Let’s talk about how we can help; UCA’s ED & Low T Clinics

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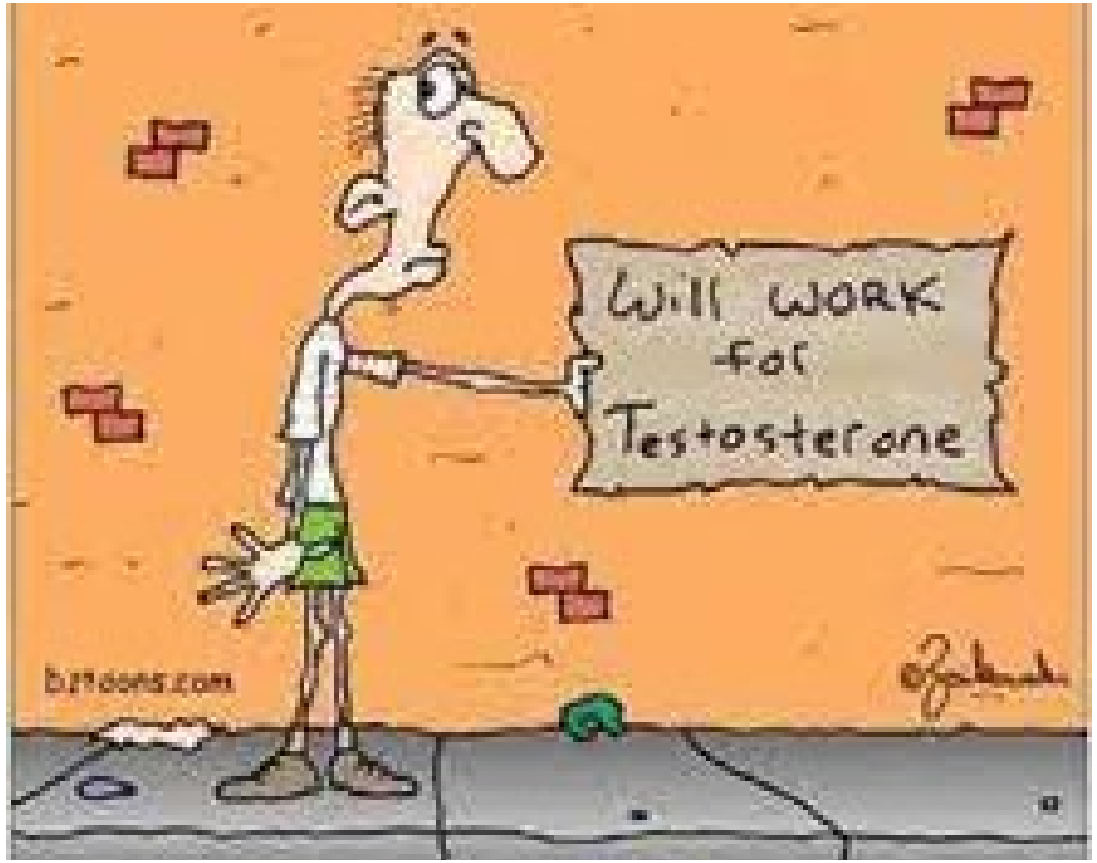
Testosterone Deficiency

- Recent surveys/studies
  - Prescriptions have nearly tripled
  - 25% of men who are on TRT had not been tested
  - Nearly 50% don't have it recheck following TRT
- Many men are hypogonadal and fear of cardiovascular complications or prostate cancer stop them from receiving therapy.
- Review is a compilation of articles, guidelines from AUA, Endocrine society and EAU



Hypogonadism

- **Primary Hypogonadism, Testicular failure**
  - Elevated LH, FSH
- **Secondary Hypogonadism, Pituitary**
  - Decreased LH, FSH
- **Mixed Hypogonadism**
  - 85% of all cases
  - Commonly referred to as “low T” and develops in aging men, beginning in the 40s through 60s and beyond

Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

Primary Hypogonadism	Secondary Hypogonadism
ORGANIC	
KS	Hypothalamic/pituitary tumor
Cryptorchidism, myotonic dystrophy, anorchia	Iron overload syndromes
Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy	Infiltrative/destructive disease of hypothalamus/pituitary
Orchitis	Idiopathic hypogonadotropic hypogonadism
Testicular trauma, torsion	
Advanced age	
FUNCTIONAL	
Medications (androgen synthesis inhibitors)	Hyperprolactinemia
End-stage renal disease[a]	Opioids, anabolic steroid use, glucocorticoids
	Alcohol and marijuana abuse[a]
	Systemic illness[a]
	Nutritional deficiency/excessive exercise
	Severe obesity, some sleep disorders
	Organ failure (liver, heart, and lung)[a]
	Comorbid illness associated with aging[a]

[a]Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin *et al.* (7).

Testosterone Deficiency Testing

- Diagnosis of Testosterone deficiency
  - TT <300 (range 230-350)
  - 2 am (fasting) readings
  - 2 low readings with symptoms
  - Who else (even without symptoms)
    - Unexplained anemia
    - Bone density loss
    - Diabetes*
    - Exposure to chemotherapy
    - Testicular radiation
    - HIV
    - Chronic narcotics
    - Male infertility
    - Chronic corticosteroid use
    - Pituitary dysfunction

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

Specific symptoms and signs
Incomplete or delayed sexual development
Loss of body (axillary and pubic) hair
Very small testes (<6 mL)
Suggestive symptoms and signs
Reduced sexual desire (libido) and activity
Decreased spontaneous erections, erectile dysfunction
Breast discomfort, gynecomastia
Eunuchoidal body proportions
Inability to father children, low sperm count
Height loss, low-trauma fracture, low BMD
Hot flushes, sweats
Nonspecific symptoms and signs associated with testosterone deficiency
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild unexplained anemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index

Adapted with permission from Bhasin *et al.* (7).

Testosterone Deficiency Testing

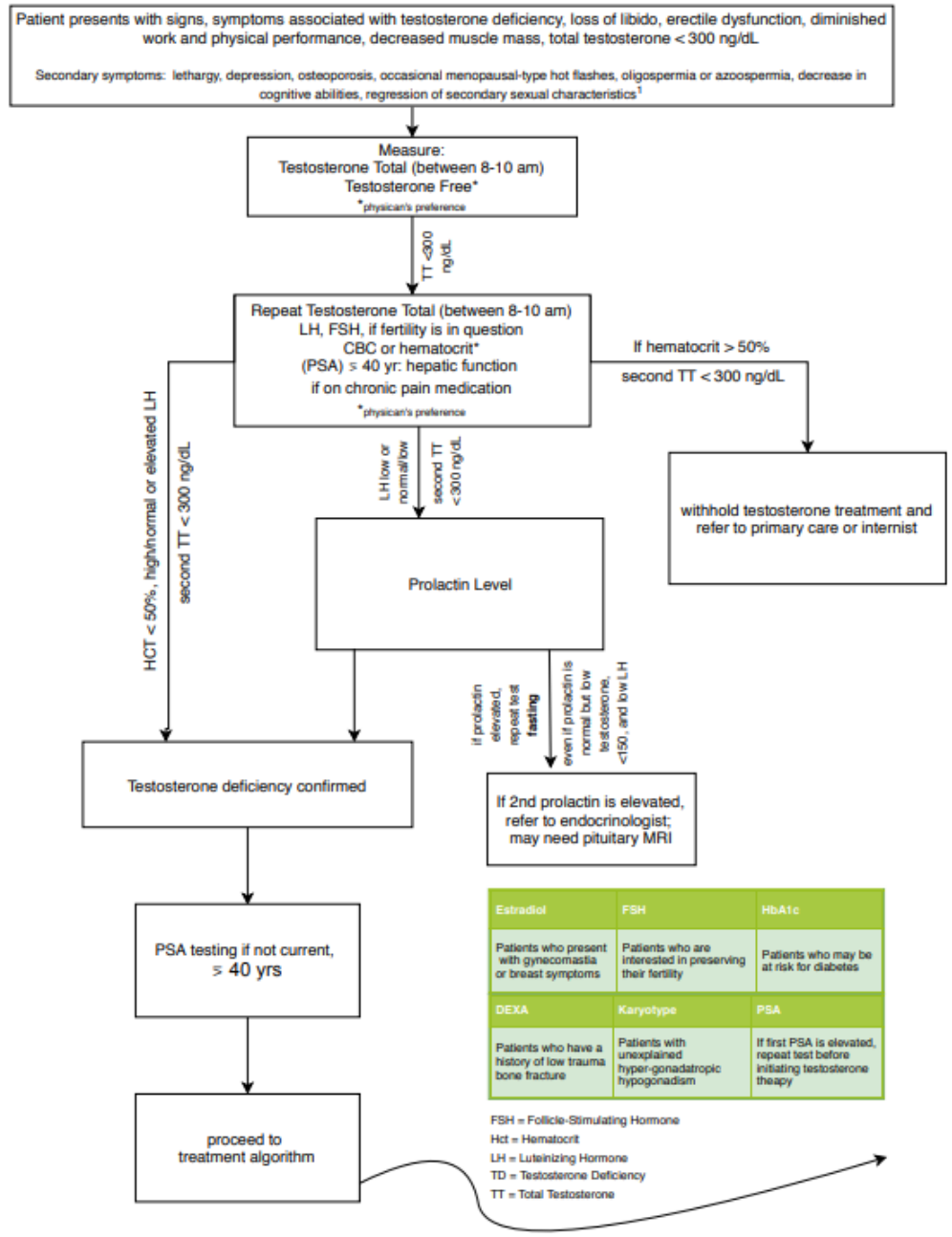
- Adjunctive Testing
  - LH
  - Prolactin
  - Hemoglobin/Hematocrit
  - PSA (if over 40)
  - FSH/Estradiol*
  - SHBG/Free T*
  - MRI*
    - High prolactin
    - Neurologic, HA or visual symptoms
    - Low T<150
    - Hypogonadotropic Hypogonadism

