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Testosterone Therapy and Cardiovascular Risk: Advances and Controversies

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Abstract

Two recent studies raised new concerns regarding cardiovascular (CV) risks with testosterone (T) therapy. This article reviews those studies as well as the extensive literature on T and CV risks. A MEDLINE search was performed for the years 1940 to August 2014 using the following key words: *testosterone*, *androgens*, *human*, *male*, *cardiovascular*, *stroke*, *cerebrovascular accident*, *myocardial infarction*, *heart attack*, *death*, and *mortality*. The weight and direction of evidence was evaluated and level of evidence (LOE) assigned. Only 4 articles were identified that suggested increased CV risks with T prescriptions: 2 retrospective analyses with serious methodological limitations, 1 placebo-controlled trial with few major adverse cardiac events, and 1 meta-analysis that included questionable studies and events. In contrast, several dozen studies have reported a beneficial effect of normal T levels on CV risks and mortality. Mortality and incident coronary artery disease are inversely associated with serum T concentrations (LOE IIa), as is severity of coronary artery disease (LOE IIa). Testosterone therapy is associated with reduced obesity, fat mass, and waist circumference (LOE Ib) and also improves glycemic control (LOE IIa). Mortality was reduced with T therapy in 2 retrospective studies. Several RCTs in men with coronary artery disease or heart failure reported improved function in men who received T compared with placebo. The largest meta-analysis to date revealed no increase in CV risks in men who received T and reduced CV risk among those with metabolic disease. In summary, there is no convincing evidence of increased CV risks with T therapy. On the contrary, there appears to be a strong beneficial relationship between normal T and CV health that has not yet been widely appreciated.

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In November 2013 and January 2014, 2 studies were published reporting increased cardiovascular (CV) risks in men who received testosterone (T) prescriptions.[1,2] These articles gained wide media attention. Media coverage of these studies was frequently combined with data indicating rapidly increased sales of T products,[3,4] raising concerns that the pharmaceutical industry was promoting a treatment associated with important risks. This view was captured best by a *New York Times* editorial entitled "Overselling Testosterone, Dangerously."[5]

The impact of these studies on patient management and the ensuing public attention has been substantial. Men discontinued treatment, occasionally criticizing their physicians for putting their health at risk; some physicians stopped prescribing T products, and others warned against treatment of T deficiency (TD) (also called *hypogonadism* or, more casually, *low T*). The Endocrine Society issued a statement cautioning against the use of T therapy in older men and in men with a history of coronary artery disease (CAD).[6] The US Food and Drug Administration (FDA) announced plans to review the CV safety of T products 2 days after publication of the second article.[7] Plaintiff attorneys began a nationwide campaign seeking cases of myocardial infarctions (MIs) and strokes in men who had used T products for a class action lawsuit. These concerns thrust T therapy into the news, where the reported CV risks anchored a variety of unrelated concerns regarding other aspects of T therapy, such as overuse and abuse, false claims by antiaging medicine, profiteering by low-T clinics, and the failure of men to accept the rigors of natural aging.

It is beyond the scope of this article to address these various issues. Instead, we wish to address the key scientific question, namely, whether T therapy is associated with increased CV risks. This review encompasses an analysis of the literature previously submitted by us to

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the FDA and to the European Medicines Agency to assist with their own investigations of this topic. This article provides in-depth analysis of studies suggesting increased CV risks with T therapy, a historical perspective, and a systematic literature review. Because of the large number of studies reviewed, much of the information is presented in tables, with text limited to summaries of data.

There are no large, long-term, placebo-controlled randomized clinical trials in the field of T therapy to provide definitive conclusions about CV risk. Nonetheless, there exists a rich literature spanning many decades that provides valuable information. As described in more detail subsequently, the 2 recent articles contradict this literature, and on careful review, neither provides credible evidence of increased CV risks. Only 2 additional studies are generally cited as support for that view. In contrast, many dozens of studies, including a modest number of randomized controlled trials (RCTs), indicate that *low* serum T concentrations are associated with increased CV risk and mortality and that T therapy may have clinically relevant CV benefits. This last point will be new to many readers. A recently published meta-analysis of 75 placebo-controlled studies, the largest to date, found no evidence of increased CV risk with T therapy and clear evidence of improved metabolic profiles.[8] Given the personal suffering of men with TD as well as the public health burden of TD, the recent controversy regarding T and CV disease presents an important opportunity to understand the science underlying this critical medical issue.

BACKGROUND

Testosterone deficiency is a clinical syndrome characterized by a set of signs and symptoms in combination with low serum T concentrations.[9,10] Symptoms include decreased libido, erectile dysfunction, difficulty achieving orgasm, reduced intensity of orgasm, fatigue, decreased energy, depressed mood, irritability, and decreased sense of well-being. Objective signs include anemia, decreased bone density, reduced muscle strength and mass, increased body fat mass (both visceral and total), and weight gain.[9,10] Androgen deprivation therapy, used in the treatment of advanced prostate cancer, causes profound TD and is associated with negative changes in body composition as well as increased risk of incident diabetes mellitus.[11] The goal of T therapy is to alleviate symptoms and signs by restoring T concentrations to optimal levels within the physiologic range.

Established benefits of T therapy in hypogonadal men include improved sexual desire and function,[12-15] improved energy, mood, and vitality,[15-19] increased lean mass,[14,19-22] decreased waist circumference,[23-27] reduced total body fat mass,[19-22] and increased bone mineral density.[28-31] Promising new data reveal that T therapy improves insulin sensitivity[32-34] and reduces blood glucose[23,25,35] and hemoglobin A_{1c} (HbA_{1c})[23,25,27,35] levels in men with type 2 diabetes or obesity.

Biochemical confirmation of TD has traditionally been made on the basis of low serum concentrations of total T (TT). Although no specific value reliably distinguishes men who will respond to treatment from those who will not, recommended thresholds for low TT range from 300 ng/dL (10.4 nmol/L)[9] to 400 ng/dL (13.9 nmol/L).[36] Because a majority of circulating T is rendered biologically unavailable due to tight binding to sex hormone—binding globulin (SHBG), the unbound fraction called *free T* and/or the portion of T weakly bound to albumin may be more indicative of a man's true androgen status.[37,38] These 2 fractions together represent bioavailable T. Men with high-normal or elevated SHBG concentrations may have TT concentrations within the normal range yet may still have TD due to reduced free T concentrations. This issue may be particularly relevant for older men because SHBG levels increase with age.[39] Levels below 65 to 100 pg/mL (<174-288 pmol/L) for calculated free T and 0.8 to 1.5 ng/dL (27-52 pmol/L) for directly measured free T have been used clinically to identify men who are candidates for treatment.[10,39,40] However, laboratory-provided reference ranges are problematic because they are not clinically based and vary widely between assays, and even among laboratories using the same assays.[41]

The prevalence of symptomatic TD ranges from 2.1% to 12.8% in middle-aged to older men, with an incidence of 12 new cases per 1000 person-years in the United States and Europe.[42] Populations at high risk for low serum T levels include men with type 2 diabetes, obesity, chronic obstructive pulmonary

disease, infection with human immunodeficiency virus, and chronic opioid use, all with prevalence rates greater than 30%.[42]

Prescription rates for T products have increased substantially over the past decade.[3,43,44] This increase has led to concerns that T products are overprescribed because of aggressive marketing. However, as recently as 2007, the FDA indicated that as few as 5% of the hypogonadal population was treated,[45] with other studies reporting similarly low treatment rates.[46] The increase in T prescriptions seems to have resulted from increased awareness of TD and the benefits of T therapy among both physicians and patients, coupled with reduced concern regarding prostate cancer risk.[47] Although it has been asserted that direct-to-consumer marketing is responsible for this growth, the evidence would suggest otherwise, as 2010 industry data failed to include any T products within the 25 most-marketed drugs in the United States.[48]

Whereas it was once believed that TD only occurred in association with several rare disorders, such as pituitary tumors, Klinefelter syndrome, or mumps orchitis, it is now understood that TD is common and often idiopathic. Symptoms and signs result directly from reduced serum concentrations of T, regardless of etiology, and can be induced experimentally in healthy volunteers of all ages simply by reducing serum T concentrations.[20] The relatively high prevalence of TD in middle-aged and older men has given rise to the concept of *male menopause*, or *andropause*. Although these terms have some conceptual appeal, TD differs importantly from menopause in that most men are unaffected, and the onset is gradual over an extended time course.[49] In addition, the age-related decline in serum T is relatively small,[39] and much of the decline can be attributed to comorbid conditions such as obesity.[39,50,51] At this time, there are insufficient data to support T therapy for disease prevention or antiaging.

Testosterone therapy has been in use for more than 70 years for the treatment of TD,[52] and several of the earliest reports documented benefits specifically for CV disease. From the late 1930s into the 1950s, several studies reported marked benefits of T therapy in patients with peripheral vascular disease[53,54] and angina pectoris.[55-59] Lesser[59] described 100 consecutive patients (92 men and 8 women) ranging from 34 to 77 years of age with angina pectoris who received T therapy with follow-up ranging from a few months to 5 years. Improvement was noted in 91%, with no appreciable improvement in patients treated with placebo.[59]

A wealth of modern data accumulated over the past 2 decades has generally revealed that a low serum T level is associated with increased risks of atherosclerosis, CV risk factors, and mortality and that T therapy has beneficial effects on multiple risk factors and risk biomarkers related to these clinical conditions. Notably, TD has been projected to be involved in the development of approximately 1.3 million new cases of CV disease, 1.1 million new cases of diabetes, and over 600,000 osteoporosis-related fractures.[60] Over a 20-year period, TD has been estimated to be directly responsible for approximately $190 to $525 billion in inflation-adjusted US health care expenditures.[60] In addition, longitudinal models predict increased outpatient visits and costs related to low baseline serum T levels independent of socioeconomic and lifestyle factors; even when controlling for age, men aged 20 to 79 years at baseline with low serum T levels had 29% more outpatient visits and 38% higher outpatient costs at 5-year follow-up.[61]

Numerous intervention studies have consistently found improvements in CV risk factors such as fat mass, obesity, waist circumference, blood pressure, and glycemic control. These important findings provide a reasonable biological mechanism to explain the frequently observed outcome of increased mortality among men with the lowest quartiles or quintiles of serum T or with frank TD.[62-68] Importantly, TD in older men is associated with increased risk of death during the 20 years after diagnosis, independent of multiple traditional risk factors and several preexisting health conditions.[63,65]

