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SPECIAL ARTICLE

Androgen Society Position Paper on Cardiovascular Risk With Testosterone Therapy

Abraham Morgentaler, MD; Sandeep Dhindsa, MD; Adrian S. Dobs, MD; Geoff Hackett, MD; T. Hugh Jones, MD; Robert A. Kloner, MD; Martin Miner, MD; Michael Zitzmann, MD, PhD; and Abdulmaged M. Traish, PhD

Abstract

The Androgen Society is an international, multidisciplinary medical organization committed to advancing research and education in the field of testosterone deficiency and testosterone therapy (TTh). This position paper is written in response to results of the TRAVERSE study, published in June 2023, which reported no increased risk of major adverse cardiovascular events (MACE) in men who received TTh compared with placebo.

In 2013-2014, 2 observational studies reported increased cardiovascular (CV) risks with TTh and received wide media attention. Despite strong criticism of those 2 studies, in 2015, the Food and Drug Administration added a CV warning to testosterone product labels and required pharmaceutical companies to perform a CV safety study, which became the TRAVERSE trial.

TRAVERSE enrolled 5246 men at high risk for MACE based on existing heart disease or multiple risk factors. Participants were randomized to daily testosterone gel or placebo gel, with a mean follow-up of 33 months. Results revealed no greater risk of MACE (myocardial infarction, stroke, or CV death) or venothrombotic events in men who received TTh compared with placebo.

Review of the prior literature reveals near uniformity of studies reporting no increased MACE with TTh. This includes 2 additional large randomized controlled trials, multiple smaller randomized controlled trials, several large observational studies, and 19 meta-analyses.

In view of these findings, it is the position of the Androgen Society that it has now been conclusively determined that TTh is not associated with increased risks of heart attack, stroke, or CV death.

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BACKGROUND

Concerns about cardiovascular (CV) risks with testosterone therapy (TTh) are a recent phenomenon. Historically, TTh was used to treat vascular disease.[1-11] The concern that TTh might be associated with increased CV risk first came to attention in 2010 with incidental reporting of a wide range of events broadly categorized as "cardiovascular" during a randomized controlled trial (RCT) designed to investigate benefits and risks of TTh in a frail population with limited mobility.[12] In 2014, a media storm followed publication of 2 observational studies that suggested possible increased risk of myocardial infarction (MI), stroke, or death with TTh.[13,14]

In the face of numerous media stories and widespread advertising by plaintiff legal firms in the United States through television, radio, and print to recruit individuals who may have experienced a stroke or MI while taking a testosterone product, the Food and Drug Administration (FDA) convened an advisory board meeting. That meeting resulted in the FDA's adding a warning label about possible CV risk to testosterone products in 2015.[15] The FDA also mandated that

From the Division of Urology, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (A.M.); Division of Endocrinology and Metabolism, St Louis University, St Louis, MO (S.D.); Division of Endocrinology, Diabetes and Metabolism, The Johns Hopkins University School of Medicine, Baltimore, MD (A.S.D.); Aston University Medical School, Birmingham, United Kingdom (G.H.);

Affiliations continued at the end of this article.

commercial testosterone drug manufacturers perform a large cardiovascular study at their own cost. These types of studies are large, multicenter, multiyear, rigorously performed RCTs in populations at high risk for major adverse cardiovascular events (MACE). This became the TRAVERSE study, with CV results published in 2023, finding no increased MACE risk with TTh compared with placebo.

The concerns about CV risk arose despite a wealth of prior evidence indicating that *low* levels of testosterone were associated with poor CV health and known risk factors for CV disease, such as obesity, diabetes, and the metabolic syndrome.[16-21] Although multiple comprehensive reviews of possible CV risks with TTh have concluded that the evidence overwhelmingly indicates no increased CV risk and several studies have found a variety of CV benefits with TTh, the publication of TRAVERSE results represents a watershed moment in that it provides a definitive and conclusive answer to this clinical concern.

Observational studies have reported that testosterone deficiency is associated with increased mortality rates in men older than 40 years.[21-24] These studies indicate that men with testosterone deficiency may have up to twice the risk of death compared with men with normal testosterone levels.[22,25] For example, one of these reported that mortality rates during an average 4.3-year period were 20.1%, 24.6%, and 34.9% for those with normal, equivocal, and low testosterone levels, respectively.[22]

A larger, longer-term study involving 2314 men aged 40 to 79 years reported that every 173 ng/dL increase in serum testosterone level was associated with a 21% lower risk of all-cause mortality.[21] This finding, which controlled for various factors such as age, body mass index, and blood pressure, excluded deaths within the first 2 years of follow-up.

The Rancho Bernardo study, involving 794 men aged 50 to 91 years, found an inverse relationship between total and bioavailable testosterone levels and the risk of death. Low total testosterone concentration also predicted a higher risk of death due to CV and respiratory diseases.[23] The most recent analysis of the UK Biobank data also suggested that low testosterone concentration is associated with increased mortality.[24] In summary, observational studies have consistently found significant associations between testosterone deficiency and increased mortality rates, particularly related to CV and all-cause mortality.

