). Thiazide-type diuretics have also been shown to be less expensive.[207,208] In an extension of the ALLHAT study, chlorthalidone was found to be more cost-effective than amlodipine and lisinopril.

Lipid and Blood Pressure Treatment

Several studies have evaluated the cost-effectiveness of the treatment of dyslipidemia and hypertension for primary prevention of coronary heart disease. In an extension of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), lifetime cost-effectiveness of atorvastatin plus amlodipine was the most expensive but also the most effective treatment compared with amlodipine-based therapy alone (ICER of €8591 per QALY in Sweden and €11 965 per QALY gain in the United Kingdom).[209] In Canada, both lipids and hypertensive therapy were found to be cost-effective (ICER of $16 700 and $37 100 per life-years saved, respectively), although statin treatment was less effective among women <50 years of age, as was hypertension treatment for men and women <50 and 60 years of age, respectively.[27]

Evidence is emerging on the use and cost-effectiveness of fixed-dose medication combinations ("polypill") for CVD prevention. Coadministration of atorvastatin and amlodipine for hyperlipidemia and hypertension has been found to be well tolerated and without adverse pharmacological interaction.[210] This combination was shown to be cost-effective in preventing CVD in a subgroup of Koreans ≥45 years of age without a history of myocardial infarction or stroke, with an approximate ICER of $6000 per QALY gained.[211] Newman et al[28] used a mathematical model to evaluate whether a fixed-dose medication (statin, angiotensin-converting enzyme inhibitor, thiazide diuretic, and β-blocker) would be cost-effective in the primary prevention of CVD in men ≥55 years of age without coronary heart disease, hypertension, or dyslipidemia. The decision model, which compared treatment and no treatment, considered medication costs and side effects, as well as direct medical costs and age-related health states, including morbidity and mortality from CVD. The fixed-dose medication treatment was less expensive and more effective, with an average cost of $70 000 compared with $93 000 for no treatment, and resulted in 13.62 QALYs compared with 12.96 QALYs without treatment. The authors concluded that the use of a fixed-dose polypharmacy approach to CVD prevention in men >55 years of age may be cost-effective.

Making the Case for Prevention to Policy Makers

The policy landscape for CVD prevention is active with considerable potential to improve health. The challenge is how to translate biological science, economic analysis, and behavioral science into policy that supports the promotion of heart health and the prevention of CVD. Brownson et al[212] describe the parallel worlds of researchers and policy makers and the diffi-

culty in connecting the two. One of the challenges described is timing. Whereas researchers' time frame is longer term with studies and analysis and publishing, the time frame of the policy maker is related to election cycles. With regard to primordial and primary prevention of CVD, the tyranny of the urgent, the acute stroke or myocardial infarction that evolves over minutes, can seem more important than the much slower, but potentially far more substantial, benefits of effective prevention strategies (ie, the rule of rescue). However, targeted population-level prevention policies can have a measurable impact even in the short time frame of policy makers.

Convincing policy makers of the importance of prevention has less to do with whether they believe prevention works and more to do with whether they believe prevention programs are effective and provide value. As previously discussed, standard cost-effective analyses are difficult to conduct, with considerable uncertainty about outcomes that occur over a period of decades. And certain types of savings are difficult to measure accurately. The interventions selected must provide evidence of improved outcome at an acceptable cost (ie, that they provide value). The assessment of cost and benefits must include the cost of intervention and anticipated reductions in medical care costs, as well as value in the workplace and society by having a healthier population and workforce.

From a government policy perspective, support for prevention policies and the necessary appropriations that support prevention can be difficult to garner when resources are limited. Congressional Budget Office scoring does not reflect long-term savings or savings that cannot be accurately measured.[213] In addition, the Congressional Budget Office considers only costs or savings to the federal government, so a program with a broader societal benefit, fiscal or otherwise, may not seem to show a positive return on investment. The Congressional Budget Office has outlined the challenges in assessing the cost savings of prevention, noting that achieving substantial savings in healthcare spending or federal outlays from prevention initiatives may take years of costly intervention and a variety of approaches to succeed; even if these initiatives change people's behavior, the resulting health benefits may take a long time to emerge, so the immediate impact on health spending may be limited; and the long-term savings on health care from reductions in the incidence of illnesses and disabilities may be substantial, but any savings to the federal government could be offset at least partially by additional expenditures as healthier individuals live longer. For example, Medicare costs could rise for the treatment of other diseases and conditions during those extra years of life, and expenditures for programs that are not directly related to health (such as Social Security) could also increase as lifespans are extended.[213] The challenge is to convince policy makers that although there may not be significant net cost savings in the short term to society (or even long term to the federal government), there is value in making an important investment in the health of our nation.

Another challenge is that the healthcare system responsible for public medical care (eg, Medicare and Medicaid) and private medical care is seen as distinct from public health rather than as an integrated system. Furthermore, the healthcare system separates the biological from the psychosocial in the socioecological model that takes into account the influence of social, cultural, and physical environments on individual and population health.

Translating evidence into policy is not as simple as knowing the science. At least 4 requirements must be satisfied to effect policy change. The policy maker has to be convinced that there is a theoretical basis for successful outcomes, that the policy is a practical one to pursue, that it is an affordable or a worthy investment, and that it is reasonable politically to pursue the new policy. In addition, in an environment of limited resources, activities undertaken must be viewed as an appropriate role of government versus the individual.

Those hoping to effect policy change must be able to articulate a rationale for policy change that, in the case of the primordial and primary prevention of CVD, adheres to the following principles: a robust evidence base on quality of life and/or prevention of future events, the impact of the health of the population on healthcare costs and medical care delivery, and the positive influence on the nation's productivity and long-term national security. In summary, the practical benefits of policies that should be adopted will promote health and prevent disease and disability with benefits accruing to both individuals and society.

Future Research Directions

By several indexes, healthcare expenditures continue to rise at the fastest rate in our history. According to a recent projection, total healthcare spending will approximate $4 trillion in 2015, or 20% of the gross domestic product, corresponding to $1 of every $5 spent in the United States.[214] This growth in healthcare spending is clearly not sustainable, making cost-effective prevention of disease a national priority. Future research in prevention should routinely include economic studies. Potential areas include the following:

- Serial assessment of participants in behavioral or multicomponent trials to confirm maintenance of the treatment effect and to assess longer-term outcomes
- Evaluation of the role of technology in facilitating and supporting lifestyle change interventions
- Assessment of motivational interviewing and related behavior-change techniques, including the impact of motivational interviewing strategies delivered in primary care settings
- Clarification of the independent and additive benefits of lifestyle modification on cardioprotective pharmacotherapies and vice versa
- Evaluation of the effects of moderate versus vigorous physical activity, with specific reference to the associated benefits, risks, and long-term compliance
- Evaluation of the advantages and limitations of selected environments to deliver primordial and primary preventive interventions, including the home, community, worksite, school, and healthcare system
- Clarification of the impact of excise taxes on the consumption/use of unhealthy foods, sugary beverages, and tobacco products
- Testing of the thesis that we are initiating treatment of hypercholesterolemia (and other risk factors) too late in life, particularly among adolescents and young adults with

high lifetime risk, clarifying the potential benefits, harms, and costs of initiating lifestyle modification interventions, drug therapy, or both early in life[199,200]
- Research on the role of genetic testing in developing more personalized approaches to prevention
- Methodological research on better approaches to evaluating value of preventive services

The medical and research communities are challenged to further clarify the effectiveness and sustainability of cost-effective preventive cardiovascular services so that proven interventions can be provided in home-, work-, school-, and community-based settings to save lives, money, and resources. Legislators, public health and planning professionals, and community representatives can help to facilitate this objective by supporting selected advocacy initiatives and empowering localities to embrace a lifestyle culture of physical activity, healthy nutrition options, smoking bans, and affordable access to health care for all Americans. The American Heart Association has developed initiatives to foster the development of a healthier population, including Go Red for Women, Power to End Stroke, Alliance for a Healthier Generation, and Start!

Cardiovascular disease is largely preventable. The mortality from CVD has fallen by two thirds since the peak in the 1960s, resulting in an unprecedented increase in longevity.[215] Approximately 55% of this decrease has been attributed to primary and secondary prevention because of improved management of cholesterol, blood pressure, and tobacco use. These gains have been offset in part by increases in obesity and diabetes mellitus.[215] These improvements have occurred despite a relatively modest investment in prevention compared with the management of acute disease. Much is yet to be accomplished to optimize the health and productivity of our nation by the economically advantageous development of healthy lifestyles, including diet, tobacco avoidance, and physical activity, and appropriate pharmacological therapy for hypertension, hyperlipidemia, tobacco cessation, and diabetes mellitus. A population with optimal health will be developed through the sustained and coordinated efforts of an informed citizenry, community participation, and the medical care system. Given the high cost of treating acute and chronic disease, prevention offers the potential of both improving health and decreasing costs.

Appendix

Primer on Cost-Effectiveness Analysis

Background on Economic Analyses

In evaluating societal choices concerning prevention, the initial and long-term direct costs and induced costs or saving of services are important considerations (see Table 1 for a glossary of terms). Given that society cannot afford unlimited medical services, all forms of care should compete for resources on the basis of effectiveness and cost. In choosing services, whether preventive or therapeutic, consumers will look to obtain value (ie, that the service is worth what is paid for it). The perspective in economic analyses will have an important impact on the assessment of value. For instance, an analysis from the perspective of a health system might not include the long-term consequences of a particular clinical strategy, whereas this issue may be vital to patients. In addition, the indirect, or nonmedical, costs or consequences are not always factored into the cost analysis. The perspective of all of the various stakeholders may be viewed in aggregate as "society." To be most useful in serving societal goals, economic analyses should be performed from a societal perspective in which an attempt to measure all of the costs and effectiveness measures associated with a particular treatment is made.[216] These costs should include those incurred by the patient, the costs of medical resources that could have been used for other patients, and any loss of income that the patient sustained because of poor health, as well as the loss of income for those who may have provided informal care to the patient. Outcomes should include events, quality of life, and survival. By evaluating the sum of all of these costs in relation to outcomes, a policy maker could decide, for example, whether the public good benefited more by allocating limited healthcare resources to preventive services or to new therapies for incident or prevalent diseases.

Determining Costs

Costs may be considered from one of several possible perspectives.[217] For hospitals, costs are their expenses related to providing a service. For payers, cost is the funds transferred to a provider or providers for services rendered plus administrative expenses. In principle, cost studies generally seek to determine societal costs, which can be used in cost-effectiveness analyses to gain the widest perspective. However, societal costs are never directly measurable; thus, combinations of cost proxies from one or several stakeholders, when measurable, are used as estimates.

Costs are often classified as direct or indirect.[218] Theoretically, direct costs are those incurred by a stakeholder for a therapy or test, and indirect related costs are those incurred by other societal groups. More commonly, direct costs relate to the provision of medical care, whereas indirect costs are nonmedical costs such as travel and related societal costs. Indirect costs reflect lost patient or business opportunity and may be referred to as productivity costs.[219]

Another issue involved in measuring hospital costs is average versus marginal or incremental cost.[220] Average cost is calculated by dividing all costs for a service by the total number provided. In contrast, the marginal cost is the cost of the next similar procedure. Average costs include all resources used, including overhead, with associated costs that would not be decreased if not used. Marginal costing accepts fixed costs as a given and focuses only on variable costs or those additional resources consumed by each additional patient. Variable costs are analytically separated from fixed costs by establishing the perspective and time frame as fixed. Because of difficulties in assessing marginal cost, most cost and cost-effectiveness studies use average costs.

Future costs should be discounted to reflect the opportunity costs of current dollars; that is, future costs should be expressed at their present value.[216] For instance, if a policy maker were given the alternative of spending $1000 now or $1000 in 5 years to treat a given condition and obtain the same outcome, the decision would always be the latter. Costs are generally discounted at a rate of 3%/y to 5%/y.[216]

Determination of Patient Utility and QALYs

In the treatment of CVD, it is unusual for 1 measurement of outcome to be of sufficient clinical importance that all other outcome measures may be ignored in clinical decision making. Although death generally overwhelms all other outcome measures in importance, patients may also suffer from considerable disability. Thus, a therapy may be justified on the basis of improved health status alone, even if not lifesaving. To incorporate health status measures into a cost-effectiveness analysis, an overall measure of health status is needed. In principle, this task may be accomplished through the determination of patient utility. The utility of a therapy or test is the sum of effects, both positive and negative, that accrue to a patient over time as the result of the procedure.[221] More technically, utility is a measure of patients' preferences for one health state over another.

Utility may be measured indirectly using either a validated survey such as the Health Utilities Index[222] or the EQ-5D[223] or by directly assessing patient preference. The patient preference methods, Standard Gamble and Time Trade-Off,[224] ask patients to directly evaluate their current state of health and what they would give up or risk to achieve optimal health. The patient preference methods are probably superior to surveys because the evaluation of a patient's view of his/her own state

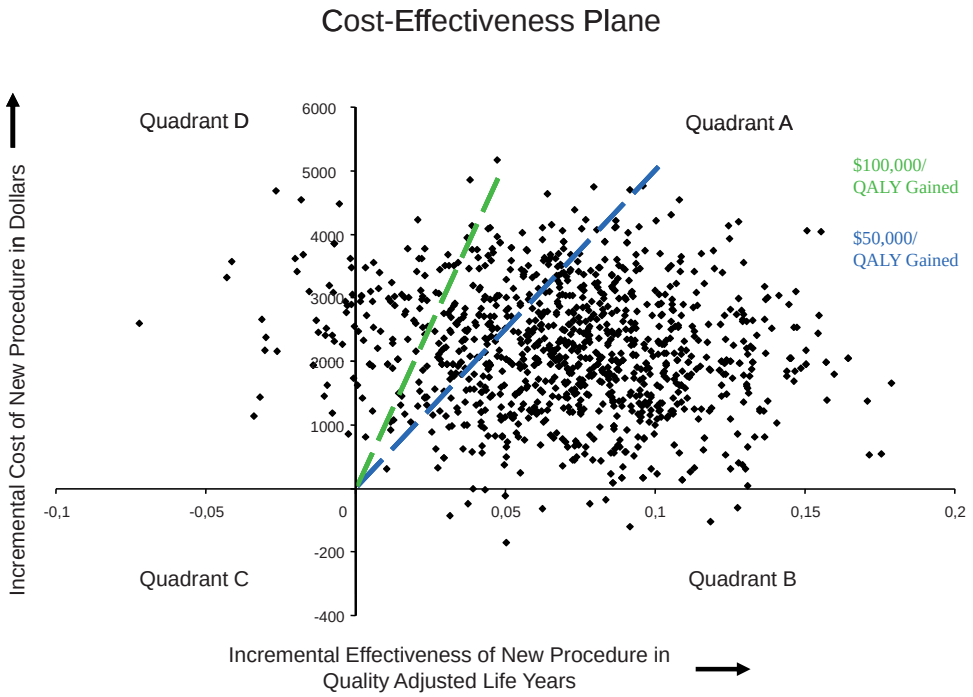

Figure 2. The distribution of cost-effectiveness in the cost-effectiveness plane. Each point represents an estimate of the incremental cost-effectiveness ratio based on dual bootstrap of cost and efficacy. Potential $50 000 and $100 000 per quality-adjusted life-year (QALY) gained threshold lines are noted. Estimates of the incremental cost-effectiveness ratio below those benchmarks would be considered cost-effective.

of health is measured directly; however, they are more difficult to administer. In the Time Trade-Off approach, patients weigh the fraction of expected survival they are willing to give up to achieve optimal health. With the Standard Gamble, patients weigh what risk of death they are willing to take to achieve optimal health. The Standard Gamble is probably superior because it includes the element of risk.

Utility alone does not provide a final summary measure of outcome because it does not include life expectancy. A summary measure can be created by combining utility and survival to obtain QALYs.[225] Survival, as with cost presented above, is generally discounted, which means that patients value a year of survival at the present time more than a year of survival in the future. The "true" discount rate for survival is unknown. Values in the literature for the discount rate have varied from 2% to 10%, with 3% being the most popular, and it should be discounted at the same rate as cost.[216] Thus, with a discount rate of 3%, next year's survival is 3% less important than this year's survival. The QALY is the best summary measure of outcome in a cost-utility analysis because it incorporates patient value, risk aversion, expected survival, and a discount rate.

Cost-Effectiveness and Cost-Utility Analysis

Cost-effectiveness analysis is by its nature incremental. Thus, it is necessary to evaluate both added cost and effectiveness compared with a control group. At times, the appropriate control is no procedure or test (eg, a placebo in pharmaceutical trials); at times, the current standard procedure (ie, the appropriate control) depends on the clinical question being asked. It is also necessary to consider the time horizon of a study. In principle, a lifetime horizon is preferred because it incorporates all downstream resource use and events.

When additional costs and incremental measures of effectiveness of a new form of therapy are available, along with description of the distribution of each, then an ICER may be calculated, along with its own distribution.[226] An ICER is a ratio of the incremental cost of the new therapy divided by the incremental measure of benefit. When the measure of benefit is expressed in life-years or QALYs, then the ICER will be measured in cost per life-year or QALYs gained.

The ICER should not be viewed only as a single number because of the uncertainty about measures of both cost and effectiveness. The first level of uncertainty is based on chance or sampling error alone. This may best be considered when patient-level data are available. The distribution of an ICER based on sampling error of the numerator and denominator is somewhat complicated because the 95% confidence interval of a ratio is not easily defined. A popular approach to this problem is to examine the confidence interval of cost and effectiveness by sampling from the distribution of each, an approach called bootstrap analysis. By sampling from both the cost and effectiveness distributions concurrently, one can make multiple estimates of the ICER.[227] The distribution of the ICER may then be displayed in a plane (Figure 2), where each point is an estimate of the ICER. In quadrant A, the new therapy is more effective but more costly than the previous standard. In quadrant B, the new therapy dominates the standard, being more effective and less expensive, whereas in quadrant D, the new therapy is dominated by the standard, being less effective and more expensive.

Cost-effectiveness analysis will almost always include a series of assumptions because it is generally not possible to accurately measure all variables necessary for a definitive analysis. In addition, even when measurements are available, they may not adequately represent values appropriate for the analysis at hand. Thus, cost-effectiveness analysis generally includes sensitivity analyses in addition to the stochastic estimates of variation discussed. With sensitivity analysis, the input variables for assessing both cost and effectiveness are varied between reasonable limits, and the ICER and its distribution are recalculated.

An ICER is an assessment of the cost-effectiveness of one treatment or test versus another; it does not say whether a service is cost-effective, and there is no scientific basis for a threshold below which an ICER must be for a new therapy to be considered cost-effective. The $50 000 per QALY threshold has been widely used because it is based on renal dialysis, and in the United States, there is general (political) agreement that there is willingness to pay for renal dialysis. Although a threshold gives cost-effectiveness studies a benchmark that may be used to compare studies, there is no scientific justification for selection of any one threshold; indeed, the optimal threshold for cost-effectiveness is a sociopolitical decision. A cost-effectiveness threshold then is an assessment of value that might vary by payer, patient, or provider.

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*Modest.

†Significant.

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†Significant.

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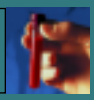
High Blood Cholesterol

Detection



Evaluation

Treatment

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

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High Blood Cholesterol

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Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

Introduction

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) constitutes the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management. The full ATP III document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary. ATP III builds on previous ATP reports and expands the indications for intensive cholesterol-lowering therapy in clinical practice. It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual.

Background

The third ATP report updates the existing recommendations for clinical management of high blood cholesterol. The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each of the guideline reports—ATP I, II, and III—has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low density lipoprotein (LDL) cholesterol (≥160 mg/dL) or those with borderline-high LDL cholesterol (130-159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For CHD patients, ATP II set a new, lower LDL cholesterol goal of ≤100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people, in accord with recent clinical trial evidence, but its core is based on ATP I and ATP II. Some of the important features shared with previous reports are shown in Table A in the Appendix.

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than recommended in ATP II. Table 1 shows the new features of ATP III.

Table 1. New Features of ATP III

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD, most of whom display multiple risk factors, to the risk level of CHD risk equivalent.
- Uses Framingham projections of 10-year absolute CHD risk (i.e., the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment.
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes.

Modifications of Lipid and Lipoprotein Classification

- Identifies LDL cholesterol <100 mg/dL as optimal.
- Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL.
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations.

Support for Implementation

- Recommends a complete lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone.
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol.
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies.
- Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL.

LDL Cholesterol: The Primary Target of Therapy

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.

Risk Assessment: First Step in Risk Management

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total cholesterol and HDL cholesterol will be usable. In such a case, if total cholesterol is ≥200 mg/dL or HDL is <40 mg/dL, a followup lipoprotein profile is needed for appropriate management based on LDL. The relationship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL levels from low to high. Therefore, ATP III adopts the classification of LDL cholesterol levels shown in Table 2, which also shows the classification of total and HDL cholesterol levels.

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Risk determinants in addition to LDL-cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL (see Table 3). (LDL is not counted among the risk factors in Table 3 because the purpose of counting those risk factors is to modify the treatment of LDL.) Based on these other risk determinants, ATP III identifies three categories of risk that modify the goals and modalities of LDL-lowering therapy. Table 4 defines these categories and shows corresponding LDL-cholesterol goals.

Table 3. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)*

* *In ATP III, diabetes is regarded as a CHD risk equivalent.*

† *HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

Table 4. Three Categories of Risk that Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
Zero to one risk factor	<160

** Risk factors that modify the LDL goal are listed in Table 3*

The category of highest risk consists of CHD and CHD risk equivalents. The latter carry a risk for major coronary events equal to that of established CHD, i.e., >20% per 10 years (i.e., more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years). CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD >20%.

Diabetes counts as a CHD risk equivalent because it confers a high risk of new CHD within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted. Persons with CHD or CHD risk equivalents have the lowest LDL cholesterol goal (<100 mg/dL).

The second category consists of persons with multiple (2+) risk factors in whom 10-year risk for CHD is ≤20%. Risk is estimated from Framingham risk scores (see Appendix). The major risk factors, exclusive of elevated LDL cholesterol, are used to define the presence of multiple risk factors that modify the goals and cutpoints for LDL-lowering treatment, and these are listed in Table 3. The LDL cholesterol goal for persons with multiple (2+) risk factors is <130 mg/dL.

The third category consists of persons having 0-1 risk factor; with few exceptions, persons in this category have a 10-year risk <10%. Their LDL cholesterol goal is <160 mg/dL.

Method of risk assessment: counting major risk factors and estimating 10-year CHD risk

Risk status in persons *without* clinically manifest CHD or other clinical forms of atherosclerotic disease is determined by a 2-step procedure.

First, the number of risk factors is counted (Table 3). Second, for persons with multiple (2+) risk factors, 10-year risk assessment is carried out with Framingham scoring (see Appendix) to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment. Estimation of the 10-year CHD risk adds a step to risk assessment beyond risk factor counting, but this step is warranted because it allows better targeting of intensive treatment to people who will benefit from it. When 0-1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention; a very high LDL level in such a person may nevertheless warrant consideration of drug therapy to reduce long-term risk. Risk factors used in Framingham scoring include age, total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking. Total cholesterol is used for 10-year risk assessment because of a larger and more robust Framingham database for total than for LDL cholesterol, but LDL cholesterol is the primary target of therapy. Framingham scoring divides persons with multiple risk factors into those with 10-year risk for CHD of >20%, 10-20%, and <10%. It should be noted that this 2-step sequence can be reversed with essentially the same results.* Initial risk assessment in ATP III uses the major risk factors to define the core risk status. Only after the core risk status has been determined should any other risk modifiers be taken into consideration for adjusting the therapeutic approach.

Role of other risk factors in risk assessment

ATP III recognizes that risk for CHD is influenced by other factors not included among the major, independent risk factors (Table 3). Among these are *life-habit risk factors* and *emerging risk factors.* The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The *life-habit risk factors* are direct targets for clinical intervention, but are not used to set a lower LDL cholesterol goal of therapy. The *emerging risk factors* do not categorically modify LDL cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.

Metabolic syndrome

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the

*If Framingham scoring is carried out *before* risk factor counting, persons with <10 percent risk are then divided into those with 2+ risk factors and 0-1 risk factor by risk factor counting to determine the appropriate LDL goal (see Table 4).

metabolic syndrome. Factors characteristic of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. ATP III recognizes the metabolic syndrome as a secondary target of risk-reduction therapy, after the primary target—LDL cholesterol. Diagnosis and treatment of the metabolic syndrome is described beginning on page 15 under "Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy."

The link between risk assessment and cost effectiveness

In ATP III, a primary aim is to match intensity of LDL-lowering therapy with absolute risk. Everyone with elevated LDL cholesterol is treated with lifestyle changes that are effective in lowering LDL levels. Persons at relatively high risk are also candidates for drug treatment, which is very effective but entails significant additional expense. The cutpoints for drug treatment are based primarily on risk-benefit considerations: those at higher risk are likely to get greater benefit. However, cutpoints for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost effectiveness. Lifestyle changes are the most cost-effective means to reduce risk for CHD. Even so, to achieve maximal benefit, many persons will require LDL-lowering drugs. Drug therapy is the major expense of LDL-lowering therapy, and it dominates cost-effectiveness analysis. However, the costs of LDL-lowering drugs are currently in flux and appear to be declining. This report recognizes that as drug prices decline it will be possible to extend drug use to lower risk persons and still be cost effective. In addition, ATP III recognizes that some persons with high long-term risk are candidates for LDL-lowering drugs even though use of drugs may not be cost effective by current standards.

Primary Prevention With LDL-Lowering Therapy

Primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including: 1) reduced intakes of saturated fat and cholesterol, 2) increased physical activity, and 3) weight control, to lower population cholesterol levels and reduce CHD risk, but the clinical approach intensifies preventive strategies for higher risk persons. One aim of primary prevention is to reduce long-term risk (>10 years) as well as short-term risk (≤10 years). LDL goals in primary prevention depend on a person's absolute risk for CHD (i.e., the probability of having a CHD

event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Any person with elevated LDL cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that increase LDL cholesterol and decrease HDL cholesterol (progestins, anabolic steroids, and corticosteroids).

Once secondary causes have been excluded or, if appropriate, treated, the goals for LDL-lowering therapy in primary prevention are established according to a person's risk category (Table 4).

Secondary Prevention With LDL-Lowering Therapy

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 2, an LDL cholesterol level of <100 mg/dL is *optimal;* therefore, ATP III specifies an LDL cholesterol <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-Lowering Therapy in Three Risk Categories

The two major modalities of LDL-lowering therapy are *therapeutic lifestyle changes* (TLC) and *drug therapy.* Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated

triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. Table 5 defines LDL cholesterol goals and cutpoints for initiation of TLC and for drug consideration for persons with three categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10-20% and <10%); and 0-1 risk factor.

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

CHD and CHD risk equivalents

For persons with CHD and CHD risk equivalents, LDL-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cut-points for initiating lifestyle and drug therapies are shown in Table 5.

- *If baseline LDL cholesterol is ≥130 mg/dL*, intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, an LDL-lowering drug will be required to achieve an LDL cholesterol <100 mg/dL; thus an LDL cholesterol lowering drug can be started simultaneously with TLC to attain the goal of therapy.

- *If LDL cholesterol levels are 100-129 mg/dL*, either at baseline or on LDL-lowering therapy, several therapeutic approaches are available:

- Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.
- Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.
- Delay use or intensification of LDL-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (e.g., nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol.

- *If baseline LDL cholesterol is <100 mg/dL,* further LDL-lowering therapy is not required. Patients should nonetheless be advised to follow the TLC Diet on their own to help keep the LDL level optimal. Several clinical trials are currently underway to assess benefit of lowering LDL cholesterol to well below 100 mg/dL. At present, emphasis should be placed on controlling other lipid and nonlipid risk factors and on treatment of the metabolic syndrome, if present.

Multiple (2+) risk factors and 10-year risk ≤20%

For persons with multiple (2+) risk factors and 10-year risk ≤ 20%, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each category is summarized in Table 5.

- *Multiple (2+) risk factors and a 10-year risk of 10-20%*. In this category, the goal for LDL cholesterol is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, TLC is initiated and maintained for 3 months. If LDL remains ≥130 mg/dL after 3 months of TLC, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal of <130 mg/dL. Use of LDL-lowering drugs at this risk level reduces CHD risk and is cost-effective. If the LDL falls to less than 130 mg/dL on TLC alone, TLC can be continued without adding drugs. In older persons (≥65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

- *Multiple (2+) risk factors and a 10-year risk of <10%*. In this category, the goal for LDL cholesterol also is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, the TLC Diet is initiated to reduce LDL cholesterol. If LDL is <160 mg/dL on TLC alone, it should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if

LDL cholesterol is ≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol <130 mg/dL; the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for CHD.

Zero to one risk factor

Most persons with 0-1 risk factor have a 10-year risk <10%. They are managed according to Table 5. The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. First-line therapy is TLC. If after 3 months of TLC the LDL cholesterol is <160 mg/dL, TLC is continued. However, if LDL cholesterol is 160-189 mg/dL after an adequate trial of TLC, drug therapy is *optional* depending on clinical judgment. Factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol);
- Multiple life-habit risk factors and emerging risk factors (if measured);
- 10-year risk approaching 10% (if measured; see Appendix).

If LDL cholesterol is ≥190 mg/dL despite TLC, drug therapy should be considered to achieve the LDL goal of <160 mg/dL.

The purpose of using LDL-lowering drugs in persons with 0-1 risk factor and elevated LDL cholesterol (≥160 mg/dL) is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus, clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when LDL cholesterol is ≥190 mg/dL after TLC.

For persons whose LDL cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic followup, and control of other risk factors are needed.

Therapeutic Lifestyle Changes in LDL-Lowering Therapy

ATP III recommends a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated *therapeutic lifestyle changes (TLC).* Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg per day) (see Table 6 for overall composition of the TLC Diet)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10-25 g/day)
- Weight reduction
- Increased physical activity

Table 6. Nutrient Composition of the TLC Diet

Nutrient	Recommended Intake
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate†	50-60% of total calories
Fiber	20-30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

** Trans fatty acids are another LDL-raising fat that should be kept at a low intake.*
† Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
‡ Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

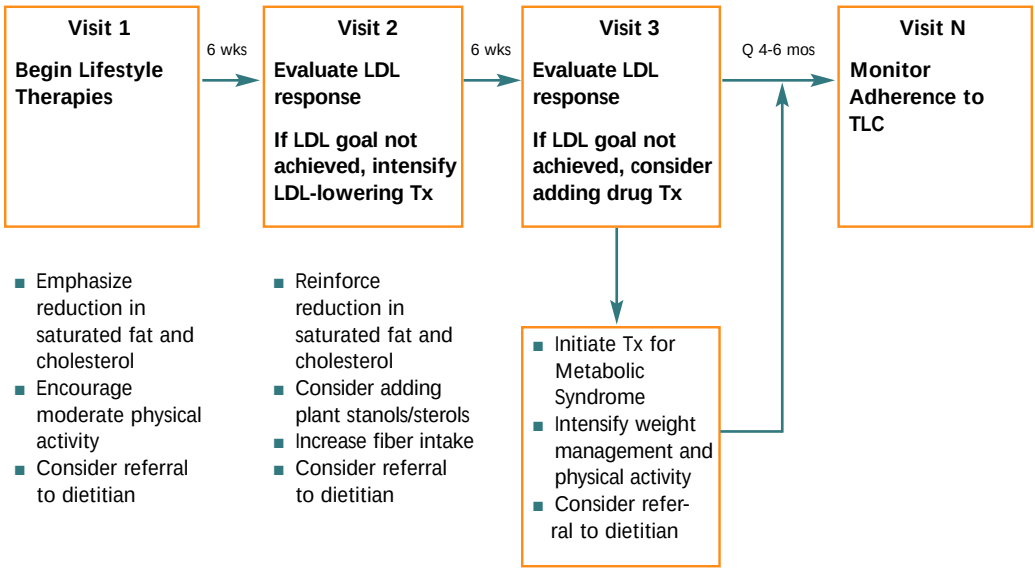
A model of steps in TLC is shown in Figure 1. To initiate TLC, intakes of saturated fats and cholesterol are reduced first to lower LDL cholesterol. To improve overall health, ATP III's TLC Diet generally contains the recommendations embodied in the Dietary Guidelines for Americans 2000. One exception is that total fat is allowed to range from 25-35% of total calories provided saturated fats and *trans* fatty acids are kept low. A higher intake of total fat, mostly in the form of unsaturated fat, can help to reduce triglycerides and raise HDL cholesterol in persons with the metabolic syndrome. In accordance with the Dietary Guidelines, moderate physical activity is encouraged. After 6 weeks, the LDL response is determined; if the LDL cholesterol goal has not been achieved, other therapeutic options for LDL lowering such as plant stanol/sterols and viscous fiber can be added.

After maximum reduction of LDL cholesterol with dietary therapy, emphasis shifts to management of the metabolic syndrome and associated lipid risk factors. The majority of persons with these latter abnormalities are overweight or obese and sedentary. Weight reduction therapy for overweight or obese patients will enhance LDL lowering and will provide other health benefits including modifying other lipid and nonlipid risk factors.

Assistance in the management of overweight and obese persons is provided by the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* from the NHLBI Obesity Education Initiative (1998). Additional risk reduction can be achieved by simultaneously increasing physical activity.

At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy,* which is the term for the nutritional intervention and guidance provided by a nutrition professional.

Figure 1. A Model of Steps in Therapeutic Lifestyle Changes (TLC)



Drug Therapy to Achieve LDL Cholesterol Goals

A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol (see Table 5). When drugs are prescribed, attention to TLC should always be maintained and reinforced. Currently available drugs that affect lipoprotein metabolism and their major characteristics are listed in Table 7.

Some cholesterol-lowering agents are currently available over-the-counter (OTC) (e.g., nicotinic acid), and manufacturers of several classes of LDL-lowering drugs (e.g., statins, bile acid sequestrants) have applied to the

Table 7. Drugs Affecting Lipoprotein Metabolism

Drug Class, Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications	Clinical Trial Results
HMG CoA reductase inhibitors (statins)*	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs†	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid Sequestrants‡	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid¥	LDL HDL TG	↓ 5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids§	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy Unexplained non-CHD deaths in WHO study	Absolute: • Severe renal disease • Severe hepatic disease	Reduced major coronary events

* *Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), cerivastatin (0.4-0.8 mg).*

† *Cyclosporine, macrolide antibiotics, various antifungal agents and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).*

‡ *Cholestyramine (4-16 g), colestipol (5-20 g), colesevelam (2.6-3.8 g).*

¥ *Immediate release (crystalline) nicotinic acid (1.5-3 g), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g).*

§ *Gemfibrozil (600 mg BID), fenofibrate (200 mg), clofibrate (1000 mg BID).*

Food and Drug Administration (FDA) to allow these agents to become OTC medications. At the time of publication of ATP III, the FDA has not granted permission for OTC status for statins or bile acid sequestrants. If an OTC cholesterol-lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting the goals of therapy, and about monitoring for therapeutic responses and side effects.

Secondary prevention: drug therapy for CHD and CHD risk equivalents

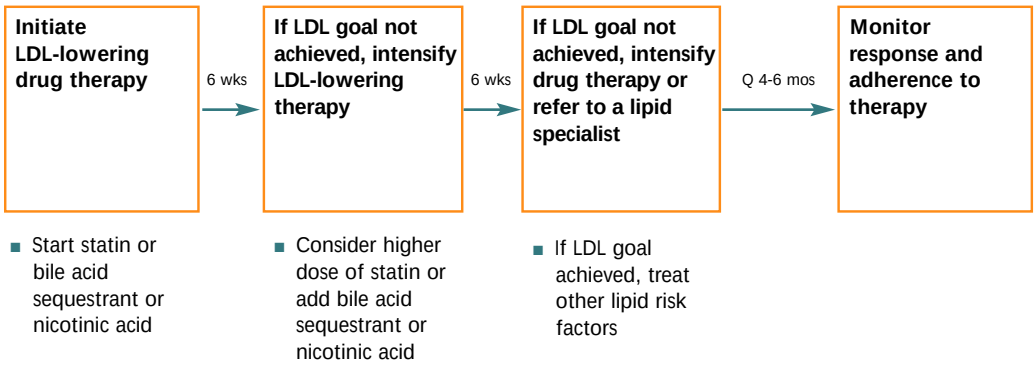
For persons with CHD and CHD risk equivalents, the goal is to attain an LDL cholesterol level <100 mg/dL. The cutpoints for initiating lifestyle and drug therapies are shown in Table 5, and the approach to treatment is discussed immediately after Table 5. Most CHD patients will need LDL-lowering drug therapy. Other lipid risk factors may also warrant consideration of drug treatment. Whether or not lipid-modifying drugs are used, nonlipid risk factors require attention and favorable modification.

In persons admitted to the hospital for a major coronary event, LDL cholesterol should be measured on admission or within 24 hours. This value can be used for treatment decisions. In general, persons hospitalized for a coronary event or procedure should be discharged on drug therapy if the LDL cholesterol is ≥130 mg/dL. If the LDL is 100–129 mg/dL, clinical judgment should be used in deciding whether to initiate drug treatment at discharge, recognizing that LDL cholesterol levels begin to decline in the first few hours after an event and are significantly decreased by 24-48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Some authorities hold drug therapy should be initiated whenever a patient hospitalized for a CHD-related illness is found to have an LDL cholesterol >100 mg/dL. Initiation of drug therapy at the time of hospital discharge has two advantages. First, at that time patients are particularly motivated to undertake and adhere to risk-lowering interventions; and second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap," because outpatient followup is often less consistent and more fragmented.

LDL-lowering drug therapy for primary prevention

Table 5 shows the cutpoints for considering drug treatment in primary prevention. The general approach to management of drug therapy for primary prevention is outlined in Figure 2.

Figure 2. Progression of Drug Therapy in Primary Prevention



When drug therapy for primary prevention is a consideration, the third visit of dietary therapy (see Figure 1) will typically be the visit to initiate drug treatment. Even if drug treatment is started, TLC should be continued. As with TLC, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason, an LDL-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. In most cases, the statin should be started at a moderate dose. In many patients, the LDL cholesterol goal will be achieved, and higher doses will not be necessary. The patient's response should be checked about 6 weeks after starting drug therapy. If the goal of therapy has been achieved, the current dose can be maintained. However, if the goal has not been achieved, LDL-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant or nicotinic acid.

After 12 weeks of drug therapy, the response to therapy should again be assessed. If the LDL cholesterol goal is still not achieved, consideration can be given to further intensification of drug therapy. If the LDL goal cannot be attained by standard lipid-lowering therapy, consideration should be given to seeking consultation from a lipid specialist. Once the goal for LDL cholesterol has been attained, attention can turn to other lipid risk factors and nonlipid factors. Thereafter, patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary.

Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy

Evidence is accumulating that risk for CHD can be reduced beyond LDL-lowering therapy by modification of other risk factors. One potential

secondary target of therapy is the metabolic syndrome, which represents a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called *insulin resistance* in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance.

The risk factors of the metabolic syndrome are highly concordant; in aggregate they enhance risk for CHD at any given LDL cholesterol level. For purposes of ATP III, the diagnosis of the metabolic syndrome is made when three or more of the risk determinants shown in Table 8 are present. These determinants include a combination of categorical and borderline risk factors that can be readily measured in clinical practice.

Table 8. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal Obesity*	Waist Circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* *Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

† *Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Management of the metabolic syndrome has a two-fold objective: (1) to reduce underlying causes (i.e., obesity and physical inactivity), and (2) to treat associated nonlipid and lipid risk factors.

Management of underlying causes of the metabolic syndrome

First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity, which will effectively reduce all of these risk factors. Therefore, after

appropriate control of LDL cholesterol, TLC should stress weight reduction and physical activity if the metabolic syndrome is present.

Weight control. In ATP III overweight and obesity are recognized as major, underlying risk factors for CHD and identified as direct targets of intervention. Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome. The recommended approaches for reducing overweight and obesity are contained in the clinical guidelines of the NHLBI Obesity Education Initiative.

Physical activity. Physical inactivity is likewise a major, underlying risk factor for CHD. It augments the lipid and nonlipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low density lipoprotein (VLDL) levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence base for this recommendation is contained in the *U.S. Surgeon General's Report on Physical Activity.*

Specific Treatment of Lipid and Non-Lipid Risk Factors

Beyond the underlying risk factors, therapies directed against the lipid and nonlipid risk factors of the metabolic syndrome will reduce CHD risk. These include treatment of hypertension, use of aspirin in patients with CHD to reduce the prothrombotic state (guidelines for aspirin use in primary prevention have not been firmly established), and treatment of elevated triglycerides and low HDL cholesterol as discussed below under Management of Specific Dyslipidemias.

Special Issues

Management of Specific Dyslipidemias

Very high LDL cholesterol (≥190 mg/dL). Persons with very high LDL cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia, familial defective apolipoprotein B, and polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD. Family testing is important to identify similarly affected relatives. These

disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering therapy.

Elevated serum triglycerides. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for CHD. Factors contributing to elevated (higher than normal) triglycerides in the general population include: obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, high carbohydrate diets (>60% of energy intake), several diseases (e.g., type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (e.g., corticosteroids, estrogens, retinoids, higher doses of beta-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia).

In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150-199 mg/dL
- High triglycerides: 200-499 mg/dL
- Very high triglycerides: ≥500 mg/dL

The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded VLDL, commonly called *remnant lipoproteins.* In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. ATP III identifies the sum of LDL+VLDL cholesterol [termed *non-HDL cholesterol* (total cholesterol minus HDL cholesterol)] as a secondary target of therapy in persons with high triglycerides (≥200 mg/dL). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than that for LDL cholesterol (Table 9) on the premise that a VLDL cholesterol level ≤30 mg/dL is normal.

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are *borderline high* (150-199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For *high triglycerides* (200-499 mg/dL), non-HDL cholesterol becomes a secondary

Table 9. Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL-C Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-HDL cholesterol goal. There are two approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; or second, nicotinic acid or fibrate can be added, if used with appropriate caution, to achieve the non-HDL cholesterol goal by further lowering of VLDL cholesterol. In rare cases in which triglycerides are *very high* (≥500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low fat diets (≤15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to <500 mg/dL should attention turn to LDL lowering to reduce risk for CHD.

Low HDL cholesterol. Low HDL cholesterol is a strong independent predictor of CHD. In ATP III, low HDL cholesterol is defined categorically as a level <40 mg/dL, a change from the level of <35 mg/dL in ATP II. In the present guidelines, low HDL cholesterol both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD.

Low HDL cholesterol levels have several causes, many of which are associated with insulin resistance, i.e., elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. Other causes are cigarette smoking, very high carbohydrate intakes (>60% of calories), and certain drugs (e.g., beta-blockers, anabolic steroids, progestational agents)

ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise HDL cholesterol. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL

cholesterol; ATP III guidelines should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL cholesterol is associated with high triglycerides (200-499 mg/dL), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined before. Also, if triglycerides are <200 mg/dL (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be considered; however, treatment for isolated low HDL is mostly reserved for persons with CHD and CHD risk equivalents.

Diabetic dyslipidemia. This disorder is essentially atherogenic dyslipidemia (high triglycerides, low HDL, and small dense LDL) in persons with type 2 diabetes. Although elevated triglycerides and/or low HDL cholesterol are common in persons with diabetes, clinical trial results support the identification of LDL cholesterol as the primary target of therapy, as it is in those without diabetes. Since diabetes is designated a CHD risk equivalent in ATP III, the LDL cholesterol goal of therapy for most persons with diabetes will be <100 mg/dL. Furthermore, when LDL cholesterol is ≥130 mg/dL, most persons with diabetes will require initiation of LDL-lowering drugs simultaneously with TLC to achieve the LDL goal. When LDL cholesterol levels are in the range of 100-129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. When triglyceride levels are ≥200 mg/dL, non-HDL cholesterol becomes a secondary target of cholesterol-lowering therapy. Several ongoing clinical trials (e.g., Antihypertensive and Lipid Lowering Heart Attack Trial [ALLHAT]) will better quantify the magnitude of the benefit of LDL-lowering treatment in older individuals with diabetes. In older persons (≥65 years of age) with diabetes but no additional CHD risk factors other than age, clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

Special Considerations for Different Population Groups

Middle-aged men (35-65 years). In general, men have a higher risk for CHD than do women. Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all CHD in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for CHD, and for those who do, intensive LDL-lowering therapy is needed.

Women (ages 45-75 years). In women, onset of CHD generally is delayed by some 10-15 years compared with that in men; thus most CHD in women occurs after age 65. All risk factors contribute to CHD in women, and most premature CHD in women (<65 years) occurs in those with multiple risk factors and the metabolic syndrome. Despite the previous belief that the gender difference in risk for CHD reflects a protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt on the use of hormone replacement therapy to reduce CHD risk in postmenopausal women. In contrast, the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for CHD risk reduction. Women should be treated similarly to men for secondary prevention. For primary prevention, ATP III's general approach is similarly applicable for women and men. However, the later onset of CHD for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs.

Older adults (men ≥ 65 years and women ≥ 75 years). Overall, most new CHD events and most coronary deaths occur in older persons (≥ 65 years). A high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. Nevertheless, the finding of advanced subclinical atherosclerosis by noninvasive testing can be helpful for confirming the presence of high risk in older persons. Secondary prevention trials with statins have included a sizable number of older persons, mostly in the age range of 65 to 75 years. In these trials, older persons showed significant risk reduction with statin therapy. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established CHD for LDL-lowering therapy. For primary prevention, TLC is the first line of therapy for older persons. However, LDL-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Younger adults (men 20-35 years; women 20-45 years). CHD is rare except in those with severe risk factors, e.g., familial hypercholesterolemia, heavy cigarette smoking, or diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature CHD in middle age. Thus, risk factor identification in young adults is an important aim for long-term prevention. The combination of early detection and early intervention on elevated LDL cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of CHD later in life. For young adults with LDL cholesterol levels ≥130 mg/dL, TLC should be instituted and emphasized.

Particular attention should be given to young men who smoke and have a high LDL cholesterol (160-189 mg/dL); they may be candidates for LDL-lowering drugs. When young adults have very high LDL cholesterol levels (≥190 mg/dL), drug therapy should be considered, as in other adults. Those with severe genetic forms of hypercholesterolemia may require LDL-lowering drugs in combination (e.g., statin + bile acid sequestrant).

Racial and ethnic groups. African Americans have the highest overall CHD mortality rate and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Although the reasons for the excess CHD mortality among African Americans have not been fully elucidated, it can be accounted for, at least in part, by the high prevalence of coronary risk factors. Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple CHD risk factors all occur more frequently in African Americans than in whites. Other ethnic groups and minority populations in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. Although limited data suggest that racial and ethnic groups vary somewhat in baseline risk for CHD, this evidence did not appear sufficient to lead the ATP III panel to modify general recommendations for cholesterol management in these populations.

