МОНГОЛ УЛСЫН ЗАСГИЙН ГАЗАР

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World Health Organization

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МОНГОЛЫН МЯНГАНЫ СОРИЛТЫН САН

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CLINICAL GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Ulaanbaatar, 2013

CONTENT PAGES

ABBREVIATIONS

ACC – American College of Cardiology
ACE - angiotensin-converting enzyme
ACS – acute coronary syndrome
ACT - activated clotting time
AF – atrial fibrillation
ANA – American Heart Association
AMI – acute myocardial infarction
APTT - activated partial prothrombin time
ARB - angiotensin receptor blocker
ASA – Acetylsalicylic acid
AV - atrio-ventricular
BB – beta adrenergic blocker
BID – twice daily
CABG - coronary artery bypass graft
CAD – coronary artery disease
CCU – coronary care unit
CK – creatine kinase
CT – computed tomography
EchoCG - echocardiography
ECG – electrocardiogram
ED – emergency department
EF - ejection fraction
EMS – emergency medical system
ESC - European Society of Cardiology
FMC - first medical contact
GP – glycoprotein
HF – heart failure
IABP - intra-aortic balloon pump
ICCU - Intensive Cardiac Care Unit
ICD - implantable cardioverter–defibrillator
ICH – intra cerebral hemorrhage
INR - international normalized ratio
IV – intravenous
LAD – – left anterior descending artery
LBBB – left bundle branch block
LCA - left circumflex artery
LDL - low-density lipoprotein
LMWH - low-molecular-weight heparin
LV - left ventricular

LVEF – left ventricular ejection fraction
HDL – high density lipoprotein
NSAID - non-steroidal anti-inflammatory drug
NSTEMI – Non ST-segment elevation myocardial infarction
NTG - nitroglycerin
OD –once daily
PCI - percutaneous coronary intervention
PO – per os
RCA – right coronary artery
SC - subcutaneous
SCD - sudden cardiac death
SK – streptokinase
STEMI - ST-segment elevation myocardial infarction
TID – three times daily
TNK - tenektasa
TIMI - thrombolysis in myocardial infarction
t-PA - tissue plasminogen activator
UFH – unfractionated heparin
VF - ventricular fibrillation
VT - ventricular tachycardia

PREFACE

AMI is a major cause of death and disability worldwide. Every year 32 million people suffer from AMI and 2.5 million people die in the world. Diseases of the circulatory system are among the

leading causes of morbidity and mortality (36.8%) in Mongolia. According to the National Health Indicators 2009, the rate of circulatory system diseases has increased from 502 per 10,000 persons in 2008 to 679 per 10,000 persons in 2009.

This guideline was developed by the working group of the Ministry of Health (MOH) of Mongolia, in co-operation with World Health Organization (WHO). The MOH working group included representatives from the Mongolian Heart Association (MHA), Health Sciences University of Mongolia, Shastin Hospital, First State Hospital, Second General Hospital a representative of general practitioners (GP) and private hospitals (Humuun hospital), School of Nursing, and Millennium Challenge Account-Mongolia (MCA-M) Health Project. The clinical guidelines have been developed based on most recent international (European, WHO) guidelines on the management of myocardial infarction.

The guideline summarizes the management of 2 typed of AMI: ST segment elevation myocardial infarction and Non ST segment elevation myocardial infarction.

A. INTRODUCTION

A.1. Definition of acute myocardial infarction

Acute myocardial infarction is defined as myocardial cell death due to prolonged myocardial ischemia

A.2. Disease code (ICD 10)*:* I 21 - I 23

A.3. Users of guideline

- General practitioners
- Family doctors
- Internal medicine doctors
- Cardiologists
- Ambulance doctor
- Interventional cardiologist
- Doctors of ED
- Patients
- Other specialists and members of committees and government and NGO working on this field.

A.4. The goal of the guideline

To improve the early detection, treatment and control of AMI and to reduce disease morbidity and mortality

A.5. Date of guideline development*:* 2012 years

A.6. Date of next revision: 2016 years

A.7. PARTICIPANTS FOR PREPARING GUIDELINE

Name	Position
U.Tsolmon	Head of working group. Associate professor , Department of Cardiology, Health Sciences University of Mongolia, Consultant cardiologist of Second General Hospital
Buing Chul Chang	Consultant Cardiologist of WHO, professor of the Yonsei University

D. Narantuya	WHO, TO/NPO, Stroke and heart attack project
Z. Lkhagvasuren	Secretary of working group. Consultant angiologist, Department of Angiology, Shastin Clinical Hospital
Dr. D.Zulgerel	Head of the Cardiology Department, Health Sciences University of Mongolia
A. Olziikhutag	President, Mongolian Heart Foundation
D.Serjee	Head of the Society of Echocardiographists, Consultant cardiologist of Second General Hospital
D.Tsegeenjav	Consultant Cardio surgeon, Department of Cardiac Surgery, Shastin Clinical Hospital
G.Dejeekhuu	Director, "Khumuun" private hospital
Kh. Tuya	Cardiologist, Shastin Clinical Hospital
Ch. Enkhtuul	Lecturer, School of Nursing, Health Sciences University of Mongolia
B.Batbold	Head, Department of Cardiolgy, Central Clinical Hospital
R.Tsevelmaa	Head, Department of Cardiolgy, Shastin Clinical Hospital
P.Otgontungalag	Cardiologist, Songino-Khairkhan District Hospital
Ts.Damdinsuren	Head, Department of Angiology, Shastin Clinical Hospital
Kh.Batmyagmar	Cardiologist, Shastin Clinical Hospital
L.Erdenekhuu	Cardiologist, Second General Hospital
G.Gereltuya	Cardiologist, Shastin Clinical Hospital
Ts. Burmaa	Officer, Standardization and Measurement Agency
N. Oyunbileg	Team leader of Health project of MCA
Salik Ram Govind	Team leader of NCD, WHO

A.8. Review, discussion and approval of guideline

Organization	Responsible for completion
MOH Sub-working group meetings of clinical guideline development for Acute Myocardial Infarction (September 2011- October 2012)	U.Tsolmon Chief , MOH Sub-working group on clinical guideline for Acute Myocardial Infarction
Consensus meeting of MOH Sub-working group of clinical guideline development for Acute Myocardial Infarction (20th December 2011)	D. Gonchigsuren Director, Department of Medical Care Policy, Implementation and Coordination, MOH
Meeting of HSUM Medical Terminology Committee (9thMarch 2012)	Prof. G. Tsagaankhuu Chairman, HSUM Medical Terminology Committee
Meeting of Mongolian cardiologist, (13-14th September 2012)	D. Narantuya, WHO/NPO Prof. Byung-Chul Chang, WHO/Consultant
Meeting of MOH Internal Medicine Professional sub-Committee (18th September 2012)	Prof. B. Tserendash, Chairman, MOH Professional Sub-Committee
The Administrative Council of MOH (15th November, 2012)	J. Khatanbaatar, State Secretary for Health

A.9. Used terminology in guideline*:*

ST-segment-elevation MI (STEMI) is one of the types MI, which presenting with ischemic symptoms and persistent ST-segment elevation on the ECG (STEMI).

Non-ST-segment-elevation MI (NSTEMI) is other one type of MI, which presenting with ischemic symptoms but without persistent ST-segment elevation.

Acute coronary syndrome (ACS) is the name given to several syndromes which are are caused by the sudden formation of blood clots (thrombosis) within a coronary artery. Acute coronary syndrome usually occurs as a result of one of three problems: ST elevation myocardial infarction , non ST elevation myocardial infarction, or unstable angina.

Coronary reperfusion is restoration of blood supply to heart tissue which is ischemic due to decrease in normal blood supply.

Coronary revascularization is any medical procedure (CABG, PTCA, stenting) performed to restore the normal blood flow in patients with atherosclerosis.

Percutaneous coronary intervention (PCI) commonly known as coronary angioplasty is a common nonsurgical procedure used to restore blood flow to blocked coronary arteries due to too narrow or new thrombus

Fibriniolytic therapy is a treatment used to break up dangerous clots inside your blood vessels.

Coronary Artery Bypass Graft is a section of vein or other conduit grafted between the aorta and a coronary artery distal to an obstructive lesion in the latter.

A10. Epidemiologic information:

AMI is a major cause of death and disability worldwide. MI may be a minor event in a lifelong chronic disease, it may even go undetected, but it may also be a major catastrophic event leading to sudden death or severe hemodynamic deterioration. Furthermore, the term MI has major psychological and legal implications for the individual and society. It is an indicator of one of the leading health problems in the world.

Epidemiology of MI in Mongolia

Diseases of the circulatory system are among the leading causes of morbidity and mortality in Mongolia. According to the National Health Indicators 2009, the rate of circulatory system diseases has increased from 502 per 10,000 persons in 2008 to 679 per 10,000 persons in 2009. The prevalence of AMI in Mongolia has increased last 20 years. According to findings of study of State Second Central Hospital, the hospital morbidity of AMI has increased 2.1 times during the 10 last years and the hospital mortality of AMI has decreased by 5.2% and was 14.5%.

B. MANAGEMENT ALGORITHM OF AMI

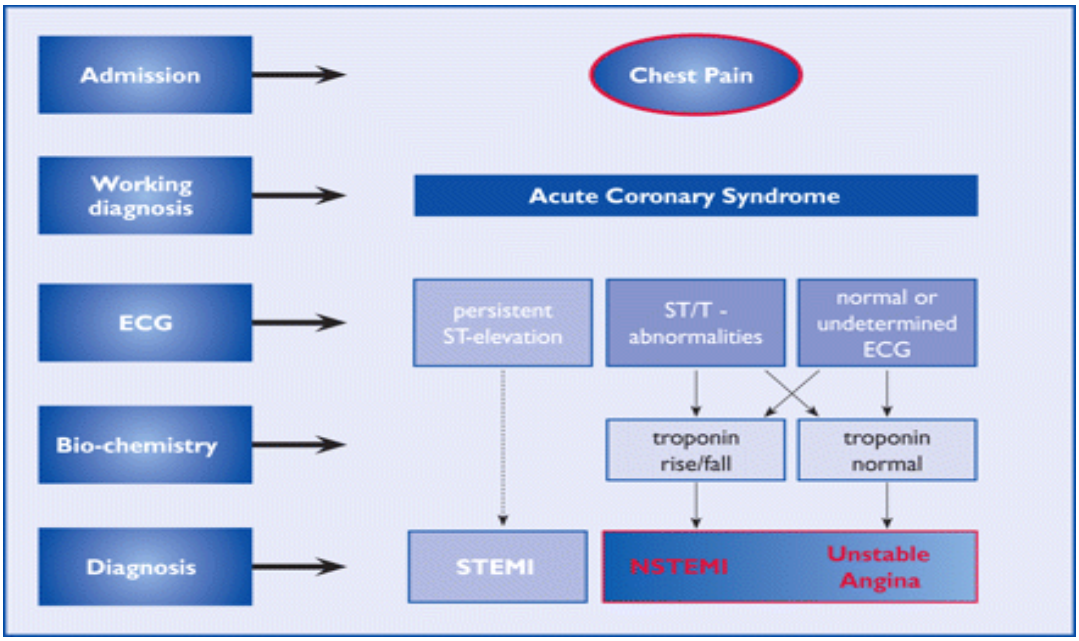

Figure 1*. The diagnostic algorithm of AMI . ECG = electrocardiogram; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