Observational studies (reviewed by Morgentaler et al[19] in 2015) have consistently found no credible evidence supporting an increased risk of CV disease with TTh. In addition, TTh has shown significant improvements in lipid profiles, blood glucose levels, and blood pressure, indicating potential benefits for individuals with metabolic syndrome. For instance, in a nested testosterone registry, Saad et al[26] conducted subgroup analyses of patients aged 65 years or younger and patients older than 65 years, finding that TTh is equally effective in improving anthropometric parameters and metabolic function in both age groups, contrary to previous assumptions about age-related differences. These findings provided additional reassuring evidence that TTh does not pose an increased risk of CV disease and may provide benefits for metabolic health.

In the Osteoporotic Fractures in Men (MrOS) study in Sweden, involving 2416 men aged 69 to 81 years, lower baseline testosterone concentrations were found to be linked with a higher risk of CV events.[27] The Health in Men Study (HIMS) involving 3690 men aged 70 to 89 years revealed that lower baseline testosterone concentrations in men were associated with an increased risk of stroke but not MI.[28]

Last, a prospective follow-up cohort study performed by Malkin et al[29] of 930 consecutive men undergoing coronary angiography with established coronary disease and observed for a mean of 6.9±2.1 years found that mortality was greater in men with bioavailable testosterone below 2.6 nmol/L compared with men with normal values (21% vs 12%, respectively).

Several of these studies suggest that normal circulating testosterone levels may

be a marker of good health, and more specifically, higher testosterone concentrations are associated with less body fat and more lean muscle mass. Both of these are markers of longevity.

STUDIES SUGGESTING INCREASED CV RISK

Of dozens of studies that have directly investigated TTh and CV risk or mortality, only 5 have suggested increased risk (Table 1).[12-14,30,31] The strength of evidence supporting increased CV risk was weak for each of these. We describe each of these in detail.

Basaria et al, 2010[12]

In this RCT, 209 frail elderly hypogonadal men (mean age, 74 years) with mobility limitations were assigned daily testosterone gel or placebo gel for 6 months.[12] The trial was designed to evaluate the change in muscle strength with TTh. However, the trial was discontinued early because of reports of greater numbers of CV event—related adverse events in the testosterone arm compared with the placebo group (23 events vs 5, respectively).

This study was not designed to investigate CV events, and no criteria for identifying CV events were set out in advance. Most events were of questionable clinical significance, including instances of peripheral edema, hypertension, tachycardia, premature ventricular contractions, and nonspecific electrocardiographic changes. Four MACE were noted, all within the testosterone arm. As the authors themselves noted, caution must be exercised in dealing with such small numbers. This is underscored by results of a similar RCT in a similar population in the same year, which reported 2 MACE, both in the placebo arm.[32] This study by Basaria et al[12] opened the door to questions about the CV safety of TTh. However, it should be evident that this study could not adequately ascertain CV risk, and the numbers of MACE were too few to be a reliable indicator of risk.

Vigen et al, 2013[13]

This 2013 retrospective observational study precipitated a major media firestorm that created the public perception that TTh is associated with serious CV risk. Investigators examined cumulative rates of mortality, MI, and stroke in men with low testosterone levels after coronary angiography, some of whom had received a testosterone prescription and others who had not.[13] The authors reported an increased absolute rate of events and greater event rate during 3 years for men who had received a testosterone prescription.

Unfortunately, the authors erred in their calculation of absolute rate of events. In fact, the absolute rate of adverse events was lower by half in the group receiving testosterone (10.1%) compared with the untreated group (21.2%). The authors subsequently admitted to additional data errors, such as inclusion of 9% women in the all-male data set. The study underwent 2 published corrections.[33,34] After these various corrections and errors, 29 medical societies called for retraction of this article.[35] Several letters to the editor and other articles also criticized the validity of the evidence presented in this study.[35-49] The FDA itself commented that "it is challenging to attribute the reported findings to testosterone treatment."[50] The lack of reliable data in this study makes it a particularly weak source of evidence in favor of increased MACE with TTh.

Finkle et al, 2014[14]

This study was published shortly after the study by Vigen et al,[13] and this timing appeared to confirm the credibility of purported CV concerns with TTh. This was a retrospective observational study based on insurance claims data, with information limited to diagnosis codes, procedure codes, and prescription data.[14] It compared rates of nonfatal MIs within the first 90 days of filling the testosterone prescription with the rates of nonfatal MI during the previous 12 months before receiving the prescription. The authors reported a higher rate of nonfatal MI after the testosterone prescription than before the prescription.

The key flaw in this study is that the 12-month period before receiving a testosterone prescription and the 3-month period after the prescription are not comparable. Because

TABLE 1. Studies Suggesting Testosterone Therapy Is Associated With Increased Risk of Cardiovascular Disease