Adherence to LDL-Lowering Therapy

Adherence to the ATP III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed in order to attain the highest possible levels of CHD risk reduction. Thus, ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, providers, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (Table 10).

Table 10. Interventions to Improve Adherence

Focus on the Patient

- Simplify medication regimens
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
- Encourage the use of prompts to help patients remember treatment regimens
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase visits for patients unable to achieve treatment goal
- Increase the convenience and access to care
- Involve patients in their care through self-monitoring

Focus on the Physician and Medical Office

- Teach physicians to implement lipid treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Remind patients of appointments and follow-up missed appointments

Focus on the Health Delivery System

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

Appendix

Shared Features of ATP III and ATP II

ATP III shares a set of core features with ATP II. These are shown in Table A.

Table A. Shared Features of ATP III and ATP II

- Continued identification of LDL cholesterol lowering as the primary goal of therapy
- Consideration of high LDL cholesterol (≥160 mg/dL) as a potential target for LDL-lowering drug therapy, specifically as follows:
  - For persons with multiple risk factors whose LDL levels are high (≥160 mg/dL) after dietary therapy, consideration of drug therapy is recommended
  - For persons with 0-1 risk factor, consideration of drug therapy (after dietary therapy) is optional for LDL 160-189 mg/dL and recommended for LDL ≥190 mg/dL
- Emphasis on intensive LDL-lowering therapy in persons with established CHD
- Identification of three categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - CHD and CHD risk equivalents* (other forms of clinical atherosclerotic disease)
  - Multiple (2+) risk factors†
  - 0-1 risk factor
- Identification of subpopulations, besides middle-aged men, for detection of high LDL cholesterol (and other lipid risk factors) and for clinical intervention. These include:
  - Young adults
  - Postmenopausal women
  - Older persons
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol

* *A CHD risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.*

† *Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD, age (male ≥45 years and female ≥55 years), and diabetes (in ATP III diabetes is regarded as a CHD risk equivalent).*

Estimating 10-Year Risk for Men and Women

Risk assessment for determining the 10-year risk for developing CHD is carried out using Framingham risk scoring (Table B1 for men and Table B2 for women). The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that the LDL cholesterol level remains the primary target of therapy. Total cholesterol and HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The blood pressure value used is that obtained at the time of assessment, regardless of whether the person is on anti-hypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk (see Tables B1 and B2). The average of several blood pressure measurements, as recommended by the Joint National Committee (JNC), is needed for an accurate measure of baseline blood pressure. The designation “smoker” means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death (hard CHD) is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above (see Table 5).

Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

Table B2. Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
<9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

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ATP III Guidelines At-A-Glance Quick Desk Reference

Step 1

1 Determine lipoprotein levels–obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Step 2

2 Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

Step 3

3 Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)*
Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

** HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

- Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

4

Step 4

If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (see Framingham tables).
Three levels of 10-year risk:

- >20% — CHD risk equivalent
- 10-20%
- <10%

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Step 5

Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

6

Step 6

Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

TLC Features

- TLC Diet:
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider increased viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2g/day) as therapeutic options to enhance LDL lowering
- Weight management
- Increased physical activity.

7

Step 7

Consider adding drug therapy if LDL exceeds levels shown in Step 5 table:

- Consider drug simultaneously with TLC for CHD and CHD equivalents
- Consider adding drug to TLC after 3 months for other risk categories.

Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications
HMG CoA reductase inhibitors (statins)	Lovastatin (20-80 mg) Pravastatin (20-40 mg) Simvastatin (20-80 mg) Fluvastatin (20-80 mg) Atorvastatin (10-80 mg) Cerivastatin (0.4-0.8 mg)	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*
Bile acid sequestrants	Cholestyramine (4-16 g) Colestipol (5-20 g) Colesevelam (2.6-3.8 g)	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL
Nicotinic acid	Immediate release (crystalline) nicotinic acid (1.5-3 gm), extended release nicotinic acid (Niaspan®) (1-2 g), sustained release nicotinic acid (1-2 g)	LDL HDL TG	↓5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg BID) Fenofibrate (200 mg) Clofibrate (1000 mg BID)	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy	Absolute: • Severe renal disease • Severe hepatic disease

* *Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).*

Identify metabolic syndrome and treat, if present, after 3 months of TLC.

Clinical Identification of the Metabolic Syndrome – Any 3 of the Following:

Risk Factor	Defining Level
Abdominal obesity*	Waist circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* *Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

† *Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Treatment of the metabolic syndrome

- Treat underlying causes (overweight/obesity and physical inactivity):
  - Intensify weight management
  - Increase physical activity.

- Treat lipid and non-lipid risk factors if they persist despite these lifestyle therapies:
  - Treat hypertension
  - Use aspirin for CHD patients to reduce prothrombotic state
  - Treat elevated triglycerides and/or low HDL (as shown in Step 9).

Treat elevated triglycerides.

ATP III Classification of Serum Triglycerides (mg/dL)

<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Treatment of elevated triglycerides (≥150 mg/dL)

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity
- If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total – HDL) 30 mg/dL higher than LDL goal.

Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

If triglycerides 200-499 mg/dL after LDL goal is reached, consider adding drug if needed to reach non-HDL goal:

- intensify therapy with LDL-lowering drug, or
- add nicotinic acid or fibrate to further lower VLDL.

If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:

- very low-fat diet (≤15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
- when triglycerides <500 mg/dL, turn to LDL-lowering therapy.

Treatment of low HDL cholesterol (<40 mg/dL)

- First reach LDL goal, then:
- Intensify weight management and increase physical activity
- If triglycerides 200-499 mg/dL, achieve non-HDL goal
- If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent consider nicotinic acid or fibrate.

Men

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Women

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Heart, Lung, and Blood Institute

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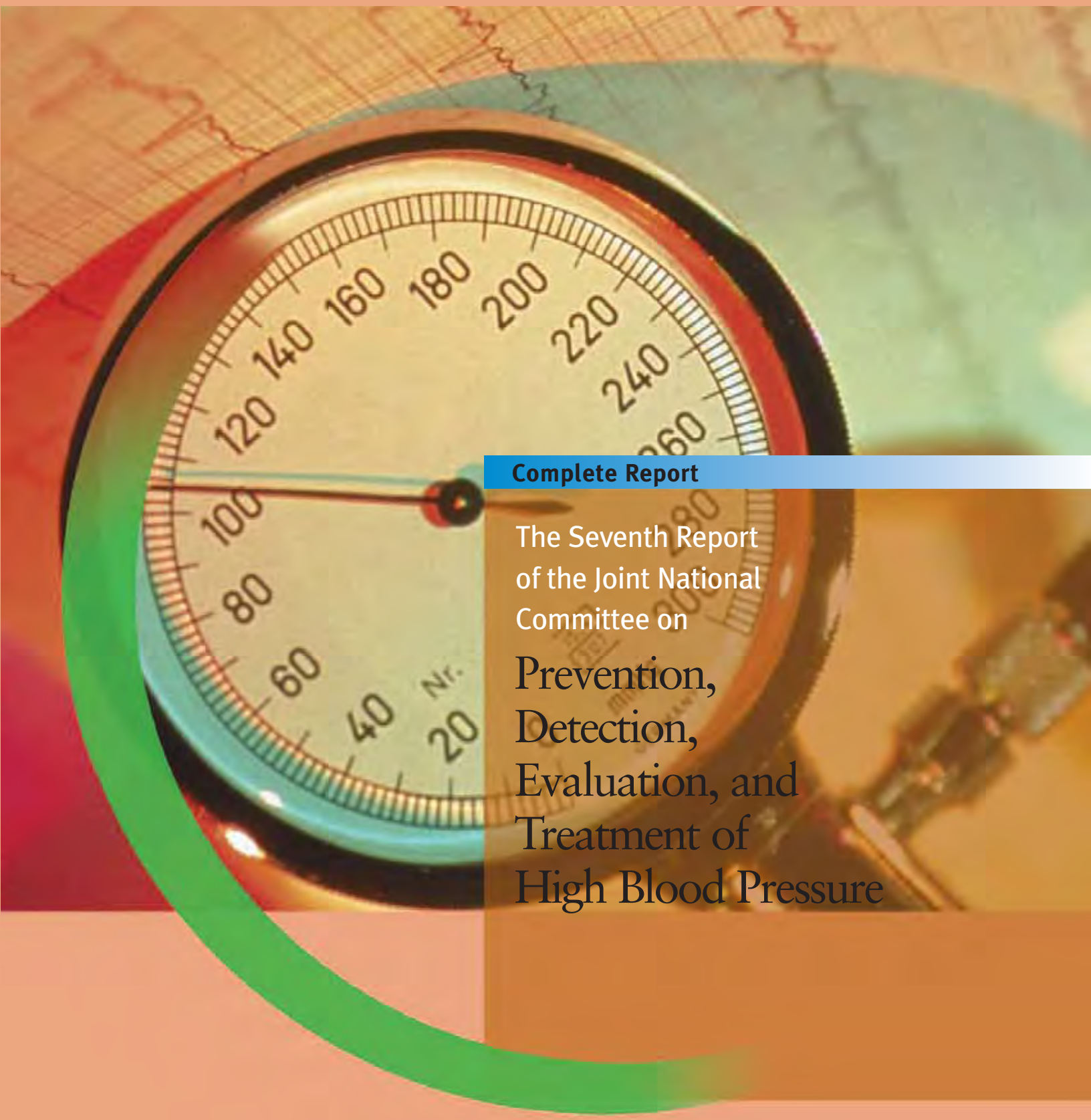
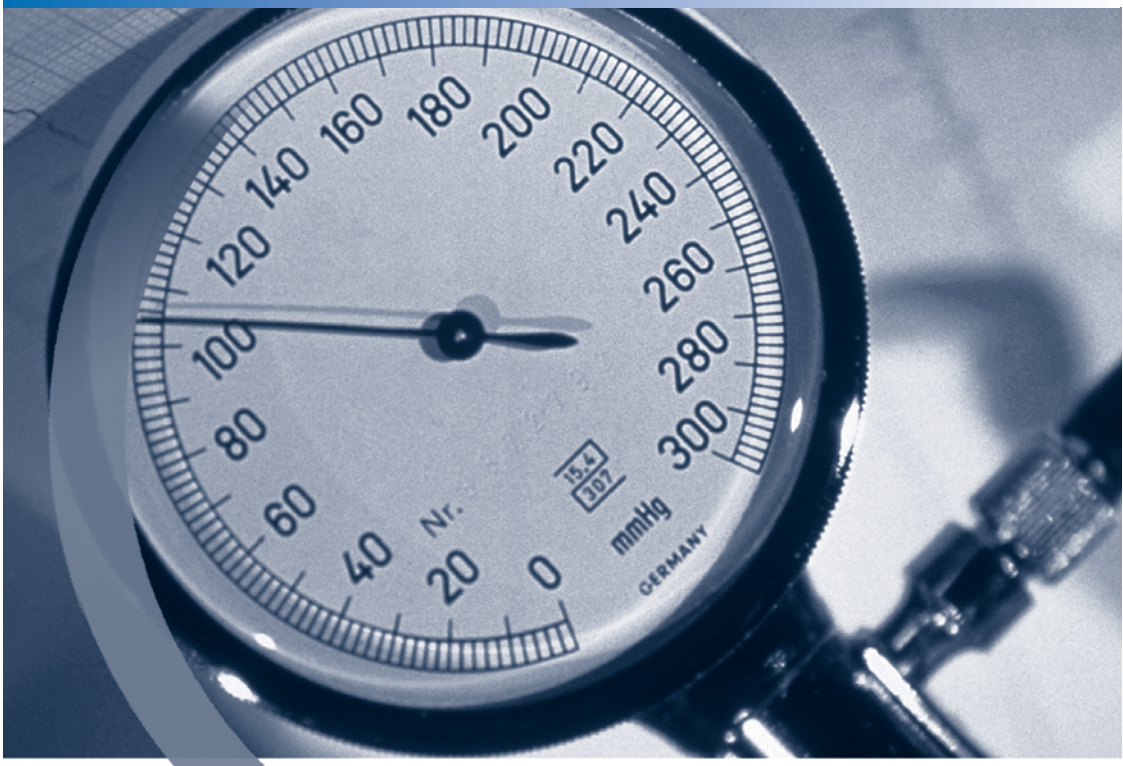


Complete Report

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

Complete Report



The Seventh Report of the Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

NIH Publication No. 04-5230
August 2004

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Dr. Bakris has received honoraria for serving as a speaker from Astra-Zeneca, Abbott, Alteon, Biovail, Boerhinger-Ingelheim, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Merck, Novartis, Sanofi, Sankyo, and Solvay; he has received funding/grant support for research projects from National Institutes of Health, Astra-Zeneca, Abbott, Alteon, Boerhinger-Ingelheim, Forest, GlaxoSmithKline, Merck, Novartis, Sankyo, and Solvay; he has served as a consultant/advisor for Astra-Zeneca, Abbott, Alteon, Biovail, Boerhinger-Ingelheim, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Merck, Novartis, Sanofi, Sankyo, and Solvay.

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American Academy of Ophthalmology
American Academy of Physician Assistants
American Association of Occupational Health Nurses
American College of Cardiology
American College of Chest Physicians
American College of Occupational and Environmental Medicine
American College of Physicians-American Society of Internal Medicine
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Department of Veterans Affairs
Health Resources and Services Administration
National Center for Health Statistics
National Heart, Lung, and Blood Institute
National Institute of Diabetes and Digestive and Kidney Diseases

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Foreword

The complete version of the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC7) provides additional scientific evidence to bolster other JNC 7 products: the *JNC 7 Express*; *Facts About the DASH Eating Plan; Your Guide to Lowering High Blood Pressure*; Reference Card from the JNC 7 for clinicians; Blood Pressure Wallet Card for patients; and Palm application of the JNC 7 recommendations. These educational materials are available on the NHLBI Web site http://www.nhlbi.nih.gov/.

The purpose of JNC reports is to synthesize the available scientific evidence and offer guidance to busy primary care clinicians. Readers of this report should remember that this document is intended as a guide, not a mandate. The National High Blood Pressure Education Program (NHBPEP) recognizes the responsible clinician's judgment regarding the management of patients remains paramount. Therefore, JNC documents are tools to be adopted and implemented in local and individual settings.

In the production of this report, much discussion was generated regarding the interpretation of the available scientific literature. However, after all of the discussions within the JNC 7 Executive Committee and the NHBPEP Coordinating Committee, as well as the many discussions at conferences and scientific meetings conducted in the United States and worldwide, the conclusion is that best management practice occurs when hypertension is treated to goal levels and blood pressure control is sustained over time. This is irrefutable but, unfortunately, hypertension treatment and control rates worldwide are simply not as good as they could be.

By developing this stellar landmark report, Dr. Aram Chobanian, the JNC 7 Executive Committee, and members of the NHBPEP Coordinating Committee, as well as the writers and the contributors to this document, have addressed the important public health issue of improving inadequate blood pressure control. Applying JNC 7 recommendations to clinical practice will prevent the devastating consequences of uncontrolled hypertension. I recommend this guideline to clinicians and public health workers with the conviction that its contents will indeed contribute to the further prevention of premature morbidity and mortality. Dr. Chobanian has our deep gratitude for leading the effort to develop this report in such a timely manner. His brilliant leadership is what made the JNC 7 and related materials possible. The NHBPEP will release other advisories as the scientific evidence becomes available.

Barbara M. Alving, M.D.
Acting Director
National Heart, Lung, and Blood Institute
and
Chair
National High Blood Pressure Education Program
Coordinating Committee

Abstract

The purpose of the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) is to provide an evidence-based approach to the prevention and management of hypertension. The key messages of this report are: in those older than age 50, systolic blood pressure (SBP) of >140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP (DBP); beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg; those who are normotensive at 55 years of age will have a 90 percent lifetime risk of developing hypertension; prehypertensive individuals (SBP 120–139 mmHg or DBP 80–89 mmHg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD; for uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes; this report delineates specific high-risk conditions, which are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers); two or more antihypertensive medications will be required to achieve goal BP (<140/90 mmHg, or <130/80 mmHg for patients with diabetes and chronic kidney disease); for patients whose BP is >20 mmHg above the SBP goal or 10 mmHg above the DBP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered; regardless of therapy or care, hypertension will only be controlled if patients are motivated to stay on their treatment plan. Positive experiences, trust in the clinician, and empathy improve patient motivation and satisfaction. This report serves as a guide, and the committee continues to recognize that the responsible physician's judgment remains paramount.

Introduction

For more than three decades, the National Heart, Lung, and Blood Institute (NHLBI) has administered the National High Blood Pressure Education Program (NHBPEP) Coordinating Committee, a coalition of 39 major professional, public, and voluntary organizations and 7 Federal agencies. One important function is to issue guidelines and advisories designed to increase awareness, prevention, treatment, and control of hypertension (high blood pressure [BP]).

Data from the National Health and Nutrition Examination Survey (NHANES) have indicated that 50 million or more Americans have high BP warranting some form of treatment.[1,2] Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension.[3] The World Health Organization reports that suboptimal BP (>115 mmHg SBP) is responsible for 62 percent of cerebrovascular disease and 49 percent of ischemic heart disease (IHD), with little variation by sex. In addition, suboptimal BP is the number one attributable risk factor for death throughout the world.[3]

Considerable success has been achieved in the past in meeting the goals of the program. The awareness of hypertension among Americans has improved from a level of 51 percent in the period 1976–1980 to 70 percent in 1999–2000 (table 1). The percentage of patients with hypertension receiving treatment has increased from 31 percent to 59 percent in the same period, and the percentage of persons with high BP controlled to below 140/90 mmHg has increased from 10 percent to 34 percent. Between 1960 and 1991, median SBP for individuals ages 60–74 declined by approximately 16 mmHg (figure 1). These changes have been associated with highly favorable trends in the morbidity and mortality attributed to hypertension. Since 1972, age-adjusted death rates from stroke and coronary heart disease (CHD) have declined by approximately 60 percent and 50 percent, respectively (figures 2 and 3). These benefits have occurred independent of gender, age, race, or socioeconomic status. Within the last two decades, better treatment of hypertension has been associated with a considerable reduction in the hospital case-fatality rate for heart failure (HF) (figure 4). This information suggests that there have been substantial improvements.

Table 1. Trends in awareness, treatment, and control of high blood pressure, 1976–2000*

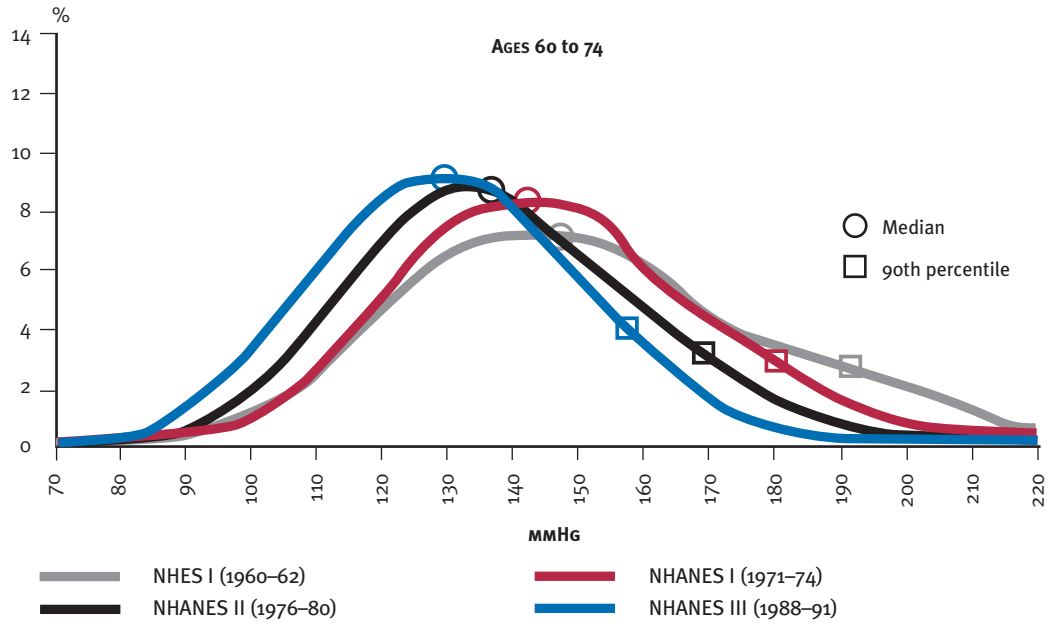
	National Health and Nutrition Examination Survey, Percent			
	1976–80[1]	1988–91[1]	1991–94[2]	1999–2000[3]
Awareness	51	73	68	70
Treatment	31	55	54	59
Control†	10	29	27	34

** Percentage of adults ages 18 to 74 years with SBP of 140 mmHg or greater, DBP of 90 mmHg or greater, or taking antihypertensive medication.*

† SBP below 140 mmHg and DBP below 90 mmHg, and on antihypertensive medication.

Sources:
1. *Data from Burt VL, et al. Prevalance of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991.* Hypertension *1995;26:60–9.*
2. *Data from The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* Arch Intern Med *1997;157:2413–46.*
3. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* JAMA *2003;289:2560–71.*

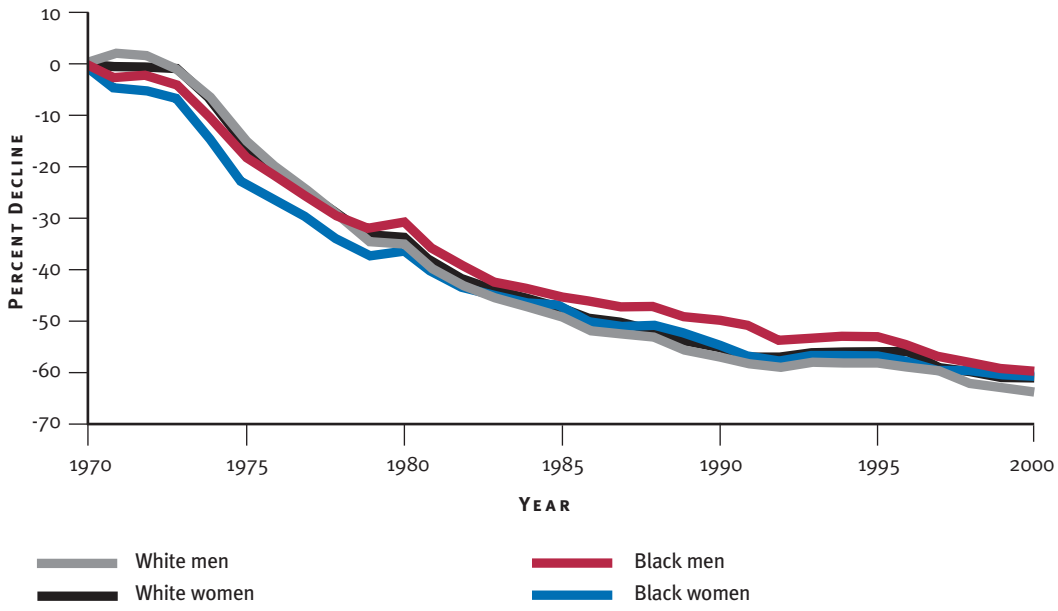
Figure 1. Smoothed weighted frequency distribution, median, and 90th percentile of systolic blood pressure for ages 60–74 years: United States, 1960–1991



NHANES, National Health and Nutrition Examination Survey; NHES, National Health Examination Survey

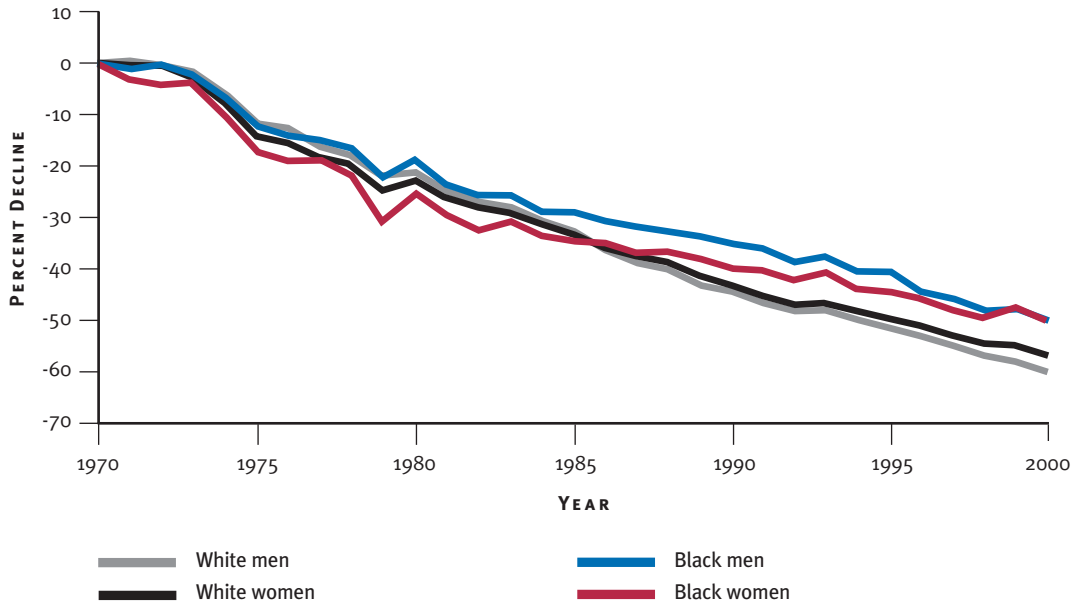
Source: Burt VL, et al. Trends in the prevalance, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. Erratum in: Hypertension *1996;7(5):1192.*

Figure 2. Percent decline in age-adjusted mortality rates for stroke by gender and race: United States, 1970–2000



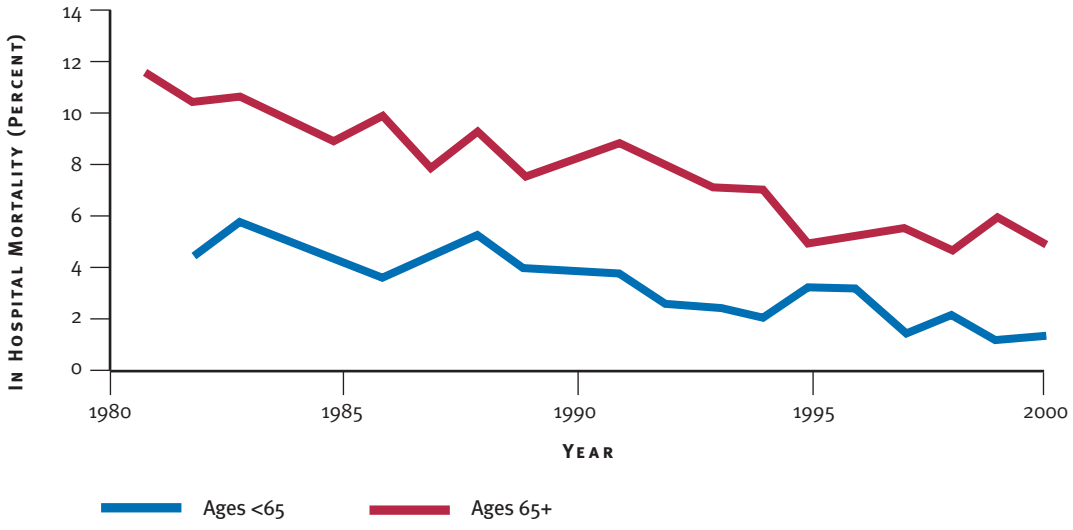
Source: Prepared by Thom T, National Heart, Lung, and Blood Institute from Vital Statistics of the United States, National Center for Health Statistics. Death rates are age-adjusted to the 2000 U.S. census population.

Figure 3. Percent decline in age-adjusted mortality rates for coronary heart disease by gender and race: United States, 1970–2000



Source: Prepared by Thom T, National Heart, Lung, and Blood Institute from Vital Statistics of the United States, National Center for Health Statistics. Death rates are age-adjusted to the 2000 U.S. census population.

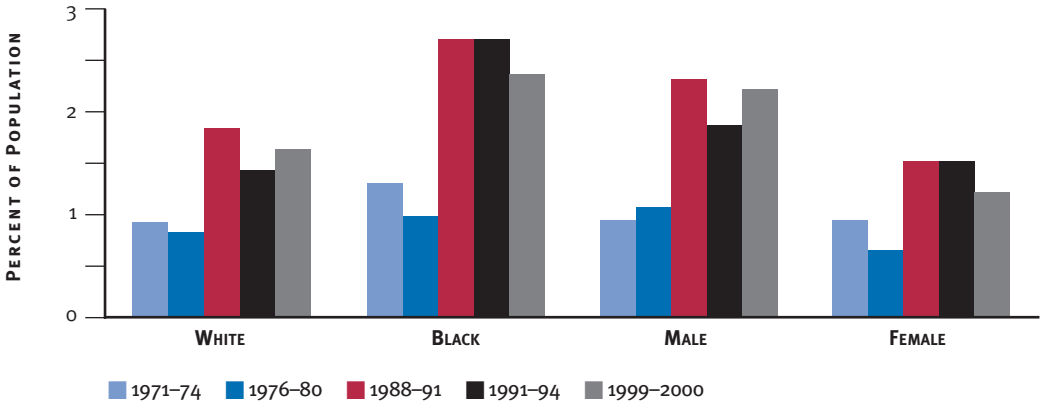
Figure 4. Hospital case-fatality rates for congestive heart failure for ages younger than 65 years and 65 years and older: United States, 1981–2000



Source: National Heart, Lung, and Blood Institute. Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. *Chart 3-36. Accessed November 2003. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm.*

However, these improvements have not been extended to the total population. Current control rates for hypertension in the United States are clearly unacceptable. Approximately 30 percent of adults are still unaware of their hypertension, >40 percent of individuals with hypertension are not on treatment, and two-thirds of hypertensive patients are not being controlled to BP levels <140/90 mmHg (table 1). Furthermore, the decline rates in CHD- and stroke-associated deaths have slowed in the past decade. In addition, the prevalence and hospitalization rates of HF, wherein the majority of patients have hypertension prior to developing HF, have continued to increase (figures 5 and 6). Moreover, there is an increasing trend in end-stage renal disease (ESRD) by primary diagnosis. Hypertension is second only to diabetes as the most common antecedent for this condition (figure 7). Undiagnosed, untreated, and uncontrolled hypertension clearly places a substantial strain on the health care delivery system.

Figure 5. Prevalence* of congestive heart failure by race and gender, ages 25–74 years: United States, 1971–74 to 1999–2000

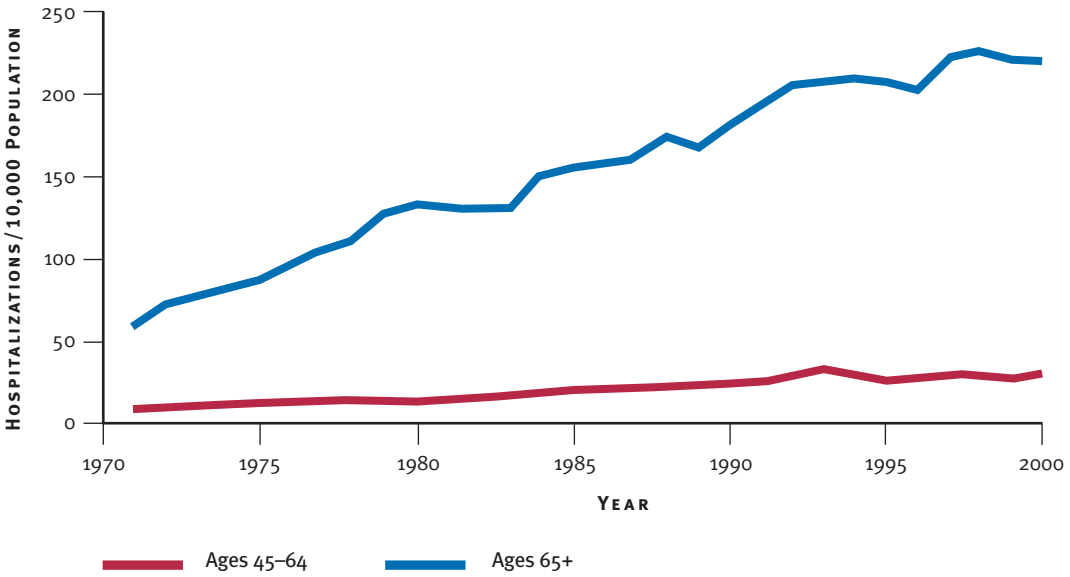


** Age-adjusted to 2000 U.S. census population.*

Note: White and Black in 1999–2000 exclude Hispanics.

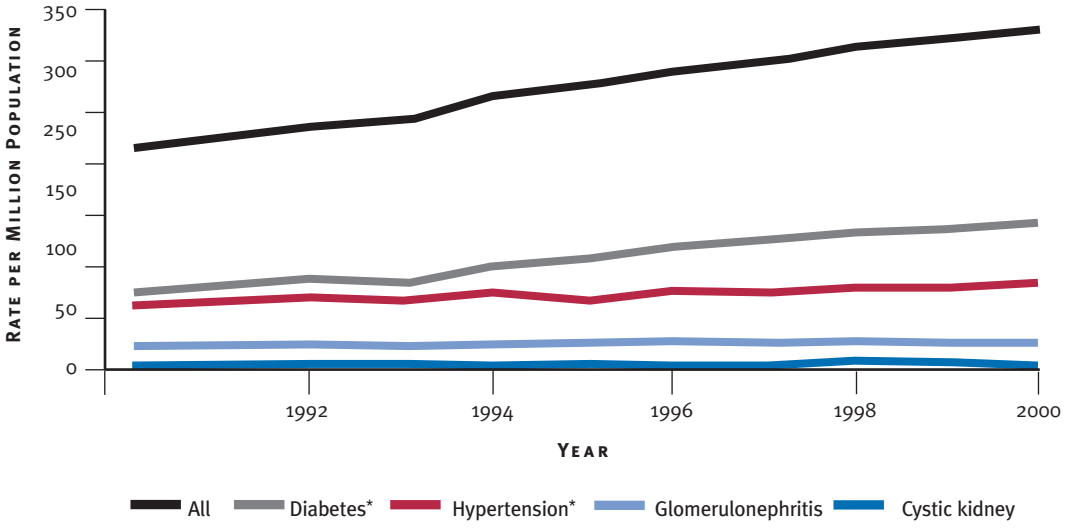
Source: National Heart, Lung, and Blood Institute. Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. *Accessed November 2003. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm and 1999–2000 unpublished data computed by Wolz M and Thom T, National Heart, Lung, and Blood Institute. June 2003.*

Figure 6. Hospitalization rates for congestive heart failure, ages 45–64 years and 65 years and older: United States, 1971–2000



Source: National Heart, Lung, and Blood Institute. Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. *Chart 3-35. Accessed November 2003. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm.*

Figure 7. Trends in incident rates of end-stage renal disease, by primary diagnosis (adjusted for age, gender, race)



* *These disease categories were treated as being mutually exclusive.*

Source: United States Renal Data System. 2002. Figure 1.14. Accessed November 2003. http://www.usrds.org/slides.htm.

Methods

The decision to appoint a committee for JNC 7 was based on four factors: the publication of many new hypertension observational studies and clinical trials since the last report was published in 1997;[4] the need for a new, clear, and concise guideline that would be useful to clinicians; the need to simplify the classification of BP; and a clear recognition that the JNC reports did not result in maximum benefit to the public. This JNC report is presented in two separate publications. The initial "Express" version, a succinct practical guide, was published in the May 21, 2003 issue of the *Journal of the American Medical Association*.[5] The current, more comprehensive report provides a broader discussion and justification for the recommendations made by the committee. As with prior JNC reports, the committee recognizes that the responsible physician's judgment is paramount in managing his or her patients.

Since the publication of the JNC 6 report, the NHBPEP Coordinating Committee, chaired by the director of the NHLBI, has regularly reviewed and discussed studies on hypertension. To conduct this task, the Coordinating Committee is divided into four subcommittees: science base; long-range planning; professional, patient, and public education; and program organization. The subcommittees work together to review the hypertension scientific literature from clinical trials, epidemiology, and behavioral science. In many instances, the principal investigator of the larger studies has presented the information directly to the Coordinating Committee. The committee reviews are summarized and posted on the NHLBI Web site.[6] This ongoing review process keeps the committee apprised of the current state of the science, and the information is also used to develop program plans for future activities, such as continuing education.

During fall 2002, the NHBPEP Coordinating Committee chair solicited opinions regarding the need to update the JNC 6 report. The entire Coordinating Committee provided, in writing, a detailed rationale explaining the necessity for updating JNC 6, outlined critical issues, and provided concepts to be addressed in the new report. Thereafter, the NHBPEP Coordinating Committee chair appointed the JNC 7 chair and an Executive Committee derived from the Coordinating Committee membership. The Coordinating Committee members served on one of five JNC 7 writing teams, which contributed to the writing and review of the document.

The concepts for the new report identified by the NHBPEP Coordinating Committee were used to create the report outline. Based on these critical issues and concepts, the Executive Committee developed relevant medical subject headings (MeSH) terms and keywords to further review the scientific literature. These MeSH terms were used to generate MEDLINE searches that focused on English-language, peer-reviewed, scientific literature from January 1997 through April 2003. Various systems of grading the evidence were considered, and the classification scheme used in JNC 6 and other NHBPEP clinical guidelines was selected.[4,7–10] This scheme classifies studies according to a process adapted from Last and Abramson (see Scheme Used for Classification of the Evidence).[11]

In reviewing the exceptionally large body of research literature on hypertension, the Executive Committee focused its deliberations on evidence pertaining to outcomes of importance to patients and with effects of sufficient magnitude to warrant changes in medical practice ("patient-oriented evidence that matters," or POEMs).[12,13] Patient-oriented outcomes include not only

mortality but also other outcomes that affect patients' lives and well-being, such as sexual function, ability to maintain family and social roles, ability to work, and ability to carry out daily living activities. These outcomes are strongly affected by nonfatal stroke, HF, CHD, and renal disease; hence, these outcomes were considered along with mortality in the committee's evidence-based deliberations. Studies of physiological endpoints ("disease-oriented evidence," or DOEs) were used to address questions where POEMs were not available.

The Coordinating Committee began the process of developing the *JNC 7 Express* report in December 2002, and the report was submitted to the *Journal of the American Medical Association* in April 2003. It was published in an electronic format on May 14, 2003, and in print on May 21, 2003. During this time, the Executive Committee met on six occasions, two of which included meetings with the entire NHBPEP Coordinating Committee. The writing teams also met by teleconference and used electronic communications to develop the report. Twenty-four drafts were created and reviewed repeatedly. At its meetings, the Executive Committee used a modified nominal group process[14] to identify and resolve issues. The NHBPEP Coordinating Committee reviewed the penultimate draft and provided written comments to the Executive Committee. In addition, 33 national hypertension leaders reviewed and commented on the document. The NHBPEP Coordinating Committee approved the *JNC 7 Express* report. To complete the longer JNC 7 version, the Executive Committee members met via teleconferences and in person and circulated sections of the larger document via e-mail. The sections were assembled and edited by the JNC 7 chair and were circulated among the NHBPEP Coordinating Committee members for review and comment. The JNC 7 chair synthesized the comments, and the longer version was submitted to the journal *Hypertension* in November 2003.

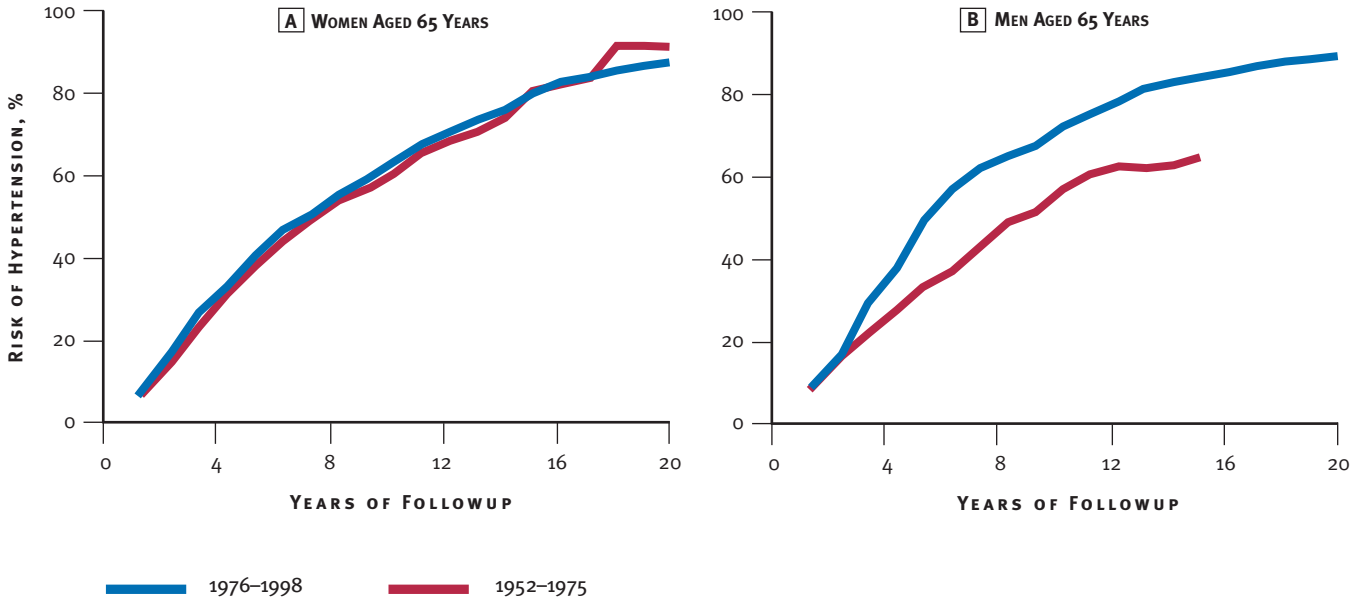
Lifetime Risk of Hypertension

Hypertension is an increasingly important medical and public health issue. The prevalence of hypertension increases with advancing age to the point where more than half of people 60–69 years of age and approximately three-fourths of those 70 years of age and older are affected.[1] The age-related rise in SBP is primarily responsible for an increase in both incidence and prevalence of hypertension with increasing age.[15]

Whereas the short-term absolute risk for hypertension is conveyed effectively by incidence rates, the long-term risk is best summarized by the lifetime risk statistic, which is the probability of developing hypertension during the remaining years of life (either adjusted or unadjusted for competing causes of death). Framingham Heart Study investigators recently reported the lifetime risk of hypertension to be approximately 90 percent for men and women who were nonhypertensive at 55 or 65 years and survived to age 80–85 (figure 8).[16] Even after adjusting for competing mortality, the remaining lifetime risks of hypertension were 86–90 percent in women and 81–83 percent in men.

The impressive increase of BP to hypertensive levels with age is also illustrated by data indicating that the 4-year rates of progression to hypertension are 50 percent for those 65 years and older with BP in the 130–139/85–89 mmHg range and 26 percent for those with BP between 120–129/80–84 mmHg range.[17]

Figure 8. Residual lifetime risk of hypertension in women and men aged 65 years



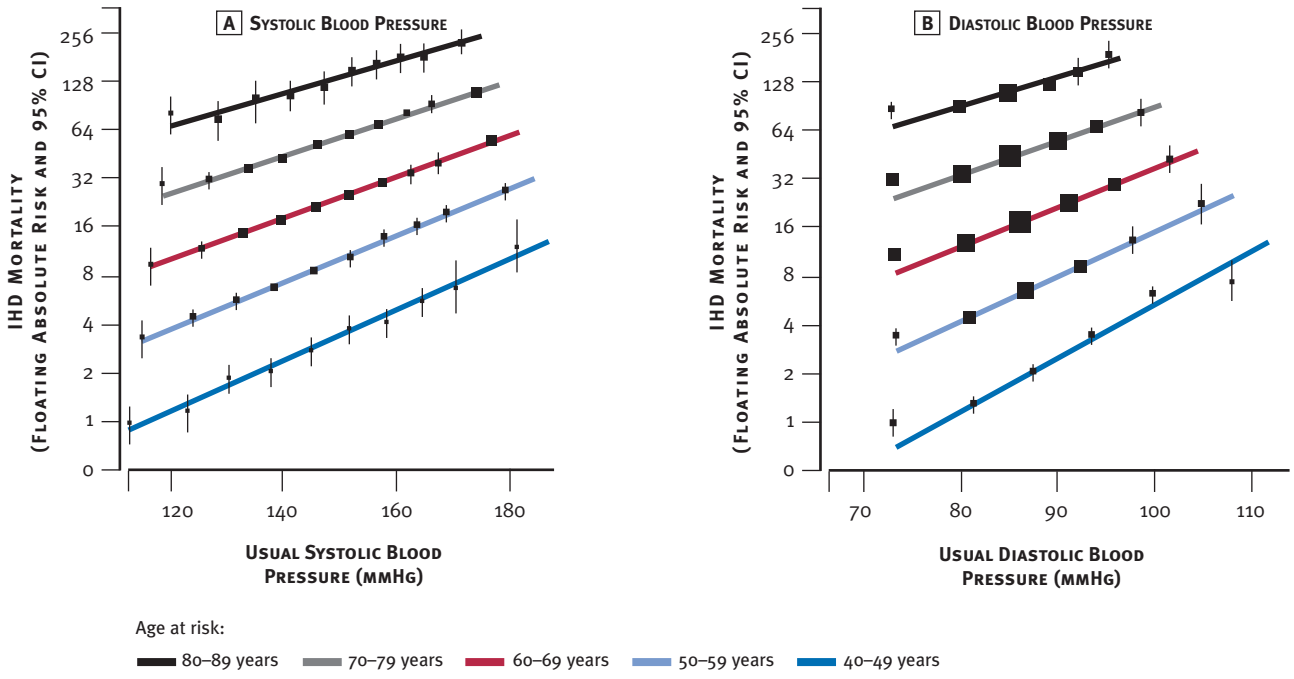
Cumulative incidence of hypertension in 65-year-old women and men. Data for 65-year-old men in the 1952–1975 period is truncated at 15 years since there were few participants in this age category who were followed up beyond this time interval.

Source: Vasan RS, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA *2002;287:1003–10. Copyright 2002, American Medical Association. All rights reserved.*

Data from observational studies involving more than 1 million individuals have indicated that death from both IHD and stroke increases progressively and linearly from levels as low as 115 mmHg SBP and 75 mmHg DBP upward (figures 9 and 10).[18] The increased risks are present in individuals ranging from 40 to 89 years of age. For every 20 mmHg systolic or 10 mmHg diastolic increase in BP, there is a doubling of mortality from both IHD and stroke.