** Resource: : ESC Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes(2007)*

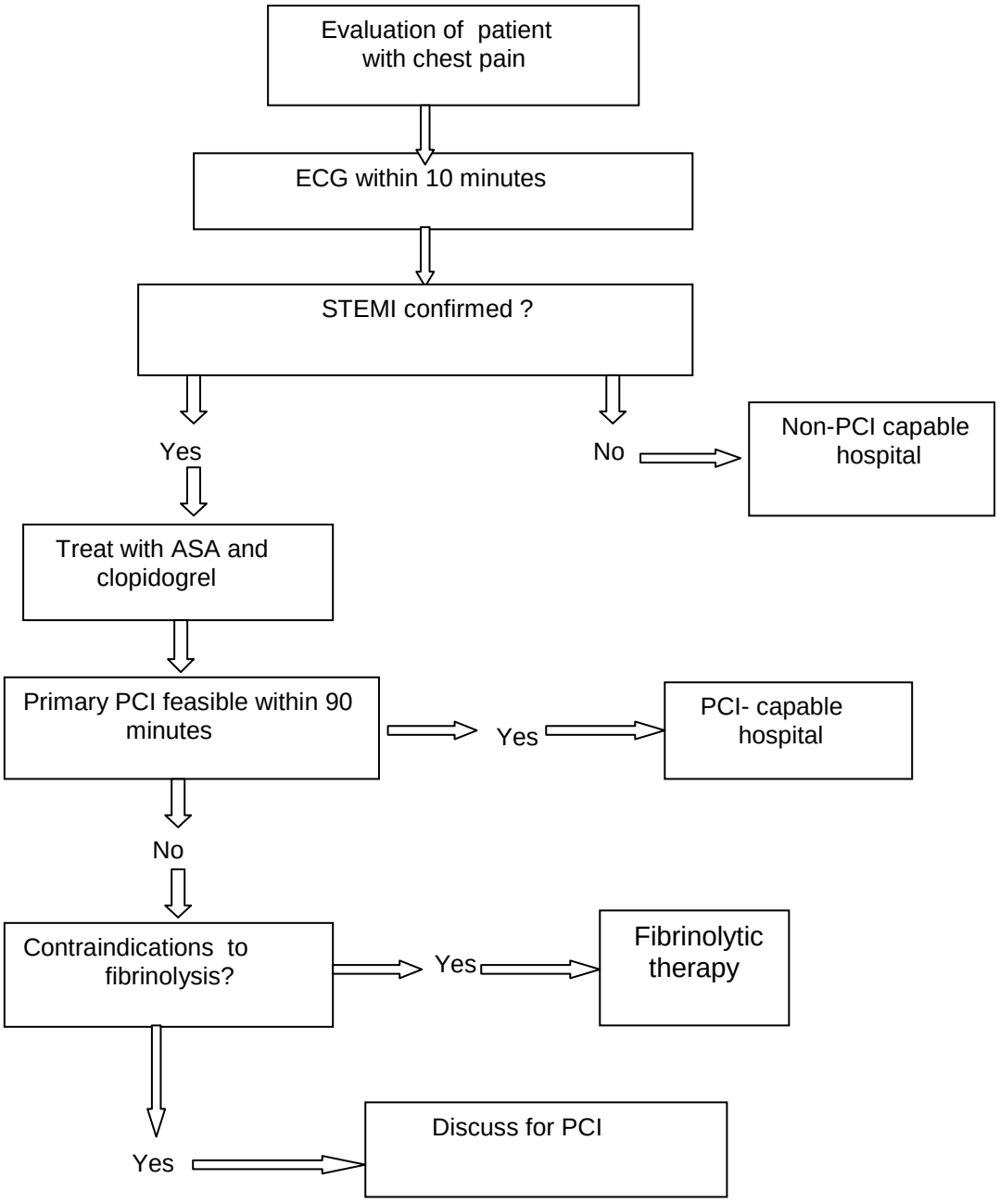

Figure 2. STEMI care algorithm*

* *Resource: Nova Scotia Guigelines for Acute Coronary Syndromes (Canada, 2008)*

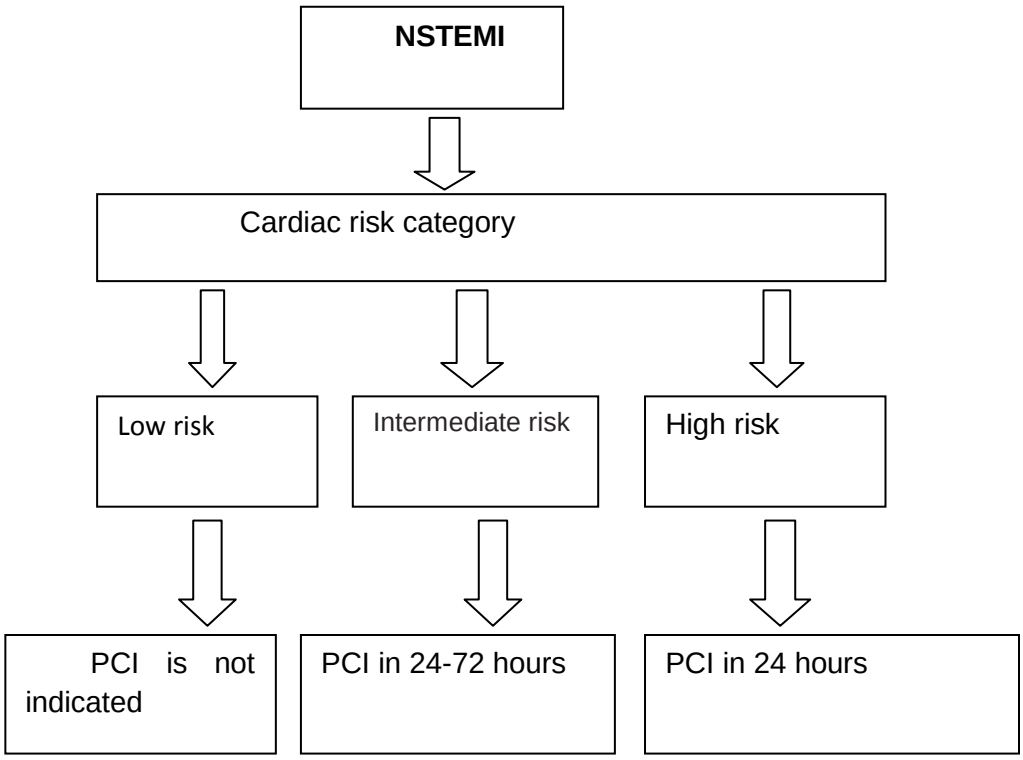

Figure 3. NSTEMI care algorithm*

** RESOURCE: ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROMES(2007)*

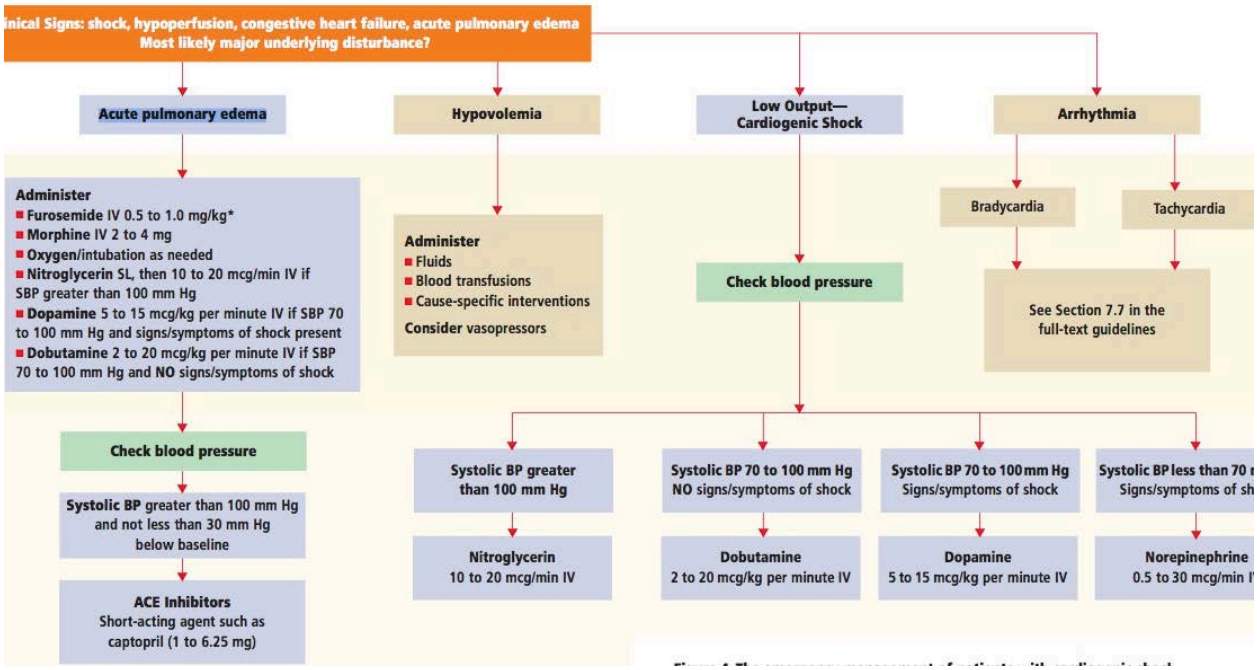

Figure 4. Treatment algorithm of the complication in AMI

C. CLASSIFICATION AND DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

C.1. Classification of acute myocardial infarction

Table 1 Clinical classification of different types of MI*

Type 1
Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2
MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3
Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a
MI associated with PCI
Type 4b
MI associated with stent thrombosis as documented by angiography or at autopsy
Type 5

MI associated with CABG

** Resource :: Expert consensus document (ECS, ACC, AHA, WHF). Universal definition of myocardial infarction (2007).*

MI is usually classified by size: microscopic (focal necrosis), small [<10% of the left ventricular (LV) myocardium], moderate (10-30% of the LV myocardium, and large (>30%of the LV myocardium), and by location.

MI can be classified temporally from clinical and other features, as well as according to the pathological appearance, as evolving (<6h), acute (6h-7 days), healing (7-28 days), and healed 29 days and beyond). It should be emphasized that the clinical and electrocardiographic timing of the onset of an acute infarction may not correspond exactly with the pathological timing. For example, the ECG may still demonstrate evolving ST-T changes and cardiac biomarkers may still be elevated (implying a recent infarct) at a time when pathologically the infarction is in the healing phase.

C.2. Diagnosis of acute myocardial infarction

Table 2. Diagnostic criteria for AMI*

Diagnostic criteria for AMI type 1 and type 2

Detection of elevated markers of myocardial necrosis (CK-MB, troponin) together with evidence of myocardial ischemia with at least one of the following:

- Chest pain
- Persistent ST segment elevation or (presumed) new left bundle-branch block
- Development of pathological Q waves in the ECG
- New regional wall motion abnormality on the 2D EchoCG

Diagnostic criteria for AMI type 3

Sudden cardiac death, often with symptoms of myocardial ischemia

- Accompanied by new ST elevation or new LBBB
- Verified coronary thrombus by angiography and/ or autopsy, but death before blood sample are obtained , or before appearance of biomarkers in blood.

Diagnostic criteria for AMI type 4A

- PCI -related increase of troponin > 3 x99th percentile of the upper reference limit(URL).

Diagnostic criteria for AMI type 4B

- Stent-thrombosis, documented by coronary angiography or autopsy.

Diagnostic criteria for AMI type 5

- CABG –related increase of troponin > 5 x99th percentile of URL plus either new Q waves or new LBBB, or angiographically verified new graft or native coronary occlusion.

*** Resource: Expert consensus document (ECS, ACC, AHA, WHF). Universal definition of myocardial infarction (2007).*

Chest pain is usually based on the following:

- chest pain/discomfort lasting for 10–20 min or more (not responding fully to nitroglycerine)
- locations such as epigastric or interscapular are possible.
- radiation of the pain to the neck, lower jaw, or left arm.
- the pain may not be severe and, in the elderly particularly
- other presentations such as fatigue, dyspnoea, faintness, or syncope are common.

ECG

- Obtain a standard 12-lead ECG within 10 minutes of first medical contact .
- Additional leads, e.g. posterior or right leads, should be considered as indicated
- Repeat ECG should be obtained in the event of recurrent of symptoms and 6 and 24 hours after admission (Consensus Nova Scotia 2007)

ECG abnormalities of myocardial ischemia or infarction may be inscribed in the PR segment, the QRS complex, and the ST segment or T-waves. The earliest manifestations of myocardial ischemia are typical T-waves and ST segment changes. Increased hyper-acute T-wave amplitude with prominent symmetrical T-waves in at least two contiguous leads is an early sign that may precede the elevation of the ST segment. Increased R-wave amplitude and width (giant R-wave with S-wave diminution) are often seen in leads exhibiting ST elevation, and tall T-waves reflecting conduction delay in the ischaemic myocardium. Transient Q-waves may be observed during an episode of acute ischemia or rarely during acute myocardial infarction with successful reperfusion. Table 3 lists ECG criteria for the diagnosis of acute myocardial ischemia that may lead to infarction.

Contiguous leads means lead groups such as anterior leads (V1–V6), inferior leads (II, III, and aVF), or lateral/apical leads (I and aVL). More accurate spatial contiguity in the frontal plane can be established by the Cabrera display: aVL, I, aVR, II, aVF, and III.24 Supplemental leads such as V3R and V4R reflect the free wall of the right ventricle.

Table 3. ECG manifestations of acute myocardial ischemia (in absence of LVH and LBBB)

ST elevation
New ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2–V3 and/or ≥0.1 mV in other leads
ST depression and T-wave changes
New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or T inversion ≥0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1

Although the criteria in Table 3 require that the ST shift be present in two or more contiguous leads, it should be noted that occasionally acute myocardial ischemia may create sufficient ST segment shift to meet the criteria in one lead but have slightly less than the required ST shift in an adjacent contiguous lead. Lesser degrees of ST displacement or T-wave inversion in leads without prominent R-wave amplitude do not exclude acute myocardial ischemia or evolving myocardial infarction.

ST elevation or diagnostic Q-waves in regional lead groups are more specific than ST depression in localizing the site of myocardial ischemia or necrosis. However, ST depression in leads V1–V3 suggests myocardial ischemia, especially when the terminal T-wave is positive (ST elevation

equivalent), and may be confirmed by concomitant ST elevation ≥0.1 mV recorded in leads V7–V9. The term 'posterior' to reflect the basal part of the LV wall that lies on the diaphragm is no longer recommended. It is preferable to refer to this territory as inferobasal. In patients with inferior myocardial infarction it is advisable to record right precordial leads (V3R and V4R) seeking ST elevation in order to identify concomitant right ventricular infarction.

During an acute episode of chest discomfort, pseudonormalization of previously inverted T-waves may indicate acute myocardial ischemia. Pulmonary embolism, intracranial processes, or peri-/myocarditis may also result in ST-T abnormalities and should be considered (false positives) in the differential diagnosis. The diagnosis of myocardial infarction is difficult in the presence of LBBB even when marked ST-T abnormalities or ST elevation are present that exceed standard criteria. A previous ECG may be helpful to determine the presence of acute myocardial infarction in this setting.

In patients with right bundle branch block (RBBB), ST-T abnormalities in leads V1–V3 are common, making it difficult to assess the presence of ischemia in these leads; however, when ST elevation or Q-waves are found, myocardial ischemia or infarction should be considered. Some patients present with ST elevation or new LBBB, and suffer sudden cardiac death before cardiac biomarkers become abnormal or pathological signs of myocardial necrosis become evident at autopsy. These patients should be classified as having had a fatal myocardial infarction.

Repeated ECG recordings should be obtained and, when possible, the current ECG should be compared with previous records. ECG monitoring should be initiated as soon as possible in all patients to detect life-threatening arrhythmias..

Prior myocardial infarction

As shown in Table 4, Q-waves or QS complexes in the absence of QRS confounders are usually pathognomonic of a prior myocardial infarction. The specificity of the ECG diagnosis for myocardial infarction is greatest when Q-waves occur in several leads or lead groupings. ST deviations or T-waves alone are non-specific findings for myocardial necrosis. However, when these abnormalities occur in the same leads as the Q-waves, the likelihood of myocardial infarction is increased. For example, minor Q-waves _0.02 and ,0.03 s that are _0.1 mV deep are suggestive of prior infarction if accompanied by inverted T-waves in the same lead group.

Table 4. ECG changes associated with prior myocardial infarction

Any Q-wave in leads V2–V3 >0.02 s or QS complex in leads V2 and V3
Q-wave >0.03 s and >0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL,V6; V4–V6; II, III, and aVF) R-wave <0.04 s in V1–V2 and R/S with a concordant positive T-wave in the absence of a conduction defect.

The electrocardiographic diagnosis of acute MI can be very straight forward or quite subtle and many pitfalls can confound the correct diagnosis (table 5).

Table 5. Common pitfalls in diagnosing MI by electrocardiography

False-positive findings
Benign early repolarization
Brugada syndrome

Cholecystitis
Failure to recognize normal limits for J-point displacement
Lead transposition or use of modified Mason-Likar configuration
Left bundle branch block
Metabolic disturbances such as hyperkalemia
Pericarditis or myocarditis
Pre-excitation
Pulmonary embolism
Subarachnoid hemorrhage
False-negative findings
Left bundle branch block
Left ventricular hypertrophy
Paced rhythm
Prior myocardial infarction with Q waves, persistent ST elevation, or both

Biomarker evaluation

Blood sampling for serum markers of necrosis is routinely done in the acute phase, but one should not wait for the results to initiate reperfusion treatment. The finding of elevated markers of necrosis may sometimes be helpful in deciding to perform coronary angiography (e.g. in patients with left bundle-branch block). Myocardial cell death can be recognized by the appearance in the blood of different proteins released into the circulation from the damaged myocytes: myoglobin, cardiac troponin T and I, CK, LDH, as well as many others. Myocardial infarction is diagnosed when blood levels of sensitive and specific biomarkers such as cardiac troponin or CKMB are increased in the clinical setting of acute myocardial ischemia.

An elevated value of cardiac troponin in the absence of clinical evidence of ischemia should prompt a search for other aetiologies of myocardial necrosis, such as myocarditis, aortic dissection, pulmonary embolism, congestive heart failure, renal failure. The preferred biomarker for myocardial necrosis is cardiac troponin (I or T), which has nearly absolute myocardial tissue specificity.

Blood samples for the measurement of troponin should be drawn on first assessment (often some hours after the onset of symptoms) and 6–9 h later. An occasional patient may require an additional sample between 12 and 24 h if the earlier measurements were not elevated and the clinical suspicion of myocardial infarction is high. Troponin values may remain elevated for 7–14 days following the onset of infarction. If troponin assays are not available, the best alternative is CKMB.

On the other hand, troponin is often elevated in plasma in conditions other than overt ischemic heart disease (table 5).

Table 6. Conditions other than MI that can elevate troponin

Acute neurologic disease, including stroke or subarachnoid hemorrhage
Aortic dissection
Aortic valve disease
Apical ballooning syndrome

Burns, especially if affecting > 30% of body surface area
Cardiac contusion or other trauma including surgery, ablation, cardioversion, defibrillation
Congestive heart failure—acute and chronic
Critical illness, especially with respiratory failure or sepsis
Drug toxicity or toxins
Extreme exertion
Hypertrophic cardiomyopathy
Infiltrative diseases, eg, amyloidosis, hemochromatosis, sarcoidosis, and scleroderma
Inflammatory diseases, eg, myocarditis or myocardial extension of endocarditis or pericarditis
Pulmonary embolism, severe pulmonary hypertension
Renal failure
Rhabdomyolysis with cardiac injury
Tachyarrhythmias, bradyarrhythmias, or heart block

The CKMB measurements should be recorded at the time of the first assessment of the patient and 6–9 h later onset of symptoms for the diagnosis myocardial infarction. An occasional patient may require an additional diagnostic sample between 12 and 24 h if the earlier CKMB measurements were not elevated and the clinical suspicion of myocardial infarction is high. Measurement of total CK is not recommended for the diagnosis of myocardial infarction, because of the large skeletal muscle distribution and the lack of specificity of this enzyme.

Commonly used imaging techniques in acute and old infarction are echocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy (MPS).. There is considerable overlap in their capabilities, but only the radionuclide techniques provide a direct assessment of myocardial viability because of the properties of the tracers used.

Echocardiography

Echocardiography is an excellent real-time imaging technique. Its strength is the assessment of myocardial thickness, thickening, and motion at rest. Echocardiography is the imaging technique of choice for detecting complications of acute infarction including myocardial free wall rupture, acute ventricular septal defect, and mitral regurgitation secondary to papillary muscle rupture or ischemia. This can be aided by tissue Doppler imaging. Echocardiographic contrast agents can improve endocardial visualization, but contrast studies are not yet fully validated for the detection of myocardial necrosis, although early work is encouraging.

Radionuclide imaging

Several radionuclide tracers allow viable myocytes to be imaged directly, including thallium-201, technetium-99m. The strength of the techniques are that they are the only commonly available direct methods of assessing viability, although the relatively low resolution of the images disadvantages them for detecting small areas of infarction.

Coronary angiography

The coronary angiography done by injecting a radio-opaque contrast agent into the coronary artery imaging using X-ray based techniques such as fluoroscopy. In coronary artery diseases mostly

used coronary angiography and determine anatomical variant coronary artery and lesion (lesion calcification, stenos, occlusion), multivessel damage, localization of lesion.

Quantitativecoronary angiography; The degree of coronary stenosis is quantitated from the cineangiogram, is usually a visual estimation of the percentage of diameter narrowing using the presumed proximal normal arterial segment and the ratio of the normal diameter to the stenosis diameter. Determine such follows;

- Left coronary artery (left main, left descending, Lxc, marginal, diagonal branches and bifurcations)
- Right coronary artery (by each segment, posterior descending artery, conus branch)

Collateral flow can be seen and classified angiographically and measure the degree of stenos by the method Petrosyan. Y. S, Zingerman L.S.

Stenos graded angiographically as follows;

Grade I - narrowing less than 50%

Grade II – stenosis between 50-75%

Grade III –stenosis between 75-99%

Grade IV - total occlusion

- To quantitative collateral flow coronary artery. Collateral flow can be seen and classified angiographilcally by the method Shlesinger. M.J.

D. EVALUATION AND MANAGEMENT OF ST ELEVATION MYOCARDIAL INFARCTION

Summary points for ST Elevation Myocardial Infarction (STEMI)*

1. Very early reperfusion of the occluded coronary artery is the mainstay in the treatment of an acute myocardial infarction with persistent ST-segment elevation.
2. Pre-hospital (ambulance) clinical and ECG diagnosis is critical for reducing the time delays between onset of symptoms and start of reperfusion.
3. Primary PCI with stenting, when performed by an experienced team within the recommended time, is the best reperfusion treatment to save lives.
4. Primary PCI should be performed within 120 min after ECG diagnosis (first medical contact) in all patients and within 90 min in patients presenting within 2 hours and with a large infarct.
5. If primary PCI cannot be performed within the recommended time, fibrinolytic therapy (preferably with a fibrin-specific agent) should be started as soon as possible, already in the ambulance.
6. In the absence of contra-indications, all patients should receive aspirin, a thienopyridine (clopidogrel) and one of the following anticoagulants as soon as possible: bivalirudin or heparin, if primary PCI will be performed; enoxaparin or heparin, if a fibrin-specific lytic agent is given; fondaparinux, enoxaparin or heparin, if streptokinase is given.
7. In case of failed fibrinolytic therapy, rescue PCI should be performed, if infarct size is large and if the procedure can be done within 12h after onset of symptoms.
8. After successful fibrinolysis, transfer to a PCI capable hospital for coronary angiography, ideally between 3 to 24 hours after start of fibrinolytic therapy, is indicated in most patients.
9. Anticoagulant therapy should be stopped shortly after the PCI procedure or after 24 to 48 hours in case of fibrinolytic therapy.
10. An oral ACE-inhibitor should be given on the first day in the absence of contraindications in patients with significant LV dysfunction. ACE inhibitors should also be considered in patients with hypertension, diabetes mellitus and chronic kidney disease. Angiotensin receptor blockers(namely valsartan) should be considered in patients who do not tolerate ACE inhibitors due to dry cough.
11. Routine IV . administration of a beta-blocker is not indicated. An oral beta-blocker should be given as soon as the patient is stable.
12. Statins should be initiated as soon as possible to achieve an LDL cholesterol < 100 mg/dl (2.5 mmol /l) or < 80 mg (2.5 mmol/l) if feasible irrespective of the initial cholesterol level. Risk factors for atherosclerosis should be identified and treatment started before hospital discharge.

13. At discharge and in the absence of contra-indications, all patients should be treated with ASA, a thienopyridine, a beta-blocker and a statin; in patients with significant LV dysfunction, an ACE-inhibitor (or an ARB) should be added.

