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Relationships between endogenous and exogenous testosterone and cardiovascular disease in men

Arthi Thirumalai[1] · **Bradley D. Anawalt**[1]

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Abstract
In this narrative review, we discuss the evidence about the controversy about the cardiovascular effects of endogenous and exogenous testosterone in men. Prospective cohort studies with follow-up of ~5–15 years generally indicate no association or a possible inverse relationship between serum endogenous testosterone concentrations and composite major cardiovascular events, cardiovascular deaths and overall mortality. Pharmacoepidemiological studies of large databases generally show no association between testosterone therapy and incident major cardiovascular events, and some pharmacoepidemiological studies demonstrate an association with decreased overall mortality. Randomized, placebo-controlled trials indicate that there is no increased incidence of overall major cardiovascular events with 1–3 years of testosterone therapy. These placebo-controlled trials have major limitations including small numbers of participants, short duration of testosterone therapy and follow-up, and lack of systematic adjudication of cardiovascular events. Overall, the evidence indicates that endogenous testosterone concentrations and testosterone therapy at physiological dosages confer no or minimal effects on the incidence of cardiovascular outcomes. There is insufficient evidence to make conclusions about testosterone therapy for patients at high risk of cardiovascular events (e.g., men with recent myocardial infarctions or stroke and men with recurrent idiopathic deep venous thromboses). In general, clinicians should avoid prescribing supraphysiological testosterone therapy to hypogonadal men or men with slightly low to low-normal serum testosterone concentrations and no identified disorder of the hypothalamus-pituitary-testicular axis because of the uncertain cardiovascular risks and the lack of proven health benefits. For most men with bona fide hypogonadism, benefits of testosterone therapy exceed the potential risk of adverse cardiovascular effects.

Keywords Testosterone · Cardiovascular risk · Myocardial infarction · Stroke · Venous thromboembolism

1 Introduction

One of the raging controversies in the field of reproductive endocrinology is the role of sex hormones in the pathophysiology of cardiovascular disease and whether testosterone and estrogen increase or decrease the risk of cardiovascular events in humans. More is known about the effects of sex steroid hormones and cardiovascular risk in women than men, and the lessons learned from randomized controlled trials in women are instructive to the nascent research and clinical care of men. It is important to understand the history of the anecdotal basis for the original simplistic hypotheses that "estrogen is good for the heart" and "testosterone is bad for the heart" for women and for men. The past three decades of women's health research have demonstrated and reinforced two key concepts: 1) epidemiological studies are typically best suited for the development of hypotheses and require randomized controlled trial for confirmation of these hypotheses; and 2) there are no simple conclusions about the effects of sex steroid hormones on cardiovascular risk: estrogen is not a cardiovascular panacea nor is testosterone a cardiovascular toxin. Although research on the effects of sex steroids on cardiovascular risk in men has lagged decades behind research on this topic in women, the same lessons seem to apply. We briefly review the poor evidence that stimulated the simplistic (and erroneous) polemical hypotheses that estrogen is beneficial and testosterone is detrimental to human cardiovascular health. We will also briefly review

✉ Bradley D. Anawalt
banawalt@medicine.washington.edu

Arthi Thirumalai
arthidoc@uw.edu

[1] Department of Medicine, University of Washington School of Medicine, Box 356420 Department of Medicine, 1959 NE Pacific Avenue, Seattle, WA 98195, USA

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the key studies of the effects of sex steroid hormones on cardiovascular risk in women to provide context for the research of men that has been largely based on epidemiology studies.

In this narrative review, we summarize the findings of a large number of epidemiological studies and the scanty evidence from randomized clinical trials of the effects of testosterone and its major metabolites (estradiol and dihydrotestosterone) on cardiovascular outcomes in men (Fig. 1). This reviewed a search of PubMed from January 1 2000, to March 1, 2022 and Google Scholar using the terms "testosterone and stroke", "testosterone and myocardial infarction" "testosterone and cardiovascular disease", "testosterone and deep venous thrombosis", "testosterone and pulmonary embolism", "hypogonadism and cardiovascular disease", "hypogonadism and myocardial infarction", and "hypogonadism and stroke". In addition, we scanned the reference section of articles derived from the above search to retrieve additional salient articles.

In men, as with women, there is a distinction between the potential risks and benefits of naturally occurring endogenous concentrations of sex steroid hormone concentrations and testosterone therapy. There is also an important distinction between sex steroid hormone replacement therapy at physiological or near-physiological dosages in hypogonadal men and women (e.g., a premenopausal woman with gonadotropin deficiency due to a pituitary macroadenoma) versus sex steroid hormone therapy for a man without hypogonadism due to an identified disorder of the hypothalamus-pituitary-testicular axis or sex steroid hormone therapy for a postmenopausal woman. We use the cautionary lessons learned from sex hormone studies in women and the current evidence in men to make conclusions and clinical recommendations about testosterone therapy for male hypogonadism.

2 Serum sex steroid hormone concentrations and risk of cardiovascular events in women

For centuries, there has been anecdotal evidence that men are more likely to have cardiovascular disease than women. William Heberden is credited as the first person to write a medical account of "dolor pectoris", and he wrote in the nineteenth century, "I have seen nearly a hundred people under this disorder, of which number there have been three women, and one boy twelve years old. All the rest were men near or past the fiftieth year of their age" [1]. William Osler in his classic "Lectures on Angina Pectoris and Allied States" noted the "remarkable preponderance of males who are attacked" and that in his "own series of forty cases to true angina, there was only one woman" [2]. Heberden recommended the administration of "wine, and spiritous liquors, and opium [to] afford considerable relief". This early impression that cardiovascular disease is significantly more prevalent in men has formed the basis for the hypothesis that circulating sex steroid hormone concentrations might be important modulators of cardiovascular risk.

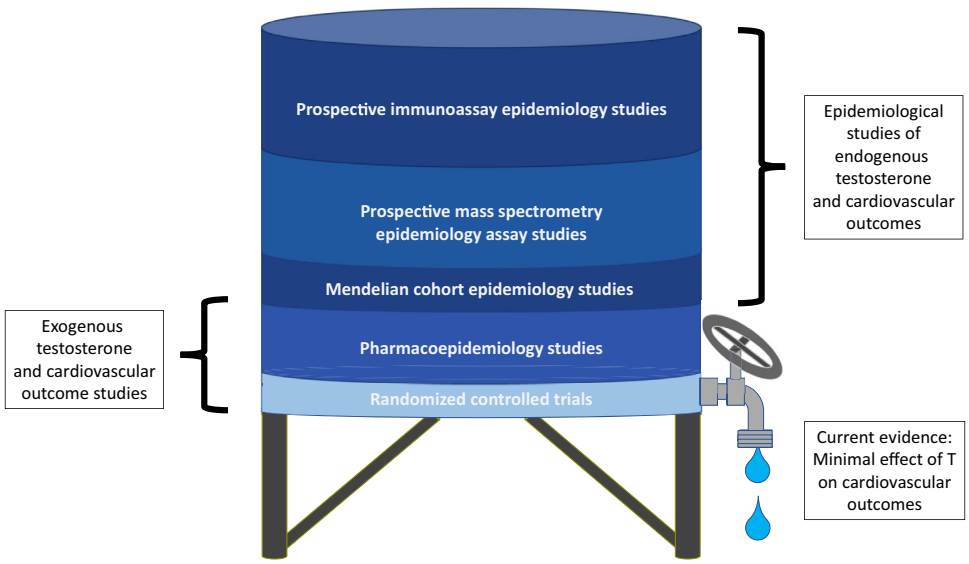

Fig. 1 Summary of the evidence about the possible association of testosterone and incident risk of cardiovascular outcomes in men. Epidemiological studies (the top 4 darker blue layers of the cistern) provide the majority of the evidence about the relationship between serum endogenous testosterone concentrations and testosterone replacement therapy (at typical dosages) and cardiovascular outcomes. There is relatively little data from high quality randomized controlled trials (the bottom pale-blue layer of the cistern). Overall, the data suggest a very small (or no) effect of endogenous testosterone or testosterone replacement therapy and incident risk of cardiovascular outcomes