Small randomized, placebo-controlled T trials have documented reduction in carotid intima-media thickness with T therapy, raising the possibility that normalizing serum T may actually cause reversal of atherosclerosis in critical vascular beds. Moreover, 2 studies published within the past 2 years, one in a Veterans Administration population[69] and the other in diabetic men,[70] found mortality reduced by half in men with TD who received T prescriptions compared with similar men who did not, It was therefore surprising that

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publication of 2 retrospective studies reporting increased risks of CV adverse events would cause such great concern. In one of these studies, Vigen et al[1] reported increased rates of MIs, strokes, and deaths in men who received T prescriptions compared with untreated men; this study used unvalidated statistical methodology that reversed the raw data, which actually revealed that the percentage of adverse events in T-treated men was lower by half compared with untreated men.[71] Large data errors revealed postpublication led to a call for retraction by no less than 29 medical societies.[72] The second study by Finkle et al[2] reported an increased rate of nonfatal MI up to 90 days after receipt of a T prescription compared with the previous 12 months. However, MI rates postprescription were low, there was no control group, and methodological issues again rendered the study results highly questionable.[73]

In response to the publication of these 2 studies and their attendant publicity, the FDA[7] announced its intention to review CV risks with T products 2 days after publication of the study by Finkle et al.[2] Although an advisory committee meeting was scheduled for September 17, 2014, the FDA had already made public its own analysis of the literature in its denial of a petition by the group Public Citizen to add black box warnings and other restrictions to T products.[74] The FDA's comments are included where appropriate in the analysis that follows.

METHODS

A MEDLINE search was performed for the years 1940 to August 2014 using the following key words: *testosterone*, *androgens*, *human*, *male*, *cardiovascular*, *stroke*, *cerebrovascular accident*, *myocardial infarction*, *heart attack*, *death*, and *mortality*. Additional studies were sought by examining publications with their own literature reviews. Tables were created with results provided by abstracts or from the full text of the article, depending on the adequacy of abstracted information.

A review of the literature was performed for 9 specific topics related to T and CV risks: mortality; incident CAD; severity of CAD; ischemic stroke; carotid intima-media thickness; obesity/fat mass; lipid profiles; glycemic control; and inflammatory markers. A summary statement was made regarding the interpretation of relevant studies in those areas, and level of evidence supporting that conclusion was adjudicated by 2 authors (M.M., A.T.).

ANALYSIS

In contrast to many dozens of studies documenting the beneficial CV effects of T therapy in humans, there appear to be only 4 articles that suggest increased CV risk. These 4 articles were also identified by the FDA analysis. These articles are the 2 retrospective large dataset analyses of Vigen et al[1] and Finkle et al,[2] a meta-analysis by Xu et al,[75] and a report of incidental CV adverse events in a placebo-controlled T gel study designed to assess muscular and functional benefits in elderly, frail men with mobility limitations by Basaria et al.[76] Although few in number, these studies have garnered considerable attention in the medical literature and lay press, and therefore merit individual analysis here.

Vigen et al, *JAMA* 2013

Vigen et al[1] conducted a retrospective analysis of men who had undergone coronary angiography within the Veterans Administration health care system. The authors reported that the overall rate of MI, stroke, and death in men with serum T levels less than 300 ng/dL (to convert to nmol/L, multiply by 0.0347) was higher in men who received a T prescription compared with untreated men. Although no statistically significant differences were noted at years 1, 2, or 3, the overall rate of events over the course of the study was reported to be significantly higher (29%) in T-treated men.

Strangely, the *actual* rate of adverse events was only half as great in the T group (123 events in 1223 men at risk, 10.1%) as in the untreated group (1587 events in 7486 men, 21.2%) (Figure).[77] The authors failed to acknowledge this fact and came to an opposite interpretation of the data based on complex statistics that included adjustment for more than 50 variables. The methodology in this study, ie, stabilized inverse propensity treatment weighting applied to Kaplan-Meier curves with time as a covariate, was described in an article by senior author Michael P. Ho just a year earlier (2012) as follows: "Clearly, assessing and confirming adequate covariate

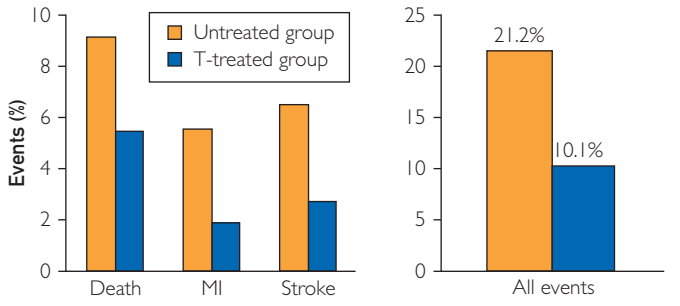

FIGURE. Actual percentage of individuals who experienced an adverse cardiovascular event in the testosterone (T)-treated and untreated groups in the study by Vigen et al.[1] The authors reported a higher rate of adverse events in the T-treated group using inverse stabilized propensity weighting in which an event was counted as more than 1 event in the T-treated group and less than 1 event in the untreated group. MI = myocardial infarction. From *J Sex Med*,[77] with permission. ©2014 International Society for Sexual Medicine.

balance in IPTW time-varying models is challenging and needs further study… Further work with simulations and contrasts to other methods and other study applications would help elucidate the advantages and disadvantages of this approach."[78] The authors fail to provide any citations or other evidence in their 2013 article by Vigen et al[1] that these major methodological concerns have been resolved and that the methodology itself is accurate or accepted by other investigators.

This article has already undergone 2 official corrections. The first, published January 15, 2014, was for misreporting of primary results as "absolute risk," a term that suggests the results were based on raw data.[79] In response to criticism following publication, the article was corrected to replace the term *absolute risk* with *Kaplan-Meier estimated cumulative percentages with events*, a term that more accurately reflects the highly statistical nature of the results. On March 5, 2014, *JAMA* published a second correction.[80] In response to a letter challenging the exclusion of 1132 men who had suffered adverse events in the non-T group, the authors revealed they had made a series of errors. The number of men in this excluded group was changed from 1132 to 128 men, a difference of greater than 1000 men. The value for a second group was found to be incorrect by more than 900 men. Most astonishingly, the all-male study group was found to include nearly 10% women. In response to these errors, 29 international medical societies and more than 160 physician-scientists from 32 countries petitioned *JAMA* to retract this article, citing "gross data mismanagement and contamination" that rendered the study "no longer credible."[72] The medical societies urging retraction are listed in Table 1.

In summary, this study used an unvalidated methodology to reverse the results of raw data, which revealed a lower percentage of adverse events in the T-treated group compared with untreated men. Putting aside the multiple disturbing data errors that undermine the integrity of the study, this lower percentage of adverse CV events in the T-treated group is consistent with the results of 2 prior studies that reported mortality reduced by half in T-treated men compared with untreated men.[69,70] Those studies are reviewed in further detail in the "Testosterone Prescriptions and CV Outcomes" section.

The FDA's concluding comment regarding Vigen et al[1] was as follows: "Given the described limitations of the study by Vigen et al it is difficult to attribute the reported findings to testosterone treatment."[74]

Finkle et al, *PLoS One* 2014

The study by Finkle et al[2] was a retrospective study of a health insurance database that reported rates of nonfatal MI in the period up to 90 days after a T prescription and compared these rates to MI rates in the previous 12 months. The postprescription period was the time to first prescription refill, which for an unspecified number of men would have been 30 days rather than 90 days. The authors reported the rate ratio of MI postprescription to preprescription was 1.36, and the rate in men older than 65 years was 2.19. In comparison, no increase in MI rate was noted for men who received a prescription for a phosphodiesterase type 5 inhibitor (PDE5i).

Because the source was an insurance claims database, available information was limited to diagnosis codes, procedure codes, and prescriptions. There was no information available regarding several standard CV risk factors, such as diabetes, hypertension, hyperlipidemia, smoking history, or obesity, and no information concerning any blood test results,

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including serum T, or lipid profiles. The weakness of the dataset as an investigative tool for assessment of CV risk is underscored by the fact that the end point in the study, nonfatal MI, was determined solely by the use of an insurance diagnosis code without verification that MI occurred and without measures to increase the likelihood of capturing a true event, such as limiting events to the primary diagnosis code at hospital discharge.[81] An error rate as high as 12% has been reported when such measures are not followed.[82]

Methodologically, it was inappropriate to compare posttreatment rates of MI to pretreatment rates because these rates measure different things.[73] The post—T prescription MI rate reasonably reflects the naturally occurring MI rate in this population, albeit with the aforementioned caveats regarding the accuracy of this type of database investigation. However, because men were included in the study on the basis of real-world receipt of a T prescription, the pre—T prescription MI reflected how often health care providers were willing to prescribe T to men with a recent (within 12 months) MI. Any reluctance to prescribe T to men with recent MI would result in a reduced preprescription MI rate. The rates of MI in the preprescription and postprescription periods thus measure different things, and the comparison is therefore meaningless.

Moreover, the reported MI rates post—T prescription were all low, overall and for all subgroups. For example, the overall postprescription MI rate reported by Finkle et al[2] was 4.75 events per 1000 person-years. This result compares with a rate of 13 expected MIs per 1000 person-years using the National Institutes of Health heart attack risk calculator, inputting age 54 years (the mean age of the study participants) and favorable risk parameters (nonsmoker; total cholesterol, 230 mg/dL [to convert to mmol/L, multiply by 0.0259]; high-density lipoprotein [HDL] cholesterol, 40 mg/dL [to convert to mmol/L, multiply by 0.0259]; systolic blood pressure, 140 mm Hg).[83] The observed MI rate among men who received a T prescription was thus approximately one-third the expected rate. In the absence of a control group of men who were untreated, it is impossible to determine whether these reported MI rates were higher, lower, or unchanged in association with a T prescription.

Finally, the comparison with men who received a PDE5i prescription is uninterpretable. These were 2 dissimilar groups treated with dissimilar medications for dissimilar indications. Phosphodiesterase type 5 inhibitors are known to have vasodilatory properties, and one medication in this class, sildenafil, is approved for treatment of pulmonary hypertension, confounding any comparison because of the possibility that PDE5i's may have beneficial effects on CV risk. This is a classic case of comparing apples and oranges.