** Resource: ESC Essential messages. ESC guidelines on the management of acute myocardial infarction. www.escardio.org/guidelines*

D.1. FIRST MEDICAL CONTACT AND EMERGENCY CARE FLOW

D.1. 1. EMERGENCY CARE FLOW

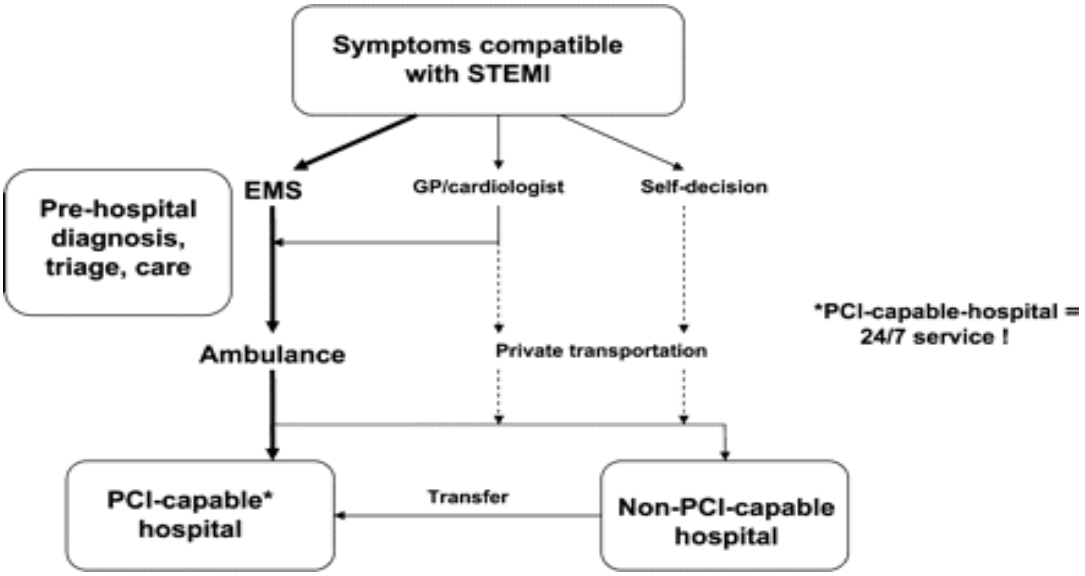

Figure 5*. Pre-hospital management. EMS = emergency medical system; STEMI = acute ST-segment elevation myocardial infarction; GP = general practitioner; PCI = percutaneous coronary intervention. Thick arrows = preferred patient flow; dotted line = to be avoided.

*Resource *: ECS guideline. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation (2008)*

D.1. 2. INITIAL DIAGNOSIS AND EARLY RISK STRATIFICATION

Rapid diagnosis and early risk stratification of patients presenting with acute chest pain are important to identify patients in whom early interventions can improve outcome. On the other hand, when the diagnosis of STEMI has been ruled out, attention can be focused on the detection of other cardiac or non-cardiac causes of the presenting symptoms such as aortic dissection, pulmonary embolism, and pericarditis. A working diagnosis of STEMI must first be made (table 7).

Table 7. Initial diagnosis of STEMI

History of chest pain/discomfort.
Persistent ST segment elevation or (presumed) new left bundle-branch block.
Elevated markers of myocardial necrosis (CK-MB, troponins). One should not wait for the results to initiate reperfusion treatment.

2D EchoCG to rule out major acute myocardial ischemia or other causes of chest pain/discomfort

A clinical history and physical examination should be obtained immediately. The time of symptom onset and first medical contact should be documented. A brief and limited neurological examination to look for evidence of prior stroke should be performed on tne STEMI patients before administration of fibrinolytic therapy.

There are no individual physical signs diagnostic of STEMI, but many patients have evidence of autonomic nervous system activation (pallor, sweating) and either hypotension or a narrow pulse pressure. Features may also include irregularities of the pulse, bradycardia or tachycardia, a third heart sound, and basal rales.

An ECG should be obtained as soon as possible. Even at an early stage, the ECG is seldom normal. In the case of STEMI or new or presumed new left bundle-branch block, reperfusion therapy needs to be given, and measures to initiate this treatment must be taken as soon as possible.

Risk stratification

Objectives of risk stratification:

- Used to predict prognosis
- Helps to determine what further investigations are needed
- Identify patients who can benefit most from early interventions to improve outcome

Considerations:

- Patient's age
- Pre-existing risk factors
- Previous infarct
- DM
- Hemodynamic status
- ECG changes, functional investigations& imaging

The following features should be considered in determining the need for and timing of PCI (Consensus Nova Scotia, Canada, 2008).

Table 8. Risk features in patients with AMI*

High- Risk features (PCI within 24-48 hours)

- Hypotension or definite evidence of HF
- Recurrent ventricular arrhythmias
- Transient ST elevation
- New ST depression ≥2mm in ≥3 leads
- Recurrent or refractory ischemia despite initial therapy
- TIMI risk score 5-7

Intermediate –risk features (PCI within 3-5 days)

- NSTEMI with no high-risk features, but known LVEF<40%
- TIMI risk score 3-4

Low -risk features (PCI within 5-7 days)

- NSTEMI with no high or intermediate -risk features

- Suspected unstable angina with recurrent symptoms but no ECG changes
- TIMI risk score 1-2

**Resource: Nova Scotia Guigelines for Acute Coranary Syndromes (Canada, 2008)*

All patients should have their metabolic risk markers measured including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol, fasting triglyceride, and plasma glucose, as well as renal function. It has been shown that mean lipid levels vary little in the 4 days after an acute coronary syndrome and can be used for clinical decisions about further therapy.

D.1.3. Relief of pain, breathlessness, and anxiety

M Morphine

O Oxygen (2-6L/min), need to keep saturation >90%

N Nitroglycerin (0.3-0.6 mg every 5 minutes, total of 3 doses) sublingually (spray or tab)

A Aspirin 160-325 mg per oral

Relief of pain is of paramount importance, not only for humane reasons but also because the pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. IV opioids are the analgesics most commonly used in this context (e.g. 4–8 mg of morphine with additional doses of 2 mg at intervals of 5–15 min until the pain is relieved); intramuscular injections should be avoided .

Side effects include nausea and vomiting, hypotension with bradycardia, and respiratory depression. Antiemetics (e.g. metoclopramide 5–10 mg I.V) may be administered concurrently with opioids. The hypotension and bradycardia will usually respond to atropine (0.5–1 mg I.V, up to a total dose of 2 mg), and respiratory depression may require ventilatory support. Oxygen (2–4 L/min by mask or nasal prongs) should be administered to those who are breathless or who have any features of heart failure or shock. Use of naloxone may be indicated for morphine induced respiratory depression.

Anxiety is a natural response to the pain and to the circumstances surrounding a heart attack. Reassurance of patients and those closely associated with them is of patient becomes excessively disturbed, it may be appropriate to administer a tranquillizer, but opioids are all that is required in many cases.

D.2 PRE-HOSPITAL OR EARLY IN-HOSPITAL CARE

D.2.1. Coronary reperfusion therapy

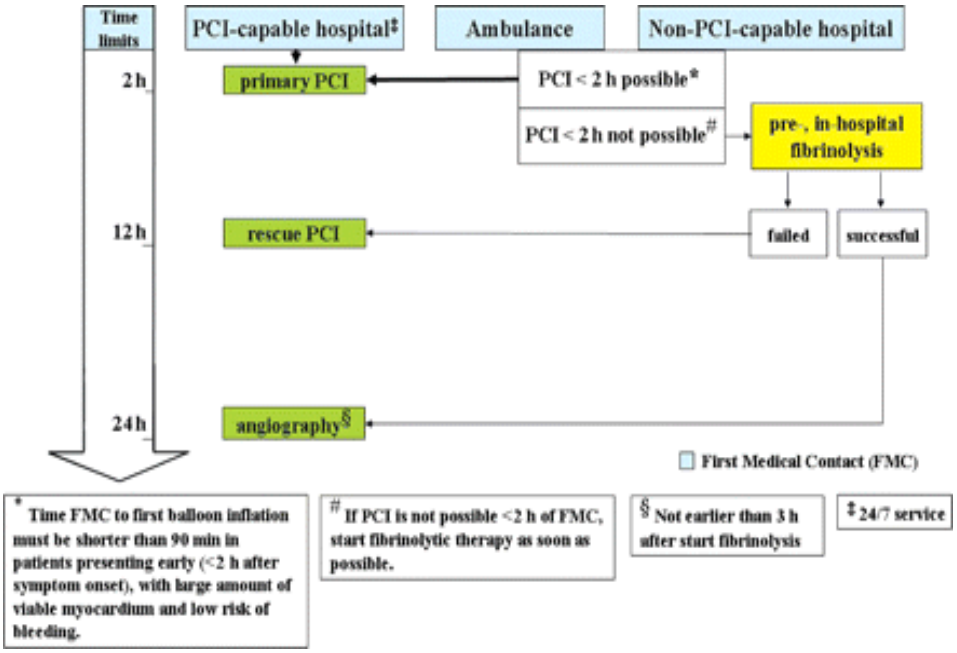

Figure 6* . Reperfusion strategies. The thick arrow indicates the preferred strategy.

* Resource*: ECS guideline. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation (2008)*

PCI, fibrinolytic therapy and CABG belong to coronary reperfusion therapy. As illustrated in Figure 6, the preferred pathway is immediate transportation of STEMI patients to a PCI-capable center offering an uninterrupted primary PCI service by a team of high-volume operators. Patients admitted to hospitals without PCI facilities should be transferred to a PCI-capable center and no fibrinolytics should be administered if the expected time delay between first medical contact (FMC) and balloon inflation is <2 h. If the expected delay is >2 h (or <90 min in patients >75 years old with large anterior STEMI and recent onset of symptoms), patients admitted to a non-PCI center should immediately receive fibrinolysis and then be transferred to a PCI-capable center where angiography and PCI should be performed in a time window of 3–24 h.

Indications for the reperfusion therapy

- Reperfusion therapy is indicated in all patients with history of chest pain/discomfort of <12 h and with persistent ST-segment elevation or (presumed) new left bundle-branch block
- Reperfusion therapy should be considered if there is clinical and/or ECG evidence of ongoing ischemia even if, according to patient, symptoms started >12 h before
- Reperfusion using PCI may be considered in stable patients presenting >.12 to 24 h after symptom onset . if there are residual symptoms or reversible ischemia during non invasive stress tests
- PCI of a totally occluded infarct artery >.24 h after symptom onset in stable patients without signs of ischemia is not indicated.

D.2.2. PCI (Percutaneous coronary intervention)

Myocardial revascularization is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life), exceed the expected negative consequences of the procedure.

Patient information needs to be objective and unbiased, patient oriented, evidence based, up-to-date, reliable, understandable, accessible, relevant, and consistent with legal requirements. Informed consent requires transparency, especially if there is controversy about the indication for a particular treatment (PCI vs. CABG vs. OMT). Informing patients about treatment choices allows them to reflect on the advantages and disadvantages associated with either strategy. Patients taking an active role throughout the decision making process have better outcomes. Potential indications for ad hoc percutaneous coronary intervention vs. revascularization at an interval Table 9.

Table 9. Potential indications for ad hoc percutaneous coronary intervention vs. revascularization at an interval

Ad hos PCI
Haemodynamically unstable patients (including cardiogenic shock).
Culprit lesion in STEMI and NSTE-ACS.
Stable low-risk patients with single or double vessel disease (proximal LAD excluded) and favourable morphology (RCA, non-ostial LCx, midor distal LAD).
Non-recurrent restenotic lesions
Revascularization at an interval
Lesions with high-risk morphology
Renal failure (creatinine clearance <60 mL/min), if total contrast volume required >4 mL/kg.
Stable patients with MVD including LAD involvement.
Stable patients with ostial or complex proximal LAD lesion.
Any clinical or angiographic evidence of higher periprocedural risk with ad hoc PCI.
chronic heart failure

PCI in ST-segment elevation myocardial Infarction

Meta-analyses comparing primary PCI with in-hospital fibrinolytic therapy in patients within 6–12 h after symptom onset treated in high-volume, experienced centres have shown more effective restoration of vessel patency, less re-occlusion, improved residual LV function, and better clinical outcome with primary PCI.

Patients admitted to hospitals without PCI facilities should be transferred to a PCI-capable centre and no fibrinolytics should be administered if the expected time delay between first medical contact (FMC) and balloon inflation is <2 h. If the expected delay is >2 h (or .90 min in patients ,75 years old with large anterior STEMI and recent onset of symptoms), patients admitted to a non-PCI centre should immediately receive fibrinolysis and then be transferred to a PCI-capable centre where angiography and PCI should be performed in a time window of 3–24 h.

Primary PCI is defined as percutaneous intervention in the setting of STEMI without previous or concomitant fibrinolytic treatment. Primary PCI should be ideally performed within 2 hours after

admission, preferably within 90 minutes. The necessary administration of antiplatelets(aspirin, clopidogrel, ticagrelor, prasugrel should be discussed). Also, the administration of unfractionated heparin during primary PCI and the target ACT(250-350sec) should be specificed.

Primary PCI

- Preferred treatment if performed by an experienced team as soon as possible after FMC
- Time from FMC to balloon inflation should be <2 h in any case and <90 min in patients presenting early (e.g. ,2 h) with large infarct and low bleeding risk
- Indicated for patients in shock and those with contraindications to fibrinolytic therapy irrespective of time delay
- nicorandil, adenosine, verapamil, Abciximab, coronary thrombus suction are needed if no reflow and microvascular obstruction during primary PCI

Facilitated PCI, or pharmaco-mechanical reperfusion, is defined as elective use of reduced or normal-dose fibrinolysis combined with glycoprotein IIb–IIIa (GPIIb–IIIa) inhibitors or other antiplateletagents. In patients undergoing PCI 90–120 min after FMC, facilitated PCI has shown no significant advantages over primary PCI.

Rescue PCI is defined as PCI performed on a coronary artery which remains occluded despite fibrinolytic therapy. The non-invasive identification of failed fibrinolysis remains a challenging issue, but ,50% ST-segment resolution in the lead(s) with the highest ST-segment elevations 60–90 min after start of fibrinolytic therapy has increasingly been used as a surrogate. Rescue PCI has been shown to be feasible and relatively safe.

Delayed PCI. In cases of persistent ST-segment elevation after fibrinolysis, defined as more than half of the maximal initial elevation in the worst ECG lead, and/or persistent ischaemic chest pain, rapid transfer to a PCI centre for rescue angioplasty should be considered. Re-administration of a second dose of fibrinolysis was not shown to be beneficial.

Patients presenting between 12 and 24 h and possibly up to 60 h from symptom onset, even if pain free and with stable haemodynamics, may still benefit from early coronary angiography and possibly PCI. Patients without ongoing chest pain or inducible ischaemia, presenting between 3 and 28 days with persistent coronary artery occlusion, did not benefit from PCI. Thus, in patients presenting days after the acute event with a fully developed Q-wave MI, only patients with recurrent angina and/or documented residual ischaemia and proven viability in a large myocardial territory are candidates for mechanical revascularization.

Guidelines for management of no reflow and microvascular obstruction during primary PCI is needed.(nicorandil, adenosine, verapamil, Abciximab, coronary thrombus suction etc)

Primary PCI should be discussed in more detail. It should be ideally performed within 2 hours after admission, preferably within 90 minutes. The necessary administration of antiplatelets(aspirin, clopidogrel, ticagrelor, prasugrel should be discussed). Also, the administration of unfractionated heparin during primary PCI and the target ACT(250-350sec) should be specificed.

D.2.3. Fibrinolytic treatment

The benefit of fibrinolytic therapy is well established: approximately 30 early deaths are evented per 1000 patients treated, with 20 deaths prevented per 1000 patients treated between 7 and 12 h after symptom onset.

Time to treatment

Time from onset of symptoms to fibrinolytic therapy is an important predictor of MI size and patient outcome. The efficacy of fibrinolytic agents in lysing thrombus diminishes with the passage of time. Fibrinolytic therapy administered within the first 2 hours (especially the first hour) can occasionally abort MI and dramatically reduce mortality. Most of these studies reported outcome data similar to those of primary PCI, provided early angiography and PCI were performed in those who needed intervention. Where appropriate facilities exist, with trained medical or paramedical staff able to analyze on-site or to transmit the ECG to the hospital for supervision, pre-hospital fibrinolysis is recommended provided that fibrinolytic therapy is the most appropriate reperfusion strategy.

The aim is to start fibrinolytic therapy within 30 min of arrival of the ambulance . For patients arriving at the hospital, a realistic aim is to initiate fibrinolysis within 30 min (door-to-needle time).

It should be noted that fibrinolytic therapy has similar outcome to primary PCI when administered within 2 hours of symptom onset. After 2 hours, primary PCI is the treatment of choice unless it can't be performed within 2 hours after admission and/or there are It should be noted that fibrinolytic therapy has similar outcome to primary PCI when administered within 2 hours of symptom onset. After 2 hours, primary PCI is the treatment of choice unless it can't be performed within 2 hours after admission and/or there are no facilities available to perform primary PCI within 2 hours of initial patient contact.no facilities available to perform primary PCI within 2 hours of initial patient contact.

Indication to FT

1. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and ST elevation greater than 0.1 mV in at least 2 contiguous precordial leads or at least 2 adjacent limb leads.
2. In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new LBBB.

Contraindications to fibrinolytic therapy

Absolute and relative contraindications to fibrinolytic therapy are shown in Table 5. Diabetes (more particularly diabetic retinopathy) and successful resuscitation are no contraindication to fibrinolytic therapy.