Table 2. Conditions in Which Measurement of FT Concentration Is Recommended

1. Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene
2. Conditions associated with increased SHBG concentrations
Aging
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of estrogens
Polymorphisms in the SHBG gene
3. Total testosterone concentrations in the borderline zone around the lower limit of the normal range (*e.g.*, 200-400 ng/dL)

Adapted with permission from Bhasin *et al.* (8).

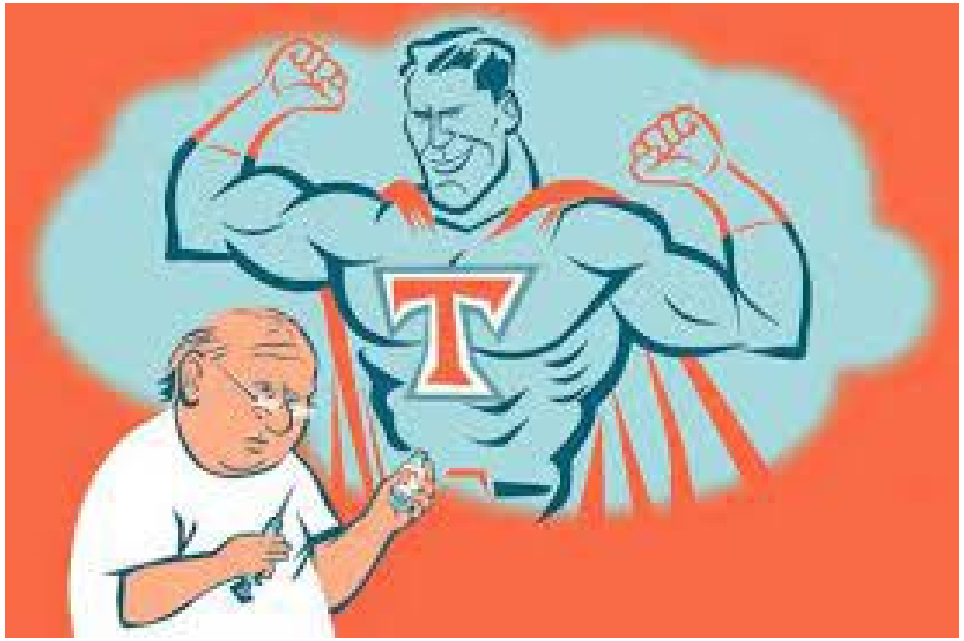
Evaluation and Management of Testosterone Deficiency: Diagnostic Algorithm