A key concept not addressed by Finkle et al[2] is that TD itself has been identified as a risk factor for CV events (reviewed in the "Testosterone and Mortality section). Given the short T exposure time of 30 to 90 days,

TABLE 1. Professional Societies Calling for Retraction of Vigen et al[1,a]

American Society for Men's Health (ASMH)
Brazilian Society of Endocrinology and Metabolism
Canadian Men's Sexual Health Council
Canadian Society for the Study of Men's Health (CSSAM)
European Society for the Study of the Aging Male (ESSAM)
European Society for Sexual Medicine (ESSM)
German Society for Men and Health
Indonesian Andrologist Association
International Society of Men's Health (ISMH)
International Society for Sexual Medicine (ISSM)
International Society for the Study of the Aging Male (ISSAM)
Irish Association of Sexual Medicine
Italian Society of Andrology
Italian Society of Andrology and Sexual Medicine
Japan ASEAN Council for Men's Health and Aging
Japanese Society for Men's Health
Korean Society for Sexual Medicine and Andrology
Malaysian Men's Health Initiative
Malaysian Society of Andrology and the Study of the Aging Male
Men's Health Initiative of British Columbia (Canada)
Mexican Association of Bone and Mineral Metabolism
Middle East Society for Sexual Medicine
Russian Society for Men's Health
South Asian Society for Sexual Medicine
Sexual Medicine Society of North America
Sociedade Latinoamericana de Medicina Sexual (Latin American Society for Sexual Medicine)
Society for Men's Health, Singapore
Society for the Study of Androgen Deficiency
Society for the Study of Andrology and Sexology, Singapore (SSASS)

[a]Current list can be found at http://www.androgenstudygroup.org/co-signers/list-of-co-signersmedical-organizations.

one unexplored possibility is that any observed increased risk of MI was due to the underlying condition rather than from the treatment. For this reason, we agree with the FDA analysis, which concluded that "it is difficult to attribute the increased risk for non-fatal MI seen in the Finkle study to testosterone alone and not consider that the study participants might have remained hypogonadic and thus at higher risk for non-fatal MI."[74]

Basaria et al, *New England Journal of Medicine* 2010

Basaria et al[76] conducted a prospective randomized trial designed to investigate whether T gel provided greater muscular and functional benefits than placebo in a population of frail elderly men treated for 6 months. The study did indeed find a benefit of T treatment over placebo for muscular and functional responses but was terminated early because of the observation of increased adverse events categorized as "cardiovascular" in the treatment arm. There were 23 of these events in the T arm and 5 in the placebo arm.

However, this study was not designed to investigate CV events, and none of these events were primary or secondary end points. Most of the reported "events" were incidentally noted, subjective, or of questionable clinical importance, such as palpitations, pedal edema, and premature ventricular contractions. None of these adverse events were defined before study enrollment, and there was no attempt to systematically investigate all participants for the presence of any of these events. The most frequently reported adverse event was pedal edema, with 5 cases in the T group and none in the placebo group. Given that the placebo group was composed of more than 100 frail elderly men with multiple comorbidities, it seems unlikely that none of them had any degree of pedal edema. This flaw underscores concerns about the interpretation of these data by Basaria et al[76] as indicative of true CV risk rates because it violated foundational concepts in clinical trials, ie, defined end points and systematic data acquisition.

Four major adverse cardiac events (MACE) occurred: 1 death, 2 MIs, and 1 stroke, all of which occurred in the T group. Although troubling, this asymmetry is not uncommon with rare events in clinical trials. In a similar study in frail elderly men performed in the United Kingdom, there were 2 MACE (1 death, 1 MI), both occurring in the placebo group.[19] As Basaria et al[76] concluded, "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 two trial groups may have been due to chance alone." A subsequent analysis suggested that events were associated with higher serum concentrations of T achieved with treatment using higher than approved doses of T, contrary to the recommendations of the Endocrine Society guidelines.[9] It is impossible to conclude from this study that T prescriptions confer an increased risk of CV events. The FDA concluded, "The Basaria study does appear to show an empirical dose-dependent association between testosterone and cardiovascular risk, but it was non-conclusive because of the small sample size and small number of events reported in the study, as well as the limitations with respect to confirming the events. The authors of this study have explicitly indicated that the differences between the groups in cardiovascular adverse events might have been due to chance alone."[74]

Xu et al, *BMC Medicine* 2013

In a meta-analysis of CV events in 27 placebo-controlled T studies of 12 weeks' duration or longer, Xu et al[75] reported that more CV events occurred in men who received T compared with those who received placebo. This study is the only one of several meta-analyses and systematic reviews to suggest any increased risk with T therapy. As with all meta-analyses, results are greatly influenced by the definitions of end points of interest and the selection of studies. In this case, the authors specifically included only studies in which one or more CV events were reported, meaning that studies without any CV events were excluded. This selection process exaggerates the apparent rate of events and distorts absolute differences in event rates between groups. In addition, just 2 of the 27 studies contributed 35% of all CV events in the T arm.

The disproportionate influence of these 2 studies on the outcome of the meta-analysis merits closer scrutiny. One is the study by Basaria et al[76] discussed previously, in which 18 of 23 events (incorrectly reported as 25

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events by Xu et al[75]) would not normally qualify as CV events. The other was the 1986 Copenhagen study[84] in which a nonapproved oral formulation of micronized T was administered at a remarkably high dose of 600 mg/d to men with cirrhosis of the liver, resulting in serum T concentrations exceeding 4000 ng/dL (approximately 140 nmol/L) in a quarter of the T group and levels as high as 21,000 ng/dL (745 nmol/L), a value approximately 20 times the upper limit of the normal range. Because these oral forms of T are known to cause liver toxicity via a first-pass effect, it should be no surprise that markedly supraphysiologic T doses in a hepatically compromised population would prove harmful. Moreover, the authors appear to have categorized any bleeding event as "cardiovascular," including the most frequently observed cause of death in this study, bleeding from esophageal varices. The authors listed 21 events as CV, yet only 1 (MI) could reasonably be considered as CV. This trial has little relevance to the question as to whether the clinical use of T therapy increases CV risks. Its inclusion and misreporting led to distorted results.

Without the contributions of the Copenhagen study[84] and the non-MACE in the study by Basaria et al,[76] the rates of adverse CV events in the T and placebo groups were similar, with a slightly lower rate in the T group (78 events in 1599 men [4.88%] vs 60 events in 1174 men [5.1%], respectively). It should be underscored that this is the only one of several previously published meta-analyses and systematic reviews to report increased risk with T treatment.[85-87] Recently, Corona et al[8] reported a meta-analysis of 75 studies, compared with the 27 analyzed by Xu et al.[75] The meta-analysis by Corona et al[8] included 3016 men treated with T and 2446 treated with placebo for a mean treatment duration of 34 weeks. They found no significant association between T therapy and CV events, either as single events or as combined CV end points. Studies in men with metabolic derangements revealed a protective effect of T treatment.[88]

Summary

None of the 4 studies cited as evidence supporting an increased CV risk with T administration provide compelling evidence of increased risk. Indeed, the articles by Vigen et al[1] and Finkle et al[2] could each arguably be described as documenting protective effects of T therapy on CV risk because the percentage of events was lower by half in the former and overall MI rates were only a fraction of expected rates in the latter. Events reported by Basaria et al[76] were not systematically investigated in all individuals, and most events were of questionable clinical importance. Finally, the results of Xu et al[75] appear to be due to the inclusion of questionable events and studies, and their conclusions are contradicted by several other meta-analyses.

REVIEW OF EXISTING LITERATURE

Any objective assessment of the literature regarding T and CV effects must recognize a broad, rich literature in which numerous studies reveal increased CV concerns with TD and improvement in a variety of CV risk factors and some CV outcomes with T therapy. That literature has been summarized and tabulated and is included here in Tables 2-9. Summary statements and levels of supporting evidence are provided in Table 10.

Testosterone Prescriptions and CV Outcomes

Three additional studies beyond those of Vigen et al[1] and Finkle et al[2] have investigated mortality or MI rates in association with T therapy.[69,70,156] Shores et al[69] studied 1031 men in the Veterans Administration health care system with serum T levels of less than 250 ng/dL. The mean age was 62 years, and mean follow-up was 40.5 months. Mortality in T-treated men was reduced by half in treated men compared with untreated men, at 10.3% vs 20.7%, respectively (P=.0001). Multivariate adjustment for age, body mass index, T level, medical morbidity, diabetes, and coronary heart disease yielded a hazard ratio (HR) of 0.61 (95% CI, 0.42-0.88; P=.008), indicating significant reduction in mortality with T therapy.

Muraleedharan et al[70] investigated a group of 581 diabetic men followed for a mean of 5.8 years. Men with low levels of serum T, defined as a serum T level of less than 10.4 nmol/L (300 ng/dL), had increased mortality compared with men with T values above this threshold. Adjusted mortality in the low T group was 17.2% compared with 9.0% in the normal T

TABLE 2. Observational Studies of Serum Testosterone Concentrations and Mortality[a]

Reference, year (study)	Subfraction of testosterone used for analysis	Sample size	Age range/mean age (y)	Mean follow-up (y)	Population	Major finding	Remarks
Studies documenting a negative (inverse) association between endogenous testosterone and mortality							
Pye et al,[89] 2014 (European Male Aging Study)	TT, FT	2599	40-79	4.3	Community-based, Europe	Testosterone deficiency is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the level of testosterone and the presence of sexual symptoms contribute independently	HR of low TT <8 nmol/L (irrespective of symptoms) for all-cause mortality, 2.3 (95% CI, 1.2-4.2) HR of low TT <8 nmol/L and FT <220 pmol/L for all-cause mortality, 5.5 (95% CI, 2.7-11.4) HR with 3 sexual symptoms (irrespective of serum testosterone level; compared with asymptomatic men), 3.2 (95% CI, 1.8-5.8) Similar risks observed for cardiovascular mortality
Haring et al,[90] 2013 (Framingham Heart Study)	TT	254	75.5	5 and 10	Community-based, United States	Higher baseline TT concentrations were associated with lower mortality risk at 5 y Correction for multiple statistical testing ($P<.005$) rendered this association statistically nonsignificant Repeated analyses at 10-y follow-up revealed no significant association between sex steroids, gonadotropins or their trajectories and mortality	HR (per quartile increment) of high FT for all-cause mortality, 0.74 (95% CI, 0.56-0.98)
Muraleedharan et al,[70] 2013		581		5.8	Type 2 diabetes	Low testosterone levels predict an increase in all-cause mortality during long-term follow-up. Testosterone replacement may improve survival in hypogonadal men with type 2 diabetes	Mortality increased in the low testosterone group (17.2%) compared with the normal testosterone group (9%; $P=.003$) when controlled for covariates In Cox regression model, multivariate-adjusted HR for decreased survival was 2.02 (95% CI, 1.2-3.4; $P=.009$). TRT (mean duration, 41.6±20.7 mo; n=64) associated with a reduced mortality of 8.4% compared with 19.2% ($P=.002$) in the untreated group (n=174) Multivariate-adjusted HR for decreased survival in the untreated group was 2.3 (95% CI, 1.3-3.9; $P=.004$)
Hyde et al,[91] 2012 (Health in Men Study)	TT, FT	4249	70-88/77	5.1	Population-based, Australia	Lower free testosterone (and higher SHBG and LH levels) were associated with all-cause mortality In cause-specific analyses, lower free testosterone (and higher LH) predicted CVD mortality, while higher SHBG predicted non-CVD mortality	HR of low FT for all-cause mortality, 1.62 (95% CI, 1.20-2.19) for 100 vs 280 pmol/L HR of low FT for CVD mortality, 1.71 (95% CI, 1.12-2.62) for 100 vs 280 pmol/L

