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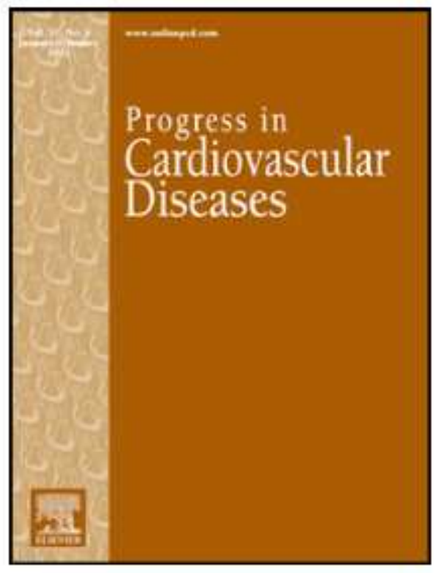

Testosterone therapy and the risk of cardiovascular disease in older, hypogonadal men

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PII: S0033-0620(24)00036-7
DOI: https://doi.org/10.1016/j.pcad.2024.02.015
Reference: YPCAD 1455

To appear in: *Progress in Cardiovascular Diseases*

Please cite this article as: S. Krishnan, J. Aldana-Bitar, I. Golub, et al., Testosterone therapy and the risk of cardiovascular disease in older, hypogonadal men, *Progress in Cardiovascular Diseases* (2023), https://doi.org/10.1016/j.pcad.2024.02.015

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Keywords: Testosterone therapy; hypogonadism; atherosclerosis and testosterone; aging, obesity, and testosterone; cardiovascular disease; coronary artery disease; coronary artery calcium; non-calcified plaque; TRAVERSE trial.

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Conflict of interest:
Matthew J. Budoff: received grants from the following companies: Novo Nordisk, Novartis, Astrazeneca, Heartflow, GE Healthcare, Amgen, and Boehringer Ingleheim, Department of Defense, Centers for Disease Control and the National Institutes of Health. Dr Budoff received honoraria from Novo Nordisk, Esperion, Astrazeneca, Merck, Janssen, and Eli Lilly

All other authors declare they have no conflict of interest.

Abstract:

The debate over the cardiovascular (CV) implications of testosterone therapy (TT) have resulted in diverging safety recommendations and clinical guidelines worldwide. This narrative review synthesizes and critically evaluates long-term studies examining the effects of TT within the context of aging, obesity, and endogenous sex hormones on CV disease (CVD) risk to support informed clinical decision-making. Observational studies have variably linked low endogenous testosterone with increased CVD risk, while randomized controlled trials (RCTs) demonstrate that TT yields cardiometabolic benefits without increasing short-term CV risk. The TRAVERSE trial, as the first RCT powered to assess CVD events, did not show increased major adverse cardiac events (MACE) incidence; however, its limitations – specifically the maintenance of testosterone at low-normal levels, a high participant discontinuation rate, and short follow-up – warrant a careful interpretation of its results. Furthermore, findings from the TTrials cardiovascular sub-study, which showed an increase in non-calcified plaque, indicate the need for ongoing research into the long-term CV impact of TT. The decision to initiate TT should consider the current evidence gaps, particularly for older men with known CVD. The CV effects of maintaining physiological testosterone levels through exogenous means remain to be fully explored. Until more definitive evidence is available, clinical practice should prioritize individualized care and informed discussions on the potential CV implications of TT.

Alphabetical list of abbreviations:

BMI - Body Mass Index

CAC - Coronary Artery Calcium

CCTA - Coronary Computed Tomography Angiography

CHF - Congestive Heart Failure

CI - Confidence Interval

CIMT - Carotid Intima-Media Thickness

CV - Cardiovascular

CVD - Cardiovascular Disease

DM - Diabetes Mellitus

GnRH - Gonadotropin-Releasing Hormone

LH - Luteinizing Hormone

MACE - Major Adverse Cardiovascular Events

NCP - Non-Calcified Plaque

RCT - Randomized Controlled Trial

SHBG - Sex Hormone-Binding Globulin

TEAAM - Testosterone's Effects on Atherosclerosis Progression in Aging Men

TOM - Testosterone in Older Men with Mobility Limitations

TPV - Total Plaque Volume

TRAVERSE - Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men

TT - Testosterone Therapy

TTrials - Testosterone Trials

1. Introduction

The interplay between testosterone and cardiovascular (CV) health has been the subject of a yearslong debate, underscored by an evolving body of evidence and a growing testosterone therapy (TT) market[1]. A lack of consensus further complicates clinical decision-making, and