In modern times, it has become clear that cardiovascular disease is much more egalitarian that Heberden and Osler concluded. There are modest, mixed differences between men and women in the epidemiology of cardiovascular disease; some specific cardiovascular outcomes are more common in men, and some more common in women. For example, in the United States, the prevalence of myocardial infarction and heart failure is slightly higher in men than women (7.4% and 2.4% in men ≥ 20 years old and 6.2% and 2.1% in women ≥ 20 years old respectively), but strokes are slightly more common in women (2.6% of women ≥ 20 years old) than men (2.5% men ≥ 20 years old) [3]. It has been tempting to invoke differences in endogenous sex steroid hormone concentrations as the cause of some of sex-specific differences in cardiovascular outcomes, but there are very little data to support this hypothesis [4]. Furthermore, the modest differences in cardiovascular risk and outcomes between men and women in industrialized countries might be due to socioeconomic factors or to factors other than differential concentrations of serum sex steroid hormone concentrations [5, 6]. For example, female gender (not female sex) might be a significant or the major determinant of differential cardiovascular risk. Early adoption of health behaviors such as physical activity, alcohol consumption and tobacco use and differential psychosocial stressors (emotional duress from factors related to work, home and financial factors) are important gender-specific social determinants of cardiovascular health [6].

2.1 Sex steroid hormone therapy and cardiovascular risk in postmenopausal women

Two clinical trials of hormone therapy in women have demonstrated that a low serum estradiol concentration is not the sole or even the primary risk factor for cardiovascular disease and outcomes in postmenopausal women. In the Women's Health Initiative (WHI), oral conjugated equine estrogen therapy with or without oral medroxyprogesterone did not reduce the risk of cardiovascular disease for postmenopausal women. The combination regimen increased the risk of overall cardiovascular events, particularly in older women and those who are more than 5 years from menopause [7, 8]. The effect was relatively small; the absolute increase in annualized event rate compared to placebo was small (0.46% *vs.* 0.44% for coronary heart disease events and 0.38% *vs.* 0.29% for stroke). The results differed for conjugated equine estrogen therapy alone that was associated with increased stroke, but no increased risk of coronary heart disease events. Furthermore, the WHI demonstrated that younger postmenopausal women and those women with recent onset of menopause might have a cardiovascular benefit from hormone therapy with decreased coronary heart disease events (but not stroke) and all-cause mortality [8, 9]. These latter findings were also demonstrated in a much smaller study, the Danish Osteoporosis Prevention study [10]. There continues to be controversy about whether early initiation of hormone therapy in women early in menopause is associated with reduced coronary heart disease events [11]. Overall, the randomized controlled studies of sex steroid hormone therapy indicate that the effects on absolute risk of coronary heart disease events is small for women over age 50 and likely depends on the formulation and dosage of hormone therapy and the age and health of the specific woman.

It is beyond the scope of this review to comprehensively discuss the role of endogenous serum testosterone concentrations or testosterone therapy and cardiovascular risk in women. In brief, there is controversy about whether higher endogenous testosterone concentrations or testosterone therapy are causally related to cardiovascular risk in women. First, there is a bidirectional relationship between serum testosterone and metabolic syndrome (a major risk factor for cardiovascular disease) in women [12]. Second, epidemiological studies have shown conflicting results between endogenous serum testosterone concentrations and risk of adverse cardiovascular events [13–15]. Third, there has been no large, long-term prospective studies of effects of endogenous or exogenous testosterone and cardiovascular risk in women [13–15].

In summary, there were early, biased observations by renowned clinicians that suggested that men are at greatly higher risk of cardiovascular disease than women and led to the general hypotheses that estrogen is "good" for cardiovascular health and testosterone is "bad" for cardiovascular health. However, the most recent epidemiological data indicates that there are small differences in the overall incidence of cardiovascular disease between men and women and that these differences vary based the specific cardiovascular disorder and the age cohort of the men and women [3]. In addition, the estrogen treatment trials of menopausal women have yielded complex results that belie a simple conclusion that estrogen is uniformly "good" or "bad" for postmenopausal women who have the highest risk of cardiovascular disease and cardiovascular death.

3 Endogenous serum sex steroid hormone concentrations and cardiovascular outcomes in men

Up until the late twentieth century, the (largely false) premise that men are significantly more likely to have cardiovascular events than women has led to the hypotheses that higher endogenous circulating testosterone and/or lower serum estrogen concentrations might adversely affect cardiovascular risk in men. More recently, there has been an alternative hypothesis that testosterone might

confer favorable benefits in cardiovascular risk based on the observation that older and more obese men are more likely to have low serum testosterone concentrations and increased risk of cardiovascular events. The epidemiological studies associating endogenous circulating testosterone concentrations with cardiovascular events have yielded mixed results. These epidemiological studies are categorized based on the type of total testosterone assay used in the study: immunoassay or mass spectrometry. Although a validated mass spectrometry assay performs with more accuracy, precision, sensitivity, and specificity in the measurement of sex steroid hormone concentrations, a validated immunoassay correlates well with mass spectrometry in the measurement of total testosterone concentrations that are within the normal range for men (9.2–30.2 nmol/L or 264–870 ng/dL) and slightly low serum concentrations (8.0–9.19 nmol or 230–263 ng/dL) [16]. The correlation drops significantly at serum total concentrations below 8.0 nmol (230 ng/dL). Because epidemiological studies have excluded men with hypogonadism with an identified disorder of the hypothalamus-pituitary-testicular axis (who account for majority of the very low serum total testosterone concentrations), immunoassays are still useful in epidemiological studies [16, 17]. However, measurement of the very low serum estradiol concentrations of normal men requires a validated chromatography-tandem mass spectrometry assay (with a derivatization step) [18, 19].

We review the epidemiological studies using immunoassays and mass spectrometry assays in the following sections. Although there are retrospective and cross-sectional studies, these are more likely to be fraught with confounding factors and biases. We will focus on the prospective, longitudinal studies and studies of cardiovascular outcomes (not markers of cardiovascular risk). For the associations of the major metabolites of testosterone—dihydrotestosterone (DHT) and estradiol—we will use only the results of mass spectrometry assay studies that are more accurate for these steroid hormones that are present in very low concentrations in the serum of men.

3.1 Prospective immunoassay cohort studies of serum endogenous sex hormones and overall cardiovascular risk and mortality in men

The initial prospective epidemiological cohort studies in men used immunoassays (Table 1) [20–29]. These studies typically adjusted for factors that are associated with lower serum testosterone concentrations including older age and higher body mass index and other known cardiovascular risk factors. However, the definition of overall cardiovascular endpoints varied between these studies. These immunoassay cohort studies typically have had cohort numbers of approximately 1000 to 5000 men and an average follow-up for 4–15 years. The participants are middle-aged or older (45–93 years old). The notable exceptions are Yeap's recent, much larger 2021 and 2022 United Kingdom Biobank studies that had approximately 150,000 and 210,000 men (ages 40–69 years old) with follow-up for 11 and 9 years, respectively [20, 21]. Collectively, the prospective immunoassay cohort studies have shown no association between initial endogenous serum testosterone concentrations and future incident rates of overall cardiovascular events, cardiovascular mortality, or overall mortality.