References:
[1]Braunstein JD. Testes. In: Greenspan FS, Strewler GJ, eds. Basic & Clinical Endocrinology
[2]"Evaluation and Management of Testosterone Deficiency: AUA Guideline" The Journal of Urology, Vol. 200, 423-432, August 2018.

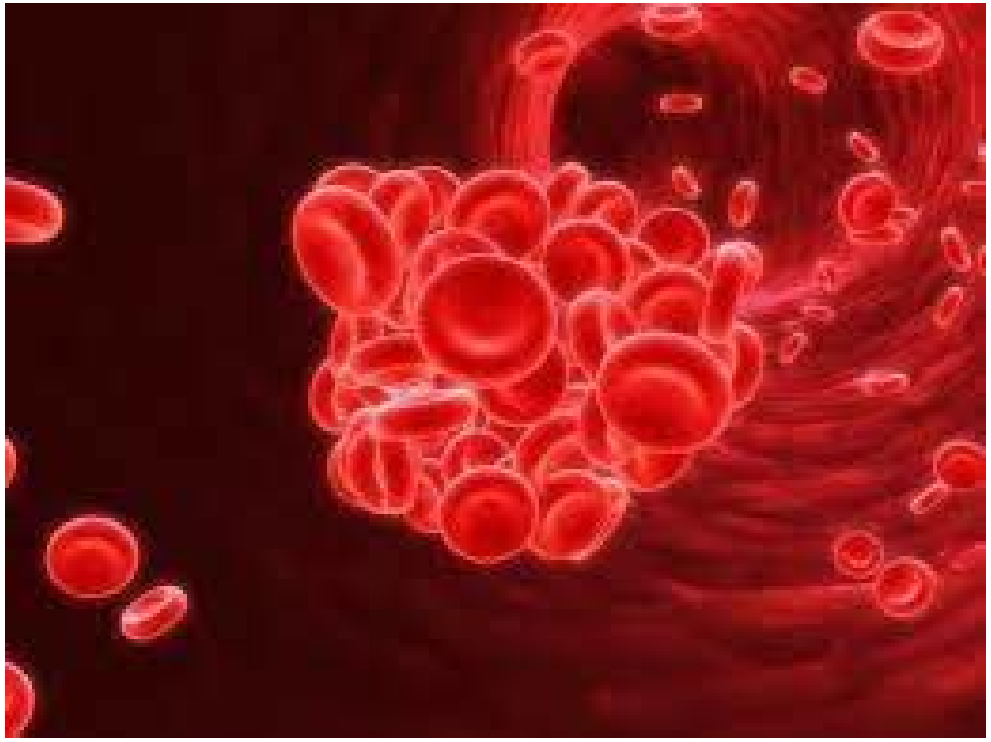
Counseling Regarding Testosterone Deficiency Treatment

- Should Improve
  - ED
  - Low sex drive
  - Anemia
  - Bone mineral density
  - Lean body mass*
  - Depressive symptoms*
- Inconclusive evidence
  - Cognitive function
  - Diabetic improvement
  - Energy
  - Fatigue
  - Lipid profiles
  - Quality of life measures



Venous Thromboembolic Events

- AUA/Endocrine recommend evaluation if hematocrit is 48-50 before initiating TRT
- FDA placed warning in 2014 based on anecdotal evidence but since that time multiple observational studies haven't shown a link
- In one study venous thromboembolism was reported in 42 cases and 40 of these had diagnosis of an underlying thrombophilia (including factor V Leiden deficiency, prothrombin mutations and homocysteinuria).