Continued on next page

TABLE 2. Continued

Reference, year (study)	Subfraction of testosterone used for analysis	Sample size	Age range/mean age (y)	Mean follow-up (y)	Population	Major finding	Remarks
Studies documenting a negative (inverse) association between endogenous testosterone and mortality, continued							
Lerchbaum et al,[92] 2012	TT, FT	2069		7.7	Coronary angiography	A combined deficiency of FT and 25(OH)D is significantly associated with fatal events in a large cohort of men referred for coronary angiography	Multivariate-adjusted HR for all-cause mortality, 2.11 (95% CI, 1.60-2.79) Multivariate-adjusted HR for CVD mortality, 1.77 (95% CI, 1.23-2.55) Multivariate-adjusted HR for non-CVD mortality, 2.33 (95% CI, 1.45-3.47)
Haring et al,[93] 2011	TT			9.9	Kidney dysfunction	Measured TT levels may help detect high-risk individuals for potential therapeutic interventions and improve mortality risk assessment and outcome	HR for all-cause mortality in men with kidney dysfunction, 1.4 (95% CI, 1.02-1.92) HR for all-cause mortality in men with kidney dysfunction and low TT, 2.52 (95% CI, 1.08-5.85)
Kyriazis et al,[94] 2011	TT	111		27 mo	HD patients	Testosterone deficiency in male HD patients is associated with increased CVD and all-cause mortality Increased arterial stiffness may be a possible mechanism explaining this association	Patients with testosterone deficiency had increased CVD and all-cause mortality, even after adjustment for age, body mass index, serum albumin and C-reactive protein levels, prevalent CVD, and HD duration Testosterone levels were inversely related to PWV ($r=-0.441$; $P<.001$) The association of testosterone with CVD mortality, but not with all-cause mortality, was lost after adjusting for PWV, an index of arterial stiffness
Carrero et al,[95] 2011	TT	260	48-67/59	3	ESRD, Sweden	Testosterone deficiency is independently associated with cardiovascular comorbidity and death in logistic regression analyses Testosterone deficiency is a common finding among male patients with ESRD, and it is independently associated with inflammation, cardiovascular comorbidity and outcome	OR of low TT for cardiovascular comorbidity was 2.51 (95% CI, 1.32-4.76) and for death was 2.0 (95% CI, 1.01-3.97)
Haring et al,[65] 2010 (Study of Health in Pomerania)	TT	1954	20-79/58.7	7.2	Population-based, Germany	Low TT is associated with increased risk of mortality from all causes and CV disease	HR of low TT for all-cause mortality, 1.92 (95% CI, 1.18-3.14; $P<.001$) HR of low TT for CV mortality, 2.56 (95% CI, 1.15-6.52; $P<.05$)
Malkin et al,[96] 2010	TT, BT	930	Not reported	6.9	CHD (positive angiographic findings)	Low BT is inversely associated with time to all-cause and vascular mortality	HR of low BT for all-cause mortality, 2.2 (95% CI, 1.4-3.6; $P<.0001$) HR of low BT for vascular mortality, 2.2 (95% CI, 1.2-3.9; $P=.007$)

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TABLE 2. Continued

Reference, year (study)	Subfraction of testosterone used for analysis	Sample size	Age range/mean age (y)	Mean follow-up (y)	Population	Major finding	Remarks
Studies documenting a negative (inverse) association between endogenous testosterone and mortality, continued							
Menke et al,[66] 2010 (Third National Health and Nutrition Examination Survey)	TT, BT, FT	1114	≥20/40	16	Population-based, United States	Decrease in FT and BT from 90th to 10th percentile is associated with increased risk of all-cause and CV mortality during the first 9 y of follow-up	HR of FT decrease for all-cause mortality, 1.43 (95% CI, 1.09-1.87) HR of BT decrease for all-cause mortality, 1.52 (95% CI, 1.15-2.02) HR of FT decrease for CV mortality, 1.53 (95% CI, 1.05-2.23) HR of BT decrease for CV mortality, 1.63 (95% CI, 1.12-2.37)
Corona et al,[97] 2010		1687		4.3	Erectile dysfunction	Testosterone levels are associated with a higher mortality of MACE Identification of low testosterone levels identifies patients with an increased cardiovascular risk	Proportion of lethal events among MACE was significantly higher in hypogonadal patients, using either 10.4 nmol/L (300 ng/dL) or 8 nmol/L (230 ng/dL) thresholds After adjustment for age and Chronic Disease Score in a Cox regression model, only the association between incident fatal MACE and testosterone <8 nmol/L (230 ng/dL) was confirmed (HR, 7.1 [95% CI, 1.8-28.6]; *P*<.001)
Ponikowska et al,[98] 2010	TT, FT	153	65±9	19 mo	Type 2 diabetes with CHD	In diabetic men with stable CAD, testosterone deficiency is common and related to high cardiovascular mortality	HR for CVD mortality per 1-SD increment in TT and FT: TT, 0.58 (95% CI, 0.39-0.87); FT, 0.65 (95% CI, 0.52-0.81)
Militaru et al,[99] 2010	TT	126		30 d	Acute MI	A low level of testosterone was independently related to total short-term mortality	OR for TT quartiles 2,3, and 4 vs 1: 0.82 (95% CI, 0.67-1.03), 0.67 (95% CI, 0.52-0.86), and 0.70 (95% CI, 0.56-0.89), respectively (P trend, <.01) The mean level of TT = 4.1±2.9 ng/mL All nonsurvivors had TT ≤3 ng/mL
Vikan et al,[100] 2009 (Tromsø Study)	TT, FT	1568	Not reported/ 59.6	11.2	Population-based, Norway	24% Higher risk of all-cause mortality for men with low FT levels	HR of low FT for all-cause mortality, 1.24 (95% CI, 1.01-1.54)
Tivesten et al,[67] 2009 (Osteoporotic Fractures in Men Study [MrOS])	TT, FT	2639 with TT, 2618 with FT	69-80/75.4	4.5	Population-based, Sweden	Increasing levels of TT and FT are associated with decreasing risk of all-cause mortality	HR of high TT for all-cause mortality, 0.59 (*P*<.001) HR of high FT for all-cause mortality, 0.50 (*P*<.001)
Carrero et al,[101] 2009		126		41 mo	Hemodialysis	In men undergoing hemodialysis, testosterone concentrations inversely correlate with all-cause and CVD-related mortality, as well as with markers of inflammation. Hypogonadism may be an additional treatable risk factor for patients with chronic kidney disease	HR for TT in the lowest tertile for all-cause mortality, 2.03 (95% CI, 1.24-3.31) HR for TT in the lowest tertile for CVD mortality, 3.19 (95% CI, 1.49-6.83) Increased risk with low TT persisted after adjustment for age, SHBG, previous CVD, diabetes, ACEi/ARB treatment, albumin, and inflammatory markers but was lost after adjustment for creatinine

Continued on next page

TABLE 2. Continued

Reference, year (study)	Subfraction of testosterone used for analysis	Sample size	Age range/mean age (y)	Mean follow-up (y)	Population	Major finding	Remarks
Studies documenting a negative (inverse) association between endogenous testosterone and mortality, continued							
Lehtonen et al,[102] 2008	TT	187	71-72	10	Population-based, Finland	Serum TT in elderly men is inversely associated with mortality Higher endogenous testosterone levels have a favorable effect on survival in elderly men	OR of low TT for all-cause mortality, 0.93 (95% CI, 0.87-0.99) Mean baseline serum testosterone concentration was ~14% higher ($P<.024$) in men who were alive at the end of the follow-up period compared with the deceased men
Laughlin et al,[63] 2008 (Rancho Bernardo Study)	TT, FT	794	63-78.9/71.2	11.8	Population-based, United States	Low TT and BT are associated with higher risk of all-cause and CV mortality	HR of low TT for all-cause mortality, 1.44 ($P<.002$) HR of low BT for all-cause mortality, 1.50 ($P<.001$) HR of low TT for CV mortality, 1.38 (95% CI, 1.02-1.85) HR of low BT for CV mortality, 1.36 (95% CI, 1.04-1.79)
Khaw et al,[62] 2007 (European Prospective Investigation Into Cancer in Norfolk)	TT	11,606	40-79/67.3	7	Population-based, Europe	Low TT is associated with higher risk of all-cause and CV mortality. Same trend was noted for CHD mortality, but statistical significance was not achieved	OR of low TT for all-cause mortality, 0.59 ($P<.001$) OR of low TT for CV mortality, 0.53 ($P<.01$)
Araujo et al,[103] 2007 (Massachusetts Male Aging Study)	TT, FT	1686	40-80	15.3	Population-based, United States	High FT and low DHT levels are associated with ischemic heart disease	TT and SHBG levels are not associated with all-cause mortality
Shores et al,[104] 2006	TT	858	≥40/61.4	4.3	Population-based, United States	Low TT is associated with higher risk of all-cause mortality	HR of low TT for all-cause mortality, 1.88 ($P<.001$)
Studies documenting no association between endogenous testosterone and mortality							
Shores et at,[105] 2014 (Cardiovascular Health Study)	TT, FT, DHT	1032	66-97/76	9	Community-based, United States	In a cohort of elderly men, DHT and calculated free DHT were associated with incident CVD and all-cause mortality	In models adjusted for cardiovascular risk factors, TT and FT were not associated with incident CVD or all-cause mortality, whereas DHT and calculated free DHT had curvilinear associations with incident CVD ($P<.002$ and $P=.04$, respectively) and all-cause mortality ($P<.001$ for both)
Studies documenting a positive association between endogenous testosterone and mortality							
None identified							

[a]ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BT = bioavailable testosterone; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; DHT = dihydrotestosterone; ESRD = end-stage renal disease; FT = free testosterone; HD = hemodialysis; HR = hazard ratio; LH = luteinizing hormone; MACE = major adverse cardiovascular events; MI = myocardial infarction; 25(OH)D = 25-hydroxyvitamin D; OR = odds ratio; PWV = pulse wave velocity; SHBG = sex hormone–binding globulin; TRT = testosterone replacement therapy; TT = total testosterone.