3.2 Prospective mass spectrometry cohort studies of serum endogenous sex hormones and overall cardiovascular risk and mortality in men

There have been a number of prospective mass spectrometry studies published in the past decade (Table 1) [30–37]. As with the prospective immunoassay cohort studies, the mass spectrometry studies generally show no association or an inverse relationship between serum testosterone concentrations and the risk of incident overall cardiovascular events, cardiovascular mortality and all-cause mortality. A 2021 meta-analysis identified 6 studies (Table 1) to create a Forest plot of the association of serum testosterone concentrations and all-cause mortality and cardiovascular mortality [38]. There was no association between endogenous serum total testosterone concentrations and all-cause mortality or cardiovascular mortality after adjustment for age, smoking status and body mass index or waist circumference. The studies were rated moderate to high quality. There was significant heterogeneity of baseline serum testosterone concentrations, but dose–response random effects meta-analyses demonstrated no significant effects of baseline serum testosterone on the relative hazard ratios for the all-cause and cardiovascular outcomes.

In several prospective mass spectrometry cohort studies, associations between serum DHT and/or estradiol concentrations and cardiovascular outcomes were reported (Table 2). Five studies examined the possible association between baseline serum DHT concentrations and the future incidence of overall cardiovascular events, cardiovascular mortality and all-cause mortality [31, 32, 35, 36]. In one study, there was no association between baseline serum DHT and any of these three outcomes [35]. In two studies, higher serum DHT was associated lower incident risk of cardiovascular mortality or overall mortality, and one study demonstrated a U-shaped curve with lower and higher serum DHT concentrations associated with higher incident risk of overall cardiovascular events and all-cause (but not cardiovascular) mortality [31, 32, 36].

Three mass spectrometry cohort studies examined the possible association between baseline serum estradiol concentrations and the incident risk of the same outcomes [35–37]. Two of these studies demonstrated no association between baseline serum estradiol and future incident

Table 1 Prospective cohort studies of baseline endogenous testosterone concentrations and future incident risk of overall major cardiovascular events, cardiovascular mortality and all-cause mortality

	Incidence of overall CV events	Incidence of CV mortality	Incidence of all-cause mortality
Immunoassay studies of serum T			
Smith et al. [22]	↔☐ risk	↔☐ risk	↔☐ risk
Arnlov et al. [23]	↔☐ risk	ND	ND
Araujo et al. [24]	ND	↔☐ risk with TT ↑ risk with ↑ cFT	↔☐ risk
Khaw et al. [26]	ND	↓ risk with ↑ TT	↓ risk with ↑ TT
Laughlin et al. [25]	ND	↑ risk with low TT	↑ risk with low TT
Vikan et al. [27]	↔☐ risk	↔☐ risk	↔ with TT ↑ risk in lowest quartile of cFT
Haring et al. [28]	↔☐ risk	ND	↔☐ risk
Soisson et al. [29]	↑ risk with lowest & highest quintiles of TT	ND	ND
Yeap et al. [20]	ND	↔☐ risk	↑ risk with low TT
Yeap et al. [21]	↔☐ risk with TT ↓ risk with ↓ cFT	ND	ND
Mass spectrometry studies of serum T			
Ohlsson et al. [30]	↓ risk with highest quartile of TT	ND	ND
Shores et al. [31]*	↔☐ risk	ND	↔☐ risk
Yeap et al. [32]*	ND	↔☐ risk	↑ risk in lowest and highest quartile of TT
Pye et al. [33]*	ND	↑ risk with low TT	↑ risk with low TT
Srinath et al. [34]*	↔☐ risk	↔☐ risk	↔☐ risk
Chan et al. [35]*	↔☐ risk	↔☐ risk	↔☐ risk
Hsu et al. [36]*	ND	↔☐ risk	↑ risk with lower TT and cFT
Collett et al. [37]	↔☐ risk	ND	ND
Meta-analysis			
Marriott et al. [38]	ND	↔☐ risk	↔☐ risk

CV cardiovascular, *ND* not determined, *T* testosterone, *TT* total testosterone, *cFT* calculated free testosterone

*Studies included in 2021 Marriott meta-analysis

risk of cardiovascular events, cardiovascular mortality and all-cause mortality, but one study demonstrated that higher baseline serum estradiol concentrations were associated with decreased cardiovascular and all-cause mortality.

Although not a sex steroid hormone, sex hormone binding globulin (SHBG) binds testosterone, DHT, and estradiol. In addition, there is some speculation that SHBG may have endocrine and paracrine activity. One prospective epidemiological study found an association between higher serum SHBG concentrations and increased incidence of major cardiovascular events and cardiovascular mortality [39], and four showed no significant association with incidence of overall cardiovascular events or cardiovascular mortality [24, 30, 35, 37]. The largest cohort study (with nearly 150,000 participants) demonstrated no association between serum SHBG concentrations and incidence of overall major cardiovascular events [20]. However, there was an association with lower serum SHBG concentrations and higher incidence of myocardial infarction, but lower incidence of cardiovascular and overall mortality, ischemic stroke, heart failure [20, 21]. Taken together, there is a suggestion that there might be an association between higher serum SHBG concentrations and increased incidence of overall cardiovascular events, but this finding must be confirmed, and plausible mechanisms must be elucidated.

3.3 Possible reverse causality between endogenous serum testosterone concentrations and overall cardiovascular risk and mortality in men

When considering the possibility that low serum endogenous testosterone concentrations might be associated

Table 2 Mass spectrometry assay epidemiology studies of baseline endogenous dihydrotestosterone and estradiol concentrations and incident risk of overall major cardiovascular events, cardiovascular mortality and all-cause mortality

Mass spectrometry studies of serum DHT	Incident overall CV events	Incident CV mortality	Incident all-cause mortality
Shores et al. [31]			
DHT	U-shaped curve ↑ with low or high DHT	ND	U-shaped curve ↑ with low or high DHT
Yeap et al. [32]			
DHT	ND	↓ risk with higher DHT	↔☐ risk
Chan et al. [35]			
DHT	↔☐ risk	↔☐ risk	↔☐ risk
Hsu et al. [36]			
DHT	ND	↔☐ risk	↓ risk with higher DHT
Mass spectrometry studies of serum E2			
Chan et al. [35]			
E2	↔☐ risk	↔☐ risk	↔☐ risk
Hsu et al. [36]			
E2	ND	↓ risk with higher E2	↓ risk with higher E2
Collet et al. [37]			
E2	↔☐ risk	↔☐ risk	↔☐ risk

CV cardiovascular, *DHT* dihydrotestosterone, *E2* estradiol

with increased cardiovascular risk, it is essential to consider reverse causality due to aging and obesity. The men in these studies generally were middle-aged or older and overweight or obese. Aging and obesity are associated with declining serum endogenous concentrations due to multiple mechanisms including co-morbidities, medications, and changes in reproductive physiology. (Please see "**Ageing and androgens: physiology and clinical implications in** this journal issue.) Aging and obesity are also both associated with increased risk of incident cardiovascular disease, cardiovascular mortality and overall mortality. It is plausible that low serum testosterone concentrations are simply markers of increased cardiovascular risk and play no causative role.

3.4 Summary of epidemiology of serum endogenous sex hormone concentrations and incident overall cardiovascular risk and mortality in men

The epidemiological data suggests that endogenous serum testosterone, DHT and estradiol concentrations are not highly associated with future incident risk of overall cardiovascular events, cardiovascular mortality or all-cause mortality. Although some studies show an inverse association between baseline serum concentrations of testosterone, DHT and estradiol, with incident risk of major cardiovascular events and/or overall mortality, there is no consistent patten among the prospective cohort studies. In addition, this inverse association might be due to reverse causality because older men with higher body mass indices or waist circumferences and multiple morbidities have lower serum testosterone concentrations and higher incident risk of major cardiovascular events and all-cause mortality.

4 Low serum testosterone due to therapeutic suppression in men: increased overall cardiovascular risk and mortality?

Although androgen deprivation therapy for treatment of prostate cancer is associated with metabolic syndrome, adverse effects of body composition, and increased incident risk of myocardial infarction and venothromboembolic events, the causal relationship has not been proven [40, 41]. An equally plausible hypothesis is that men with more advanced prostate cancer that is treated with androgen deprivation therapy tend to have worse general health and higher risk of major cardiovascular outcomes than the control comparator groups in the published epidemiological studies [40].