Table 10. Contraindications to fibrinolytic therapy

Absolute contraindications
Haemorrhagic stroke or stroke of unknown origin at any time
Ischaemic stroke in preceding 6 months
Central nervous system trauma or neoplasms
Recent major trauma/surgery/head injury (within preceding 3 weeks)
Gastrointestinal bleeding within the last month
Known bleeding disorder
Aortic dissection

Non-compressible punctures (e.g. liver biopsy, lumbar puncture)
Relative contraindications
Transient ischemic attack in preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week post-partum
Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure,<110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Refractory resuscitation

Hazards of fibrinolysis

Fibrinolytic therapy is associated with a small but significant excess of strokes, with all of the excess hazard appearing on the first day after treatment. The early strokes are largely attributable to cerebral hemorrhage, later strokes are more frequently thrombotic or embolic. Advanced age, lower weight, female gender, prior cerebrovascular disease, and systolic and diastolic hypertension on admission are significant predictors of intracranial hemorrhage[5]

In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied[6,7] Major non-cerebral bleeds (bleeding complications requiring blood transfusion or that are life threatening) can occur in 4–13% of the patients treated[8]

The Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Routine administration of hydrocortisone is not indicated. Streptokinase should never be readministered because of antibodies which can impair its activity and because of the risk of allergic reactions

The occurrence of a change in neurological status during or after reperfusion therapy, particularly within the first 24 hours after initiation of treatment, is considered to be due to ICH until proven otherwise. Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until brain imaging scan shows no evidence of ICH. Neurology and/or neurosurgery or hematology consultations should be obtained for STEMI *patients who have ICH as dictated by clinical circumstances. In patients with ICH, infusions of cryoprecipitate, fresh frozen plasma, protamine, and platelets should be given, as dictated by clinical circumstances.

Fibrinolytic agents

Table 11. Doses of fibrinolytic agents

Names of agents	Initial treatment
Alteplase	15 mg i.v. bolus , 0.75 mg/kg over 30 min then 0.5 mg/kg over 60 min I.V. The treatment lasts for 1.5 hours. Total dosage not to exceed 100 mg.
Urokinase	1.0 million units I.V bolus or 1.5 million units bolus followed by 1.5

1.5 million units over 60 min infusion

The dosage of urokinase needs verification as I cannot find the dosage recommended for AMI. In fact, urokinase is currently not recommended as treatment of AMI. Is the omission of tPA or TNK due to the lack of these drugs in Mongolia. This is important as fibrin specific thrombolytics are the recommended drugs for thrombolysis in STEMI. I believe the guideline should contain both tPA and TNK as well as streptokinase because it should contain ideal, up to date information.

☐ Fondaparineux needs verification as administration of periprocedural Fondaparineux is associated with non significant 1% increase of death or recurrent MI in STEMI patients undergoing primary PCI. The European guideline currently does not recommend the use of Fondaprineux in STEMI patients undergoing primary PCI

☐ To use bivalirudin, it is recommended to use unfractionated heparin during the primary PCI as bivalirudin is associated with increased incidence of catheter thrombosis.

☐ I think it is safe to say that both unfractionated heparin and low molecular weight heparin may be used in STEMI. The statement that unfractionated heparin should be used only when low molecular weight heparin is unavailable should be deleted.(As stated in the ESC guideline, there is little evidence to suggest the beneficial effect of LMWH over unfractionated heparin in STEMI)

Guideline for use of GP IIb/IIIa inhibitor, namely abciximab. is needed. The periprocedural use of abciximab has been demonstrated to reduce the 30 day mortality rate by 32% without increasing the risk of hemorrhagic stroke and major bleeding. (Guideline for ACT when using periprocedural GP II b/IIIa during primary PCI: 200-250sec)

The fibrinolytic therapy for the AMI is not common in our country . Results of the study of the Second General Hospital in Ulaanbaatar relieved that fibrinolytic therapy was given to 4% of patients with AMI treated in 2009-2010 years.

Assessment of efficacy of the fibrinolytic therapy

The fibrinolysis with streptokinase was successful in 55% of patients with STEMI. Criteria for the evaluation of the fibrinolytic therapy :

- Disappearance of chest pain
- ST-segment resolution of >50% at 60–90 min
- Elevated marker of myocardial necrosis (CK-MB)
- Finding of the coronary angiography

Angiography during hospital stay after fibrinolytic therapy:

- Evidence of successful fibrinolysis: within 3–24 h after start of fibrinolytic therapy
- Evidence of failed fibrinolysis or uncertainty about success: immediate
- Recurrent ischemia, reocclusion after initial successful fibrinolysis: immediate

If there is evidence of persistent occlusion, re-occlusion, or reinfarction with recurrence of ST-segment elevation the patient should be immediately transferred to a hospital with PCI capabilities. If rescue PCI is not available, a second administration of a non-immunogenic fibrinolytic agent may be considered, if there is a large infarct and if the risk of bleeding is not high.

D.2.4. Coronary bypass surgery

The number of patients who need a coronary artery bypass graft (CABG) in the acute phase is limited, but CABG may be indicated after failed PCI, coronary occlusion not amenable for PCI, presence of refractory symptoms after PCI, cardiogenic shock, or mechanical complications such as ventricular rupture, acute mitral regurgitation, or ventricular septal defect .

GENERAL PRINCIPLES OF CABG

Median sternotomy.

A median sternotomy is made in the usual manner.

Aorta is directly cannulated for arterial perfusion during the cardiopulmonary bypass. Small bites of the adventitia and media as high up on the aorta as feasible are taken with 3/0 prolene sutures on noncutting needles to form a single or double purse string. A stab wound is made within the purse string sutures. The tip of the aortic cannula is then introduced atraumatically into the opening. The tubing is then tied to the aortic cannula.

Venous drainage is accomplished through a single atriocaval cannula in most patients undergoing CABG. Bicavalcannulation is used when concomitant procedures necessitating an opening into the right side of the heart indicated.

Techniques for greater vein harvesting

Traditional open vein harvesting through one long incision or multiple interrupted incision can result in significant wound morbidity including infection and chronic leg edema.

Saphenous vein grafts must be divided at a point that ensure a comfortable length of the graft when heart is fully filled.

Myocardial Preservation:

Cold blood cardioplegia is infused into the aortic root to achievecardioplegic arrest of the heart initially and repeated every 20-25 minutes during the cross clamp time. Additionally cardioplegic solution is infused directly into the vein graft after the distal anastomosis is completed. Retrograde cardioplegic perfusion through a coronary sinus catheter is a useful adjunct for optimal myocardial protection during coronary revascularization.

Distal anastomoses:

The arteriotomy is made at the selected side. The distal anastomosis are using 7/0-8/0 prolene sutures, double armed needles. The first needle is passed from the outside of the graft 2 mm to the surgeon’s side of the heel. It is then passed from the inside to the outside of the lumen of the coronary artery, 2 to 3 mm to the right of its heel. The same needle is now passed again from the outside to the inside of the graft, adjacent to the previous suture in a clockwise direction. The needle is then passed from the inside to the outside of coronary artery, adjacent to the previous stitch and similarly in a clockwise direction.

Proximal anastomoses:

All proximal anastomoses are being performed with the aortic cross-clamp in place. Another technique is under cardiopulmonary bypass. The proximal anastomosis must be used long 6/0 or 7/0

Prolene double armed sutures. The first stitch is passed from the inside of the graft to the outside and then passed from the outside to the inside of the aorta in counterclockwise direction. After three to five rounds of suturing, the graft is lowered into position, and the needle is clamped. Then the needle at the other end of the suture is now from the inside to the outside of the aorta, followed by outside to inside of the vein graft in a clockwise direction. When the proximal anastomosis are completed, the vein grafts are each occluded with atraumatic bulldog clamps.

D.2.5 ANTITHROMBOTIC (ANTITHROMBIN) THERAPY

Antithrombotic therapy (antiplatelet agents and anticoagulant) depends on methods of treatment for the STEMI patients. Antithrombotic therapy without reperfusion therapyiIn patients presenting within 12 h after symptom onset and in whom reperfusion therapy was not given, or in patients presenting after 12 h aspirin, clopidogrel and an antithrombin agent (heparin, enoxaparin, or fondaparinux) should be given as soon as possible.

Aspirin should be given to all patients with a STEMI as soon as possible after the diagnosis is deemed probable. NSAIDs apart from aspirin have been demonstrated to increase the risk of death, reinfarction, cardiac rupture, and other complications in STEMI patients: discontinuation of these drugs is indicated at the time of STEMI.

Fondaparineux needs verification as administration of periprocedural Fondaparineux is associated with non significant 1% increase of death or recurrent MI in STEMI patients undergoing primary PCI. The European guideline currently does not recommend the use of Fondaprineux in STEMI patients undergoing primary PCI

To use bivalirudin, it is recommended to use unfractionated heparin during the primary PCI as bivalirudin is associated with increased incidence of catheter thrombosis.

I think it is safe to say that both unfractionated heparin and low molecular weight heparin may be used in STEMI. The statement that unfractionated heparin should be used only when low molecular weight heparin is unavailable should be deleted.(As stated in the ESC guideline, there is little evidence to suggest the beneficial effect of LMWH over unfractionated heparin in STEMI)

Guideline for use of GP IIb/IIIa inhibitor, namely abciximab. is needed. The periprocedural use of abciximab has been demonstrated to reduce the 30 day mortality rate by 32% without increasing the risk of hemorrhagic stroke and major bleeding. (Guideline for ACT when using periprocedural GP II b/IIIa during primary PCI: 200-250sec)

Table 12. Antithrombotic therapy with PCI

Antiplatelet agent • Aspirin, oral dose of 150-325 mg • Clopidogrel, oral loading dose of 300-600mg
Anticoagulant • Heparin is standard anticoagulant therapy during PCI. Heparin is given as an I.V. bolus at a usual starting dose of 100 U/kg weight. Heparin should be given at a dose able to maintain an ACT of 250–350 s. Infusion should be stopped at the end of the procedure.

Low-molecular-weight heparins (LMWHs) have been studied in a limited number of STEMI patients undergoing primary PCI. Thus, there is little evidence to support their use instead of heparin in this setting. • Bivalirudin: I.V bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h and terminated at the end of procedure.

Table 13. Antithrombotic therapy with fibrinolytic treatment (SK)

Antiplatelet agent • Aspirin, oral dose of 150-325 mg • Clopidogrel, loading dose of 300 mg if age ≤75 years, 75 mg if age >75 years
Anticoagulant • Fondaparinux I.V bolus of 2.5 mg followed 24 hours later by s.c dose of 2.5 mg once daily up to 8 days or hospital discharge • If Fondaparinux is not available, Enoxaparin: in patients < 75 years and creatinine level < 2mg/ml, I.V bolus of 30mg followed 15 min later s.c dose 1mg/kg every 12 hours until hospital discharge for a maximum of 8 days. In patients >75 years, no I.V bolus, start with s.c dose 0.75mg/kg . • If Enoxaparin is not available, Heparin: I.V bolus of 60 U/kg with a maximum of 4000 U followed by an I.V infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 sec, to be monitored at 3, 6, 12, and 24 h.

Table 14. Antithrombotic therapy without reperfusion therapy in patients with STEMI

Antiplatelet agent

- Aspirin should be started at a dose of 150–325 mg in a chewable form, followed by 80-160 mg An alternative approach, especially if oral ingestion is not possible, is I.V. administration of aspirin at a dose of 250–500 mg
- Clopidogrel, oral dose of 75 mg

Anticoagulant

- Fondaparinux I.V bolus of 2.5 mg followed 24 hours later by s.c dose of 2.5 mg once daily up to 8 days or hospital discharge
- If Fondaparinux is not available, Enoxaparin: in patients < 75 years and creatinine level < 2mg/ml, I.V bolus of 30mg followed 15 min later s.c dose 1mg/kg every 12 hours until hospital discharge for a maximum of 8 days. In patients >75 years, no I.V bolus, start with s.c dose 0.75mg/kg .
- If Enoxaparin is not available, Heparin: I.V bolus of 60 U/kg with a maximum of 4000 U followed by an I.V infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 sec, to be monitored at 3, 6, 12, and 24 h.

D.2.6 ANTIISCHEMIC MEDICAL THERAPY

Beta blockers (BB)

The benefit of long-term b-blockers after STEMI is well established, but the role of routine early I.V administration is less firmly established.

- Oral BB therapy should be initiated within 24 hours for most STEMI patients who have no evidence of hypotension or heart failure
- Early I.V use of BB should be considered in patients with suspected STEMI who are hypertensive or have ongoing chest pain and who do not have contraindication to treatment

Nitrates

- No significant reduction in mortality was observed with the routine oral and transdermal administration. The routine oral use of nitrates in the initial phase of a STEMI not recommended (GISSI-3, ISSI-4 trial)
- In the absence of contraindications, intravenous NTG (10-20 mmg /min infusion) can be considered in patients with persistent ischemia, HF or hypertension.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

- A systematic overview of trials of ACE-inhibition early in STEMI indicated that this therapy is safe, well tolerated, and associated with a small but significant reduction in 30-day mortality, with most of the benefit observed in the first week
- ACE-inhibitors should be started in the first 24 h if no contraindications are present
- ACE-inhibitors should be given to patients who have an impaired ejection fraction (EF≤40%) or hypertension and diabetes

- Patients who do not tolerate an ACE-inhibitor should be given an ARB(valsartan, candesartan)

D.2.7 PUMP FAILURE AND SHOCK

Pump failure

Heart failure during the acute phase of STEMI is associated with a poor short and long-term prognosis. The clinical features are those of breathlessness, sinus tachycardia, a third heart sound, and pulmonary rales, which are basal, but may extend throughout both lung fields. The degree of failure may be categorized according to the Killip classification:

Table 15. Killip classification of acute heart failure

Class	Clinical features
class 1	No lung rales or third heart sound
class 2	Pulmonary congestion with rales over 50% of the lung fields or third heart sound
class 3	Pulmonary edema with rales over 50% of the lung fields
class 4	Shock

General measures include monitoring for arrhythmias, checking for electrolyte abnormalities and for the presence of concomitant conditions such as valvular dysfunction or pulmonary disease. Pulmonary congestion can be assessed by portable chest X-rays. Echocardiography is the key diagnostic tool and should be performed to assess the extent of myocardial damage and possible complications, such as mitral regurgitation and ventricular septal defect.

Cardiogenic shock

Cardiogenic shock is a clinical state of hypoperfusion characterized by a systolic pressure ,90 mmHg and a central filling pressure (wedge pressure). 20 mmHg, or a cardiac index ,1.8 L/min/m2 and caused by extensive loss of viable myocardial tissue. The diagnosis of cardiogenic shock should be made when other causes of hypotension have been excluded, such as hypovolaemia, vasovagal reactions, electrolyte disturbances, pharmacological side effects, tamponade, or arrhythmias. It is usually associated with extensive LV damage, but may occur in right ventricular infarction. LV function and associated mechanical complications should be evaluated urgently by two-dimensional Doppler echocardiography.

Table 16. Treatment of acute heart failure

Treatment of mild heart failure (Killip class II)

- O2
- Loop diuretics, i.e. furosemide: 20–40 mg I.V. repeated at 1–4 hourly intervals if necessary
- Nitrates if no hypotension
- ACE-inhibitor in the absence of hypotension, hypovolaemia or renal failure
- ARB (valsartan) if ACE-inhibitor is not tolerated

Treatment of severe heart failure (Killip class III)

- O2

- Ventilatory support according to blood gasses
- Furosemide
- Nitrates if no hypotension
- Inotropic agents: dopamine and/or dobutamine
- Haemodynamic assessment with balloon floating catheter
- Early revascularization

Treatment of shock (Killip class IV)

- O2
- Mechanical ventilatory support according to blood gasses
- Haemodynamic assessment with balloon floating catheter
- Inotropic agents: dopamine and dobutamine
- Intra-aortic balloon pump
- LV assist devices
- Early revascularization

D.2.8 MECHANICAL COMPLICATIONS: cardiac rupture and mitral regurgitation

Free wall rupture

This is characterized by cardiovascular collapse with electromechanical dissociation, i.e. continuing electrical activity with a loss of cardiac output and pulse. It is usually fatal within a few minutes, and does not respond to standard cardiopulmonary resuscitation. Only very rarely is there time to bring the patient to surgery.

In <25% of cases the presentation is sub acute (thrombus or adhesions seal the rupture), giving time for intervention. The clinical picture may simulate reinfarction because of the recurrence of pain and re-elevation of ST-segments. The classical signs of cardiac tamponade occur and can be confirmed by echocardiography. Although echocardiography is not always able to show the site of rupture, it can demonstrate pericardial fluid with or without signs of tamponade The presence of pericardial fluid alone is not sufficient to diagnose a sub acute free wall rupture, because it is relatively common after acute myocardial infarction. The typical finding is an echo-dense mass in the pericardial space consistent with clot (heamopericardium). Immediate surgery should be considered.

Ventricular septal rupture

The diagnosis of ventricular septal rupture, first suspected because of sudden severe clinical deterioration, is confirmed by the occurrence of a loud systolic murmur, by echocardiography and/or by detecting an oxygen step-up in the right ventricle. Echocardiography reveals the location and size of the ventricular septal defect; the left-to-right shunt can be depicted by colour Doppler and further quantified by pulsed Doppler technique.

Mitral regurgitation

Mitral regurgitation is common and it occurs usually after 2–7 days. There are three mechanisms of acute mitral regurgitation in this setting: (i) mitral valve annulus dilatation due to LV dilatation and dysfunction; (ii) papillary muscle dysfunction usually due to inferior myocardial

infarction; and (iii) rupture of the trunk or tip of the papillary muscle. In most patients, acute mitral regurgitation is secondary to papillary muscle dysfunction rather than rupture.

The most frequent cause of partial or total papillary muscle rupture is a small infarct of the posteromedial papillary muscle in the right or circumflex coronary artery distribution. Papillary muscle rupture typically presents as a sudden haemodynamic deterioration. Due to the abrupt and severe elevation of left atrial pressure, the murmur is often of low intensity. Chest radiography shows pulmonary congestion (this may be unilateral). The presence and severity of mitral regurgitation are best assessed by colour Doppler-echocardiography. Most patients with acute mitral regurgitation should be operated early because they may deteriorate sudden.

D.2.9 ARRHYTHMIAS AND CONDUCTION DISTURBANCES

A life-threatening arrhythmia, such as ventricular tachycardia (VT), VF, and total atrio-ventricular (AV) block may be the first manifestation of ischemia and requires immediate correction. These arrhythmias may cause many of the reported sudden cardiac deaths (SCDs) in patients with acute ischemic syndromes. VF or sustained VT has been reported in up to 20% of patients who present with STEMI.