In addition, longitudinal data obtained from the Framingham Heart Study have indicated that BP values between 130–139/85–89 mmHg are associated with a more than twofold increase in relative risk from cardiovascular disease (CVD) as compared with those with BP levels below 120/80 mmHg (figure 11).[19]

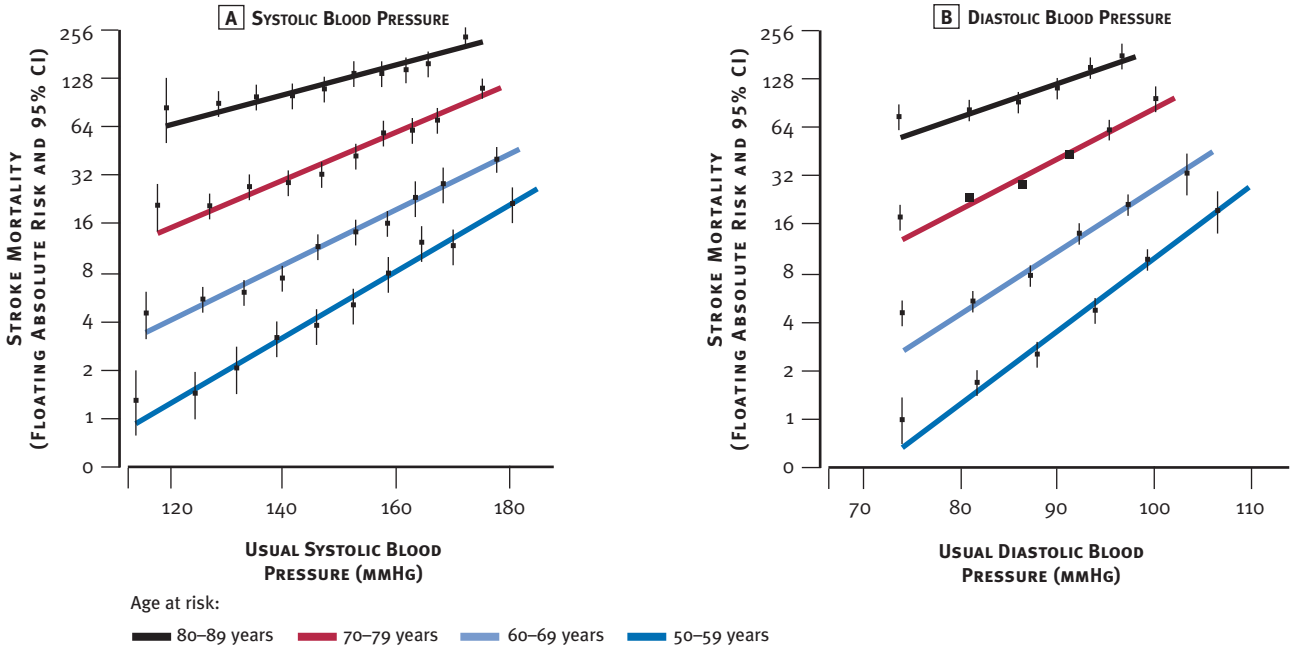
Figure 9. Ischemic heart disease mortality rate in each decade of age versus usual blood pressure at the start of that decade



IHD, ischemic heart disease

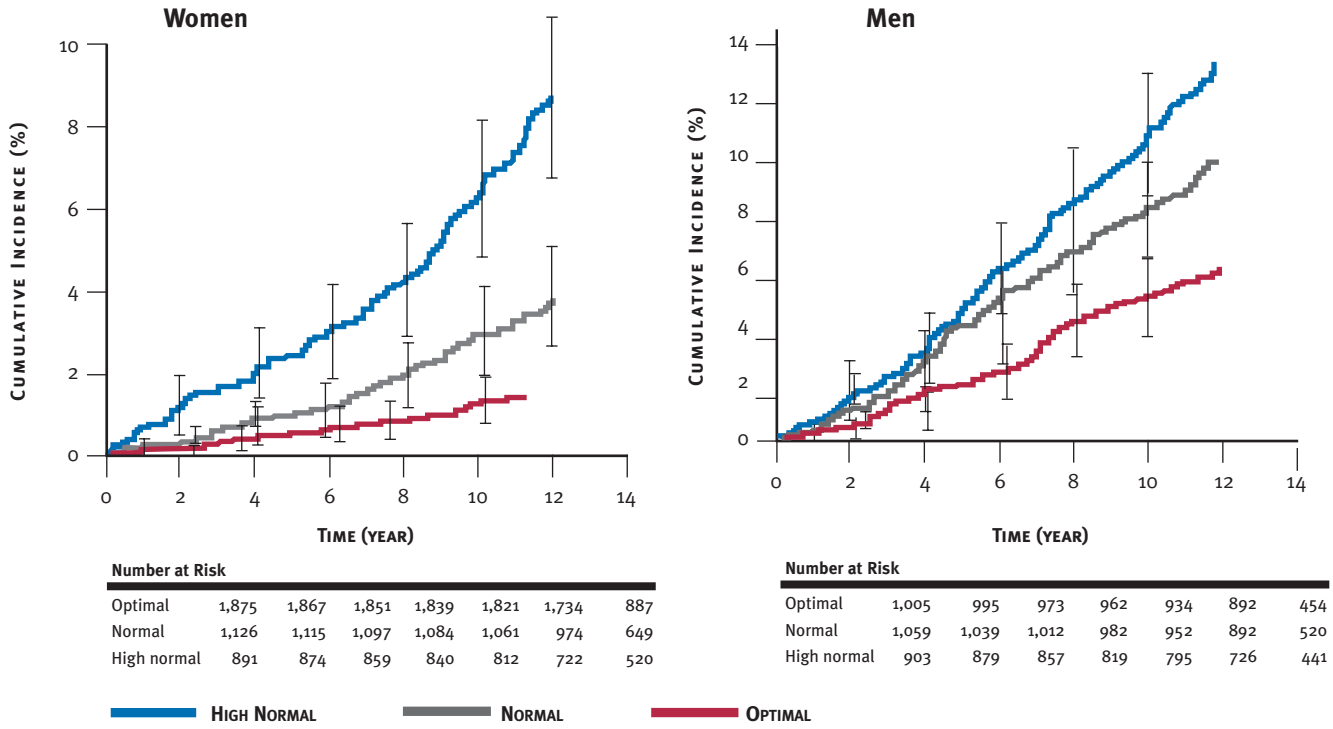
*Source: Reprinted with permission from Elsevier. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. (*The Lancet *2002:360:1903–13).*

Figure 10. **Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade**



*Source: Reprinted with permission from Elsevier. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. (*The Lancet *2002; 360:1903–13).*

Figure 11. **Impact of high normal blood pressure on the risk of cardiovascular disease**



Number at Risk

Optimal	1,875	1,867	1,851	1,839	1,821	1,734	887
Normal	1,126	1,115	1,097	1,084	1,061	974	649
High normal	891	874	859	840	812	722	520

Number at Risk

Optimal	1,005	995	973	962	934	892	454
Normal	1,059	1,039	1,012	982	952	892	520
High normal	903	879	857	819	795	726	441

Cumulative incidence of cardiovascular events in women (panel A) and men (panel B) without hypertension, according to blood pressure category at the base-line examination. Vertical bars indicate 95 percent confidence intervals. Optimal BP is defined here as a systolic pressure of <120 mmHg and a diastolic pressure of <80 mmHg. Normal BP is a systolic pressure of 120–129 mmHg or a diastolic pressure of 80–84 mmHg. High-normal BP is a systolic pressure of 130–139 mmHg or a diastolic pressure of 85–89 mmHg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used.

Source: Vasan RS, et al. Impact of high-normal blood pressure on risk of cardiovascular disease. N Engl J Med *2001;345:1291–7. Copyright 2001, Massachusetts Medical Society. All rights reserved.*

Basis for Reclassification of Blood Pressure

Because of the new data on lifetime risk of hypertension and the impressive increase in the risk of cardiovascular complications associated with levels of BP previously considered to be normal, the JNC 7 report has introduced a new classification that includes the term "prehypertension" for those with BPs ranging from 120–139 mmHg systolic and/or 80–89 mmHg diastolic. This new designation is intended to identify those individuals in whom early intervention by adoption of healthy lifestyles could reduce BP, decrease the rate of progression of BP to hypertensive levels with age, or prevent hypertension entirely.

Another change in classification from JNC 6 is the combining of stage 2 and stage 3 hypertension into a single stage 2 category. This revision reflects the fact that the approach to the management of the former two groups is similar (table 2).

Table 2. Changes in blood pressure classification

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	<120/80	→ Normal
Normal	120–129/80–84	→ Prehypertension
Borderline	130–139/85–89	
Hypertension	≥140/90	→ Hypertension
Stage 1	140–159/90–99	→ Stage 1
Stage 2	160–179/100–109	→ Stage 2
Stage 3	≥180/110	

DBP, diastolic blood pressure; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure

Sources: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med *1997;157:2413–46.*

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA *2003;289:2560–71.*

Table 3 provides a classification of BP for adults 18 years and older. The classification is based on the average of two or more properly measured, seated, BP readings on each of two or more office visits.

Prehypertension is **not** a disease category. Rather, it is a designation chosen to identify individuals at high risk of developing hypertension, so that both patients and clinicians are alerted to this risk and encouraged to intervene and prevent or delay the disease from developing. Individuals who are prehypertensive are **not** candidates for drug therapy based on their level of BP and should be firmly and unambiguously advised to practice lifestyle modification in order to reduce their risk of developing hypertension in the future (see Lifestyle Modifications). Moreover, individuals with prehypertension, who **also** have diabetes or kidney disease, should be considered candidates for appropriate drug therapy if a trial of lifestyle modification fails to reduce their BP to 130/80 mmHg or less.

Table 3. Classification of blood pressure for adults

Blood Pressure Classification	SBP mmHg	DBP mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 Hypertension	140–159	or 90–99
Stage 2 Hypertension	≥160	or ≥100

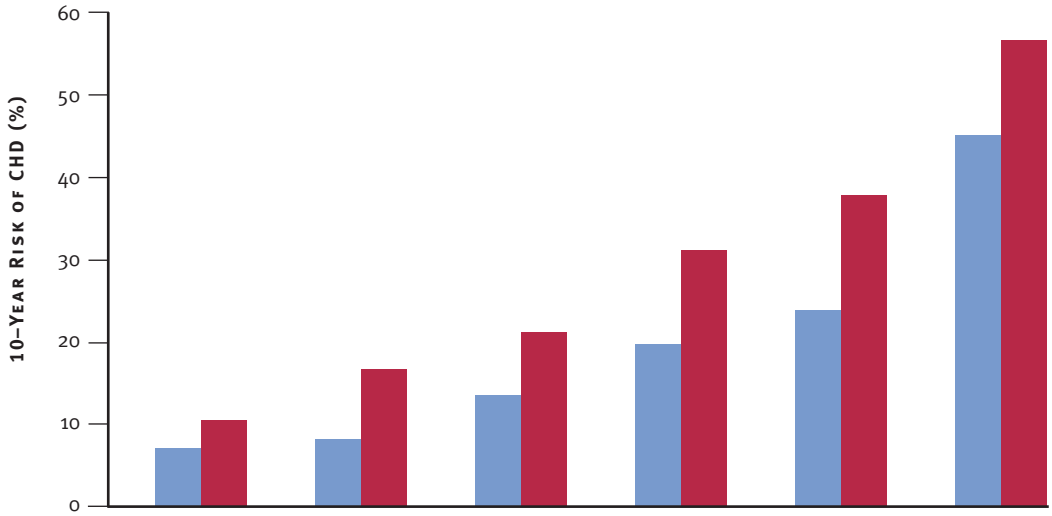
SBP, systolic blood pressure; DBP, diastolic blood pressure

This classification does not stratify hypertensive individuals by the presence or absence of risk factors or target organ damage in order to make different treatment recommendations, should either or both be present. JNC 7 suggests that **all** people with hypertension (stages 1 and 2) be treated. The treatment goal for individuals with hypertension and no other compelling conditions is <140/90 mmHg (see Compelling Indications). The goal for individuals with prehypertension and no compelling indications is to lower BP to normal levels with lifestyle changes, and prevent the progressive rise in BP using the recommended lifestyle modifications (see Lifestyle Modifications).

Cardiovascular Disease Risk

The relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance of heart attack, HF, stroke, and kidney diseases. The presence of each additional risk factor compounds the risk from hypertension as illustrated in figure 12.[20] The easy and rapid calculation of a Framingham CHD risk score using published tables[21] may assist the clinician and patient in demonstrating the benefits of treatment. Management of these other risk factors is essential and should follow the established guidelines for controlling these coexisting problems that contribute to overall cardiovascular risk.

Figure 12. Ten-year risk for coronary heart disease by systolic blood pressure and presence of other risk factors



Cholesterol	180	240	240	240	240	240
HDL	50	50	35	35	35	35
Smoking	No	No	No	Yes	Yes	Yes
Diabetes	No	No	No	No	Yes	Yes
LVH	No	No	No	No	No	Yes

SBP 120 **SBP 180**

CHD, coronary heart disease; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure

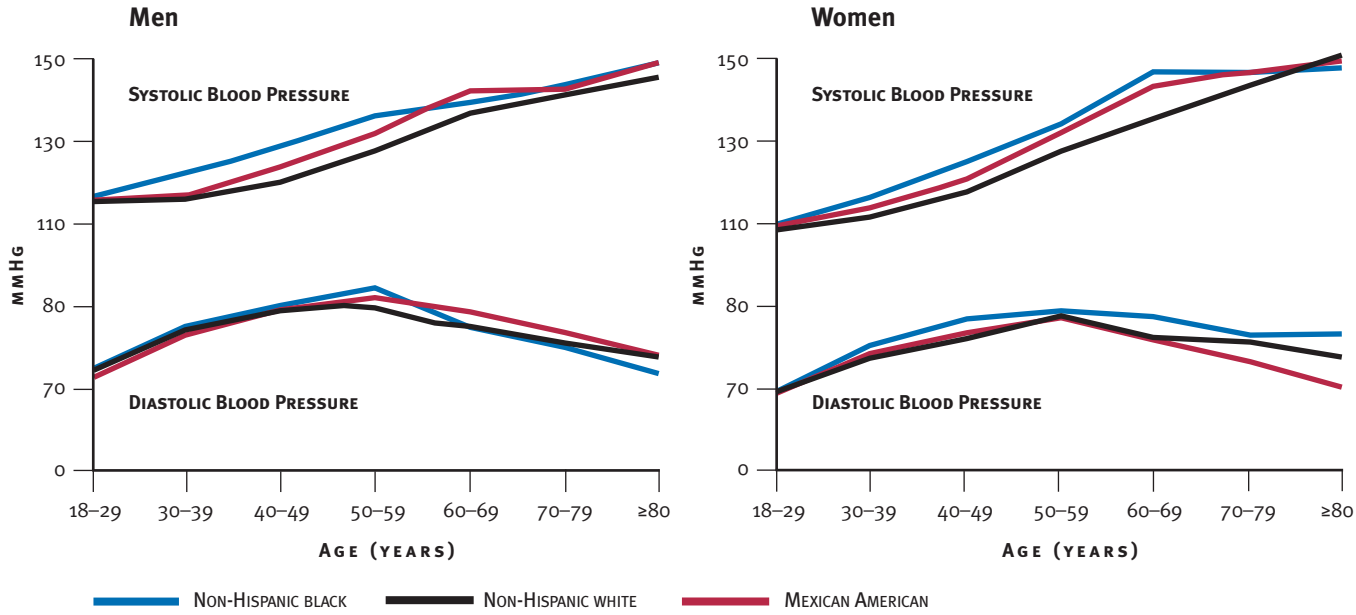
Source: Derived from Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation *1991;83:356–62.*

Importance of Systolic Blood Pressure

Impressive evidence has accumulated to warrant greater attention to the importance of SBP as a major risk factor for CVDs. Changing patterns of BP occur with increasing age. The rise in SBP continues throughout life in contrast to DBP, which rises until approximately age 50, tends to level off over the next decade, and may remain the same or fall later in life (figure 13).[1,15] Diastolic hypertension predominates before age 50, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above 50 years of age, systolic hypertension represents the most common form of hypertension. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important (figure 14).[22]

Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, cardiovascular mortality, stroke, and HF events.[23–25] Both observational studies and clinical trial data suggest that poor SBP control is largely responsible for the unacceptably low rates of overall BP control.[26,27] In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial, DBP control rates exceeded 90 percent, but SBP control rates were considerably less (60–70 percent).[28,29] Poor SBP control is at least in part related to physician attitudes. A survey of primary care physicians indicated that three-fourths of them failed to initiate

Figure 13. Changes in systolic and diastolic blood pressure with age

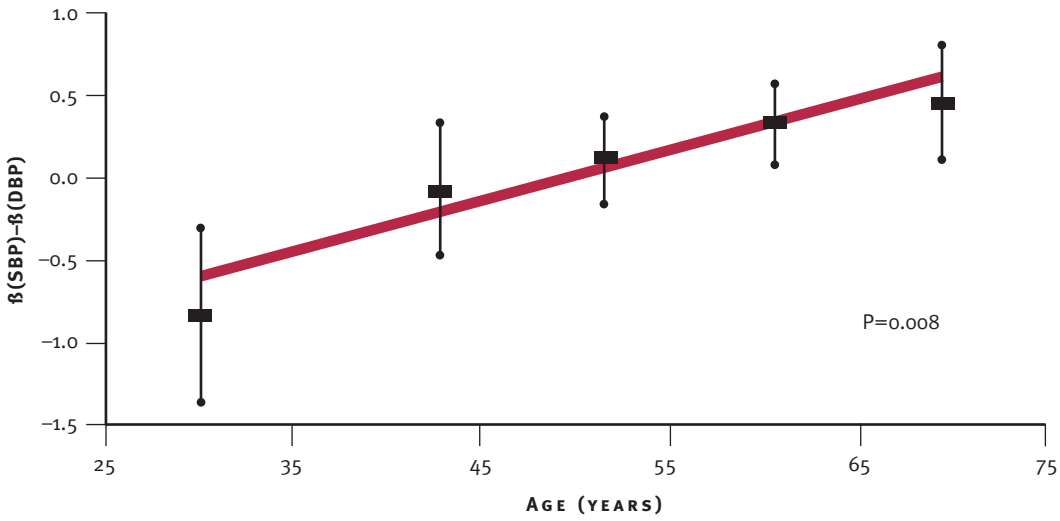


SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988–1991.

Source: Burt VL, et al. Prevelance of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension *1995;25(3):305–13.*

antihypertensive therapy in older individuals with SBP of 140–159 mmHg, and most primary care physicians did not pursue control to <140 mmHg.[30,31] Most physicians have been taught that the diastolic pressure is more important than SBP and thus treat accordingly. Greater emphasis must clearly be placed on managing systolic hypertension. Otherwise, as the United States population becomes older, the toll of uncontrolled SBP will cause increased rates of CVDs and renal diseases.

Figure 14. Difference in coronary heart disease prediction between systolic and diastolic blood pressure as a function of age



DBP, diastolic blood pressure; SBP, systolic blood pressure

The strength of the relationship as a function of age is indicated by an increase in the ß coefficient. Difference in ß coefficients (from Cox proportional-hazards regression) between SBP and DBP is plotted as a function of age, obtaining this regression line: ß(SBP) – ß(DBP) = 1.4948 + 0.0290 x age (P=0.008). A ß coefficient level <0.0 indicates a stronger effect of DBP on CHD risk, while levels >0.0 suggest a greater importance of systolic pressure.

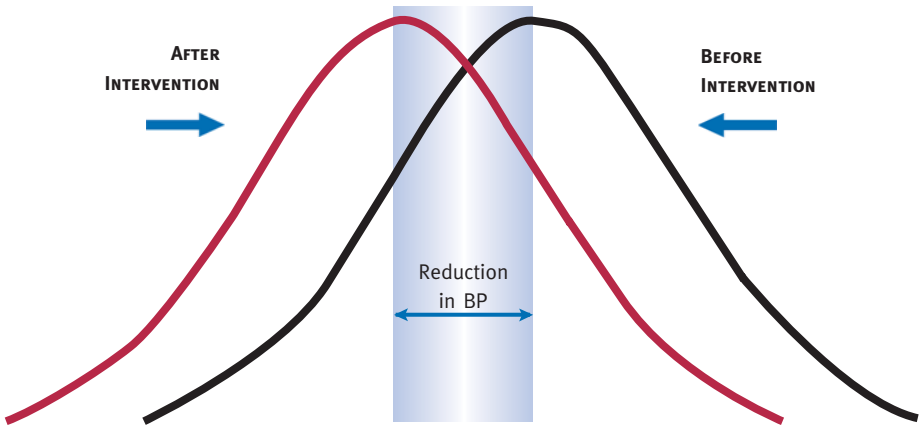
Source: Franklin SS, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation *2001;103:1245–9.*

Prevention of Hypertension: Public Health Challenges

The prevention and management of hypertension are major public health challenges for the United States. If the rise in BP with age could be prevented or diminished, much of hypertension, cardiovascular and renal disease, and stroke might be prevented. A number of important causal factors for hypertension have been identified, including excess body weight; excess dietary sodium intake; reduced physical activity; inadequate intake of fruits, vegetables, and potassium; and excess alcohol intake.[10,32] The prevalence of these characteristics is high. At least 122 million Americans are overweight or obese.[33] Mean sodium intake is approximately 4,100 mg per day for men and 2,750 mg per day for women, 75 percent of which comes from processed foods.[34,35] Fewer than 20 percent of Americans engage in regular physical activity,[36] and fewer than 25 percent consume five or more servings of fruits and vegetables daily.[37]

Because the lifetime risk of developing hypertension is very high (figure 8), a public health strategy, which complements the hypertension treatment strategy, is warranted. To prevent BP levels from rising, primary prevention measures should be introduced to reduce or minimize these causal factors in the population, particularly in individuals with prehypertension. A population approach that decreases the BP level in the general population by even modest amounts has the potential to substantially reduce morbidity and mortality or at least delay the onset of hypertension. For example, it has been estimated that a 5 mmHg reduction of SBP in the population would result in a 14 percent overall reduction in mortality due to stroke, a 9 percent reduction in mortality due to CHD, and a 7 percent decrease in all-cause mortality (figure 15).[10,38]

Figure 15. Systolic blood pressure distributions



Reduction in SBP mmHg	% Reduction in Mortality		
	Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

BP, blood pressure; CHD, coronary heart disease; SBP, systolic blood pressure

Source: Whelton PK, et al. Primary prevention of hypertension: Clinical and public health advisory from The National High Blood Pressure Education Program. JAMA *2002;288:1882–8.*

Barriers to prevention include cultural norms; insufficient attention to health education by health care practitioners; lack of reimbursement for health education services; lack of access to places to engage in physical activity; larger servings of food in restaurants; lack of availability of healthy food choices in many schools, worksites, and restaurants; lack of exercise programs in schools; large amounts of sodium added to foods by the food industry and restaurants; and the higher cost of food products that are lower in sodium and calories.[10] Overcoming the barriers will require a multipronged approach directed not only to high-risk populations, but also to communities, schools, worksites, and the food industry. The recent recommendations by the American Public Health Association and the NHBPEP Coordinating Committee that the food industry, including manufacturers and restaurants, reduce sodium in the food supply by 50 percent over the next decade is the type of approach which, if implemented, would reduce BP in the population.[39,40]

Community Programs

Healthy People 2010 has identified the community as a significant partner and vital point of intervention for attaining healthy goals and outcomes.[41] Partnerships with community groups such as civic, philanthropic, religious, and senior citizen organizations provide locally focused orientation to the health needs of diverse populations. The probability of success increases as interventional strategies more aptly address the diversity of racial, ethnic, cultural, linguistic, religious, and social factors in the delivery of medical services. Community service organizations can promote the prevention of hypertension by providing culturally sensitive educational messages and lifestyle support services and by establishing cardiovascular risk factor screening and referral programs. Community-based strategies and programs have been addressed in prior NHLBI publications and other documents (*Facts About the DASH Eating Plan*,[42] *Your Guide to Lowering High Blood Pressure*,[43] National High Blood Pressure Education Month,[44] The Heart Truth: A National Awareness Campaign for Women About Heart Disease,[45] *Mobilizing African American Communities to Address Disparities in Cardiovascular Health: The Baltimore City Health Partnership Strategy Development Workshop Summary Report*,[46] NHLBI Healthy People 2010 Gateway,[47] Cardiovascular Disease Enhanced Dissemination and Utilization Centers [EDUCs] Awardees,[48] Hearts N' Parks,[49] Healthbeat Radio Network,[50] Salud para su Corazón [For the Health of Your Heart][51]).

Calibration, Maintenance, and Use of Blood Pressure Devices

The potential of mercury spillage contaminating the environment has led to the decreased use or elimination of mercury in sphygmomanometers as well as in thermometers.[52] However, concerns regarding the accuracy of nonmercury sphygmomanometers have created new challenges for accurate BP determination.[53,54] When mercury sphygmomanometers are replaced, the new equipment, including all home BP measurement devices, must be appropriately validated and checked regularly for accuracy.[55]

Accurate Blood Pressure Measurement in the Office

The accurate measurement of BP is the sine qua non for successful management. The equipment—whether aneroid, mercury, or electronic—should be regularly inspected and validated. The operator should be trained and regularly retrained in the standardized technique, and the patient must be properly prepared and positioned.[4,56,57] The auscultatory method of BP measurement should be used.[58] Persons should be seated quietly for at least 5 minutes in a chair (rather than on an exam table), with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. Measurement of BP in the standing position is indicated periodically, especially in those at risk for postural hypotension, prior to necessary drug dose or adding a drug, and in those who report symptoms consistent with reduced BP upon standing. An appropriately sized cuff (cuff bladder encircling at least 80 percent of the arm) should be used to ensure accuracy. At least two measurements should be made and the average recorded. For manual determinations, palpated radial pulse obliteration pressure should be used to estimate SBP—the cuff should then be inflated 20–30 mmHg above this level for the auscultatory determinations; the cuff deflation rate for auscultatory readings should be 2 mmHg per second. SBP is the point at which the first of two or more Korotkoff sounds is heard (onset of phase 1), and the disappearance of Korotkoff sound (onset of phase 5) is used to define DBP. Clinicians should provide to patients, verbally and in writing, their specific BP numbers and the BP goal of their treatment.

Followup of patients with various stages of hypertension is recommended as shown in table 4.

Table 4. Recommendations for followup based on initial blood pressure measurements for adults without acute end organ damage

Initial Blood Pressure (mmHg)*	Followup Recommended†
Normal	Recheck in 2 years
Prehypertension	Recheck in 1 year‡
Stage 1 Hypertension	Confirm within 2 months‡
Stage 2 Hypertension	Evaluate or refer to source of care within 1 month. For those with higher pressures (e.g., >180/110 mmHg), evaluate and treat immediately or within 1 week depending on clinical situation and complications.

** If systolic and diastolic categories are different, follow recommendations for shorter time followup (e.g., 160/86 mmHg should be evaluated or referred to source of care within 1 month).*

† Modify the scheduling of followup according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.

‡ Provide advice about lifestyle modifications (see Lifestyle Modifications).

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activities and sleep.[59] BP has a reproducible "circadian" profile, with higher values while awake and mentally and physically active, much lower values during rest and sleep, and early morning increases for 3 or more hours during the transition of sleep to wakefulness.[60] These devices use either a microphone to measure Korotkoff sounds or a cuff that senses arterial waves using oscillometric techniques. Twenty-four hour BP monitoring provides multiple readings during all of a patient's activities. While office BP values have been used in the numerous studies that have established the risks associated with an elevated BP and the benefits of lowering BP, office measurements have some shortcomings. For example, a white-coat effect (increase in BP primarily in the medical care environment) is noted in as many as 20–35 percent of patients diagnosed with hypertension.[61]

Ambulatory BP values are usually lower than clinic readings. Awake hypertensive individuals have an average BP of >135/85 mmHg, and during sleep, >120/75 mmHg. The level of BP measurement using ABPM correlates better than office measurements with target organ injury.[15] ABPM also provides a measure of the percentage of BP readings that are elevated, the overall BP load, and the extent of BP fall during sleep. In most people, BP drops by 10–20 percent during the night; those in whom such reductions are not present appear to be at increased risk for cardiovascular events. In addition, it was reported recently that ABPM patients whose 24-hour BP exceeded 135/85 mmHg were nearly twice as likely to have a cardiovascular event as those with 24-hour mean BPs <135/85 mmHg, irrespective of the level of the office BP.[62,63]

Indications for the use of ABPM are listed in table 5. Medicare reimbursement for ABPM is now provided to assess patients with suspected white-coat hypertension.

Table 5. Clinical situations in which ambulatory blood pressure monitoring may be helpful

- Suspected white-coat hypertension in patients with hypertension and no target organ damage
- Apparent drug resistance (office resistance)
- Hypotensive symptoms with antihypertensive medication
- Episodic hypertension
- Autonomic dysfunction

Self-Measurement

Self-monitoring of BP at home and work is a practical approach to assess differences between office and out-of-office BP prior to consideration of ABPM. For those whose out-of-office BPs are consistently <130/80 mmHg despite an elevated office BP, and who lack evidence of target organ disease, 24-hour monitoring or drug therapy can be avoided.

Self-measurement or ABPM may be particularly helpful in assessing BP in smokers. Smoking raises BP acutely, and the level returns to baseline about 15 minutes after stopping.

Evaluation of hypertensive patients has three objectives: (1) to assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment (table 6); (2) to reveal identifiable causes of high BP (table 7); and (3) to assess the presence or absence of target organ damage and CVD.

Patient evaluation is made through medical history, physical examination, routine laboratory tests, and other diagnostic procedures. The physical examination should include: an appropriate measurement of BP, with verification in the contralateral arm; an examination of the optic fundi; a calculation of body mass index (BMI) (measurement of waist circumference is also very useful); an auscultation for carotid, abdominal, and femoral bruits; a palpation of the thyroid gland; a thorough examination of the heart and lungs; an examination of the abdomen for enlarged kidneys, masses, distended urinary bladder, and abnormal aortic pulsation; a palpation of the lower extremities for edema and pulses; and neurological assessment.

Data from epidemiological studies and clinical trials have demonstrated that elevations in resting heart rate and reduced heart-rate variability are associated with higher cardiovascular risk. In the Framingham Heart Study, an average resting heart rate of 83 beats per minute was associated with a substantially higher risk of death from a cardiovascular event than the risk associated with lower heart rate levels.[64] Moreover, reduced heart-rate variability was also associated with an increase in cardiovascular mortality.[65]

No clinical trials have prospectively evaluated the impact of reduced heart rate on cardiovascular outcomes.

Table 6. Cardiovascular risk factors

Major Risk Factors
Hypertension*
Age (older than 55 years for men, 65 years for women)†
Diabetes mellitus*
Elevated LDL (or total) cholesterol, or low HDL cholesterol*
Estimated GFR <60 mL/min
Family history of premature CVD (men <55 years of age or women <65 years of age)
Microalbuminuria
Obesity* (BMI ≥30 kg/m^2)
Physical inactivity
Tobacco usage, particularly cigarettes
Target Organ Damage
Heart
LVH
Angina/prior MI
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
Dementia
CKD
Peripheral arterial disease
Retinopathy

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction

* *Components of the metabolic syndrome. Reduced HDL and elevated triglycerides are components of the metabolic syndrome. Abdominal obesity also is a component of metabolic syndrome.*

† *Increased risk begins at approximately 55 and 65 years of age for men and women, respectively. Adult Treatment Panel III used earlier age cut points to suggest the need for earlier action.*

Table 7. Identifiable causes of hypertension

Chronic kidney disease
Coarctation of the aorta
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy
Drug induced or drug related (see table 18)
Obstructive uropathy
Pheochromocytoma
Primary aldosteronism and other mineralocorticoid excess states
Renovascular hypertension
Sleep apnea
Thyroid or parathyroid disease

Laboratory Tests and Other Diagnostic Procedures

Routine laboratory tests recommended before initiating therapy include a 12-lead electrocardiogram; urinalysis; blood glucose and hematocrit; serum potassium, creatinine (or the corresponding estimated glomerular filtration rate [eGFR]), and calcium;[66] and a lipoprotein profile (after a 9- to 12-hour fast) that includes high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Optional tests include measurement of urinary albumin excretion or albumin/creatinine ratio (ACR) except for those with diabetes or kidney disease where annual measurements should be made. More extensive testing for identifiable causes is not generally indicated unless BP control is not achieved or the clinical and routine laboratory evaluation strongly suggests an identifiable secondary cause (i.e., vascular bruits, symptoms of catecholamine excess, or unprovoked hypokalemia). (See Identifiable Causes of Hypertension for a more thorough discussion.) The presence of decreased GFR or albuminuria has prognostic implications as well. Studies reveal a strong relationship between decreases in GFR and increases in cardiovascular morbidity and mortality.[67,68] Even small decreases in GFR increase cardiovascular risk.[67] Serum creatinine may overestimate glomerular filtration. The optimal tests to determine GFR are debated, but calculating GFR from the recent modifications of the Cockcroft and Gault equations is useful.[69]

The presence of albuminuria, including microalbuminuria, even in the setting of normal GFR, is also associated with an increase in cardiovascular risk.[70-72] Urinary albumin excretion should be quantitated and monitored on an annual basis in high-risk groups, such as those with diabetes or renal disease.

Additionally, three emerging risk factors (1) high-sensitivity C-reactive protein (HS-CRP); a marker of inflammation; (2) homocysteine; and (3) elevated heart rate may be considered in some individuals, particularly those with CVD but without other risk-factor abnormalities. Results of an analysis of the Framingham Heart Study cohort demonstrated that those with a LDL value within the range associated with low cardiovascular risk, who also had an elevated HS-CRP value, had a higher cardiovascular event rate as compared to those with low CRP and high LDL cholesterol.[73] Other studies also have shown that elevated CRP is associated with a higher cardiovascular event rate, especially in women.[74] Elevations in homocysteine have also been linked higher cardiovascular risk; however, the results with this marker are not as robust as those with high HS-CRP.[75,76]

Additional diagnostic procedures may be indicated to identify causes of hypertension, particularly in patients whose (1) age, history, physical examination, severity of hypertension, or initial laboratory findings suggest such causes; (2) BP responds poorly to drug therapy; (3) BP begins to increase for uncertain reason after being well controlled; and (4) onset of hypertension is sudden. Screening tests for particular forms of identifiable hypertension are shown in table 8.

Pheochromocytoma should be suspected in patients with labile hypertension or with paroxysms of hypertension accompanied by headache, palpitations, pallor, and perspiration.[77] Decreased pressure in the lower extremities or delayed or absent femoral arterial pulses may indicate aortic coarctation; and truncal obesity, glucose intolerance, and purple striae suggest Cushing's syndrome. Examples of clues from the laboratory tests include unprovoked hypokalemia (primary aldosteronism), hypercalcemia (hyperparathyroidism), and elevated creatinine or abnormal urinalysis (renal parenchymal disease). Appropriate investigations should be conducted when there is a high index of suspicion of an identifiable cause.[78–81]

The most common parenchymal kidney diseases associated with hypertension are chronic glomerulonephritis, polycystic kidney disease, and hypertensive nephrosclerosis. These can generally be distinguished by the clinical setting and additional testing. For example, a renal ultrasound is useful in diagnosing polycystic kidney disease. Renal artery stenosis and subsequent renovascular hypertension should be suspected in a number of circumstances including: (1) onset of hypertension before age 30, especially in the absence of family history, or onset of significant hypertension after age 55; (2) an abdominal bruit especially if a diastolic component is present; (3) accelerated hypertension; (4) hypertension that had been easy to control but is now resistant; (5) recurrent flash pulmonary edema; (6) renal failure of uncertain etiology especially in the absence of proteinuria

Table 8. Screening tests for identifiable hypertension

Diagnosis	Diagnostic Test
Chronic kidney disease	Estimated GFR
Coarctation of the aorta	CT angiography
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy	History; dexamethasone suppression test
Drug induced/related (see table 18)	History; drug screening
Pheochromocytoma	24-hour urinary metanephrine and normetanephrine
Primary aldosteronism and other mineralocorticoid excess states	24-hour urinary aldosterone level or specific measurements of other mineralocorticoids
Renovascular hypertension	Doppler flow study; magnetic resonance angiography
Sleep apnea	Sleep study with O_2 saturation
Thyroid/parathyroid disease	TSH; serum PTH

CT, computed tomography; GFR, glomerular filtration rate; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone

or an abnormal urine sediment; and (7) acute renal failure precipitated by therapy with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) under conditions of occult bilateral renal artery stenosis or moderate to severe volume depletion.

In patients with suspected renovascular hypertension, noninvasive screening tests include the ACEI-enhanced renal scan, duplex Doppler flow studies, and magnetic resonance angiography. While renal artery angiography remains the gold standard for identifying the anatomy of the renal artery, it is not recommend for diagnosis alone because of the risk associated with the procedure. At the time of intervention, an arteriogram will be performed using limited contrast to confirm the stenosis and identify the anatomy of the renal artery.

Genetics of Hypertension

The investigation of rare genetic disorders affecting BP has led to the identification of genetic abnormalities associated with several rare forms of hypertension, including mineralocorticoid-remediable aldosteronism, 11beta-hydroxylase and 17alpha-hydroxylase deficiencies, Liddle's syndrome, the syndrome of apparent mineralocorticoid excess, and pseudohypoaldosteronism type II.[82] The individual and joint contributions of these genetic mutations to BP levels in the general population, however, are very small. Genetic association studies have identified polymorphisms in several candidate genes (e.g., angiotensinogen, alpha-adducin, beta- and DA-adrenergic receptors, and beta-3 subunit of G proteins), and genetic linkage studies have focused attention on several genomic sites that may harbor other genes contributing to primary hypertension.[83–85] However, none of these various genetic abnormalities has been shown, either alone or in joint combination, to be responsible for any applicable portion of hypertension in the general population.

Blood Pressure Control Rates

Hypertension is the most common primary diagnosis in America (35 million office visits as the primary diagnosis).[5] Current control rates (SBP <140 mmHg and DBP <90 mmHg), though improved, are still far below the Healthy People goal of 50 percent, which was originally set as the year 2000 goal and has since been extended to 2010 (see table 1). In the majority of patients, reducing SBP has been considerably more difficult than lowering DBP. Although effective BP control can be achieved in most patients who are hypertensive, the majority will require two or more antihypertensive drugs.[28,29,86] Failure to prescribe lifestyle modifications, adequate antihypertensive drug doses, or appropriate drug combinations may result in inadequate BP control.

Goals of Therapy

The ultimate public health goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Since most persons with hypertension, especially those >50 years of age, will reach the DBP goal once the SBP goal is achieved, the primary focus should be on attaining the SBP goal. Treating SBP and DBP to targets that are <140/90 mmHg is associated with a decrease in CVD complications.[87] In patients with hypertension and diabetes or renal disease, the BP goal is <130/80 mmHg.[88,89]

Benefits of Lowering Blood Pressure

In clinical trials, antihypertensive therapy has been associated with reductions in (1) stroke incidence, averaging 35–40 percent; (2) myocardial infarction (MI), averaging 20–25 percent; and (3) HF, averaging >50 percent.[90] It is estimated that in patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the added presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death.[91]

Lifestyle Modifications

Adoption of healthy lifestyles by all persons is critical for the prevention of high BP and is an indispensable part of the management of those with hypertension.[10] Weight loss of as little as 10 lbs (4.5 kg) reduces BP and/or prevents hypertension in a large proportion of overweight persons, although the ideal is to maintain normal body weight.[92,93] BP is also benefited by adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan[94] which is a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of dietary cholesterol as well as saturated and total fat (modification of whole diet). It is rich in potassium and calcium content.[95] Dietary sodium should be reduced to no more than 100 mmol per day (2.4 g of sodium).[94–96] Everyone who is able should engage in regular aerobic physical activity such as brisk walking at least 30 minutes per day most days of the week.[97,98] Alcohol intake should be limited to no more than 1 oz (30 mL) of ethanol, the equivalent of two drinks per day in most men and no more than 0.5 oz of ethanol (one drink) per day in women and lighter weight persons. A drink is 12 oz of beer, 5 oz of wine, and 1.5 oz of 80-proof liquor (see table 9).[99] Lifestyle modifications reduce BP, prevent or delay the incidence of hypertension, enhance antihypertensive drug efficacy, and decrease cardiovascular risk. For example, in some individuals, a 1,600 mg sodium DASH eating plan has BP effects similar to single drug therapy.[94] Combinations of two (or more) lifestyle modifications can achieve even better results.[100] For overall cardiovascular risk reduction, patients should be strongly counseled to quit smoking.

Table 9. Lifestyle modifications to prevent and manage hypertension*

Modification	Recommendation	Approximate SBP Reduction (Range)†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m²).	5–20 mmHg/10kg[92,93]
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg[94,95]
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg[94-96]
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg[97-98]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons.	2–4 mmHg[99]

DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure

* *For overall cardiovascular risk reduction, stop smoking.*

† *The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.*

Pharmacologic Treatment

A large number of drugs are currently available for reducing BP. Tables 10 and 11 provide a list of the commonly used antihypertensive agents, and their usual dose range and frequency of administration.

More than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes.[28,87,101–103] For example, in ALLHAT, 60 percent of those whose BP was controlled to <140/90 mmHg received two or more agents, and only 30 percent overall were controlled on one drug.[28] In hypertensive patients with lower BP goals or with substantially elevated BP, three or more antihypertensive drugs may be required.

Since the first VA Cooperative Trial, published in 1967, thiazide-type diuretics have been the basis of antihypertensive therapy in the majority of placebo-controlled outcome trials, in which CVD events, including strokes, CHD, and HF have been reduced by BP lowering.[104–108] However, there are also excellent clinical trial data proving that lowering BP with other classes of drugs, including ACEIs, ARBs, beta blockers (BBs), and calcium channel blockers (CCBs) also reduces the complications of hypertension.[90,101,102,107,109–112] Several randomized controlled trials have demonstrated reduction in CVD with BBs, but the benefits are less consistent than with diuretics.[107,108] The European Trial on Systolic Hypertension in the Elderly (Syst-EUR) showed significant reductions in stroke and all CVD with the dihydropyridine CCB, nitrendipine, as compared with placebo.[113] The Heart Outcomes Prevention Evaluation (HOPE) Study, which was not

restricted to hypertensive individuals but which included a sizable hypertensive subgroup, showed reductions in a variety of CVD events with the ACEI, ramipril, compared with placebo in individuals with prior CVD or diabetes mellitus combined with other risk factor(s).[110] The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study in which the ACEI, perindopril, was added to existent therapy in patients with stable coronary disease and without HF also demonstrated reduction in CVD events with ACEIs.[114]

Since 1998, several large trials comparing "newer" classes of agents, including CCBs, ACEIs, an alpha-1 receptor blocker, and an ARB, with the "older" diuretics and/or BBs have been completed.[101,102,109,112,115–118] Most of these studies showed the newer classes were neither superior nor inferior to the older ones. One exception was the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study, in which CVD events were 13 percent lower (because of differences in stroke but not CHD rates) with the ARB, losartan, than with the BB, atenolol.[102] There has not been a large outcome trial completed yet comparing an ARB with a diuretic. All of these trials together suggest broadly similar cardiovascular protection from BP-lowering with ACEIs, CCBs, and ARBs, as with thiazide-type diuretics and BBs, although some specific outcomes may differ between the classes. There do not appear to be systematic outcome differences between dihydropyridine and nondihydropyridine CCBs in hypertension morbidity trials. On the basis of other data, short-acting CCBs are not recommended in the management of hypertension.