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TABLE 3. Association Between Testosterone Level and Incident Coronary Artery Disease[a]

Reference, year (type of study, No. of patients)	Subfraction of testosterone used for analysis	Primary end point measured (method)	Main finding of study	Potential confounding factors
Studies documenting an association between low testosterone levels and incident CAD				
Zhao & Lil,[107] 1998 (CCS, 201)	TT	CAD (H&P, ECG, cardiac catheterization in 27 patients)	Men with CAD have lower levels of TT	BT not used for analysis Limited number of patients underwent catheterization Small sample size
English et al,[108] 2000 (CCS, 90)	TT, FT, BT, FAI	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of FT, BT, and FAI	Small sample size
Dobrzycki et al,[109] 2003 (CCS, 96)	TT, FT, FAI	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT, FT, and FAI	BT not used for analysis Small sample size
Akishita et al,[110] 2010 (CS, 171)	TT	Cardiovascular events[b] (H&P, physician and hospital records)	Men with lower levels of endogenous TT are more likely to have cardiovascular events	BT not used for analysis Small sample size End points other than CAD were pulled in the analysis Patients did not undergo cardiac catheterization
Rosano et al,[111] 2007 (CCS, 129)	TT, FT, BT	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT and BT	Small sample size
Hu et al,[112] 2011 (CCS, 87)	TT	CAD (cardiac catheterization)	Men with catheterization-proven CAD have lower levels of TT	BT not used for analysis Small sample size
Studies documenting a complex association between serum testosterone concentrations and incident CAD				
Soisson et al,[113] 2013 (PCS [French 3C], 3650 men aged >65 y)	TT, BT	CHD and stroke	After adjustment for cardiovascular risk factors, a J-shaped association between plasma TT and IAD risk was found ($P<.01$) The HRs associated with the lowest and the highest TT quintiles relative to the second quintile were 2.23 (95% CI, 1.02-4.88) and 3.61 (95% CI, 1.55-8.45), respectively	Additional analysis for CHD had similar results (HR, 3.11 [95% CI, 1.27-7.63] and 4.75 [95% CI, 1.75-12.92], respectively) Similar J-shaped association was observed between BT and IAD risk ($P=.01$) No significant association of estradiol and SHBG with IAD was found
Studies documenting no association between testosterone levels and incident CAD				
Cauley et al,[114] 1987 (CCS, 163)	TT, FT	Acute, nonfatal myocardial infarction, death from cardiovascular disease (ECG, hospital records)	No difference in TT or FT levels between cases and controls	BT not used for analysis Small sample size Patients did not undergo cardiac catheterization
Barrett-Connor & Khaw,[115] 1988 (CS, 1009)	TT	Cardiovascular disease or mortality, ischemic heart disease morbidity or mortality (death certificates, hospital records)	No statistically significant association between levels of TT and primary end points	BT not used for analysis Patients did not undergo cardiac catheterization
Kabakci et al,[116] 1999 (CCS, 337)	TT, FT	CAD (cardiac catheterization)	No statistically significant difference in FT or TT levels between cases and controls	BT not used in analysis Small sample size Suboptimal method used for measurement of FT
Amlöv et al,[117] 2006 (PCS, 2084)	TT	Cardiovascular disease[c] (physician and hospital records)	No significant association between levels of endogenous TT and incidence of CAD	BT not used for analysis End points other than CAD were pooled in the analysis Patients did not undergo cardiac catheterization
Studies documenting an association between high serum concentrations of testosterone and incident CAD				
None identified				

[a]BT = bioavailable testosterone; CAD = coronary artery disease; CCS = case-control study; CHD = coronary heart disease; CS = cohort study; ECG = electrocardiography; FAI = free androgen index; FT = free testosterone; H&P = history and physical examination; HR = hazard ratio; IAD = ischemic arterial disease; PCS = prospective cohort study; SHBG = sex hormone–binding globulin; TT = total testosterone.

[b]Cardiovascular events included stroke, CAD, sudden cardiac death, and peripheral arterial disease.

[c]Cardiovascular disease included CAD, myocardial infarction, angina pectoris, coronary insufficiency, death from CAD, stroke, transient ischemic attack, congestive heart failure, and peripheral vascular disease.

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TABLE 4. Association Between Serum Testosterone Concentrations and Severity of Coronary Artery Disease[a]

Reference, year (type of study, No. of patients)	Subfraction of testosterone used for analysis	Method of measuring CAD severity	Main finding of study	Comment
Negative (inverse) correlation				
Dobrzycki et al,[109] 2003 (CCS, 96)	TT, FT, FAI	Duke index[b]	Inverse correlation between FT and CAD severity	r=−0.69, *P*=.048
Li et al,[118] 2012 (CCS, 803)	TT	Gensini score[c]	Inverse correlation between TT and CAD severity	r=−0.188, *P*<.001
Phillips et al,[119] 1994 (CCS, 55)	TT, FT	Visual estimation of coronary artery occlusion and calculation of mean percent occlusion[d]	Inverse correlation between TT and FT levels and CAD severity	TT: r=−0.43, *P*<.02; FT: r=−0.62, *P*<.001
Rosano et al,[111] 2007 (CCS, 129)	TT	Coronary artery score[e]	Inverse correlation between TT and CAD severity	r=−0.52, *P*<.01
Positive correlation				
None identified				

[a]CAD = coronary artery disease; CCS = case-control study; FAI = free androgen index; FT = free testosterone; TT = total testosterone.
[b]Duke prognostic coronary artery index: a prognostic tool involving the extent and severity of atherosclerotic lesions in coronary arteries.
[c]Genisi score: Calculation based on location and number of stenotic coronary artery segments and degree of luminal narrowing.
[d]Authors visually estimated the maximum percent reduction in luminal diameter of the left main, left anterior descending, left circumflex, and right coronary arteries. The mean of these 4 values was used to estimate CAD severity.
[e]Coronary artery score: authors multiplied the degree of coronary artery obstruction by the number of stenoses.
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group (*P*=.003). In these populations, the multivariate-adjusted HR for decreased survival was 2.02 (95% CI, 1.2-3.4; *P*=.009). Untreated men with low T concentrations had mortality of 19.2%, compared with treated men, in whom mortality was again reduced by approximately half, at 8.4%. Notably, this value approximated the mortality in men with normal serum T concentrations. After multivariate adjustment, the HR for decreased survival in the untreated group was 2.3 (95% CI, 1.3-3.9; *P*=.004).

After publication of the study by Finkle et al,[2] Baillargeon et al[156] studied 25,420 US Medicare recipients aged 65 years and older. In this study, a cohort of 6355 men treated with at least 1 injection of T between January 1, 1997, and December 31, 2005, were matched to 19,065 T nonusers at a 1:3 ratio based on a composite MI prognostic score. A significant trend toward reduced MI rates with T administration was noted with increasing quartiles of risk.[156] For men in the highest prognostic MI risk quartile, treatment with T therapy was associated with significantly reduced risk (HR, 0.69; 95% CI, 0.53-0.92). Eisenberg et al[157] found no difference in 10-year mortality between T users and nonusers using an andrology database from Baylor College of Medicine.

Testosterone and Mortality

A substantial number of observational studies have investigated mortality as a function of serum T concentrations (Table 2).[62,63,65-67,70,89-105] The majority have reported a significant association of low T with mortality in community cohorts as well as in populations with medical conditions, including renal disease, diabetes, erectile dysfunction, and prostate cancer treated with androgen deprivation. A meta-analysis by Araujo et al,[158] which investigated 16,184 community-based participants with a mean follow-up of 9.7 years, found that low T levels were associated with an increased risk of CV-related mortality with an HR of 1.35 (95% CI, 1.13-1.62; *P*<.001). Androgen deprivation therapy has also been associated with increased CV events and mortality.[159] Although no study has documented a direct association between high serum T and mortality, Yeap et al[68] reported that the third quartile for serum T was associated with the lowest mortality and higher mortality occurred in men in the lowest 2 quartiles as well as the highest quartile.

Summary Statement. Low levels of TT, bioavailable T, and free T are associated with increased risk of mortality from all causes and CV disease.