5 Testosterone therapy and overall cardiovascular risk and mortality in men

There have been several pharmaco-epidemiological studies of the relationship between testosterone therapy and incident risk of overall major cardiovascular events. The largest study, published in 2021, included over 80,000 male veterans who had filled a testosterone prescription and over 120,000 who had not [42]. The mean follow-up was 4.3 years. There was no association between transdermal or intramuscular testosterone therapy and the composite outcome of incident myocardial infarction, ischemic stroke or venous thromboembolic disease. Three other pharmaco-epidemiological studies also demonstrated no association [43–45], two found an association with decreased risk [46, 47], and two found an association with increased risk of composite cardiovascular outcomes [48, 49]. The definition of composite cardiovascular outcomes differed between all studies, and there was considerable variation in the patient populations (Table 3).

There are no published studies of randomized, placebo-controlled trials of testosterone therapy that were designed to assess incident cardiovascular risk as a primary outcome. Several meta-analyses of randomized controlled trials of testosterone and major cardiovascular outcomes have been published [50, 51]. The two most recently published meta-analyses of randomized placebo-controlled trials of testosterone therapy concluded there was no association between testosterone therapy and major cardiovascular events [50, 51]. Both meta-analyses were limited by the small number of aggregate participants (< 4,000 men) in the included studies, the short duration of testosterone exposure (generally ≤ 1 year), the heterogeneity of the studies, and lack of uniform and precise adjudication of cardiovascular events.

Table 3 Studies of testosterone therapy and incident risk of composite cardiovascular events

Pharmaco-epidemiological studies of T therapy		
	Incident overall CV events	**Definition of composite CV events**
Vigen et al. [48]	↑	MI + ischemic CVA + all-cause mortality
Anderson et al. [46]	↓	MI + all CVA + all-cause mortality
Wallis et al. [45]	↔□	MI + VTE + ischemic CVA
Cheetham et al. [47]	↓	MI + ischemic CVA + TIA + unstable angina + revascularization procedure + sudden cardiac death
Layton et al. [43]	↔□	MI + ischemic CVA + TIA + unstable angina
Argalious et al. [44]	↔□	MI + all CVA + total mortality
Loo et al. [49]	↑	MI + ischemic CVA + TIA
Shores et al. [42]	↓	MI + ischemic CVA + VTE

Selected randomized, controlled T therapy trials			
	Primary Study Outcome	**Study Design**	**Absolute rate of major CV events**
Copenhagen Study [52]	Effects of oral T on mortality in men with cirrhosis	~Study of 134 men treated with oral T vs. 87 treated with placebo for ~28 months	1 in T-treated group vs. 0 in placebo-treated group
TOM Trial [53]	Effects of T gel on physical function in men ≥ 65 years old with low serum T	Study of 106 men treated with T gel vs. 103 treated with placebo gel stopped early	4 in T-treated group vs. 0 in placebo-treated group
T Trials [54]	Effects of T gel on several outcomes in men ≥ 65 years old with low serum T	Study of 790 men randomized to T gel vs. placebo gel for 1 year	4 in T-treated group vs. 0 in placebo-treated group
TEAAM Study [56]	Effects of T gel on atherosclerosis in men ≥ 60 years old with low to low-normal serum T	Study of 308 men randomized to T gel vs. placebo gel for 3 years	11 in T-treated group vs. 6 in placebo-treated group

T testosterone, *CV* cardiovascular, *MI* myocardial infarction, *VTE* venous thromboembolic disease, *CVA* cerebrovascular accident, *TIA* transient ischemic attack

In addition, the number of major cardiovascular events was very low in both testosterone- and placebo-treated men reflecting the short duration and likely bias toward inclusion of healthier men in these studies.

There are 4 randomized, placebo-controlled trials (that were included in the above meta-analysis) that merit comment. The Copenhagen Study Group trial was designed to examine the effects of a high dosage of oral micronized testosterone (200 mg three times daily) on mortality in men with alcohol cirrhosis [52]. The study was stopped early (after a median of 28 months of treatment) due to a trend of increased mortality in the testosterone-treated group (adjusted relative mortality 1.17.; 95% CI = 0.66–2.15). Of the 33 deaths in the testosterone-treated group ($n = 134$), only 1 was considered to be due to a cardiovascular cause (myocardial infarction) compared to 18 deaths overall and 0 cardiovascular-related deaths in the placebo group ($n = 87$). The TOM trial was designed to determine whether testosterone therapy improved strength and physical function in men ≥ 65 years old with low serum testosterone and limited mobility [53]. It was discontinued early due to increased cardiovascular events in the testosterone-treated group (23 *vs.* 5 in the placebo group). The adverse cardiovascular events in the testosterone group ($n = 106$) included the following: 2 self-reported episodes of syncope, 5 episodes of edema, 1 episode of self-reported tachycardia with fatigue and 1 episode of premature ventricular contractions on electrocardiogram. There were 4 major cardiovascular events (2 myocardial infarctions, 1 stroke and 1 cardiovascular death) in the testosterone-treated group ($n = 106$) and 0 in the placebo group ($n = 103$). The T trials were a set of studies designed to evaluate effects of testosterone therapy on sexual function, physical function, vitality, bone mass, cognition, anemia and coronary plaque development in men ≥ 65 years old with low serum testosterone concentrations. In the principal study, 790 men were randomized to transdermal testosterone gel adjusted to achieve a normal serum testosterone or transdermal placebo gel for one year [54]. The number of major cardiovascular events was 7 in both groups during the treatment period, and 2 men in the testosterone-treated group and 9 in the placebo-treated group had major cardiovascular events in the year after the treatment period. In the cardiovascular substudy of the T Trials, the investigators reported no significant differences in the progression of calcified plaque volume or coronary calcium scores between the testosterone- and placebo-treated groups, but there was a significantly greater increase in absolute non-calcified plaque volume and total plaque volume in the testosterone-treated group [55]. The T Trials investigators did not comment on the baseline differences between the two groups; the baseline non-calcified, calcified and total plaque volumes and coronary artery calcium scores were about 50% higher compared to the baseline values of the placebo-treated group. Finally, the TEAAM trial was a three-year study of the effects of testosterone gel at a typical replacement dosage (75 mg 1% testosterone) on carotid intima medial thickness or coronary artery calcification assessed by coronary artery calcium scores (similar to the T trial) [56]. There were no differences in either outcome between the testosterone-treated and placebo-treated groups, and the incidence of major cardiovascular events was infrequent and similar in both groups (11 in the testosterone-treated group *vs.* 6 in the placebo group).

In summary, the data from pharmaco-epidemiological studies are mixed, but the majority of the studies demonstrate no association between testosterone therapy and incident risk of major cardiovascular events. The limited data from modest-sized randomized clinical trials for testosterone replacement therapy at typical physiological or near-physiological dosages indicates that short term therapy (up to three years) is not associated with increased incidence of major cardiovascular events. These data are reassuring that there is not an early, large risk of testosterone, but longer-term follow-up of randomized controlled studies of testosterone therapy must be done. The majority of the evidence indicates that there is no increased risk of adverse major cardiovascular outcomes associated with testosterone therapy when administered at typical replacement dosages for hypogonadism.

6 The effects of endogenous and exogenous testosterone (and its major metabolites) on the risk of specific cardiovascular outcomes in men

There are five specific important cardiovascular disorders that have been studied in more detail than other cardiovascular outcomes that we will briefly review here: myocardial infarction, stroke, venous thromboembolism, heart failure and atrial fibrillation.