Ventricular arrhythmias

The incidence of VF occurring within 48 h of the onset of STEMI may be decreasing owing to increased use of reperfusion treatment and beta blockers. Use of prophylactic beta blockers in the setting of STEMI reduces the incidence of VF. Similarly, correction of hypomagnesaemia and hypokalaemia is encouraged because of the potential contribution of electrolyte disturbances to VF. Prophylaxis with lidocaine may reduce the incidence of VF but appears to be associated with increased mortality probably owing to bradycardia and asystole, and has therefore been abandoned. In general, treatment is indicated to prevent potential morbidity or reduce the risk of sudden death. There is no reason to treat asymptomatic ventricular arrhythmias in the absence of such potential benefit.

Ventricular ectopic rhythms

Ventricular ectopic beats are common during the initial phase. Irrespective of their complexity (multiform QRS complex beats, short runs of ventricular beats, or the R-on-T phenomenon) their value as predictors of VF is questionable. No specific therapy is required.

Supraventricular arrhythmias

Atrial fibrillation (AF), which complicates 10–20% of STEMIs, is more prevalent in older patients and in those with severe LV damage and heart failure. Stroke rates are higher in patients with STEMI and AF compared with those without AF. AF is associated with increased in-hospital mortality. Specific recommendations for management of patients with AF in the setting of STEMI are based primarily on consensus.

Sinus bradycardia and heart block

Sinus bradycardia is common (9–25%) in the first hour, especially in inferior infarction. In some cases, opioids are responsible. If associated with hemodynamic compromise it should be treated AV block.

Data from four large, randomized trials suggest that AV block occurs in almost 7% and persistent bundle-branch block in up to 5.3% of cases of STEMI. While pacing has not been shown to increase long-term survival, it may still be indicated in symptomatic brady-arrhythmias associated with STEMI.

First-degree AV block needs no treatment. AV block associated with inferior wall infarction is usually transient, with a narrow QRS escape rhythm above 40 bpm and low mortality, whereas AV block related to anterior wall infarction is more often located below the AV node and associated with an unstable, wide QRS escape rhythm due to the extensive myocardial necrosis. A new left bundle-branch block usually indicates extensive anterior infarction with a high likelihood for developing complete.

AV block and pump failure

The preventive placement of a temporary pacing electrode may be warranted. The sub clavian route should be avoided following fibrinolysis or in the presence of antithrombin therapy. Recommendations for permanent cardiac pacing for persistent conduction disturbances (_14 days) due to STEMI are outlined in the ESC Guidelines for cardiac pacing.

Table 17. Management of arrhythmias and conduction disturbances in the acute phase

Haemodynamically unstable VT and VF

- Electrical cardioversion

Monomorphic VT

- I.V amiodarone or beta blocker(sotalol)

Polymorphic VT

If baseline QT is normal

- I.V amiodarone or beta blocker(sotalol) or lidocaine

If baseline QT is prolonged

- Correct electrolytes or lidocaine
- Urgent angiography should be considered

Atrial fibrillation

- I.V Beta blocker if no clinical sign of HF, AV block and bronchospasm
- I.V verapamil if no clinical sign of HF, AV block
- I.V amiodarone
- I.V digitalis if severe HF
- Electrical cardioversion if severe haemodynamic compromise or intractable ischemia or when adequate rate control cannot be achieved with pharmacological agents
- I.V heparin or LMWH

Sinus bradycardia associated with hypotension, AV block I (Mobitz II), AV block III

- I.V atropine
- Temporary pacing if atropine fails

D.3. MANAGEMENT OF SPECIFIC TYPES OF INFARCTION

Right ventricular infarction

The recognition of right ventricular infarction is important because it may manifest itself as cardiogenic shock, but the appropriate treatment strategy is quite different from that for shock due to severe LV dysfunction. Right ventricular infarction may be suspected by the specific, but insensitive, clinical triad of hypotension: hypotension, clear lung fields, and raised jugular venous pressure in a patient with inferior STEMI. ST-segment elevation in V4R is very suggestive of the diagnosis, this lead should certainly be recorded in all cases of inferior STEMI and shock, if not done as a routine. Q-waves and ST-segment elevation in V1–3 also suggest right ventricular infarction. Echocardiography may confirm the diagnosis.

Various degrees of right ventricular involvement in inferior STEMI can be found. When right ventricular infarction can be implicated in hypotension or shock, it is important to maintain right ventricular preload. It is desirable to avoid (if possible) vasodilator drugs such as the opioids, nitrates, diuretics, and ACE-inhibitors/ARBs. I.V. fluid loading is effective in many cases: initially, it should be administered rapidly. Careful haemodynamic monitoring is required during I.V. fluid loading. Right ventricular infarction is often complicated by AF. This should be corrected promptly as the atrial contribution to right ventricular filling is important in this context. Likewise, if heart block develops, dual chamber pacing should be undertaken. Direct PCI should be performed as soon as possible as it may result in rapid haemodynamic improvement.. There has been some question of the effectiveness of fibrinolytic therapy in right ventricular infarction,150 but it certainly seems appropriate in the hypotensive patient if PCI is not available.

Myocardial infarction in diabetic patients

Up to 20% of all patients with an infarction have diabetes, and this figure is expected to increase. Importantly, patients with diabetes may present with atypical symptoms, and heart failure is a common complication. Diabetic patients who sustain a STEMI still have doubled mortality compared with non-diabetic patients. Despite this, patients with diabetes do not receive the same extensive treatment as non-diabetic patients. This has been shown to be associated with poorer outcome, and is presumably triggered by fear of treatment-related complications. Fibrinolysis should not be withheld in patients with diabetes when indicated.

D.4. MANAGEMENT OF THE LATER IN-HOSPITAL COMPLICATIONS

Ambulation

Patients with significant LV damage should rest in bed for the first 12–24 h, by which time it will be apparent whether the infarction is going to be complicated. In uncomplicated cases, the patient can sit out of bed late on the first day, be allowed to use a commode, and undertake self-care and self-feeding. Ambulation can start the next day, and such patients can be walking up to 200 m on the flat, and walking up stairs within a few days. Those who have experienced heart failure, shock, or serious arrhythmias should be kept in bed longer, and their physical activity increased slowly, dependent upon their symptoms and the extent of myocardial damage.

Deep vein thrombosis and pulmonary embolism

These complications are now relatively uncommon after infarction, except in patients kept in bed because of heart failure. In such patients, they can be prevented by prophylactic doses of a LMWH and the application of compression stockings. When they occur, they should be treated with therapeutic doses of a LMWH, followed by oral anticoagulation for 3–6 months.

Intraventricular thrombus and systemic emboli

Echocardiography may reveal intraventricular thrombi, especially in patients with large anterior infarctions. If the thrombi are mobile or protuberant, they should be treated initially with I.V. unfractionated heparin or LMWH, and subsequently with oral anticoagulants for at least 3–6 months.

Pericarditis

Acute pericarditis may complicate STEMI with transmural necrosis. It gives rise to chest pain that may be misinterpreted as recurrent infarction or angina. The pain is, however, distinguished by its sharp nature, and its relationship to posture and respiration. The diagnosis may be confirmed by a pericardial rub. If the pain is troublesome, it may be treated by high-dose I.V. aspirin (1000 mg/24 h) or NSAIDs. (Intravenous NSAIDS may be used, but high dose aspirin or NSAIDS should be preferred). A haemorrhagic effusion with tamponade is uncommon and is particularly associated with antithrombin treatment. It can usually be recognized echocardiographically. Treatment is by pericardiocentesis if haemodynamic compromise occurs. Antithrombin therapy must be interrupted unless there is an absolute indication for its continuous use.

Late ventricular arrhythmias

VT and VF occurring during the first 24–48 h have a low predictive value for recurring risk of arrhythmias over time. Arrhythmias developing later are liable to recur and are associated with an increased risk of sudden death.

Post-infarction angina and ischemia

Angina or recurrent ischemia or reinfarction in the early postinfarction phase following either successful fibrinolysis or PCI is an absolute indication for urgent (repeated) coronary angiography and, if indicated, (repeated) PCI or CABG. Although analyses from several trials have identified a patent infarct-related vessel as a marker for good long-term outcome, it has not been shown that late PCI with the sole aim of restoring patency is beneficial. Coronary artery bypass surgery may be indicated if symptoms are not controlled by other means or if coronary angiography demonstrates lesions, such as left main stenosis or three-vessel disease with poor LV function.

D.5. SECONDARY PREVENTION

Coronary heart disease is a chronic condition, and patients who have recovered from a STEMI are at high risk for new events and premature death. Eight to 10% of post-infarction patients have a recurrent infarction within a year after discharge and mortality after discharge remains much higher than in the general population.

Smoking cessation

Unselected acute coronary syndrome patients who are smokers are twice as likely to present as STEMI, compared with non smokers ,indicating a strong prothrombotic effect of smoking. Stopping smoking is potentially the most effective of all secondary prevention measures, and much effort should be devoted to this end. Patients do not smoke during the acute phase of a STEMI, and the

convalescent period is ideal for health professionals to help smokers to quit. However, resumption of smoking is common after returning home, and continued support and advice is needed during rehabilitation. Nicotine replacement, buproprione, and antidepressants may be useful. Nicotine patches have been demonstrated to be safe in acute coronary syndrome patients.

Diet, dietary supplements, and weight control

Evidence from systematic reviews of randomized controlled trials on food and nutrition in secondary prevention has recently been published. Current guidelines on prevention recommend (i) to eat a wide variety of foods; (ii) adjustment of calorie intake to avoid overweight; (iii) increased consumption of fruit and vegetables, along with wholegrain cereals and bread, fish (especially oily), lean meat, and low-fat dairy products; (iv) to replace saturated and trans fats with monounsaturated and polyunsaturated fats from vegetable and marine sources and to reduce total fats to ,30% of total calorie intake, of which less than one-third should be saturated; and (v) to reduce salt intake if blood pressure

Physical activity

Exercise therapy has long been used for rehabilitation purposes following STEMI and the benefit of regular physical exercise in stable coronary artery disease patients is also well established. Four mechanisms are considered to be important mediators of a reduced cardiac event rate: (i) improvement of endothelial function; (ii) reduced progression of coronary lesions; (iii) reduced thrombogenic risk; and (iv) improved collateralization. Thirty minutes of moderate intensityaerobic exercise at least five times per week is recommended.

Blood pressure control

According to the ESC Guidelines for the management of arterial hypertension the goal is to achieve a blood pressure <130/80 mmHg in patients with stroke, myocardial infarction, renal disease, and diabetes.

Management of diabetes

Glucometabolic disturbances are common in patients with coronary disease and should be actively searched for. Since an abnormal glucose tolerance test is a significant risk factor for future cardiovascular events after myocardial infarction, In patients with established diabetes, the aim is to achieve HbA1c levels <6.5%.

Interventions on lipid profile

Several trials have unequivocally demonstrated the benefits of long-term use of statins in the prevention of new ischaemic events and mortality in patients with coronary heart disease. The targets established by the Fourth Joint Task Force of the ESC and other societies in patients after infarction are: for total cholesterol <175 mg/dL (4.5 mmol/L) with an option of 155 mg/dL (4.0 mmol/L) if feasible, and for lower LDL cholesterol 100 mg/dL (2.5 mmol/L) with an option of 80 mg/dL (2.0 mmol/L) if feasible.

Table 18. Long-term medical treatment after STEMI

Recommendations
Antiplatelets/anticoagulants
Aspirin for ever (75–100 mg daily) in all patients without allergy

Clopidogrel (75 mg daily) for 12 months in all patients irrespective of the acute treatment

Clopidogrel (75 mg daily) in all patients with contraindication to aspirin

Oral anticoagulant at INR 2–3 in patients who do not tolerate aspirin and clopidogrel

Oral anticoagulant at recommended INR when clinically indicated (e.g. atrial fibrillation, LV thrombus, mechanical valve)

Oral anticoagulant (at INR 2–3) in addition to low-dose aspirin (75–100 mg) in patients at high risk of thromboembolic events

Oral anticoagulant in addition to aspirin and clopidogrel (recent stent placement plus indication for oral anticoagulation)

Oral anticoagulant in addition to clopidogrel or aspirin (recent stent placement plus indication for oral anticoagulation and increased risk of bleeding)

b-Blockers

Oral b-blockers in all patients who tolerate these medications and without contraindications, regardless of blood pressure or LV function

ACE-inhibitor and ARB

ACE-inhibitor should be considered in all patients without contraindications, regardless of blood pressure or LV function

ARB in all patients without contraindications who do not tolerate ACE-inhibitors, regardless of blood pressure or LV function

Aldosterone blockade

Aldosterone blockade may be considered for post-STEMI patients with an EF <40% and heart failure or diabetes provided that creatinine is <2.5 mg/dL in men and 2.0 mg/dL in women, and potassium is <5.0 mEq/L

Statins

Statins in all patients, in the absence of contraindications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDL cholesterol <100 mg/dL (2.5 mmol/L)

Influenza immunization

In all patients

Mentioning of the VALIANT trial for valsartan, which demonstrated the non inferiority of valsartan, compared to captopril, in post infarction heart failure is needed. As such, in post MI patients with LV dysfunction, the ARB of choice in patients who cannot tolerate ACE inhibitors are valsartans.

D.6. LOGISTICS OF CARE

Pre-hospital care

Patient delay

The most critical time of a STEMI is the very early phase, during which the patient is often in severe pain and liable to cardiac arrest. Furthermore, the earlier that some treatments, notably reperfusion therapy, are given, the greater the beneficial effect (‘time is muscle’). Yet, it is often an hour or more after the onset of symptoms before medical aid is requested. Older patients, likely to delay seeking care. It should be a normal part of the care of patients with known coronary heart

disease to inform their partners and family about the symptoms of a heart attack and how to respond to it. The benefit of education of the general public for reducing delay times is uncertain. The public must at least be aware of how to call the EMS.

Emergency medical system

An EMS with a well-known unique telephone number for medical emergencies only is important to avoid further delays. Dispatchers have variable degrees of medical training. A tele-consultation with a reference cardiological center is ideal but available in a limited number of countries only. An updated and shared written management protocol is critically important. Although the use of an EMS decreases delay time , it is underutilized in many countries.

The ambulance service

The ambulance (helicopter) service has a critical role in the management of a STEMI and should be considered not only a mode of transport but a place for initial diagnosis, triage, and treatment. Ambulances should be able to reach the great majority of chest pain patients within 15 min of the call. The quality of the care given depends on the training of the staff concerned. At the most simple level, all ambulance personnel should be trained to recognize the symptoms of a STEMI, administer oxygen, relieve pain, and provide basic life support. All emergency ambulances should be equipped with 12-lead ECG recorders and defibrillators, and at least one person on board should be trained in advanced life support. Ambulance staff should be able to record an ECG for diagnostic purposes and either interpret it or transmit it so that it can be reviewed by experienced staff in an Intensive Cardiac Care Unit (ICCU) or elsewhere. The recording of an ECG prior to hospital admission can greatly accelerate in-hospital management and increase the probability of reperfusion therapy.

Networks

As indicated above, the implementation of a network of hospitals connected by an efficient ambulance (helicopter) service and using a common protocol is key for an optimal management of patients with STEMI. With such a network in place, target delay times should be: <10 min for ECG transmission; ≤5 min for tele-consultation; <30 min for ambulance arrival to start fibrinolytic therapy; and ≤120 min for ambulance arrival to first balloon inflation. Quality of care, appropriateness of reperfusion therapy, delay times, and patient outcomes should be measured and compared at regular times, and appropriate measures for improvement should be taken.

General practitioners

In many countries, general practitioners still play a major role in the early care of STEMI. In these countries they are often the first to be called by patients. If they respond quickly, they can be very effective since they usually know the individual patient and can take and interpret the ECG, are able to administer opioids, to call the ambulance service, and undertake defibrillation if needed. In other circumstances, consultation with a general practitioner is one of the reasons for an increased pre-hospital delay.

Admission procedures

The processing of patients once they arrive in hospital must be speedy, particularly with regard to the diagnosis and administration of fibrinolytic agents or the performance of a primary PCI, if

indicated. Candidates for primary PCI must be admitted directly to the cath lab, bypassing the emergency room and/or ICCU, while patients candidate for fibrinolysis must be treated directly in the emergency room.

The Intensive Cardiac Care Unit (ICCU , CCU)

STEMI patients should be admitted to ICCUs after the initial reperfusion therapy, which is given in the ambulance, in the emergency room, or in the cath lab. ICCUs should be equipped adequately and staffed with dedicated and properly trained physicians and nurses, due to the increased complexity of older and sicker patients.

Non-invasive monitoring

ECG monitoring for arrhythmias and ST-segment deviations should be started immediately in any patient suspected of having sustained a STEMI. This should be continued for at least 24 h. Further ECG monitoring for arrhythmias is dependent upon the perceived risk and upon the equipment available. When a patient leaves the ICCU, monitoring of rhythm may be continued, if necessary, by telemetry. A more prolonged stay at the ICCU is appropriate for those who have sustained heart failure, shock, or serious arrhythmias in the acute phase, as the risk of further events is high.

Invasive monitoring

All ICCUs should have the skills and equipment to undertake invasive monitoring of the arterial and pulmonary artery pressures. Arterial pressure monitoring should be undertaken in patients with cardiogenic shock. Pulmonary artery catheters have been used for a long time in ICCUs in haemodynamically unstable patients. However, recent studies did not show a benefit of a routine use of these procedures on mortality or on the length of the hospital stay. A restricted use is recommended.

E. EVALUATION AND MANAGEMENT OF NON-ST ELEVATION MYOCARDIAL INFARCTION

Summary points for Non ST Elevation Myocardial Infarction (NSTEMI)*

1. NSTEMI compared to STEMI:
    - More frequent
    - Patients are older and with more comorbidities
    - Initial mortality lower, 6 months mortality equal and long term mortality higher
2. Initial strategy for patients with NSTEMI:
    - Admit to specialized coronary care units
    - Alleviate: ischemia and symptoms
    - Monitor: ECGs and troponins
3. Electrocardiogram
    - Should be obtained within 10min of first medical contact.

