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Testosterone Therapy and Cardiovascular Disease

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to explain how the literature suggests testosterone therapy could alter cardiovascular risk, describe the effects of testosterone on cardiovascular risk factors and state different medical societies' positions on testosterone therapy and potential cardiovascular risk.

This AUA Update aligns with the American Board of Urology Module on Impotence, Infertility, Infection and Andrology. Additional information on this topic can be found in the AUA Core Curriculum section on Sexual Medicine.

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Since the discovery of testosterone in the 1930s, the beneficial effects of testosterone therapy have been well established. Beneficial effects of T that have been reported include improvements in sexual function, libido, bone mineral density, muscle mass and fat deposition.[1] However, over the past decade, there has been increasing concern with testosterone therapy and the potential increased risk of cardiovascular events. Prior to 2010, numerous studies failed to find any increased cardiovascular risk with the use of testosterone therapy. In fact, during this time numerous studies found that *low* levels of T increased the risk of CVEs, and in some studies testosterone therapy actually was beneficial in reducing CVEs.[2] **However, from 2010 to 2014 there were 4 studies that raised concern with testosterone therapy and cardiovascular safety.** In light of these studies, the U.S. Food and Drug Administration (FDA) in 2015 mandated a label warning change about the unknown cardiovascular safety with testosterone therapy. Since 2015, numerous studies and society guidelines have been published to better understand the association between testosterone therapy and cardiovascular risk, and to further guide management of hypogonadal patients. There are several potential mechanisms by which testosterone can influence the cardiovascular system.

EFFECT OF TESTOSTERONE ON CARDIOVASCULAR RISK FACTORS

Lipids. **The reported effects of testosterone therapy on lipid parameters are inconsistent.** Mechanistic studies suggest the potential for testosterone to reduce low-density lipoprotein cholesterol levels, but clinical studies in aggregate imply a neutral effect. **A more frequent observation is the reduction of high-density lipoprotein cholesterol with testosterone therapy.[3]** Biologically, testosterone can increase hepatic lipase activity, which is known to facilitate breakdown of HDL particles.[4] However, there is growing controversy about whether low HDL-C concentrations alone result in increased cardiovascular risk. Recent studies have focused on other HDL properties, which include efflux capacity, or the ability of HDL particles to shuttle cholesterol out of the vascular tissues. HDL efflux capacity is not affected by testosterone.[5] **As described below, testosterone therapy can improve insulin resistance, which corresponds to lowering of triglyerides and increasing HDL-C**. In a meta-analysis of randomized trials of testosterone therapy in patients with diabetes, testosterone therapy resulted in lower triglyceride and total cholesterol levels, with no effect on LDL-C and a heterogeneous effect on HDL-C.[5] Given the overall inconsistent and modest relationship between testosterone therapy and lipids, it is unlikely that lipid changes play a significant role in the relationship between testosterone therapy and cardiovascular disease.

Diabetes and metabolic syndrome. Several observational studies demonstrate an association between lower testosterone levels and the risk of diabetes, and individuals with diabetes have lower testosterone levels than non-diabetic individuals.[6] **Furthermore, some randomized trials have shown improvements in insulin resistance with testosterone therapy in hypogonadal individuals with diabetes and metabolic syndrome.[7]** Testosterone therapy in such individuals can improve body composition by reducing visceral and subcutaneous fat mass and increasing lean muscle mass.[8] Visceral adipose tissue is thought to increase hepatic gluconeogenesis by increasing triglyceride delivery to the liver via portal vein,[9] while lean skeletal muscle is the predominant site of ingested glucose utilization. Testosterone therapy may also improve skeletal muscle insulin sensitivity by activating glucose metabolism-related signaling pathways, and upregulates insulin signaling genes in adipose tissue.[10] While diabetes and metabolic syndrome are strongly associated with the development of cardiovascular disease, testosterone therapy has not uniformly improved glycemic parameters across all studies. Furthermore, any beneficial effects of testosterone therapy on glucose parameters do not necessarily translate into reductions in cardiovascular disease. For example, statin drugs increase blood glucose and the risk of diabetes but consistently and significantly lower the risk of cardiovascular disease, even in those with diabetes.[11]