6.1 Effects of endogenous and exogenous testosterone on the risk of myocardial infarction

Most observational studies of endogenous serum testosterone have shown no association between endogenous serum testosterone concentrations and incident risk of myocardial infarction [22, 27, 57, 58]. A recent Mendelian genetic analysis demonstrated a possible association between genes associated with increased serum endogenous testosterone concentrations and incident risk of myocardial infarction [59]. However, this Mendelian study showed no association between the gene variants of interest (*JMJD1C)* in the test population and a weak association in the validation population (odds ratio per each unit increase in log-transformed of testosterone = 1.37; CI 1.03–1.82). This study was also

limited by the lack of a defined physiological mechanism of *JMJD1C* regulation of testosterone production.

In 2013 and 2014, two retrospective pharmaco-epidemiological studies using large pharmacy databases showed an association between testosterone prescriptions and increased myocardial infarction or composite cardiovascular outcomes [48, 60]. These studies were instrumental in leading to the United States Food and Drug Administration (FDA) to issue a warning about the possible link between exogenous testosterone therapy and increased incident risk of myocardial infarction and overall cardiovascular risk. The first of these two studies used a United States national database of military veterans with a low serum total testosterone and who had undergone a coronary angiogram [48]. In adjusted analyses, there was a 29% increased risk of the composite endpoint of myocardial infarction, stroke or cardiovascular death; in the unadjusted analysis, the absolute event rate of the composite cardiovascular was much lower in the group of men treated with testosterone compared to the untreated men (10% in the testosterone-treated group *vs.* 21% in the untreated group). There were a number of methodological criticisms levied against this study including a failure to discuss and explain this discrepant, unadjusted absolute rate or to fully describe the statistical adjustments that resulted in the complete reversal of absolute events. The second study published shortly after this angiogram study showed an increased risk of myocardial infarction in middle-aged men after they were prescribed testosterone compared to men who were prescribed sildenafil [60]. This study also had a number of flaws including the lack of an appropriate control group, retrospective design, lack of any clinical data other than diagnostic codes and prescription refills, lack of formal adjudication of myocardial infarctions, and an assumption that men prescribed a phosphodiesterase inhibitor (sildenafil) had similar cardiovascular risk as the group that was prescribed testosterone. Subsequent large pharmaco-epidemiological studies demonstrated no association or decreased risk of myocardial infarction with testosterone therapy, and the largest pharmacy database study of testosterone-treated men demonstrated a 24% decreased risk of myocardial infarction associated with testosterone therapy [42, 46, 47, 49, 61–67]. A 2018 meta-analysis of pharmaco-epidemiological studies demonstrated a decreased risk of myocardial infarction with testosterone therapy [50].

There are limited data about cardiovascular safety from randomized controlled studies of testosterone therapy. The most rigorous recent (2017) meta-analysis that included 16 randomized controlled trials with myocardial infarction as an outcome concluded that there was no significant association between testosterone therapy and incident risk of myocardial infarction, but the evidence was rated very low quality [68]. (Note that the 2017 meta-analysis attempted a separate meta-analysis of epidemiological studies and determined that the heterogeneity was too great to perform a meta-analysis.) A 2021 systematic review and meta-analysis identified six observational studies and two randomized controlled studies of hypogonadal men treated with testosterone *vs.* no testosterone therapy that included data on myocardial infarction [69]. The authors included studies that defined hypogonadism based solely on serum total testosterone concentrations < 300 ng/mL, and these studies did not have data on symptoms or signs of hypogonadism. To achieve low heterogeneity, the authors performed a sensitivity analysis and eliminated two of the six epidemiological studies. In a combined meta-analysis of just 4 epidemiological studies and 2 randomized controlled trials, the odds ratio of myocardial infarction was not statistically different between the testosterone-treated and non-testosterone-treated groups (testosterone-treated *vs.* non-testosterone-treated: 2.2% *vs.* 2.7%, OR 0.87, 95% CI 0.75–1.01; P = 0.08). Although this 2021 meta-analysis included over 10,000 testosterone-treated men, > 85% were in a single epidemiological study [47], and only 256 were in the two randomized-controlled studies [53, 56].

The findings of the 2017 and 2021 meta-analyses were concordant and similar to earlier meta-analyses of randomized controlled studies that also demonstrated no effect of testosterone therapy on incident risk of myocardial infarction [70]. The published meta-analyses have varied widely in the inclusion of studies, but all of the meta-analyses have been limited by the inclusion of studies that were underpowered for cardiovascular outcomes, lack of rigorous criteria for cardiovascular events, and relatively short follow-up [68, 70].

In summary, the current data suggest that there is no association between serum endogenous testosterone concentrations or exogenous testosterone therapy and risk of myocardial infarction. However, the current evidence is too weak to make a firm conclusion. It is likely that any beneficial or adverse effect of endogenous testosterone concentrations or testosterone replacement therapy on myocardial risk is small, and it will require very large numbers of men in randomized, controlled studies and carefully designed, large prospective cohort studies to determine if there is an effect [68].

6.2 The effects of endogenous and exogenous testosterone (and its major metabolites) on the risk of stroke

Epidemiological studies of endogenous testosterone concentrations generally have demonstrated no association or an inverse relationship between serum endogenous testosterone and stroke [23, 29, 30, 34, 57, 71–75]. A 2015 meta-analysis of cohort four studies demonstrated no association between serum endogenous testosterone concentrations and

strokes [74]. None of the above epidemiological studies distinguished between ischemic or hemorrhagic stroke, but a 2022 study of > 200,000 men demonstrated no association between serum endogenous testosterone concentration and ischemic or hemorrhagic stroke [58].

One epidemiological study showed an association between higher serum endogenous estradiol concentrations and increased incident risk of stroke, but one showed no such association [57, 71]. Two other cohort studies demonstrated an increased risk of stroke with low serum endogenous DHT concentrations with one study demonstrating a J-shaped curve between serum endogenous DHT concentration and stroke [57, 73]. A fifth cohort study found an association between higher serum estradiol concentrations and lower risk of stroke [23].

Two Mendelian studies linked variants in the *JMJD1C* gene with higher serum endogenous concentrations with a possible small increase in incident risk of ischemic stroke in men [59, 76]. However, these variants have no clearly defined physiologic mechanism of regulating testosterone production and might be affecting stroke risk by other mechanisms [57, 76]. As acknowledged by the investigators of the two studies, this "tentative conclusion represents the current limit of what can be learned using a Mendelian randomization approach with these variants" [76].

Large pharmaco-epidemiological studies have shown no change in incident risk or decreased incident risk of stroke associated with testosterone therapy [46, 47, 49, 64, 65]. As with myocardial infarction, the current data suggest that testosterone replacement therapy for male hypogonadism (defined as symptoms and signs of testosterone deficiency, reproducibly low serum testosterone concentrations, and an identified disorder of the hypothalamus-pituitary axis) has no effect on the risk of stroke. B.

6.3 The effects of endogenous and exogenous testosterone (and its major metabolites) on the risk of venous thromboembolic disease (deep venous thrombosis and/or pulmonary embolism)

Epidemiological studies have shown no association between endogenous serum testosterone concentrations and venous thromboembolic disease (VTE) [77, 78]. More recently, Mendelian studies demonstrated an association between genes associated with increased endogenous serum testosterone (and an inverse association with endogenous serum estradiol) concentrations and an incident risk of VTE [59, 79].

The potential causal relationship between exogenous testosterone use and an increased risk of VTE has been highly controversial since the United States FDA issued a "black box" warning in 2014. There are mixed data about the biological plausibility of exogenous testosterone and increased thrombophilia [80, 81] and the original basis for the original FDA warning was based on case reports [82]. All but one [82] of the pharmaco-epidemiological studies of testosterone therapy indicate that there is no increased risk of VTE with testosterone replacement therapy [42, 83–87].

A 2021 systematic review and meta-analysis of > 5000 men in 13 clinical studies of exogenous testosterone therapy and incident VTE concluded that the "evidence suggests that [testosterone replacement therapy] is not associated with increased risk of VTE" [82]. The majority of the studies that formed the basis of this conclusion had moderate to high risk of bias due to unclear or suboptimal methodology for detection of VTE or unclear randomization of study participants. A 2018 systematic meta-analysis made similar conclusions [88].