TABLE 5. Association Between Endogenous Testosterone Level and Carotid Intima-Media Thickness[a]

Reference, year (type of study)	Sample size	Age range/ mean age (y)	Main findings
Negative (inverse) correlation			
De Pergola et al,[120] 2003 (CS)	127 Overweight or obese men	18-45/34	After adjustment for age, total body fat, central obesity, and fasting glucose concentration, carotid artery IMT was inversely associated with FT
Fu et al,[121] 2008 (CCS)	106 Men	50-70/64	FT was independently inversely associated with carotid artery IMT
Fukui et al,[122] 2003 (CS)	154 Diabetic men	62	FT was inversely associated with carotid artery IMT Free testosterone was inversely associated with carotid artery plaque score Carotid artery IMT and plaque score were significantly higher in patients with lower levels of FT
Mäkinen et al,[123] 2005 (CCS)	96 Nondiabetic men	40-70/57	After adjustment for age, BMI, blood pressure, smoking, and total cholesterol, TT was inversely associated with carotid artery IMT
Muller et al,[124] 2004 (CS)	195 Men	73-91/77	FT was inversely associated with mean progression of carotid artery IMT independent of age FT was inversely associated with mean progression of carotid artery IMT after adjustment for cardiovascular risk factors[b]
Soisson et al,[125] 2012 (CS)	354 Men	≥65	Analyses with and without adjustment for cardiovascular risk factors revealed that carotid IMT was inversely and significantly correlated with TT and bioavailable testosterone levels but not with SHBG and estradiol levels
Svartberg et al,[126] 2006 (CS)	1482 Men	25-84/60	After adjustment for age, smoking, physical activity, blood pressure, and lipid levels, TT was inversely associated with carotid artery IMT The association between TT and carotid artery IMT was not independent of BMI There was no association between FT and carotid artery IMT
Tsujimura et al,[127] 2012 (CS)	176 Men	≥40	A multivariate model adjusted for age, BMI, mean arterial pressure, and treatment for hypertension revealed a significant association between FT and carotid artery IMT Even after adjustment for other clinically relevant factors, the significant association between FT and carotid artery IMT was not attenuated After adjustment for all other clinically relevant factors, both univariate and multivariate models ascertained the stepwise association that an FT level of ≤10.0 pg/mL was significantly associated with carotid artery IMT
van den Beld et al,[128] 2003 (CS)	403 Men	73-94/77.8	After adjustment for age, serum TT was inversely related to carotid artery IMT
Vikan et al,[129] 2009 (CS)	2290 Men	55-74/66	After adjustment for age, systolic blood pressure, smoking, and use of lipid-lowering medications, TT was inversely associated with total carotid plaque area SHBG was not associated with changes in carotid artery IMT or plaque area
Positive correlation			
None identified			

[a]BMI = body mass index; CCS = case-control study; CS = cross-sectional study; FT = free testosterone; IMT = intima-media thickness; SHBG = sex hormone–binding globulin; TT = total testosterone.
[b]Cardiovascular risk factors included body mass index, waist-to-hip ratio, hypertension, diabetes, smoking, and serum cholesterol levels.

Level of Evidence. IIa

Testosterone and Incident CAD

Eleven studies have reported on the association of serum T concentrations and incident CAD (Table 3).[107-117] Six of these studies reported an association between CAD and lower T levels, and 4 showed no significant relationship. None found an association with higher serum T concentrations. However, Soisson et al[113] reported a J-shaped curve for a combined end point of MI and ischemic stroke, with the first and fifth T quintiles having greater event rates than the second quintile. Nevertheless, overall these data are congruent with the finding that men in the highest quartile of T (≥550 ng/dL) have a lower risk of CV events compared with men in the 3 lower quartiles (HR, 0.70; 95% CI, 0.56-0.88), even after adjustment for traditional CV risk factors and exclusion of men with known CV disease at baseline.[160]

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Summary Statement. Incident CAD is associated with lower levels of TT, bioavailable T, or free T.

Level of Evidence. IIa

Severity of CAD

Severity of CAD has also been investigated as a function of serum T concentrations (Table 4).[109,111,118,119] Four of 4 studies noted an inverse relationship between serum androgen concentrations and CAD severity, indicating that higher serum androgen concentrations are associated with reduced severity and lower androgen concentrations are associated with more severe disease.

Summary Statement. Severity of CAD is inversely correlated with serum concentrations of TT, bioavailable T, or free T.

Level of Evidence. IIa

Testosterone and Ischemic Stroke

Three studies have investigated the relationship of androgens to incident ischemic stroke. One found no relationship to serum T,[161] another found a significant association with low levels of TT and free T,[162] and a third found no significant association with TT but an inverse relationship with serum dihydrotestosterone concentrations.[105]

Summary Statement. The available evidence is insufficient to conclude whether there exists a relationship between ischemic stroke and serum androgens.

Level of Evidence. Not available.

Testosterone, Carotid Intima-Media Thickness, and Atherosclerosis

Carotid intima-media thickness has been found to be a marker for atherosclerosis. Ten studies have examined the association between endogenous serum T concentrations and carotid intima-media thickness. All 10 documented an inverse relationship with TT, free T, or bioavailable T (Table 5).[120-129] None has reported a significant relationship between higher T and increased carotid intima-media thickness. Hak et al[163] investigated 1032 men in the Rotterdam

TABLE 6. Changes in Parameters of Obesity With Testosterone Treatment vs Placebo

Reference, year	Testosterone preparation	Treatment duration	Change T group	Change P group	Net change T over P
Total fat mass (kg)					
Mårin et al,[130] 1993	Gel	9 mo	−1.8	0.6	−2.4
Snyder et al,[131] 1999	Patch	36 mo	−3.3	−1.3	−2.0
Kennyet al,[132] 2001	Patch	12 mo	−1.7	0.3	−2.0
Ferrando et al,[133] 2002	TE	6 mo	−3.6	0.3	−3.9
Boyanov et al,[134] 2003	Oral TU	3 mo	−1.65	−0.25	−1.4
Crawford et al,[135] 2003	Mixed esters	12 mo	−2.3	0.7	−3.0
Steidle et al,[136] 2003	Gel	3 mo	−0.8	−0.1	−0.7
	Patch	3 mo	−0.4	−0.1	−0.3
Wittert et al,[137] 2003	Oral TU	12 mo	−0.2	0.85	−1.05
Casaburi et al,[138] 2004					
No training	TE	10 wk	−1.01	−0.08	−0.93
Training	TE	10 wk	−1.41	−0.13	−1.28
Svartberg et al,[28] 2008	Inj TU	12 mo	−5.4	−0.6	−4.8
Allan et al,[139] 2008	Patch	12 mo	−0.5	0.1	−0.6
Emmelot-Vonk et al,[140] 2008	Oral TU	6 mo	−1.0	−0.1	−0.9
Srinivas-Shankar et al,[19] 2010	Gel	6 mo	−0.8	−0.3	−0.5
Visceral adipose tissue (kg)					
Mårin et al,[130] 1993	Gel	9 mo	−0.6	0.2	−0.8
Allan et al,[139] 2008	Patch	12 mo	−0.2	0.5	−0.7
Trunk fat (kg)					
Casaburi et al,[138] 2004					
No training	TE	10 wk	−0.55	0.34	−0.89
Training	TE	10 wk	−0.67	0.11	−0.78
Page et al,[21] 2005	TE	36 mo	−1.9	−0.4	−1.5
Allan et al,[139] 2008	Patch	12 mo	0.1	0.0	0.1
Visceral adipose tissue (cm^3)					
Svartberg et al,[28] 2008	Inj TU	12 mo	−38	−11	−27
Subcutaneous adipose tissue (kg)					
Mårin et al,[130] 1993	Gel	9 mo	−1.2	0.5	−1.7
Allan et al,[139] 2008	Patch	12 mo	−0.1	0.0	−0.1
Subcutaneous adipose tissue (cm^3)					
Svartberg et al,[28] 2008	Inj TU	12 mo	−49	−10	−39
Total adipose tissue (cm^3)					
Svartberg et al,[28] 2008	Inj TU	12 mo	−86	−27	−59
Right leg fat (kg)					
Page et al,[21] 2005	TE	36 mo	−0.9	0.1	−1.0
Percentage total body fat (%)					
Sih et al,[141] 1997	TC	12 mo	−1.9	19.3	−21.2
Boyanov et al,[134] 2003	Oral TU	3 mo	−3	−0.1	−2.9
Crawford et al,[135] 2003	Mixed esters	12 mo	−10.9	3.4	−14.3
Steidle et al,[136] 2003	Gel	3 mo	−1.2	−0.2	−1.0
	Patch	3 mo	−0.5	−0.2	−0.3
Casaburi et al,[138] 2004					
No training	TE	10 wk	−6	−0.1	−5.9
Training	TE	10 wk	−9.4	−2.2	−7.2
Page et al,[21] 2005	TE	36 mo	−17.0	1.0	−18.0
Kapoor et al,[142] 2007	Mixed esters	3 mo	−3.7	−1.5	−2.2

Continued on next page

TABLE 6. Continued

Reference, year	Testosterone preparation	Treatment duration	Change T group	Change P group	Net change T over P
Percentage total body fat (%), continued					
Kapoor et al,[143] 2006	Mixed esters	3 mo	−3.0	−1.8	−1.2
Svartberg et al,[28] 2008	Inj TU	12 mo	−18.9	−1.9	−17.0
Allan et al,[139] 2008	Patch	12 mo	−2.9	0.4	−3.3
Emmelot-Vonk et al,[140] 2008	Oral TU	6 mo	−4.7	0.0	−4.7
Aversa et al,[33] 2010	Inj TU	24 mo	−18.5	0.5	−19
Aversa et al,[144] 2010	Inj TU	12 mo	−18.4	0.6	−19.0
Waist circumference (cm)					
Mårin et al,[130] 1993	Gel	9 mo	−2.5	−0.6	−1.9
Kapoor et al,[142] 2007	Mixed esters	3 mo	−2.0	0.1	−2.1
Kapoor et al,[143] 2006	Mixed esters	3 mo	−1.6	NA	NA
Svartberg et al,[28] 2008	Inj TU	12 mo	−3.0	−1.0	−2.0
Heufelder et al,[34] 2009	Gel	12 mo	−14.6	−6.7	−7.9
Aversa et al,[33] 2010	Inj TU	24 mo	−8.5	−0.5	−8.0
Kalinchenko et al,[145] 2010	Inj TU	30 wk	−5.8	−1.5	−4.3
Aversa et al,[144] 2010	Inj TU	12 mo	−8.7	1.1	−9.7

Inj TU = parenteral testosterone undecanoate; Mixed esters = mixed parenteral testosterone esters; NA = not available; TC = parenteral testosterone cypionate; TE = parenteral testosterone enanthate; TU = testosterone undecanoate.

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study and found an inverse relationship between serum T and atherosclerosis of the abdominal aorta. Another study similarly found an inverse relationship between serum T and intima-media thickness of the thoracic aorta.[164]

In a placebo-controlled trial, Aversa et al[33] documented reduction in carotid intima-media thickness among T-deficient men, with a positive correlation between the magnitude of the increase in serum T with treatment and the magnitude of the reduction in intima-media thickness. In a separate study of severely obese hypogonadal men randomized to 54 weeks of diet and exercise alone vs diet and exercise plus T treatment with intramuscular injections of T undecanoate, T-treated men had significant improvements in cardiac ejection fraction, carotid intima-media thickness, endothelial function, and epicardial fat, the lattermost being associated with CAD.[165] Cessation of T therapy resulted in return of CV factors to baseline 24 weeks later. These results suggest a direct contribution of T therapy to CV health in T-deficient men.[165]

Summary Statement. Carotid intima-media thickness and/or carotid plaque volume are inversely correlated with serum concentrations of TT, bioavailable T, or free T.