Reference, year	Aim of study	Study results	Comments and concerns
Basaria et al, 2010[12]	This randomized controlled study was designed to determine the effects of TTh vs placebo on improvements in physical strength, including leg-press and chest-press strength, and in stair climbing while carrying a load in men with limited mobility and a high prevalence of chronic diseases.	Study population: 209 men aged 65 years and older; mean age, 74 years; serum T level <350 ng/dL or free T <50 pg/mL required. Compared with the placebo group, the T group had significantly greater improvements in leg-press and chest-press strength and in stair climbing while carrying a load. A total of 23 participants in the T group compared with 5 in the placebo group had CV event–related adverse events.	○ Study not designed to investigate CV risks; events were not adjudicated ○ Trial terminated early ○ CV events: 23 T arm vs 5 placebo. Most "events" were of uncertain significance (eg, pedal edema, palpitations, nonspecific electrocardiographic changes). ○ 4 MACE: 2 MI, 1 stroke, 1 death, all in the T group ○ Most CV events were self-reported by patients or by outside physicians, ie, not determined by study investigators. ○ Number of MACE was small. A similar study in a similar population reported 2 MACE, both in placebo arm.[32] ○ Authors' comments about CV event results: "The cardiovascular adverse events reported in the TOM trial were diverse and may have variable clinical importance. 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."
Vigen et al, 2013[13]	The aim of this retrospective study was to assess the association between TTh and MACE, consisting of cumulative all-cause mortality, MI, and ischemic stroke among male veterans with low T levels who underwent coronary angiography and to determine whether this association is modified by underlying coronary artery disease.	Study population: 8709 men with a total T level <300 ng/dL; 1223 patients started TTh a median of 531 days after coronary angiography. Of 7486 patients not receiving T therapy, 681 died, 420 had MIs, and 486 had strokes. Of 1223 patients receiving TTh, 67 died, 23 had MIs, and 33 had strokes. At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no-T group vs 25.7% in the TTh group, with an absolute risk difference of 5.8% (95% CI, −1.4% to 13.1%).	○ Publication of the original article stated in the abstract and text that the absolute rate of events was higher in the group that received TTh at 25.7% compared with 19.9% in the no-T group. This result appeared prominently in the accompanying editorial and in media reports but was incorrect. ○ The correct absolute rate of events showed that the T group had a lower rate of MACE by half at 10.1% compared with 21.2% for the no-T group. One week after publication, the article was corrected, replacing the term "absolute rate of events" with "Kaplan-Meier estimated cumulative percentage of events." ○ This was the first publication to report results using the statistical methodology called stabilized inverse probability of treatment weighting, adjusting in this case for 52 variables. One year earlier, the senior author had indicated that the strengths and weaknesses of this methodology were not yet adequately understood. ○ The article underwent 2 published corrections.

Continued on next page

TABLE 1. Continued

Reference, year	Aim of study	Study results	Comments and concerns
			○ Study design inappropriately excluded >1000 individuals who suffered stroke/MI from the non-T arm and should have been included in the analysis. ○ A second published correction revised this number downward and noted also that review of this population included 9% women in the "all-male" study population. ○ Twenty-nine medical societies petitioned the publisher to retract the article based on results not being "credible" in light of these failures.
Xu et al, 2013[30]	This study was designed to assess the effect of TTh on CV events using a meta-analysis of data from randomized clinical trials.	The authors analyzed 27 trials involving 2994 men who experienced 180 adverse events they deemed CV in nature. They reported that TTh increased the risk of a CV event (odds ratio, 1.54; 95% CI, 1.09-2.18). The effect of TTh varied with source of funding (*P* value for interaction, .03) but not with baseline T level (*P* value for interaction, .7).	○ This is the only meta-analysis of 19 such studies to report increased CV risk with TTh. ○ Number of events used in this study analysis did not match numbers from original published studies. ○ The authors included the 1986 Copenhagen study, in which investigators used their own formulation of oral T (never commercially available) in men with cirrhosis, delivered at extremely high supraphysiologic doses 4× the upper limit of normal. ○ Two component studies with incorrect values for adverse events accounted for 46% of all events in this study. ○ Unreliable data acquisition and inclusion of questionable studies explain the contradictory results of this meta-analysis vs all others.
Finkle et al, 2014[14]	This retrospective observational study was designed to evaluate whether T prescriptions might increase the risk of acute nonfatal MI and whether this effect might be particularly strong in men with preexisting cardiac disease. Investigators compared MI rates in the 3 months after receipt of a T prescription with the 12 months before the prescription.	Data were derived from a US commercial insurance database. Study population was composed of 55,593 men who had received a T prescription. The authors reported the rate ratio for post/pre prescription for T was 1.36 (1.03-1.81). In men aged 65 years and older, the rate ratio was 2.19 (1.27-3.77). A similar analysis for a comparison population that received a prescription for a phosphodiesterase type 5 inhibitor showed no increase in the post/pre rate for nonfatal MI.	○ This study inappropriately compared rates of MI during 2 periods that are not comparable. One was a naturally occurring rate of MI, and the other was determined by prescribing decisions by health care providers. ○ No laboratory data were presented to confirm the diagnosis of hypogonadism or to assess whether patients demonstrated continued use of T. ○ No adequate controls