Blood pressure. Overall, the data suggest a limited impact of testosterone therapy on blood pressure. An older meta-analysis of randomized trials reported no effects of testosterone therapy on systolic or diastolic blood pressure.[12] However, animal studies report activation of the renin-angiotensin system and salt and water retention with testosterone,[13,14] which can potentially raise blood pressure. However, testosterone therapy can also have a vasodilatory effect, lowering systemic vascular resistance, which may have an offsetting effect on blood pressure.[15] While for most individuals testosterone therapy is unlikely to have a meaningful impact on blood pressure, there may be individualized responses depending on age and co-morbidity status.[13]

Blood hematocrit and viscosity. A known side effect of testosterone therapy is elevation in hematocrit.[16] Mechanistically, this increased erythropoiesis may partially relate to increases in erythropoietin but also to direct stimulatory effects on bone marrow hematopoietic cells.[17] These increases correlate with circulating testosterone concentrations, and there may be some differences in mode of testosterone therapy delivery and short-term elevations in hematocrit, possibly due to a rapid rise in testosterone levels.[18] Higher hematocrit levels can increase blood viscosity, potentially impairing blood flow and promoting thrombosis.[19] Although very high hematocrit levels (>60%) can result in hyperviscocity symptoms such as headache, weakness and paresthesias, and rarely cardiovascular or neuro-occlusive events, the occurrence of severe vascular events directly related to higher hematocrit with testosterone therapy is quite rare. **Currently, the AUA recommends against starting testosterone therapy in men with hematocrit levels >50% until after an evaluation is completed,[1] while the Endocrine Society uses a lower cutoff of >48% to withhold testosterone therapy.[20]**

HEART FAILURE

Patients with congestive heart failure, specifically with reduced ejection fraction, have altered hemodynamics consisting of

ABBREVIATIONS: AUA=American Urological Association, C=cholesterol, CHF=congestive heart failure, CV=cardiovascular, CVE=cardiovascular event, FDA=U.S. Food and Drug Administration, HDL=high-density lipoprotein, LDL=low-density lipoprotein, MACE=major adverse cardiovascular event, MI=myocardial infarction, T=testosterone

elevated filling pressures, lower cardiac output and frequently increased systemic vascular resistance. Furthermore, they have impaired quality of life due to reduced exercise capacity and symptoms of fatigue and dyspnea. Observational studies demonstrate an association between lower testosterone levels and increased mortality in patients with CHF.[21]

There are several potential mechanisms by which testosterone therapy can favorably impact those with CHF. In one carefully conducted small randomized trial of patients with stable chronic heart failure with invasive hemodynamic measurement, oral testosterone acutely lowered systemic vascular resistance and increased cardiac output, effects that were maximal at highest serum testosterone concentrations.[15] Although there do not seem to be improvements in ejection fraction with testosterone therapy, it can improve peripheral muscle function and alter muscle fiber type, which can enhance oxygen utilization and exercise capacity.[22] Increases in hematocrit, particularly in those with anemia, which is more common with heart failure, can also augment exercise capacity.

In one meta-analysis of 4 randomized controlled trials involving 198 patients with heart failure and at least moderately reduced ejection fraction, testosterone therapy resulted in a favorable increase in 6-minute walk distance of 54 meters compared with placebo, as well as significant improvement in peak oxygen consumption.[23] Thus, beneficial effects correlated with increase in free or bioavailable testosterone. Importantly, the New York Heart Association Functional Classification (graded 1 to 4, where I=no limitation and IV=symptoms at rest) improved by ≥1 grade in 35% of those in the testosterone groups vs 9.8% in the placebo groups. There were no changes in left ventricular ejection fraction with testosterone therapy and there was no difference in adverse cardiovascular events. Importantly, the patients in these studies had stable heart failure and were excluded if they had recent heart failure admissions.