The largest study (accounting for > 30% of weight of the findings) in the meta-analysis was a pre-defined subset of the United States Testosterone Trial. In this one-year study, 390 older men (mean age 72) with low serum testosterone but no identified cause of hypogonadism were randomized to transdermal testosterone gel or placebo; 4 incidents of VTE occurred in the testosterone-treated group and 5 in the placebo-treated group [54]. Although some investigators have suggested that there might be an early effect (< 6 months) of increased VTE risk with testosterone replacement therapy [85], the results of the Testosterone Trial argues against the likelihood of this early adverse effect [54, 82].

In summary, based on several epidemiological studies and a small number of clinical trials that were generally short in duration (≤ 1 year) and potentially biased, the evidence suggests that testosterone replacement therapy does not increase the risk of idiopathic VTE. The evidence does not exclude the possibility that testosterone replacement therapy might increase the risk of VTE in men with underlying thrombophilia or that pharmacological dosages of testosterone (including men with baseline normal serum testosterone concentrations and no identified cause of hypogonadism) might increase the risk of VTE.

6.4 The effects of endogenous and exogenous testosterone on the risk of heart failure

One prospective cohort study in the United States demonstrated an association between lower serum endogenous testosterone concentrations and increased incident risk of heart failure in men, but another prospective study in Europe found no such association [89, 90]. A very large study using a United Kingdom national database demonstrated no association between low baseline serum endogenous total and calculated free testosterone concentrations and incident risk of heart failure at follow-up (mean follow-up = 9 years) [58]. Curiously, that study found an association between lower sex hormone binding globulin and lower incident risk of

heart failure [58]. A 2020 meta-analysis that included 7 randomized, placebo-controlled trials of men with heart failure demonstrated a small increase in average systolic blood pressure (~6 mm Hg), but no significant association with change in left ventricular dysfunction, functional outcomes such as exercise capacity, or clinical outcomes such as death or hospital admissions for heart failure [91]. These studies did not enroll patients with classic hypogonadism, and many of the participants had normal baseline serum testosterone concentrations. Three of the 7 studies used lower than typical replacement dosages of testosterone, and all of the studies were short in relatively short term (3–12 months).

Based on limited data, testosterone does not appear to have a major role in the pathogenesis, exacerbation or treatment of heart failure, but low serum testosterone concentrations might be a marker of poor prognosis in men with heart failure.

6.5 The effects of endogenous and exogenous testosterone (and dihydrotestosterone) on the risk of atrial fibrillation

There is a modest number of prospective cohort studies of the association of testosterone and incident risk of atrial fibrillation in men, and these studies have yielded mixed results. Two prospective cohort studies have demonstrated an inverse relationship between baseline serum endogenous testosterone concentrations and incident risk of atrial fibrillation in middle-aged to older men, and a third such study found the same association in men > 80 years old [75, 92, 93]. Another prospective cohort study found increased incident risk of atrial fibrillation with baseline low serum endogenous DHT concentrations, but no association between baseline serum testosterone concentrations [94]. Two prospective cohort studies found an association between higher baseline serum total or bioavailable testosterone (testosterone not bound to sex hormone binding globulin) concentrations and incident risk of atrial fibrillation [95, 96]. There is one pharmaco-epidemiological study examining the association of testosterone therapy with atrial fibrillation in male veterans with low serum baseline testosterone concentrations [97]. In this database study, the group of men who achieved serum testosterone concentrations in the normal range during testosterone concentrations in the normal had a lower incident risk of atrial fibrillation than the group of men with low serum testosterone concentrations and no testosterone replacement therapy or the group who had low or high serum testosterone concentrations during testosterone replacement therapy. This study is difficult to interpret because the relationship of the timing of testosterone administration and serum testosterone concentration assessment was not determined. However, the study suggests that testosterone therapy at typical replacement dosages is unlikely to increase the risk of atrial fibrillation for men with low serum testosterone concentrations.

The current evidence precludes a firm conclusion about the role of testosterone in the pathophysiology and incidence of atrial fibrillation, but it seems unlikely that serum endogenous testosterone concentrations or testosterone replacement have a large effect on this common cardiac arrhythmia.

6.6 Summary of the effects of endogenous and exogenous T on specific cardiovascular outcomes: myocardial infarction, stroke, VTE, heart failure or atrial fibrillation

Overall, the current evidence is reassuring that testosterone replacement therapy at typical dosages for bona fide male hypogonadism is unlikely to greatly increase the risk of myocardial infarction, stroke, VTE, heart failure or atrial fibrillation (Fig. 2a). The available evidence is inconclusive to determine there might be small effects on the risk of these specific cardiovascular disorders. It is also possible that testosterone replacement therapy might increase cardiovascular risk in specific cohorts of men such as men with a recent myocardial infarction (< 1 month prior) or men with recurrent idiopathic VTE. In those populations, the benefits and risks of testosterone replacement therapy must be carefully assessed.

7 High-dosage testosterone use and androgenic steroid abuse

Chronic abuse of high dosages of androgens has been associated with myocardial infarction, stroke, cardiomyopathy, arrhythmia, conduction abnormalities, hypercoagulability, increased atherosclerosis hypertension and dyslipidemia [98, 99]. The evidence for these adverse cardiovascular is weak and is based on case reports and series, case–control studies and cross-sectional studies [98, 99]. Moreover, men who abuse high dosages of androgens are more likely to use tobacco products and abuse alcohol, cocaine, methamphetamine and other illicit drugs [98, 99]. These significant confounders are known to cause many adverse cardiovascular outcomes. Nonetheless, the potential cardiovascular risks of high dosages of testosterone and other androgens outweigh the unknown health benefits for athletes and body builders who are using these compounds as performance enhancers (Fig. 2b).

Uncertainty about the potential adverse effect of supraphysiological dosages of androgens is clinically important and factors in the decision-making for dosage