regulatory perspectives on TT's CV safety diverge internationally. 2015 Food and Drug Administration guidelines recommend the reservation of TT for symptomatic hypogonadism only. They caution against TT's use for age-related testosterone decline, citing potential CV disease (CVD) risks observed in several observational studies and metanalyses[2-7]. These alerts are not mirrored by European counterparts. Rather, the European regulatory body emphasizes a lack of conclusive and consistent evidence: insufficient to link TT with CVD[8].

This discord pervades the sphere of literature, trials, and meta-analyses as well[9]. Numerous randomized controlled trials (RCT's) have shown cardiometabolic improvements with TT, including improved lipid profiles and glycemic control. In turn, observational studies have not evidenced increased CVD risk in the short- to medium-term. And yet, retrospective studies present conflicting results. Some retrospective analyses demonstrate increased CVD events post-TT, while others show neutral or beneficial effects[2-7, 10-11]. This complex evidence landscape has left clinicians to carefully navigate the potential risks and benefits of TT.

In light of these considerations, this narrative review will examine the broader context of sex hormones and CV risk profiles. Here, we aim to synthesize and critically evaluate an extensive list of long-term studies which assess TT's CVD risk profile. In doing so, we hope to empower clinicians' informed, shared decision making with their patients regarding TT and its associated CV risks.

2. A Multi-Faceted Intersection: Aging, Obesity, and Sex Hormones with CVD Risk

Before synthesizing literature to assess TT's CVD risk profile, this review will first examine the relationship between endogenous sex hormones, aging, and obesity upon CVD risk.

Endogenous estrogens in pre-menopausal women are thought to have vasculoprotective effects. This understanding contrasts directly with the observed increase in CVD risks associated with androgenic hormone patterns in aging men: particularly within the context of obesity[12]. However, there is little data to support the hypothesis that elevated testosterone levels may be linked to the higher age-adjusted CVD event rates in men. Rather than via sole differences in sex hormone concentrations, CVD outcomes are instead influenced by diverse factors such as age, disease type, and potentially extrinsic factors such as socioeconomic status. Building from these themes, numerous studies challenge the notion that the impacts of estrogen and testosterone can be categorized as uniformly beneficial or harmful[13-16].

An alternative hypothesis suggests that testosterone may, instead, confer uniquely positive CV benefits. This is based specifically upon observations that low testosterone levels have been associated with increased risk for adverse cardiometabolic conditions, including inflammation and atherosclerosis[17]. Even so, prospective and longitudinal studies do not show a strong association between testosterone concentrations and the likelihood of future CVD events, CVD-related mortality, or mortality from all causes[18-20].

Risk for adverse cardiometabolic conditions is particularly prevalent in context of aging and obesity. Age-related decline in the hypothalamus-pituitary-testicular axis function leads to impaired hypothalamic secretion of gonadotropin-releasing hormone (GnRH), ultimately resulting in decreased pituitary gland secretion of luteinizing hormone (LH)[21-22]. Testicular Leydig cells of older men also become less responsive to LH compared to young men. This pattern yields a gradual annual decline of approximately 2% per year in bioavailable testosterone levels in aging men, beginning around the fourth decade of life[23]. Physiology partially mitigates this downward trend, via decreased testosterone metabolism and increased organ-specific

androgen sensitivity[24]. These mechanisms to conserve testosterone in aging men may, in turn, amplify the effects of androgen replacement or supplementation therapy. In doing so, they reveal implications regarding the safety of TT.