Despite the acute favorable hemodynamic effects of testosterone therapy and improvements in exercise capacity in those with CHF, there are some potential cautionary concerns as well. As noted above, testosterone can cause salt and water retention, potentially exacerbating volume overload in those with tenuous volume status. Furthermore, a mainstay of CHF treatment is neurohormonal blockade with renin-angiotensin-aldosterone system blocking agents, including angiotensin-converting enzyme inhibitors, which reduce mortality and improve left ventricular remodeling in patients with CHF.[24] Given the potential activation of the renin-angiotensin pathway by testosterone, the long-term consequences of testosterone therapy in patients with CHF are unknown. **Although the approach to patients with CHF was not specifically delineated in the AUA guideline on testosterone deficiency, other societies have cautioned against testosterone therapy in those with New York Heart Association Functional Classification IV symptoms (CHF symptoms at rest) or with severe or uncontrolled heart failure.**[20, 25, 26]

SUBCLINICAL ATHEROSCLEROSIS

Animal models and *in vitro* studies suggest that testosterone may have a beneficial effect by limiting the development of atherosclerosis. Testosterone administration blunted atherosclerosis development in castrated male rabbits and also reduced neointimal plaque development in an endothelial cell injury model.[27,28] Some of this beneficial effect may be via estradiol after conversion of testosterone to estradiol by aromatase.[29] In humans, experimental effects on atherosclerosis can be assessed using serial imaging modalities.

Two large randomized clinical trials have been performed to evaluate the effects of testosterone therapy on subclinical atherosclerosis.[30, 31] In the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial, 308 men ≥60 years old with low/low-normal testosterone levels (100–400 ng/dl; free testosterone <50 pg/ml) were randomized to treatment with 1% testosterone gel or matching placebo gel daily for 3 years. The co-primary outcomes were change in mean common carotid artery intima-media thickness and coronary artery calcium score. Carotid intima-media thickness is an established marker of cardiovascular risk that correlates with risk factor burden and risk of cardiovascular disease events.[32] Similarly, coronary artery calcium measurement is a well-established clinically used tool that harnesses the close correlation between calcium and atherosclerotic plaque in the coronary arteries to estimate the total burden of coronary atherosclerosis and thus cardiovascular disease risk. In this study, despite increases in total testosterone to 565 ng/dl in the treatment arm vs 330 ng/dl in the placebo arm, there was no difference in the change in coronary artery calcium or carotid intima-media thickness score between the groups.

While these findings may be interpreted as lack of effect of testosterone therapy on atherosclerosis, both carotid intima-media thickness and coronary artery calcium change have been found to be poor surrogate end points in cardiovascular trials. For example, statins consistently lower cardiovascular disease events in clinical trials, but the change in coronary artery calcium with statins and placebo is similar in randomized studies.[33] The cardiovascular study of the Testosterone Trials (TTrials) employed coronary computerized tomography angiography measures in their end point, which can quantify and characterize atherosclerotic plaque subcomponents, including non-calcified atherosclerotic plaque. Here, 138 older men (mean age 71 years) at higher cardiovascular disease risk with low serum testosterone (<275 mg/dl) were randomized to testosterone gel or placebo for 12 months. **Paired coronary computerized tomograms showed an increase in non-calcified coronary plaque volume, the primary end point, by 40 mm^3 in the testosterone therapy arm vs 4 mm^3 in the placebo arm (p=0.003).** There was also a greater increase in total coronary plaque volume in the testosterone therapy arm, but no difference between arms in change in coronary artery calcium score. Despite these intriguing findings, studies of subclinical atherosclerosis cannot take the place of large clinical end point trials in determining risks or benefits of testosterone therapy on cardiovascular disease.

STUDIES RAISING FDA CONCERN WITH TESTOSTERONE THERAPY AND CARDIOVASCULAR RISK

There were 4 studies from 2010 to 2014 that raised concern with the use of testosterone therapy and increased cardiovascular risk (table 1). In 2010, Basaria et al conducted a randomized placebo controlled trial to investigate testosterone therapy use and greater functional and muscular benefits compared to placebo in an elderly (average age 74 years) frail population of men treated for 6 months.[34] The study was terminated early due to an increased number of CVEs in the testosterone

therapy arm compared to placebo (23 vs 5). However, the study did demonstrate that testosterone therapy improved functional and muscular responses compared to placebo. There were several limitations with this study. The study was not designed to assess CVEs. CVEs were not a primary or secondary end point. As a result, the 2 groups receiving T and placebo were not balanced for CV risk factors at baseline. In addition, there were a small number of major adverse cardiovascular events, none of which was confirmed or adjudicated. There were 4 MACEs in the T arm and none in the placebo arm. The authors themselves concluded that "the lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the 2 trial groups may have been due to chance alone."