Level of Evidence. IIa

Effects of Testosterone Therapy on Fat, Muscle, and Obesity

More than 2 dozen RCTs and a similar number of observational studies have consistently revealed that T therapy in T-deficient men results in increased lean and muscle mass, improved strength, decreased total and visceral fat, decreased percent body fat, reduced body mass index, and decreased waist circumference (Table 6).[19,21,28,33,34,130-145] This result appears consistent and reliable over a wide range of investigational tools and measures. There are no studies documenting increased fat or obesity as a result of T therapy.

Consistent with these results, men undergoing androgen deprivation therapy for advanced prostate cancer have increased fat mass, decreased lean mass, and increased waist circumference[166-168] and an increased risk of incident diabetes and CV disease.[11] An experimental trial in humans in which endogenous T was suppressed by luteinizing hormone–releasing hormone followed by graded doses of T gel with or without an aromatase inhibitor revealed that improvements in fat and lean mass corresponded to serum T dose and concentration.[169] Estradiol concentrations were unrelated to lean mass but contributed to reductions in fat mass.[169] Studies with dihydrotestosterone found similar improvements in lean and fat mass.[170]

Summary Statement. Testosterone therapy is associated with a significant reduction in obesity and fat mass.

Level of Evidence. Ib

Diabetes, Metabolic Syndrome, Glycemic Control, Lipids, and Inflammatory Markers

Longitudinal population-based studies have revealed that men with the lowest quartile of endogenous serum T concentrations are at double the risk of subsequent development of new-onset diabetes and the metabolic syndrome.[171-173] In addition, studies have found that as many as 40% to 50% of diabetic men are T deficient.[174-176] In 4 placebo-controlled or

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parallel open-label studies performed for 3 to 12 months in hypogonadal men with metabolic syndrome or diabetes, insulin resistance improved in all 4 studies[32,34,143,145] and fasting glucose and HbA_{1c} were improved in 3[32,34,143] and unchanged in 1.[145] Several meta-analyses investigating the impact of T treatment on lipids revealed relatively small but significant reductions in total cholesterol, HDL cholesterol, and low-density lipoprotein cholesterol, with no effect on triglycerides (Table 7).[87,147,148]

Studies of glycemic control generally found improvement in HbA_{1c} and reduced insulin resistance in men who received T therapy. None showed worsening of glycemic control or increased insulin resistance (Table 8).[32,34,143,145,149,150] With regard to inflammatory markers, several studies revealed reduction in C-reactive protein or highly-specific C-reactive protein as well as tumor necrosis factor α, whereas others found no change. None reported increased inflammatory markers (Table 9).[33,142,145,151-155]

Summary Statement. Testosterone therapy is associated with small decreases in serum concentrations of total cholesterol, HDL cholesterol, and low-density lipoprotein cholesterol. No clear effect on triglycerides has been documented.

Level of Evidence. IIa

Summary Statement. Testosterone therapy is associated with a decrease in serum glucose concentrations, HbA_{1c}, and insulin resistance in diabetic and prediabetic men.

Level of Evidence. Ia

Summary Statement. Testosterone therapy is associated with an inconsistent reduction in serum concentrations of inflammatory markers.

Level of Evidence. Ib

Testosterone in Men With Angina

Three randomized, placebo-controlled studies[177-179] investigated the effect of T administration in men with known angina by treadmill testing, using time to 1-mm ST-segment depression as an indication of myocardial ischemia. In 2 of these studies, T was administered intravenously 30 minutes before treadmill testing,[178,179] and in the third, T was administered via topical patch.[177] An increase in time to ischemia was noted in all 3 trials.[177-179] These results are consistent with those of other studies in humans in which T administration has been found to cause vasodilation of the coronary[180] and brachial[181,182] arteries and animal studies that have documented vasodilation of the coronary arteries in rabbit,[183] dog,[184] and pig[185] models.

TABLE 7. Meta-analyses Regarding the Effects of Testosterone Administration on Lipid Concentrations

Reference, year	Main findings
Haddad et al,[87] 2007	In patients with low levels of baseline testosterone, exogenous testosterone did not affect any of the lipid subfractions In patients with normal levels of baseline testosterone, exogenous testosterone resulted in a significant decrease in total cholesterol levels In patients with normal levels of baseline testosterone, exogenous testosterone did not affect the levels of LDL, HDL, or triglyceride levels In patients with chronic disease or in those on glucocorticoid therapy, exogenous testosterone resulted in a small decrease in levels of HDL In patients with chronic disease or in those on glucocorticoid therapy, exogenous testosterone did not affect the levels of total cholesterol, LDL, or triglycerides
Isidori et al,[147] 2005	Exogenous testosterone resulted in reduced levels of total cholesterol The improvement in total cholesterol was more significant for patients with reduced levels of baseline testosterone No significant change in total cholesterol in patients with baseline testosterone of >10 nmol/L Exogenous testosterone did not affect levels of LDL or HDL The effect of testosterone replacement therapy on triglyceride levels was not examined in this meta-analysis
Whitsel et al,[148] 2001	Exogenous testosterone resulted in small but significant reduction in the levels of total cholesterol, LDL, and HDL Exogenous testosterone did not affect triglyceride levels

HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.
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Summary Statement. Testosterone therapy improves time to onset of symptomatic angina with exercise.

Level of Evidence. Ib

Testosterone and Congestive Heart Failure

An association between low levels of TT and/or free T has been reported for mortality due to congestive heart failure (CHF).[186,187] Four

TABLE 8. Effects of Testosterone Therapy on Indices of Glycemic Control[a]

Reference, year (study type)	Testosterone formulation used	Sample size	End points measured	Main findings
Studies documenting a beneficial effect of testosterone therapy on indices of glycemic control				
Corona et al,[149] 2011 (meta-analysis, 37 studies)	Various formulations (meta-analysis)	1822 Diabetic men and 10,009 nondiabetic men (meta-analysis)	HbA_{1c}, fasting plasma glucose, triglycerides	HgA_{1c} decreased by 0.76% with TRT Fasting plasma glucose decreased by 1.18 mmol/L with TRT TG decreased by 0.67 with TRT
Heufelder et al,[34] 2009 (SBRCT)	TD[b]	16 Hypogonadal men with T2DM	HOMA-IR, HbA_{1c}, fasting plasma glucose	HOMA-IR decreased by 4.2 in TRT group ($P<.001$) HbA_{1c} decreased by about 1% after 13 wk in TRT group ($P<.001$) HbA_{1c} decreased by about 1.5% after 52 wk in TRT group ($P<.001$) Fasting plasma glucose decreased by 1.9 mmol/L in TRT group ($P=.062$)
Jones et al,[32] 2011 (DBRCT)	TD[c]	220 Hypogonadal men with T2DM and/or MetS	HOMA-IR, HbA_{1c}, body composition	HOMA-IR decreased by 15.2% after 6 mo with TRT ($P=.018$) HOMA-IR decreased by 16.4% after 12 mo with TRT ($P=.006$) HbA_{1c} decreased by 0.44% after 9 mo with TRT ($P=.035$)
Kalinchenko et al,[145] 2011 (DBRCT)	IM[d]	113 Hypogonadal men with MetS	HOMA-IR, fasting plasma glucose, BMI, WC, waist-to-hip ratio	HOMA-IR decreased by 1.49 in TRT group (overall $P=.04$) No significant change in fasting plasma glucose in TRT group Significant reduction in BMI, weight, waist-to-hip ratio, hip circumference, and WC in TRT group ($P<.001$ for all except for waist-to-hip ratio; $P=.04$ for waist-to-hip ratio)
Kapoor et al,[143] 2006 (DBPCC)	IM[e]	24 Hypogonadal men with T2DM	HOMA-IR, HgA_{1c}, fasting plasma glucose	HOMA-IR decreased by 1.73 in TRT group ($P=.02$) HgA_{1c} decreased by 0.37% in TRT group ($P=.03$) Fasting plasma glucose decreased by 1.58 mmol/L in TRT group ($P=.03$)
Malkin et al,[150] 2007 (SBPCC)	IM[f]	13 Men with CHF and no T2DM	HOMA-IR, fasting plasma glucose, glucose tolerance, body composition	HOMA-IR decreased by 1.9 in TRT ($P=.03$) Fasting plasma glucose decreased by 0.61 mmol/L in TRT ($P=.03$) Total body mass increased by 1.5 kg in TRT ($P=.008$) Percent body fat decreased by 0.8% in TRT ($P=.02$)
Studies documenting a detrimental effect of testosterone therapy on indices of glycemic control				
None identified				

[a]BMI = body mass index; CHF = congestive heart failure; DBPCC = double-blind placebo-controlled crossover study; DBRCT = double-blind randomized controlled trial; HgA_{1c} = hemoglobin A_{1c}; HOMA-IR = homeostatic model of insulin resistance; IM = intramuscular; MetS = metabolic syndrome; SBPCC = single-blind placebo-controlled crossover study; SBRCT = single-blind randomized controlled trial; T2DM = type 2 diabetes mellitus; T = transdermal; TG = triglycerides; TRT = testosterone replacement therapy; WC = waist circumference.

[b]Heufelder et al[34] administered testosterone gel, 50 mg TD, for 52 wk.

[c]Jones et al[32] administered testosterone 2% gel, 3-g metered dose (60 mg testosterone), for 12 mo.

[d]Kalinchenko et al[145] administered testosterone undecanoate, 1000 mg IM, given at baseline and after 6 and 18 wk.

[e]Kapoor et al[143] administered testosterone, 200 mg IM once every 2 wk for 3 mo.

[f]Malkin et al[150] administered Sustanon 250 (testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/mL) IM injection. Two IM injections were given 2 wk apart.

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RCTs[188-191] involving T therapy or placebo in individuals with CHF were analyzed in a meta-analysis by Toma et al[192] in 2012. Three of the RCTs studied men and 1 studied women. Individuals who received T therapy had significant functional improvements in the 6-minute walk test, incremental shuttle walk test, and/or peak oxygen consumption.[188-191] Overall exercise capacity was increased compared with placebo. No significant adverse CV events were noted.[188-191] Two additional, more recent placebo-controlled trials have confirmed beneficial functional results of T therapy in men with CHF.[80,81]

Summary Statement. Testosterone therapy improves exercise capacity and peak oxygen consumption in men with symptomatic CHF as defined by New York Heart Association functional class II.