Malkin, C.J., et al. Low serum testosterone and increased mortality in men with coronary heart disease. Heart, 2010. 96: 1821. EUA

MACE Events

- 2010-2014 4 studies of concern led to 2015 warning of “unknown cardiovascular safety”
- Current evidence shows that low testosterone could be a risk factor for MACE events
- TRT shouldn’t commence until 3-6 months after a MACE event
- CHF Class IV at rest or uncompensated CHF shouldn’t have TRT
- TRAVERSE Trial
  - 6,000 men enrolled, expected completion 06/2022
  - Primary outcome-time to MACE
  - Secondary outcomes
    - MACE/cardiac procedures/CABG
    - High grade prostate cancer

- Prior to the 2015 FDA testosterone label change, Morgentaler et al published a systematic review of all articles from 1940 to 2014 relating to T and cardiovascular disease. They identified over 200 articles, with only 4 articles (as previously described) suggesting increased cardiovascular risk with T. Benefit of testosterone with reduced CV risk in many of these
- 2014 Corona et al meta analysis 75 studies over 3000 treated no MACE, + effects of T
- 2018 Miner eta al systemic review of 23 studies to evaluate for an increase in MACE. They found no relationship In fact men who normalized T had lower risk of MI and death.

Key Studies Showing Increased CV Risk with Testosterone Replacement

Study	Key Features of Study
Basaria et al	•Randomized placebo controlled trial of frail elderly men •Testosterone treatment for 6 months •Some patients were given off-label high dose of 15 grams of testosterone •CV disease was not an end point •Treatment arm patients had greater CV risk factors •5 vs 2 major CVEs (ie MI) •No difference in CVEs if excluding CHF patients
Vigen et al	•Retrospective analysis of 8709 men who had undergone coronary angiography within VA Health Care System •No randomization or placebo •2 major corrections • "Absolute risk"of MI (19.9% vs 25.7%) vs (21% vs 10%) • Exclusion of 1132 men •Retraction requested by 29 international societies

Key Studies Showing Increased CV Risk with Testosterone Replacement

Xu et al	•Meta-analysis of CVEs in 27 placebo controlled studies of >12 weeks •Just 2 studies provided 1/3 of all CVEs in T treatment arm •If excluding 2 studies, CVEs in T and placebo arms are identical
Finkle et al	•Retrospective study of a health insurance database •Reported rates of non-fatal myocardial infarction in the period up to 90 days following a testosterone prescription and compared these to MI rates in the prior 12 months •Pre-prescription MI rate 3.48/1000 and post-prescription MI rate 4.75/1000 •No information on concomitant co-morbid conditions •No information on compliance with T medication •No data on serum testosterone values

Prostate Events and Testosterone Replacement

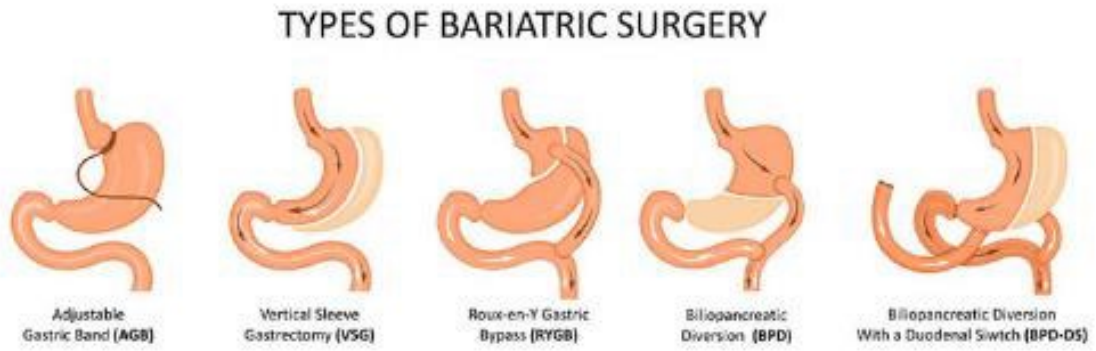
- Meta analysis PSA 0.3-0.43 increase
- Other meta analyses of randomized controlled trials
  - Boyle etal
    - No increased risk of PSA>4
    - Change in PSA
    - No increased risk of biopsy
    - No increased risk of prostate cancer
- Prostate cancer
  - TRT after definitive treatment
    - Multiple retrospective trials showed no increased risk of recurrence after definitive treatment
    - Shared decision model
  - Untreated prostate cancer
    - Shared decision making on active surveillance
    - Locally advanced or metastatic recommend against