In 2013, Vigen et al conducted a retrospective analysis of a database of 8709 men who had undergone coronary angiography within the VA Health Care System.[35] This study found that the overall rate of stroke, myocardial infarction and death in hypogonadal men was higher in men who received a T prescription compared with untreated men. However, there was no statistically significant difference in CVEs between the testosterone therapy and untreated groups at year 1, 2 or 3. There were several methodological concerns with the manuscript, which resulted in numerous medical societies requesting retraction of the paper. Furthermore, there was no way to determine compliance with testosterone therapy in the T group, and only 60% of men had a T level checked after starting therapy. The average T level after initiating testosterone therapy was 332.2 ng/dl, suggesting that many of the men were still hypogonadal in the T group. In the same year, Xu et al published a meta-analysis of 27 placebo controlled studies assessing the effects of testosterone replacement therapy on CVEs.[36] The studies had to be 12 weeks' duration or longer and had to report "cardiovascular-related events." These authors discovered that CVEs were greater in men who received T compared with placebo. This is the only one of several prior meta-analyses and systematic reviews to report increased CV risk with testosterone therapy.[37–39] The studies in this meta-analysis were inconsistent in numerous aspects of clinical trial design, including age, baseline T levels, inclusion and exclusion criteria, baseline health status, drug formulation, route of administration, dose and duration, as well as the type of CVE reported and confirmed. In addition, just 2 of the 27 studies contributed 35% of all CVEs in the T group. One was the study by Basaria et al,[34] already described, and the other was the 1986 Copenhagen study,[40] in which 600 mg oral daily T was given to men with cirrhosis of the liver. In one-quarter of the T group, men had serum T concentrations above 4000 ng/dl, reaching as high as 21,000 ng/dl. The authors reported 21 events as cardiovascular, yet there was only one MI.

In 2014, Finkle et al conducted a retrospective study of a health insurance database that reported rates of non-fatal MI in the period up to 90 days following a T prescription, and compared these to MI rates in the prior 12 months.[41] These authors found that the ratio of MI post-prescription to pre-prescription was 1.36 when 4 subgroups of patients were combined (age $<$ or $\geq$65 years, with and without heart disease history). The ratio was 2.19 in men 65 years or older. The concerns with this study were that there was no control group, no information on concomitant co-morbid conditions and no information on compliance with T medication, and there were no data on serum testosterone values. These limitations make it is difficult to draw conclusions on CV risk with the use of testosterone therapy.

In summary, there were several significant concerns with these 4 aforementioned studies that suggested that testosterone therapy increased the risk of cardiovascular events. The studies by Vigen[35] and Finkle[41] et al had no randomization and no placebo group. In addition, there was no control group in the analysis by Finkle et al. In both of these studies, there was no information on compliance of the testosterone utilization, and there were limited or no data on serum testosterone values. These concerns, among others regarding statistical methodology and inappropriate exclusion/inclusion of patients, led to a request for retraction of the Vigen article by 29 international societies. In the meta-analysis by Xu et al, studies were inconsistent in age, baseline T levels, inclusion and exclusion criteria, baseline health status, drug formulation, route of administration, dose and duration, as well as the type of CVEs reported and confirmed.[36] This meta-analysis was the only one of several prior meta-analyses and systematic reviews to report increased cardiovascular risk with testosterone therapy. Finally, in the study by Basaria et al, cardiovascular disease was not a primary end point.[34] The treatment arm had patients with greater cardiovascular risk factors, and when patients with CHF were excluded, there were no differences in cardiovascular events. The patients were frail elderly men who in some cases were being treated with off-label high doses of testosterone. The authors themselves concluded that "the lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the 2 trial groups may have been due to chance alone."

FDA LABELING CHANGES ON CARDIOVASCULAR RISK AND INDICATIONS FOR T USE

From 2010 to 2014, 4 studies as previously described raised questions about whether testosterone therapy gave rise to increased cardiovascular risk. In 2014, the FDA conducted an independent review of these studies and rejected requests that cardiovascular risk be included as a "black box" warning in the labels of T products. In September 2014, the FDA convened an Advisory Committee to evaluate the benefits and CVE risks and indications for T treatment**. In March 2015, the FDA issued a statement which said it was "requiring [testosterone therapy] manufacturers to add information to the label about the *possible* increased risk of heart attacks and strokes in patients taking testosterone."**[42,43] The testosterone label in the "Warnings and Precautions" section now was required to state that "Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining risk of major adverse cardiovascular events, such as non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with the use testosterone compared to non-use. Some studies, but not all, have reported an increased risk of MACE in association with the use of testosterone replacement therapy in men." Interestingly, the European Medicines Agency, which in Europe is equivalent to the FDA, did not mandate a T label change regarding cardiovascular risk with testosterone therapy after its review of the literature.