Table 10. Oral antihypertensive drugs*

Class	Drug (Trade Name)	Usual Dose Range in mg/Day	Usual Daily Frequency*
Thiazide diuretics	chlorothiazide (Diuril)	125–500	1–2
	chlorthalidone (generic)	12.5–25	1
	hydrochlorothiazide (Microzide, HydroDIURIL†)	12.5–50	1
	polythiazide (Renese)	2–4	1
	indapamide (Lozol†)	1.25–2.5	1
	metolazone (Mykrox)	0.5–1.0	1
	metolazone (Zaroxolyn)	2.5–5	1
Loop diuretics	bumetanide (Bumex†)	0.5–2	2
	furosemide (Lasix†)	20–80	2
	torsemide (Demadex†)	2.5–10	1
Potassium-sparing diuretics	amiloride (Midamor†)	5–10	1–2
	triamterene (Dyrenium)	50–100	1–2
Aldosterone receptor blockers	eplerenone (Inspra)	50–100	1
	spironolactone (Aldactone†)	25–50	1
BBs	atenolol (Tenormin†)	25–100	1
	betaxolol (Kerlone†)	5–20	1
	bisoprolol (Zebeta†)	2.5–10	1
	metoprolol (Lopressor†)	50–100	1–2
	metoprolol extended release (Toprol XL)	50–100	1
	nadolol (Corgard†)	40–120	1
	propranolol (Inderal†)	40–160	2
	propranolol long-acting (Inderal LA†)	60–180	1
	timolol (Blocadren†)	20–40	2
BBs with intrinsic sympathomimetic activity	acebutolol (Sectral†)	200–800	2
	penbutolol (Levatol)	10–40	1
	pindolol (generic)	10–40	2

Table 10. Oral antihypertensive drugs* (continued)

Class	Drug (Trade Name)	Usual Dose Range in mg/Day	Usual Daily Frequency*
Combined alpha- and BBs	carvedilol (Coreg)	12.5–50	2
	labetalol (Normodyne, Trandate†)	200–800	2
ACEIs	benazepril (Lotensin†)	10–40	1
	captopril (Capoten†)	25–100	2
	enalapril (Vasotec†)	5–40	1–2
	fosinopril (Monopril)	10–40	1
	lisinopril (Prinivil, Zestril†)	10–40	1
	moexipril (Univasc)	7.5–30	1
	perindopril (Aceon)	4–8	1
	quinapril (Accupril)	10–80	1
	ramipril (Altace)	2.5–20	1
	trandolapril (Mavik)	1–4	1
Angiotensin II antagonists	candesartan (Atacand)	8–32	1
	eprosartan (Teveten)	400–800	1–2
	irbesartan (Avapro)	150–300	1
	losartan (Cozaar)	25–100	1–2
	olmesartan (Benicar)	20–40	1
	telmisartan (Micardis)	20–80	1
	valsartan (Diovan)	80–320	1–2
CCBs—nondihydropyridines	diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac†)	180–420	1
	diltiazem extended release (Cardizem LA)	120–540	1
	verapamil immediate release (Calan, Isoptin†)	80–320	2
	verapamil long acting (Calan SR, Isoptin SR†)	120–480	1–2
	verapamil (Coer, Covera HS, Verelan PM)	120–360	1
CCBs—dihydropyridines	amlodipine (Norvasc)	2.5–10	1
	felodipine (Plendil)	2.5–20	1
	isradipine (Dynacirc CR)	2.5–10	2
	nicardipine sustained release (Cardene SR)	60–120	2
	nifedipine long-acting (Adalat CC, Procardia XL)	30–60	1
	nisoldipine (Sular)	10–40	1
Alpha-1 blockers	doxazosin (Cardura)	1–16	1
	prazosin (Minipress†)	2–20	2–3
	terazosin (Hytrin)	1–20	1–2
Central alpha-2 agonists and other centrally acting drugs	clonidine (Catapres†)	0.1–0.8	2
	clonidine patch (Catapres-TTS)	0.1–0.3	1 wkly
	methyldopa (Aldomet†)	250–1,000	2
	reserpine (generic)	0.1–0.25	1
	guanfacine (Tenex†)	0.5–2	1
Direct vasodilators	hydralazine (Apresoline†)	25–100	2
	minoxidil (Loniten†)	2.5–80	1–2

ACEIs, angiotensin converting enzyme inhibitors; BBs, beta blockers; CCBs, calcium channel blockers

* *In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (trough effect). BP should be measured just prior to dosing to determine if satisfactory BP control is obtained. Accordingly, an increase in dosage or frequency may need to be considered. These dosages may vary from those listed in the* Physician's Desk Reference *(57th ed.).*

† *Available now or becoming available soon in generic preparations.*

Source: Physician's Desk Reference. *57th ed. Montvale, NJ: Thompson PDR, 2003.*

Table 11. Combination drugs for hypertension

Combination Type*	Fixed-Dose Combination, mg†	Trade Name
ACEIs and CCBs	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel
	Enalapril-felodipine (5/5)	Lexxel
	Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)	Tarka
ACEIs and diuretics	Benazepril-hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
	Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril-hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
	Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5)	Monopril/HCT
	Lisinopril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic
	Moexipril-hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
ARBs and diuretics	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan-hydrochlorothiazide (600/12.5, 600/25)	Teveten-HCT
	Irbesartan-hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
	Losartan-hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
	Olmesartan medoxomil-hydrochlorothiazide (20/12.5, 40/12.5, 40/25)	Benicar HCT
	Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5)	Micardis-HCT
	Valsartan-hydrochlorothiazide (80/12.5, 160/12.5, 160/25)	Diovan-HCT
BBs and diuretics	Atenolol-chlorthalidone (50/25, 100/25)	Tenoretic
	Bisoprolol-hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
	Metoprolol-hydrochlorothiazide (50/25, 100/25)	Lopressor HCT
	Nadolol-bendroflumethiazide (40/5, 80/5)	Corzide
	Propranolol LA-hydrochlorothiazide (40/25, 80/25)	Inderide LA
	Timolol-hydrochlorothiazide (10/25)	Timolide
Centrally acting drug and diuretic	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
	Reserpine-chlorthalidone (0.125/25, 0.25/50)	Demi-Regroton, Regroton
	Reserpine-chlorothiazide (0.125/250, 0.25/500)	Diupres
	Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic and diuretic	Amiloride-hydrochlorothiazide (5/50)	Moduretic
	Spironolactone-hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene-hydrochlorothiazide (37.5/25, 75/50)	Dyazide, Maxzide

** ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta blockers; CCBs, calcium channel blockers*

† Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

Rationale for Recommendation of Thiazide-Type Diuretics as Preferred Initial Agent

In trials comparing diuretics with other classes of antihypertensive agents, diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension. In the ALLHAT study, which involved more than 40,000 hypertensive individuals,[109] there were no differences in the primary CHD outcome or mortality between the thiazide-type diuretic, chlorthalidone; the ACEI, lisinopril; or the CCB, amlodipine. Stroke incidence was greater with lisinopril than chlorthalidone therapy, but these differences were present primarily in African Americans who also had less BP lowering with lisinopril than diuretics. The incidence of HF was greater in CCB-treated and ACEI-treated individuals as compared with those receiving the diuretic in both African Americans and Whites. In the Second Australian National Blood Pressure (ANBP2) Study, which compared the effects of an ACEI-based regimen against diuretics-based therapy in 6,000 White hypertensive individuals, cardiovascular outcomes were less in

the ACEI group, with the favorable effect apparent only in men.[112] CVD outcome data comparing ARB with other agents are limited.

Clinical trial data indicate that diuretics are generally well tolerated.[103,109] The doses of thiazide-type diuretics used in successful morbidity trials of "low-dose" diuretics were generally the equivalent of 25–50 mg of hydrochlorothiazide or 12.5–25 mg of chlorthalidone, although therapy may be initiated at lower doses and titrated to these doses if tolerated. Higher doses have been shown to add little additional antihypertensive efficacy, and are associated with more hypokalemia and other adverse effects.[119–122]

Uric acid will increase in many patients receiving a diuretic, but the occurrence of gout is uncommon with dosages ≤50 mg/day of hydrochlorothiazide or ≤25 mg of chlorthalidone. Some reports have described an increased degree of sexual dysfunction when thiazide diuretics (particularly at high doses) are used. In the Treatment of Mild Hypertension Study (TOMHS), participants randomized to chlorthalidone reported a significantly higher incidence of erection problems through 24 months of the study; however, the incidence rate at 48 months was similar to placebo.[123] The VA Cooperative study did not document a significant difference in the occurrence of sexual dysfunction using diuretics when compared with other antihypertensive medications[103] (see section on erectile dysfunction). Adverse metabolic effects may occur with diuretics. In ALLHAT, diabetes incidence after 4 years of therapy was 11.8 percent with chlorthalidone therapy, 9.6 percent with amlodipine, and 8.1 percent with lisinopril. However, those differences did not translate to fewer cardiovascular events for the ACEI or CCB groups.[109] Those who were already diabetic had fewer cardiovascular events in the diuretic group than with ACEI treatment. Trials of longer than 1 year's duration using modest doses of diuretics generally have not shown an increase in serum cholesterol in diuretic-treated patients.[124,125] In ALLHAT, serum cholesterol did not increase from baseline in any group, but it was 1.6 mg/dL lower in the CCB group and 2.2 mg/dL lower in the ACEI group than in diuretic-treated patients.[109] Thiazide-induced hypokalemia could contribute to increased ventricular ectopy and possible sudden death, particularly with high doses of thiazides in the absence of a potassium-sparing agent.[121] In the Systolic Hypertension in the Elderly Program (SHEP) Trial, the positive benefits of diuretic therapy were not apparent when serum potassium levels were below 3.5mmol/L.[126] However, other studies have not demonstrated increased ventricular ectopy as a result of diuretic therapy.[127] Despite potential adverse metabolic effects of diuretics, with laboratory monitoring, thiazide-type diuretics are effective and relatively safe for the management of hypertension.

Thiazide diuretics are less expensive than other antihypertensive drugs, although as members of other classes of drugs have become available in generic form, their cost has been reduced. Despite the various benefits of diuretics, they remain underutilized.[128]

Achieving Blood Pressure Control in Individual Patients

The algorithm for the treatment of hypertensive patients is shown in figure 16. Therapy begins with lifestyle modification, and if BP goal is not achieved, thiazide-type diuretics should be used as initial therapy for most patients, either alone or in combination with one of the other classes (ACEIs, ARBs, BBs, CCBs) that have also been shown to reduce one or more hypertensive complications in randomized controlled outcome trials. Selection of one of these other agents as initial therapy is recommended when a diuretic cannot be used or when a compelling indication is present that requires the use of a specific drug, as listed in table 12. If the initial drug selected is not tolerated or is contraindicated, then a drug from one of the other classes proven to reduce cardiovascular events should be substituted.

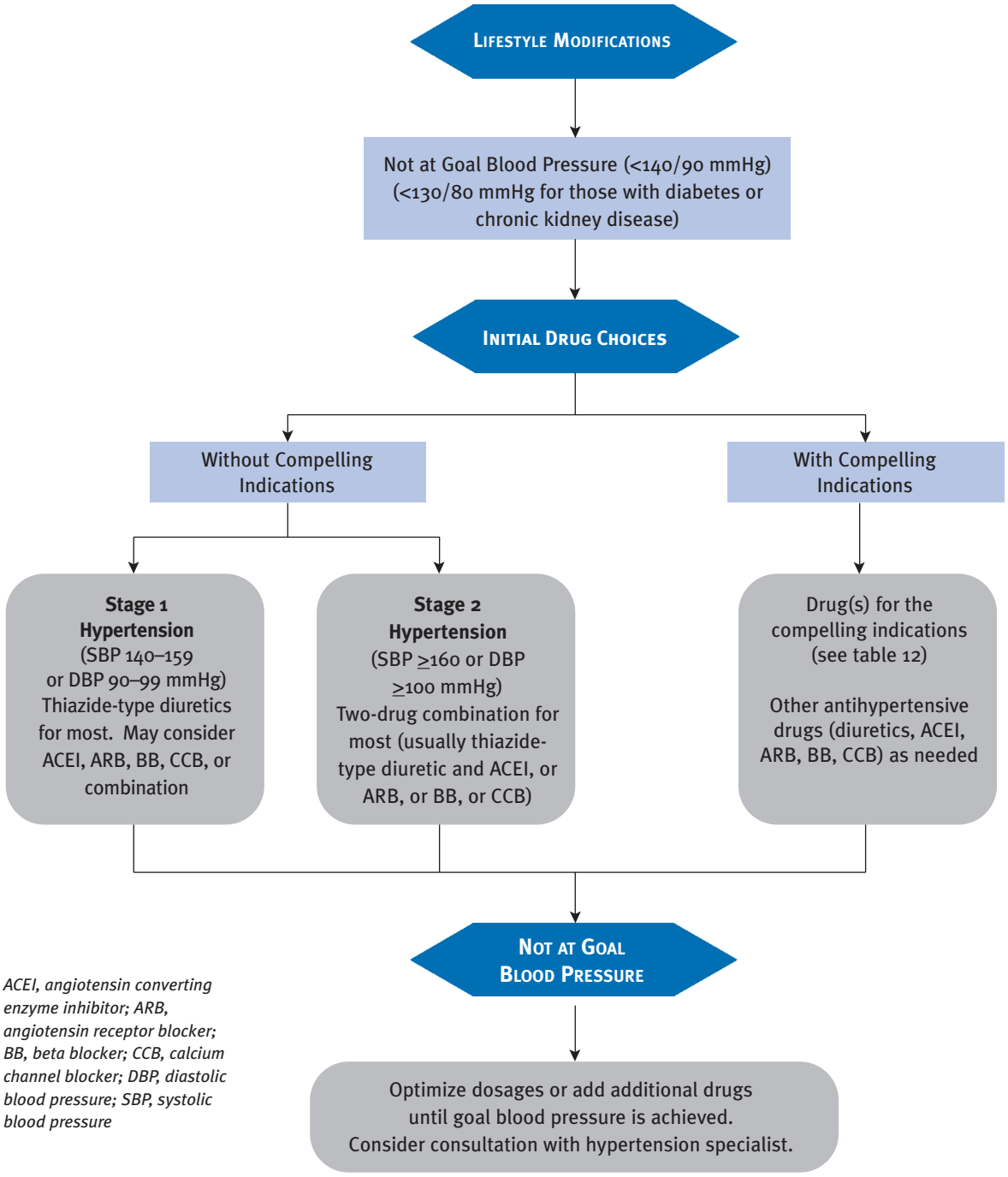
Since most hypertensive patients will require two or more antihypertensive medications to achieve their BP goals, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. When BP is >20 mmHg above systolic goal or 10 mmHg above diastolic goal, consideration should be given to initiate therapy with two drugs, either as

separate prescriptions or in fixed-dose combinations.[129] (See figure 16.)

The initiation of therapy with more than one drug increases the likelihood of achieving BP goal in a more timely fashion. The use of multidrug combinations often produce greater BP reduction at lower doses of the component agents, resulting in fewer side effects.[129,130]

The use of fixed-dose combinations may be more convenient and simplify the treatment regimen, and may cost less than the individual components prescribed separately. Use of generic drugs should be considered to reduce prescription costs, and the cost of separate prescription of multiple drugs available generically may be less than nongeneric, fixed-dose combinations. The starting dose of most fixed-dose combinations is usually below the doses used in

Figure 16. Algorithm for treatment of hypertension



ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure

clinical outcome trials, and the doses of these agents should be titrated upward to achieve the BP goal before adding other drugs. However, caution is advised in initiating therapy with multiple agents, particularly in some older persons and in those at risk for orthostatic hypotension, such as diabetics with autonomic dysfunction.

Followup and Monitoring

Once antihypertensive drug therapy is initiated, most patients should return for followup and adjustment of medications at monthly intervals or until the BP goal is reached. More frequent visits will be necessary for patients with stage 2 hypertension or with complicating comorbid conditions. Serum potassium and creatinine should be monitored at least one to two times per year. After BP is at goal and stable, followup visits can usually be at 3- to 6-month intervals. Comorbidities such as HF, associated diseases such as diabetes, and the need for laboratory tests influence the frequency of visits. Other cardiovascular risk factors should be monitored and treated to their respective goals, and tobacco avoidance must be promoted vigorously. Low-dose aspirin therapy should be considered only when BP is controlled because of the increased risk of hemorrhagic stroke when the hypertension is not controlled.[131]

Compelling Indications

Hypertension may exist in association with other conditions in which there are compelling indications for use of a particular treatment based on clinical trial data demonstrating benefits of such therapy on the natural history of the associated condition (table 12). Compelling indications for specific therapy involve high-risk conditions that can be direct sequelae of hypertension (HF, IHD, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes,

Table 12. Clinical trial and guideline basis for compelling indications for individual drug classes

Compelling Indication*	Recommended Drugs						Clinical Trial Basis†
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT	
Heart failure	●	●	●	●		●	ACC/AHA Heart Failure Guideline,[132] MERIT-HF,[133] COPERNICUS,[134] CIBIS,[135] SOLVD,[136] AIRE,[137] TRACE,[138] ValHEFT,[139] RALES,[140] CHARM[141]
Postmyocardial infarction		●	●			●	ACC/AHA Post-MI Guideline,[142] BHAT,[143] SAVE,[144] Capricorn,[145] EPHESUS[146]
High coronary disease risk	●	●	●		●		ALLHAT,[109] HOPE,[110] ANBP2,[112] LIFE,[102] CONVINCE,[101] EUROPA,[114] INVEST[147]
Diabetes	●	●	●	●	●		NKF-ADA Guideline,[88,89] UKPDS,[148] ALLHAT[109]
Chronic kidney disease			●	●			NKF Guideline,[89] Captopril Trial,[149] RENAAL,[150] IDNT,[151] REIN,[152] AASK[153]
Recurrent stroke prevention	●		●				PROGRESS[111]

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACEI, angiotensin converting enzyme inhibitor; AIRE, Acute Infarction Ramipril Efficacy; Aldo ANT, aldosterone antagonist; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin receptor blocker; BB, beta blocker; BHAT, β-Blocker Heart Attack Trial; Capricorn, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CCB, calcium channel blocker; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, The International Verapamil-Trandolapril Study; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Peridopril Protection against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial

* *Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.*

† *Conditions for which clinical trials demonstrate the benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve BP goal to test outcomes.*

high coronary disease risk). Therapeutic decisions in such individuals should be directed at both the compelling indication and BP lowering.

The absence of a positive indication can signify a lack of information for a particular drug class. For example, in recurrent stroke, there is no study employing CCBs or ARBs. Different stages of the conditions may dictate different strategies. In HF management, thiazide-type diuretics are recommended for reducing the incidence of HF but not in lengthening survival in individuals who already have the condition. Furthermore, widespread use of combination therapy in clinical trials confounds interpretation of the effects of single drugs. In the Perindopril Protection against Recurrent Stroke Study (PROGRESS), recurrent stroke rate was reduced only when a thiazide-type diuretic was added to ACEI background therapy.

Ischemic Heart Disease

Hypertensive patients are at increased risk for MI or other major coronary events and may be at higher risk of death following an acute MI. Myocardial oxygen supply in hypertensive individuals may be limited by coronary artery disease (CAD), while myocardial oxygen demand is often greater because of the increased impedance to left ventricular ejection and the frequent presence of left ventricular hypertrophy (LVH).[154] Lowering both SBP and DBP reduces ischemia and prevents CVD events in patients with CAD, in part by reducing myocardial oxygen demand. One caveat with respect to antihypertensive treatment in patients with CAD is the finding in some studies of an apparent increase in coronary risk at low levels of DBP. For example, in the SHEP study, lowering DBP to <55 or 60 mmHg was associated with an increase in cardiovascular events, including MI.[155] No similar increase in coronary events (a J-shaped curve) has been observed with SBP. Patients with occlusive CAD and/or LVH are put at risk of coronary events if DBP is low. Overall, however, many more events are prevented than caused if BP is aggressively treated.

Stable angina and silent ischemia. Therapy is directed toward preventing MI and death and reducing symptoms of angina and the occurrence of ischemia. Unless contraindicated, pharmacologic therapy should be initiated with a BB.[142,156] BBs will lower BP; reduce symptoms of angina; improve mortality; and reduce cardiac output, heart rate, and AV conduction. The reduced inotropy and heart rate decrease myocardial oxygen demand. Treatment should also include smoking cessation, management of diabetes, lipid lowering, antiplatelet agents, exercise training, and weight reduction in obese patients.

If angina and BP are not controlled by BB therapy alone, or if BBs are contraindicated, as in the presence of severe reactive airways disease, severe peripheral arterial disease, high-degree AV block, or the sick sinus syndrome, either long-acting dihydropyridine or nondihydropyridine type CCBs may be used. CCBs decrease total peripheral resistance, which leads to reduction in BP and in wall tension. CCBs also decrease coronary resistance and enhance post-stenotic coronary perfusion. Nondihydropyridine CCBs also can decrease heart rate; when in combination with a BB however, they may cause severe bradycardia or high degrees of heart block. Therefore, long-acting dihydropyridine CCBs are preferred for combination therapy with BBs. If angina or BP is still not controlled on this two-drug regimen, nitrates can be added, but these should be used with caution in patients taking phosphodiesterase-5 inhibitors such as sildenafil. Short-acting dihydropyridine CCBs should not be used because of their potential to increase mortality, particularly in the setting of acute MI.

Heart Failure

The HF syndrome occurs when the heart is incapable of maintaining sufficient flow to accommodate tissue perfusion and metabolic requirements. Forty to fifty percent of patients with symptoms of HF may have preserved systolic function. These patients are more likely to have hypertension, LVH, and isolated diastolic dysfunction, and are more likely to be women.[141,157] A variety of neurohormonal systems, especially the renin-angiotensin-aldosterone and sympathetic nervous systems may be activated in response to the left ventricular dysfunction, but such activation may lead to abnormal ventricular

remodeling, further left ventricular enlargement, and reduced cardiac contractility. The inexorable progression to more severe stages of left ventricular dysfunction can be significantly reduced by effective therapy with ACEIs, BBs, and diuretics.

Hypertension precedes the development of HF in approximately 90 percent of patients and increases risk for HF by two- to threefold. Hypertension is especially important in HF affecting African American and elderly persons. CAD is the cause of HF in approximately two-thirds of HF patients in the United States. The true incidence of HF has been unchanged in men and has declined among women over the past 50 years.[158] However, HF hospitalization rates have more than doubled in the past 20 years[159] because of the improved therapy resulting in increased life expectancy. HF will probably become even more prevalent in the future as our population ages.

Optimal therapy for HF may require the use of specialized HF disease-management programs and utilization of a variety of health professionals to reinforce treatment recommendations. American College of Cardiology/American Heart Association guidelines are available to manage HF.[132] In the stage A group (New York Heart Association [NYHA] class I), for those at high risk for HF but with no demonstrable clinical symptoms or left ventricular dysfunction, treatment should include fastidious risk-factor management to control BP, hypercholesterolemia, and hyperglycemia. ACEIs may be appropriate due to their beneficial effects on mortality in patients at high risk for CVD.[110,114] The ALLHAT study also has suggested that thiazide-diuretic therapy is useful in preventing disease progression.[109] In stage B HF (NYHA class I), defined by the presence of reduced left ventricular function (ejection fraction [EF] ≤40 percent) in otherwise asymptomatic individuals, ACEIs and BBs are recommended. Stage C HF patients (NYHA class II–III) manifest left ventricular dysfunction and overt symptoms; in these individuals, ACEIs and BBs are again indicated. Aldosterone antagonists also may be of value in this situation.[140] Loop diuretics are often necessary to control volume retention. However, there is no evidence that diuretics prevent progression of disease, and diuretics can also increase serum creatinine levels when used in excess. Patients with stage D HF (NYHA class IV) may require advanced care, such as inotropic drugs, implantable defibrillators, biventricular pacemakers, mechanical-assist devices, or transplantation, in addition to the treatment described above for stage C patients.

HF is a "compelling indication" for the use of ACEI. Abundant evidence exists to justify their use with all stages of HF (table 12). In patients intolerant of ACEIs, ARBs may be used. BBs are also recommended in HF because of clinical studies demonstrating decreased morbidity and mortality, and improvement in HF symptoms (table 12).

Aldosterone antagonists may provide additional benefit in patients with severe left ventricular dysfunction, usually late stage C (NYHA class III–IV). In the Radomized Aldactone Evaluation Study (RALES), low dose spironolactone (12.5–25 mg daily), when added to standard therapy, decreased mortality by 34 percent.[140] In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced mortality by 15 percent in patients following a recent MI with left ventricular ejection fraction (LVEF) ≤40 percent, 90 percent of whom had HF symptoms.[140] Hyperkalemia is a risk with aldosterone antagonists even at low doses (especially since most patients also are taking ACEIs or ARBs), but its incidence can be reduced by limiting therapy to patients with serum Cr <2.5 mg/dL and monitoring serum potassium carefully.

BP targets in HF have not been firmly established, but lowering SBP is almost uniformly beneficial. In most successful trials, systolic blood pressures were lowered to the range of 110–130 mmHg. One trial demonstrated benefits of beta blockade in patients with SBP >85 mmHg,[134] suggesting that very low BPs (e.g., SBP <100 mmHg) may be desirable in some HF patients.

Digoxin continues to be used in HF despite inconsistent clinical results. In the DIG trial, it did not reduce mortality in NYHA class II–III patients taking ACEIs and diuretics, but did reduce HF symptoms and hospitalizations.[160]

Diabetes and Hypertension

The combined unadjusted prevalence of total diabetes and impaired fasting glucose in those over age 20 is 14.4 percent and is the leading cause of blindness, ESRD, and nontraumatic amputations.[161–165] Type 2 diabetes comprises >90 percent of diabetes in the United States and is associated with a 70–80 percent chance of premature death from CVD and stroke.[166–170] The concordance of hypertension and diabetes is increased in the population; hypertension is disproportionately higher in diabetics,[171] while persons with elevated BP are two and a half times more likely to develop diabetes within 5 years.[172,173] The common absence of normal nocturnal "dipping" of BP in diabetics is linked to other CVD surrogates such as LVH and microalbuminuria.[171]

The coexistence of hypertension in diabetes is particularly pernicious because of the strong linkage of the two conditions with all CVD,[168,169] stroke,[87,109,110,168,169,174–176] progression of renal disease,[165,175,177,178] and diabetic retinopathy.[179] The United Kingdom Prospective Diabetes Study (UKPDS)[174] demonstrated that each 10 mmHg decrease in SBP was associated with average reductions in rates of diabetes-related mortality (15 percent), myocardial infarction (11 percent), and the microvascular complications of retinopathy or nephropathy (13 percent). Randomized controlled trials that have included large diabetic populations including UKPDS, Hypertension Optimal Treatment (HOT) Trial, SHEP, the Syst-EUR,[67] HOPE Study,[110] LIFE, and ALLHAT, have demonstrated that adequate BP control improves CVD outcomes, especially stroke, when aggressive BP targets are achieved.[87,88,109,164,175,180]

Microalbuminuria (30–300 mg/day) is associated with increased CVD risk in diabetics and other high-risk patients.[67,181] Overt albuminuria (>300 mg/day or >200 mg/g creatinine on spot urine) or renal insufficiency (estimated GFR <60 mL/min, corresponding to serum creatinine >1.5 mg/dL in men or >1.3 mg/dL in women) defines the presence of chronic kidney disease (CKD) in diabetic patients. SBP correlates better than DBP with renal disease progression in diabetics.[171,177,178,182,183] The rate of decline in renal function among patients with diabetic nephropathy has been reported to be a continuous function of arterial pressure down to approximately 125–130 mmHg SBP and 70–75 mmHg DBP.[177,178,182,183]

The JNC 7 recommendations are consistent with guidelines from the American Diabetes Association (ADA),[88,164] which has also recommended that BP in diabetics be controlled to levels of 130/80 mmHg or lower (although available data are somewhat sparse to justify the low target level of 130/80 mmHg). Whatever the goal level, rigorous control of BP is paramount for reducing the progression of diabetic nephropathy to ESRD.[88,164,177,178,181–183]

Regarding the selection of medications, clinical trials with diuretics, ACEIs, BBs, ARBs, and calcium antagonists have a demonstrated benefit in the treatment of hypertension in both type 1 and type 2 diabetics.[87,88,109,164,175,180] The question of which class of agent is superior for lowering BP is somewhat moot because the majority of diabetic patients will require two or more drugs to achieve BP control.[164,171,184]

Thiazide-type diuretics are beneficial in diabetics, either alone or as part of a combined regimen. In the prespecified diabetic subgroup of ALLHAT, therapy that began with chlorthalidone reduced the primary endpoint of fatal CHD and MI to the same degree as therapy based on lisinopril or amlodipine. Of potential concern is the tendency for thiazide-type diuretics to worsen hyperglycemia, but this effect tended to be small and did not produce more cardiovascular events compared to the other drug classes.[185]

Therapy with an ACEI also is an important component of most regimens to control BP in diabetic patients.[67,172,173,178,179] ACEIs may be used alone for BP lowering but are much more effective when combined with a thiazide-type diuretic or other antihypertensive drugs. The ADA has recommended ACEIs for diabetic patients older than 55 years of age at high risk for CVD, and BBs for those with known CAD.[88] In the Micro-Hope subanalysis of the HOPE Study, which included both hypertensive and normotensive individuals,[186] high-risk diabetic patients treated with

ACEI added on to conventional therapy showed a reduction in combined MI, stroke, and CVD death of about 25 percent and a reduction in stroke by about 33 percent compared to placebo plus conventional therapy. With respect to microvascular complications, the ADA has recommended both ACEIs and ARBs for use in type 2 diabetic patients with CKD because these agents delay the deterioration in GFR and the worsening of albuminuria.[88,164,171,181]

BBs, especially beta1-selective agents, are beneficial to diabetics as part of multidrug therapy, but their value as monotherapy is less clear. A BB is indicated in a diabetic with IHD but may be less effective in preventing stroke than an ARB as was found in the LIFE study.[187] Although BBs can cause adverse effects on glucose homeostasis in diabetics, including worsening of insulin sensitivity and potential masking of the epinephrine-mediated symptoms of hypoglycemia, these problems are usually easily managed and are not absolute contraindications for BB use.

CCBs may be useful to diabetics, particularly as part of combination therapy to control BP. They were shown to reduce CVD events in diabetics compared to placebo in several clinical outcome trials.[87,101,113,118] In the diabetic cohort of ALLHAT, amlodipine was as effective as chlorthalidone in all categories except HF, where it was significantly inferior.[109] The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial in diabetics was stopped prematurely when it was found that the dihydropyridine nitrendipine was inferior to lisinopril in reducing the incidence of ischemic cardiac events.[188] However, in normotensive diabetics in the ABCD2 Trial, nitrendipine was equivalent to lisinopril in stroke prevention and in retardation of the development of albuminuria.[189]

Chronic Kidney Disease

Age and kidney function. Renal excretory function, as represented by GFR, deteriorates with age beginning in the third or fourth decade of life. By the sixth decade, GFR commonly declines by 1–2 mL/min per year. This age-related loss of renal function is proportional to BP level, and the rate of GFR deterioration can accelerate to 4–8 mL/min per year if SBP remains uncontrolled.[165] Such rates of deterioration may lead to the development of ESRD and the need for dialysis or transplantation, especially in those with other coexistent renal diseases.

CKD is defined as either: (1) reduced excretory function with an eGFR <60 mL/min/1.73 m^2 (approximately corresponding to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women); or (2) the presence of albuminuria (>300 mg/d or 200 mg/g creatinine). In a number of laboratories, serum creatinine is being replaced as an index of renal function by eGFR, the values of which are derived from newer algorithms that include adjustments for gender, race, and age. These algorithms are available on Web sites.[66] The measurements appear to be of greater value than 24-hour urine collections for creatinine clearance.

Urinary albumin excretion has diagnostic and prognostic value equivalent to reduced eGFR. To avoid inaccuracies associated with 24-hour urine collections, spot urine samples may be used and the albumin/creatinine ratio (ACR) determined. Microalbuminuria is present when the spot urine ACR is between 30–200 mg albumin/g creatinine. ACR values >200 mg albumin/g creatinine signify the presence of CKD.

CVD risk in CKD. CVD is the most common cause of death in individuals with CKD, and CKD is an independent risk factor for CVD. Individuals with eGFR <60 mL/min have an approximate 16 percent increase in CVD mortality, and individuals with eGFR <30 mL/min have a 30 percent increase.[190] CVD risk also exhibits a continuous relationship with albuminuria; the presence of microalbuminuria confers a 50 percent increase in risk and the presence of macroalbuminuria, a 350 percent increase.[191]

Therapy. NHANES III data indicated that about 3 percent of adults (5.6 million people) in the United States had elevated serum creatinine values, and 70 percent of these people had hypertension.[192] While 75 percent of individuals received treatment, only 11 percent with hypertension and elevated serum creatinine had BPs <130/85 mmHg,

and only 27 percent had BPs <140/90 mmHg.[193] In the prevention of CKD, the value of vigorous antihypertensive therapy is most pronounced in those individuals with the greatest degrees of albuminuria. In the Modification of Diet and Renal Disease (MDRD) Study, individuals with proteinuria had slower rates of progression to ESRD if their SBP values were <130 mmHg. A meta-analysis of individuals with CKD and albuminuria found that positive predictors of outcome were lower SBP levels (110–129 mmHg), lower albumin excretion ratio (AER) (<1.0 g/day), and the presence of ACEI therapy.[194,195] However, in the African American Study of Kidney Disease and Hypertension (AASK) study of African Americans with hypertensive CKD, those achieving a mean BP of 128/78 mmHg experienced renal deterioration at the same rate as those achieving a mean of 141/85 mmHg.[196] Many studies demonstrate that antihypertensive regimens that include an ACEI or ARB are more effective in slowing progression of CKD than other antihypertensive regimens.[149–152,196]

The joint recommendations of the American Society of Nephrology and the National Kidney Foundation provide useful guidelines for management of hypertensive patients with CKD. They recommend a goal BP for all CKD patients of <130/80 mmHg and the need for more than one antihypertensive drug to achieve this goal. The guidelines indicate that most patients with CKD should receive an ACEI or an ARB in combination with a diuretic, and many will require a loop diuretic rather than a thiazide. In addition, if there is a conflict between the goals of slowing progression of CKD and CVD risk reduction, individual decision making is recommended based on risk stratification.

Patients With Cerebrovascular Disease

The risk of clinical complications of cerebrovascular disease including ischemic stroke, hemorrhagic stroke, and dementia increases as a function of BP levels. Given the population distribution of BP, most ischemic strokes occur in individuals with prehypertension or stage 1 hypertension. The incidence of ischemic or hemorrhagic stroke is reduced substantially by treatment of hypertension. No specific agent has been proven to be clearly superior to all others for stroke protection. In the LIFE study, there were fewer strokes in the losartan-treated group than in the group treated with atenolol.[102] In the ALLHAT study, the stroke incidence was 15 percent greater with ACEI than with thiazide-type diuretic or dihydropyridine CCB, but the BP reduction in the lisinopril group was also less than with chlorthalidone or amlodipine.[109]

With respect to the prevention of recurrent stroke, PROGRESS demonstrated that addition of the diuretic, indapamide, to the ACEI, perindopril, caused a 43 percent reduction in stroke occurence.[111] The reduced incidence of stroke appeared related to the BP reduction obtained by the combination therapy even though many patients on entry into the study were not hypertensive.[197] No significant reduction was present in those on perindopril alone whose BP was only 5/3 mmHg lower than in the control group.

The management of BP during an acute stroke remains controversial. BP is often elevated in the immediate poststroke period and is thought by some to be a compensatory physiologic response to improve cerebral perfusion to ischemic brain tissue. As a result, it has been common practice after acute cerebral infarction to reduce or withhold BP treatment until the clinical condition has stabilized. There still are no large clinical studies upon which to base definitive recommendations. Nevertheless, the American Stroke Association has provided the following guidelines: in patients with recent ischemic stroke whose SBP is >220 mmHg or DBP 120–140 mmHg, cautious reduction of BP by about 10–15 percent is suggested, while carefully monitoring the patient for neurologic deterioration related to the lower pressure. If the DBP is >140 mmHg, carefully monitored infusion of sodium nitroprusside should be used to reduce the BP by 10–15 percent.[198]

BP control affects the use of thrombolytic agents in ischemic stroke. SBP >185 mmHg or diastolic pressures >110 mmHg are contraindications to the use of tissue plasminogen activator (tPA) within the first 3 hours of an ischemic stroke. Once a thrombolytic agent has been initiated, BP should be monitored closely, especially in the first 24

hours after initiation of treatment. SBP ≥180 mmHg or DBP ≥105 mmHg usually necessitates therapy with intravenous agents to prevent intracerebral bleeding.[199]

Other Special Situations

Minorities

The prevalence, impact, and control of hypertension differ across racial and ethnic subgroups of the U.S. population. In African Americans, hypertension is more common, more severe, develops at an earlier age, and leads to more clinical sequelae than in age-matched non-Hispanic Whites.[200] Mexican Americans and Native Americans have lower control rates than non-Hispanic Whites and African Americans.[201,202] The pathogenesis of hypertension in different racial subgroups may differ with respect to the contributions of such factors as salt, potassium, stress, cardiovascular reactivity, body weight, nephron number, sodium handling, or hormonal systems, but in all subgroups, the etiology is multifactorial.[200,203] African Americans have a greater prevalence of other cardiovascular risk factors, especially obesity.[200,203] Much of the variance in hypertension-related sequelae across racial or ethnic groups may be attributable to differences in socioeconomic conditions; access to healthcare services; or attitudes, beliefs, and deficits in accurate health-related information.[200,203] For example, when medications and provider services were provided free of charge, as in the Hypertension Detection and Follow-up Program, African American men treated with the intensive "Stepped-Care Approach" actually benefited more than Whites.[204]

Weight reduction and sodium reduction are recommended for all prehypertensive and hypertensive patients but may be particularly effective in minorities. The salt content of some minorities' traditional diets may be very high.[205] The low-sodium DASH eating plan was associated with greater reductions in BP in African Americans than in other demographic subgroups.[94] In clinical trials, lowering BP prevents sequelae of hypertension in all racial or ethnic groups.[200,203] Nonetheless, monotherapy with BBs, ACEIs, or ARBs lowers BP to a somewhat lesser degree in African Americans than Whites.[109,206–208] In the ALLHAT trial with more than 15,000 Blacks, ACEI was less effective in lowering blood pressure than either the thiazide-type diuretic or the CCB. This was associated with a 40 percent greater risk of stroke, 32 percent greater risk of HF, and 19 percent greater risk of CVD in those randomized to the ACEI versus the diuretic.[109] The interracial differences in BP lowering observed with these drugs are abolished when they are combined with a diuretic.[109,203,208]

Racial differences in the incidence of antihypertensive drug side effects may occur; African Americans and Asians have a three- to fourfold higher risk of angioedema[109,209,210] and have more cough attributed to ACEIs than Caucasians.[211]

Several other benefits of treatment have been demonstrated in minority populations. A 28 percent reduction in mortality was observed in African Americans who received BB therapy after acute MI compared to those not receiving a BB.[212] A greater degree of preservation of renal function occurred in African Americans with hypertensive nephrosclerosis treated with a regimen containing an ACEI compared to a BB or a calcium antagonist.[196] No large outcome studies have been carried out with ARBs in African American and other minority patients. Unfortunately, sufficient numbers of Mexican Americans, other Hispanic Americans, Native Americans, or Asian/Pacific Islanders have not been included in most of the major clinical trials to allow reaching strong conclusions about their responses to individual antihypertensive therapies.

Irrespective of whether race or ethnicity should be a significant consideration in the choice of individual antihypertensive drugs, in minority groups the use of combination or multiple antihypertensive drug therapy that usually includes a thiazide-type diuretic will lower BP and reduce the burden of hypertension-related CVD and renal disease.

Metabolic Syndrome

Definition and associations. The term "metabolic syndrome" describes a constellation of cardiovascular risk factors related to hypertension,

abdominal obesity, dyslipidemia, and insulin resistance. The definition adopted by the National Cholesterol Education Program (Adult Treatment Panel [ATP] III) guidelines in 2001[21] is the presence of three or more of the five risk factors (table 13). The World Health Organization has a somewhat different definition of the metabolic syndrome, but for consistency, JNC 7 has adopted the ATP III definition.

Several other associated features have been reported, including hyperinsulinemia, insulin resistance, and higher density of LDL-cholesterol particles.[213] The metabolic syndrome has also been associated with high levels of inflammatory risk markers,[214] reduced fibrinolysis (including elevated plasminogen activator inhibitor-1),[215] heightened magnitude of oxidative stress,[216,217] microalbuminuria,[218] abnormalities in autonomic regulation,[219] and activation of the renin-angiotensin-aldosterone axis.[220]

Table 13. Clinical criteria defining the metabolic syndrome in Adult Treatment Panel III

- Waist circumference:
  >102 cm (>40 inches) for men
  >88 cm (>35 inches) for women
- Blood pressure:
  ≥130 mmHg systolic and/or
  ≥85 mmHg diastolic
- Fasting glucose:
  ≥110 mg/dL or 6.1 mmol/L
- Triglycerides:
  ≥150 mg/dL or 1.69 mmol/L
- HDL-cholesterol:
  <40 mg/dL (1.04 mmol/L) in men
  <50 mg/dL (1.29 mmol/L) in women

HDL, high-density lipoprotein

Source: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA *2001;285:2486–97.*

Prevalence

When the ATP III criteria were applied to the data from the NHANES III survey (1988–1994), the prevalence of the metabolic syndrome in adults in the United States was estimated at 23.7 percent or about 47 million individuals.[221] BMI, kg/m^2 is related to the metabolic syndrome in both men and women (table 14).[222] In addition, because abdominal obesity is also correlated with the metabolic syndrome, ATP III uses it rather than BMI. This becomes important in overweight individuals with a BMI of 25–29.9 kg/m^2 and large waist circumference (>40 inches in men, >35 inches in women) who may have metabolic syndrome despite not being obese.

The metabolic syndrome will likely increase further in the next several years, primarily because of the rapid increase in obesity. The health problems related to the metabolic syndrome will likely escalate dramatically.

Table 14. Estimated prevalence of the metabolic syndrome using the Adult Treatment Panel III definition among normal weight, overweight, and obese men and women in the National Health and Nutrition Examination Survey III

Category	BMI, kg/m^2	Metabolic Syndrome Prevalence, Percent	
		Men	Women
Normal weight	<25.0	4.6%	6.2%
Overweight	25.0–29.9	22.4%	28.1%
Obese	>30	59.6%	50.0%

BMI, body mass index

Source: Park YW, et al. The metabolic syndrome: Prevalance and associated risk factor findings in the US population from The Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med *2003;163:427–36.*

Age Trends

The prevalence of the metabolic syndrome is highly age dependent. A prevalence of 7 percent among adults 20–29 years of age rises to 40 percent or more among Americans over age 60.

Clinical Impact

The metabolic syndrome is associated in men with a fourfold increase in risk for fatal CHD, and a twofold greater risk of CVD and all-cause mortality, even after adjustment for age, LDL-cholesterol, smoking, and family history of CHD.[223] The metabolic syndrome is associated with increased CHD risk in women.[224] Patients with the metabolic syndrome have a five- to nine-fold increased risk of developing diabetes.[225,226]

Clinical Management of the Metabolic Syndrome

The cornerstone for clinical management in adults is appropriate lifestyle changes.

Overweight and obesity. Treatment of overweight and obesity is summarized in the next section, using key principles in the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*.[227]

Physical activity. The metabolic syndrome can improve with increased physical activity.[228] (See Prevention and Lifestyle Modification for Overweight and Obesity.)

Prehypertension and hypertension. The vast majority of individuals with the metabolic syndrome will fall into the categories of prehypertension or stage 1 hypertension. Lifestyle modification is the cornerstone of management in all patients with prehypertension or with the metabolic syndrome, but if BP exceeds 140/90 mmHg, pharmacological therapy is indicated as described in the hypertension treatment algorithm (figure 16).

Lipids. Elevated triglycerides and reduced HDL are typical lipid abnormalities in metabolic syndrome. Elevated LDL is not a prime feature of metabolic syndrome but is important in clinical management.[21]

Impaired glucose tolerance and diabetes. Modest lifestyle change including healthful nutrition and increased physical activity can reduce the development of diabetes by nearly 60 percent in high-risk individuals.[229] Management guidelines published by the ADA are appropriate for individuals with impaired fasting glucose and diabetes.[230]

Lipids

All patients with lipid abnormalities for LDL, HDL, or triglycerides should be treated according to the ATP III recommendations.[21]

Overweight and Obesity

Prevalence and epidemiology. Using the NHANES databases for the periods 1988–1994 vs. 1999–2000, the age-adjusted prevalence of obesity (BMI ≥30 kg/m^2) among U.S. adults increased from 22.9 percent to 30.5 percent,[33] while the prevalence of overweight (BMI ≥25 kg/m^2) increased from 55.9 percent to 64.5 percent. Obese subjects, especially men, with no other risk factors, have increased relative risk for CVD (table 15).[231]

Obesity occurs more often among Hispanics, Native Americans, and African Americans than Caucasians in the United States. These demographic differences extend to children, where obesity and related health problems are increasing at nearly double the rate in ethnic minorities compared to Caucasians.[232,233] The rapid increase in the population of ethnic minorities in the United States is another factor that will lead to a rise in the prevalence of obesity and its complications unless effective, culturally diverse, population-based health promotion strategies are encouraged.

Table 15. Relative 10-year risk for diabetes, hypertension, heart disease, and stroke over the next decade among men initially free of disease stratified by baseline body mass index

BMI	Diabetes	Hypertension	Heart Disease	CVA
18.5–21.9	1.0	1.0	1.0	1.0
22.0–24.9	1.8	1.5	1.1	1.1
25.0–29.9	5.6	2.4	1.7	1.3
30.0–34.9	18.2	3.8	2.2	2.1
>35.0	41.2	4.2	2.4	2.5

BMI, body mass index; CVA, cerebrovascular accident

Source: Field AE, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med *2001;161:1581–6.*

Prevention and lifestyle modifications for overweight and obesity. The major goal of management of both the metabolic syndrome and overweight and obesity is to reduce the age-related rate of weight gain. This challenging task will require a complex combination of healthy behaviors, including decrease in sedentary activities, increase in physical activity, and reduction in calorie intake (table 16). Simple yet practical suggestions include reducing time spent watching television or being online, and increasing time spent walking or in activities that raise the heart rate. The emphasis for weight management should be on avoidance of excess total energy intake and a regular pattern of physical activity. Reducing food portion sizes and limiting fat intake can assist in reducing overall calorie intake. High-sodium diets may be especially deleterious in obese subjects.[234]

Specific nutrient intakes for individuals should be based on lipoprotein levels, BP, and the presence of coexisting heart disease, diabetes, and other risk factors. For example, adoption of the well-studied low sodium DASH eating plan[94] provides heart healthy foods that can be used to promote weight loss, reduce BP in both hypertensive and prehypertensive individuals, and reduce LDL. The benefits of modest lifestyle changes on cardiovascular risk factors are well documented. In the Framingham Heart Study, weight loss of 5 lbs or greater was associated with reductions in cardiovascular risk of about 40 percent.[235] A 10 percent reduction in body weight can reduce disease risk factors.[227]

Physical activity is a key feature of treatment. Increased physical activity, when combined with a reduction in calories, is essential to weight loss success. Based on the available evidence, the recommendation is to engage in regular physical activity at least 30 minutes per day, most days of the week (see table 9). In addition, physical activity is critical to the maintenance of weight loss and is important for overall reduction in cardiovascular risk; 60–90 minutes per week of walking can reduce CHD mortality by about 50 percent.[236] The CVD benefits of slow walking appear to be comparable to those of walking more quickly, suggesting that the most important predictor of benefit was walking time, not speed. Exercise programs appear beneficial at any age and are associated with overall reductions in CVD outcomes by about 50 percent.[237] Although aerobic fitness may negate much of the cardiovascular risk associated with obesity,[238] studies report that individuals who are obese have much lower levels of physical activity and poorer aerobic fitness than leaner individuals.[239]

Table 16. Lifestyle changes beneficial in reducing weight*

- Decrease time in sedentary behaviors such as watching television, playing video games, or spending time online.
- Increase physical activity such as walking, biking, aerobic dancing, tennis, soccer, basketball, etc.
- Decrease portion sizes for meals and snacks.
- Reduce portion sizes or frequency of consumption of calorie-containing beverages.

* *For more detailed information refer to the* Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. *National Institutes of Health.* Obes Res *1998;6(suppl)2:51S–209S.*

Left Ventricular Hypertrophy

The common feature of all forms of LVH is increased left ventricular mass, although there are many different presentations and subtypes, each with a different prognosis and therapy.[240] LVH subclasses can be characterized generally by the relative wall thickness, the presence or absence of reduced contractility, and the end-diastolic chamber size. LVH can occur in endurance athletes with normal or supranormal systolic function, large end-diastolic volumes, and elongation of myofibrils (eccentric hypertrophy). LVH due to hypertension is usually characterized by "concentric" hypertrophy with circumferential hypertrophy of myofibrils, normal or increased contractility, increased relative wall thickness, normal or low end-diastolic volumes, and at times, impaired relaxation ("diastolic dysfunction"). In population-based samples, 30–50 percent of individuals with stages 1 and 2 hypertension have impaired left ventricular relaxation, and in more severe forms of hypertension, about two-thirds have abnormal left ventricular relaxation. In untreated or poorly treated individuals, LVH becomes a major risk factor for dilated cardiomyopathy and HF.[241]

Detection and risk. Echocardiography is much more sensitive than electrocardiography (ECG) for detection of LVH although ECG-LVH is a highly specific indicator for the condition. Individuals with LVH, are more than twice as likely to suffer premature cardiovascular events or death. Current ECG algorithms defining LVH produce a high false-positive rate in African Americans and overestimate the prevalence of LVH in this population.[242,243] The attributable risk of LVH for all-cause mortality is greater than that of single or multivessel coronary artery disease or low EF.