Level of Evidence. Ia

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TABLE 9. Effects of Testosterone Therapy on Markers of Inflammation[a]

Reference, year (type of study)	Sample size	Testosterone formulation used	Duration of TTh	Main outcomes measured	Major findings
Studies documenting beneficial effect of testosterone therapy on markers of inflammation					
Aversa et al,[33] 2010 (DBRCT)	50 Men (40 received TRT and 10 received placebo)	Testosterone undecanoate, 1000 mg IM once every 12 wk	24 mo	hsCRP, HOMA-IR, CIMT	Significant reduction in hsCRP with TTh Significant reduction in HOMA-IR with TTh Significant reduction in CIMT with TTh
Guler et al,[151] 2006 (CCS)	41 Men (25 received TRT and 16 received placebo)	Sustanon 250 IM once weekly[b]	3 wk	hsCRP, IL-6, TNF-α	Significant reduction in hsCRP with TTh Significant reduction in IL-6 with TTh Significant increase in TNF-α in both groups
Kalinchenko et al,[145] 2010 (DBRCT)	171 Men (105 received TRT and 65 received placebo)	Testosterone undecanoate, 1000 mg IM	Given at baseline and after 6 and 18 wk	CRP, IL-1β, IL-6, IL-10, TNF-α	Significant reduction in CRP with TTh Significant reduction in TNF-α with TTh Significant reduction in IL-1β with TTh
Kapoor et al,[142] 2007 (DBPCC)	20 Men	Sustanon 200 IM once every 2 wk[c]	3 mo	CRP, IL-6, TNF-α, leptin, adiponectin, resistin	No significant change in levels of CRP with TTh No significant change in levels of TNF-α with TTh No significant change in levels of IL-6 with TTh
Malkin et al,[152] 2004 (SBRCT)	27 Men	Sustanon 100 IM once every 2 wk[d]	1 mo	TNF-α, IL-1β, IL-10	Significant reduction in TNF-α with TTh Significant reduction in IL-1β with TTh Significant increase in IL-10 with TTh
Studies documenting no effect of testosterone therapy on markers of inflammation					
Nakhai-Pour et al,[153] 2007(DBRCT)	237 Men	Testosterone undecanoate, 160 mg PO daily	26 wk	hsCRP	No significant change in levels of hsCRP with TTh
Ng et al,[154] 2002 (CCS)	33 Men (16 received TTh and 17 were controls)	Dihydrotestosterone, 70 mg TD daily	3 mo	hsCRP, sIL-6, sICAM-1, sVCAM-1	No significant change in levels of hsCRP with TTh No significant change in sICAM-1 with TTh No significant change in sVCAM-1 with TTh
Singh et al,[155] 2002 (DBRCT)	61 Men	Patients randomized to 1 of 5 treatment groups, each group receiving varying doses of testosterone enanthate[e]	20 wk	Total cholesterol, LDL, HDL, VLDL, TG, CRP, apolipoprotein B, apolipoprotein C-III	No significant correlation between endogenous testosterone levels and levels of CRP No change in CRP levels with T therapy, regardless of the testosterone dose
Studies documenting negative effect of testosterone therapy on markers of inflammation					
None identified					

[a]CCS = case-control study; CIMT = carotid artery intima-media thickness; CRP = C-reactive protein; DBPCC = double-blind placebo-controlled crossover study; DBRCT = double-blind randomized controlled trial; HDL = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model of insulin resistance; hsCRP = high-sensitivity CRP; IL = interleukin; IM = intramuscular; LDL = low-density lipoprotein cholesterol; PO = by mouth; SBRCT = single-blind randomized controlled study; sICAM-1 = soluble intracellular adhesion molecule 1; sIL = soluble IL; sVCAM-1 = soluble vascular cell adhesion molecule 1; TD = transdermal; TG = triglycerides; TNF-α = tumor necrosis factor α; TRT = testosterone replacement therapy; TTh = testosterone therapy; VLDL = very low-density lipoprotein cholesterol.

[b]Sustanon 250 contains 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate.

[c]Sustanon 200 contains 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate.

[d]Sustanon 100 contains 20 mg testosterone propionate, 40 mg testosterone phenylpropionate, and 40 mg testosterone isocaproate.

[e]Singh et al[155] study: group 1 (n=12) received testosterone enanthate, 25 mg IM weekly; group 2 (n=12) received testosterone enanthate, 50 mg IM weekly; group 3 (n=12) received testosterone enanthate, 125 mg IM weekly; group 4 (n=11) received testosterone enanthate, 300 mg IM weekly; and group 5 (n=14) received testosterone enanthate, 600 mg IM weekly.

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TABLE 10. Summary Statements

Testosterone and cardiovascular risk summary assessments	Evidence level
Low levels of total, bioavailable, and free testosterone are associated with increased risk of mortality from all causes and CV disease	IIa
Incident CAD is associated with lower levels of total, bioavailable, or free testosterone	IIa
Severity of CAD is inversely correlated with serum concentrations of total, bioavailable, or free testosterone	IIa
The available evidence is insufficient to conclude whether there exists a relationship between ischemic stroke and serum androgens	NA
Carotid intima-media thickness and/or carotid plaque volume are inversely correlated with serum concentrations of total, bioavailable, or free testosterone	IIa
Testosterone therapy is associated with a significant reduction in obesity and fat mass	Ib
Testosterone therapy is associated with small decreases in serum concentrations of total cholesterol, HDL, and LDL. No clear effect on triglycerides has been documented	IIa
Testosterone therapy is associated with a decrease in serum glucose concentrations, HbA_{1c}, and insulin resistance in diabetic and prediabetic men	Ia
Testosterone therapy is associated with an inconsistent reduction in serum concentrations of inflammatory markers	Ib
Testosterone therapy improves time to onset of symptomatic angina with exercise	Ib
Testosterone therapy improves exercise capacity and peak oxygen consumption in men with symptomatic congestive heart failure as defined by NYHA functional class II	Ia

CAD = coronary artery disease; CV = cardiovascular; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NA = not available; NYHA = New York Heart Association.

DISCUSSION

A large body of scientific and clinical evidence accumulated over several decades has revealed a broad and robust relationship between serum T and CV health. Specifically, low T levels are strongly associated with increased mortality in multiple studies, as well as with atherosclerosis, incident CAD, and severity of CAD. Men with relatively low endogenous T concentrations are at increased risk of subsequent development of diabetes and the metabolic syndrome.[163,193,194] Creation of a T-deficient state, via androgen deprivation for medical indications or experimentally, results in worsening of CV risk factors such as obesity, fat mass, and insulin resistance.[20,195] Conversely, T therapy in T-deficient men increases lean mass,[14,19-22,28,30,139,150,196-202] reduces fat mass,[14,17-28,30,33-35,139,143-145,196,198,201-211] improves insulin resistance,[32-34,143,150,188,196-198,201,204,206,207] decreases carotid intima-media thickness,[33] and reduces risk of mortality and improves survival.[69,70]

It was therefore surprising when 2 recently published studies suggested increased CV risks associated with T prescriptions.[1,2] Although these 2 studies gained enormous media attention and prompted an FDA safety review, neither appears to provide credible evidence of increased risk. Only 2 additional studies are generally cited as providing support for the concern that T therapy may be associated with increased CV risk, each with important limitations that preclude drawing conclusions of increased CV risk.[75,76] These studies have undergone serious criticism in the scientific literature.[72,73,77,212] The FDA itself has provided commentary on these studies, concluding that none provide compelling evidence of increased CV risk.[74] However, final comments by the FDA following the report based on an advisory committee meeting in September 2014 have not yet been published.

These negative reports have had a chilling effect on the medical community with regard to the treatment of men with TD, and the concern regarding CV risks has fueled a wide variety of complaints and opinions on the merits of T therapy in general. It is anticipated that further clarity will be achieved with reporting of results from the Testosterone Trials,[213] the largest prospective T trial to date, in which approximately 800 men were followed for 12 months. This trial may provide suggestive results regarding CV risk markers, but is underpowered for a comparison of CV outcomes in T-treated vs placebo-treated men. Results are anticipated in 2015.

In the meantime, clinicians must make decisions based on the best available evidence. One potential benefit of the increased attention to this issue is recognition of the strong positive relationship between serum androgens and CV health. This relationship is not widely recognized. With regard to the strong association of low T values and mortality in observational studies, it is possible that a low T concentration merely serves as a surrogate marker for poor health, with poor prognosis. Although nearly all studies attempted to adjust for relevant confounders, it may be impossible to adjust for all known and unknown confounders. Nonetheless, the consistent improvements in CV risk factors seen with T therapy in T-deficient men do provide a plausible biological mechanism whereby normal

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serum T concentrations favor CV health and support the perspective that T therapy may help establish and maintain CV health in T-deficient men.

CONCLUSION

In the absence of large, prospective, placebo-controlled studies of several years' duration, it is impossible to provide any definitive comment on the absolute safety or risk of T therapy with regard to CV outcomes. However, review of the literature clearly reveals a strong relationship between higher serum T concentrations, endogenous or via T therapy, as beneficial for reduction of CV disease and CV risk factors. Public health may be harmed not only by inadequate appreciation of an actual risk but also by the failure to offer beneficial treatment for a medical condition because of *false* claims of risk concerns. On the basis of the current state of evidence, placing restrictions on the appropriate use of T therapy for T-deficient men is likely to result in compromise of public health and a substantially increased future financial burden on the US health care system.

In summary, we find no scientific basis for the suggestion that T therapy increases CV risk. In fact, as of this date, we are unaware of *any* compelling evidence that T therapy is associated with increased CV risk. On the contrary, the weight of evidence accumulated by researchers around the world over several decades clearly indicates that higher levels of T are associated with amelioration of CV risk factors and reduced risk of mortality.

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Abbreviations and Acronyms: **CAD** = coronary artery disease; **CHF** = congestive heart failure; **CV** = cardiovascular; **FDA** = Food and Drug Administration; **HbA_{1c}** = hemoglobin A_{1c}; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **MACE** = major adverse cardiac events; **MI** = myocardial infarction; **PDE5i** = phosphodiesterase type 5 inhibitor; **RCT** = randomized controlled trial; **SHBG** = sex hormone–binding globulin; **T** = testosterone; **TD** = T deficiency; **TT** = total T

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