During the 2014 FDA Advisory Committee meeting, concerns were also raised that 28% of men had no T levels obtained prior to T prescription and 21% had no T levels monitored after testosterone therapy was initiated. The committee theorized that the rapid growth of the T market at that time was partly due to treatment of age-related hypogonadism, asymptomatic men with low serum testosterone and symptomatic men with normal or unknown serum T levels. In March 2015 the FDA issued a safety announcement stating, "The U.S. Food and Drug Administration cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications." That year, the word "idiopathic" was removed as a possible etiology for hypogonadism, suggesting that hypogonadal men had to have a known associated medical condition to be considered "on-label" for testosterone therapy usage.

Following the FDA 2015 label change, the FDA required companies that manufactured T products to conduct a large, randomized, placebo controlled trial to evaluate the effects of testosterone therapy on cardiovascular outcomes. **This trial, the TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men) study, began enrollment in May 2018 and the primary outcome of the trial is time to MACE.** Secondary outcomes include incidence of MACE or cardiac revascularization procedures/cardiac percutaneous coronary intervention and coronary artery bypass graft. Secondary outcomes also include prostate safety, assessing the incidence of high grade prostate cancer. The study is expected to be completed in June 2022 with approximately 6000 participants.

LOW SERUM T LEVELS ASSOCIATED WITH INCREASED CARDIOVASCULAR RISK

The 2018 AUA testosterone guideline states that "Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease."[1] This was a strong recommendation with a grade B level of evidence. This statement was based on the body of literature suggesting that hypogonadal men are more likely to have a CVE.

In 2018, a meta-analysis of observational studies assessing endogenous T levels and cardiovascular risk found that low T was a marker for cardiovascular risk.[44] This study had a total of 10,479 subjects with a mean age of 63.5 years and a mean follow-up time of over 6 years. The investigators found that lower T levels were predictive of a higher risk of CVEs, cardiovascular mortality and all-cause mortality. Another study in 2019 followed 18,238 Danish men for 5 years and found that lower T levels were associated with higher 1-year and 5-year risks of MI, stroke, venous thromboembolism and all-cause mortality.[45] Even after adjusting for co-morbidity and age, the association between low T and all-cause mortality remained significant.

While low T may be associated with increased cardiovascular risk, its causality has not been well established. Many of the risk factors associated with hypogonadism are the same risk factors associated with cardiovascular disease. For example, both conditions are much more prevalent in patients with obesity, diabetes and metabolic syndrome. **In fact, Maseroli et al found that roughly 63% of men with secondary hypogonadism had obesity, diabetes or metabolic syndrome**.[46] Thus, the increased cardiovascular risk in hypogonadal men may be indirectly associated with the higher prevalence of similar co-morbid conditions in both hypogonadism and cardiovascular disease.

STUDIES DEMONSTRATING TESTOSTERONE THERAPY WITH NO INCREASED CARDIOVASCULAR RISK

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.[2] They identified over 200 articles, with only 4 articles (as previously described) suggesting increased cardiovascular risk with T. They found several dozen studies demonstrating beneficial effects of normal T on cardiovascular risk and mortality. They also found that low levels of T were associated with increased risk of mortality and cardiovascular disease. Finally, these authors noted that the severity of coronary artery disease was inversely correlated with serum T levels.

In 2014, Corona et al published a meta-analysis of 75 studies.[47] This meta-analysis included 3016 men treated with T and 2446 treated with placebo for a mean treatment duration of 34 weeks. These investigators found no significant association between testosterone therapy and CVEs, either as single events or as combined cardiovascular end points. In fact, they found a protective effect of testosterone therapy in men with metabolic disorders.[46]

In 2018, Miner et al performed a systematic review of 23 studies (12 clinical trials and 11 observational studies) published after the FDA 2015 labeling change which assessed testosterone therapy and cardiovascular risk.[48] No study reported an increased MACE with testosterone therapy. In fact, men whose T normalized with testosterone therapy had a reduced risk of MI and death compared with men whose T levels failed to normalize.

