Testosterone and cardiovascular disease: controversy or wake-up call?

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In men with hypogonadism due to diseases of the hypothalamus, pituitary, or testis, testosterone therapy is generally safe and has been shown to induce beneficial effects. Conversely, in men with age-related low testosterone levels, the significance of this change and the effects of testosterone therapy are debatable. Studies have linked low testosterone levels with increased cardiovascular morbidity and mortality, with testosterone therapy being reported to improve cardiovascular risk profiles. However, two recent retrospective studies have fueled the controversy on testosterone therapy by reporting increased cardiovascular events. Because placebo-controlled, randomized clinical trials on testosterone therapy in older men with age-related decline in testosterone levels are lacking, long-term cardiovascular health following testosterone therapy in this patient population remains unclear. Therefore, a careful approach should be adopted when considering therapy of hypogonadism and coexisting cardiovascular disease in older men. Adequately powered, long-term prospective randomized trials on testosterone in older men are urgently needed. ***Cardiovasc Endocrinol*** **00:000–000 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Male hypogonadism is a frequent and potentially undertreated condition. Recent estimates indicate that hypogonadism affects ~2.4 million men aged between 40 and 69 years in the USA, with almost 500 000 new cases of hypogonadism diagnosed annually within the same age group [1]. Testosterone in men reaches a maximum level at ~30 years of age, after which levels gradually decline by 1–2% annually [1]. Controversy exists on whether the age-related decline in testosterone levels is a normal physiologic process or whether it is a functional process as a result of chronic comorbidities and lifestyle choices. Testosterone levels are known to be lower in patients with chronic diseases such as end-stage renal disease, malignancy, AIDs, chronic obstructive pulmonary disease, diabetes mellitus (DM), obesity, and several genetic conditions such as Klinefelter's and Kallman's syndromes [2,3]. Trauma to the testis, castration, cranial or whole-body irradiation, chemotherapy, severe and prolonged illness, chronic opioid therapy, traumatic brain injury, hypothalamic–pituitary tumors, and medications such as cytotoxic agents, glucococorticoids, and ethanol are other well-known causes of male hypogonadism [2,4, 5].

The past two decades have witnessed a substantial increase in the number of prescriptions for testosterone therapy. Estimates suggest that since 1993, prescriptions for testosterone, regardless of the formulation, have increased by nearly five-fold [6], with primary care providers (family practice 36.0%, internal medicine 20.1%) being the most common prescribers, followed by endocrinologists (13.5%) and urologists (6.6%) [7]. The possible reasons behind the increase in testosterone prescriptions include increased prevalence of physiologic testosterone deficiency secondary to the aging population, increased media coverage of testosterone therapy, and aggressive marketing by pharmaceutical companies of the new testosterone formulations. This recent flurry of direct consumer advertising and marketing of testosterone products on television, the internet, and in print is difficult to ignore. Another reason behind the increased prescription of testosterone is the inappropriate prescription of testosterone by healthcare providers themselves to patients with 'low T' symptoms [8]. Interestingly, Baillargeon *et al.* [9] recently analyzed 10 years of clinical data from about 10 million men aged 40 years or older who were in a large employer-based health plan and found that over 25% of those for whom testosterone was prescribed had not even undergone testosterone level assessments in the preceding year.

In contrast, the relationship between circulating testosterone levels and various aspects of cardiovascular health is not clearly understood. The effects of testosterone therapy on risk factors of cardiovascular disease and major adverse cardiovascular outcomes remain controversial because of the lack of data from well-designed randomized trials that include sufficient numbers of men for an adequate length of time. In fact, there is no equivalent study involving men that is comparable to the scale of the Women's Health Initiative [10], nor is there likely to be a

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trial of such magnitude in the foreseeable future. Because testosterone therapy is readily available, several investigators have taken the initiative to perform observational studies on existing cohorts of men on testosterone therapy to assess its therapeutic risk for cardiovascular disease. To this end, two recent observational studies derived from large health databases have reported an increased risk for cardiovascular events following testosterone therapy [11,12], raising the question of whether testosterone therapy might be harmful from a cardiovascular standpoint in men. This has prompted the US Food and Drug Administration and the Endocrine Society to issue a call for more extensive and detailed assessments of the risks and benefits of testosterone therapy in older men with declining testosterone levels.

Definitions of hypogonadism

The expert panel of the Endocrine Society in 2010 defined hypogonadism as a clinical syndrome characterized by low serum testosterone levels, below the lower limit of the normal range for healthy young men (280–300 ng/dl), which results from failure of the testes to produce physiological levels of testosterone and a normal number of spermatozoa due to disruption of the hypothalamic–pituitary–testicular axis at one or more levels [13]. They go on to further classify hypogonadism as abnormalities of the hypothalamic–pituitary–testicular axis at the testicular level caused by primary testicular failure, and central defects of the hypothalamus or pituitary, causing secondary testicular failure [13]. Hypogonadism can also reflect combined defects that result in low testosterone levels, impairment of spermatogenesis, and variable gonadotropin levels, depending on whether primary or secondary testicular failure predominates [13].