Therapy. Several studies suggest that LVH regression is associated with a lower overall CVD risk. Weight loss, salt restriction, and BP lowering with most antihypertensive agents produce LVH regression. Selection of individual drugs appears to be less important, but certain trends have emerged. Fifty studies of LVH regression conducted before 1996 were subjected to meta-analysis.[244] In these studies, predictors of left ventricular mass reduction during treatment were higher pretreatment left ventricular mass, greater fall in SBP or DBP, and longer duration of treatment. The most consistent reduction in left ventricular mass was achieved with ACEIs, the least reduction occurred with BBs, and intermediate benefits occurred for diuretics and calcium antagonists. However, in both the Treatment of Mild Hypertension study and the VA Cooperative Monotherapy trial, diuretic therapy achieved the greatest benefit in left ventricular mass reduction.[245,246] The LIFE study found that LVH, defined by ECG, was reduced significantly more by a losartan-based than atenolol-based regimen despite equivalent BP lowering.[102]

Peripheral Arterial Disease

Major risk factors for peripheral arterial disease (PAD) are hypertension, diabetes, and smoking. Symptomatic PAD is associated with a greatly increased risk of death from CVD, in part because diffuse atherosclerosis, CAD, and renovascular disease frequently coexist in these patients. Therefore, more intensive screening for these related cardiovascular disorders is appropriate in persons with PAD. Renovascular hypertension should be strongly considered in this population if BP is uncontrolled and if ACEI or ARB treatment is being considered.

Antihypertensive drug treatment is ineffective in relieving the symptoms of PAD, and vasodilator agents such as ACEIs, CCBs, alpha-adrenergic blockers, and direct vasodilators do not improve walking distance or symptoms of claudication.[247–249] This lack of efficacy may be due to: (1) inability of maximally dilated diseased vessels to dilate further during exercise; (2) redistribution of flow caused by the creation of a "steal" phenomenon where blood flow increases in nondiseased vascular beds at the expense of diseased beds; or (3) alteration of pressure-flow relationships distal to the occluded areas by BP reduction. BBs may cause peripheral vasoconstriction and have the potential to increase the frequency of intermittent claudication in individuals with PAD. However, recent studies have shown that BBs have little effect on walking distance or calf blood flow in patients with intermittent claudication.[250] Thus,

BBs can be used in PAD patients, especially if needed for treatment of CAD or HF.

No selective outcome benefit has been demonstrated for any individual class of antihypertensive medication in patients with PAD.[109] Therefore, antihypertensive drug choices should be made on the basis of the presence or absence of compelling indications. If Raynaud's phenomenon is present, CCBs can be used.[251] LDL lowering will reduce the risk for CVD events in people with PAD.[252]

Therapy. Treating hypertension in PAD patients reduces the risk of MI, stroke, heart failure, and death.[253] A structured walking program has been shown to increase the pain-free and maximum walking distance in patients with intermittent claudication.[254] Smoking cessation may be the single most important factor whether PAD progresses. Patients should be encouraged and assisted to stop smoking. Lipid abnormalities should be controlled using lifestyle modification or drugs as appropriate. Coexisting glucose intolerance or insulin resistance calls for increased exercise and weight reduction, and aggressive management of diabetes is indicated. Table 17 outlines medical therapies of PAD.

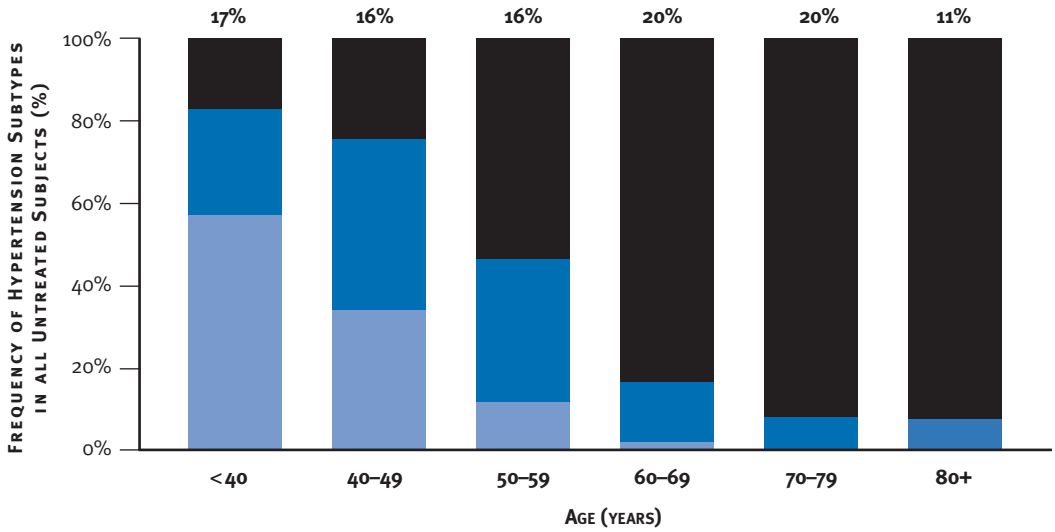
Table 17. Medical therapies of peripheral arterial disease

- Stop smoking.
- Achieve ideal body weight.
- Engage in structured exercise program.
- Achieve goal blood pressure.
- Control lipids (goal: low-density lipoprotein <100 mg/dL).
- Prevent or control diabetes.
- Administer antiplatelet therapy (aspirin, clopidogrel, or both).
- Consider use of Cilostazol for symptoms of claudication if exercise alone is ineffective.

Hypertension in Older People

The number of Americans 65 years of age or older has increased from 24.2 million to 32.6 million from 1980 to 2000 and is expected to continue to rise.[255] SBP increases almost linearly with age in industrialized societies (figure 12) as does the overall prevalence of hypertension and the proportion of hypertensives with isolated SBP elevation (ISH) (figure 17).[192] In contrast, DBP increases in parallel with SBP until about age 55, after which it declines as a manifestation of age-related increases in central arterial stiffness. By age 60, about two-thirds of those with hypertension have ISH; by age 75, almost all hypertensive

Figure 17. Frequency distribution of untreated hypertensive individuals by age and hypertension subtype



Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the tops of bars represent the overall percentage distribution of untreated hypertension in that age group. ■ *ISH (SBP ≥140 mmHg and DBP <90 mmHg);* ■ *SDH (SBP ≥140 mmHg and DBP ≥90 mmHg);* ■ *IDH (SBP <140 mmHg and DBP ≥90 mmHg).*

Source: Franklin SS, et al. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives. Analysis based on National Health and Nutrition Examination Survey (NHANES III). Hypertension *2001;37:869–74.*

individuals have systolic hypertension and about three-fourths have ISH.

Individuals over age 60 represent the most rapidly growing segment of the U.S. population, and even in those who remain normotensive between 55 and 65 years of age, there remains a lifetime risk of developing hypertension that exceeds 90 percent.[16] At the same time, there is a three- to fourfold increase in CVD risk in older compared to younger individuals. These facts prompted the NHBPEP to issue a clinical advisory statement in May 2000 stating that SBP should be the primary target for the diagnosis and management of older people with hypertension.[256] Currently, BP control rates (systolic <140 mmHg and diastolic <90 mmHg) are only about 20 percent in older hypertensive individuals, largely due to poor control of SBP.[257]

Treatment benefits. In the SHEP study involving hypertensive individuals over age 60 with pretreatment SBP >160 and DBP <90 mmHg, individuals treated with chlorthalidone (with or without BB) had reductions in the primary endpoint of stroke (36 percent), as well as HF events (54 percent), MI (27 percent), and overall CVD (32 percent)[24] as compared with the placebo group. Using a similar design and sample size, the Syst-EUR study compared a regimen based on nitrendipine to placebo and found a significant reduction in stroke (41 percent) as well as overall CVD events (31 percent).[113] A meta-analysis of eight placebo-controlled trials in 15,693 elderly patients followed for 4 years found that active antihypertensive treatment reduced coronary events (23 percent), strokes (30 percent), cardiovascular deaths (18 percent), and total deaths (13 percent), with the benefit particularly great in those older than 70 years.[258] Benefits of therapy have been demonstrated even in individuals over 80 years of age.[116,259] Analyses of treatment trials in the elderly by the Hypertension Trialists group have suggested that the choice of initial agent is less important than the degree of BP reduction achieved.[90]

Accurate and representative BP measurement can pose special problems in some older individuals (see Accurate Blood Pressure Measurement in the Office). BP is more variable in older patients, often due to stiff large arteries and age-related decreases in baroreflex buffering. Exaggerated BP drops may occur in the elderly during postural change (see next section), after meals,[260] and after exercise.[97] Pseudohypertension, where cuff BP overestimates the actual intra-arterial pressure due to relative inability of the BP cuff to compress a thickened, stiff, or calcified brachial artery is an uncommon condition in older persons. But this condition should be strongly considered if usual treatment does not reduce BP, especially in those patients who complain of symptoms consistent with postural hypotension.[261] A relatively small percentage of elderly patients have a reversible form of hypertension, most commonly due to renovascular disease, which is seen most often in smokers.[262]

SBP provides more appropriate classification and risk stratification than DBP in the elderly. In the Framingham Heart Study, SBP alone correctly classified the BP stage in 94 percent of adults over the age of 60, while DBP alone correctly classified 66 percent.[192] Pulse pressure (PP) (SBP–DBP) is only marginally stronger than SBP for risk stratification in individuals over age 60, but under age 60, PP is not useful as a CVD risk predictor.[18] PP generally decreases as a result of SBP lowering,[24,263] but no prospective clinical trial has used PP as the primary clinical endpoint. Thus, on balance, SBP is superior to PP and DBP as a way to stratify patients and as a target for treatment in older persons.

Although no randomized prospective clinical trial has conclusively proven the benefits of treatment in individuals with stage 1 systolic hypertension (140–159 mmHg), hypertension therapy should not be withheld in these patients, and therapy should not be withheld on the basis of age. There is no definitive evidence of an increase in risk of aggressive treatment (a J-curve) unless DBP is lowered to <55 or 60 mmHg by treatment.[155]

Treatment. Weight loss and reduced sodium intake are particularly beneficial in older people. In the Trial of Nonpharmacologic Interventions in the Elderly (TONE), reducing sodium to 80 mmol (2 grams) per day reduced BP over 30 months, and about 40 percent of those on the low-salt diet

were able to discontinue their antihypertensive medications.[264] When weight loss was combined with salt reduction, an additional BP decrease was seen. Older persons should also be encouraged to avoid excessive alcohol intake and to remain as physically active as is feasible.

Use of specific drug classes in older people is largely similar to that recommended in the general algorithm and for individual compelling indications. Combination therapy with two or more drugs is generally needed to achieve optimal BP control. In routine practice, if the systolic goal is achieved, the diastolic goal will almost always be reached as well.

A significant number of elderly individuals have widely variable BP with exaggerated high and low extremes. Such individuals deserve consideration for a slow titration approach as do individuals with a history of medication side effects and those with orthostatic hypotension (OH). Unfortunately, the misperception that many elderly have "brittle hypertension" has contributed to widespread inadequacy of drug titration and to poor BP control.

Orthostatic Hypotension

BP measurements are typically recorded in the sitting position. This practice, while convenient for the practitioner, limits the ability to diagnose OH. Normally, standing is accompanied by a small increase in DBP and a small decrease in SBP when compared to supine values. OH is present when there is a supine-to-standing BP decrease >20 mmHg systolic or >10 mmHg diastolic. There is more OH in diabetic individuals. OH occurred in about 7 percent of men over 70 years of age in the Honolulu Heart Study, was highly age-dependent, and carried with it a 64 percent increase in age-adjusted mortality compared with a control population.[265] There is a strong correlation between the severity of OH and premature death as well as increased incidents of falls and fractures.[265-267] The causes of OH include severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and certain venodilator antihypertensive drugs, especially alpha blockers and alpha-beta blockers. Diuretics and nitrates may further aggravate OH.

In treating older hypertensive patients, clinicians should be alert to potential OH symptoms such as postural unsteadiness, dizziness, or even fainting. Lying and standing BPs should be obtained periodically in all hypertensive individuals over age 50. OH is a common barrier to intensive BP control that should be clearly documented; if present, drug therapy should be adjusted accordingly and appropriate warnings given to patients.

Resistant Hypertension

Resistant hypertension is defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. Several causes of resistant hypertension may be present.

Improper BP measurement can lead to overestimation of intra-arterial pressure (see Accurate Blood Pressure Measurement in the Office). Falsely high readings may also be observed in those whose brachial arteries are heavily calcified or arteriosclerotic and cannot be fully compressed.[268] Clinic or "white-coat" hypertension may also lead to transient high readings that are not experienced throughout the day. This can be documented by home BP or ambulatory BP readings (see prior sections).

Inadequate diuretic therapy is common in resistant hypertension. Volume overload, once recognized, can be managed by use of appropriate diuretics. While a thiazide-type diuretic is recommended for the majority of hypertensive patients, a loop diuretic is often required for patients who have a decreased GFR or HF.

Failure to receive adequate medications can be the result of reluctance on the part of the patient or practitioner to use effective medication doses. Causes and approaches to nonadherence are discussed in subsequent sections.

Drug interactions that induce resistance may be difficult to detect unless the patient is asked open-ended questions regarding what they take when experiencing pain and what food supplements, health-food preparations, over-the-counter and Internet-purchased medications, and supplements

they use. Nonsteroidal anti-inflammatory drugs and pressor agents in cold remedies, nasal vasodilators, and some nontraditional remedies may counter the antihypertensive effects of prescribed medications. If resistant hypertension persists after remediable causes are identified and corrected, then a concerted search for a cause of secondary hypertension should be conducted (table 7). If resistance still persists, consultation with a hypertension specialist is the next logical step.

Specific causes of resistant hypertension are listed in table 18. They usually can be identified by appropriate evaluation, and once identified, can almost always be treated effectively. The prevalence of truly resistant hypertension is small.

Table 18. Causes of resistant hypertension

Improper Blood Pressure Measurement

Volume overload

- Excess sodium intake
- Volume retention from kidney disease
- Inadequate diuretic therapy

Drug-induced or other causes

- Nonadherence
- Inadequate doses
- Inappropriate combinations
- Nonsteroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
- Cocaine, amphetamines, other illicit drugs
- Sympathomimetics (decongestants, anorectics)
- Oral contraceptive hormones
- Adrenal steroid hormones
- Cyclosporine and tacrolimus
- Erythropoietin
- Licorice (including some chewing tobacco)
- Selected over-the-counter dietary supplements and medicines (e.g., ephedra, ma huang, bitter orange)

Associated conditions

- Obesity
- Excess alcohol intake

Identifiable causes of hypertension (see table 7).

Cognitive Function and Dementia

Dementia and cognitive impairment occur more commonly in people with hypertension. Reduced progression of cognitive impairment may occur with effective antihypertensive therapy.[269,270] Narrowing and sclerosis of small penetrating arteries in the subcortical regions of the brain are common findings on autopsy in chronic hypertension.[271–274] These changes are believed to contribute to hypoperfusion, loss of autoregulation, compromise of the blood-brain barrier, and ultimately to subcortical white matter demyelination, microinfarction, and cognitive decline. Magnetic resonance imaging (MRI) studies in persons with chronic hypertension have revealed greater numbers of subcortical white matter lesions and microinfarcts, astrogliosis, ventricular enlargement, and extracellular fluid accumulation than in age-matched controls.[275–285]

Mild cognitive impairment (MCI) is a diagnostic category that represents a transitional state between normal aging and mild dementia in which patients exhibit signs of poor recent memory but can still perform daily tasks such as managing finances, driving, shopping, and preparing meals.[286] Hypertension and hypercholesterolemia are risk factors for MCI and for other signs of cognitive decline, such as impaired attention, reaction time, verbal fluency, or executive function.[275,276,278,287–289]

Effective antihypertensive therapy strongly reduces the risk of developing significant white matter changes on MRI.[290] However, existing white matter changes, once established, do not appear to be reversible.[291,292] The optimal SBP/DBP to prevent cognitive decline in older individuals is thought by some to be in the SBP 135–150 mmHg and DBP 70–79 mmHg range.[287,288] In the SystEUR trial, CCB therapy was superior to placebo in slowing the decline in cognitive function,[293] but no comparative data are available regarding whether certain classes of antihypertensive drugs are superior to others in preventing cognitive decline.

Hypertension in Women

Nonpregnant Women

Sexual dimorphism of BP and hypertension prevalence in women. There is a sexual dimorphism in BP, such that women have lower SBP levels than men during early adulthood, while the opposite is true after the sixth decade of life. DBP tends to be just marginally lower in women than men regardless of age.[294] Similarly, in early adulthood, hypertension is less common among women than men. However, after the fifth decade of life, the incidence of hypertension increases more rapidly in women than men, and the prevalence of hypertension in women is equal to or exceeds that in men during the sixth decade of life. The highest prevalence rates of hypertension are observed in elderly black women, with hypertension occurring in >75 percent of women older than 75 years of age.[295]

Awareness, treatment, and control of high BP in women. Women are more likely than men to know that they have hypertension, to have it treated, and to have it controlled.[1] In NHANES III, approximately 75 percent of hypertensive Black and White women were aware of their high BP in contrast to 65 percent of hypertensive men in these ethnic groups. Overall, 61 percent of hypertensive women, but only 44 percent of men, were being treated with antihypertensive medications. The higher treatment rates in women have been attributed to increased numbers of physician contact.

Menopause and blood pressure. The effect of menopause on BP is controversial. Longitudinal studies have not documented a rise in BP with menopause, while cross-sectional studies have found significantly higher SBP and DBP in postmenopausal versus premenopausal women.[294] In NHANES III, the rate of rise in SBP tended to be steeper in postmenopausal compared to premenopausal women until the sixth decade, when the rate of increase tended to slow. Staessen et al. reported that, even after adjustment for age and BMI, postmenopausal women are more than twice as likely to have hypertension as premenopausal women.[296] In a prospective study of conventional and ambulatory BP levels, postmenopausal women had higher SBP (4–5 mmHg) than pre- and perimenopausal controls.[297] The increase in SBP per decade was 5 mmHg greater in the peri- and postmenopausal women than in the premenopausal group. Thus, there is evidence that at least part of the rise in BP (particularly SBP) seen later in life in women is due to menopause. A menopause-related increase in BP has been attributed to a variety of factors, including estrogen withdrawal, overproduction of pituitary hormones, weight gain, or a combination of these and other yet undefined neurohumoral influences.[298]

Postmenopausal hormone therapy and BP. Results of studies evaluating the effects of hormone replacement therapy (HRT) on BP have been inconsistent. The Women's Health Initiative (WHI), the largest longitudinal study to address this question, found an average 1 mmHg increase in SBP over 5.6 years of followup among 8,506 postmenopausal women randomized to conjugated equine estrogen and medroxyprogesterone acetate as compared to a placebo group.[299] There was no difference in DBP between the hormone treatment groups. Further, in the WHI cross-sectional analysis of almost 100,000 women 50–79 years of age, current hormone use was associated with a >25 percent likelihood of having hypertension compared to past use or no prior use.[300]

Smaller observational and interventional studies have found different results. In the Baltimore Longitudinal Study on Aging (BLSA), women receiving HRT had a significantly smaller increase in SBP over time than nonusers, but DBP was not affected. The Postmenopausal Estrogen/Progestin Intervention trial showed no effect of HRT on SBP or DBP.[301] In small studies that used 24-hour ABPM to evaluate the effects of HRT on BP, while overall results were inconsistent, several of the studies suggest that HRT improves or restores the normal nighttime reduction ("dipping") in BP that may be diminished in postmenopausal women. Such an effect would tend to reduce total BP load and thereby reduce target organ damage.[298]

Overall, HRT-related change in BP is likely to be modest and should not preclude hormone use in normotensive or hypertensive women. All hyper-

tensive women treated with HRT should have their BP monitored closely at first and then at 6-month intervals.

Oral contraceptives and BP. Many women taking oral contraceptives experience a small but detectable increase in BP; a small percentage experience the onset of frank hypertension. This is true even with modern preparations that contain only 30 µg estrogen. The Nurses' Health Study found that current users of oral contraceptives had a significantly increased (relative risk [RR]=1.8; 95 percent confidence interval [CI]=1.5–2.3) risk of hypertension compared with those who had never used oral contraceptives.[302] Absolute risk was small: only 41.5 cases of hypertension per 10,000 person/years could be attributed to oral contraceptive use. Controlled prospective studies have demonstrated a return of BP to pretreatment levels within 3 months of discontinuing oral contraceptives, indicating that their BP effect is readily reversible.

Oral contraceptives occasionally may precipitate accelerated or malignant hypertension. Family history of hypertension, including preexisting pregnancy-induced hypertension, occult renal disease, obesity, middle age (>35 years), and duration of oral contraceptive use increase susceptibility to hypertension. Contraceptive-induced hypertension appears to be related to the progestogenic, not the estrogenic, potency of the preparation.

Regular monitoring of BP throughout contraceptive therapy is recommended, and it has been suggested that contraceptive prescriptions be limited to 6 months to ensure at least semiannual reevaluations. Withdrawal of the offending contraceptive agent is generally desirable in cases of contraceptive-induced hypertension, but such therapy may have to be continued in some women (e.g., if other contraceptive methods are not suitable) and combined with antihypertensive therapy.

Outcomes of antihypertensive trials in women. Relative benefits of antihypertensive therapy do not appear to differ between the sexes.[303] Absolute risk reduction for stroke was also similar in men and women, but for coronary events, it was greater in men. Similarly, a placebo-controlled trial of CCB treatment showed treatment benefits for both sexes.[113,304] More recent outcome trials comparing ACEIs, ARBs, or CCBs to diuretics and BBs in older, high-risk patients have generally shown similar benefits for women and men.[101,102,109] The current evidence indicates that the sex of the patient should not play a role in decisions about whether to treat high BP.

Choice of antihypertensive drugs for women. While women generally respond to antihypertensive drugs similarly to men, some special considerations may dictate treatment choices for women. ACEIs and ARBs are contraindicated for women who are or intend to become pregnant because of the risk of fetal developmental abnormalities. Diuretics are particularly useful in elderly individuals because of a decreased risk of hip fracture. Some antihypertensive drugs have gender-specific adverse effect profiles. For example, in the TOMHS, women reported twice as many adverse effects as men.[305] Women are more likely to develop diuretic-induced hyponatremia, and men are more likely to develop gout. Hypokalemia is more common in women taking a diuretic. ACEI-induced cough is twice as common in women as in men, and women are more likely to complain of CCB-related peripheral edema and minoxidil-induced hirsutism.

Pregnant Women

Hypertensive disorders in pregnancy are a major cause of maternal, fetal, and neonatal morbidity and mortality. Hypertension in pregnancy is classified into one of five categories (table 19), and it is critical to differentiate preeclampsia, a pregnancy-specific syndrome of exaggerated vasoconstriction and reduced organ perfusion, from pre-existing chronic hypertension.[7,306]

Prepregnancy assessment. Women should be evaluated prior to conception to define their BP status, and if hypertensive, to assess its severity, possible secondary causes, and presence of target organ damage, and to plan treatment strategies. Many hypertensive women who plan to become pregnant should be screened for pheochromocytoma due to the high morbidity and mortality of this condition if not diagnosed antepartum.

Table 19. Classification of hypertension in pregnancy

Chronic hypertension	■ BP ≥140 mmHg systolic or 90 mmHg diastolic prior to pregnancy or before 20 weeks gestation ■ Persists >12 weeks postpartum
Preeclampsia	■ BP ≥140 mmHg systolic or 90 mmHg diastolic with proteinuria (>300 mg/24 hrs) after 20 weeks gestation ■ Can progress to eclampsia (seizures) ■ More common in nulliparous women, multiple gestation, women with hypertension for ≥4 years, family history of preeclampsia, hypertension in previous pregnancy, renal disease
Chronic hypertension with superimposed preeclampsia	■ New onset proteinuria after 20 weeks in a woman with hypertension ■ In a woman with hypertension and proteinuria prior to 20 weeks gestation ■ Sudden two- to threefold increase in proteinuria ■ Sudden increase in BP ■ Thrombocytopenia ■ Elevated AST or ALT
Gestational hypertension	■ Hypertension without proteinuria occurring after 20 weeks gestation ■ Temporary diagnosis ■ May represent preproteinuric phase of preeclampsia or recurrence of chronic hypertension abated in midpregnancy ■ May evolve to preeclampsia ■ If severe, may result in higher rates of premature delivery and growth retardation than mild preeclampsia
Transient hypertension	■ Retrospective diagnosis ■ BP normal by 12 weeks postpartum ■ May recur in subsequent pregnancies ■ Predictive of future primary hypertension

ALT, alanine aminotransferase; AST, aspartate aminotransaminase; BP, blood pressure

In hypertensive women planning to become pregnant, it may be prudent prior to conception to change to antihypertensive medications known to be safe during pregnancy, such as methyldopa or BBs. ACEIs and ARBs should be discontinued prior to attempts at conception or as soon as pregnancy is confirmed. Those with progressive renal diseases should be encouraged to complete their childbearing while their renal function is relatively well preserved. Mild renal disease (serum creatinine <1.4 mg/dL) has a minimal effect on fetal survival, and the underlying renal disease does not generally worsen during pregnancy. However, moderate or severe renal insufficiency in pregnancy may accelerate both hypertension and the underlying disease and markedly reduce fetal survival.

Treatment of chronic hypertension during pregnancy. Women with stage 1 hypertension are at low risk for cardiovascular complications during pregnancy and are candidates for lifestyle modification therapy only, as there is no evidence that pharmacologic treatment improves neonatal outcomes. Further, BP usually falls during the first half of pregnancy; therefore, hypertension may be easier to control with reduced or no medications. With lifestyle modification, aerobic exercise should be restricted based on theoretical concerns that inadequate placental blood flow may increase the risk of preeclampsia, and weight reduction should not be attempted, even in obese pregnant women. Although the data on pregnant women are sparse, many experts recommend restriction of sodium intake to the same 2.4 g sodium intake recommended for those with

primary hypertension.[7] Use of alcohol and tobacco must be strongly discouraged.

Use of antihypertensive drugs in pregnant women with chronic hypertension varies greatly among centers. Some clinicians prefer to stop antihypertensive medications while maintaining close observation, including use of home BP monitoring. This approach reflects concern about the safety of antihypertensive drug treatment during pregnancy. A meta-analysis of 45 randomized controlled studies of treatment with several classes of antihypertensive drugs in stages 1 and 2 hypertension during pregnancy showed a direct linear relationship between treatment-induced fall in mean arterial pressure and the proportion of small-for-gestational-age infants.[307] This relationship was independent of type of hypertension, type of antihypertensive agent, and duration of therapy.

However, for pregnant women with target organ damage or a prior requirement for multiple antihypertensive agents for BP control, antihypertensive medication should be continued as needed to control BP. In all cases, treatment should be re-instituted once BP reaches 150–160 mmHg systolic or 100–110 mmHg diastolic, in order to prevent increases in BP to very high levels during pregnancy. Aggressive treatment of severe chronic hypertension in the first trimester is critical, since fetal loss rates of 50 percent and significant maternal mortality have been reported in these patients.[308] Most of the poor outcomes are related to superimposed preeclampsia (table 19). Further, women with chronic hypertension are also at higher risk for adverse neonatal outcomes if proteinuria is present early in pregnancy. Fetal loss and acceleration of maternal renal disease increase at serum creatinine levels >1.4 mg/dL at conception.

Antihypertensive drug selection. The primary goal of treating chronic hypertension in pregnancy is to reduce maternal risk, but the choice of antihypertensive agent(s) is largely driven by the safety of the fetus. Methyldopa is preferred by many as first-line therapy, based on reports of stable uteroplacental blood flow and fetal hemodynamics and the absence of long-term (7.5-year followup) adverse effects on development of children exposed to methyldopa in utero.[309,310] Other treatment options are summarized in table 20.

Preeclampsia. Preeclampsia is more common in women with chronic hypertension, with an incidence of approximately 25 percent. Risk factors for superimposed preeclampsia include renal insufficiency, a history of hypertension for 4 years or longer, and hypertension in a previous pregnancy. Prevention of preeclampsia relies on: (1) identification of high-risk women; (2) close clinical and laboratory monitoring aimed at its early recognition; and

Table 20. Treatment of chronic hypertension in pregnancy

Agent	Comments
Methyldopa	■ Preferred based on long-term followup studies supporting safety
BBs	■ Reports of intrauterine growth retardation (atenolol) ■ Generally safe
Labetalol	■ Increasingly preferred to methyldopa due to reduced side effects
Clonidine	■ Limited data
Calcium antagonists	■ Limited data ■ No increase in major teratogenicity with exposure
Diuretics	■ Not first-line agents ■ Probably safe
ACEIs, angiotensin II receptor antagonists	■ Contraindicated ■ Reported fetal toxicity and death

ACEIs, angiotensin converting enzyme inhibitors; BBs, beta-blockers

(3) institution of intensive monitoring or delivery when indicated. Treatment of preeclampsia includes hospitalization for bed rest, control of BP, seizure prophylaxis in the presence of signs of impending eclampsia, and timely delivery. Importantly, many women with preeclampsia have previously been normotensive, so acute BP elevations even to modest levels (i.e., 150/100 mmHg) may cause significant symptomatology and require treatment. Treatment does not alter the underlying pathophysiology of the disease, but it may slow its progression and provide time for fetal maturation. Preeclampsia rarely remits spontaneously and in most cases worsens with time.

While delivery may be appropriate therapy for the mother, it may compromise a fetus of <32 weeks gestation. Regardless of gestational age, delivery should be strongly considered when there are signs of fetal distress or intrauterine growth retardation or signs of maternal problems, including severe hypertension, hemolysis, elevated liver enzymes, low platelet count, deteriorating renal function, visual disturbance, and headache or epigastric pain. Vaginal delivery is preferable to cesarean delivery to avoid the added stress of surgery.

Antihypertensive drug therapy. Antihypertensive therapy should be prescribed only for maternal safety; it does not improve perinatal outcomes and may adversely affect uteroplacental blood flow. Selection of antihypertensive agents and route of administration depends on anticipated timing of delivery. If delivery is likely more than 48 hours away, oral methyldopa is preferred due to its safety record. Oral labetalol is an alternative, and other BBs and calcium antagonists are also acceptable based on limited data (table 20). If delivery is imminent, parenteral agents are practical and effective (table 21). Antihypertensives are administered before induction of labor for persistent DBPs of 105–110 mmHg or higher, aiming for levels of 95–105 mmHg.

Treating hypertension during lactation. Hypertensive mothers can usually breast-feed safely. However, all antihypertensive drugs that have been studied are excreted into human breast milk. Therefore, in mothers with stage 1 hypertension who wish to breast-feed for a few months, it might be prudent to withhold antihypertensive medication, with close monitoring of BP, and reinstitute antihypertensive therapy following discontinuation of nursing. No short-term adverse effects have been reported from exposure to methyldopa or hydralazine. Propanolol and labetalol are preferred if a BB is indicated. ACEIs and ARBs should be avoided, based on reports of adverse fetal and neonatal renal effects. Diuretics may reduce milk volume and thereby suppress lactation. Breast-fed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.

Recurrence of hypertension. Hypertension recurs in a large proportion (20–50 percent) of subsequent

Table 21. Treatment of acute severe hypertension in preeclampsia

Hydralazine	■ 5 mg iv bolus, then 10 mg every 20–30 minutes to a maximum of 25 mg, repeat in several hours as necessary
Labetalol (second-line)	■ 20 mg iv bolus, then 40 mg 10 minutes later, 80 mg every 10 minutes for two additional doses to a maximum of 220 mg
Nifedipine (controversial)	■ 10 mg po, repeat every 20 minutes to a maximum of 30 mg ■ Caution when using nifedipine with magnesium sulfate, can see precipitous blood pressure drop ■ Short-acting nifedipine is not approved by the Food and Drug Administration for managing hypertension
Sodium nitroprusside (rarely, when others fail)	■ 0.25 ug/kg/min to a maximum of 5 ug/kg/min ■ Fetal cyanide poisoning may occur if used for more than 4 hours

pregnancies. Risk factors for recurrence include early onset of hypertension in the first pregnancy, a history of chronic hypertension, persistent hypertension beyond 5 weeks postpartum, and elevated BP early in pregnancy. Women with preeclampsia have a greater tendency to develop hypertension than those with normotensive pregnancies.

Hypertension in Children and Adolescents

In children and adolescents, hypertension is defined as elevated BP that persists on repeated measurement at the 95th percentile or greater for age, height, and gender (table 22). As with adults, the fifth Korotkoff sound is used to define DBP.[311]

Clinicians should be alert to the possibility of identifiable causes of hypertension in younger children. Secondary forms of hypertension are more common in children and in individuals with severe hypertension (>20 mmHg above the 95th percentile). Chronic hypertension is becoming increasingly common in adolescence and is generally associated with obesity, sedentary lifestyle, and a positive family history of hypertension and other CVDs. As in adults, children and adolescents with established hypertension develop target organ damage including LVH. Appropriate assessment for LVH, including echocardiography, should be considered in children who have significant and persistant hypertension.

Lifestyle interventions should be recommended for all children with hypertension, with pharmacologic therapy instituted for higher levels of BP or if insufficient response to lifestyle modifications occurs. Teenage children with BP below but near the 95th percentile should adopt healthy lifestyles similar to adults with prehypertension. Although the recommendations for choice of drugs are generally similar in children and adults, dosages of antihypertensive medication for children should be smaller and adjusted very carefully. ACEIs and ARBs should not be used if the patient is pregnant. These agents should be used with extreme caution in sexually active teenage girls and only when careful counseling and effective pregnancy precautions are established.

The presence of uncomplicated hypertension is not a reason to restrict children from participating in physical activities, particularly because exercise may lower BP. Use of anabolic steroid hormones for the purpose of bodybuilding should be strongly discouraged. Efforts should be made to identify other modifiable risk factors in children (e.g., obesity, lack of physical activity, smoking), and vigorous interventions should be made when these factors are present. Detailed recommendations regarding hypertension in children and adolescents can be found in the 1996 *NHBPEP Working Group Report on Hypertension Control in Children and Adolescents*.[311]

Table 22. The 95th percentile of blood pressure by selected ages, by the 50th and 75th height percentiles, and by gender in children and adolescents

Age	Girls' SBP/DBP		Boys' SBP/DBP	
	50th Percentile for Height	75th Percentile for Height	50th Percentile for Height	75th Percentile for Height
1	104/58	105/59	102/57	104/58
6	111/73	112/73	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/88

DBP, diastolic blood pressure; SBP, systolic blood pressure

Source: Adapted from the National High Blood Pressure Education Program. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics *1996;98(pt 1):649–58.*

Hypertensive Crises: Emergencies and Urgencies

Hypertensive emergencies are characterized by severe elevations in BP (>180/120 mmHg) complicated by evidence of impending or progressive target organ dysfunction. They require immediate BP reduction (not necessarily to normal) to prevent or limit target organ damage.[312,313] Examples include hypertensive encephalopathy, intracerebral hemorrhage, acute MI, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, or eclampsia. Hypertensive urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction. Examples include upper levels of stage II hypertension associated with severe headache, shortness of breath, epistaxis, or severe anxiety. The majority of these patients present as noncompliant or inadequately treated hypertensive individuals, often with little or no evidence of target organ damage.

Early triage to establish the appropriate therapeutic strategies for these patients is critical to limiting morbidity and mortality.[314] Patients presenting with severe hypertension may represent as much as 25 percent of all patient visits to busy urban emergency rooms (ERs).[315]

Patients with hypertensive emergencies should be admitted to an intensive care unit for continuous monitoring of BP and parenteral administration of an appropriate agent (table 23). The initial goal of therapy in hypertensive emergencies is to reduce mean arterial BP by no more than 25 percent (within minutes to 1 hour), then if stable, to 160/100–110 mmHg within the next 2–6 hours. Excessive falls in pressure that may precipitate renal, cerebral, or coronary ischemia should be avoided. For this reason, short-acting nifedipine is no longer considered acceptable in the initial treatment of hypertensive emergencies or urgencies. If this level of BP is well tolerated and the patient is clinically stable, further gradual reductions toward a normal BP can be implemented in the next 24–48 hours. There are exceptions to the above recommendation—patients with an ischemic stroke in which there is no clear evidence from clinical trials to support the use of immediate antihypertensive treatment, patients with aortic dissection who should have their SBP lowered to <100 mmHg if tolerated, and patients in whom BP is lowered to enable the use of thrombolytic agents (see Stroke).

Some patients with hypertensive urgencies may benefit from treatment with an oral, short-acting agent such as captopril, labetalol, or clonidine followed by several hours of observation. However, there is no evidence to suggest that failure to aggressively lower BP in the ER is associated with any increased short-term risk to the patient who presents with severe hypertension. Such a patient may also benefit from adjustment in their antihypertensive therapy, particularly the use of combination drugs, or reinstitution of medications if noncompliance is a problem. Most importantly, patients should not leave the ER without a confirmed followup visit within several days.

Unfortunately, the term "urgency" has led to overly aggressive management of many patients with severe, uncomplicated hypertension. Aggressive dosing with intravenous drugs or even oral agents, to rapidly lower BP is not without risk. Oral loading doses of antihypertensive agents can lead to cumulative effects causing hypotension, sometimes following discharge from the ER. Patients who continue to be noncompliant will often return to the ER within weeks.

Erectile Dysfunction and Hypertension

Erectile dysfunction (ED), defined as the inability to have and maintain an erection adequate for intercourse, becomes increasingly common in men over age 50 and is even more common if they are hypertensive.[316] In a survey of over 3,000 health professionals, the frequency of ED was 4 percent in men under age 50, 26 percent in those 50–59, and 40 percent in those 60–69.[316] The frequency was significantly higher if they were hypertensive, diabetic, obese, smokers, or were taking antidepressants or BBs.

Whereas hypertension per se may be associated with ED,[317] the use of various antihypertensive medications may increase the incidence, in part because BP lowering itself may cause reduction of perfusion of genital organs. Available data

Table 23. Parenteral drugs for treatment of hypertensive emergencies*

Drug	Dose	Onset of Action	Duration of Action	Adverse Effects†	Special Indications
Vasodilators					
Sodium nitroprusside	0.25–10 µg/kg/min as IV infusion‡	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocynate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5–15 mg/h IV	5–10 min	15–30 min, may exceed 4 hrs	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 µg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 µg/min as IV infusion‡	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 hrs IV	15–30 min	6–12 hrs	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV 10–40 mg IM	10–20 min IV 20–30 min IM	1–4 hrs IV 4–6 hrs IM	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Adrenergic Inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min 0.5–2.0 mg/min IV infusion	5–10 min	3–6 hrs	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 µg/kg/min IV bolus, then 50–100 µg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 µg/min	1–2 min	10–30 min	Hypotension, nausea, asthma, first degree heart block, heart failure	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

h or hr, hour; IM, intramuscular; IV, intravenous; min, minute(s)

* *These doses may vary from those in the* Physicians' Desk Reference *(51st ed.)*

† *Hypotension may occur with all agents*

‡ *Require special delivery system*

regarding individual effects of antihypertensive drug therapy are confounded by age, vascular disease, and hormonal status. In the TOHMS study involving antihypertensive drugs from five different classes (excluding ARBs) participants randomized to chlorthalidone reported a significantly higher incidence of erection problems, at 24 months of the study, than participants randomized to placebo. Incidence rates through 48 months were more similar among treatment groups than at 24 months, with nonsignificant differences between chlorthalidone and placebo groups.[123] In the VA Cooperative Trial, no difference on incidence of sexual dysfunction was noted

between a CCB, ACEI, hydrochlorothiazide, or BB compared to placebo.[103] In other studies centrally acting alpha agonists have been associated with ED, while ACEIs, ARBs, and CCBs have not been observed to increase its incidence.[317,318]

A lower risk of ED was reported among men who were physically active, not obese, and nonsmokers.[316] Therefore, lifestyle modifications should be encouraged to forestall ED. If ED appears after institution of antihypertensive drug therapy, the offending agent should be discontinued and treatment restarted with another agent. Sildenafil or other phosphodiesterase-5 inhibitors may be prescribed without a significant likelihood of adverse reactions in those with concomitant antihypertensive therapy so long as nitrates are avoided.[319]

There are no definitive data on a relation between sexual dysfunction and hypertension in women. Regardless of gender, clinicians should be willing to discuss sexual dysfunction problems and offer counseling to improve the patient's quality of life.

Urinary Outflow Obstruction

Symptoms of urinary outflow obstruction or a known history of obstruction should be elicited as part of the hypertension work-up. When a normal bladder is distended beyond approximately 300 mL, sympathetic nervous system stimulation may cause a substantial increase in BP. Patients with high spinal cord injuries in particular may exhibit large acute BP increases similar to individuals with autonomic dysfunction. BP control can be improved by keeping the bladder volume below 300 mL and by the use of sympatholytic drugs. Nonsurgical treatment of patients with urinary outflow obstruction includes the use of alpha-1 blockers such as terazosin, doxazosin, or prazosin, which indirectly dilate prostatic and urinary sphincter smooth muscle and also lower BP.[320]

Patients Undergoing Surgery

Uncontrolled hypertension is associated with wider fluctuations of BP during induction of anesthesia and intubation, and may increase the risk for perioperative ischemic events. BP levels of >180/110 mmHg should be controlled prior to surgery.[321] For elective surgery, effective BP control can be achieved over several days to weeks of outpatient treatment. In urgent situations, rapidly acting parenteral agents, such as sodium nitroprusside, nicardipine, and labetalol, can be utilized to attain effective control very rapidly. Surgical candidates with controlled hypertension should maintain their medications until the time of surgery, and therapy should be reinstated as soon as possible postoperatively. Adequate potassium supplementation should be provided, if needed, to correct hypokalemia well in advance of surgery. Older patients may particularly benefit from treatment with beta-1 selective BBs before and during the perioperative period.[322]

Sudden intraoperative hypertension is managed by many of the same parenteral antihypertensive agents that are utilized in the management of hypertensive emergencies (see prior section).[323] Intravenous infusions of sodium nitroprusside, nicardipine, and labetalol can be effective. Nitroglycerin is often an agent of choice in patients with coronary ischemia, while the very short-acting BB, esmolol, may be of benefit in managing intraoperative tachycardia.

Hypertension is very common in the early postoperative period and is related to increased sympathetic tone and vascular resistance.[324] Contributing factors include pain and increased intravascular volume, which may require parenteral dosing with a loop diuretic such as furosemide. If resumption of oral treatment must be interrupted postoperatively, periodic dosing with intravenous enalaprilat or transdermal clonidine hydrochloride may be useful.

Dental Issues in Hypertensive Individuals

A concern in dental care is the use of epinephrine in local anesthetic solutions. Many dental providers do not use catecholamine-containing local anesthetic formulations for any patient with elevated BP, as they are concerned with an adverse cardiovascular response. A systematic review of this topic[325] concluded that, although adverse events may occur in uncontrolled hypertensive patients during dental procedures, the use of epinephrine had a minimal effect. BP should be

monitored closely in the dental office if general anesthesia is administered to hypertensive individuals because of potential wide fluctuations in BP and the risk of hypotension in those receiving antihypertensive drugs. CCBs and other vasodilators may cause hypertrophy of the gums.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) occurs in 2–4 percent of the adult population, and >50 percent of individuals with OSA have hypertension.[263,326–333] Obesity is so common in OSA that the index of suspicion for OSA should be high in any hypertensive patient whose BMI is above 27 kg/m^2.[331] These individuals should be questioned thoroughly for symptoms of OSA, including snoring, witnessed apnea, irregular breathing during sleep, restless sleeping, and chronic morning fatigue. Frequently it is the sleep partner who provides the most reliable history, especially regarding snoring, because the affected individual may deny or be unaware of the problem. If the diagnosis is suspected clinically, confirmation by a formal sleep study is indicated. The impact of sleep apnea on CVD is probably related in large part to its association with elevated BP. However, OSA may act through a number of mechanisms to elicit myocardial and vascular damage, including an increase in catecholamine release,[333,334] activation of inflammatory mechanisms,[335] insulin resistance,[336,337] and endothelial dysfunction.[338] Other cardiovascular conditions associated with OSA include arrhythmias, HF, MI, and stroke.[331,332,339–344]

Previous debate about whether OSA is an etiologic factor in hypertension has focused largely around the strong association of OSA with obesity. While obesity is known to contribute in large part to OSA,[345-348] patients with OSA may also be at increased risk for weight gain,[349] and treatment of OSA may reduce visceral fat.[350] It now appears that the potential causal association between OSA and hypertension involves both the obesity-hypertension link and an independent role of OSA in chronic BP elevation. Episodes of apnea with repeated oxygen desaturation in OSA have been shown to stimulate strong sympathetic nervous system discharges that directly elevate BP.[333,334] Poorer quality of sleep and shorter sleep periods may play a reinforcing role in the fatigue and daytime somnolence. Sleep deprivation alone may raise BP[351] and impair glucose tolerance.[352] There is also a direct relationship between the severity of sleep apnea and the level of BP. Finally, sustained and effective treatment of OSA with continuous positive airway pressure (CPAP) has been reported to lower nighttime and daytime BP in hypertensive individuals with OSA.[353–355]

In addition to weight loss, improvements in the quality of sleep in OSA patients can occur as a result of a variety of positioning measures during sleep, particularly sleeping on one's side. Treatment with CPAP can be useful in overall BP lowering and may also improve cardiac ischemia[356,357] and HF symptoms.[331,332] The role of oral prostheses and surgical approaches remains to be fully defined.[354] No specific class of antihypertensive drugs has yet been demonstrated to be superior for BP lowering in OSA patients.[354]

Hypertension and the Eye

Hypertension can affect the retina, choroid, and optic nerve of the eye, particularly with stage 2 hypertension. These changes can be appreciated with inspection of the retinal vessels by direct ophthalmoscopy, photography, or angiography. Hypertensive retinopathy is most commonly manifested by generalized or focal narrowing of retinal arterioles. In acute or advanced hypertension, the retinal vasculature may be injured sufficiently to cause occlusion or leakage. These changes may be manifested as nerve fiber layer infarcts ("soft" exudates or cotton-wool patches), extravascular edema ("hard" exudates), intraretinal hemorrhages, and retinal arterial macroaneurysms.

Hypertensive choroidopathy is most frequently seen in young patients with acute hypertension, including cases of eclampsia or pheochromocytoma. Findings include Elschnig spots (nonperfused areas of the choriocapillaris) and Siegrist streaks (linear hyperpigmentation over choroidal arteries). Hypertensive optic neuropathy occurring with severe hypertension may present with flame hemorrhages, optic disc edema, venous congestion, and macular exudates.[358–360]

Renal Transplantation

Hypertension is a relatively common occurrence in patients receiving organ transplants; in those receiving kidney allografts, the prevalence of hypertension probably exceeds 65 percent.[361] Nocturnal hypertension, a reversal of diurnal BP rhythm, may be present in these individuals, who may need ABPM to evaluate overall BP control.