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TABLE 1. Continued

Reference, year	Aim of study	Study results	Comments and concerns
Budoff et al, 2017[31]	This randomized controlled study was nested within the T Trials and tested the hypothesis that T treatment of older men with low circulating T levels reduces progression of noncalcified coronary artery plaque volume, as determined by coronary computed tomography angiography.	In this trial, 138 completed the study; 73 were treated with T, and 65 men received placebo. At baseline,70 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units, reflecting severe atherosclerosis. At 12 months, the T-treated group demonstrated greater increase in noncalcified plaque volume from baseline compared with placebo. Median volume rose in the T group from 204 mm^3 to 232 mm^3 and with a mean change of 40 mm^3 (95% CI, 23-56 mm^3). The placebo group rose from median of 317 mm^3 to 325 mm^3 with mean change of 4 mm^3 (95% CI, −14 to 22 mm^3). The estimated difference between groups was 41 mm^3 (95% CI, 14-67 mm^3; P=.003). A secondary end point of change in total plaque volume was also significantly greater in the T group. There was no significant change in calcium scores for either group. No MACE occurred in either group.	○ A major concern in the interpretation of this study is the imbalance of the baseline burden of noncalcified plaque between groups, raising questions as to whether the groups are comparable. Median plaque volume was >50% greater in the placebo group vs the T group at baseline (317 mm^3 vs 204 mm^3, respectively) and was still substantially greater at completion of the study, 325 mm^3 vs 232 mm^3. ○ The clinical significance of a greater increase in noncalcified plaque is uncertain, particularly when known prognostic markers such as coronary artery calcium scores showed no differences between groups. ○ Although the authors reported greater increase in total plaque volume (noncalcified and calcified) for the T treatment vs placebo, the absolute increase in volume was nearly identical (46 mm^3 vs 42 mm^3, respectively). Presumably, the reported difference was due to lower total plaque volume at baseline in the T group, which itself is a limitation in the interpretation of these results. ○ The increase in noncalcified plaque was confined to the fibrous component, which is believed to offer plaque stability compared with fatty or necrotic components, which have been associated with plaque rupture. These latter components were unchanged. ○ Importantly, none of the 170 men enrolled in this study suffered a MACE.

CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; T, testosterone; TTh, testosterone therapy.

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having testosterone prescribed was required for this study, the MI rate for 12 months before the prescription did not reflect a naturally occurring MI rate in an identified population. Instead, it was determined by how willing physicians were to offer a testosterone prescription to men with recent MI. Any hesitancy to prescribe testosterone within 12 months after an MI would suppress the reported MI rate and thus artificially increase the ratio of post-prescription to pre-prescription MI rates. This study was also highly criticized for absence of an appropriate control population and for providing insufficient information about the study population.[35-48]

Xu et al, 2013[30]

This is the only study of 19 meta-analyses to report increased CV risks with TTh. The difference in results between this study and other meta-analyses can be explained by inclusion of studies of questionable relevance and use of incorrect values for adverse events. For example, unlike other meta-analyses, the authors included the Copenhagen study, in which investigators administered micronized oral testosterone of their own preparation to men with cirrhosis at doses that resulted in on-study testosterone concentrations of more than 4 times the upper level of normal (nearly 150 nmol/L or >4000 ng/dL).[51] In their data acquisition from that study alone, the authors reported 16 of 134 adverse CV events in the testosterone group and 5 of 87 in the placebo group; however, there were only 4 events that could be considered CV (1 MI and 3 thromboses in portal or hepatic veins) in the testosterone arm and none in the placebo group.

Budoff et al, 2017[31]

This RCT was nested within the Testosterone Trials and reported a greater increase in noncalcified coronary artery plaque volume with TTh compared with placebo, as measured by computed tomography angiography.[31] Changes in calcified plaque and computed tomography–derived calcium scores were no different between groups.

The importance of the noted difference in noncalcified plaque is difficult to assess. Noncalcified plaque volume was approximately 50% greater in the placebo group at baseline, and despite a greater increase in the testosterone arm during the study, the final noncalcified plaque burden was still greater in the placebo group. A later assessment revealed that the difference in plaque volume in the TTh group was largely confined to the fibrous component of the plaque, which is believed to provide plaque stability.[52] Fatty and necrotic portions (which are indicative of a vulnerable plaque) as well as calcified plaque volume were not different.[53] Thus, TTh may have resulted in stabilization of coronary plaques. There were no CV events in this study population.[31]

STUDIES INDICATING NO INCREASED OR REDUCED RISK WITH TTH

As shown in Table 2, a moderately sized body of evidence derived from RCTs has found no increased MACE risk with TTh, and RCTs have found benefits for other CV disease or risks.[31,54-76] These include greater exercise tolerance without angina,[72] improved physical activity and Vo_2max in men and women with heart failure,[65,69-71] reduced atherosclerosis,[68,74] improved components of the metabolic syndrome, and improved glycemic control in men with type 2 diabetes or metabolic syndrome.[55,61-63,73-76] A 3-year RCT reported no difference in carotid-intima media thickness, coronary calcifications, or MACE between men who received TTh and men who received placebo.[58]

Observational and prospective registry studies (Table 3) have provided additional evidence that TTh is not associated with increased MACE and may even be protective.[77-103] One large cohort study (n=91,012) reported TTh to be associated with a reduction in MI, stroke, all-cause mortality, and a composite end point when testosterone prescriptions were associated with normalization of serum testosterone, but not when testosterone levels failed to normalize. Men who received a testosterone

TABLE 2. Selected RCTs Investigating TTh Effects on Cardiovascular or Metabolic Disease