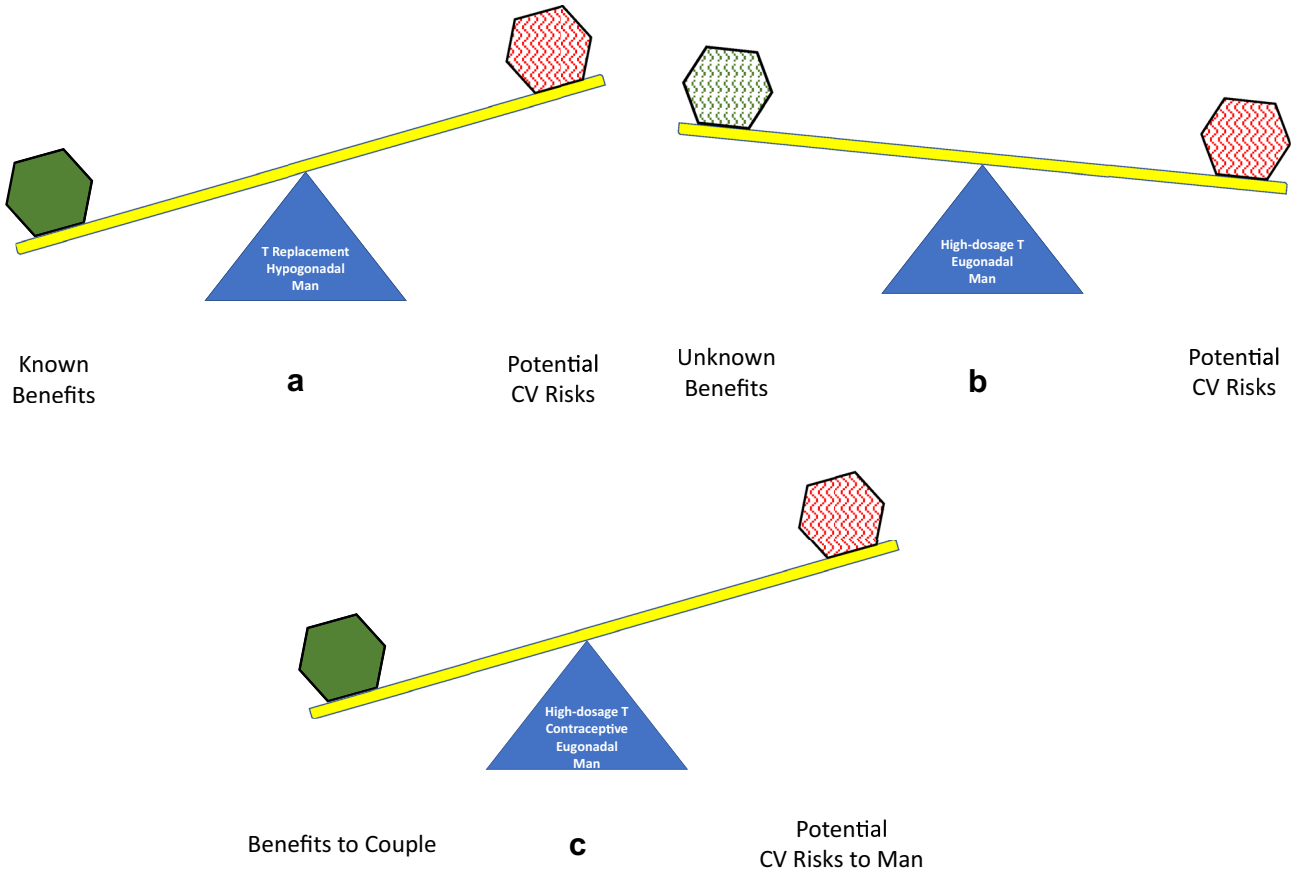

Fig. 2 The benefit *vs.* risk ratio for testosterone-based therapies in hypogonadal men, eugonadal men and for a prototype male hormonal contraception. **a** For hypogonadal men, the proven benefits of testosterone replacement therapy (e.g., improved sexual function, muscle mass and strength, bone mass and strength and overall sense of well-being) exceed the small potential (unproven) adverse effects on incident cardiovascular risk; **b** For eugonadal men who are taking testosterone therapy to increase muscle mass and strength above the level achieved with exercise, the small potential adverse effects on incident cardiovascular risk outweigh the (unproven) potential benefits; **c** For an effective (≥95% efficacy) androgen-based prototype male hormonal contraceptive, the benefits to the couple include agency over reproduction for the man and increased overall health safety for the couple (e.g., decreased anxiety about unwanted conceptions for the man and woman and decreased health risks associated with pregnancy and with female contraceptives for the woman). These benefits would be greater than the small potential (unproven) adverse effects on incident cardiovascular risk for the man

adjustment of testosterone replacement therapy and for the initiation of testosterone therapy. It is good practice to generally avoid prescribing amounts of testosterone that provide significantly more than 5–10 mg of testosterone daily, an amount that approximates the usual daily of testosterone production of 5–7 mg in eugonadal men. Most men with slightly low or low-normal serum testosterone concentrations, no specific symptoms or signs of male hypogonadism, and no identifiable disorder of the hypothalamus-pituitary–testicular axis are eugonadal and would require supraphysiological dosages of testosterone to increase their serum testosterone concentrations. The potential cardiovascular risks of exogenous testosterone might outweigh the unproven health benefits for the majority of these men (Fig. 2b).

8 Exogenous estrogen trials and cardiovascular risk

High dosages of oral estrogen have been demonstrated to increase the risk of nonfatal cardiovascular events and VTE in men with a history of myocardial infarction; the Coronary Drug Project clearly demonstrated that conjugated equine estrogen at dosages of 2.5 and 5.0 mg were deleterious to this cohort [100]. It remains uncertain whether lower, physiologic dosages of estrogen in the form of estradiol would affect cardiovascular risk in men. Because exogenous estradiol therapy suppresses circulating gonadotropins and testosterone in men, only men being treated with low serum estrogen and testosterone concentrations due to androgen deprivation therapy (e.g.,

men with high grade or metastatic prostate cancer) might benefit from studies of physiological estradiol replacement or selective estrogen receptor modulators to determine if bone health can be maintained while improving or at least not increasing the incident risk of cardiovascular and VTE events.

9 Exogenous dihydrotestosterone trials and cardiovascular risk

A single study of exogenous DHT has been reported [101]. In this study, 114 healthy men > 50 years old were randomized to high dosage DHT for 2 years that resulted in about a tenfold increase in mean serum DHT concentrations and significant suppression of serum gonadotropin, testosterone and estradiol concentrations. The DHT dosage was sufficient to cause a net increase in androgen effect with an increase in hematocrit, lean body mass and hand grip strength and a decrease in fat mass. At the end of treatment, the DHT-treated group had a small but significant increase in systolic blood pressure (6 mm Hg), but no significant differences in major serum lipoprotein concentrations and carotid intimal thickness compared to the placebo group. There were two major cardiovascular events in each group.

10 Investigational male hormonal contraceptives and cardiovascular risk

There has been interest in development of effective, reversible, androgen-based male hormonal contraceptive regimens for decades. There have been six bona fide efficacy trials (and one descriptive study) of testosterone or testosterone plus a progestin regimen [102–108]. These contraceptive trials have demonstrated ≥ 95% efficacy— a rate that is superior to male condoms and compares favorably to female hormonal contraceptives. There have been no adverse cardiovascular events in any of these trials. However, these studies have been short in duration (≤ 2.5 years of drug exposure), and the participants have been young (18–50 years old) and healthy.

In these clinical trials of androgen-based male hormonal contraceptives, potential adverse cardiometabolic effects have included weight gain (average ~1–4 kg) and modest suppression of serum high density cholesterol (HDL) concentrations (average ~5–25%). There has been no documentation of adverse effects on systolic or diastolic blood pressure or serum LDL or non-HDL cholesterol concentrations, but these data were not systematically measured or reported in all of the efficacy studies. Although these initial studies did not demonstrate any safety signal for potential male hormonal contraceptives, these studies were not designed to determine cardiovascular safety with longer-term use or in older men, men with significant cardiometabolic risk factors or known cardiovascular disease.

The calculation of the benefit to risk ratio for prospective androgen-based male hormonal contraceptive is more complex than an analysis of the man taking the male hormonal contraceptive because the man's female sexual partner(s) has significant health benefits (Fig. 2c). The benefits to the female include decreased risk of pregnancy and delivery with their attendant health risks (e.g., VTE and pre-eclampsia). The cardiovascular risks due to testosterone (or another androgen) are likely to be minimal because the dosages used in prototype contraceptives are similar to typical replacement regimens for treatment of male hypogonadism.

11 Potential mechanisms of cardiovascular risk effects of testosterone and its metabolites

There are several potential mechanisms for testosterone to affect cardiovascular risk (Fig. 3). There are effects that might be deleterious including decreased HDL cholesterol, erythrocytosis and increased blood viscosity, and salt and water retention or beneficial including decreased lipoprotein(a), improved cardiac function and aerobic function, coronary arterial vasodilation, and decreased fat mass, and possible decreased risk or delay in development of diabetes mellitus (Fig. 3; for recent reviews, please see Gagliano-Juca and Jones) [109, 110].

12 Future studies of testosterone therapy and cardiovascular risk

There are three broad groups of men that would most benefit from more extensive study of the cardiovascular effects of testosterone therapy: hypogonadal males, middle-aged to older men with low serum testosterone concentrations and no identifiable disorder of the hypothalamus-pituitary–testicular axis, and eugonadal men taking pharmacological dosages of testosterone. For hypogonadal males, prospective case–control of studies boys and men with enrollment at the time of initiation of testosterone would be invaluable. These studies could be done in countries with regional or national health registries and could be funded by manufacturers of testosterone formulations. For middle-aged and older men with low serum testosterone concentrations and no identifiable disorder of the hypothalamus-pituitary–testicular axis, randomized, placebo-controlled studies are key. The United States TRAVERSE study is the first such study. It is a 5-year study of 5,246 men, ages 45–80 years old, at high risk of cardiovascular events and a serum total testosterone concentration < 300 ng/dL (https://www.clinicaltrials.