TESTOSTERONE GUIDELINES AND CARDIOVASCULAR RISK

Since the 2015 FDA label change relating to cardiovascular risk, there have been numerous guidelines published from different societies addressing testosterone therapy and cardiovascular risk (table 2). **The majority of guidelines state that there is inconclusive evidence to support the link between CVEs and testosterone therapy.** Some societies recommend waiting 3 and up to 6 months before reinitiating testosterone therapy after a CVE. Several societies have recommended assessing cardiovascular risk before testosterone therapy is initiated. Finally, the European Association of Urology Testosterone Guidelines state that in hypogonadal men testosterone treatment has been demonstrated to have a positive impact on cardiovascular risks.

CLINICAL RECOMMENDATIONS FOR USE OF TESTOSTERONE IN PATIENTS WITH CARDIOVASCULAR DISEASE

As described in table 2, several societies have provided recommendations for the use of testosterone therapy in patients with

cardiovascular disease. Notably, there are currently no official recommendations from the American Heart Association or the American College of Cardiology. However, a prudent approach considering both potential benefits and potential harms is advisable while awaiting results from ongoing randomized trials.

Prior to starting testosterone therapy, patients with cardiovascular disease should be assessed for any active cardiac conditions, including recent MI or stroke (past 6 months) or CHF with higher risk features (see figure). These include patients with CHF who are currently volume overloaded, have tenuous volume status (ie recent CHF admission or more than 1 admission in the prior year) or have CHF symptoms at rest. If such conditions are encountered, testosterone therapy should not be initiated, in line with most other society recommendations. **However, in the absence of these higher risk conditions, patients should be engaged in a process of shared decision making, as is advocated for other therapies with potential cardiovascular effects.**[49] Elements of this discussion should include the degree of hypogonadal symptoms experienced by the patient and degree of expected benefit for these symptoms from testosterone therapy. In addition, current cardiovascular guidelines differentiate all patients with atherosclerotic cardiovascular disease into those at "very high risk" and those "not at very high risk." Those at very high risk include those with multiple atherosclerotic cardiovascular disease events (ie those with recurrent MI, or MI and stroke) or those with one atherosclerotic cardiovascular disease event and multiple uncontrolled risk factors, which is in contrast to a patient with coronary revascularization several years prior and no interval event.[49] If there is any adverse cardiovascular effect of testosterone therapy, these individuals at very high risk will have the greatest absolute increase in risk. Most important in this conversation is determining the goals of the patient. Some may weigh improvement in hypogonadal symptoms more heavily than concerns over uncertainty in cardiovascular events. If after a shared decision making conversation the decision is to initiate testosterone therapy, these individuals should be monitored periodically for any changes in hematocrit, cardiovascular risk factors and cardiovascular symptoms.

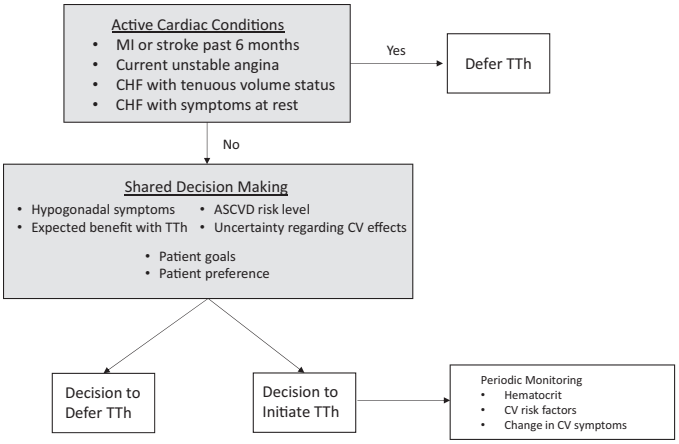

Figure. Proposed algorithm for considering testosterone therapy in patients with cardiovascular disease. ASCVD, atherosclerotic cardiovascular disease. TTh, testosterone therapy.

DID YOU KNOW?

- Based mainly on 4 studies, the FDA issued a label change in 2015 requiring testosterone manufacturers to add information to the label about the *possible* increased risk of heart attacks and strokes in patients taking testosterone.
- The majority of testosterone guidelines suggest that there is inconclusive evidence to support the link between testosterone therapy and cardiovascular events.
- Many of the risk factors associated with hypogonadism are the same risk factors associated with cardiovascular disease.