Endocrine Society Guidelines Key Points

- We recommend confirming the diagnosis by repeating the measurement of morning fasting total T concentrations. In men whose total T is near the lower limit of normal or who have a condition that alters sex hormone–binding globulin, we recommend obtaining a free T concentration using either equilibrium dialysis or estimating it using an accurate formula.
- Albumin, total testosterone and sex hormone binding globulin and calculating free testosterone.
- We recommend against starting T therapy in patients who are planning fertility in the near term or have any of the following conditions:
  - breast or prostate cancer
  - a palpable prostate nodule or induration
  - prostate-specific antigen level of 4 ng/mL
  - prostate-specific antigen 3 ng/mL in men at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer) without further urological evaluation
  - elevated hematocrit
  - untreated severe obstructive sleep apnea
  - severe lower urinary tract symptoms
  - uncontrolled heart failure
  - myocardial infarction or stroke within the last 6 months
  - thrombophilia
- If PSA increases by 1.4 over 1st year need GU evaluation.

Lifestyle Modifications

- Weight loss and diet
- Increase after a low- calorie diet and physical activity is small (1-2 nmol)→29-58 [102,103].
- It should also be recognized that 60-86% of weight lost is regained after 3 years and 75-121% after 5 years [104].
- Bariatric surgery results in an average increase of about 10 nmol/L→289 depending on the degree of weight loss [103].