- Consider additional leads, if normal
- Check for: ST-segment depression and/or T wave inversion.
- Comparison with previous ECG - if obtainable - useful.
- Always serial ECGs or continuous monitoring
- A normal ECG does not exclude the diagnosis (hidden ischemia in CX and right ventricular Involvement).

4. Biomarkers
   - Troponin I or T are gold standard.
   - Troponins rise within 2 to 4 hours
   - Minor elevations usually resolve within 2-3 days, but with larger necrosis elevations may remain for up to 2 weeks.
   - High sensitivity assays yield a negative predictive value of 95% as a single test on admission and nearly 100% by a repeat sample after 3 hours.
5. Echocardiography
   - Echocardiography should be routinely available in emergency rooms or chest pain units, and used early in all patients.
   - Evaluation of global LV function.
   - Diagnose regional hypokinesia by wall motion analysis.
   - Rule out some differential diagnosis.
   - Stress testing (e.g. exercise ECG) to rule out obstructive CAD in pain free patients with normal ECG and negative biomarkers.
6. Coronary angiography
   - Should be performed urgently for diagnostic purpose in patients at high risk.
7. Assess individual risk
   - Ischemic risk (TIMI, GRACE score).
   - Bleeding risk (CRUSADE score).
8. Markers of increased risk

   Clinical
   - Continuous or frequent episodes of pain
   - Tachycardia.
   - Hypotension.
   - Heart failure.

   Electrocardiogram
   - ST-segment depression or T-wave inversion on admission.
   - Deep T- wave inversion in anterior leads.
   - ST-segment depression ≥ 0.1mV or ≥0.05 mV in two or more contiguous leads.
   - ST-segment elevation (≥0.1 mV) in lead aVR.
9. Antischemic therapy
   - Nitrates (oral or intravenous) to relieve angina.

- Beta adrenergic blocker (BB) in patients with tachycardia and/or hypertension. The maintenance of beta adrenergic blockers should be considered in subjects without complete revascularization and residual angina.
- BB indicated in all patients with LV dysfunction.
- Non-dihydropyridine calcium channel blocker considered in patients without heart failure with continued symptoms already on BB or with contraindication to BB.

10. Antiplatelet treatment
    - Aspirin lifelong for all.
    - A P2Y12 inhibitor should be added and kept for 12 months unless there are contraindications such as excessive bleeding risk.
    - Ticagrelor indicated in all-comers, prasugrel only prior PCI in clopidogrel naïve patients without prior stroke/TIA whose anatomy is known, clopidogrel if ticagrelor and prasugrel are not an option
    - Glycoprotein IIb/IIIa in high risk PCI patients, but not routinely upstream.
11. Anticoagulation
    - Fondaparinux best benefit/ risk profile.
    - Add UFH on top of fondaparinux in patients undergoing PCI.
    - Enoxaparin in low bleeding risk patients.
    - Other low molecular weight heparins or unfractionated heparin are less recommended options as they were not compared to fondaparinux.
    - Bivalirudin in high risk bleeding as alternative to GP IIb/IIIa + UFH in patients undergoing PCI.
12. Invasive management
    - Timing of revascularization customized according to risk.
    - Within 72 hours all patients at risk, but
    - Within 2 hours for very high risk patients (life-threatening symptoms)
    - Within 24 hours for patients with high risk criteria
    - Prefer DES stents for PCI.
    - Non invasive evaluation for low risk patients
13. Special populations and situations
    - Special attention to diabetes, elderly, women, chronic kidney disease, anaemia.
    - Adjust medication doses according to renal function.
14. Long term management, secondary prevention
    - Statins for all initiated early with aim of LDL < 1,8 mmol/L (70 mg/dL).
    - Beta adrenergic blockers to all with LVEF < 40%.
    - ACE inhibitors to all with LVEF < 40%, patients with symptomatic heart failure, hypertension, diabetes or kidney disease.
    - Consider ACE inhibitors for all other as a general preventive medication.
    - ARB with proven efficiency to ACE intolerant patients.
    - Aldosterone antagonists to patients already on BB/ACEI with LVEF < 35%.

- Enrollment in secondary prevention program with intervention on diet, exercise and lifestyle.

** Resource: ESC Essential messages. ESC guidelines on the management of acute myocardial infarction. www.escardio.org/guidelines*

E.1. DIAGNOSIS AND RISK ASSESSMENT

Diagnosis and short-term risk stratification of NSTEMI should be based on a combination of clinical history, symptoms, ECG, biomarkers, and risk score results.

Clinical presentation and history.

The typical clinical presentation of NSTE-ACS is retrosternal pressure or heaviness ('angina') radiating to the left arm, neck, or jaw, which may be intermittent (usually lasting several minutes) or persistent. However, atypical presentations of NSTE-ACS are not uncommon. These include epigastric pain, recent-onset indigestion, stabbing chest pain, chest pain with some pleuritic features, or increasing dyspnoea. Atypical complaints are often observed in younger (25–40 years) and older (>75 years) patients, in women, and in patients with diabetes, chronic renal failure, or dementia.

Physical examination

The physical examination is frequently normal. An important goal of the physical examination is to exclude non-cardiac causes of chest pain and nonischaemic cardiac disorders (e.g. pulmonary embolism, aortic dissection, pericarditis, valvular heart disease, pneumothorax, pneumonia, pleural effusion).

Diagnostic tools

Electrocardiogram

ST-segment shifts and T-wave changes are the ECG indicators of unstable CAD.The number of leads showing ST-depression and the magnitude of ST-depression are indicative of the extent and severity of ischaemia and correlate with prognosis. ST-segment depression >0.5 mm(0.05 mV) in two or more contiguous leads is suggestive of NSTEMI and linked to prognosis. Minor (0.5 mm) ST-depression may be difficult to measure in clinical practice. More relevant is ST-depression of >1 mm (0.1 mV) which is associated with an 11% rate of death and MI at 1 year. ST-depression of >2 mm carries about a six-fold increased mortality risk. ST-depression combined with transient ST-elevation also identifies a high-risk subgroup. The finding of persistent (>20 min) ST-elevation suggests STEMI which requires different treatment.

Patients with ST-depression have a higher risk for subsequent cardiac events compared with those with isolated T-wave inversion (.> 1 mm) in leads with predominant R-waves, who in turn have a higher risk than those with a normal ECG on admission. Some studies have cast doubt on the prognostic value of isolated T-wave inversion. However, deep symmetrical inversion of the T-waves in the anterior chest leads is often related to a significant stenosis of the proximal left anterior descending coronary artery or main stem.

It should be appreciated that a completely normal ECG does not exclude the possibility of NSTE-ACS. In several studies, around 5% of patients with normal ECG who were discharged from the emergency department were ultimately found to have either an acute MI or an unstable angina.

Particularly, ischaemia in the territory of the circumflex artery frequently escapes the common 12-lead ECG, but may be detected in lead V4R and V3R as well as in leads V7–V9. Transient episodes of bundle branch block occasionally occur during ischaemic attacks.

Recommendations for ECG diagnosis

- A 12-lead ECG should be obtained within 10 min after first medical contact and immediately read by an experienced physician.
- In the absence of ST-elevation, additional recordings (V3R and V4R, V7–V9) should be obtained
- Comparison with a previous ECG, if available, is valuable, particularly in patients with co-existing cardiac disorders such as LV hypertrophy or a previous MI.
- ECG recordings should be repeated at least at 6 and 24 h, and in the case of recurrence of chest pain/symptoms. A pre-discharge ECG is advisable.

Biochemical markers

Several biomarkers have been investigated in recent years to be used for diagnostic and risk stratification. These reflect different pathophysiological aspects of NSTE-ACS, such as minor myocardial cell injury, inflammation, platelet activation, or neurohormonal activation. For the long-term prognosis, indicators of LV and renal dysfunction or diabetes also play an important role.

Markers of myocardial injury

Troponin (cTnT or cTnI)are the preferred markers of myocardial injury, because they are more specific and more sensitive than the traditional cardiac enzymes such as creatinine kinase (CK) or its isoenzyme MB (CK-MB). In this setting, myoglobin is not specific and sensitive enough to allow the detection of myocardial cell injury and therefore not recommended for routine diagnosis and risk stratification. It is believed that the elevation of cardiac troponins reflects irreversible myocardial cellular necrosis typically ESC Guidelines resulting from distal embolization of platelet-rich thrombi from the site of a ruptured plaque.

Accordingly, troponins may be seen as a surrogate marker of active thrombus formation. Troponins are the best biomarker to predict short-term (30 days) outcome with respect to MI and death. The prognostic value of troponin measurements has also been confirmed for the long term (1 year and beyond).

It is important to stress that other life-threatening conditions presenting with chest pain, such as dissecting aortic aneurysm or pulmonary embolism, may also result in elevated troponins and should always be considered as a differential diagnosis. Elevation of cardiac troponins also occurs in the setting of non-coronary-related myocardial injury (Table 3). This reflects the sensitivity of the marker for myocardial cell injury and should not be labeled as false-positive test results. True ‘false-positive’ results have been documented in the setting of skeletal myopathies or chronic renal failure.

There is no fundamental difference between troponin T and troponin I. Differences between study results are predominantly explained by varying inclusion criteria, differences in sampling patterns, and the use of assays with different diagnostic cut-offs. The diagnostic cut-off for MI using cardiac troponins should be based on the 99th percentile of levels among healthy controls as recommended by the Consensus committee. Acceptable imprecision (coefficient of variation) at the

99th percentile for each assay should be ≤10%. Each individual laboratory should regularly assess the range of reference values in their specific setting.

In patients with MI, an initial rise in troponins in peripheral blood occurs after 3–4 h. Troponin levels may persist elevated for up to 2 weeks caused by proteolysis of the contractile apparatus. In NSTE-ACS, minor elevation of troponins may be measurable only over 48–72 h (Figure 2).

Recommendations for diagnosis

- Blood must be drawn promptly for troponin (cTnT or cTnI) measurement. The result should be available within 60 min .
- A single negative test for troponins on arrival of the patient in hospital is not sufficient for ruling out an elevation, as in many patients an increase in troponins can be detected only in the subsequent hours.
- The test should be repeated after 6–12 h if the initial test is negative . A second sample in the absence of any other suspicious findings may be omitted only if the patient's last episode of chest pain was more than 12 h prior to the initial determination of troponins.
- The diagnosis of NSTEMI should never be made only on the basis of cardiac biomarkers, whose elevation should be interpreted in the context of other clinical findings.

Markers of inflammatory activity

Of the numerous inflammatory markers that have been investigated over the past decade, C-reactive protein measured by high-sensitive (hsCRP) assays is the most widely studied and linked to higher rates of adverse events. The exact source of elevated hsCRP levels among patients with NSTE-ACS remains unclear.

Markers of neurohumoral activation

Neurohumoral activation of the heart can be monitored by measurements of systemic levels of natriuretic peptides secreted from the heart. Natriuretic peptides, such as braintype [B-type natriuretic peptide (BNP)] or its N-terminal prohormone fragment (NT-proBNP), are highly sensitive and fairly specific markers for the detection of LV dysfunction.

The level is strongly associated with the risk of death even when adjusted for age, Killip class, and LV ejection fraction (EF). Values taken a few days after onset of symptoms seem to have superior predictive value when compared with measurements on admission. Natriuretic peptides are useful markers in the emergency room in evaluating chest pain or dyspnoea and were shown to be helpful in differentiating between cardiac and non-cardiac causes of dyspnoea.

Markers of renal function

Impaired renal function is a strong independent predictor for long-term mortality in ACS patients. Serum creatinine concentration is a less reliable indicator of renal function than creatinine clearance (CrCl) or glomerular filtration rate (GFR), because it is affected by a multitude of factors, including age, weight, muscle mass, race, and various medications. Cystatin C is considered to be a surrogate marker of renal function superior to CrCl or GFR estimation.

Echocardiography and non-invasive myocardial imaging

An echocardiogram is recommended to rule in/out differential diagnoses. LV systolic function is an important prognostic variable in patients with ischaemic heart disease and can be easily and

accurately assessed by echocardiography. In experienced hands, transient localized hypokinesia or akinesia in segments of the left ventricle wall may be detected during ischaemia, with normal wall motion on resolution of ischaemia. Furthermore, differential diagnoses such as aortic stenosis, aortic dissection, pulmonary embolism, or hypertrophic cardiomyopathy may be identified. Therefore, echocardiography should routinely be used in emergency units.

In patients without recurrence of pain, normal ECG findings, and negative troponins tests, a non-invasive stress test for inducible ischaemia is recommended before discharge. MRI is useful to assess myocardial viability. Rest myocardial scintigraphy was shown to be helpful for initial triage of patients presenting with chest pain without ECG changes or evidence of ongoing MI.

Imaging of the coronary anatomy

The gold standard is still conventional invasive coronary angiography. At the current state of development, cardiac computed tomography (CT) cannot be recommended as the coronary imaging modality in NSTEMI, because of suboptimal diagnostic accuracy. CT or MRI may, however, be indicated for evaluation of differential diagnoses, such as pulmonary embolism or aortic dissection.

Differential diagnoses

There are several cardiac and non-cardiac conditions that may mimic NSTEMI (Table).

Table 19. Cardiac and non-cardiac conditions that can mimic non-ST-elevation acute coronary Syndromes

Cardiac	Pulmonary	Haematological	Vascular	Gastrointestinal	Orthopaedic
Myocarditis	Pulmonary embolism	Sickle cell anaemia	Aortic dissection	Oesophageal spasm	Cervical discopathy
Pericarditis	Pulmonary infarction		Aortic aneurysm	Oesophagitis	Rib fracture
Cardiomyopathy	Pneumonia		Aortic coarctation	Peptic ulcer	Muscle injury
Valvular disease	Pleuritis		Cerebrovascular disease	Pancreatitis	Muscle inflammation
Apical ballooning (Tako-Tsubo syndrome)	Pneumothorax			Cholescystitis	Costochondritis

Risk scores

Several risk stratification scores have been developed and validated in large patient populations. In clinical practice, only simple risk scores are useful. Established risk scores (such as TIMI. GRACE) should be implemented for initial and subsequent risk assessment.

The TIMI risk score is derived from the TIMI trial population and was validated . It is less accurate in predicting events, but its simplicity makes it useful and widely accepted.

Table 20*. TIMI Risk score

One point each for:

- ≥ 65 years of age
- At least 3 risk factors for CAD*
- Significant coronary stenosis (≥50%)
- ST deviation on presentation
- Severe angina symptoms ( )

- Use of ASA in last 7 days
- Elevated serum troponin or CK-MB

Total number of points= TIMI risk score

*family history coronary artery disease, hypertension, dyslipidemia, diabetes, current smoking

**Resource ;Antman EM et al, 2000*

Table 21. TIMI risk score and recommended timing of PCI

Cardiac risk category	TIMI risk score	Recommended timing of PCI
Low risk	1-2	5-7 days
Intermediate risk	3-4	3-5 days
High risk	5-7	24-48 hours

The GRACE risk scores are based upon a large unselected population of an international registry of the full spectrum of ACS patients. The risk factors were derived with independent predictive power for in-hospital deaths and post-discharge deaths at 6 months (Table 24). On the basis of direct comparisons, the GRACE risk score is recommended as the preferred classification to apply on admission and at discharge in daily clinical routine practice.

Table 22. Mortality in hospital and at 6 months in low-,intermediate-, and high-risk categories in registry populations according to the GRACE risk score

Risk category	GRACE risk score	In-hospital deaths (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category	**GRACE risk score**	**Post-discharge to 6 months deaths (%)**
Low	≤88	<3
Intermediate	89–118	3–8
High	>118	>8

For calculations, see http://www.outcomes.org/grace

Recommendations for diagnosis and risk stratification

The following predictors of long-term death or MI should be considered in risk stratification.

- Clinical indicators: age, heart rate, blood pressure, Killip class, diabetes, previous MI/CAD.
- ECG markers: ST-segment depression.
- Laboratory markers: troponins, GFR/CrCl/ cystatin C, BNP/NT-proBNP, hsCRP;
- Imaging findings: low EF, main stem lesion, three vessel disease
- Risk score result.

E. 2. TREATMENT .

Four categories of acute treatment are discussed: antiischaemic agents, anticoagulants, antiplatelet agents, and coronary revascularization.Generally, the therapeutic approach is based on whether the patient is to be onlymedically treated**,** or in addition referred to angiography and revascularization.

E.2.1. ANTI-ISCHAEMIC TREATMENT

Anti-ischaemic drugs decrease myocardial oxygen consumption (decreasing heart rate, lowering blood pressure, or depressing LV contractility) and/or induce vasodilatation.

Beta-blockers

In NSTEMI, the primary benefits of beta-blockers are related to their effects on beta-1 receptors that result in a decrease in myocardial oxygen consumption. A meta analysis suggested that beta-blocker treatment was associated with a 13% relative reduction in risk of progression to NSTEMI.

- Beta-blockers are recommended in the absence of contraindications particularly in patients with hypertension or tachycardia. In most cases, oral treatment is sufficient. The target heart rate for a good treatment effect should be between 50 and 60 b.p.m. Oral beta blocker therapy should be continued throughout the hospital stay and after discharge.
- IV beta blocker therapy (metoprolol 5 mg every 5 minutes, up to 3 times) can be considered in hemodynamically stable patients with continuing symptoms despite administration of oxygen and nitroglycerin.
- Patients with significantly impaired atrioventricular conduction and a history of asthma or of acute LV dysfunction should not receive beta-blockers

Nitrates

The major therapeutic benefit is probably related to the venodilator effects that lead to a decrease in myocardial pre-load and LV end diastolic volume, resulting in a decrease in myocardial oxygen consumption. In addition, nitrates dilate normal as well as atherosclerotic coronary arteries and increase coronary collateral flow. There are no randomized placebo controlled trials to confirm the benefits of this class of drugs either in relieving symptoms or in reducing major adverse cardiac events.

- Intravenous nitrates may be considered in the absence of contraindications. IV NTG is indicated in first 48 hours, for treatment of persistent ischemia, HF or NTN. The dose should be titrated upwards until symptoms (angina and/or dyspnoea) are relieved unless side effects (notably headache or hypotension) occur. When symptoms are controlled, intravenous nitrates may be replaced by non-parenteral alternatives with appropriate nitrate-free intervals.
- Nitrates were contraindicated in patients taking phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil) because of the risk of profound vasodilatation and blood pressure drop in the case of concomitant administration.