Table 1. Key features of 4 studies suggesting testosterone increases cardiovascular risk

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

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

Table 2. Six international societies and their guideline recommendations on T therapy and CV risk over prior 5 years

T Guidelines	T Therapy and Cardiovascular Recommendations	Type of Analysis Utilized
AUA 2018	• Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B) • Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (eg myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B) • Testosterone therapy should not be commenced for a period of 3 to 6 months in patients with a history of cardiovascular events. (Expert Opinion)	• **Systematic review** • **Articles published between January 1, 1980 and February 6, 2017 and yielded 15,217 references, 546 studies (enrolling approximately 350,000 men)**

Endocrine Society 2018	• "We recommend against starting T therapy in patients who (have)…. heart failure, myocardial infarction or stroke within the last 6 months."
	• "…there is no conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men."
	• "Thus, there are insufficient data to establish a causal link between T therapy and cardiovascular events."
		• Two systematic reviews and used the best available evidence from other published systematic reviews and individual studies
		• First review:
		  • 11 reports of 4 trials with 1779 participants.
		  • All included trials tested transdermal therapy with a duration of therapy that ranged from 12 to 52 weeks
		• Second review:
		  • 9 studies of 3 trials with 1581 patients
		  • Studies were placebo controlled trials that used randomization or allocation by minimization with low to moderate risk of bias

European Association of Urology 2016	• There is no substantive evidence that testosterone treatment, when replaced to the normal physiological range, is related to the development of major adverse cardiovascular events. (Level of Evidence 1a) • In hypogonadal men, testosterone treatment has been demonstrated to have a positive impact on cardiovascular risks. (Level of Evidence 1b)	• Studies included from 2011 to April 2016 • Studies limited to reviews, meta-analyses or meta-analysis of randomized controlled trials • 2252 unique records were identified, of which 51 publications were selected for inclusion
British Society for Sexual Medicine 2017	• Assess CV risk before T replacement therapy is initiated and monitor CV risk factors throughout therapy. (Level of Evidence 1b: Grade A)	• Studies included from May 2005 to May 2015 • 1714 articles, including 52 clinical trials and 32 placebo controlled, randomized, controlled trials
Canadian Men's Health Foundation 2015	• Men with testosterone deficiency syndrome and stable cardiovascular disease are candidates for testosterone treatment. (Weak recommendation; low-quality evidence)	• Studies included from January 2009 to April 2014 • Reports from meta-analyses, practice guidelines, clinical conferences and major reviews were also examined, and papers were manually searched for additional references
American College of Physicians 2020	• "…inadequate evidence to make definitive conclusions about cardiovascular and other long-term harms." • "However, our findings do not suggest an increased risk for death with testosterone treatment."	• 38 randomized controlled trials of at least 6 months' duration • Studies evaluated transdermal or intramuscular testosterone therapies vs placebo or no treatment • Studies had to report pre-specified patient centered outcomes • 20 long-term observational studies were also included

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Study Questions Volume 40 Lesson 26

1. A 46-year-old man with a family history of cardiovascular disease had an MI 5 months ago. He has a serum testosterone value of 167 ng/dl, low energy and low libido, and wishes to initiate testosterone therapy. He should be counseled that
   a. low testosterone is a risk factor for cardiovascular disease
   b. testosterone therapy increases the risk of cardiovascular disease
   c. following an MI, men should wait at least 9 months before restarting testosterone therapy
   d. men with a family history of cardiovascular disease should be discouraged from initiating testosterone therapy

2. The primary end point of the TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men) trial is the
   a. time to development of prostate cancer
   b. time to major adverse cardiovascular events
   c. incidence of major adverse cardiovascular events
   d. incidence of cardiac revascularization procedures

3. The most common risk factor associated between hypogonadism and cardiovascular disease is
   a. obstructive sleep apnea
   b. smoking
   c. obesity
   d. age

4. The cardiovascular risk factor most likely to improve with testosterone therapy is
   a. abnormal lipid profile
   b. increased weight
   c. increased blood glucose
   d. increased blood pressure

5. Testosterone therapy should be avoided, pending medical evaluation, when the hematocrit is
   a. >45%
   b. >50%
   c. >55%
   d. There is no hematocrit threshold at which testosterone therapy should be withheld