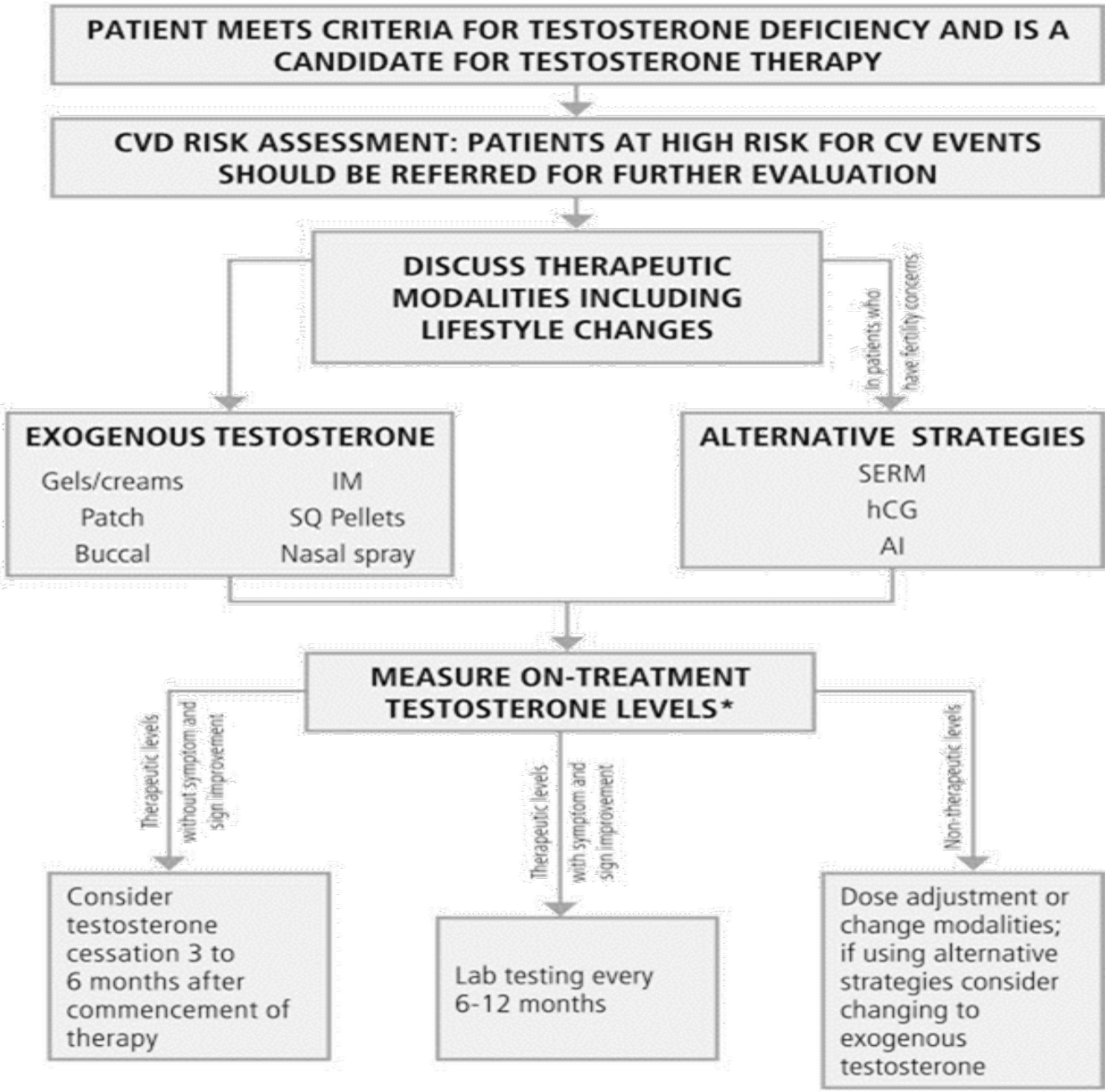


102. Haring, R., et al. Association of low testosterone levels with all-cause mortality by different cut-offs from recent studies. Eur Heart J, 2010. 31.
103. Morgentaler, A. Testosterone, cardiovascular risk, and hormonophobia. J Sex Med, 2014. 11: 1362.
104. Santos M. R, et al. Testosterone deficiency increases hospital readmission and mortality rates in male patients with heart failure. Arq Bras Cardiol, 2015. 105:256.

Lifestyle Modifications

- Lifestyle changes represent an essential part of the management of obesity;
- However, some evidence suggests that when compared to lifestyle modifications alone, testosterone therapy-treated obese men benefit most from relief of their symptoms associated with testosterone deficiency, whereas those not treated did not benefit [79].

EVALUATION AND MANAGEMENT OF TESTOSTERONE DEFICIENCY: TREATMENT ALGORITHM



*Testosterone levels should be driven to the normal physiological range of 450-600 ng/dL (approximately equivalent to the middle tertile of the normal range).

AI = Aromatase Inhibitor
CVD = Cardiovascular Disease
hCG = Human Chorionic Gonadotropin.
IM = Intramuscular Testosterone Injection
SERM = Selective Estrogen Receptor Modulator
SQ = Subcutaneous

Notes:

Treatment

Testosterone Level <300 all men or <350 for symptomatic men below age 65
Testosterone treatment may be initiated with the patient having input/choice of the following (based on insurance coverage or lifestyle/convenience): ▪ **Gels** – Androgel, Testim, Axiron, Fortesta ▪ **Compounded Creams** ▪ **Injections** – Testosterone Cypionate 200 mg/milliliters every 1-2 weeks, Aveed* ▪ **Sub-Q** - Xyosted ▪ **Patch** – Androderm ▪ **Pellet** – Testopel (procedure completed by urologist) ▪ **Oral**** – Clomid (primary choice if LH is normal/low and if fertility is current or future concern; starting dose 50 mg ½ tablet qod to help prevent tachyphylaxis; Titrate dose based on follow-up labs) ▪ **Arimidex** (1 mg po q M/W/F if Estradiol level is significantly elevated) *5 injections/year, additional lab tests, insurance PA, written consent, provider education enrollment required; protocol maintained in nurse manager's office; patient observation for 30 minutes post injection **based on if have low T yet seeking pregnancy with spouse; requires additional labs including FSH, LH
Testosterone Level >350
Offer to repeat lab in 3 months unless very symptomatic; mid-level provider to consult with urologist to consider course of treatment