In addition to its effects upon the endocrine system, aging is associated with increased body mass index (BMI) and visceral fat. These physical changes correlate with lower serum Sex Hormone-Binding Globulin (SHBG) levels, a protein essential for transporting sex hormones, including testosterone. While aging is associated with increased serum SHBG, increased BMI is associated with lower SHBG. The latter's influence is significantly more pronounced, and BMI often serves as a tipping point to lower SHBG levels in older men. The interplay between aging, obesity, and the hypothalamus-pituitary-testicular axis is multifaceted — each affecting SHBG with its own weight of influence and, as a result, the levels of both total and free testosterone levels. To make matters more nuanced, BMI and specific functional impairments in these axes may titrate SHBG levels even further. Obesity often impacts the hormonal axis independently, by reducing the secretion of GnRH due to the action of leptin on hypothalamic neurons, and subsequently reducing testosterone biosynthesis[21,25].

Aging and obesity are not only linked with decreased circulating testosterone levels but are themselves independent risk factors for CVD. Age is a central component of pooled cohort CVD risk calculators[26]. Obesity represents a modifiable risk factor for the development and progression of CVD[27]. This dual association emphasizes the importance of understanding this complex interplay, especially given an aging global demographic.

The Multiethnic Study of Atherosclerosis (MESA) demonstrated a correlation between lower testosterone levels in men and a higher incidence of metabolic diseases and atherosclerosis, as evidenced by increased coronary artery calcium (CAC) scores[28]. These scores,

obtained from non-contrast computed tomography (CT), measure the calcified plaque burden in coronary arteries. CAC scoring serves as a predictive tool for future CVD events and mortality, an integral component in CVD risk assessment[29].

Although causality cannot be inferred from the MESA, implications of its findings are twofold. First, if low testosterone contributes to CVD risk, then targeting this hormonal pathway may offer a preventative strategy for preserving health in aging men. Alternatively, if testosterone levels have no causative role in CVD risk and serve simply as a biomarker for health status and CV risk, they might prove valuable in risk stratification. In other words, testosterone levels may help identify individuals who receive benefit from targeted, non-hormonal interventions that address traditional CVD risk factors.

3. Review of Literature: TT and its Impact upon CVD

This review has now detailed a thorough physiological background, exploring the complex and multi-faceted intersection of aging, obesity, and sex hormones with CVD risk. Now, we transition to discuss the extensive breadth of literature surrounding TT and CVD.

3A. Early TT Trials

Initial trials evaluated the relationship between TT and CV health in specific populations, such as those with chronic stable angina or congestive heart failure (CHF)[30-38]. Most trials utilized exercise capacity as a primary outcome and surrogate for CV health. Several studies evidenced TT's impact upon exercise capacity improvement, angina reduction, and diminished ischemic electrocardiogram changes. These trials were instrumental to initiating the exploration of TT's effects on CV health, yet many limitations prevented their generalizability. Limitations

included the following: sample size, study duration, use of indirect measures of CV health rather than events, as well as a focus on specific populations such as CHF and chronic stable angina.

The Copenhagen Study Group trial was one of the first to report increased mortality with TT[39]. The study, conducted in 1986, was not designed to evaluate CVD risk specifically. Rather, the Copenhagen Study Group investigated the effects of high-dose oral testosterone in men with alcohol cirrhosis. The trial was terminated early after a median of 28 treatment months, given a trend toward increased mortality. Adjusted relative mortality was 1.17 (95% CI: 0.66–2.15). Despite early termination, only one of the 33 deaths in the TT group was attributed to a CVD event (myocardial infarction). This limited number of CVD deaths suggests that the increased mortality was likely related to complications from cirrhosis, rather than direct CV effects of TT.