	Reference, year	No.	Age (y)	Duration	Comments
1	Lincoff et al, 2023[54]	5246	45-80	21-33 months	Rate of MACE was no greater in men who received TTh compared with placebo.
2	Wittert et al, 2021[55]	1007	50-74	2 years	Number of MACE were 2 in TTh group and 6 in placebo group. TTh group showed lower progression to T2DM in men with prediabetes and greater remission of type 2 DM.
3	Snyder et al, 2016[56]	790	65 or older	1 year	With 2 years of follow-up, there were 9 MACE in TTh group and 16 in placebo group.
4	Snyder et al, 2001[57]	108	65 or older	36 months	Changes in lipids and apolipoprotein parameters did not differ for TTh compared with placebo. Reported adverse CV events included were 2 MI and 2 coronary revascularizations in the T group and 1 MI and 2 coronary revascularizations in the placebo group.
5	Budoff et al, 2017[31]	170	65 or older	1 year	TTh for 1 year compared with placebo was associated with greater increase in coronary artery noncalcified plaque volume. Calcium scores and calcified plaque did not differ. The clinical significance of noncalcified plaque is uncertain.
6	Basaria et al, 2015[58]	308	60 or older	3 years	TTh showed no greater increase in common carotid artery intima-media thickness or coronary artery calcium than placebo.
7	Basaria et al, 2010[12]	209	75 or older	Terminated	TTh was associated with greater numbers of adverse events categorized as CV than placebo. These included 4 MACE, all in the TTh group.
8	Khripun et al, 2019[59]	80	51.6	9 months	TTh in men with T2DM was accompanied with decrease in inflammatory markers such as leptin, resistin, ICAM-1, P-selectin, and CRP.
9	Mohler et al, 2018[60]	788	65 or older	12 months	TTh was associated with small reductions in cholesterol and insulin but not with other glucose markers, markers of inflammation or fibrinolysis, or troponin.
10	Groti et al, 2018[61]	55	Mean 60	1 year	TTh improved glycemic control and endothelial function.
11	Kalinchenko et al, 2010[62]	184	35-70	30 weeks	TTh compared with placebo resulted in greater improvement in MetS components and inflammatory markers.
12	Kapoor D et al, 2006[63]	24	Mean 64	3 months	TTh demonstrated reductions in insulin resistance and improved glycemic control in men with type 2 diabetes.
13	Malkin CJ et al, 2004[64]	10	Mean 60	1 month	Compared with placebo, TTh caused a reduction in the serum cytokines TNF-α and IL-1β.
14	Malkin et al, 2006[65]	76	64 $\pm$ 9.9	12 months	TTh improved functional exercise capacity, New York Heart Association class, left ventricular length, and systolic blood pressure.
14	Francomano et al, 2016[66]	10	18-40	4 days	TTh caused greater endothelial vasodilatory response than placebo.
15	Comoldi et al, 2010[67]	87	Mean 74	12 weeks	TTh compared with placebo demonstrated greater reductions in serum cholesterol and triglyceride levels in patients with CAD and was associated with lower rates of anginal/ischemic episodes.
16	Mathur et al, 2009[68]	13	Mean 64.8	12 months	TTh resulted in a protective effect on myocardial ischemia that was maintained throughout treatment without decrement.
17	Dos Santos et al, 2016[69]	39	Mean 52	4 months	TTh together with exercise training improved muscle sympathetic nerve activity and functional capacity in patients with heart failure.
18	Caminiti et al, 2009[70]	35	Median 70	3 months	In men with heart failure, TTh compared with placebo demonstrated greater improvement in exercise capacity, muscle strength, and glucose metabolism.
19	Pugh et al, 2004[71]	20	Mean 62	12 weeks	TTh produced significant improvements in exercise capacity and symptoms in men with heart failure.

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TABLE 2. Continued

	Reference, year	No.	Age (y)	Duration	Comments
20	English et al, 2000[72]	46	Mean 62	12 weeks	TTh in men with exercise-induced angina demonstrated ability to exercise longer without precipitating angina compared with placebo.
21	Dhindsa et al, 2016[73]	23	Mean 52	6 months	TTh reduced subcutaneous fat, increased lean mass, improved insulin resistance, decreased inflammation, and decreased fasting blood glucose concentration, suggesting improvement in CV and diabetes risk profiles.
22	Aversa et al, 2010[74]	50	Mean 57	24 months	TTh vs placebo improved HOMA-IR, reduced carotid intima-media thickness and hs-CRP in men with MetS
23	Jones et al, 2011[75]	220	Mean 60	12 months	TTh vs placebo improved insulin resistance, total and low-density lipoprotein cholesterol, lipoprotein (a), and sexual health in hypogonadal men with T2DM and/or MetS.
24	Hackett et al, 2014[76]	211		30 weeks	TTh reduced HbA_{1c}, weight, waist circumference, and body mass index in men with T2DM.

CAD, coronary artery disease; CRP, C-reactive protein; CV, cardiovascular; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IL-1β, interleukin 1β; MACE, major adverse cardiovascular events; MetS, metabolic syndrome; MI, myocardial infarction; RCTs, randomized controlled trials; T, testosterone; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor α; TTh, testosterone therapy.

prescription but never achieved a normal testosterone concentration showed no benefit over an untreated group with low testosterone concentrations.[82] This is an important finding that not all men who receive a testosterone prescription are adequately treated. Several additional large longitudinal and cohort studies have similarly reported that TTh is associated with a reduction in MACE.[78,79,81,89,93,97]

In a recently published analysis of 9 studies with prospectively collected data that provided individual participant data and at least 5 years of follow-up, for a total of 255,830 participant-years, the investigators found that baseline serum testosterone concentration below 7.4 nmol/L (213 ng/dL) had higher all-cause mortality.[103] For men with baseline serum testosterone level below 5.3 nmol/L (153 ng/dL), there was an increased CV mortality risk. Additional findings included greater all-cause mortality risk with lower sex hormone–binding globulin concentration, luteinizing hormone concentration above 10 IU/L, and estradiol concentrations below 5.1 pmol/L.