Continued Care

- Follow-up Testosterone Care Plan
  - 1st Follow up visit: 4-6 weeks
  - Continued follow up visits: 6-month schedule
- Follow-up Visits With Primary Urologist
  - Testosterone clinic will treat testosterone and may refill ED medications; however, annual urology visits will be continued with primary urologist

UCA Men's Health Center: ED Clinic

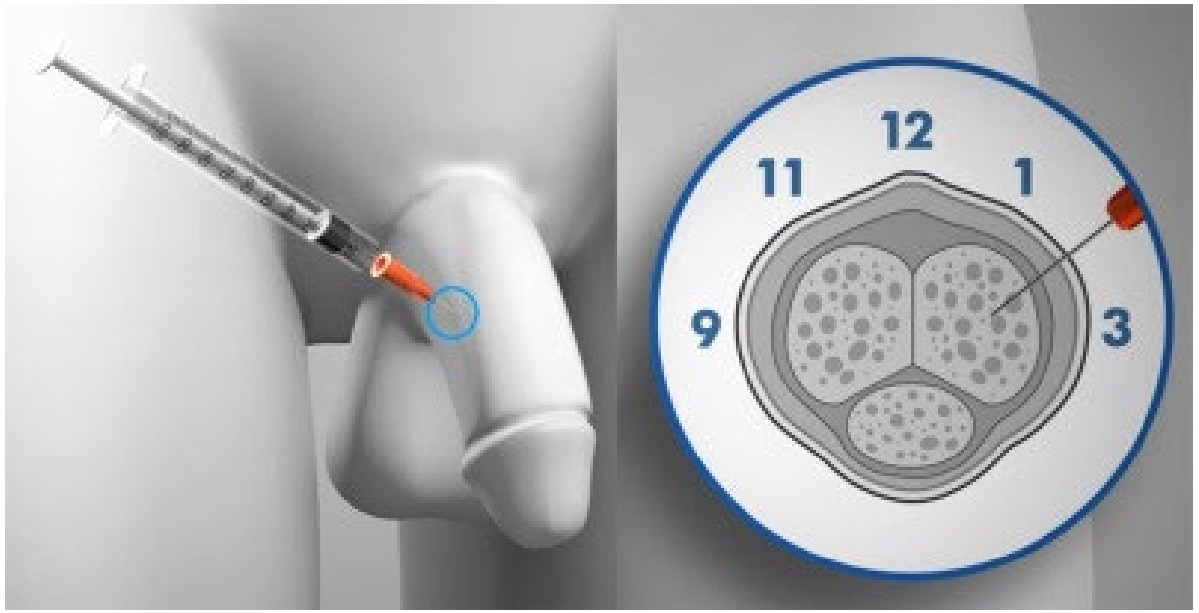
- 3 Main Options
  - ED consult
  - VED teaching and purchase
  - Penile injection teaching

Vacuum Assist Device

- French Physician Vincent Marie Mondat in the early 1800s developed the vacuum assist device for ED.
- The pump works by applying negative pressure to the penis to increase corporal blood flow and result in an erection (Jonas, 2001).

Erectile Dysfunction: A Review of Historical Treatments With a Focus on the Development of the Inflatable Penile Prosthesis
Kristen Gurtner, BS,[1] Amanda Saltzman, MD,[2] Kristi Hebert, MD,[2] and Eric Laborde, MD[2]Am J Mens Health. 2017 May; 11(3): 479–486.

Intracavernosal Injections



- 1977-incidentally injected Papaverine in patient with known ED and induced an erection
- 1983 AUA Las Vegas meeting
  - Dr. Brindley
  - Phenoxybenzamine
- Trimix
  - Phenoxybenazmine
  - Papaverine
  - Alprostadil

Reproductive Medicine Jack Grinnan, ... Stanton C. Honig, in Encyclopedia of Reproduction (Second Edition), 2018

Thank You

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UCA | Women's Center

UCA | Van Scott Cancer Center

UCA | Men's Health Center