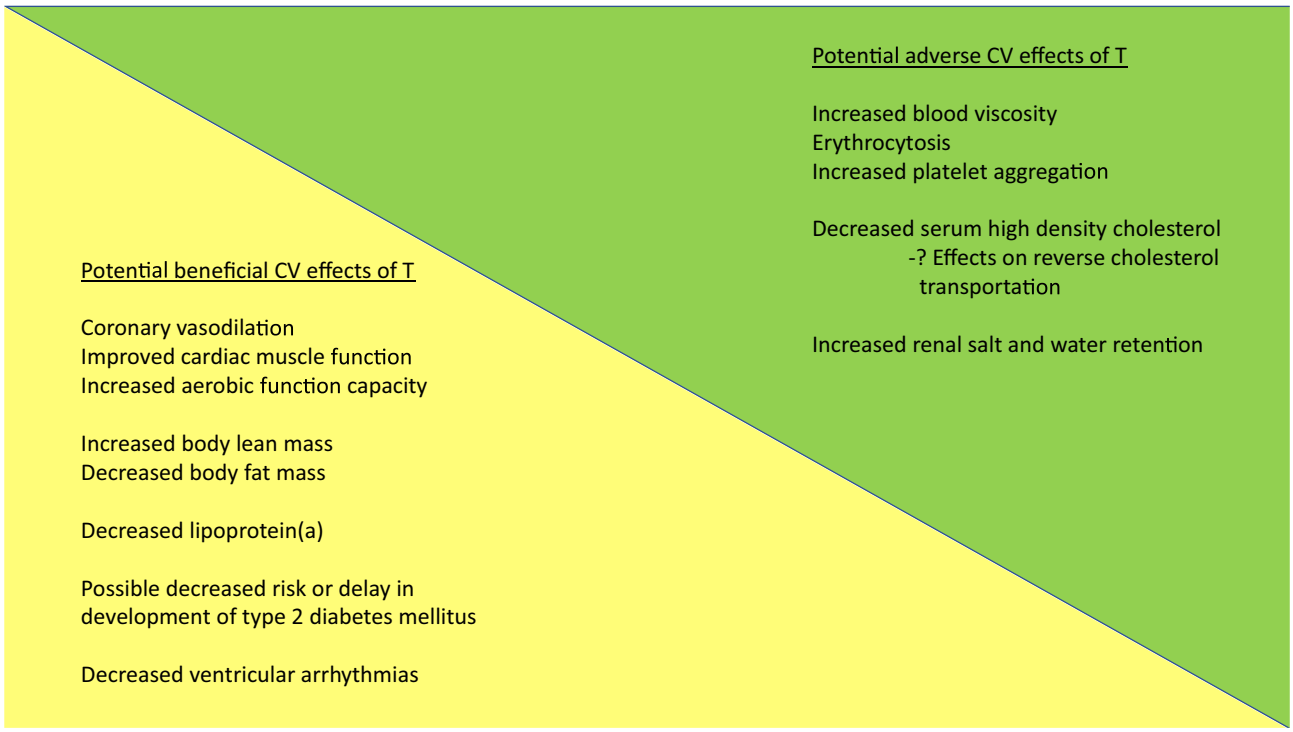

Fig. 3 Potential mechanisms for beneficial and adverse cardiovascular effects of testosterone

gov/ct2/show/NCT0351803). The primary outcome is the time to the aggregate of nonfatal myocardial infarction, nonfatal stroke, cardiovascular revascularization or cardiovascular death. Enrollment has been completed, and there has been no early discontinuation of the study—suggesting no clear safety signal. The initial results are expected to be announce in 2023. For eugonadal men using androgenic steroids, the most useful initial studies would be follow-up cohort studies using national registries; the use of randomized response questionnaire techniques and enrollment into a de-identified database that is linked to the cardiovascular risk factors and outcomes in a national health registry would ensure anonymity and greatly enhance recruitment and reliability of results.

13 Summary

Most of the data on the effects of endogenous and exogenous testosterone is derived from epidemiological studies (Fig. 1). The majority of the epidemiological studies demonstrate no association between serum concentrations of endogenous testosterone on major cardiovascular outcomes including overall mortality, cardiovascular deaths, myocardial infarction, stroke, and VTE, heart failure and atrial fibrillation. Some epidemiological studies demonstrate an inverse relationship between serum endogenous testosterone concentrations and major cardiovascular outcomes, but that inverse association is likely due to reverse causation.

Based on pharmacoepidemiological studies and a small number of randomized controlled studies that were not designed to assess cardiovascular outcomes, there is no adverse safety signal for major cardiovascular outcomes in men treated with testosterone therapy at typical replacement or near-replacement dosages.

14 Conclusions and clinical guidance

The past 50 years of research have clarified that testosterone and estradiol are not Manichean hormones: testosterone is not "bad for the human heart" nor is estradiol "good for the human heart". Although epidemiological studies suggest a strong benefit of estrogen therapy for menopausal women, randomized controlled trials failed to confirm this benefit. Based on randomized, controlled trials of estrogen therapy with or without the addition of a progestin, there is a small increased risk of major cardiovascular events in certain cohorts of women such as women over age 60 years initiating this hormone therapy years after menopause. However younger women who initiate hormone therapy early on the onset of menopause might benefit or at least to have little or no increased cardiovascular risk. There is no equivalent evidence base derived from randomized, placebo-controlled

trials of testosterone therapy for men with low serum testosterone concentrations. However, as with menopausal women treated with estrogen therapy, the cardiovascular risk associated with testosterone therapy for hypogonadal men is likely to have a small effect. As women and estrogen, the cardiovascular risk is also likely to vary based on the age and underlying health (including the hypothalamus-pituitary–testicular axis function) of the man, the dosage of testosterone and possibly the formulation of testosterone.

For clinicians and patients, the current evidence about the cardiovascular risk of testosterone therapy in men favors the following conclusions:

1. Testosterone therapy should not be initiated to men with low serum endogenous testosterone concentrations in order to reduce cardiovascular risk.
2. The benefits of testosterone therapy for improved quality of life, sexual function, increased muscle mass and strength, and bone health outweigh the potential cardiovascular safety concerns in most men with hypogonadism due to an identified disorder of the hypothalamus-pituitary-testicular axis. (Fig. 2a)
3. For men with borderline low-normal serum testosterone concentrations, the potential adverse cardiovascular effects of testosterone outweigh the unproven benefits of exogenous testosterone therapy (Fig. 2b).
4. Men who are initiated on testosterone therapy should be informed the United States Food and Drug Administration and Health Canada agencies have issued warnings about possible increased risk of myocardial infarction, stroke and venous thromboembolic disease with testosterone therapy, but the European Medicines Agency and Australian Therapeutic Goods Administration concluded there was no consistent evidence or a weak signal (respectively) for concerns about cardiovascular safety with testosterone therapy.
5. For hypogonadal men with hypogonadism due to an identified disorder of the hypothalamus-pituitary-testicular axis with high risk of cardiovascular events (e.g., men with a myocardial infarction in the past month or men with recurrent venothromboembolic events), the benefit-ratio should be considered before initiation of testosterone therapy and alternative therapies for specific conditions (e.g., bisphosphonates to increase bone density in men at higher risk of developing osteoporosis) should be considered.

The current evidence for testosterone and incident risk of cardiovascular events is weak, but the evidence supports the conclusion that, at worst, any increase in absolute risk of adverse cardiovascular effects is likely to be small. However, that small possible risk is enough to discourage clinicians and patients to avoid promiscuous testosterone prescription without a strong rationale for such therapy.

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Declarations

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