Calcium channel blockers

Calcium channel blockers are vasodilating drugs. In addition, some have significant direct effects on atrioventricular conduction and heart rate. There are three subclasses of calcium blockers, which are chemically distinct and have different pharmacological effects: the dihydropyridines (nifedipine), the benzothiazepines (diltiazem), and the phenylalkylamines (verapamil). The agents in each

subclass vary in the degree to which they cause vasodilatation, decrease myocardial contractility, and delay atrioventricular (A-V) conduction. A-V block may be induced by non-dihydropyridines. Nifedipine and amlodipine produce the most marked peripheral arterial vasodilatation, whereas diltiazem has the least vasodilatory effect. All subclasses cause similar coronary vasodilatation. A meta-analysis of the effects of calcium channel blockers on death or non-fatal MI in unstable angina suggests that this class of drugs does not prevent the development of acute MI or reduce mortality.

- Consider oral or IV administration of a non-dihydropyridine calcium channel blockers (e.g. verapamil or diltiazem) in hemodynamically stable patients with suspected NSTEMI who have continuing symptoms and contraindications to beta-blocker.
- Nifedipine, or other dihydropyridines, should not be used unless combined with beta-blockers

New drugs

New antianginal drugs with different modes of action have been investigated in recent years. Ivabradine selectively inhibits the primary pacemaker current in the sinus node and may be used in patients with beta-blocker contraindications. Trimetazidine (preductal) exerts metabolic effects without haemodynamic changes. Ranolazine exerts antianginal effects by inhibiting the late sodium . Nicorandil has nitrate-like properties.

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E.2.2. ANTICOAGULANTS

Anticoagulants are used in the treatment of NSTEMI to inhibit thrombin generation and/or activity, thereby reducing thrombus-related events. There is clear evidence that anticoagulation is effective in addition to platelet inhibition and that the combination of the two is more effective than either treatment alone. With all anticoagulants, there is an increased risk of bleeding.

Several anticoagulants, which act at different levels of the coagulation cascade, have been investigated in NSTMI: Unfractionated heparin (UFH) as intravenous infusion, Low molecular weight heparin (LMWH) as subcutaneous injection, Fondaparinux as subcutaneous injection, Direct thrombin inhibitors (DTIs) as intravenous infusion, Vitamin K antagonists (VKAs) as oral medication.

Recommendations for anticoagulation

- Anticoagulation is recommended for all patients in addition to antiplatelet therapy.
- Anticoagulation should be selected according to the risk of both ischaemic and bleeding events. Also the choice depends on the initial strategy.
- In an urgent invasive strategy, UFH , enoxaparin, or bivalirudin should be immediately started. In a medical strategy, Enoxaparain or fondaparinux are preferable to UFH.
- At PCI procedures, the initial anticoagulant should also be maintained during the procedure regardless of whether this treatment is UFH, enoxaparin or bivalirudin whereas addititional UFH in standard dose (50–100 IU/kg bolus) is necessary in the case of fondaparinux.
- Anticoagulation can be stopped within 24 h after an invasive procedure. In a conservative strategy, fondaparinux, enoxaparin, or other LMWH may be maintained up to hospital discharge.

Unfractionated heparin (UFH)

UFH is poorly absorbed by the subcutaneous route, so that intravenous infusion is the preferred route of administration. A pooled analysis of six trials testing short-term UFH vs. placebo or untreated controls showed a significant risk reduction for death and MI of 33%. In trials comparing the combination of UFH plus aspirin vs. aspirin alone in NSTE-ACS, a trend towards a benefit was observed in favour of the UFH–aspirin combination, but at the cost of an increase in the risk of bleeding.

- UFH should be used instead of fondaparinux in patients with NSTEMI under the following circumstances:
  - Severe renal impairment (creatinine clearance <30ml/min)
  - Patients with mechanical heart valves
  - Patients with very high risk features mandating urgent (within 12 hours) PCI or CABG
- The therapeutic window is narrow, requiring frequent monitoring of the activated partial thromboplastin time (a PTT), with an optimal target level of 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal. At higher aPTT values, the risk of bleeding complications is increased, without further antithrombotic benefits. At aPTT values lower than 50 s, the antithrombotic effect is limited and the number of ischaemic events not reduced.
- A weight-adjusted dose of UFH is recommended, at an initial bolus of 60–70 IU/kg with a maximum of 5000 IU, followed by an infusion of 12–15 IU/kg/h, to a maximum of 1000 IU/h. This regimen is that currently recommended as being the most likely to achieve the target aPTT values.
- In UFH treated patients undergoing PCI, UFH should be stopped after the procedure. In patients managed with a conservative strategy, UFH should be continued for at least 48 hours. The anticoagulant effect of UFH is rapidly lost within a few hours after interruption. During the first 24 h after termination of treatment, there is a risk of reactivation of the coagulation process.

Low molecular weight heparin (LMWH)

The advantages of LMWH are an almost complete absorption after subcutaneous administration, less protein binding, less platelet activation, and, thereby, a more predictable dose–effect relationship. Furthermore, there is a lower risk of heparin-induced thrombocytopenia (HIT) with LMWH when compared with UFH due to less interaction with platelet factor 4. The risk of bleeding with LMWH is dose-related and is increased with higher age, female gender, lower body weight, reduced renal function, and interventional procedures.

Several trials have assessed the respective efficacy and safety of various LMWHs in comparison with UFH. Dalteparin and nadroparin were shown to be equally efficacious and safe as UFH in aspirin-treated patients. Dalteparin was shown to have greater efficacy in troponin-positive than in troponin-negative patients.

- Enoxaparin with a less favourable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low .
- As the efficacy/safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown, these anticoagulants cannot be recommended over fondaparinux.

- LMWHs are commonly administered subcutaneously every 12 h
- They are contraindicated in the case of renal failure with CrCl <30 mL/min.

Factor-Xa inhibitors

The only selective factor-Xa inhibitor available for clinical use is fondaparinux. No dose adjustment and no monitoring of anti-Xa activity. Fondaparinux has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting time (ACT), prothrombin, and thrombin times.

- Fondaparinux is preferred anticoagulant if patient at increased risk of bleeding. Fondaparinux is superior safety to enoxaparin, but cannot be used as sole anticoagulant during PCI procedures.
- 2.5 mg SC fixed dose of fondaparinux is recommended.
- In fondaparinux treated patients undergoing PCI, fondaparinux should be stopped after the procedure. In patients managed with a conservative strategy, fondaparinux should be maintained for up to 5 days or until hospital discharge.
- Fondaparinux is contraindicated if CrCl is lower than 30 mL/min.

Direct thrombin inhibitors

DTIs bind directly to thrombin (factor-IIa) and thereby inhibit the thrombin-induced conversion of fibrinogen to fibrin. Currently, several DTIs (hirudin, bivalirudin) are available. Hirudin and bivalirudin prolong aPTT and ACT. Coagulation tests correlate well with plasma concentrations. Therefore, these two tests can be used to monitor the anticoagulant activity of these compounds.

Intravenous direct thrombin inhibition with hirudin has been compared with aPTT-monitored UFH infusion in several large-scale randomized trials. In a meta-analysis including all these trials, there was a significantly lower event rate with hirudin vs. UFH infusion. However, these differences were not sustained during long-term follow-up.

Vitamin K antagonists (VKAs)

The VKAs produce their anticoagulant effect by interfering with the hepatic metabolism of vitamin K Their therapeutic effects are not observed until after 3–5 days of treatment. This treatment is therefore not useful in the acute phase of NSTEMI. In order to maintain anticoagulation efficacy without an excessive risk of bleeding, laboratory monitoring of the prothrombin time aiming for international normalized ratio (INR) levels 2.0–3.0 is required in the setting of MI.

VKA treatment, especially VKAs in combination with aspirin, was shown to be more effective than aspirin alone in the long-term prevention of death, re-MI, and stroke, but at the cost of a higher risk of major bleeding. In the current era of combining aspirin with clopidogrel in NSTEMI, VKAs are mostly used in the presence of other indications for anticoagulation, such as atrial fibrillation, or after implantation of a mechanical heart valve.

Anticoagulants during percutaneous coronary intervention procedures in NSTEMI

The use of platelet inhibition with aspirin and UFH has been the standard of care for PCI from the beginning. The current recommendation, based on empiric evidence, is to give UFH as an intravenous bolus of 100 IU/kg or 50–60 IU/kg if GP IIb/IIIa inhibitors are given. The efficacy of UFH is

monitored by ACT. However, the relationship between ACT and the rate of clinical events, and the real utility of ACT monitoring remain controversial.

Direct thrombin inhibition with bivalirudin and GP IIb/IIIa inhibitor infusion has been shown to be at least as effective as and associated with a lower risk of bleeding than UFH/LMWH plus GP IIb/IIIa inhibitors in the setting of planned PCI.

More recent data have shown that no additional UFH is needed if PCI is carried out within 6–8 h following the last subcutaneous dose of enoxaparin. After 6–8 h, an additional 0.3 mg/kg intravenous bolus of enoxaparin is recommended.

A standard dose of UFH (50–100 IU/kg bolus) is needed in addition to fondaparinux at the time of PCI, if fondaparinux was initiated prior to the procedure.

E.2.3. ANTIPLATELET AGENTS

Platelet activation plays a key pathophysiological role in NSTEMI. Antiplatelet therapy is necessary for the acute event, and subsequent maintenance therapy. Three related but complementary strategies provide effective antiplatelet therapy: cyclooxygenase (COX)-1 inhibition aspirin), inhibition of adenosine diphosphate (ADP)-mediated platelet aggregation with thienopyridines (ticlopidine and clopidogrel), and GP IIb/IIIa inhibition (tirofiban, eptifibatide, abciximab).

Acetylsalicylic acid (aspirin)

Aspirin irreversibly inhibits COX-1 in platelets, thereby limiting the formation of thromboxane A2, thus inhibiting platelet aggregation. In the meta-analysis of the Antithrombotic Trial lists Collaboration, a 46% reduction in the rate of vascular events was evidenced.

- Aspirin is recommended for all patients presenting with NSTEMI without contraindication at an initial loading dose of 160–325 mg (non-enteric) , and at a maintenance dose of 75–100 mg long-term.
- For all patients with contraindication to aspirin, clopidogrel should be given instead.
- The most common side effect of aspirin is gastrointestinal intolerance, reported in 5–40% of aspirin-treated patients. Gastrointestinal bleeding appears to increase with higher doses. In the CAPRIE study, the rate of gastrointestinal bleeding leading to aspirin discontinuation was 0.93%.

Thienopyridines

Both ticlopidine and clopidogrel are ADP receptor antagonists, which block the ADP-induced pathway of platelet activation by specific inhibition of the P2Y12 ADP receptor. Ticlopidine was replaced by clopidogrel over time. In the CURE trial, clopidogrel was administered for 9–12 months in addition to aspirin (75–325 mg) vs. aspirin alone in 12 562 patients suffering from NSTEMI. The benefit was obtained early, with a significant 34% risk reduction of cardiovascular death, MI, stroke, or severe ischaemia at 24 h in the clopidogrel group.

- For all patients, an immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily.

- In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function.
- In patients pre-treated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible.
- Clopidogrel can be administered with all statins.
- The triple association of aspirin, clopidogrel, and a VKA should only be given if a compelling indication exists.
- Newer P2Y12 inhibitors with more potent receptor affinity and more rapid onset of action are currently under evaluation (e.g. prasugrel, cangrelor).

Glycoprotein IIb/IIIa receptor inhibitors

Three GP IIb/IIIa inhibitors have been approved for clinical use, namely abciximab, eptifibatide, and tirofiban.

Recommendations for glycoprotein IIbIIIa inhibitors

- In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment is recommended in addition to oral antiplatelet agents.
- Patients who receive initial treatment with eptifibatide or tirofiban prior to angiography should be maintained on the same drug during and after PCI.
- In high-risk patients not pre-treated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography.
- GP IIb/IIIa inhibitors must be combined with an anticoagulant

Table 23. Clinical use of antithrombotic therapy

Anticoagulants
Fondaparinux* 2.5 mg subcutaneously daily
Enoxaparin* 1 mg/kg subcutaneously every 12 h
Dalteparin* 120 IU/kg every 12 h
Nadroparin* 86 IU/kg every 12 h
UFH intravenous bolus 60–70 U/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 U/h) titrated to aPTT 1.5–2.5 times control
Bivalirudina intravenous bolus of 0.1 mg/kg and infusion of 0.25 mg/kg/h. Additional intravenous bolus of 0.5 mg/kg and infusion increased to 1.75 mg/kg/h before PCI
Oral antiplatelet therapy
Aspirin initial dose: 160–325 mg non-enteric formulation, followed by 75–100 mg daily
Clopidogrel 75 mg/day after a loading dose of 300 mg (600 mg when rapid onset of action is wanted)
GP IIb/IIIa inhibition*
Abciximab 0.25 mg/kg intravenous bolus followed by infusion of 0.125 mg/kg/min (maximum 10 mg/min) for 12–24 h
Eptifibatide 180 mg/kg intravenous bolus (second bolus after 10 min for PCI) followed by infusion of 2.0 mg/kg/min for 72–96 h
Tirofiban 0.4 mg/kg/min intravenously for 30 min followed by infusion of 0.10 mg/kg/min for 48–96 h.

*See Chronic kidney disease for specific rules of prescription in the case of renal failure

E.2.4. CORONARY REVASCULARIZATION

NSTEMI is the most frequent manifestation of ACS and represents the largest group of patients undergoing PCI. Despite advances in medical and interventional treatments, the mortality and morbidity remain high and equivalent to that of patients with STEMI after the initial month. Therefore, early risk stratification is essential for selection of medical as well as interventional treatment strategies. The ultimate goals of coronary angiography and revascularization are mainly two-fold: symptom relief, and improvement of prognosis in the short and long term.

The indications for myocardial revascularization and the preferred approach (PCI or CABG) depend on the extent and severity of the lesions as identified by coronary angiography, the patient's condition, and co-morbidity. Data from TIMI show that 30–38% of the patients with unstable coronary syndromes have single vessel disease and 44–59% have multivessel disease (>50%diameter stenosis).

Invasive vs. conservative strategy

Choice of strategy

Coronary angiography should be planned as soon as possible (urgent invasive strategy) in patients with severe ongoing angina, profound or dynamic ECG changes, major arrhythmias, or haemodynamic instability upon admission or thereafter. These patients represent 2–15% of the patients admitted with NSTE-ACS.

In patients with intermediate to high-risk features, but without the aforementioned life threatening features, early coronary angiography (within 72 h) followed by revascularization when possible and indicated, or initial medical stabilization and selective performance of coronary angiography based on the clinical course have been tested as alternative strategies.

In low-risk patients, a non-invasive assessment of inducible ischaemia should be performed prior to discharge. If this is positive, coronary angiography should be performed.

Recommendations for invasive evaluation and revascularization

- Urgent coronary angiography is recommended in patients with refractory or recurrent angina associated with dynamic ST-deviation, heart failure, life threatening arrhythmias, or haemodynamic instability
- Early (<72 h) coronary angiography followed by revascularization (PCI or CABG) in patients with intermediate to high-risk features is recommended .
- Routine invasive evaluation of patients without intermediate to high-risk features is not recommended, but non-invasive assessment of inducible ischaemia is advised.
- PCI of non-significant lesions is not recommended.
- After critical evaluation of the risk–benefit ratio, and depending on known co-morbidities and potential need for non-cardiac surgery in the short/medium term (e.g. planned intervention or other conditions) requiring temporary withdrawal of dual antiplatelet therapy, consideration should be given to the type of stent to be implanted (BMS or DES).

E.3. COMPLICATIONS AND THEIR MANAGEMENT

Bleeding complications

Bleeding complications are the most frequent non-ischaemic complications observed in the management of NSTEMI. Bleeding is graded a major or minor. It is estimated that the frequency of major bleeding ranges from 2 to 8% across the spectrum of NSTEMI. The independent predictors of major bleeding were advanced age, female sex, history of bleeding, history of renal insufficiency, use of GP IIb/IIIa inhibitors.

Prevention of bleeding has become a target as important as the prevention of ischaemic events. Prevention of bleeding encompasses the choice of safer drugs, appropriate dosage, reduced duration of antithrombotic treatment, use of combination of antithrombotic and antiplatelet agents.

Recommendations for bleeding complications:

- Minor bleeding should preferably be managed without interruption of active treatments
- Major bleeding such as gastrointestinal, retro-peritoneal bleeding, intracranial haemorrhage, or severe blood loss requires the interruption and neutralization of both antiplatelet and anticoagulant treatment.
- Blood transfusion has been shown to improve prognosis in elderly patients suffering from acute MI with haematocrit levels <25%.
- In mild to moderate anaemia (haematocrit >25% or haemoglobin levels >8 g/dL), blood transfusion may be associated with increased risk of death and should be avoided

Thrombocytopenia

Thrombocytopenia is defined as a decrease in platelet count to <100 000 or a drop of >50% from baseline platelet count. Thrombocytopenia is considered to be moderate if the platelet count is between 20 000 and 50 000 and severe if it is less than 10 000. Thrombocytopenia can occur during UFH or LMWH and Glycoprotein IIb/inhibitor treatment. Mild and transient decline in platelet count occurring 1–4 days after initiation of therapy is common and observed in up to 15% of UFH-treated patients.

Recommendations for thrombocyopenia

- Significant thrombocytopenia (<100 000 or >50% drop in platelet count) occurring during treatment with GP IIb/IIIa inhibitors and/or heparin (LMWH or UFH) requires the immediate interruption of these drugs .
- Severe thrombocytopenia (<10 000) induced by GP IIb/IIIa inhibitors requires platelet transfusion with fresh–frozen plasma in the case of bleeding
- Prevention of heparin-induced thrombocytopenia (HIT) can be achieved with the use of anticoagulants devoid of risk of HIT, such as fondaparinux or bivalirudin, or brief prescription of LMWH in cases where these compounds are chosen as anticoagulant .