Hypertension is less common in other forms of transplantation. The mechanisms of hypertension in transplant patients are multifactorial, but vasoconstriction and long-term vascular structural changes caused by chronic immunosuppressive drugs, which are calcineurin inhibitors (cyclosporin and tacrolimus) and corticosteroids, are among the most important.[362] Impaired renal function is another exacerbating factor; despite successful renal transplantation, most patients have enough impairment in renal function to cause relative salt and water retention. Transplant renal artery stenosis may also be a factor.

Observational studies suggest that hypertension correlates with deterioration in graft function. Large-scale, controlled, clinical trials on the effects of BP control on decline in GFR or on CVD incidence are lacking in this population. The high risk of graft occlusion and cardiovascular events has suggested that BP should be lowered to 130/80 mmHg or less. Because of the absence of compelling data, no particular class of antihypertensives can be considered superior to any other. The difficulty of lowering BP in this group makes combination drugs necessary in almost all patients. As with other renal diseases, serum creatinine and potassium should be monitored 1–2 weeks following initiation or escalation in therapy with ACEIs or ARBs. A >1 mg/dL increase in serum creatinine should raise the question of renal artery stenosis.

Patients With Renovascular Disease

Hemodynamically significant renal artery stenosis may be associated with all stages of hypertension, but it is more commonly recognized in patients with stage 2 or resistant hypertension, since these are the individuals in whom special evaluation for the problem is carried out. If present bilaterally, renal artery stenosis can lead to reduced kidney function (ischemic nephropathy).[363]

Clinical clues to renovascular disease include (1) onset of hypertension before age 30 (especially without a family history) or recent onset of significant hypertension after age 55; (2) an abdominal bruit, particularly if it continues into diastole and is lateralized; (3) accelerated or resistant hypertension; (4) recurrent (flash) pulmonary edema; (5) renal failure of uncertain etiology, especially with a normal urinary sediment; (6) coexisting diffuse atherosclerotic vascular disease, especially in heavy smokers; or (7) acute renal failure precipitated by antihypertensive therapy, particularly ACEIs or ARBs.[78,79,81]

In patients with indications of renovascular disease, captopril-enhanced radionuclide renal scan, duplex Doppler flow studies, and magnetic resonance angiography may be used as noninvasive screening tests. Three-dimensional images can be obtained by spiral computed tomography, a technique that necessitates the use of intravenous contrast.[81] Definitive diagnosis of renovascular disease requires renal angiography, which carries some risk, particularly of radiocontrast-induced acute renal failure or atheroembolism.[364]

In patients, usually women, with fibromuscular dysplasia, results of percutaneous transluminal renal angioplasty (PTRA) have been excellent and comparable to surgical revascularization.[365] Patients with normal renal function and atherosclerotic renal artery stenosis that is focal, unilateral, and nonostial also may be managed by angioplasty.[365] Renal artery stenting has become an important adjunct to PTRA, being used to counteract elastic recoil and to abolish the residual stenosis often observed after PTRA.[366]

Even though many patients with high-grade renal artery stenosis remain stable for prolonged periods if BP is well controlled,[367] surgical revascularization or PTRA with renal artery stenting may be needed to preserve renal function.[81]

Drugs and Other Agents Affecting Blood Pressure

Many prescription drugs and some over-the-counter agents and herbal supplements may affect BP and complicate BP control in treated hypertensive individuals. Consequently, searching for the presence of these agents in a person's medical history can identify a "secondary" component contributing to BP elevation. Such recognition may negate the need to employ unnecessary and potentially hazardous testing.

Use of agents that can affect BP in a given patient should be suspected in the following situations: (1) loss of control of previously well-controlled hypertension; (2) presence of comorbidities (particularly osteoarthritis); (3) biochemical evidence of intercurrent drug usage (such as an increase in serum potassium or creatinine concentrations with nonsteroidal anti-inflammatory drugs); and (4) atypical hypertension (such as severe but transient hypertension in a young patient presenting with chest pain and ECG changes accompanying possible cocaine usage).

Table 24 provides a list of agents that may alter BP. They may affect BP in several ways, such as affecting sodium balance; increasing adrenergic or suppressing parasympathetic neural activity; altering the production, release, or effectiveness of vasoactive hormones; or exerting direct effects on the endothelium or vascular smooth muscle.

Table 24. Common substances associated with hypertension in humans

Prescription Drugs	Street Drugs and Other "Natural Products"
Cortisone and other steroids (both cortico- and mineralo-), ACTH	**Cocaine and cocaine *withdrawal***
Estrogens (usually just oral contraceptive agents with high estrogenic activity)	**Ma Huang, "herbal ecstasy," and other phenyl propanolamine analogues**
Nonsteroidal anti-inflammatory drugs	**Nicotine and *withdrawal***
Phenylpropanolamines and analogues	Anabolic steroids
Cyclosporine and Tacrolimus	Narcotic *withdrawal*
Erythropoietin	Methylphenidate
Sibutramine	Phencyclidine
Ketamine	Ketamine
Desflurane	Ergotamine and other ergot-containing herbal preparations
Carbamazepine	St. John's Wort
Bromocryptine	**Food Substances**
Metoclopramide	**Sodium chloride**
Antidepressants (especially venlafaxine)	**Ethanol**
Buspirone	Licorice
Clonidine, BB combination	Tyramine-containing foods (with MAO-I)
Pheochromocytoma: BB without alpha blocker first; glucagon	**Chemical Elements and Other Industrial Chemicals**
Clozapine	Lead
	Mercury
	Thallium and other heavy metals
	Lithium salts, especially the chloride

ACTH, adrenocorticotropic hormone; BB, beta blocker

Note: Bold-faced items within the list represent the substances of more current clinical importance.

Alcohol

Modest consumption of alcohol (e.g., <30 grams of ethanol a day or approximately two "drinks" daily) is not generally associated with BP increases. Larger amounts of alcohol ingestion have a dose-related effect on BP, both in hypertensive and normotensive subjects.[10] The use of ABPM has highlighted the biphasic effects of alcohol on BP, underscoring the importance of the timing of BP measurement. A large intake of alcohol (>30 grams) may lower BP in the first 4 hours after ingestion. Approximately 10–15 hours later (perhaps at the time a patient is seen for an office visit or in the ER during withdrawal), BP increase may be noted. This accounts for some of the discrepancies reported in the literature about alcohol's effect on BP. The mechanism(s) of alcohol's effect on BP are unclear but appear predominantly to result from sympathetic neural activation, although changes in cortisol and cellular calcium concentrations also may play a role.

Nonaspirin Nonsteroidal Anti-Inflammatory Drugs

Nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) represent one of the most common medication classes consumed by hypertensive patients. Among the NANSAIDs, older agents like Indomethacin are the most extensively studied. BP responses vary within the class of the NANSAIDs; however, increases in pressure are often accompanied by peripheral edema and weight gain, supporting a salt-retention mechanism of hypertension associated with the loss of natriuretic prostaglandins such as PGE2.[368,369] Reduction in the well-described vasodilatory effects of some prostaglandins are another mechanism. Cyclooxygenase-2 (COX-2) inhibitors also may cause elevation in BP.[370–372] Recently, a double-blind randomized trial was conducted evaluating the effects of celecoxib, rofecoxib, and naproxen on 24-hour BP in type 2 diabetic patients with osteoarthritis whose hypertension was treated with ACEIs or ARBs. At equally efficacious doses for the management of osteoarthritis, treatment with rofecoxib (but not celecoxib or naproxen) induced a significant increase in average 24-hour SBP in type 2 diabetic patients receiving ACEIs or angiotensin-II receptor blockers.[373] Thus, current data suggest that certain NSAIDs and COX-2 inhibitors may have destabilizing effects on BP control in diabetic hypertensive patients. This is a major concern because diabetic patients are often older and obese, and both obesity and aging predispose to osteoarthritis as well as diabetes.

Issues Dealing With Adherence to Regimens

Behavioral models suggest that the most effective therapy prescribed by the most careful clinician will control hypertension only if the patient is motivated to take the medication as directed and to establish and maintain a health-promoting lifestyle. Motivation improves when patients have positive experiences with, and trust in, their clinicians. Better communication improves outcomes; empathy builds trust and is a potent motivator (table 25).[374]

Table 25. Provide empathetic reinforcement

- Adopt an attitude of concern coupled with hope and interest in the patient's future.
- Provide positive feedback for blood pressure and behavioral improvement.
- If blood pressure is not at goal, ask about behaviors to achieve blood pressure control.
- Hold exit interviews to clarify regimen. A patient may tell you that they understand but tell the exit interviewer that they do not.
- Schedule more frequent appointments and health care personnel contact with patients who are not achieving goal blood pressure.

What Can the Clinician Do?

Clinician-patient partnerships that are based on trust, respect, and a holistic knowledge of the patient correlate with positive outcomes of care, such as adherence, satisfaction, and improved health status. Patients often evaluate a clinician's competence by their customer service skills, not their clinical skills.[375] Customer service includes ease of access, minimal waiting time, and a positive regard from the office staff; all are known to influence provider satisfaction and patient adherence. Clinicians are the role model and should train staff by providing a positive, interactive, empathetic environment. This will increase patients' comfort and willingness to participate in their own care.

Clinical Inertia

There is a broad range of clinician commitment to optimal hypertension therapy (table 26). Failure to titrate or combine medications and to reinforce lifestyle modifications, despite knowing that the patient is not at goal BP, represents clinical inertia which must be overcome. This may be due in part to clinician focus on relieving symptoms, a lack of familiarity with clinical guidelines, or discomfort in titrating to a goal.[376]

Table 26. Clinician awareness and monitoring

- Anticipate adherence problems for young men.
- Consider nonadherence as a cause of:
  - Failure to reach goal blood pressure
  - Resistant hypertension
  - Sudden loss of control.
- Encourage patients to bring in all medications from all physicians and other sources, whether prescription, complementary, or over-the-counter, to each visit for review and to rule out iatrogenic causes of elevated blood pressure.
- Ask what the patient takes for pain.
- Recognize depression and other psychiatric illnesses, including panic attacks, and manage appropriately.
- Be willing to change unsuccessful regimens and search for those more likely to succeed.

A number of approaches are available to overcome clinical inertia. One of the most effective is to use decision support systems that prompt the clinician to advance therapy when a goal has not been achieved (table 27). Such systems can be electronic (computer- or personal digital assistant-based) or paper-based (flow charts, algorithms, guidelines). Feedback reminders from any source (computer-based, automated telephone-based, nurse care managers, outside auditors) can be very effective in not only helping to achieve BP goals but to alert clinicians to missed patient appointments, necessary prescription refills, and laboratory abnormalities.[377]

Table 27. Organize care delivery systems

- Schedule next appointment before patient leaves office.
- Use appointment reminders, preferably computer-based, and contact patients to confirm appointments.
- Follow up with patients who missed appointments.
- Use an office-based system approach for monitoring and followup (e.g., educate staff to provide patient encouragement, computer or chart reminders, disease management aids).

Patient-centered behavioral interventions, such as counseling, improve BP control (table 28).[378] Nurse clinicians and pharmacists have proven their effectiveness in helping to achieve goal BP.[379] Commercial health plans may provide resources for chart auditing or other assistance to improve BP control.[380] Clinicians should periodically audit their own patient files to assess their degree of compliance and success with established goals and treatment interventions.

Table 28. Patient education about treatment

- Assess the patient's understanding and acceptance of the diagnosis of hypertension.
- Discuss patient's concerns, and clarify misunderstandings.
- Tell the patient the blood pressure reading, and provide a written copy.
- Come to agreement with the patient on goal blood pressure.
- Ask the patient to rate from 1 to 10 his or her chance of staying on treatment.
- Inform the patient about recommended treatment, and provide specific written information about the role of lifestyle including diet, physical activity, dietary supplements, and alcohol intake; use standard brochures when available.
- Elicit concerns and questions, and provide opportunities for the patient to state specific behaviors to carry out treatment recommendations.
- Emphasize:
  - Need to continue treatment
  - Control does not mean cure
  - One cannot tell if blood pressure is elevated by "feeling or symptoms"; blood pressure must be measured.

The National Committee for Quality Assurance (NCQA) has established the Health Plan Employer Data and Information Set (HEDIS), a set of standardized performance measures designed to ensure that purchasers and consumers have the information they need to reliably assess quality of health care (http://www.ncqa.org/Programs/HEDIS). Enforcement of HEDIS guidelines by managed care organizations has successfully increased the appropriate use of ACEIs in HF and of BBs in patients who have suffered an MI. NCQA now monitors physician records for the percent of patients whose BP is <140/90 mmHg.[381] BP control rates by monitored physicians have increased to as high as 59 percent. Patients should be told their BP on each visit and encouraged not only to ask for those numbers but to also inquire as to why BP is above the goal, if that is the case. They also should be given a written record to keep as their part of this commitment.

Role of Other Health Care Professionals

Clinicians must work with other health care professionals (e.g., nurse case managers and other nurses, physician assistants, pharmacists, dentists, registered dietitians, licensed nutritionists, nutrition educators, optometrists, and podiatrists) to influence or reinforce instructions to improve patient lifestyles and BP control (table 29). Nurse-managed hypertension clinics, worksite occupational health departments, managed care organizations, pharmacists, and lay community workers have all contributed to better hypertension control. Public health nurses and community outreach workers in high-risk communities are also helpful through their efforts to screen, identify cases, refer and track followup appointments, and educate patients. All health care professionals must be committed to enhancing BP control through reinforcing messages about the risks of hypertension, the importance of managing both SBP and DBP and achieving goal BP, education about effective lifestyle interventions, pharmacologic therapies, and adherence to treatment.

Table 29. Collaborate with other health professionals

- Use complementary skills and knowledge of nurses, physician assistants, pharmacists, registered dietitians, optometrists, dentists, and podiatrists.
- Refer selected patients for more intensive counseling.

Patient Factors

Patient attitudes are greatly influenced by cultural differences, beliefs, and previous experiences with the health system.[382] These attitudes must be understood and respected if the clinician is to build trust and increase communication with patients and families (table 30). Clinicians should explain to patients that the terms "hypertension" and "high BP" are used interchangeably and that neither indicates an anxiety state. In addition to motivation, patients need specific education designed to help them modify their lifestyle and to take medications as prescribed to feel better and to reduce risks.

Table 30. Individualize the regimen

- Include patient in decision making.
- Simplify the regimen to once-daily dosing, if possible.
- Incorporate treatment into patient's daily lifestyle; e.g., take medications just before or after brushing teeth.
- Agree with the patient on realistic short-term objectives for specific components of the medication and lifestyle modification plan.
- Encourage discussion of diet and physical activity.
- Encourage discussion of adverse drug effects and concerns.
- Encourage self-monitoring with validated blood pressure devices.
- Minimize the cost of therapy; recognize financial issues and enlist local community and national programs to assist in affording medications.
- Indicate that adherence to the regimen will be a subject of discussion at each visit.
- Encourage gradual sustained weight loss.

Characterization of Patients Leading to Tailored Therapy

There is a broad range of patient involvement in, and commitment to, hypertension therapy. Management strategies need to be focused on the patient's goals when providing advice and encouraging adherence. Optimal management strategies are likely to differ for patient types. Healthy lifestyles influence adherence to medication as well as a patient's beliefs and involvement with behaviors including food, beverages, physical activity, healthy weight, salt and alcohol consumption, and smoking. A cluster analysis of 727 hypertensive patients found that the individuals fell into 4 categories.[383] The largest group (39 percent) was health-oriented, informed about hypertension, and took their medication. The second group (16 percent) tended to rely on medication rather than lifestyle to control their BP. The third group (22 percent) had the highest BMI, did not practice health-promoting lifestyles (except for low rates of alcohol consumption and tobacco abuse), often forgot to take their medication, and had a lower BP control rate. These patients may benefit most from clinical counseling and help with achieving lifestyle modifications; they will likely require more frequent office visits or contact with nurses or other providers. The patients in the last group (23 percent) were more likely to be male and young, knew less about hypertension, were least afraid of the consequences of hypertension or failure to take their medication, and were most likely to consume alcohol, abuse tobacco, and stop medication without informing their physician. This last group will probably require persistent reinforcement, information on the hazards related to lack of BP control, and small incremental goal setting by allied health care personnel. Involvement of family members or other social supports also may be useful (table 31).

Table 31. Promote social support systems

- With full permission of the patient, involve caring family members or other social support (e.g., faith-based or community organizations) in the treatment process.
- Suggest common interest group activities (e.g., a walking group) to enhance mutual support and motivation.

Goal Setting and Behavioral Change

The clinician and patient must agree upon BP goals and an estimated achievement time, and those goals should be clearly recorded in the chart. With the support of the clinician, the patient must be empowered with the understanding that making behavioral changes is ultimately his or her responsibility. As people make behavioral changes, they progress through a series of stages (precontemplation, contemplation, preparation, action, and maintenance). Behavioral changes are more successfully facilitated using this approach, along with motivational interviewing, rather than assigning the same intervention to every patient.[384,385]

Patients can be asked to use a 1–10 ranking to indicate how likely they are to follow the plan. If not likely, the clinician can use motivational interviewing to identify the barriers to adherence. At visits where BP is above goal, alterations in the treatment plan should be made and documented accordingly. Home BP devices can be very useful in involving many patients in their own care. Clinicians must calibrate these devices (see Self-Measurement). This should be done, in part, by having the patient determine their BP with the device in the presence of the clinician. Home-determined BP tends to be approximately 5 mmHg lower than office BP, and this information should be considered when assessing progress toward the goal. However, office BP should still be used to determine whether a patient is at goal.

Patient satisfaction with health care providers predicts compliance with treatment. All clinicians need to provide positive, patient-centered care to satisfy and enable their patients to follow treatment. Some patient-centered behavioral interventions, like counseling, have been shown to improve BP control, while the evidence for structured training or self-monitoring is less clear.

Economic Barriers

The cost of medications may be a barrier to effective treatment. Patients often perceive that lifestyle modifications such as following the DASH eating plan are expensive, but following these plans can be accomplished even on modest budgets. Nutrition educators offer classes in schools, communities, and worksites on food budgeting and meal planning. Clinicians should refer their patients to these classes. Medical nutrition therapy by registered dietitians improves the health of patients who have high cholesterol, diabetes, obesity, or other chronic disease risk factors.[386] Patients should be advised that most lifestyle modifications may be cost-free or may even save money (e.g., smoking cessation and reduction of alcohol consumption). Further, the beneficial effects of lifestyle modification may include reduction in the amount and cost of prescribed medications and the cost of insurance. A patient adhering to the DASH eating plan may require less medication and save money. Patients need to understand the important difference between the price of a medication and the cost of nonadherence. The price of medication is the amount of money needed for purchase, and the cost is the outcome or consequences of not adhering to this treatment advice, which may include impaired quality of life, CVD, kidney failure, stroke, and even premature death. The identification of persons who can assist the patient with insurance concerns and social services may be important to overall adherence. Most pharmaceutical companies have special needs programs that are often handled through their marketing departments.

Additional Sources of Information

Additional information is available at the NHLBI Web site http://www.nhlbi.nih.gov/.

Scheme Used for Classification of the Evidence

M Meta-analysis; use of statistical methods to combine the results from clinical trials

RA Randomized controlled trials; also known as experimental studies

RE Retrospective analyses; also known as case-control studies

F Prospective studies; also known as cohort studies, including historical or prospective followup studies

X Cross-sectional surveys; also known as prevalence studies

PR Previous review or position statements

C Clinical interventions (nonrandomized)

These symbols are appended to the citations in the reference list. The studies that provided evidence supporting the recommendations of this report were classified and reviewed by the staff and the Executive Committee. The classification scheme is from the JNC 6 report and other NHBPEP Working Group Reports.[3,4,6,9]

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For More Information

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National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

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Reference Card From the

Seven Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

EVALUATION

Classification of Blood Pressure (BP)*

Category	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

* See *Blood Pressure Measurement Techniques* (reverse side)

Key: SBP = systolic blood pressure DBP = diastolic blood pressure

Diagnostic Workup of Hypertension

- Assess risk factors and comorbidities.
- Reveal identifiable causes of hypertension.
- Assess presence of target organ damage.
- Conduct history and physical examination.
- Obtain laboratory tests: urinalysis, blood glucose, hematocrit and lipid panel, serum potassium, creatinine, and calcium. Optional: urinary albumin/creatinine ratio.
- Obtain electrocardiogram.

Assess for Major Cardiovascular Disease (CVD) Risk Factors

- Hypertension
- Obesity (body mass index ≥30 kg/m^2)
- Dyslipidemia
- Diabetes mellitus
- Cigarette smoking
- Physical inactivity
- Microalbuminuria, estimated glomerular filtration rate <60 mL/min
- Age (>55 for men, >65 for women)
- Family history of premature CVD (men age <55, women age <65)

Assess for Identifiable Causes of Hypertension

- Sleep apnea
- Drug induced/related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Cushing's syndrome or steroid therapy
- Pheochromocytoma
- Coarctation of aorta
- Thyroid/parathyroid disease

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TREATMENT

Principles of Hypertension Treatment

- Treat to BP <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or chronic kidney disease.
- Majority of patients will require two medications to reach goal.

Algorithm for Treatment of Hypertension

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for patients with diabetes or chronic kidney disease)
See *Strategies for Improving Adherence to Therapy*

Initial Drug Choices

Without Compelling Indications

Stage 1 Hypertension
(SBP 140–159 or DBP 90–99 mmHg)

Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension
(SBP ≥160 or DBP ≥100 mmHg)

2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB).

With Compelling Indications

Drug(s) for the compelling indications
See *Compelling Indications for Individual Drug Classes*

Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

Not at Goal Blood Pressure

Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.

See *Strategies for Improving Adherence to Therapy*

Blood Pressure Measurement Techniques

Method	Notes
In-office	Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.
Ambulatory BP monitoring	Indicated for evaluation of "white coat hypertension." Absence of 10–20 percent BP decrease during sleep may indicate increased CVD risk.
Patient self-check	Provides information on response to therapy. May help improve adherence to therapy and is useful for evaluating "white coat hypertension."

Causes of Resistant Hypertension

- Improper BP measurement
- Excess sodium intake
- Inadequate diuretic therapy
- Medication
  - Inadequate doses
  - Drug actions and interactions (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), illicit drugs, sympathomimetics, oral contraceptives)
  - Over-the-counter (OTC) drugs and herbal supplements
- Excess alcohol intake
- Identifiable causes of hypertension (see reverse side)

Compelling Indications for Individual Drug Classes

Compelling Indication	Initial Therapy Options
• Heart failure	THIAZ, BB, ACEI, ARB, ALDO ANT
• Post myocardial infarction	BB, ACEI, ALDO ANT
• High CVD risk	THIAZ, BB, ACEI, CCB
• Diabetes	THIAZ, BB, ACEI, ARB, CCB
• Chronic kidney disease	ACEI, ARB
• Recurrent stroke prevention	THIAZ, ACEI

Key: THIAZ = thiazide diuretic, ACEI= angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = beta blocker, CCB = calcium channel blocker, ALDO ANT = aldosterone antagonist

Strategies for Improving Adherence to Therapy

- Clinician empathy increases patient trust, motivation, and adherence to therapy.
- Physicians should consider their patients' cultural beliefs and individual attitudes in formulating therapy.

The National High Blood Pressure Education Program is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health. Copies of the JNC 7 Report are available on the NHLBI Web site at **http://www.nhlbi.nih.gov** or from the NHLBI Health Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; Phone: 301-592-8573 or 240-629-3255 (TTY); Fax: 301-592-8563.

Principles of Lifestyle Modification

- Encourage healthy lifestyles for all individuals.
- Prescribe lifestyle modifications for all patients with prehypertension and hypertension.
- Components of lifestyle modifications include weight reduction, DASH eating plan, dietary sodium reduction, aerobic physical activity, and moderation of alcohol consumption.

Lifestyle Modification Recommendations

Modification	Recommendation	Avg. SBP Reduction Range†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2).	5–20 mmHg/10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and lowfat dairy products with reduced content of saturated and total fat.	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to ≤100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week.	4–9 mmHg
Moderation of alcohol consumption	Men: limit to ≤2 drinks* per day. Women and lighter weight persons: limit to ≤1 drink* per day.	2–4 mmHg

* 1 drink = 1/2 oz or 15 mL ethanol (e.g., 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey).

† Effects are dose and time dependent.

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National High Blood Pressure Education Program

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Table 14. Secondary Prevention for Patients With Coronary and Other Vascular Disease

2004 STEMI Guideline Recommendations	2007 STEMI Focused Update Recommendations	2007 COR and LOE	Comments
	Smoking		
	2007 Goal: Complete cessation, no exposure to environmental tobacco smoke		
Assess tobacco use.	1. Status of tobacco use should be asked about at every visit.	*I (B)*	Modified recommendation (changed text)
Strongly encourage patient and family to stop smoking and to avoid secondhand smoke.	2. Every tobacco user and family members who smoke should be advised to quit at every visit.	*I (B)*	Modified recommendation (changed text)
	3. The tobacco user's willingness to quit should be assessed.	*I (B)*	New recommendation
Provide counseling, pharmacological therapy (including nicotine replacement and bupropion), and formal smoking cessation programs as appropriate. (See Section 7.12.4 in the 2004 STEMI Guideline for further discussion.)	4. The tobacco user should be assisted by counseling and developing a plan for quitting.	*I (B)*	Modified recommendation (changed text)
	5. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and pharmacological treatment) should be arranged.	*I (B)*	Modified recommendation (changed text)
	6. Exposure to environmental tobacco smoke at work and home should be avoided.	*I (B)*	New recommendation
	Blood Pressure Control:		
	2007 Goal: Less than 140/90 mm Hg or less than 130/80 if patient has diabetes or chronic kidney disease		
If blood pressure is 120/80 mm Hg or greater, initiate lifestyle modification (weight control, physical activity, alcohol moderation, moderate sodium restriction, and emphasis on fruits, vegetables, and low-fat dairy products) in all patients.	1. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is recommended to initiate or maintain lifestyle modification—weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.	*I (B)*	Modified recommendation (changed text)
If blood pressure is 140/90 mm Hg or greater, or 130/80 mm Hg or greater for individuals with chronic kidney disease or diabetes, add blood pressure–reducing medications,* emphasizing the use of beta blockers and inhibitors of the renin-angiotensin-aldosterone system. (See Sections 7.12.6, 7.12.7, and 7.12.8 in 2004 STEMI Guideline.)[15]	2. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for patients with diabetes or chronic kidney disease), it is useful as tolerated, to add blood pressure medication, treating initially with beta blockers and/or ACE inhibitors, with the addition of other drugs such as thiazides as needed to achieve goal blood pressure.	*I (A)*	Modified recommendation (changed text)
	Lipid Management		
	2007 Goal: LDL-C substantially less than 100 mg per dL (If triglycerides are greater than or equal to 200 mg per dL, non–HDL-C should be less than 130 mg per dL†.)		
Start dietary therapy in all patients (less than 7% of total calories as saturated fat and less than 200 mg/d cholesterol).	1. Starting dietary therapy is recommended for all patients. Reduce intake of saturated fats (to less than 7% of total calories), trans fatty acids, and cholesterol (to less than 200 mg per day).	*I (B)*	Modified recommendation (changed text)
	2. Adding plant stanol/sterols (2 g per day) and/or viscous fiber (greater than 10 g per day) is reasonable to further lower LDL-C.	*IIa (A)*	New recommendation
Promote physical activity and weight management.	3. Promotion of daily physical activity and weight management is recommended.	*I (B)*	Modified recommendation (changed text)
Encourage increased consumption of omega-3 fatty acids.	4. It may be reasonable to encourage increased consumption of omega-3 fatty acids in the form of fish‡ or in capsules (1 g per day) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction.	*IIb (B)*	Modified recommendation (changed text)
Assess fasting lipid profile in all patients, preferably within 24 h of STEMI. Add drug therapy according to the following guide. (See Section 7.12.2 in the STEMI 2004 Guideline.)	5. A fasting lipid profile should be assessed in all patients and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiation of lipid-lowering medication is indicated as recommended below before discharge according to the following schedule:	*I (A)*	Modified recommendation (changed text)
LDL-C less than 100 mg/dL (baseline or on treatment), statins should be used to lower LDL-C.	• LDL-C should be less than 100 mg per dL.	*I (A)*	Modified recommendation (changed text)
	• Further reduction of LDL-C to less than 70 mg per dL is reasonable.	*IIa (A)*	New recommendation

Table 14. Continued

2004 STEMI Recommendations	2007 STEMI Recommendations	2007 COR and LOE	Comments
LDL-C greater than or equal to 100 mg/dL (baseline or on treatment), intensify LDL-C-lowering therapy with drug treatment, giving preference to statins.	• If baseline LDL-C is greater than or equal to 100 mg per dL, LDL-lowering drug therapy§ should be initiated.	*I (A)*	Modified recommendation (changed text)
	• If on-treatment LDL-C is greater than or equal to 100 mg per dL, intensifying LDL-lowering drug therapy (may require LDL-lowering drug combination‖) is recommended.	*I (A)*	Modified recommendation (changed text)
	• If baseline LDL-C is 70 to 100 mg per dL, it is reasonable to treat to LDL-C less than 70 mg per dL.	*IIa (B)*	New recommendation
If triglycerides are greater than or equal to 150 mg/dL or HDL-C is less than 40 mg/dL, emphasize weight management and physical activity. Advise smoking cessation.	• If triglycerides are greater than or equal to 150 mg per dL or HDL-C is less than 40 mg per dL, weight management, physical activity, and smoking cessation should be emphasized.	*I (B)*	Modified recommendation (changed text)
If triglycerides are 200 to 499 mg/dL after LDL-C–lowering therapy¶, consider adding fibrate or niacin.**	• If triglycerides are 200 to 499 mg per dL,†† non–HDL-C target should be less than 130 mg per dL.	*I (B)*	Modified recommendation (changed text)
	• If triglycerides are 200 to 499 mg per dL,†† further reduction of non–HDL-C to less than 100 mg per dL is reasonable.	*IIa (B)*	New recommendation
	6. Therapeutic options to reduce non–HDL-C include:		
	• More intense LDL-C–lowering therapy is indicated.	*I (B)*	New recommendation
	• Niacin** (after LDL-C–lowering therapy) can be beneficial.	*IIa (B)*	Modified recommendation (changed text)
	• Fibrate therapy‡‡ (after LDL-C–lowering therapy) can be beneficial.	*IIa (B)*	Modified recommendation (changed text)
If triglycerides are greater than or equal to 500 mg/dL:**‡‡ Consider fibrate or niacin‡‡ before LDL-C–lowering therapy.‖**‡‡ Consider omega-3 fatty acids as adjunct for high triglycerides. (See Section 7.12.2 in the 2004 STEMI Guideline.)	7. If triglycerides are greater than or equal to 500 mg per dL,††§§ therapeutic options indicated and useful to prevent pancreatitis are fibrate‡‡ or niacin** before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieving non–HDL-C less than 130 mg per dL is recommended.	*I (C)*	Modified recommendation (changed text)
	Physical Activity Goal: 30 minutes, 7 days per week (minimum 5 days per week)		
Cardiac rehabilitation programs are recommended for patients with STEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is warranted. (See Sections 7.12.12 and 8.2 in the 2004 STEMI Guideline.)	1. Advising medically supervised programs (cardiac rehabilitation) for high-risk patients (e.g., recent acute coronary syndrome or revascularization, HF) is recommended.	*I (B)*	Modified recommendation (changed text)
Assess risk, preferably with exercise test, to guide prescription.	2. For all patients, it is recommended that risk be assessed with a physical activity history and/or an exercise test to guide prescription.	*I (B)*	Modified recommendation (changed text)
Encourage minimum of 30 to 60 min of activity, preferably daily but at least 3 or 4 times weekly (walking, jogging, cycling, or other aerobic activity) supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work).	3. For all patients, encouraging 30 to 60 minutes of moderate-intensity aerobic activity is recommended, such as brisk walking on most—preferably all—days of the week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work).	*I (B)*	Modified recommendation (changed text)
	4. Encouraging resistance training 2 days per week may be reasonable.	*IIb (C)*	New recommendation
	Weight Management Goal: BMI: 18.5 to 24.9 kg/m^2 Waist circumference: Men less than 40 inches (102 cm), women less than 35 inches (89 cm)		
Calculate BMI and measure waist circumference as part of evaluation. Monitor response of BMI and waist circumference to therapy.	1. It is useful to assess BMI and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2.	*I (B)*	Modified recommendation (changed text)

Table 14. Continued

2004 STEMI Recommendations	2007 STEMI Recommendations	2007 COR and LOE	Comments
Start weight management and physical activity as appropriate. Desirable BMI range is 18.5 to 24.9 kg/m^2.	2. The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment.	*I (B)*	Modified recommendation (changed text)
If waist circumference is greater than or equal to 35 inches in women or greater than or equal to 40 inches in men, initiate lifestyle changes and treatment strategies for metabolic syndrome. (See Section 7.12.3 of STEMI 2004 Guideline.)	3. If waist circumference (measured horizontally at the iliac crest) is 35 inches (89 cm) or greater in women and 40 inches (102 cm) or greater in men, it is useful to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated.	*I (B)*	Modified recommendation (changed text)
	Diabetes Management Goal: HbA_{1c} less than 7%		
Appropriate hypoglycemic therapy to achieve near-normal fasting plasma glucose, as indicated by HbA_{1c}.	1. It is recommended to initiate lifestyle and pharmacotherapy to achieve near-normal HbA_{1c}.	*I (B)*	Modified recommendation (changed text)
Treatment of other risk factors (e.g., physical activity, weight management, blood pressure, and cholesterol management). (See Section 7.12.9 in the 2004 STEMI Guideline.)	2. Beginning vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management as recommended above) is beneficial.	*I (B)*	Modified recommendation (changed text)
	3. Coordination of diabetic care with the patient's primary care physician or endocrinologist is beneficial.	*I (C)*	New recommendation
	Antiplatelet Agents/Anticoagulants: Aspirin		
Start and continue indefinitely aspirin 75 to 162 mg/d if not contraindicated.	**1. For all post-PCI STEMI stented patients without aspirin resistance, allergy, or increased risk of bleeding, aspirin 162 mg to 325 mg daily should be given for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long-term aspirin use should be continued indefinitely at a dose of 75 mg to 162 mg daily.**	***I (B)***	Modified recommendation (changed text)
	2. In patients for whom the physician is concerned about risk of bleeding lower-dose 75 mg to 162 mg of aspirin is reasonable during the initial period after stent implantation.	***IIa (C)***	New recommendation
	Antiplatelet Agents/Anticoagulants: Clopidogrel		
Consider clopidogrel 75 mg/d or warfarin if aspirin is contraindicated.	**1. For all post-PCI patients who receive a DES, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. For post-PCI patients receiving a BMS, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks).**	***I (B)***	Modified recommendation (changed text)
	2. For all STEMI patients not undergoing stenting (medical therapy alone or PTCA without stenting), treatment with clopidogrel should continue for at least 14 days.	***I (B)***	New recommendation
	3. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy.	***IIa (C)***	New recommendation
	Antiplatelet Agents/Anticoagulants: Warfarin		
Manage warfarin to INR 2.5 to 3.5 in post-STEMI patients when clinically indicated or for those not able to take aspirin or clopidogrel. (See Sections 7.12.5 and 7.12.11 and Figure 37 in the 2004 STEMI Guideline for further details of antiplatelet and anticoagulant therapy at hospital discharge.)	1. Managing warfarin to an INR equal to 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus).	*I (A)*	Modified recommendation (changed text)
	2. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.	*I (B)*	New recommendation

Table 14. Continued

2004 STEMI Recommendations	2007 STEMI Recommendations	2007 COR and LOE	Comments
	3. In patients requiring warfarin, clopidogrel, and aspirin therapy, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75 mg dose of clopidogrel.	***I (C)***	New recommendation
	Renin-Angiotensin-Aldosterone System Blockers: ACE Inhibitors		
ACE inhibitors in all patients indefinitely; start early in stable high-risk patients (anterior MI, previous MI, Killip class greater than or equal to II [S3 gallop, rales, radiographic CHF], LVEF less than 0.40).	1. ACE inhibitors should be started and continued indefinitely in all patients recovering from STEMI with LVEF less than or equal to 40% and for those with hypertension, diabetes, or chronic kidney disease, unless contraindicated.	*I (A)*	Modified recommendation (changed text)
	2. ACE inhibitors should be started and continued indefinitely in patients recovering from STEMI who are not lower risk (lower risk defined as those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed), unless contraindicated.	*I (B)*	New recommendation
	3. Among lower risk patients recovering from STEMI (i.e., those with normal LVEF in whom cardiovascular risk factors are well controlled and revascularization has been performed) use of ACE inhibitors is reasonable.	*IIa (B)*	New recommendation
	Renin-Angiotensin-Aldosterone System Blockers: Angiotensin Receptor Blockers		
Angiotensin receptor blockers in patients who are intolerant of ACE inhibitors and with either clinical or radiological signs of heart failure or LVEF less than 0.40.	1. Use of angiotensin receptor blockers is recommended in patients who are intolerant of ACE inhibitors and have HF or have had an MI with LVEF less than or equal to 40%.	*I (A)*	Modified recommendation (changed text)
	2. It is beneficial to use angiotensin receptor blocker therapy in other patients who are ACE-inhibitor intolerant and have hypertension.	***I (B)***	New recommendation
	3. Considering use in combination with ACE inhibitors in systolic dysfunction HF may be reasonable.	*IIb (B)*	New recommendation
	Renin-Angiotensin-Aldosterone System Blockers: Aldosterone Blockade		
Aldosterone blockade in patients without significant renal dysfunction‖‖ or hyperkalemia¶¶ who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either diabetes or heart failure. (See Section 7.12.6 in the 2004 STEMI Guideline.)	1. Use of aldosterone blockade in post-MI patients without significant renal dysfunction‖‖ or hyperkalemia¶¶ is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, have an LVEF of less than or equal to 40%, and have either diabetes or HF.	*I (A)*	Modified recommendation (changed text)
	Beta Blockers		
Start in all patients. Continue indefinitely. Observe usual contraindications. (See Section 7.12.7 in the 2004 STEMI Guideline.)	1. It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or LV dysfunction with or without HF symptoms, unless contraindicated.	*I (A)*	Modified recommendation (changed text)
	Influenza Vaccination		
	1. Patients with cardiovascular disease should have an annual influenza vaccination.	*I (B)*	New recommendation

Recommendations in bold type are those the writing committee felt deserved extra emphasis. The 2007 STEMI recommendations are written in complete sentences, in accordance with ACC/AHA Guidelines methodology. "No content change" indicates the updated recommendation now includes an LOE and COR and a verb consistent with that LOE and COR as outlined in the ACC/AHA LOE/COR table (Table 1).

*For compelling indications for individual drug classes in specific vascular diseases, see the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[87a]).

†Non–HDL-C indicates total cholesterol minus HDL-C.

‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C less than 70 mg per dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C less than 70 mg per dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of greater than 50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

‖Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin.

¶Treat to a goal of non–HDL-C substantially less than 130 mg per dL.

**Dietary supplement niacin must not be used as a substitute for prescription niacin.

††The use of resin is relatively contraindicated when triglycerides are greater than 200 mg per dL.

‡‡The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination.

§§Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are greater than 200 mg per dL.

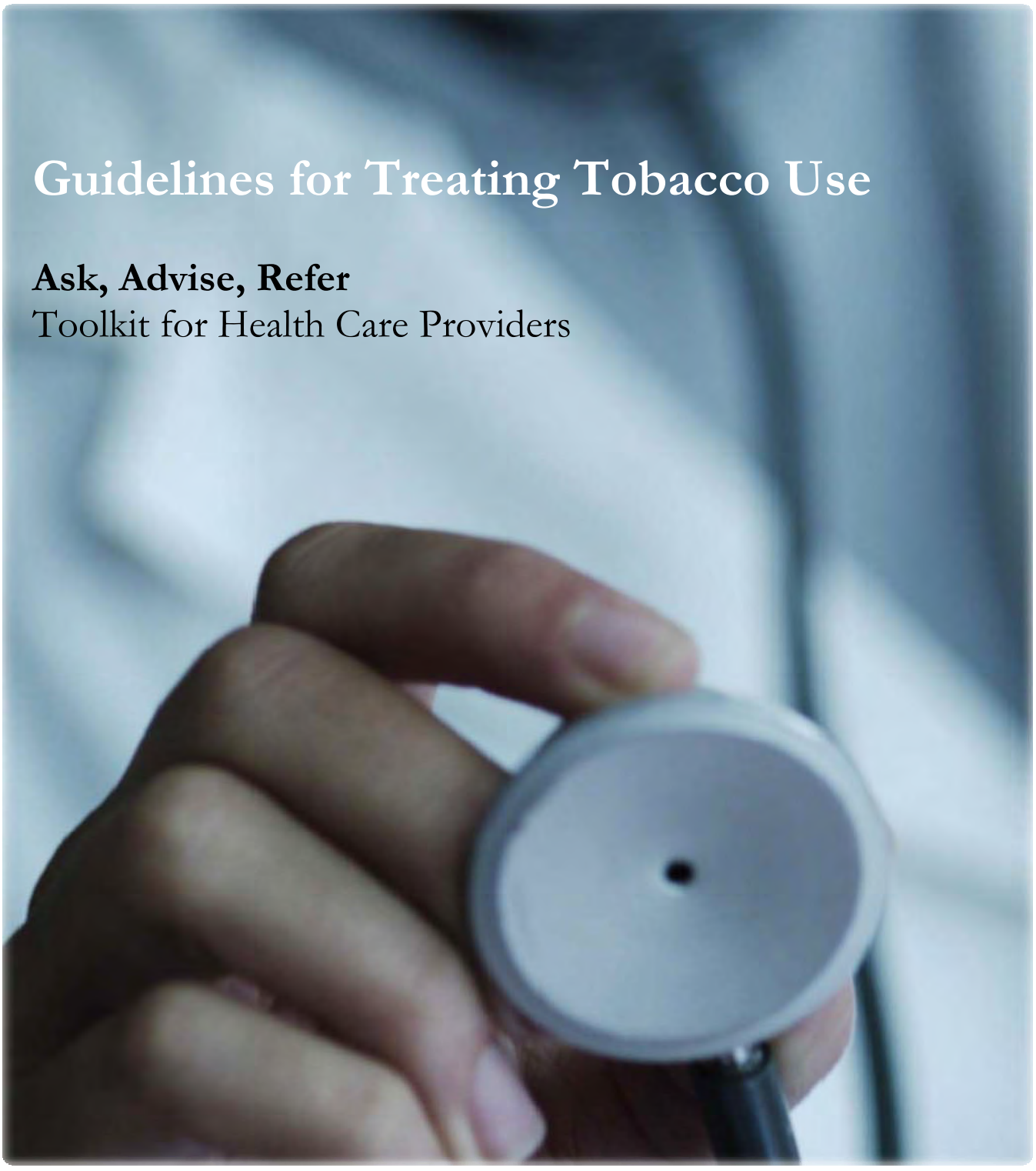
‖‖Creatinine should be less than 2.5 mg per dL in men and less than 2.0 mg per dL in women.

¶¶Potassium should be less than 5.0 mEq/L.

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CHF, congestive heart failure; COR, classification of recommendation; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-elevation myocardial infarction.

Guidelines for Treating Tobacco Use

Ask, Advise, Refer
Toolkit for Health Care Providers



County of Los Angeles Public Health
Tobacco Control & Prevention Program

L.A. Care Health Plan

Introduction

This toolkit is based on information from the U.S. Public Health Service-sponsored *Treating Tobacco Use and Dependence* Clinical Practice Guidelines. The guidelines provide evidence-based strategies and recommendations designed to assist clinicians in delivering and supporting effective treatments for tobacco use and dependence. This toolkit provides an overview for clinicians with information including:

- The Ask, Advise, Refer (AAR) Model
- Cessation resources for patients
- Pharmacotherapy guidelines
- Resources for clinicians and patients

This toolkit was developed by the Los Angeles County Tobacco Control and Prevention Program in collaboration with LA Care (2008). For questions, please contact the Los Angeles County Tobacco Control and Prevention Program at (213) 351-7890.

Acknowledgements

The Los Angeles County Department of Public Health Tobacco Control and Prevention Program would like to acknowledge the following individuals and organizations who contributed their time, experience, and information to this toolkit: Steven Schroeder, Smoking Cessation Leadership Center UCSF; Catherine Saucedo, Smoking Cessation Leadership Center UCSF; Kirsten Hansen, Center for Tobacco Cessation; Marsha Epstein, Los Angeles County Division of Chronic Disease and Injury Prevention; Linda Aragon, Los Angeles County Tobacco Control and Prevention Program; Gigi Talbott, Los Angeles County Tobacco Control and Prevention Program; Donna Sze, Los Angeles County Tobacco Control and Prevention Program.

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Table of Contents

Section 1: Why Should We Promote Smoking Cessation?

Smoking is the leading cause of preventable death in the United States, accounting for an estimated 435,000 deaths each year. In Los Angeles County, nearly 9,000 lives and $4.3 billion dollars are lost due to smoking and smoking-related diseases annually. Smokers who die of tobacco-related diseases lose an average of 14 years of life, but quitting reduces the risk of tobacco related disease and prolongs life.

Although the rate of smoking in Los Angeles County has decreased dramatically, more than 1 million residents continue to smoke. Highest rates are among those who have mental health or substance abuse problems or who are African-Americans, on Medi-Cal, without health insurance, living in poverty or lesbian, gay or bisexual. African-American children in Los Angeles County have the highest rates of exposure to tobacco smoke in their homes.

Quitting has immediate and long-term benefits. **Most smokers want to stop smoking**—and every year, more than half of them try. Only 9% or fewer are successful with each attempt because most try without counseling or medication. Studies have consistently shown that counseling, especially when combined with medication, doubles or triples the proportion of patients who successfully stop smoking, achieving long-term quit rates as high as 30% with each attempt. In fact, tobacco use interventions are more cost effective than most other routine preventive medical interventions. And smokers offered assistance in stopping smoking were more satisfied with their medical care, even if they did not want to stop.

By using the following recommended guidelines, effective tobacco use interventions can take as little as 30 seconds. Your advice to your patients to stop smoking is the most cost-effective use of time to increase the quality and length of their lives.

Section 2: Effective Intervention (Ask, Advise, Refer)

Many physicians understandably cite time, energy, and resources as major barriers in preventing them from talking to their patients about not smoking. The "Ask, Advise, and Refer" format was created to give physicians a simple, practical plan that can be implemented with all patients and it can take 30 seconds or less.

1. ASK PATIENTS ABOUT TOBACCO USE AT EVERY VISIT.

Also ask about tobacco exposure to secondhand smoke in the home.
Make tobacco-use screening a regular part of your practice. Have office systems in place (e.g. vital signs stamp or an electronic prompt). Such reminders will enable you to systematically document tobacco-use status and referrals. (see sample.)