Of 20 meta-analyses directly assessing CV risk with TTh, 19 have found no increased risk (Table 4).[30,104–121] The 1 exception is by Xu et al,[30] described before. For example, 1 meta-analysis of 93 RCTs and 15 pharmacoepidemiologic studies in 2018 concluded that TTh "was not associated with an increased CV risk and may have a beneficial effect in some subpopulations."[111]

Large RCTs

There have been 3 large, multicenter RCTs involving TTh published since 2016, including TRAVERSE. None of these found increased MACE in men receiving TTh compared with placebo.

The Testosterone Trials (T Trials) were a set of 7 placebo-controlled, double-blind studies of 790 men to assess the effect of testosterone treatment on a number of parameters in men 65 years and older with baseline testosterone levels of less than 275 ng/dL and symptoms of testosterone deficiency.[56] Parameters measured in these trials included sexual function, physical function, vitality, cognition, anemia, bone health, and coronary artery noncalcified plaque volume. Patients with high CV risk were excluded. Treatment was randomized to testosterone gel or placebo gel administered daily. Treatment was administered for 1

TABLE 3. Selected Observational and Registry Studies Investigating Cardiovascular Risk with Testosterone Therapy

Reference, year	No. of patients	Study type	Comment
Baillargeon et al, 2014[77]	6355	Observational	No increased risk of MI with TTh, moderately protective effect of TTh in high-risk patients
Anderson et al, 2016[78]	4713	Observational	Reduced incidence of MACE with TTh
Janmohamed et al, 2015[79]	217	Observational	Reduced incidence of MACE with TTh
Ali et al, 2015[80]	3115	Observational	No increased risk of CV events with TTh
Tan et al, 2015[81]	19,968	Observational	Reduced incidence of MI and stroke with TTh
Sharma et al, 2016[82]	43,931	Observational	Reduced incidence of MI, stroke, and mortality with TTh
Hackett et al, 2016[83]	857	Observational	Reduction of all-cause mortality in men with T2DM with TTh
Etminan et al, 2015[84]	3197	Observational	No increased risk of MI with TTh, including men with prior CV events
Ramasamy et al, 2015[85]	153	Observational	No increased all-cause mortality, MI, TIA/CVA, DVT/PE in men >65 years who received TTh
Bair et al, 2015[86]	878	Observational	Reduced incidence of MACE with TTh
Bair et al, 2016[87]	755	Observational	Reduced MACE in men with severe CAD treated with TTh to normal and high levels of T
Shoskes et al, 2016[88]	23	Prospective open label	Endothelial function improved with TTh
Wallis et al, 2016[89]	10,311	Observational	Reduction of all-cause and CV mortality in men with the highest tertile of T exposure
Sharma et al, 2015[90]	59,553	Observational	No increased risk of DVT or pulmonary embolism in men who received TTh compared with men who did not
Haider et al, 2016[91]	77	Prospective observational study	During 8 years of follow-up with TTh, none of the patients suffered a MACE
Traish et al, 2017[92]	656	Prospective observational	No CV events and reduced all-cause mortality for men treated with TTh compared with an untreated control group with median follow-up of 7 years
Cheetham et al, 2017[93]	8808	Retrospective cohort study	33% reduction in composite CV end points with TTh
Eisenberg et al, 2015[94]	284	Observational	No increased mortality risk with TTh
Li et al, 2016[95]	102,650	Observational	No increased risk of VTE with TTh
Baillargeon et al, 2015[96]	663	Observational	No increased risk of VTE with TTh
Oni et al, 2019[97]	1470	Observational	TTh was associated with decreased all-cause mortality compared with those with nonnormalized T levels and the untreated group
Bhattacharya et al, 2011[98]	849	Registry	TTh resulted in an improvement in metabolic syndrome components
Miner et al, 2013[99]	849	Registry	TTh improved T deficiency symptoms in men including sexual function and mood/depression
Traish et al, 2014[100]	255	Registry	TTh ameliorates metabolic syndrome components
Haider et al, 2014[101]	156	Registry	TTh for up to 6 years produced significant and sustained improvements in weight, T2DM, and other cardiometabolic risk factors in obese, diabetic men
Maggi et al, 2016[102]	999	Registry	No difference in CV events between treated and untreated men
Yeap et al, 2024[103]	24,109	Prospective cohort study	Increased all-cause and CV mortality for men with low serum T

CAD, coronary artery disease; CV, cardiovascular; DVT, deep venous thrombosis; MACE, major adverse cardiovascular events; MI, myocardial infarction; PE, pulmonary embolism; T, testosterone; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack; TTh, testosterone therapy; VTE, venothrombotic event.