E.4. SPECIAL POPULATION AND CONDITIONS

The elderly (>65 years)

Recommendations for the elderly

- Elderly patients often have atypical symptoms (shortness of breath, diaphoresis, , nausea–vomiting, and syncope)
- The bleeding risk linked to LMWH is higher in elderly patients.
- Elderly patients should be considered for routine early invasive strategy, after careful evaluation of their inherent raised risk of procedure-related complications.

Diabetes mellitus

The presence of diabetes mellitus is an independent predictor of higher mortality among patients with NSTEMI and is associated with a two-fold higher risk of death when compared with non-diabetic patients. About 20–30% of all patients with NSTEMI have diabetes type 2.

In the case of angiography and/or angioplasty, the use of contrast medium raises the risk of contrast-induced nephropathy (CIN). Metformin should be interrupted ideally 24 h before the examination or at the latest on the day of the procedure. The risk of lactic acidosis is very low, but is increased in the case of renal failure. Metformin can be re-introduced 48 h after the use of contrast medium, if renal failure has not developed.

Recommendations for diabetes

- Tight glycaemic control to achieve normoglycaemia as soon as possible is recommended in all diabetic patients with NSTEMI in the acute phase .
- Insulin infusion may be needed to achieve normoglycaemia in selected NSTE-ACS patients with high blood glucose levels at admission.
- An early invasive strategy is recommended for diabetic patients with NSTE-ACS.

- Diabetic patients with NSTE-ACS should receive intravenous GP IIb/IIIa inhibitors as part of the initial medical management which should be continued through the completion of PCI.

Chronic kidney disease (CKD)

Chronic kidney disease as a marker of risk of coronary artery disease. The presence of renal dysfunction complicates the management of patients suffering from NSTE-ACS. In case of severe renal failure (CrCl <30 mL/min), many drugs with exclusive or substantial renal elimination need to be down-titrated or might even be contraindicated, particularly LMWH, fondaparinux, bivalirudin and GP IIb/IIIa inhibitors.

Contrast-induced nephropathy (CIN)

Baseline renal dysfunction may increase the risk of CIN in the case of angiography. Risk of CIN is particularly high in patients with older age, diabetes, dehydration, high volume contrast medium injection. Patients who need to undergo coronary angiography and/or angioplasty must receive special care in order to reduce or avoid CIN. Current protocols recommend hydration with 250–500 mL of sodium chloride 0.9% before and after the procedure, being cautious in those patients with a history of heart failure. The amount of contrast medium should be limited to a maximum of 50 mL for a diagnostic procedure. Assessment of creatinine level up to day 3 after contrast injection is necessary to detect CIN.

Recommendations for patients with CKD

- CrCl and/or GFR should be calculated for every patient hospitalized for NSTEMI.
- In patients with CrCl <30 mL/min or GFR <30 mL/min/1.73 m2, a careful approach to the use of anticoagulants is recommended, since dose adjustment is necessary with some, while others are contraindicated.
- UFH infusion adjusted according to aPTT is recommended when CrCl <30 mL/min or GFR <30 mL/min/1.73 m2.
- GP IIb/IIIa inhibitors can be used in the case of renal failure. Dose adaptation is needed with eptifibatide and tirofiban. Careful evaluation of the bleeding risk is recommended for abciximab
- Patients with CKD with CrCl <60 mL/min are at high risk of further ischaemic events and therefore should be submitted to invasive evaluation and revascularization whenever possible.
- Appropriate measures are advised in order to reduce the risk of CIN.

E.5. SECONDARY PREVENTION OF NSTEMI

Non-pharmacologic secondary preventive therapy

Smoking cessation

- Cigarette smokers should be urged to quit to reduce their risk of recurrent cardiac events and death.
- Active counseling and drug interventions, such as nicotine replacement is necessary.

Exercise

- Regular physical activity must be encouraged. Thirty minutes of moderate intensity aerobic activity, if possible every day, or at least five times per week is recommended.

Weight reduction

- The theoretical goal is to achieve a body mass index (BMI) <25 kg/m2 or a waist circumference ,102 cm in men and ,88 cm in women. An initial weight loss of 10% from baseline is a first step.

Nutrition intervention

- Healthy diet based on low salt intake with reduced intake of saturated fats is essential.
- Encourage regular in take of fruit and vegetables

Blood pressure control

- The goal is to achieve blood pressure <140/90 mmHg in non-diabetic patients and <130/80 mmHg in patients with diabetes or chronic renal dysfunction.
- Lifestyle interventions are an important means of achieving blood pressure control, particularly physical activity, in addition to weight loss and pharmacotherapy.

Management of diabetes

- In patients with established diabetes, the aim is to achieve HbA1c levels <6.5%.
- Counselling with endocrinologists is advisable.
- Lifestyle measures, in addition to weight loss in obese patients, and adapted pharmacotherapy are of great importance.
- Patients with diabetes should be offered a needs based diabetes education

Pharmacologic secondary preventive therapy

Antiplatelet agents and anticoagulants

- Aspirin (81-160 mg daily) should be continued in all NSTEMI patients without contraindications. The dose of ASA should be minimized (81 mg daily) in patients also taking clopidogrel or warfarin to reduce the risk of bleeding complications.
- Clopidogrel (75 mg daily), in addition to ASA is recommended on discharge for all NSTEMI patients in the absence of contraindications. The duration of clopidogrel therapy (3-12 months) should be tailored according to patient risk and the type of stent.

Beta-blocker therapy

- Beta-blockers should be given to all patients without contraindications.
- Use of cardioselective beta blockers (bisoprolol, carvedilol) is generally recommended in NSTEMI patients with preserved LV function.
- In patients with ongoing symptoms , with contraindications to beta blockade, treatment with a calcium channel blocker(verapamil, diltiazem) can be considered.
- Long-term therapy of beta blocker may not be necessary in low-risk patients (e.g. normotensive preserved LV function who have been completely revascularized.

ACE inhibitors

- ACE inhibitors are indicated long-term in all patients with LVEF <40% and in patients with diabetes, hypertension, or CKD, unless contraindicated

Angiotensin receptor blockers

- ARBs should be considered in patients who are intolerant to ACE inhibitors and/or who have heart failure or MI with LVEF <40%.

Aldosterone receptor antagonists

- Aldosterone blockade should be considered in patients after MI who are already treated with ACE inhibitors and beta-blockers and who have an LVEF <40% and either diabetes or heart failure, without significant renal dysfunction or hyperkalaemia.

Statins

- This beneficial effect was shown in all subgroups, including men and women, the elderly, smokers, diabetic patients, hypertensive patients, or patients with chronic kidney disease (CKD).
- Statins are recommended for all NSTEMI patients (in the absence of contraindications), irrespective of cholesterol levels, initiated early (within 1–4 days) after admission, with the aim of achieving LDLc levels <100 mg/dL (<2.6 mmol/L)

E.6. MANAGEMENT STRATEGIES

First step: initial evaluation

Chest pain or discomfort will be the symptom that leads to the patient seeking medical attention or hospitalization. A patient with suspected NSTE-ACS must be evaluated in a hospital and immediately seen by a qualified physician. Specialized chest pain units provide the best and most expeditious care. The initial step is to assign the patient without delay to a working diagnosis on which the treatment strategy will be based. The criteria are the following:

- Quality of chest pain and a symptom-oriented physical examination.
- Assessment of the likelihood of CAD (e.g. age, risk factors, previous MI, CABG, PCI);
- ECG (ST-deviation or other ECG abnormalities).

On the basis of these findings which should be available within 10 min after first medical contact, the patient can be assigned to one of the three major working diagnoses:

- STEMI requiring immediate reperfusion;
- NSTEMI
- Unstable angina.

Additional ECG leads (V3R and V4R, V7–V9) should be recorded, especially in patients with persisting chest pain. Blood is drawn on arrival of the patient in hospital and the result should be available within 60 min to be used in the second strategy step. Initial blood tests must at least include: troponin T or troponin I, CK (-MB), creatinine, haemoglobin, and leukocyte count. The assignment to the category NSTEMI will result in the second strategy step.

Second step: diagnosis validation and risk assessment

Diagnosis validation

After the patient is assigned to the group NSTEMI intravenous and oral treatments will be started. The first-line treatment should be made up of at least nitrates, beta-blockers, aspirin, clopidogrel, and anticoagulation, the type depending on the management strategy, i.e. urgent invasive, early invasive, or conservative.

The further management will be based on additional information/data:

- routine clinical chemistry, particularly troponins (on prese tation and after 6–12 h) and other markers according to working diagnoses (e.g. D-dimers, BNP, NT-proBNP).
- repeat, preferably continuous, ST-segment monitoring.
- Echocardiogram, MRI, CT, or nuclear imaging for differential diagnoses (e.g. aortic dissection, pulmonary embolism).
- responsiveness to antianginal treatment.
- risk score assessment.
- bleeding risk assessment

During this step, other diagnoses may be confirmed or excluded, such as acute anaemia, pulmonary embolism, and aortic aneurysm

Risk assessment

Risk assessment is an important component of the decision making process and is subject to constant re-evaluation. It encompasses assessment of both ischaemic and bleeding risk. The risk factors for bleeding and ischaemic events overlap considerably, with the result that patients at high risk of ischaemic events are also at high risk of bleeding complications. Therefore, the choice of the pharmacological environment (dual or triple antiplatelet therapy, anticoagulants) has become critical, as has the dosage of the drugs. In addition, in cases where invasive strategy is needed, the choice of the vascular approach is very important, since the radial approach has been shown to reduce the risk of bleeding when compared with the femoral approach. In this context, particular attention has to be paid to renal dysfunction, shown to be particularly frequent in elderly patients and among diabetics.

During this step, the decision has to be made whether the patient should go on to cardiac catheterization or not.

Third step: invasive strategy

Cardiac catheterization is advised to prevent early complications and/or to improve long-term outcome . Accordingly, the need for and timing of an invasive strategy has to be tailored according to the acuteness of risk into three categories: conservative, early invasive, or urgent invasive.

Conservative strategy

Patients that fulfil all the below criteria may be regarded as low risk and should not be submitted to early invasive evaluation:

- no recurrence of chest pain
- no signs of heart failure
- no abnormalities in the initial ECG or a second ECG (6–12 h)
- no elevation of troponins (arrival and at 6–12 h);

Low risk as assessed by a risk score can support the decision-making process for a conservative strategy. Before discharge, a stress test for inducible ischaemia is useful for further decision-making.

Patients who cannot be excluded by the above criteria should go on to cardiac catheterization.

Urgent invasive strategy

Urgent invasive strategy should be undertaken for patients who are early in the process of developing major myocardial necrosis escaping the ECG (e.g. occlusion of the circumflex

artery) or are estimated to be at high risk of rapid progression to vessel occlusion.

These patients are characterized by:

- refractory angina (e.g. evolving MI without ST-abnormalities).
- recurrent angina despite intense antianginal treatment associated with ST-depression (>2 mm) or deep negative T-waves
- clinical symptoms of heart failure or haemodynamic instability ('shock')
- life-threatening arrhythmias (ventricular fibrillation or ventricular tachycardia).

Early invasive strategy

Most patients initially respond to the antianginal treatment, but are at increased risk and need early angiography. The timing depends on the local circumstances, but it should be performed within 72 h. The following features indicate patients who should undergo routine early angiography.

- elevated troponin levels.
- dynamic ST or T-wave changes (symptomatic or silent) (>0.5 mm)
- diabetes mellitus
- reduced renal function (GFR,60 mL/min/1.73 m2)
- depressed LVEF<40%.
- early post-MI angina
- PCI within 6 months, previous CABG
- intermediate to high risk according to a risk score

Fourth step: revascularization modalities

If the angiogram shows no critical coronary lesions, patients will be referred for medical therapy. The diagnosis of NSTEMI may be reconsidered and particular attention should be paid to other possible reasons for symptoms at presentation before the patient is discharged. However,
the absence of critical coronary lesions does not rule out the diagnosis if clinical presentation was suggestive of ischaemic chest pain and if biomarkers were positive. In this situation, patients should receive treatment according to recommendations in NSTEMI.

Recommendations for the choice of a revascularization modality in NSTE-ACS are similar to those for elective revascularization procedures. In patients with single vessel disease, PCI with stenting of the culprit lesion is the first choice. In patients with multivessel disease, the decision for PCI or CABG must be made individually. The anticoagulant should not be changed for PCI. In patients pre-treated with fondaparinux, UFH must be added before PCI. In patients pre-treated with tirofiban or eptifibatide, the infusion should be maintained throughout the intervention. Patients untreated with GP IIb/IIIA inhibitors should preferably receive abciximab before PCI.

If CABG is planned, clopidogrel should be stopped and surgery deferred for 5 days, if the clinical condition and the angiographic findings permit this. If angiography shows no options for revascularization, owing to the extent of the lesions and/or poor distal run off, freedom from angina at rest should be achieved by intensified medical therapy, and secondary preventive measures should be instituted.

Fifth step: Discharge and post-discharge management

Although in NSTEMI most adverse events occur in the early phase, the risk for MI or death remains elevated over several months. Patients treated with early revascularization are at low (2.5%) risk for developing life-threatening arrhythmias, with 80% occurring during the first 12 h after onset of symptoms.500 Accordingly, monitoring of the patients beyond 24–48 h is not warranted. Discharge from hospital depends on clinical and angiographic findings. Patients with NSTEMI should be hospitalized for at least 24 h after successful stenting of the culprit lesion. Intense risk factor modification is warranted in all patients following the diagnosis of NSTEMI.

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APPENDIXES

Appendex 1. International classification of AMI (ICD-10)

Disease code	AMI
I21	**Acute myocardial infarction**
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	**Subsequent myocardial infarction**
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	**Certain current complications following acute myocardial infarction (AMI)**
I23.0	Haemopericardium as current complication following AMI
I23.1	Atrial septal defect as current complication following AMI
I23.2	Ventricular septal defect as current complication following AMI
I23.3	Rupture of cardiac wall without haemopericardium as current complication following AMI
I23.4	Rupture of chordae tendineae as current complication following AMI
I23.5	Rupture of papillary muscle as current complication following AMI
I23.6	Thrombosis of atrium and ventricle as current complications following AMI
I23.8	Other current complications following AMI

Appendex 2. Sample Alteplase PROTOCOL FOR STEMI*

Patient's full name:

Patient's gender, age:

Patient's height (cm) and weight (kg):

Door-to-needle time for initiation of SK therapy (minutes):

(or medical contact-to-needle)

Name of hospital:

Ward's name:

Absolute contraindications

- ☐ Haemorrhagic stroke or stroke of unknown origin at any time
- ☐ Ischaemic stroke in preceding 6 months
- ☐ Neoplasms
- ☐ Recent major trauma/surgery/head injury (within preceding 3 weeks)
- ☐ Gastrointestinal bleeding within the last month
- ☐ Known bleeding disorder
- ☐ Aortic dissection
- ☐

Relative contraindications

- ☐ Transient ischemic attack in preceding 6 months
- ☐ Oral anticoagulant therapy
- ☐ Pregnancy or within 1 week post-partum
- ☐ Refractory hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg)
- ☐ Advanced liver disease
- ☐ Pregnant
- ☐ Active peptic ulcer

1. Vital signs

Baseline, then q15 minx3h after initiation of Alteplase, then q30 minx2h, then, q1hx24h.

2. Neurological signs

Baseline and q4hx24h

3. ECG (before the therapy)

☐ ST elevation greater than 0.1 mV in at least contiguous leads

4. Blood work

☐BC ☐PT, INR, PTT ☐Creatinine

□Glucose □Troponin □CK-MB

5. Antiplatelet agent

□ Aspirin, oral dose of 150-325 mg

□ Clopidogrel, loading dose of 300 mg if age ≤75 years, 75 mg if age >75 years

6. □ Oxygen

7. Administer of Alteplase as follows:

Initially 15 mg i.v. bolus , then 0.75 mg/kg over 30 min (maximum dosage not to exseed 50 mg), then 0.5 mg/kg over 60 min I.V (maximum dosage not to exseed 35 mg). The treatment lasts for 1.5 hours. Total dosage not to exceed 100 mg.

8 .Anticoagulation

□ Heparin is given for 24-48 hours.

Physician's name and signature:

Date(YYYY/MM/DD):

*****Resource: *Nova Scotia clinical guideline (Canadian) for acute STEMI(2008).*

Appendex 3.

Unfractionated heparin (UFH) in AMI

A weight-adjusted dose of UFH is recommended, at an initial bolus of 60–70 IU/kg with a maximum of 5000 IU, followed by an infusion of 12–15 IU/kg/h, to a maximum of 1000 IU/h. This regimen is that currently recommended as being the most likely to achieve the target aPTT values. The optimal target level of 50–75 s, corresponding to 1.5–2.5 times the upper limit of normal. Next dose of heparin depends on aPPT value.

Heparin dosing by using aPPT values*

aPPT (sec)	IV bolus dose of heparin (unit)	Time to stop heparin infusion (min)	Changes of speed for heparin infusion ml/hours (unit/hours)	Time for control of aPPT
<50	5000	0	+3 (+120)	6 hours
50-59	0	0	+3 (+120)	6 hours

60-85	0	0	0 (0)	Next morning
86-95	0	0	-2 (-80)	Next morning
96-120	0	30	-2(-80)	6 hours
>120	0	60	-4 (-160)	6 Hours

**Resource: Hirsh J., Anand S., Halperin J.L., Fuster V. Guide to anticogulant therapy: Heparin. American Heart Association. 2001*

Appendex 8.

The management of MI and health service delivery level

Three levels	Diagnosis	Treatment	Others
1 level (ambulance, family and soum hospital)	ECG	First medical treatment (MONA)	Referral to hospital
2 level (Aimag and district)	ECG Troponin Echocardiography	Medical treatment Fibrinolytic therapy	Risk assessment Follow-up by cardio-monitor Referral to the tertiary level hospital
3 level (State central hospitals)	ECG Troponin Echocardiography Angiography	Medical treatment Fibrinolytic therapy PCI	Risk assessment Follow-up by cardio-monitor Follow-up patient's hemodynamic by invasive method