Vital Signs:
BP: _____ PULSE: _____ RR: _____
WT: _____ HT: _____ BMI: _____

Tobacco Use:
Current_____ Former _____ Never _____

☐ **Referred for tobacco counseling/ treatment**

Smoke-free Home:
Yes____ No____

2. ADVISE TOBACCO USERS TO STOP.

Smokers say their clinician's advice is an important motivator to stop smoking. Advice must be clear, strong, and personalized, for example: **"As your physician and someone who cares about you and your health, I would encourage you to stop smoking because it is the most important thing you can do to protect your health."**

Patients for whom tobacco poses a special risk should receive tailored advice. For example,
- "Smoking is strongly linked with snoring and sleeping problems. Your sleep could improve if you stopped smoking."
- "Stopping smoking reduces your chance of a heart attack or a stroke."

3. REFER PATIENTS TO RESOURCES.

• **Provide patients with the phone number of the FREE California Smokers' Helpline: 1-800-NO-BUTTS** or local tobacco cessation resources. Let them know that counseling can double the chances of quitting and staying free of tobacco. Long-term quit rates can be as high as 20% with either consistent follow-up counseling or pharmacotherapy and rise to 30% when counseling is combined with pharmacotherapy.

The California Smokers' Helpline offers quitting materials, referrals to local resources, and up to six sessions with a trained counselor. The Helpline provides services in English, Chinese (Mandarin and Cantonese), Korean, Spanish, Vietnamese, and TDD for the hard of hearing. Services are also available for pregnant women, teens, and tobacco chewers.

• **Offer self-help materials** that include tips to help patients stop smoking. If you have time, just 3 to 5 minutes of personalized counseling by a clinician doubles quit rates. (See page 14.)

Section 3: Prescribing Pharmacotherapy

Pharmacotherapy doubles or triples the chances of successfully quitting with each attempt. It is a key part of a multi-component approach to assisting patients with their tobacco dependence. Therefore, offer and prescribe pharmacotherapy to help all tobacco users, unless contraindicated. Determine regimen-based contraindications and precautions **(Table 1)**, level of addiction **(Table 2)**, and patient preference. Use clinical judgment in providing tobacco use treatment to pregnant and adolescent smokers (see page 8). Encourage your patients to consider medications: "**Medication improves your success in becoming free of tobacco. Would you like to discuss which medication is best for you?"**

Nicotine replacement therapy (NRT) **doubles** successful quit rates. NRT is FDA-approved for adults 18 and over. In recommended doses, NRT is safe for most patients, including those with stable heart disease. Medi-Cal pays for nicotine replacement therapy if combined with counseling, e.g. the California Smokers' Helpline (check with specific plans).

NRT is available in several forms. The nicotine patch is the most effective and convenient form for most smokers. Combining daily use of the nicotine patch with other forms of NRTs results in long-term quit rates higher than those observed when a single form of NRT is used. Some smokers who have stopped smoking continue to use self-dosing NRT formulations such as nicotine gum or lozenges, as needed. The long-term use of these therapies is not known to present health risks.

Bupropion SR **doubles** successful quit rates with each attempt. First marketed as the antidepressant Wellbutrin SR®, it is now also marketed as Zyban®** for treatment of smoking addiction. Due to its anti-depressant effects, it is the best choice of medication for patients with a history of depression. For patients who are heavily addicted, substance abusers or schizophrenic, use bupropion combined with NRT for increased effectiveness. Contraindications include a history of seizures, bipolar disorder, or an eating disorder. Medi-Cal requires an order specifically for Zyban®. The FDA has approved bupropion SR for long-term maintenance.

Varenicline (Chantix®)** combined with counseling can **double** successful quit rates with each attempt. Varenicline does not contain nicotine. It mimics the effects of nicotine and activates nicotine receptors to prevent cravings. At the same time, Varenicline possesses antagonist properties that eliminate the pleasurable effects of smoking. Adding nicotine replacement increases side effects without increasing quit rates. Varenicline plus bupropion has not been studied yet. Healthcare professionals, patients, patients' families, and caregivers should monitor changes in mood and behavior. Varenicline is being investigated for long term use.

Nortriptyline and clonidine are not approved for cessation by the FDA and have significant adverse effects. Other drugs, including additional antidepressants, have *not* been shown to increase smoking quit rates. Neither acupuncture nor hypnosis has been shown to be effective.

**Use of brand names is for informational purposes only and does not imply endorsement.

Table 1. FDA-Approved Medications for Tobacco Dependence

Pharmaco-therapy	Common Side Effects	Advantages	Disadvantages	Dosage	Duration	Availability
Bupropion SR	• Insomnia • Dry mouth	• Easy to use (pill) • No concerns for cardiac patients • Effective in patients with depression • Limits weight gain • Can be used with NRT	• Prescription needed • Precautions: Pregnancy Category C • **Do not use for patients who:** • Use a monoamine oxidase (MAO) inhibitor, levodopa or bupropion in any other form (Zyban, Wellbutrin) • Have a history of seizures or stroke • Have a history of anorexia or bulemia • Have other seizure-threshold-lowering conditions (e.g., alcohol dependence, head trauma)	150 mg every morning for 3 days, then 150 mg twice daily Begin 1-2 weeks before first tobacco free day Check BP if combine with NRT	7-12 weeks, maintenance up to 6 mos.	Zyban® Wellbutrin SR® Generic SR (Prescription only)
Nicotine Patch	• Local skin reaction • Insomnia	• Easy to use • Provides steady levels of nicotine • Unobtrusive • No prescription needed- OTC • Three strengths: 7, 14, 21 mg • Fewer compliance issues associated with the patch	• Do not use if have severe eczema or psoriasis; allergic reactions to adhesive may occur • Dose is not adjustable if cravings occur • 16-hr patch may lead to morning nicotine cravings • Use clinical judgment in pregnancy/teens • Contraindications: Pregnancy Category D. Severe or unstable angina pectoris, serious arrhythmias. For one month after acute MI	See Table 2. For most patients: 21 mg/24 hours ……. Then 14 mg/24 hours … Then 7 mg/24 hours ….	 4-6 weeks 2-4 wks 2-4 wks	Nicoderm CQ® Nicotrol® Habitrol® Generic Patches (Available prescription & OTC)
Nicotine Gum	• Mouth soreness • Jaw ache • Dyspepsia • Hiccups	• Can use with patches to control urge in addicted smokers • User controls dose • No prescription needed- OTC • May delay weight gain	• Caution with dentures; proper technique required • Do not use with acidic beverages during use • Contraindications: Pregnancy Category D; TMJ disease. Also see contraindications for patch.	1-24 cigarettes/day 2mg gum 25+ cigarettes/day 4mg gum Chew each piece slowly 30 minutes, up to 24 pieces/day 10-12/day usually	Up to 12 Weeks Taper 7-12 weeks	Nicorette® Nicorette Mint® (All flavors OTC)
Nicotine lozenge	• Nausea • Throat irritation • Hiccups • Dyspepsia	• Easy to use and conceal • Can use with patches to control urge in addicted smokers • User controls dose • No prescription needed- OTC • May satisfy oral cravings	• Do not eat or drink 15 minutes before or during use • Acidic beverages limit absorption • Limit 20 in 24 hours • Gastrointestinal side effects (nausea, hiccups, and heartburn) may be bothersome • Contraindications: Pregnancy Category D. Also see patch.	If 1st cigarette more than 30 min. after waking – 2mg PRN If 1st cigarette less than 30 min. after waking- 4mg PRN Up to 20 lozenges/day	Up to 12 weeks	Commit® Generic (All OTC)
Nicotine Inhaler	• Local irritation of mouth and throat • Mild cough and rhinitis initially	• Can be used with patches to control urges in addicted smokers • User controls dose • Mimics hand-to-mouth ritual of smoking	• Prescription needed • Do not use with acidic beverages • Frequent continuous puffing needed for up to 20 minutes per cartridge • Does not work in cold (<40 degrees F) • Contraindications: Pregnancy Category D; Reactive airway disease. Also see patch.	6-16 Cartridges/day PRN Inhale 80 times/cartridge 20 minutes/cartridge Taper dosage after 3-6 months	Up to 6 mos.	Nicotrol Inhaler® (Prescription only)
Nicotine Nasal Spray	• Nasal irritation • Dyspepsia • Sneezing • Red, watery eyes initially	• Can use with patches to control urges in addicted smokers • User controls dose • Most rapid nicotine delivery; simulates smoking • Highest effectiveness of nicotine products	• Prescription needed • Localized adverse effects limit use • Change in sense of smell or taste • Dependence can result • Patients with chronic nasal disorders should not use • Contraindications: Pregnancy Category D; Reactive airway disease. Also see patch.	Recommend 1-2 doses/hr PRN 5 doses/hr, 40 doses/day maximum One dose equals two sprays, one spray in each nostril (nearly equals nicotine from one cigarette)	3 to 6 mos.	Nicotrol NS® (Prescription only)
Varenicline	• Nausea/ Vomiting • Insomnia • Abnormal dreams • Dry mouth	• Easy to use (pill) • Blocks nicotine & therefore pleasure of smoking • No drug interactions • An oral formulation with twice-a-day dosing • Offers new mechanism of action for persons who previously failed using other medications • Early industry-sponsored trials suggest agent is superior to bupropion SR	• Prescription needed • Do not use while nursing • Precautions: Pregnancy Category C; • Avoid in chronic renal failure • Post-marketing data just emerging- new warning about rare but important psychiatric symptoms; hard to distinguish from nicotine withdrawal. Monitor for changes in mood, behavior, psychiatric symptoms or suicidal ideation	Begin 1-2 weeks before stop date Days 1-3: 0.5 mg tablet every morning Days 4 – 7: 0.5 mg tablet twice daily Days 8 to end of treatment: 1 mg tablet twice daily	3 to 6 mos.	Chantix® (Prescription only)

Table 2. Suggested Initial Dosages for Nicotine Replacement Therapy

Patient Characteristics	Nicotine Replacement Therapy
1-10 cigarettes/day; smokes 1 hour after waking.	14 mg/24 hr patch and/or 2 mg gum or lozenges PRN.*
11-24 cigarettes/day; smokes 1 hour after waking.	21 mg/24 hr patch.* Consider combining with 2 mg gum or lozenge PRN.
> 25 cigarettes/day; smokes within 30 minutes of waking. **Has condition that complicates treatment.**** **Prior failed quit attempts despite NRT or bupropion.**	21 mg/24 hr patch and PRN 4 mg gum and/or lozenges strongly recommended. Consider combining patch and nasal spray if patient has a psychiatric condition. See **Table 1** and **Issues That May Complicate Treatment** below.

* If patient exhibits moderate or severe withdrawal when stopping, increase dose, and/or add rescue NRT and/or add bupropion. See Minnesota Withdrawal Scale at http://www.uvm.edu/~hbpl/?Page=minnesota/default.html
** Conditions include depression, psychiatric conditions, alcohol and substance use, pregnancy, adolescence.

ISSUES THAT MAY COMPLICATE TREATMENT

Pregnancy: Intensive counseling is recommended as a first-line intervention. Patients who continue to smoke are usually highly addicted or have other co-morbid conditions; screen for alcohol and other drug use, depression and refer for treatment. The California Smokers' Helpline offers counseling for pregnant smokers.

NRT nicotine gum or lozenges or bupropion SR may be used during pregnancy when non-drug treatments have failed. Fetal risk from these drugs should be balanced against the greater risk of maternal smoking. Do not prescribe nicotine nasal spray because of higher peak levels of nicotine.

Adolescence: Screen pediatric and adolescent patients and their parents for tobacco use and strongly urge total abstinence from tobacco. Offer advice and medications to parents who smoke.

Long-term efficacy for bupropion SR in adolescents has not been established. Neither NRT nor bupropion SR is approved by the FDA for use in people 17 years of age and younger, so use clinical judgment.

Weight gain: Provide strategies for monitoring weight gain. Bupropion SR and NRTs, e.g., gum or patch, can delay weight gain, and should be considered for longer use in those with weight issues, diabetics, etc.

Psychiatric or substance abuse problems: Smoking prevalence is high (40-90%); treatment is more complicated and relapse is more common. Treat underlying psychiatric conditions concurrently.

When using NRT, care should be taken not to under-dose. In persons with schizophrenia, consider prescribing nicotine nasal spray, as its higher peak levels are the closest to inhaled smoke from a cigarette; evidence suggests that success is improved when NRT is combined with bupropion SR.

Because smoking induces cytochrome P450, psychotropic drug doses may need to be adjusted in patients who have stopped smoking. Closely follow patients with a history of depression; reduction or abstinence from nicotine may exacerbate depression and other psychiatric conditions.

Depression: Consider bupropion (unless contraindicated) alone or in combination with NRT.
Alcohol or substance abuse or a psychiatric condition: Consider bupropion with NRT.

Heavily addicted: Consider bupropion with NRT, patch plus rescue NRT, or varenicline. Consider bupropion in combination with NRT especially if patient also has depression, substance abuse, or a psychiatric condition.

Special populations: Interventions should be culturally, language, and educationally appropriate. In general, the treatments that were found to be effective in the guideline can be used with members of special populations, including hospitalized smokers, members of racial and ethnic minorities, older smokers, and others.

HEALTH INSURANCE COVERAGE FOR CESSATION AIDS

Medi-Cal Coverage:

Medi-Cal enrollees may receive coverage for medications to stop smoking. Medi-Cal alone covers the patch and bupropion, however coverage within different Medi-Cal plan formularies vary. All Medi-Cal plans cover various forms of NRT, such as the nicotine patch. Medi-Cal plans may also cover additional medications such as Zyban (Bupropion SR) or Chantix. Check with each plan to see what is covered and if the following are needed for each medication:

1. Prior authorization
2. Prescription
3. Certificate of enrollment from a behavior-modification program, such as the California Smoker's Helpline.

The California Smokers' Helpline will fax a certificate to the pharmacy when the patient enrolls. The smoker presents the prescription to the pharmacist, who then submits the request to Medi-Cal with the certificate.
http://www.californiasmokershelpline.org/quittingaids.shtml

Medicare Coverage:

Medicare Part B covers counseling and medications for tobacco use dependence. Formularies vary. Check the Medicare formulary. http://formularyfinder.medicare.gov/formularyfinder

Los Angeles County:

Department of Health Services, LA County Public-Private Partners (PPPs) and LA County Community Health Plan (CHP, the County's HMO for indigent patients): All plans cover various NRT options, such as the patch and/or bupropion as routine medications.

Private Insurance Coverage:

Individual plans vary.

Section 4: What Else Can Providers Do to Help Patients Stop Smoking?

Follow up with patients who are trying to stop smoking.

Your concern emphasizes the importance of stopping. Reinforce the use of the California Smokers' Helpline and other counseling sources. Assess for abstinence at all subsequent contacts.

Educate all patients about the dangers of secondhand smoke and encourage patients to maintain a smoke-free home. Secondhand smoke increases the risk of serious respiratory problems, e.g. a greater number and severity of asthma attacks and lower respiratory tract infections or an increased risk for middle ear infections in children. Inhaling secondhand smoke can cause lung cancer and coronary heart disease in nonsmoking adults. **Smokers are up to ten times more likely to successfully stop if their home is smoke-free**.

Prevent and treat relapse.

Former users who stopped in the last 6 months are at risk of relapse. Many patients alternate between thinking about stopping, making attempts to stop smoking, relapsing, and trying to stop again over the course of years. Relapse is not a sign of personal failure of the tobacco user or the clinician; it often takes multiple tries to successfully stop smoking. Most smokers who relapse want to try again soon. A relapse should be viewed as a learning experience. When the patient relapses, he or she can become aware of their triggers, their reasoning (e.g. one cigarette won't hurt) and the steps that led to picking up that first cigarette.

- Ask patients if they are willing to make another attempt to stop smoking.
- Discuss the circumstances surrounding the relapse and help patients determine what worked and what didn't work at their last attempt. Refer to the California Smokers' Helpline and/or other counseling resources again.
- Suggest additional medication or a different medication at next attempt: a longer course of NRT or other medication, or a combination of medications, e.g. bupropion plus nicotine replacement therapy, or nicotine patch plus a short acting nicotine (gum, lozenge or spray). Varenicline (Chantix®) may have a higher successful quit rate than a single form of NRT or bupropion alone.
- Suggest using additional cessation resources such as Nicotine Anonymous Meetings.

For tobacco users unwilling to stop smoking

Reiterate that **"stopping smoking is the most important thing you can do to protect your health."** Give them the phone number of the California Smokers' Helpline. If possible, provide the "5 R's": Relevance, Risks, Rewards, Roadblocks, and Repetition to motivate smokers who are unwilling to stop smoking at this time.

5 "R's" FOR TOBACCO USERS UNWILLING TO STOP SMOKING

Relevance: Make your advice personally relevant to the patient, being as specific as possible.

Risks: Ask the patient to identify potential negative consequences of tobacco use.

Rewards: Ask the patient to identify potential benefits of stopping tobacco use.

Roadblocks: Ask the patient to identify their barriers and note elements of treatment (problem solving, pharmacotherapy) to address barriers.

Repetition: Repeat the motivational intervention at every visit. Inform them that most people make repeated attempts to become free of tobacco before they are successful.

Section 5: Resources for Providers

Ask-Advise-Refer

Intervention Cues

STEP 1: ASK patients about tobacco use at every visit.

- Systematically ask every patient about tobacco use at every visit.
- Determine if the patient is current, former, or was never a tobacco user.
- Determine what form of tobacco is used.
- Determine frequency of use.
- Document tobacco use status in the patient's medical record.
- Determine if others in the household also use tobacco.

Step 1 Sample Intervention Cues

For the patient who never regularly used tobacco:

- "Congratulations, you have made a wise choice to protect your health."

For the patient who quit using tobacco:

- "Congratulations on quitting tobacco use. We have some good programs to help you remain tobacco-free. I can give you the contact information for the program."

For the patient who uses tobacco:

- "How many cigarettes per day do you smoke?"
- "How many cigars per day do you smoke?"

STEP 2: ADVISE tobacco users to stop.

- In a clear, strong, and personalized manner, urge every tobacco user to quit.
- Tobacco users who have failed in previous quit attempts should be told that most people make repeated quit attempts before they are successful.
- Employ the teachable moment: link health issues with advice.

Step 2 Sample Intervention Cues

For the patient who currently uses tobacco:

- "Make it a priority to quit smoking – It is important for your health."
- "I can help you stop smoking. Let me give you the phone number for the California Smokers' Helpline. You can receive free counseling on how to stop and remain tobacco-free."

STEP 3: REFER patients to resources.

- Give them a California Smokers' Helpline Gold Card/Brochure.
- Give them information (fact sheets or brochures) on smoking or tips to help them stop.
- Discuss using pharmacotherapy.
- Document in patient's medical record.

Step 3 Sample Intervention Cues

For the patient who currently uses tobacco:

- "I know stopping smoking is very difficult. Most people who want to stop are successful. Sometimes it takes more than one try. I know you can do it. Let me refer you to the California Smokers' Helpline, they can help you stop."

Local Cessation Resources

California Smokers' Helpline: 1-800-NO-BUTTS or 1-800-662-8887

http://www.californiasmokershelpline.org/

Section 5: Resources for Providers

Tobacco Impacts on Medical Specialties

All Specialties
Sleep Disorders (longer latency, less total sleep time, lighter sleep, daytime sleepiness)
Desired wound healing
Post-surgical infections
Increased irritability while in hospital
Many medication interactions

Circulatory Diseases
Myocardial infarction
Angina pectoris/Ischemic heart disease
Congestive heart failure
Strokes
Transient ischemic attack
Atherosclerosis
Aortic aneurysm
Peripheral vascular disease
Low HDL
High triglyceride levels

Dermatology
Skin aging
Palmoplantar pustulosis
Psoriasis (OR 1.4-2.4)
Pustular psoriasis (OR 10)
Premature hair loss
Premature grey hair
Yellow fingers

Dental (Also see ENT)
Stained teeth
Bad breath (halitosis)
Periodontal disease
Tooth loss
Oral cancers
Reduced lower jaw bone density

Emergency Medicine
Asthma/COPD exacerbations
Burn injuries
Hip and other fractures
Mls/CHF/ Strokes/TIAs
Pneumonia

Endocrinology
Insulin resistance/metabolic syndrome
Increased Diabetes Type 2
Diabetes complications: amputations

ENT
Hearing loss
Oral cavity, pharynx, head & neck cancers
Obstructive sleep apnea
Snoring
Increased respiratory infections

ENT (cont.)
Smell & taste disturbances
Bad breath (halitosis)

Gastroenterology
GI cancers: esophagus, stomach, pancreas
Stomach ulcers
Increased HCV viremia

Hematology/Oncology
Polycythemia
High leukocyte count
Higher lead level in lead workers

Cancers:
Lung, bronchus
Pharynx, larynx, oral cavity
Esophagus
Stomach
Urinary bladder
Kidney, renal pelvis
Acute myeloid leukemia
Penile
Cervix uteri
Breast (OR 1.4-1.8 Premenopausal)

HIV/AIDS
Increased HIV viremia, lower CD4 counts
Joint occurrence oral candidacies and hairy leukoplakia
Increased symptom burden
Increased Pneumocystis colonization
Accounts for 60% of cardiovascular risk

Infectious Diseases
Tuberculosis
Influenza
Pneumonia (pneumococcal and others)
Worse outcomes in disseminated cryptococcosis

Nephrology
Onset of progression of lupus nephritis
Progression of chronic kidney disease in diabetics, polycystic kidney disease, IgA nephropathy, other chronic kidney disease

Ob-Gyn
Cervical cancer
Infertility, miscarriage, stillbirth
Premature, low birth weight
Ectopic pregnancy
Early menopause
Osteoporosis
Pre-menopausal breast cancer

Ophthalmology
Macular degeneration
Cataracts
Retinal arterial and venous occlusions

Orthopedics
Hip fractures
Increased other fractures
Osteoporosis

Pediatrics
Short gestation/low birth weight
Respiratory distress syndrome
Other respiratory- newborn
Cleft lip/palate
SIDS
Food and inhalant allergies

Psychiatry/Neurology
Sleep Disorders (longer latency, less total sleep time, lighter sleep)
Obstructive sleep apnea
Daytime sleepiness
Highest rates of smoking in schizophrenics, bipolar, depression, anxiety disorders, ADHD, drug abuse
Large contribution to early death rate in chronic mental illness
Relative risk of suicide compared to former smokers: double to triple
Risk of signing out AMA
Reduced levels of some epilepsy meds

Pulmonary
Cough, shortness of breath
Asthma onset, attacks more frequent and severe
Lung cancer
Pneumonia, pneumococcal & others
Influenza
Bronchitis, emphysema, COPD
Pneumocystis colonization

Rheumatology
Increased onset and complications of autoimmune diseases; rheumatoid nodules & multiple joint involvement in rheumatoid arthritis, digital ischemia in systemic sclerosis & Reynaud's, nephritis and dermatologic manifestations in SLE

Urology
Penile cancer (OR 4.5)
Erectile dysfunction
Kidney cancer
Lower sperm count and concentration
Abnormally shaped sperm-teratozoospermia

Section 5: Resources for Providers

CME Course Listing for Providers

1. Medscape: Challenges of Treating Tobacco Users in High-Risk Populations (Slides With Audio) by Linda H Ferry, MD, MPH Charles J Bentz, MD, November 2007. The American College of Preventive Medicine designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit™.
http://www.medscape.com/viewarticle/565309

2. Medscape Smoking Resource Center
Six additional online CME activities plus links to other helpful resources.
http://www.medscape.com/resource/smoking

3. NY City Treating Nicotine Addiction CME April 2005
CME must be printed out and mailed in.
http://www.nyc.gov/html/doh/downloads/pdf/chi/chi24-4.pdf

4. **Rx Consultant: CE for pharmacists.** "Smoking Cessation for the Busy Clinician" covers NRT and oral medications with CE questions to mail in with $7.50 for CE.
http://www.rxconsultant.com/issues/0709smoking.pdf

Online Resources for Providers

1. Rx for Change provides materials to facilitate the training of clinicians
http://rxforchange.ucsf.edu/faculty

2. Treatobacco.net by the Society for Research on Nicotine and Tobacco www.srnt.org
PowerPoint presentations on tobacco cessation medication efficacy and safety
http://www.treatobacco.net/resource_library/slide_kits.cfm

3. University of California San Francisco Smoking Cessation Leadership Center
http://smokingcessationleadership.ucsf.edu/Resources.html

4. California Smokers' Helpline: Information for physicians and materials for physicians to give their patients.
http://www.californiasmokershelpline.org/Healthcare%20Provider%20Subpage.shtml

5. Surgeon General's Treating Tobacco Use and Dependence
http://www.surgeongeneral.gov/tobacco/clinpack.html

6. AHRQ Supported Clinical Practice Guidelines
Clinical Practice Guideline: *Treating Tobacco Use and Dependence*
http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf

7. An Algorithm for Optimal Smoking Cessation Treatment by John.Hughes@uvm.edu John R Hughes, University of Vermont with PowerPoint presentation at 2007 UK National Smoking Cessation Conference.
http://www.uknscc.org/2007_UKNSCC/presentations/john_hughes.html

8. Redefining the Role of Tobacco Cessation Specialists by John Hughes
http://www.uknscc.org/2007_UKNSCC/presentations/john_hughes_web.html

9. Varenicline: Implications for the field by Alex Bobak, GP
http://www.uknscc.org/2007_UKNSCC/presentations/alex_bobak_web.html

Section 6: Patient Education Fact Sheets

For reproducible education resources, see the following pages:

Free Smoking Cessation Materials Available from the California Smokers' Helpline

Gold Card
"Take Charge of your life" says this referral tool. A mock credit card, the Gold Card lists the smoke, chew, and TDD/TTY phone numbers.

General Audience Brochure
For smokers interested in quitting, provides service information including hours of operation, phone numbers, and what to expect when you call. Available in English, Spanish, Chinese, Vietnamese, and Korean.

American Indian Brochure
This culturally relevant brochure provides service information including hours of operation, phone number, and what to expect when you call.

Teen Provider Brochure
Designed for adults who want to help a teen quit smoking. Includes questions frequently asked by adults who refer teens to the Helpline and answers questions about free services.

Chew Tobacco Brochure
For chew tobacco users interested in quitting. Provides service information including hours of operation, phone numbers, and what to expect when you call.

For a complete listing of FREE promotional materials available from the California Smokers' Helpline and information about how to order, visit http://www.californiasmokershelpline.org/Order.php

Smoking and Your Health

Stopping smoking is hard because Nicotine is a very powerful drug. For some people, it can take several tries before they can stop smoking. But each time you try to stop smoking, the more likely you will be able to stop for good.

Smoking hurts almost every organ of the body. It causes many diseases and hurts the health of smokers in general:

Cancer

- Smoking causes cancers of the bladder, mouth, pharynx, larynx, esophagus, cervix, kidney, lung, pancreas, and stomach, and causes leukemia.

Cardiovascular Disease (Heart and Circulatory System)

- Smoking causes heart disease.
- Smoking can double a person's risk for stroke.
- Smoking lowers the blood flow in the body. Smokers are 10 times more likely than nonsmokers to develop peripheral vascular disease, which is a disease that hurts blood flow.

Respiratory Disease and Other Effects

- Cigarette smoking increases the risk of dying from lung disease.
- Cigarette smoking causes about 90% of all deaths from lung diseases.

Secondhand Smoke

Secondhand smoke is a harmful mix of gases that is released into the air when tobacco products burn or when smokers blow their smoke out. Secondhand smoke can cause disease and early death in children and adults who do not smoke. Secondhand smoke affects us right away and can cause heart disease and lung cancer in adults who do not smoke.

Good Reasons to Stop Smoking

- ✓You will live longer and live better.
- ✓You will lower your chance of having a heart attack, stroke or cancer.
- ✓The people you live with, like your children, will have better health.
- ✓If you are pregnant, stopping smoking will give you a better chance of having a healthy baby.
- ✓You will have more money to spend on things other than cigarettes.

How Your Health Gets Better When You Stop Smoking

20 minutes:	Heart rate drops.
12 hours:	Carbon monoxide level in blood drops to normal.
48 hours:	Ability to smell and taste starts to improve.
2–3 weeks:	Chance of heart attack drops, circulation improves, walking becomes easier, and lung function improves.
1–9 months:	Coughing and shortness of breath decrease.
1 year:	Excess risk of coronary heart disease is half that of a smoker.
5 years:	Risk of stroke is reduced to that of a non-smoker.
10 years:	Lung cancer death rate is about half that of a smoker; Risk of cancer of the mouth, throat and esophagus decreases.
15 years:	Risk of coronary heart disease returns to that of a non-smoker.

5 Tips to Stop Smoking

Congratulations on taking the first step! As your health care provider, I'm here to help you stop smoking. Here are some things you can do to help you stop.

1. Get Ready.

- Set a date to stop smoking.
- Change the things around you. Get rid of cigarettes and ashtrays in your home, car, and workplace.
- Do not let people smoke in your home.
- If you have tried to stop smoking before, think about what worked and what did not work.

2. Get Help.

- Tell your friends, family, and coworkers that you are going to stop smoking. Ask them not to smoke around you or leave cigarettes out.
- Talk to your health care doctor or provider.
- Get counseling. The more counseling you have, the better your chances of stopping. Call 1-800-NO-BUTTS.

3. Learn New Ways of Living.

- Stay busy.
- Change the things that you do every day. Take a different road to work or eat in a different place.
- Let go of stress. Exercise is a good way to do this.
- Plan something fun to do every day.
- Drink a lot of water.

4. Use Medications in the Right Way.

- Talk to your health care provider, or doctor, about how to use medications.
- Read and follow the directions. Call your doctor if you have any questions.

5. Be Ready for Hard Work.

- Most people try to stop smoking several times before they finally stop.
- If you smoke again, think about what caused you to smoke. Try to stay away from those situations in the future. Do not give up. Try again!

Resources for Patients

L.A. Care (for information about coverage plans)
1-888-839-9909
www.lacare.org

The California Smokers' Helpline
1-800-NO-BUTTS
(1-800-662-8887)
www.californiasmokershelpline.org

American Legacy Foundation
202-454-5555
www.americanlegacy.org

It's Quitting Time LA!
www.laquits.com

American Cancer Society
1-800-ACS-2345
(1-866-228-4327)
www.cancer.org

American Heart Association
www.americanheart.org
1-800-AHA-USA-1 or
1-800-242-8721

American Lung Association of California
(510) 638-LUNG
www.californialung.org
Freedom From Smoking Online:
www.lungusa.org/ffs/index.html-

Nicotine Anonymous
1-877-879-6422
http://www.nicotine-anonymous.org/

Additional Online Resources:

Tobacco Free California
http://www.tobaccofreeca.com/

Quit Net
www.quitnet.com

National Cancer Institute
www.cancer.gov/cancertopics/smoking

VideoJug.com -- Videos and online discussion boards
http://www.videojug.com/tag/quit-smoking

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CHOLESTEROL

Cholesterol is a fatty substance that you body needs to work. It is made in the liver and found in food that comes from animals, such as meat, eggs, milk products, butter and lard.

Too much cholesterol in your blood can be harmful to your body and can increase your risk for heart disease. You are at risk for high blood cholesterol if:

- Your body makes too much cholesterol
- You eat food high in saturated fats and cholesterol
- You have diabetes, low thyroid level called hypothyroidism, or kidney disease

There are 3 main types of fats in your blood:

- High Density Lipoproteins (HDL): This "good" cholesterol takes extra cholesterol in your blood back to your liver so your body can get rid of it.
- Low Density Lipoproteins (LDL): This "bad" cholesterol in your blood builds up in your blood vessels. This can cause your vessels to narrow, making it hard for blood to flow.
- Triglycerides: Eating too many carbohydrates can increase your triglyceride level.

Blood fats are measured by a blood test. Your results will tell you:

Your total cholesterol level

- A healthy level is less than 200.
- If your total cholesterol is above 200, your doctor will check your HDL, LDL and triglycerides.

Your HDL blood cholesterol level

This is the "good" cholesterol: the higher the number, the better.

- A healthy level is 60 and above.
- Talk to your doctor about treatment if your level is less than 40.

Your LD blood cholesterol level
This is the "bad" cholesterol: the lower the number, the better.

- A healthy level is less than 100.
- Your doctor may want your LDL less than 70 if you have had a recent heart problem.
- Talk to your doctor about treatment if your level is 130 and above.

Your triglyceride blood level

- A healthy level is less than 150.
- Talk to your doctor about treatment is your level is 200 and above.

To lower your blood cholesterol levels

- See your doctor and get your cholesterol checked regularly.
- Talk to your doctor, nurse or dietitian about a diet and exercise plan.
- Medicine may be needed if diet and exercise are not enough.
- Eat plenty of high fiber food, such as whole grains, beans, and fresh fruits and vegetables.
- Limit food that contains high amounts of cholesterol and saturated and polyunsaturated fats, such as beef, pork, cheese, whole milk, or lard. Eat more low fat foods, such as skinless chicken breasts, fish or skim milk.
- Choose foods high in monounsaturated fats, such as olive or canola oils and nuts.
- Bake, broil, grill or roast foods rather than fry them.

Talk to your doctor, nurse, or dietitian about how to manage your cholesterol levels.

6/2005. Developed through a partnership of the Ohio State University Medical Center, Mount Carmel Health and OhioHealth, Columbus Ohio.

Colesterol

El colesterol es una sustancia grasa que su cuerpo necesita para funcionar. Se fabrica en el hígado y se encuentra en alimentos de origen animal, tales como la carne, los huevos, los productos lácteos, la mantequilla y la manteca.

Demasiado colesterol en la sangre puede ser dañino para el cuerpo y puede aumentar su riesgo de sufrir un ataque cardíaco. Usted tiene riesgo de tener el colesterol alto en la sangre si:

- su cuerpo produce demasiado colesterol;
- come alimentos con un alto contenido de grasas saturadas y colesterol;
- sufre de diabetes, un funcionamiento débil de la tiroides llamado hipotiroidismo o enfermedad renal.

Existen 3 tipos principales de grasas en la sangre:

- Lipoproteínas de alta densidad (HDL, por sus siglas en inglés): Este colesterol “bueno” saca el colesterol adicional de la sangre y lo devuelve al hígado, de manera que el cuerpo pueda deshacerse de él.
- Lipoproteínas de baja densidad (LDL, por sus siglas en inglés): Este colesterol “malo” se acumula en los vasos sanguíneos, lo que produce el estrechamiento de los vasos sanguíneos, dificultando así la circulación de la sangre.
- Triglicéridos: Comer demasiados **carbohidratos** puede aumentar su nivel de triglicéridos.

Un examen de sangre mide las grasas en la sangre. Los resultados le informarán:

El nivel total de colesterol en la sangre

- Un nivel saludable es menor a 200.
- Si el colesterol total es mayor a 200, el médico le controlará los niveles de HDL, LDL y triglicéridos.

El nivel de colesterol de HDL en la sangre

Éste es el colesterol “bueno”: mientras más alto, mejor.

- Un nivel saludable es de 60 o más.
- Converse con su médico sobre el tratamiento si su nivel es menor a 40.

Por Una Vida Sana

El nivel de colesterol de LDL en la sangre
Éste es el colesterol "malo": mientras más bajo, mejor.

- Un nivel saludable es menor a 100.
- Es probable que su médico desee que su LDL sea menor a 70 si ha tenido un problema cardíaco reciente.
- Converse con su médico sobre el tratamiento si su nivel es de 130 o más.

El nivel de triglicéridos en la sangre

- Un nivel saludable es menor a 150.
- Converse con su médico sobre el tratamiento si su nivel es de 200 o más.

Para disminuir sus niveles de colesterol en la sangre

- Visite a su médico y controle su colesterol regularmente.
- Hable con su médico, enfermera o nutricionista sobre una dieta y un plan de ejercicios.
- Es posible que necesite medicamentos si la dieta y los ejercicios no son suficientes.
- Coma muchos alimentos con fibra, tales como los granos enteros, frijoles, y frutas y verduras frescas.
- Restrinja los alimentos que contienen grandes cantidades de colesterol y grasas saturadas y poliinsaturadas, tales como la carne de res, la carne de cerdo, el queso, la leche entera o la manteca.
- Coma más alimentos bajos en grasas, tales como pechuga de pollo sin piel, pescado o leche descremada.
- Elija alimentos altos en grasas monosaturadas, tales como el aceite de olive o canola y los frutos secos.
- En lugar de freír los alimentos, hornéelos o áselos a la parrilla o a las brasas.

Hable con su médico, enfermera o nutricionista sobre cómo manejar sus niveles de colesterol.

6/2005. Developed through a partnership of The Ohio State University Medical Center, Mount Carmel Health and OhioHealth, Columbus, Ohio.

Tips for Kids With High Cholesterol

You may think only "old" people have high cholesterol. This is not the case — even kids can have high cholesterol.

What is cholesterol?

Cholesterol is a type of fat made in your body. We all need some for good health, but too much can lead to health problems such as heart disease. Cholesterol comes from two sources:

- Your liver
- Foods you eat like milk, cheese, yogurt, eggs, meats

Are there different kinds of cholesterol?

Yes! HDL is also called "good" cholesterol because it helps get rid of the "bad" cholesterol called LDL. LDL builds up on artery walls☹, HDL carries it away☺.

- The *higher* your HDL the better!
- The *lower* your LDL the better!

Turn the page for tips to stay healthy!

For a Healthy Life

Accreditation of Medi-Cal, Healthy Kids and Healthy Families Program.

Tips for kids!

Get more HDL☺ and less LDL☹

1. Be active at least 1 hour each day.
2. Limit time spent watching TV, playing video games, and sitting at the computer.
3. Reach or stay at a healthy weight.
4. Eat more fruits, vegetables, and whole grains.
5. Eat more foods that say “non fat” or “low fat” on the label.
6. Replace soda and other sugary drinks with water.

Let’s play a word game!

Find and circle the healthy words below:

P	E	A	R	Z	H	E	A	R	T
T	C	V	P	L	A	Y	P	U	I
V	E	G	G	I	E	S	P	N	U
S	L	R	M	O	W	A	L	K	R
W	E	A	V	W	A	T	E	R	F
I	R	I	L	O	W	F	A	T	I
M	Y	N	N	O	N	F	A	R	H
G	O	S	P	O	R	T	S	B	Y

Pear	Grains	Apple	Veggies
Heart	Walk	Nonfat	Play
Run	Sports	Lowfat	Celery
Water	Fruit		

Consejos para niños con colesterol alto

Es posible que crea que solamente los “ancianos” tienen colesterol alto. No es así pues hasta los niños pueden tener colesterol alto.

¿Qué es el colesterol?

El colesterol es un tipo de grasa que se produce en su cuerpo. Todos necesitamos algo de grasa para mantener la buena salud, pero demasiada cantidad puede generar problemas de salud, tales como enfermedades cardíacas. El colesterol proviene de dos fuentes:

- De su hígado
- De los alimentos que ingiere, como la leche, el queso, el yogur, los huevos y las carnes

¿Existen diferentes clases de colesterol?

Sí. El HDL también se conoce como colesterol “bueno” porque ayuda a eliminar el colesterol “malo” conocido como LDL. El LDL se acumula en las paredes arteriales☹, el HDL lo transporta☺.

- Cuanto *más alto* sea su HDL, mejor.
- Cuanto *más bajo* sea su LDL, mejor.

Vea al dorso consejos para mantenerse sano.

For a Healthy Life

¡Consejos para niños!

Tenga más HDL☺ y menos LDL☹

1. Haga actividades físicas al menos 1 hora por día.
2. Reduzca el tiempo que pasa mirando televisión, jugando videojuegos y sentado en la computadora.
3. Alcance o manténgase en un peso saludable.
4. Coma más frutas, verduras y granos integrales.
5. Coma más alimentos que digan “sin grasa” o “bajos en grasa” en la etiqueta.
6. Reemplace los refrescos y otras bebidas azucaradas por agua.

¡Hagamos un juego de palabras!

Encuentre y marque con un círculo las palabras saludables que aparecen a continuación:

G	R	A	F	Z	A	S	A	R	G	N	I	S
B	P	E	R	A	Z	G	Z	U	R	I	R	T
E	O	N	U	C	F	G	U	G	A	U	E	Y
Ò	P	E	T	S	O	M	V	A	N	D	M	P
T	A	S	A	R	G	N	E	S	O	J	A	B
A	P	V	Ò	Y	C	J	R	P	S	E	N	S
G	I	N	Z	A	O	O	D	J	Z	R	Z	O
C	O	R	R	E	R	C	U	D	U	B	A	N
L	O	L	Y	E	R	H	R	A	V	G	N	R
D	E	P	O	R	T	E	A	G	Z	E	A	H
H	A	N	M	A	N	H	S	B	A	Ò	O	R
M	L	I	C	A	M	I	N	A	R	V	N	C

Pera	Granos	Manzana	Verduras	Corazón	Caminar
Sin grasa	Jugar	Correr	Deportes	Bajos en grasa	
Apio	Agua	Fruta			

L.A. Care HEALTH PLAN

82044

Controlling High Blood Pressure

High blood pressure (hypertension) is called the silent killer. This is because many people who have it don't know it. Normal blood pressure is less than 120/80. Know your blood pressure and remember to check it regularly. Doing so can save your life. Here are some things you can do to help control your blood pressure.

Choose heart-healthy foods

- Select low-salt, low-fat foods.
- Limit canned, dried, cured, packaged, and fast foods. These can contain a lot of salt.
- Eat 8–10 servings of fruits and vegetables every day.
- Choose lean meats, fish, or chicken.
- Eat whole-grain pasta, brown rice, and beans.
- Eat 2–3 servings of low-fat or fat-free dairy products
- Ask your doctor about the DASH eating plan. This plan helps reduce blood pressure.

Maintain a healthy weight

- Ask your healthcare provider how many calories to eat a day. Then stick to that number.
- Ask your healthcare provider what weight range is healthiest for you. If you are overweight, weight loss of only 10 lbs can help lower blood pressure.
- Limit snacks and sweets.
- Get regular exercise.

Get up and get active

- Choose activities you enjoy. Find ones you can do with friends or family.
- Park farther away from building entrances.
- Use stairs instead of the elevator.
- When you can, walk or bike instead of driving.
- Rake leaves, garden, or do household repairs.
- Be active for at least 30 minutes a day, most days of the week.

Manage stress

- Make time to relax and enjoy life. Find time to laugh.
- Visit with family and friends, and keep up with hobbies.

Limit alcohol and quit smoking

- Men: Have no more than 2 drinks per day.
- Women: Have no more than 1 drink per day.

- Talk with your healthcare provider about quitting smoking. Smoking increases your risk for heart disease and stroke. Ask about local or community programs that can help.

Medications

If lifestyle changes aren’t enough, your healthcare provider may prescribe high blood pressure medicine. Take all medications as prescribed.

Cómo controlar la alta presión arterial

La **alta presión arterial** (hipertensión) se conoce también como “el asesino silencioso”, ya que muchas personas la tienen sin saberlo. La presión arterial normal es inferior a 120/80. Sepa cuál es su presión arterial y recuerde que debe revisarla con regularidad, ya que hacer esto puede salvarle la vida. Estas son algunas cosas que usted puede hacer para ayudar a controlar su presión arterial.

Elija alimentos que sean saludables para el corazón

- Elija alimentos con bajo contenido de sal y de grasa.
- Limite el consumo de alimentos enlatados, curados, secos o de paquete, y las comidas rápidas, ya que pueden contener una gran cantidad de sal.
- Coma todos los días de 8–10 porciones de frutas y verduras.
- Elija carnes magras, pescado o pollo.
- Coma pasta y arroz integrales, así como frijoles.
- Consuma de 2–3 porciones de productos lácteos descremados o bajos en grasa.
- Consulte con su médico acerca del plan de alimentación DASH. Este plan ayuda a reducir la presión arterial.

Mantenga un peso saludable

- Pregunte a su proveedor de atención médica cuántas calorías puede comer cada día y no sobrepase la cantidad indicada.
- Pregunte a su proveedor de atención médica cuáles son los límites de peso más adecuados para usted. Si tiene exceso de peso, perder aunque sea 10 libras puede ayudarle a reducir su presión arterial.
- Limite los bocaditos entre comidas y los dulces.
- Haga ejercicio con regularidad.

Levántese y haga ejercicio

- Elija actividades que le agraden. Encuentre algunas que pueda hacer con sus familiares y amigos.
- Estaciónese más lejos de las entradas de los edificios.
- Utilice las escaleras en vez del ascensor.
- Cuando pueda, camine o vaya en bicicleta en vez de ir en automóvil.
- Rastrille las hojas en el jardín o haga reparaciones en la casa.
- Manténgase activo durante por lo menos 30 minutos diarios la mayoría de los días de la semana.

Controle el estrés

- Reserve tiempo para relajarse y disfrutar de la vida. Encuentre tiempo para reírse.
- Visite a sus familiares y amigos, y mantenga sus pasatiempos favoritos.

Limite el alcohol y deje de fumar

- Hombres: limite su consumo de alcohol a no más de 2 bebidas diarias.
- Mujeres: limite su consumo de alcohol a no más de1 bebida diaria.
- Hable con su proveedor de atención médica acerca de dejar de fumar. Fumar aumenta los riesgos de enfermedades cardíacas y ataque cerebral. Averigüe sobre los programas locales que le puedan ayudar.

Medicamentos

Si los cambios en su estilo de vida no son suficientes, su proveedor de atención médica podría recetarle medicamentos para la alta presión arterial. Tome todos sus medicamentos según las indicaciones.

Keep Your Balance

There is a new food guide, called **MyPlate**. **MyPlate** promotes balancing healthier food choices with daily physical activity.

Following **MyPlate** means eating healthy foods and balancing what you eat with exercise. Make a plan that's right for you based on your age, sex and activity level.

Exercise

Making small changes one step at a time will get you where you need to go. Move your body every day.

To lose weight you need to eat less and move more.

EAT LESS!
MOVE MORE!

Stay informed and up to date by visiting one of L.A. Care's Family Resource Centers. The Centers offer FREE health education and physical fitness classes.

Inglewood
Corner of Century & Crenshaw
3111 W. Century Blvd, Ste. 100
Inglewood, CA 90303
1-310-330-3130

Lynwood
In Plaza Mexico
3180 E. Imperial Highway
Lynwood, CA 90262
1-310-661-3000

If you are an L.A. Care member you can attend special L.A. Care Member Only workshops offered by Health In Motion™. Please contact your provider for more information or visit us at **www.lacare.org**.

Developed by L.A. Care Health Plan working with our contracted health plan partners. Together, we provide Medi-Cal managed care services in Los Angeles County.

LA0534 12/11

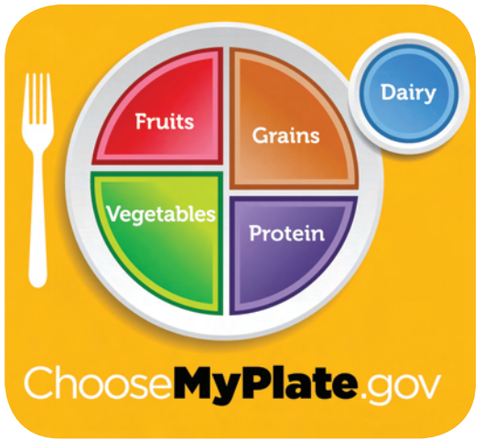
L.A. Care
HEALTH PLAN

FINDING YOUR
BALANCE

Balance What You Eat With Exercise

For a healthier you, keep a balanced diet and an active lifestyle.