In contrast, the 2009 Testosterone in Older Men with Mobility Limitations (TOM) trial investigated the safety of TT in older men with mobility limitations and low to low-normal serum testosterone levels[40]. This trial randomized participants to receive either 10 grams of 1% testosterone gel or placebo. Like the Copenhagen Study Group before it, TOM was prematurely stopped due to a rise in CVD events in the testosterone group. However, several limitations should be considered when interpreting this study. First, the primary aim was to evaluate improvements in functional status, not CVD outcomes. Second, the TT dose in the study was higher than commonly used in clinical practice. Mean serum testosterone levels during treatment were comparable to those observed in other studies involving older men; however, those studies included healthier men without significant CVD risk factors or existing CVD. TOM's cohort, in contrast, included participants with the following characteristics: 25% had diabetes, 50% were obese, more than 80% had hypertension, and about 50% had preexisting CVD. These comorbidities, combined, were likely to have contributed to the observed CV events as opposed

to TT alone. Moreover, the CVD events were diverse. They included atherosclerotic and non-atherosclerotic related events, suggesting multiple potential mechanisms rather than a single cause. This combination of study design, TT dosage, CVD event variety, with high cohort prevalence of CVD risk factors and CVD limits the interpretation of TOM's results.

3B. The TEAAM Trial

Now we transition from the earlier testosterone therapy trials, with poorer generalizability and greater limitations, to discuss instead RCT's that relied upon sub-clinical atherosclerosis as a marker for CVD.

The 2015 Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial assessed TT's impact on the progression of subclinical atherosclerosis in older men with low or low-normal testosterone[41]. TEAAM investigators randomized participants to either 7.5g of 1% transdermal testosterone gel or placebo. Over a three-year treatment period, there were no differences in the rates of change of carotid intima-media thickness (CIMT) (0.012 mm/year in the TT group and 0.010 mm/year in the placebo group, $p = 0.89$), CAC (31.4 Agatston units/year in the TT group and 41.4 Agatston units/year in the placebo group, $p = 0.54$), serum lipids, or blood glucose. The trial also found a similarly low incidence of MACE between the two subgroups. Limitations of the study included its three-year duration, which may not have been sufficient to detect long-term CVD risk associated with TT. Moreover, TEAAM's study design focused on detecting changes in CIMT and CAC, rather than CVD events themselves.

3C. Biomarkers in Assessing Sub-Clinical Atherosclerosis

To better understand the role of TT in primary CVD risk prevention, let us pause our literature review and shift our focus to upstream indicators of CVD events. In other words, let us investigate platforms for assessing sub-clinical atherosclerosis.

CIMT, an ultrasound measure of thickness in the carotid artery lining, is a potential marker of early atherosclerosis. Compared to ultrasound assessment of carotid plaque presence, however, CIMT is less predictive. CAC scoring, in turn, has been directly compared to CIMT and carotid plaque scoring, within several observational and prospective studies[42-43]. Initial hypotheses predicted that CAC would not predict stroke as effectively as CIMT. However, despite its anatomical distance from the carotid artery bed, coronary artery calcium presence and burden are strong predictors for CVD events (including stroke and transient ischemic attack). This well-established finding is likely rooted in atherosclerosis being a systemic process. CAC presence and CAC score, in fact, are both superior to CIMT for predicting CV events.

While CAC is a well-established prognostic tool, it is not a comprehensive measure of atherosclerotic burden. Focusing solely upon CAC, without also considering non-calcified plaque (NCP) in the coronary arteries, may overlook changes in other categories of plaque relevant to CVD risk. Honing into CAC alone also ignores the timeline of atherosclerosis development; CAC typically manifests in the later stages of atherogenesis. Coronary atherosclerosis initiates as fatty streaks within the arterial wall, which then develop into noncalcified plaque – composed of lipids, inflammatory cells, and fibrous tissue. Over time, these plaques evolve and undergo calcification as calcium hydroxyapatite deposits within the fibrous cap, the stabilizing layer above the plaque's lipid core[44]. This process signifies plaque maturation, and calcified plaques typically develop in the later stages of atherosclerosis. These

calcified deposits are associated with stable coronary artery disease (CAD), and they possess a lower risk of rupture[45].

3D. The TTrials

Having discussed markers of subclinical atherosclerosis, this review will now explore literature that evaluates upstream indicators of CVD. The 2017 Testosterone Trials (TTrials), for instance, were a series of seven coordinated, placebo-controlled studies. TTrials investigated TT's effects on various health outcomes in older men, specifically those with low testosterone levels not attributable to factors other than age[46]. The cardiovascular arm of the trial examined a subset of these men and focused on TT's impact upon coronary artery plaque morphology and volume, as assessed by coronary computed tomography angiography (CCTA). TTrials' primary outcome was volume of NCP, while secondary outcomes included total coronary artery plaque volume (TPV) and CAC.