TABLE 4. Meta-analyses Investigating Cardiovascular Risks With Testosterone Therapy

Reference, year	Comments
Alexander et al, 2017[104]	TTh not associated with MI, stroke, or mortality
Borst et al, 2014[105]	TTh not associated with increased CV risk
Calof et al, 2005[106]	TTh not associated with increased CV risk
Cannarella et al, 2022[107]	TTh associated with reduced risk of arterial thrombotic events, MI, VTE, and mortality
Cannarella et al, 2024[108]	TTh not associated with increased CV risk in men with heart failure
Carson et al, 2012[109]	TTh not associated with increased CV risk
Corona et al, 2014[110]	TTh not associated with increased CV risk
Corona et al, 2018[111]	TTh associated with reduced overall mortality and CV morbidity in pharmacoepidemiologic studies; neither benefit nor harm reported with RCTs
Elliott et al, 2017[112]	TTh not associated with increased CV events, including CV death, stroke, or MI
Fallara et al, 2022[113]	TTh associated with reduced all-cause mortality
Fernandez-Balsells et al, 2010[114]	TTh not associated with increased CV events or death
Haddad et al, 2007[115]	TTh not associated with increased CV events
Hudson et al, 2022[116]	TTh not associated with increased CV events or mortality
Lee et al, 2021[117]	TTh not associated with increased risk of MI
Sood et al, 2024[118]	TTh not associated with increased CV risks, including MI, stroke, CV mortality, heart failure, AF, PE, VTE
Ayele et al, 2021[119]	TTh not associated with increased risk of VTE
Houghton et al, 2018[120]	TTh not associated with increased VTE
Toma et al, 2012[121]	TTh improved exercise capacity in men with heart failure; no CV events occurred
Xu et al, 2013[30]	TTh increased CV risks compared with placebo; analysis included a study in which testosterone was administered in pharmacologic doses and reported incorrect values for component studies

AF, atrial fibrillation; CV, cardiovascular; MI, myocardial infarction; PE, pulmonary embolism; RCTs, randomized controlled trials; TTh, testosterone therapy; VTE, venothrombotic event.

year, and there was an additional year of follow-up. The number of MACE—defined in this study as nonfatal MI, nonfatal stroke, and CV death—was 7 in both the testosterone and placebo groups in the first year. In the second year, there were 9 MACE in the placebo group and 2 in the testosterone group. The total number of MACE during 2 years thus totaled 16 in the placebo group and 9 in the testosterone group.[56]

The T4DM trial was a randomized, double-blind, placebo-controlled, 2-year study performed at 6 centers in Australia.[55] It aimed to evaluate whether testosterone treatment could prevent progression of or reverse early type 2 diabetes in men with impaired glucose tolerance or newly diagnosed type 2 diabetes in conjunction with a community-based lifestyle program. The study enrolled 1003 men aged 50 to 74 years with a waist circumference of 95 cm or higher, impaired glucose tolerance, and serum testosterone level of less than 14 nmol/L (approximately 400 ng/dL). Men at high risk for CV events were excluded. The results found that testosterone treatment for 2 years reduced the proportion of participants with type 2 diabetes and progression to type 2 diabetes. The number of MACE (stroke, MI, or CV death) were 6 in the placebo group and 2 in the testosterone group.[55]

The TRAVERSE study was performed in response to the FDA mandate in 2015 requiring testosterone manufacturers to perform a large CV trial investigating whether TTh is associated with increased MACE.[54] The study enrolled 5246 men, 45 to 80 years of age, who had symptoms of hypogonadism and 2 fasting serum testosterone levels of less than 300 ng/dL (10.4 nmol/L). Inclusion was limited to men at high risk for MACE because of known preexisting CV disease or having 3 or more risk factors, including hypertension, dyslipidemia, smoking, chronic kidney disease, diabetes mellitus, elevated high-sensitivity C-reactive protein concentration, age of 65 years or older, and high coronary calcium score on computed tomography scan. Patients were randomized to daily transdermal testosterone gel (1.62%) or placebo gel.

At baseline, mean age was 63 years, median serum testosterone level was 227 ng/dL, and 55% had preexisting CV disease. The primary end point was cumulative MACE, defined as nonfatal MI, nonfatal stroke, and CV death. With median follow-up of 33.0 months, the rate of MACE was 7.0% in the testosterone group and 7.3% in the placebo group. There was also no difference between groups for any of the 3 component end points (ie, stroke, MI, CV death). A secondary end point added coronary revascularization to the cumulative MACE rate. This also found no difference between testosterone and placebo groups.[54]

The TRAVERSE trial stands alone as a large CV trial designed to provide a definitive answer to the question of whether TTh in testosterone-deficient men causes increased risk of MACE compared with placebo. The results were clear and unequivocal that TTh does not increase MACE. In fact, the results of all 3 large RCTs were consistent; none reported greater rates of MACE in the TTh arms compared with placebo, and there were numerically fewer events in the TTh groups.

OTHER CV RISKS

In addition to the results for primary, secondary, and tertiary end points, the TRAVERSE authors reported a higher incidence of atrial fibrillation (AF) and pulmonary embolism (PE). Specifically, AF was reported in 91 men who received TTh and 63 who received placebo. Pulmonary embolism was reported in 24 men who received TTh and in 12 who received placebo.[54]

In any large clinical trial, it is to be expected, on the basis of chance alone, that there will be a discrepancy in number of events between groups for 1 or more medical conditions. In particular, the PE data represented just 1 component within the category of venothrombotic events (VTEs) that did not differ significantly between testosterone and placebo arms in TRAVERSE.[54] Isolated examples of such differences are of questionable significance.

The association with testosterone has previously been studied for both AF and PE. Multiple individual studies and meta-analyses have failed to indicate increased risk of VTE, including PE, in men receiving TTh.[95,96] Baillargeon et al[96] conducted a case-control study of 30,572 men 40 years and older. Exposure to TTh in the 15, 30, or 60 days before an event was not associated with increased risk of VTE. A meta-analysis by Houghton et al[120] investigated 6 RCTs and 5 observational studies and found no significant association between TTh and VTE.