Great health starts with eating healthy food. The foods you eat give you the energy your body needs every day. Making small changes in the foods you eat can make a big difference in your health. Learn good eating habits by following MyPlate.



MyPlate is made up of **5** food groups and oils. Each group on the guide is a different color:

- Fruits
- Grains
- Vegetables
- Protein
- Dairy
- Fats & Oils

Eat foods from each of the **5** groups and oils every day, but follow **2** basic rules:

1. Eat more grains, vegetables, fruits and milk.
2. Eat less high-fat, high-sugar foods.

You can learn more about **MyPlate** by visiting **www.choosemyplate.gov**.

Fruits

2 cups a day
Focus on fruits.

- ✓ Eat a variety of fruits, fresh or frozen.
- ✓ Go easy on fruit juices.

Helpful Hints

1 cup = Size of a baseball
OR
A medium piece of fruit

Grains

6 oz a day
Make half your grains whole.

- ✓ Eat whole grain bread, cereal, pasta or brown rice every day.

Helpful Hints

1 oz = 1 slice of bread
OR
1 cup of dry cereal
OR
½ cup of rice or pasta

Dairy

3 cups a day
Get your calcium-rich foods.

- ✓ Try low-fat (1%) or fat-free milk, cheese, yogurt and ice cream.
- ✓ If you don't or can't drink milk, try lactose-free products or other calcium foods like broccoli and almonds.

Helpful Hints

1 cup = 8 oz glass of milk
OR
1 ½ oz of low-fat cheese
(1 oz of cheese looks like four dice)

Vegetables

2 ½ cups a day
Vary your veggies.

- ✓ Eat more dark green veggies like broccoli and orange veggies like carrots.
- ✓ Choose fresh or frozen.

Helpful Hints

1 cup = Size of a baseball
OR
1 cup of cooked vegetables

Protein

5 ½ oz a day
Go lean on protein.

- ✓ Choose low-fat or lean meats and poultry.
- ✓ Bake, broil or grill, but don't fry.
- ✓ Eat more dry beans and legumes.

Helpful Hints

1 oz meat = 1 tablespoon of peanut butter (looks like a ping-pong ball)
OR
2-3 oz of meat (looks like a deck of cards)

Fats & Oils

You need to eat a little fat every day.

- ✓ Healthier fats come from plants such as olives, avocados, nuts and vegetable oils. Choose these more often.
- ✓ Less healthy fats come from animals like red meat, whole milk, lard, butter and mayonnaise. Choose these less often.

Mantenga su equilibrio

Existe una nueva guía alimenticia, denominada ***MyPlate***. ***MyPlate*** promueve el equilibrio de alimentos sanos con la actividad física diaria.

Seguir ***MyPlate*** significa comer alimentos sanos y equilibrar lo que usted come con ejercicio. Haga un plan que sea correcto para usted con base en su edad, sexo y nivel de actividad.

Ejercicio

Hacer cambios pequeños poco a poco lo llevará a donde tiene que estar. Mueva su cuerpo todos los días.

Para bajar de peso necesita comer menos y moverse más.

Coma menos
Muévase más

Manténgase usted y a su familia sana y informada visitando uno de los Centros de Recursos Familiar de L.A. Care. Los centros ofrecen educación para la salud y clases de ejercicio físico sin costo.

Inglewood
En la esquina de Century y Crenshaw
3111 W. Century Blvd, Ste. 100
Inglewood, CA 90303
1-310-330-3130

Lynwood
En Plaza Mexico
3180 E. Imperial Highway
Lynwood, CA 90262
1-310-661-3000

Si usted es miembro de L.A. Care, puede asistir a clases especiales exclusivos para miembros de L.A. Care que ofrece Health In Motion™. Comuníquese con su proveedor para obtener más información o visite **www.lacare.org/es**.

Desarrollado por L.A. Care Health Plan en colaboración con los asociados de nuestro plan de salud contratado. Juntos, proporcionamos los servicios médicos administrados de Medi-Cal en el condado de Los Ángeles.

LA0534 12/11 SP

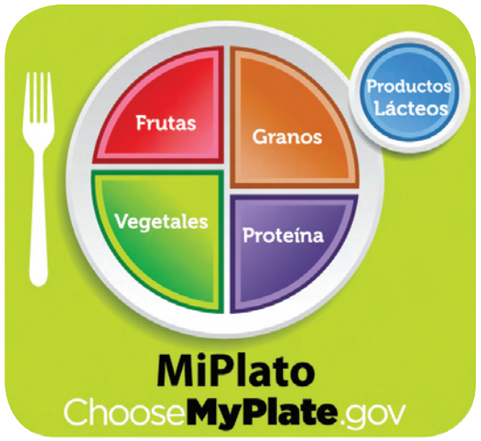
L.A. Care
HEALTH PLAN

ENCUENTRE SU
EQUILIBRIO

Equilibre lo que come con ejercicio

Para tener una mejor salud, lleve una dieta balanceada y un estilo de vida activo.

La buena salud comienza con una alimentación sana. Los alimentos que usted consume le dan la energía que su cuerpo necesita todos los días. Hacer pequeños cambios con los alimentos que consume puede hacer una gran diferencia en su salud. Aprenda buenos hábitos alimenticios siguiendo *MyPlate*.



MyPlate consta de **5** grupos alimenticios y aceites. Cada grupo que aparece en la guía tiene un color diferente:

- Frutas
- Granos
- Verduras
- Proteínas (carnes y legumbres)
- Lácteos (leche y derivados)
- Fats & Oils

Consuma alimentos de cada uno de los **5** grupos y aceites todos los días, pero siga **2** reglas básicas:

1. Coma más granos, verduras, frutas y leche.
2. Coma menos alimentos ricos en grasa y en azúcar.

Puede conocer más acerca de ***MyPlate*** visitando a **http://www.choosemyplate.gov/sp-index.html**.

Frutas

2 tazas diarias

Concéntrese en comer frutas.

- ✓ Coma distintas frutas, frescas o congeladas.
- ✓ No tome muchos jugos de frutas.

Datos útiles

1 taza = del tamaño de una pelota de béisbol
O
Una pieza mediana de fruta

Verduras

2 ½ tazas diarias

Consuma verduras variadas.

- ✓ Coma más verduras de color verde oscuro, como el brócoli, y de color naranja, como la zanahoria.
- ✓ Elija verduras frescas o congeladas.

Datos útiles

1 taza = del tamaño de una pelota de béisbol
O
1 taza de verduras cocidas

Granos

6 onzas o una taza al día

La mitad de los granos que consuma deben ser integrales.

- ✓ Coma pan integral (como tres rebanadas), cereales integrales, arroz o pasta integral.

Datos útiles

1 onza = 1 tortilla de maíz
O
1 taza de cereal sin leche
O
½ taza de arroz o pasta

Proteínas

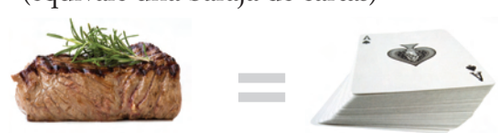
5 ½ onzas al día

Coma proteínas bajas en grasas.

- ✓ Elija carnes y carnes de ave bajas en grasa o sin grasa.
- ✓ Ase, hornee o cocine la carne a la plancha, no la fría.
- ✓ Coma más frijoles y legumbres.

Datos útiles

1 onza de carne = 1 cucharada de mantequilla de maní (equivale al tamaño de una pelota de ping-pong)
O
2-3 onzas de carne
(equivale una baraja de cartas)



Lácteos

3 tazas diarias

Consuma alimentos ricos en calcio.

- ✓ Coma lácteos bajos en grasa (1%) o sin grasa como la leche, el queso, el yogurt y el helado.
- ✓ Si no puede o no quiere tomar leche, elija productos sin lactosa u otras fuentes de calcio como el brócoli y las almendras.

Datos útiles

1 taza = 1 vaso de 8 onzas de leche
O
1 ½ onza de queso
(1 onza equivale a cuatro dados)

Grasas y aceites

Usted necesita comer un poco de grasa todos los días.

- ✓ Las grasas más saludables son aceites de origen vegetal como el de oliva, aguacate, nueces y los aceites vegetales. Elija éstas con mayor frecuencia.
- ✓ Las grasas menos saludables son las grasas de origen animal como las que contienen la carne roja, la leche entera, la manteca, la mantequilla y la mayonesa. Elija éstas con menor frecuencia.

Step 1: Moving more

Increase your daily moving with these ideas.

Walk the dog
Work in the garden
Walk to the store
Walk to the mall
Walk in the house

Play ball
Carry wood
Climb stairs
Play golf
Play with your kids or grandkids

Park further away when you shop.

Begin with what you are doing now and do a little more.

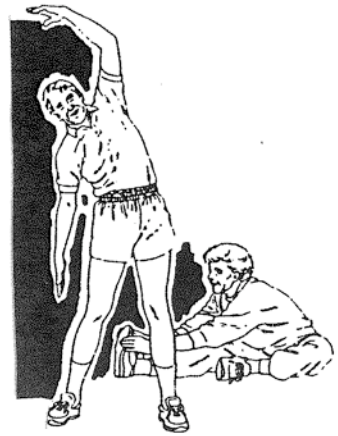
Step 2: Moving into exercise

When you're ready, choose one or two activities you like and practice them 5 times a week.

Brisk walking
Swimming
Rowing
Jogging
Dancing

Jumping rope
Volleyball
Skiing
Playing active games
Biking

When you start to exercise



Start slowly. Do 5 minutes at first. If you <u>feel</u> you are working too hard, you are- slow down. Check with your doctor if you have health problems or if you are not used to hard exercise. Using the whole body is heart healthy (aerobic) exercise.

Step 3: Follow the rules for safe exercise

1. <u>Warm up.</u> Walk or do the exercise slowly for 5 minutes.
2. <u>Begin with 5 minutes</u> of exercise. Add 5 minutes more each week until you reach 30 minutes. Aim for 5 times per week.
3. <u>Cool down.</u> Walk slowly for 5 minutes.

If you have any pain when you exercise, STOP. Call your doctor.

Remember:

1. Choose what you like best. Try different exercises on different days.
2. Don't give up. It takes time to form new habits.
3. Exercise with a friend.
4. Always warm up and cool down.
5. Work up to 30 minutes of exercise.
6. Exercise 5 times a week.

Do it! Stick to it! Exercise!

Pamphlet development supported by the Maine Statewide AHEC System, the University of New England, and the Bingham Program in cooperation with the Cardiac Rehabilitation Program, Kennebec Valley Medical Center, June 1992

Every body is made to move

Do you want

- ☺ more energy?
- ☺ to feel better?
- ☺ to reduce stress?
- ☺ to look better?
- ☺ to have fun?

Get moving! As easy as 1, 2, 3

Primer paso: Moviéndose más

Aumente su actividad física con estas ideas.

Camine al perro
Haga trabajo en el jardín
Camine a la tienda
Camine al centro comercial
Camine en la casa

Juegue pelota
Cargue leña
Suba escalones
Juegue golf
Juegue con sus niños o nietos

Estaciónese más lejos cuando vaya de compras.

Empiece con lo que está haciendo ahora y haga un poco más.

Segundo paso: Ahora al ejercicio

Cuando esté listo(a), elija una o dos actividades que le gustan y practiquelas 5 veces a la semana.

Caminar rápido	Brincar la cuerda
Nadar	Esquíar
Remar	Jugar voleibol
Trotar	Jugar juegos activos
Bailar	Ciclismo

Cuando empiece a hacer ejercicio

Empiece lentamente. Haga 5 minutos primero. Si usted siente que se está esforzando mucho, si lo está, disminúyale un poco. Pregúntele a su doctor si usted tiene problemas de salud o si usted no debe de estar haciendo ejercicio fuerte. Usando todo su cuerpo es un ejercicio saludable para el corazón (aeróbico).

Tercer paso: Siga las reglas para hacer ejercicio seguro

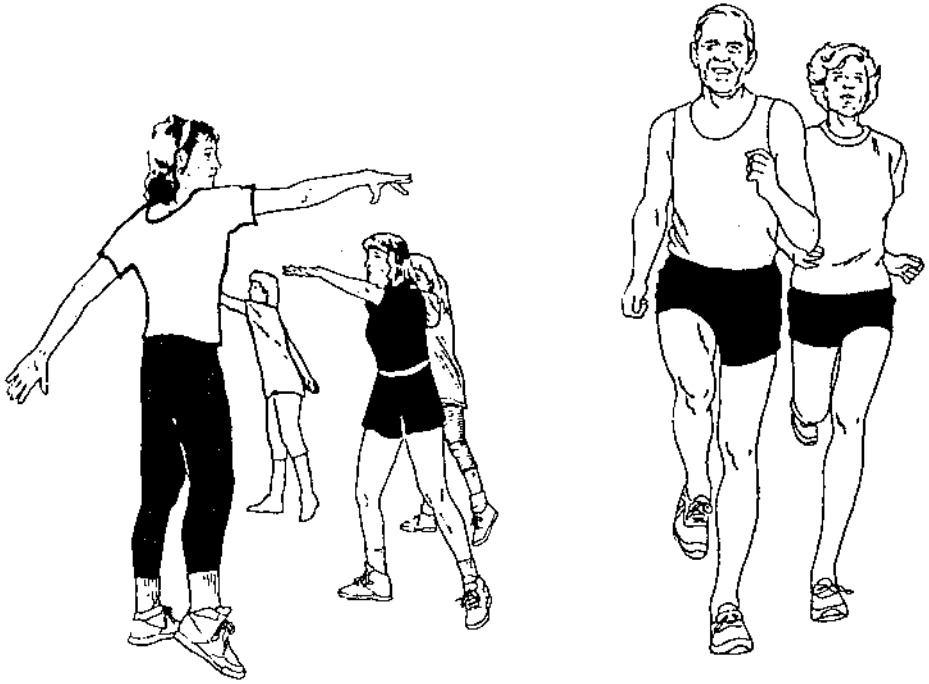
1. Calentamiento. Camine o haga ejercicio lentamente por 5 minutos.
2. Empiece con 5 minutos de ejercicio. Aumente 5 minutos más cada semana hasta llegar a 30 minutos. Su meta es 5 veces por semana.
3. Enfriamiento. Camine lentamente por 5 minutos.

Si tiene dolor cuando hace ejercicio, PARE. Llame a su doctor.

Recuerde:

1. Elija lo que a usted le gusta más. Intente diferentes ejercicios en diferentes días.
2. No se desanime. Toma tiempo formar nuevos habitos.
3. Haga ejercicio con un amigo.
4. Siempre haga ejercicios de calientamiento y enfriamento.
5. Siga hasta llegar a 30 minutos de ejercicio.
6. Haga ejercicio 5 veces por semana.

¡Hágalo! ¡No lo deje! ¡Haga Ejercicio!



Desarrollo del folleto apoyado por el sistema estatal de Maine AHEC, la universidad de Nueva Inglaterra, y el programa de Bingham en cooperación con el programa cardiaco de rehabilitación, centro médico del valle kennebec, junio de 1992

La traducción de este folleto fue financiada por Care1st Health Plan.

04 Spanish

Todo cuerpo está hecho para moverse

¿Quiere usted

- ☺ más energía?
- ☺ sentirse mejor?
- ☺ reducir la tensión nerviosa (estrés)?
- ☺ verse mejor?
- ☺ divertirse?

¡Muévase! Es tan fácil como 1, 2, 3

MY ACTION PLAN

Visited doctor on: _____

My weight goal: _____

3 steps I plan to take:

1.

2.

3.

HELPFUL TIP: To keep track of your progress, fill out "My Food and Activity Tracker" for one week. Make copies of the Tracker for the weeks to come. Here's a sample:

	FRUITS 2–3 a day	VEGGIES 3–5+ a day	ACTIVITIES 30–60 min.
M	1 cup of orange juice 1 apple 1 cup of grapes	6 baby carrots 1 cup of lettuce 1 cucumber ½ of a tomato	I walked for 45 minutes!

L.A. Care Health Plan Member Services:
1-888-839-9909

My Food and Activity Tracker

	FRUITS 2–3 a day	VEGGIES 3–5+ a day	ACTIVITIES 30–60 min.
M			
T			
W			
TH			
F			
SA			
SU			

LA0523 11/08

L.A. Care HEALTH PLAN

My Easy Steps to a **Healthy Weight**

Take your first step today!

For a **Healthy Life**

3 EASY STEPS TO A HEALTHY WEIGHT

1 Talk with your doctor

Choose steps to take:

- Eat a healthy breakfast
- Cut down on fastfood and sweets
- Cut out soda
- Limit juice to one small cup of 100% juice a day
- Drink more water
- Move your body 1 hour a day
- Take the TV out of the bedroom

2 Eat more fruits and vegetables

5 or more a day

- 2 to 3 fruits
- 3 to 5 vegetables
- Eat less high-fat, high-sugar foods like cookies, cake, chips, and fries

3 Move your body

1 hour a day

- Run
- Dance
- Jump
- Play
- Bike

TAKE YOUR FIRST STEP TODAY!

MI PLAN DE ACCIÓN

Fui al médico: _____

Peso deseado: _____

Tres pasos que pienso dar:

1.
2.
3.

CONSEJO: Para seguir su progreso, complete el cuadro de "Mi diario de comida y actividades" durante una semana. Haga copias del diario para las próximas semanas. Por ejemplo:

	FRUTA 2 a 3 al día	VERDURA 3 a 5+ al día	ACTIVIDAD 30–60 min.
LUNES	1 taza de jugo de naranja 1 manzana 1 taza de uvas	6 zanahorias pequeñas 1 taza de lechuga ½ tomate 1 pepino	Caminé 45 minutos

Llame a nuestro Departamento de servicio para miembros al 1-888-839-9909

Mi diario de comida y actividades

	FRUTA 2 a 3 al día	VERDURA 3 a 5+ al día	ACTIVIDAD 30–60 min.
LUNES			
MARTES			
MIÉRCOLES			
JUEVES			
VIERNES			
SÁBADO			
DOMINGO			

LA0523 11/08 SP

L.A. Care HEALTH PLAN

Mis pasos fáciles hacia un **peso saludable**

¡Dé el primer paso hoy!

Por Una **Vida Sana**

3 PASOS FÁCILES PARA MANTENER UN PESO SALUDABLE

1 Hable con su doctor

Decida qué pasos seguir:

- Coma un desayuno sano
- Evite las comidas rápidas y los dulces
- Disminuya el consumo de bebidas gaseosas
- Limite el consumo de jugos (100% de jugo natural) a tan sólo 1 pequeña taza diaria
- Tome más agua
- Mueva su cuerpo 1 hora cada día
- Quite la televisión de la recámara

2 Coma más fruta y verdura

por lo menos 5 al día

- 2-3 frutas
- 3-5 vegetales
- Coma menos alimentos altos en grasas y azúcares, como galletas, papitas tostadas y fritas

3 Mueva su cuerpo

1 hora diaria

- Corra
- Baile
- Salte
- Juegue
- Monte en bicicleta

¡DÉ EL PRIMER PASO HOY!

Patient's Guide to Stop Smoking

Introduction

This booklet is based on information from the U.S. Public Health Service Consumer Guide, *Help for Smokers and Other Tobacco Users,* May 2008. The booklet provides strategies and recommendations designed to assist tobacco users to quit.

This material was developed by the Los Angeles County Tobacco Control and Prevention Program. For questions, please contact the Los Angeles County Tobacco Control and Prevention Program at (213) 351-7890 or go to http://publichealth.lacounty.gov/tob/

Funding for this material provided by a generous grant from L.A. Care Health Plan.

Welcome!

Congratulations on taking the first step to stop smoking! We all know that quitting smoking is not easy. But there is hope! All of the information in this booklet is based on the best ways to help you quit. These steps will give you the best chance of stopping smoking for good.

Nicotine: A Strong Drug

Stopping smoking is hard because nicotine is a very strong drug. For some people, it can take many tries before they can stop smoking. But each time you try to stop, the more likely you will be able to stop for good.

Good Reasons to Stop Smoking

- ✓ You will feel better, have more energy and breathe easier.
- ✓ You will have less chance of getting sick.
- ✓ The people around you, especially children, will be healthier. Breathing other people's smoke can cause health problems.
- ✓ If you are pregnant, you and your baby will be healthier.
- ✓ You will save more money.

If you smoke one pack per day, look what you can save if you stop smoking for…

One day:	$5
One week:	$35
One month:	$150
One year:	$1,820
10 years:	$18,200
20 years:	$36,400

Prices are based on a 2007 average of $5.00 per pack.

Smoking and Your Health

Smoking is bad for your health. Smoking hurts almost every organ of the body and causes many health problems such as:

- Cancer
- Heart disease
- Stroke
- Lung disease
- Unhealthy effects on pregnancy and baby

Special Cases

Everyone can stop smoking. The best reasons to quit are the ones which are personal for you.

Pregnant women or new mothers: Quitting will help your baby be healthier.

People who have had heart attacks: Quitting can lower your risk of another heart attack.

Cancer patients: Quitting lowers your chance of getting cancer again.

Parents of children and teenagers: Quitting can keep your family from getting sick from secondhand smoke.

Your Health Gets Better When You Stop Smoking

After 20 minutes:	Heart rate slows down.
After 12 hours:	Carbon monoxide level in blood drops to normal.
After 48 hours:	Sense of smell and taste gets better.
After 2–3 weeks:	Chance of heart attack is lower, blood flow gets better, walking becomes easier, breathing gets better.
After 1–9 months:	Coughing and shortness of breath happen less often.
After 1 year:	Risk of heart disease is half that of a smoker.
After 5 years:	Risk of stroke is the same as that of a non-smoker.
After 10 years:	Lung cancer death risk is about half that of a smoker; risk of cancer of the mouth and throat is lower.
After 15 years:	Risk of heart disease goes down to that of a non-smoker.

Secondhand Smoke and Health

Secondhand smoke, or the smoke you breath when someone else smokes, is not good. Cigarettes, cigars, and pipes all give off secondhand smoke. It is not safe to be around any amount of secondhand smoke.

How Secondhand Smoke Can Hurt Us

- Secondhand smoke causes disease and early death in children and adults who do not smoke.

Secondhand Smoke and Children

- Secondhand smoke can hurt children. It can cause Sudden Infant Death Syndrome (SIDS), lung problems, and ear problems. It can also make asthma attacks worse and happen more often.
- Smoking can slow lung growth and cause breathing problems in children.

So How Do I Stop Smoking?

Follow these simple steps and you can be on your way to a life without smoking.

Step 1: **Get Ready**
Step 2: **Get Help**
Step 3: **Get Medicine**

Stay Quit!

Step 1: Get Ready

- **Choose a day to stop smoking.**
  After you quit, do not smoke – not even a puff!
  Do not use any tobacco.

- **Change the things around you.**
  Stop buying cigarettes.
  Get rid of ashtrays in your home, car and workplace.
  Do not let people smoke in your home.

Questions to think about...
Think about these questions before you try to stop smoking. You may want to talk about your answers with your doctor.

1. Why do you want to stop smoking?

2. If you tried to stop smoking in the past, what helped you? What did not help you?

3. What situations will be hard for you after you stop smoking? How will you plan to handle them?

4. What pleasures do you get from smoking? What ways can you still get pleasure if you stop smoking?

Your Quit Date:

_____

Follow this 5-day countdown to your quit date:

5 days before	• Think about why you want to stop smoking. • Tell your friends and family you are planning to stop. • Stop buying cigarettes.
4 days before	• Pay attention to when and why you smoke. • Think of other things to hold in your hand, like a rubber band or a stress ball. • Think of habits or things that you do every day that you can change.
3 days before	• Think of who you can ask for help.
2 days before	• Get medicine to help you stop smoking. See your doctor to get a prescription.
1 day before	• Throw away cigarettes, matches and lighters. Put away ashtrays. • Clean your clothes to get rid of the smell of cigarettes.
Quit Day!	• Keep very busy. • Tell family and friends that today is your quit day. • Stay away from alcohol. • Give yourself a treat or do something special.

Step 2: Get Help

You have a better chance of quitting if you have help.

- **Tell your family, friends and people you work with** that you are going to stop smoking. Ask for their help.

- **Talk to your doctor, nurse, or other health care worker. They can help you quit.** Here are some questions you can ask your doctor:
  - How can you help me stop smoking?
  - What medicine is best for me? How do I use it?
  - What should I do if I need more help?
  - What is it like to stop smoking?

- Call the **CALIFORNIA SMOKERS' HELPLINE** for **FREE** help.

1-800-NO-BUTTS (or 1-800-662-8887) English
1-800-45-NO-FUME (or 1-800-45-66-3863) Spanish
1-800-838-8917 Chinese
1-800-556-5564 Korean
1-800-778-8440 Vietnamese
1-800-933-4TDD Hearing Impaired
1-800-844-CHEW Chewers' Helpline

There are programs for pregnant women, teens and tobacco chewers too. You can also go to: www.californiasmokershelpline.org

Step 3: Get Medicine

If you are trying to stop smoking, medicine can help raise your chances of stopping for good. **Talk to your doctor about getting the right medicine for you**.

If you are pregnant or trying to become pregnant, nursing, under age 18, smoking fewer than 10 cigarettes per day or have a health problem, tell your doctor**.**

Ask your doctor about medicines that can help you stop smoking:

Nicotine Patch
Nicotine Gum
Nicotine Lozenge
Nicotine Nasal Spray
Nicotine Inhaler
Bupropion SR (pill)
Varenicline (pill)

How to get medicine to help you stop smoking

1 **Talk to your doctor**

- Tell your doctor that you want to stop smoking.
- Ask your doctor about getting a prescription for medicine that is right for you.
- If you have Medi-Cal, you may need prior authorization. Check your health plan to see if your medicine is covered. Ask your doctor for help.

2 **Call the California Smokers' Helpline**
1-800-NO-BUTTS
(1-800-662-8887)

- A trained person will help you with a plan to stop smoking.
- After the first call, the Helpline will send you a certificate of enrollment.

3 **Go to a pharmacy or drug store**

- Choose a pharmacy that works with your health plan.
- Bring your prescription to the pharmacy.
- Give the pharmacy your certificate from the California Smokers' Helpline.
- Also remember to bring your health plan member ID card.

Stay Quit!

If you "slip" or start smoking again, do not give up. Keep trying. Remember, many people try many times before they finally stop smoking for good.

- **Stay away from alcohol**.
- **Stay away from other people when they smoke.** If you can, go to a place where smoking is not allowed.
- **Eat healthy food and get exercise.** This will help you manage your weight, and it will help keep your mood up.

Talk to your doctor if you are having problems with any of these situations, and remember:

Step 1: **Get ready**

Step 2: **Get help**

Step 3: **Get medicine**

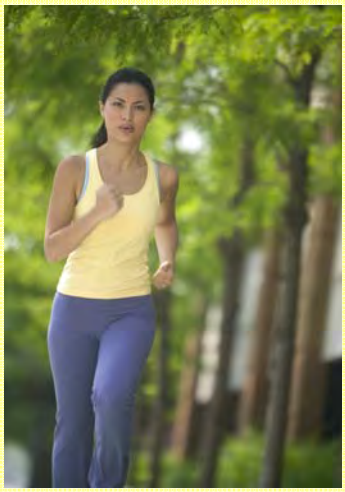
Stay Quit!

More ideas to help you stop smoking:

- ✓ Keep busy! Go for a walk or talk to your friends and family.
- ✓ Drink a lot of water.
- ✓ After meals, brush your teeth or use mouthwash.
- ✓ Take a deep breath through your nose and blow out slowly through your mouth. Do this 10 times.
- ✓ Do not allow smoking in your home or your car.

Keep Moving!

Be active and exercise. Choose activities you enjoy and slowly add more time that you do them. It's also a good idea to check with your doctor before starting any type of activity.



- ✓ Find ways to walk, bike or jog more.
- ✓ Park the car further away so you can walk more.
- ✓ Take the stairs instead of the elevator.
- ✓ Play with your children.
- ✓ Go dancing!

Eat Healthy Foods

- ✓ Eat more vegetables, whole grains, and fat-free or low-fat milk products. Drink fat-free or low-fat milk.
- ✓ Eat lean meats, chicken, fish, beans, eggs and nuts.
- ✓ Cut down on fat, salt and sugar.

More Information to Help You Stop Smoking

L.A. Care
1-888-4LA-Care
or 1-888-452-2273
www.lacare.org

American Legacy Foundation
1-202-454-5555
www.americanlegacy.org

It's Quitting Time LA!
www.laquits.com

California Smokers' Helpline
1-800-NO-BUTTS or
1-800-662-8887
www.californiasmokershelpline.org

American Cancer Society
1-800-ACS-2345 (1-866-228-4327 for TTY)
www.cancer.org

American Heart Association
1-800-AHA-USA-1 or
1-800-242-8721
www.americanheart.org

American Lung Association of California
(510) 638-LUNG
www.californialung.org

1-800-QUIT-NOW
1-800-784-8669
www.smokefree.gov

Guía del paciente para dejar de fumar

L.A. Care HEALTH PLAN

County of Los Angeles Public Health

Introducción

Este folleto se basa en información de la guía del consumidor de servicios de salud pública de los Estados Unidos *Help for Smokers and Other Tobacco Users ("Ayuda para fumadores y otros consumidores de tabaco"),* de mayo de 2008. El folleto ofrece estrategias y recomendaciones diseñadas para ayudar a los consumidores de tabaco a dejar de fumar.

Este material ha sido desarrollado por el Programa de prevención y control del tabaco del condado de Los Ángeles. Si tiene alguna pregunta, póngase en contacto con el Programa de prevención y control del tabaco del condado de Los Ángeles llamando al (213) 351-7890 o visitando http://publichealth.lacounty.gov/tob/

El financiamiento de estos materiales proviene de un generoso subsidio de L.A. Care Health Plan.

¡Bienvenidos!

¡Felicitaciones por tomar el primer paso para dejar de fumar! Todos sabemos que dejar de fumar no es sencillo. Pero ¡hay esperanza! Toda la información de este folleto se basa en los mejores métodos para ayudarle a dejar de fumar. Estos pasos le darán la mejor oportunidad para dejar de fumar para siempre.

La nicotina: Una droga poderosa

Dejar de fumar es difícil porque la nicotina es una droga muy poderosa. Algunas personas tienen que intentarlo muchas veces antes de dejar de fumar. Pero cada vez que intenta dejar de fumar tiene más probabilidades de dejarlo para siempre.

Buenos motivos para dejar de fumar

- ✓ Se sentirá mejor, tendrá más energía y respirará mejor.
- ✓ Tendrá menos probabilidades de enfermarse.
- ✓ Las personas a su alrededor, sobre todo los niños, estarán más saludables. Respirar el humo de otras personas puede causar problemas de salud.
- ✓ Si está embarazada, usted y su bebé estarán más saludables.
- ✓ Ahorrará más dinero.

Si fuma un paquete al día, fíjese cuánto puede ahorrar si deja de fumar por…

Un día:	$5
Una semana:	$35
Un mes:	$140
Un año:	$1,820
10 años:	$18,200
20 años:	$36,400

Los precios se basan en el promedio de $5.00 por paquete en 2007.

Fumar y su salud

Fumar es malo para su salud. Fumar afecta casi todos los órganos y causa muchos problemas de salud como:

- Cáncer
- Enfermedades de corazón
- Ataque cerebral
- Enfermedad pulmonar
- Efectos no saludables en el embarazo y el bebé

Casos especiales

Toda persona puede dejar de fumar. Los mejores motivos para dejar de fumar son los motivos personales de cada uno.

Mujeres embarazadas o nuevas mamás: Dejar de fumar ayudará a que su bebé esté más saludable.

Personas que han tenido un ataque al corazón: Dejar de fumar puede disminuir el riesgo de tener otro ataque al corazón.

Enfermos de cáncer:
Dejar de fumar disminuye las probabilidades de volver a tener cáncer.

Padres de niños y adolescentes:
Dejar de fumar puede evitar que la familia se enferme por el humo de fumador pasivo.

Su salud mejora cuando deja de fumar

Después de 20 minutos:	Disminuye el ritmo del corazón.
Después de 12 horas:	El nivel de monóxido de carbono en la sangre vuelve a lo normal.
Después de 48 horas:	Mejoran el sentido del gusto y el olfato.
Después de 2 ó 3 semanas:	Disminuye la probabilidad de tener un ataque al corazón, mejora el flujo sanguíneo, es más fácil caminar y mejora la respiración.
Después de 1 a 9 meses:	Se tose y falta la respiración con menos frecuencia.
Después de 1 año:	El riesgo de tener un ataque al corazón es 50% menor que el de un fumador.
Después de 5 años:	El riesgo de ataque cerebral es el mismo que el de los no fumadores.
Después de 10 años:	Tiene aproximadamente 50% menos riesgo de morir por cáncer de pulmón que un fumador; el riesgo de tener cáncer de boca y de garganta es menor.
Después de 15 años:	El riesgo de tener una enfermedad del corazón disminuye al mismo nivel de los no fumadores.

El humo de fumador pasivo y la salud

El humo de fumador pasivo, es decir, el humo que se respira cuando fuma otra persona, no es bueno. Los cigarrillos, los puros y las pipas producen todos humo de fumador pasivo. Hay riesgo por estar cerca de cualquier cantidad de humo de fumador pasivo.

Cómo nos puede perjudicar el humo de fumador pasivo

- El humo de fumador pasivo es causa de enfermedad y muerte temprana en niños y adultos que no fuman.

El humo de fumador pasivo y los niños

- El humo de fumador pasivo puede perjudicar a los niños. Puede causar muerte de cuna, problemas de pulmón y de oído. También puede empeorar los ataques de asma y hacer que se produzcan con más frecuencia.
- Fumar puede retrasar el crecimiento de los pulmones y causar problemas respiratorios en los niños.

Entonces, ¿cómo dejo de fumar?

Si sigue estos pasos sencillos, irá de camino hacia una vida sin tabaco.

Paso 1: **Prepárese**
Paso 2: **Pida ayuda**
Paso 3: **Obtenga medicamentos**

¡Siga sin fumar!

Paso 1: **Prepárese**

- **Escoja un día para dejar de fumar.**
  Cuando deje de fumar, no vuelva a hacerlo, ¡ni siquiera una probadita! No use nada de tabaco.

- **Cambie las cosas a su alrededor.**
  Deje de comprar cigarrillos.
  Tire los ceniceros de su casa, su carro y su lugar de trabajo.
  No deje que la gente fume en su casa.

Preguntas en las que pensar...
Piense en estas preguntas antes de tratar de dejar de fumar. Puede que desee comentar sus respuestas con su médico.

1. ¿Por qué quiere dejar de fumar?

2. Si intentó dejar de fumar en el pasado, ¿qué le ayudó? ¿Qué no le ayudó?

3. ¿Qué situaciones serán difíciles para usted cuando deje de fumar? ¿Cómo piensa manejarlas?

4. ¿Qué placer obtiene de fumar? ¿Cómo puede seguir obteniendo placer si deja de fumar?

El día que deje de fumar:

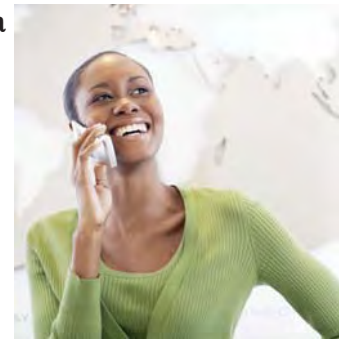
_____

Siga esta cuenta hacia atrás 5 días antes de dejar de fumar:

5 días antes	• Piense por qué quiere dejar de fumar. • Dígale a sus amigos y a su familia que piensa dejar de fumar. • Deje de comprar cigarrillos.
4 días antes	• Preste atención a cuándo y por qué fuma. • Piense en otras cosas que pueda tener en la mano como una liga o una pelota anti-estrés. • Piense en hábitos o cosas que hace cada día y que puede cambiar.
3 días antes	• Piense a quién puede pedir ayuda.
2 días antes	• Consiga una medicina que le ayude a dejar de fumar. Vea al médico para que le dé una receta.
1 día antes	• Tire los cigarrillos, los cerillos y los encendedores. Guarde los ceniceros. • Lave su ropa para deshacerse del olor a cigarrillo.
El día que deje de fumar	• Manténgase muy ocupado. • Dígale a su familia y a sus amigos que hoy es el día que deja de fumar. • Aléjese del alcohol. • Dese un gusto o haga algo especial para usted.

Paso 2: **Pida ayuda**

Tiene más probabilidades de dejar de fumar si recibe ayuda.



- **Dígale a su familia, a sus amigos y a la gente con la que trabaja** que va a dejar de fumar. Pida ayuda.

- **Hable con su médico, su enfermera u otro trabajador de atención médica. Ellos pueden ayudarle a dejar de fumar.** Algunas preguntas que puede hacerle a su médico:
  - ¿Cómo puede ayudarme a dejar de fumar?
  - ¿Qué medicina es mejor para mí? ¿Cómo la utilizo?
  - ¿Qué debo hacer si necesito más ayuda?
  - ¿Cómo es dejar de fumar?

- Llame a la **LÍNEA DE AYUDA PARA FUMADORES DE CALIFORNIA** para recibir **AYUDA** gratuita.

  1-800-NO-BUTTS (o 1-800-662-8887) inglés
  1-800-45-NO-FUME (o 1-800-45-66-3863) español
  1-800-838-8917 chino
  1-800-556-5564 coreano
  1-800-778-8440 vietnamita
  1-800-933-4TDD personas con deficiencia auditiva
  1-800-844-CHEW Línea de ayuda para los que mastican tabaco

También hay programas para mujeres embarazadas, adolescentes y mascadores de tabaco. También puede visitar: www.californiasmokershelpline.org

Paso 3: **Obtenga medicamentos**

Si trata de dejar de fumar, la medicina puede ayudar a aumentar sus probabilidades de dejarlo para siempre. **Hable con su médico sobre cómo obtener el medicamento apropiado para usted**.

Si está embarazada o tratando de quedar embarazada, si está amamantando, tiene menos de 18 años, fuma menos de 10 cigarrillos al día o tiene un problema de salud, dígaselo a su médico**.**

Pregúntele a su médico sobre medicamentos que pueden ayudarle a dejar de fumar:

El parche de nicotina
Chicle de nicotina
Caramelos de nicotina
Rociador nasal de nicotina
Inhalador de nicotina
Bupropion SR (píldora)
Varenicline (píldora)

Cómo conseguir medicina que le ayude a dejar de fumar

1 Hable con su médico

- Dígale a su médico que quiere dejar de fumar.
- Pregúntele a su médico cómo obtener una receta para una medicina apropiada para usted.
- Si tiene Medi-Cal, puede que necesite autorización previa. Pregunte en su plan de salud para ver si su medicina está cubierta. Pida ayuda a su médico.

2 Llame a la Línea para fumadores de California
1-800-NO-BUTTS
(1-800-662-8887)

- Una persona capacitada le ayudará con un plan para dejar de fumar.
- Después de la primera llamada, la línea de ayuda le enviará un certificado de inscripción.

3 Vaya a una farmacia

- Elija una farmacia que trabaje con su plan de salud.
- Lleve su receta a la farmacia.
- Dele a la farmacia su certificado de la línea de ayuda para fumadores de California.
- Recuerde también llevar su tarjeta de miembro del plan de salud.

¡Siga sin fumar!

Si "cae" o empieza a fumar otra vez, no se rinda. Siga intentándolo. Recuerde, mucha gente lo intenta muchas veces antes de dejar de fumar para siempre.

- **Aléjese del alcohol**.
- **Aléjese de otras personas cuando fumen.** Si puede, vaya a un lugar donde no se permita fumar.
- **Coma alimentos saludables y haga ejercicio.** Esto le ayudará a controlar su peso y a tener un buen estado de ánimo.

Hable con su médico si tiene problemas en alguna de estas situaciones, y recuerde:

Paso 1: **Prepárese**

Paso 2: **Pida ayuda**

Paso 3: **Obtenga medicamentos**

¡Siga sin fumar!

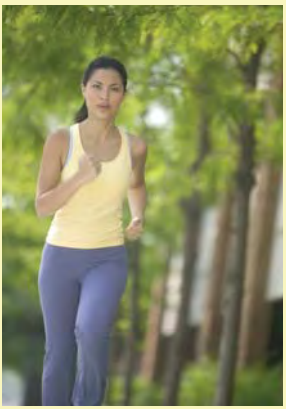
Más ideas para ayudarle a dejar de fumar:

- ✓ ¡Manténgase ocupado! Salga a pasear o hable con sus amigos y su familia.
- ✓ Tome mucha agua.
- ✓ Después de las comidas, cepíllese los dientes o utilice un enjuague bucal.
- ✓ Respire profundamente por la nariz y exhale lentamente por la boca. Haga esto 10 veces.
- ✓ No deje que fumen en su casa ni en su carro.

¡Manténgase en movimiento!

Permanezca activo y haga ejercicio. Elija actividades que disfrute y dedíqueles más tiempo poco a poco. También es buena idea hablar con su médico antes de empezar cualquier tipo de actividad.

- ✓ Busque maneras de caminar, andar en bicicleta o correr más.
- ✓ Estacione su carro más lejos para poder caminar más.
- ✓ Tome las escaleras en vez del elevador.
- ✓ Juegue con sus hijos.
- ✓ ¡Vaya a bailar!



Coma alimentos saludables

- Coma más verduras, granos enteros y productos lácteos sin grasa o con poca grasa. Tome leche sin grasa o con poca grasa.
- Coma carnes magras, pollo, pescado, frijoles, huevos y nueces.
- Reduzca las grasas, la sal y el azúcar.

Más información para ayudarle a dejar de fumar

L.A. Care
1-888-4LA-Care
o 1-888-452-2273
www.lacare.org

American Legacy Foundation
1-202-454-5555
www.americanlegacy.org

It's Quitting Time LA!
www.laquits.com

Línea de ayuda para fumadores de California
1-800-NO-BUTTS or
1-800-662-8887
www.californiasmokershelpline.org

Sociedad americana contra el cáncer
1-800-ACS-2345 (1-866-228-4327 for TTY)
www.cancer.org

Asociación americana del corazón
1-800-AHA-USA-1 o
1-800-242-8721
www.americanheart.org

Asociación del pulmón de California
(510) 638-LUNG
1-800-LUNG-USA o
1-800-586-4872
www.californialung.org

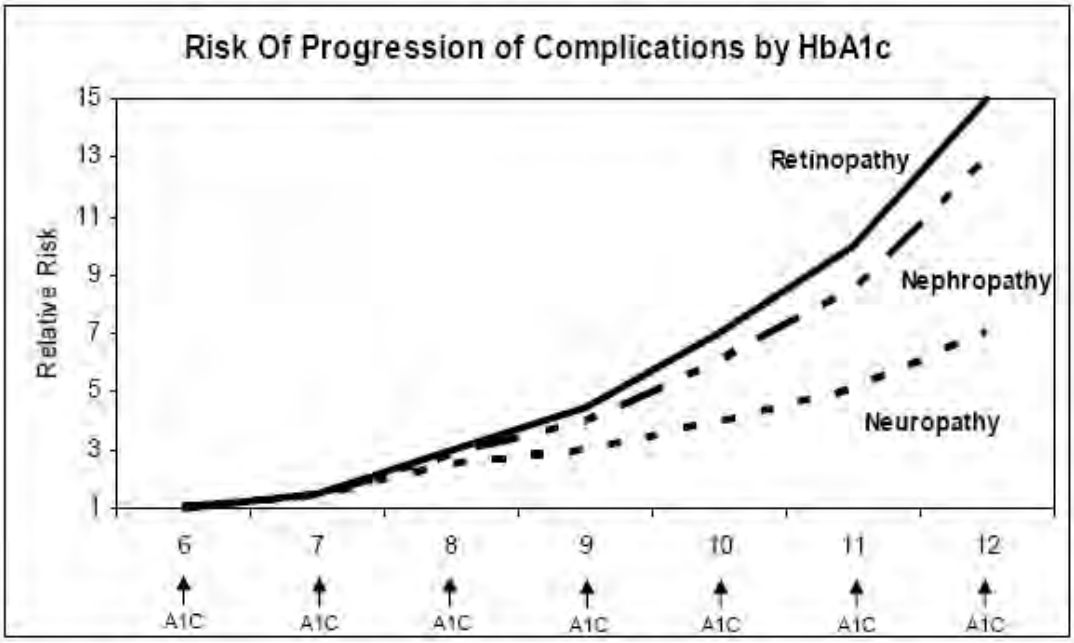
1-800-QUIT-NOW
1-800-784-8669
www.smokefree.gov

CARDIOVASCULAR FLOW SHEET

Name:	**Medical Record #:**			**D.O.B:**	
Basic Guidelines for Cardiovascular Care					
	Date:	Date:	Date:	Date:	Date:
Blood Pressure (every visit) Goal:					
Weight (every visit) Goal:					
Height					
BMI (every visit) Goal:					
Lipid Profile (annual) Total Cholesterol, < 200 mg/dl Goal:					
HDL (annual) > 40 mg/dl (male), > 50 mg/dl (female) Goal:					
LDL (annual) < 100 mg/dl Goal:					
Triglycerides (annual) < 150 mg/dl Goal:					
A1C (annual)					
Ejection Fraction (%) or degree of LV dysfunction					
ACE Inhibitor/ARB for Heart Failure					
ACE Inhibitor/ARB for Post MI					
Beta-Blocker/HF					
Beta-Blocker/Post MI					
Statin Therapy (elevated LDL or ischemic heart disease)					
Aspirin Therapy (if age >40 yrs or high risk for CVD)					
Smoking Cessation (California Smokers' Helpline 1-800-NO-BUTTS)					
Behavioral Issues / Depression					
Physical Activity (frequency)					
Influenza (Annual)					
Pneumococcal Immunization (as recommended by CDC)					

L.A. Care HEALTH PLAN

IS THIS POWERFUL?



Please ask your patient to visit an ophthalmologist or optometrist for their check-up today!

Source: Skyler. Endocrinol Metab Clin North Am 1996;25:243-254

Order of Importance for Predicting Fatal and Nonfatal MI

1.	LDL Cholesterol	P=0.0022
2.	Diastolic BP	P=0.012
3.	Smoking	P=0.025
4.	HDL Cholesterol	P=0.026
5.	A1C	P=0.053

High Risk

Low Risk

Please check your patients LDL levels today!

Source: Turner RC, Millus H, Neil HA, et al. BMJ.1998;316:823-828

For more information please contact L.A. Care's Utilization Management Medical Director, Dr. Z. Joseph Wanski, at (213) 694-1250 ext 4388 or email: jwanski@lacare.org