After 12 months, TT was associated with a significantly higher increase in NCP volume; median values rose from 204 mm^3 to 232 mm^3 in the TT group versus an increase from 317 mm^3 to 325 mm^3 in the placebo group. This yielded a net difference of 41 mm^3 (95% CI: 14 to 67 mm^3; P = .003). Additionally, TTrials noted an increase in median TPV from 272 mm^3 to 318 mm^3 in the TT group, versus an increase from 499 mm^3 to 541 mm^3 in the placebo group. The estimated difference in median TPV increase between subgroups was 47 mm^3 (95% CI: 13 to mm^3; P = .006). Even so, neither significant changes in CAC scores nor major adverse CVD events were reported in either group.

The progression of NCP volume has important implications regarding the mechanism of CVD events with TT. Several studies have investigated the association of atherosclerotic plaque

types and future risk of coronary events[47-50]. Plaque classifications are distinguished via CCTA, and CCTA consistently demonstrates concordance with invasive imaging modalities such as intravascular ultrasound and optical coherence tomography. Several retrospective analyses of plaque type assessed by CCTA have demonstrated that features such as NCP volume, progression of NCP volume, and progression of TPV are the strongest determinants of future acute coronary syndromes (ACS). In contrast, increasingly dense calcified plaques are associated with lower rates of ACS[51].

In this regard, atherosclerotic CVD events observed after TT initiation may result from the rupture and thrombosis of NCP. However, larger and longer-term studies have yet to understand the clinical significance of TT upon the development or progression of atherosclerotic plaques, as well as the long-term CV safety of TT.

3E. The T4DM Trial

The 2021 T4DM study was a 2-year, multi-center RCT exploring the effectiveness of TT in preventing type 2 diabetes mellitus (DM). Study participants included overweight or obese men, aged 50-74 with low testosterone levels[52]. Patients were randomized to depot intramuscular testosterone injections vs placebo, alongside a lifestyle intervention program by Weight Watchers. TT yielded an impressive 40% relative risk reduction in DM by the two-year mark (RR 0.59, 95% CI: 0.43-0.80; p=0.0007). In conjunction with lifestyle optimization, TT may thus be beneficial for DM prevention within this unique demographic.

In terms of CV safety, T4DM results were consistent with those of the TTrials before it. T4DM suggested no increased risk of MACE, when TT was used at replacement dosages for

treating symptomatic hypogonadism. A comparable incidence in CVD events between the TT and placebo groups provide reassurance regarding TT's short-term CV safety.

3F. Meta-Analyses and the TRAVERSE Trial

Prior to the TRAVERSE trial, no RCTs had been designed to assess incident CVD risk as a primary outcome. Instead, meta-analyses of many RCTs had been published: thus enabling the aggregation and synthesis of available evidence. One metanalysis included both RCTs and non-randomized studies. There, Elliot et al. employed traditional pairwise and Bayesian network analyses to compare multiple interventions in a single analysis, an important feature considering the inclusion of studies with a wide array of formulations and dosages (including transdermal gel, oral treatments, and intramuscular injections)[53]. Another meta-analysis by Corona et al. pooled both RCTs and pharmaco-epidemiological studies, without restricting inclusion to studies with CV events as primary endpoints[54]. The meta-analysis by Hudson et al. was notable for incorporating individual participant data, thereby empowering a detailed investigation of interactions between treatment effects and participant-level characteristics[55]. Despite their comprehensive approaches, however, these meta-analyses did not find an association between TT and MACE. Perhaps it is these studies' numerous limitations that explain this lack of TT-MACE correlation: number of aggregate participants (which may limit power to detect differences in MACE outcomes), a low incidence of MACE (making it challenging to assess the relationship between TT and MACE), short-term TT exposure durations (precluding the evaluation of long-term CVD risk), or short follow-up periods (which may ineffectively capture potential delayed CVD risks of TT).

The TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men) trial, in contrast, was the first of its kind. TRAVERSE was uniquely powered to assess CVD events, and included a cohort of 5,246 men aged 45 to 80 with testosterone levels <10.4 nmol/L (<300 ng/dl) with CVD or at high risk for its development[56]. Participants received either 1.62% testosterone gel or placebo, with doses titrated to maintain testosterone levels within a target range of 350 to 750 ng/dL. After a mean treatment duration of 22 months, no significant difference was observed in terms of MACE incidence: with a hazard ratio of 0.96 (95% CI: 0.78-1.17). Apart from MACE, TRAVERSE found a higher rate of non-fatal arrhythmia warranting intervention with TT (5.2% vs 3.3% placebo, p = 0.001) and a non-statistically significant trend towards atrial fibrillation (3.5% vs 2.4% placebo, p = 0.02). Additionally, there was a higher incidence of acute kidney injury (2.3% vs 1.5%, p = 0.04) and pulmonary embolism (0.9% vs 0.5%) in the TT group.

The TRAVERSE trial's methodology, while comprehensive, presented limitations[57,58]. The treatment arm's testosterone levels were on the lower end of the normal range, with a mean increase of 148 ng/dL from a baseline of 227ng/dL, achieving a median level around 350ng/dL for most of the trial period – values which are at the bottom threshold of the normal range (300-1000 ng/dL). This may have obscured certain effects of TT. The trial also had a high discontinuation rate of over 60%, raising questions about its underlying reasons, be it due to lack of perceived benefit, adverse effects, or other factors. Furthermore, an 18% loss to follow-up could potentially affect the study's conclusions. These limitations warrant careful consideration when interpreting TRAVERSE's findings, highlighting the importance of restraint in generalizing the implications for TT.

4. Conclusion

The therapeutic approach for TT for symptomatic hypogonadism and low testosterone levels associated with aging, obesity, and systemic illness presents challenges. These conditions are intricately linked with CVD outcomes, and may confound the relationship between low testosterone and CVD[59,60]. Although observational studies suggest an association between low testosterone and increased risk of CVD, results from testosterone supplementation are inconsistent. RCTs indicate that short-term TT at standard replacement is not associated with increased CVD risk. Nevertheless, the cardiovascular sub-study of TTrials observed increases in NCP and CAC, signaling the need for further investigation into potential long-term implications of TT.

The TRAVERSE trial, a landmark study unique in its capacity to evaluate CVD events, contributes valuable insights into the short-term safety of TT at lower physiological levels. However, the long-term effects and implications of mid to high physiological testosterone levels are not yet fully understood. The trials' limitations – achievement of only low-normal testosterone levels, high discontinuation rates, brief follow-up period, and high loss to follow-up rate – suggest that the findings should be interpreted with caution. It is important to avoid generalizing the safety of TT based on these results alone and to approach the extrapolation of TRAVERSE's conclusions to higher dosages or longer-term therapy with caution.

The decision to initiate TT requires a nuanced approach, which must account for current gaps in evidence regarding CV safety. A personalized assessment and management of CVD risk factors is essential for older men with known CVD. The CV effects of exogenous testosterone, when given to maintain physiological levels, remain to be fully explored. In this regard, an important question remains: the identification of male patients with symptomatic hypogonadism

who may benefit from TT. This topic continues to be the subject of ongoing debate. Hopefully, future trials will provide clarity on whether TT confers beneficial, neutral, or adverse cardiovascular effects in middle-aged and older men. Until definitive evidence surfaces, clinical practice should exercise caution and prioritize individualized care with informed discussions regarding the potential CV implications of TT.

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Conflict of interest:
Matthew J. Budoff: received grants from the following companies: Novo Nordisk, Novartis, Astrazeneca, Heartflow, GE Healthcare, Amgen, and Boehringer Ingleheim, Department of Defense, Centers for Disease Control and the National Institutes of Health. Dr Budoff received honoraria from Novo Nordisk, Esperion, Astrazeneca, Merck, Janssen, and Eli Lilly

All other authors declare they have no conflict of interest.