Multiple studies have investigated the relationship of AF with endogenous serum testosterone concentrations. Most report that *low* endogenous testosterone levels are associated with increased risk of AF,[122,123] although at least 2 studies have reported an association between higher naturally occurring androgen concentrations and AF.[124,125] A rat model suggested that low testosterone levels are arrhythmogenic for AF.[126] Sharma et al[127] investigated 76,639 veterans with low testosterone concentrations and found that normalization of serum testosterone concentration with TTh resulted in a decreased incidence of AF compared with men with low testosterone levels who were untreated or who received a testosterone prescription but never normalized their serum testosterone concentrations. We are

unaware of any prior TTh intervention studies reporting increased AF risk.

A final speculative CV concern has been that TTh-induced erythrocytosis may contribute to MACE or VTE. However, as noted by the Endocrine Society guidelines, "The frequency of neuro-occlusive events in men with hypogonadism enrolled in RCTs of T who developed erythrocytosis has been very low."[128] In light of strong evidence provided by TRAVERSE and prior literature that TTh is not associated with increased MACE or VTE with TTh, the concern about erythrocytosis bears reevaluation.

DISCUSSION

For more than 2 decades, the scientific literature has reported with near uniformity that testosterone *deficiency* (hypogonadism) is associated with a variety of CV concerns and that TTh incurs no increased CV risk and in several circumstances may provide clinically important CV benefits. The reassuring safety results from TRAVERSE represent a watershed moment as it provides definitive evidence that TTh is not associated with increased MACE.

The concern about CV risk that arose suddenly, just 10 to 14 years ago, provides an interesting perspective on medical science.[12-14,30,31] The adoption of the narrative that TTh may be associated with serious CV risks demonstrates that even weak evidence can create a perception of risk once media promote the story broadly. Moreover, once a risk has been raised as a concern, there is an extremely high bar to demonstrate safety. In light of the results of TRAVERSE and other supporting literature, it is remarkable how the false concern that arose for CV risk with TTh has influenced nearly every facet of medical education, research, and most important, patient care. Since the FDA contributed to the public misperception that TTh was associated with increased MACE risk by adding a CV warning to testosterone labels, we believe it is incumbent on the FDA to remove this warning now that the study it mandated to investigate this issue has found no increased risk of MACE.

The emphasis on CV risks during this last decade also obscured awareness of evidence that TTh appears to have cardiometabolic *benefits*. For example, TTh has been found in RCTs to improve clinical response in men and women with heart failure; to allow greater exercise tolerance in men with exercise-induced angina; to decrease fat mass; to increase muscle mass; to improve insulin resistance, to reduce progression to type 2 diabetes, and to increase remission of type 2 diabetes; and in long-term registry studies, to greatly improve obesity.

Other benefits of TTh in men with age-related testosterone deficiency, as found in TRAVERSE and numerous other studies, include increased sexual activity and libido, improved bone mineral density and strength, improved mood, resolution of unexplained anemia, greater physical activity, and sense of vigor/vitality.[56]

The impact of testosterone deficiency on health and mortality and the benefits of TTh in testosterone-deficient men have been largely overlooked or dismissed by much of the mainstream medical community. This occurred in part owing to what can now be recognized as meritless concerns about increased MACE that have dominated the field for the last decade. With this concern resolved, there is now an exciting opportunity for all stakeholders in medicine—governments, policymakers, health insurance companies, businesses, health care providers, and the public—to focus on the consequences of the clinical condition of testosterone deficiency and the benefits of TTh in testosterone-deficient men.

CONCLUSION

The TRAVERSE trial, supported by an extensive prior literature, has found beyond any reasonable doubt that TTh in testosterone-deficient individuals is not associated with increased risk of MACE. This has been studied in multiple populations, all with the same result, including in men 65 years and older who were relatively healthy, in a diabetic and prediabetic population, and in men at high risk for MACE. We believe

this is now "settled science" and see no reason to expend valuable resources to investigate this issue further.

It is the position of the Androgen Society that it has been conclusively determined that TTh is not associated with increased risk of heart attacks, stroke, or CV deaths.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

Abbreviations and Acronyms: **AF,** atrial fibrillation; **CV,** cardiovascular; **FDA,** Food and Drug Administration; **MACE,** major adverse cardiovascular events; **MI,** myocardial infarction; **PE,** pulmonary embolism; **RCT,** randomized controlled trial; **TTh,** testosterone therapy; **VTE,** venothrombotic event

Affiliations (Continued from the first page of this article.): Department of Endocrinology, Barnsley Hospital, Barnsley, United Kingdom (T.H.J) Endocrinology and Andrology, University of Sheffield, Sheffield, United Kingdom (T.H.J.); Cardiovascular Division, Department of Medicine, Keck School of Medicine of University of Southern California, Los Angeles, CA (R.A.K.); Departments of Family Medicine and Urology, Warren Alpert School of Medicine, Brown University, Providence, RI (M.M.); Department of Clinical and Surgical Andrology, Centre of Reproductive Medicine and Andrology, Münster University Hospital, Münster, Germany (M.Z.); and Departments of Biochemistry and Urology, Boston University School of Medicine, Boston, MA (A.M.T.).

Correspondence: Address to Abraham Morgentaler, MD, 200 Boylston St, suite A309, Chestnut Hill, MA 02467 (amorgent@bidmc.harvard.edu).

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