The debate over risks versus benefits of testosterone therapy is often confounded by the difficulty in distinguishing hypogonadism secondary to diseases of the hypothalamus, pituitary, or the testis from age-related decline in testosterone levels. However, it is well-accepted that testosterone therapy in young men (defined as age < 50 years) with classic hypogonadism is generally safe and induces several beneficial effects, including the development of secondary sexual characteristics, improved sexual function, mood, and well-being, increased skeletal muscle mass and strength, increased bone mineral density, and decreased fat mass [13]. Conversely, in older men (defined as age > 65 years) with age-related decline in testosterone levels, the clinical benefits and the long-term risks of testosterone therapy remain controversial, especially in frail elderly men with underlying comorbid conditions. Testosterone therapy should only be used in elderly men who have known pathologic conditions of the hypothalamus, pituitary, and testis, those on long-term opioid and/or glucocorticoid therapy, those with a previous history of cranial irradiation for brain tumors, those who have undergone pituitary tumor surgery, and those with a history of traumatic brain injury. For obese men with no history of obvious pathologic conditions, intensive lifestyle intervention, nutritional counseling, and physical activity to induce weight loss can consequently raise endogenous testosterone secretion, which may obviate the need for testosterone therapy [14]. In men with clinical signs and symptoms of hypogonadism, testosterone therapy can be considered on an individualized basis if the potential benefits of treatment outweigh the potential risks after a thorough discussion with the patient.

Controversy of testosterone and cardiovascular risks

Previous studies have demonstrated the association of low testosterone levels with increased cardiovascular risks [15,16], raising the question of whether a low testosterone level is a cause or a consequence of cardiovascular disease. If hypogonadism were a consequence of cardiovascular disease, it is then tempting to infer that patients with more severe cardiovascular disease will have lower testosterone levels than those with milder disease, but this has yet to be proven. The prevalence of hypogonadism in men with an asymptomatic coronary plaque is similar to the prevalence in men with symptomatic cardiovascular disease, and both groups have lower levels of testosterone than men with normal coronary arteries, supporting a causative role more so than a symptomatic consequence [17].

Although many cross-sectional cohort studies have reported an association of low testosterone levels with increased risk for DM [18], metabolic syndrome [19], dyslipidemia [20], and cardiovascular disease [17], the data from longitudinal studies have not found any association between testosterone levels and incident cardiovascular disease [21]. Conversely, some studies have reported that testosterone therapy improves glycemic control, body composition, lipid profiles, and coronary perfusion [22,23]. In fact, in an observational retrospective cohort study of 1031 men aged older than 40 years with a high degree of comorbidities (DM, sexual dysfunction, and coronary artery disease), Shores *et al.* [24] reported that testosterone therapy (89% of men received testosterone injections) was associated with lower mortality compared with no testosterone therapy (10.3 vs. 20.7%, $P < 0.0001$). These findings were recently substantiated by Muraleedharan *et al.* [25] in a prospective 6-year follow-up study of 581 men with type 2 DM treated mainly with testosterone gel in a single center by experienced doctors who were aware of the importance of monitoring testosterone levels and the maintenance of these levels within the therapeutic range. This study demonstrated that low testosterone levels at baseline increases the risk for all-cause and cardiovascular

mortality in men with type 2 DM, and that subsequent testosterone therapy may reduce the mortality compared with that among those who were untreated (8.4 vs. 19.2%, $P = 0.002$).

Individuals with severe primary hypogonadism such as men with Klinefelter's syndrome are known to have increased insulin resistance, dyslipidemia, and central obesity [26], all the constituents that define the metabolic syndrome [27]. In contrast, accelerated coronary artery disease has been demonstrated in patients treated with testosterone-suppressive therapy. In a study of 73 196 men treated with androgen suppressive therapy for prostate cancer, there was a 44% increase in the risk of developing DM and a 16% increase in the risk for cardiovascular death or myocardial infarction, effects that were evident as early as 1–4 months [28]. Similar conclusions were drawn from a study of men treated by orchidectomy, in which over a 10-year period there was a two-fold increase in cardiovascular mortality [29]. However, one must add a note of caution and acknowledge the difference between the severely low testosterone levels associated with these conditions and moderately low testosterone levels associated with aging. Whether low testosterone is a cause or a consequence of cardiovascular disease remains debatable, but there appears to be some evidence supporting both sides of this controversy.

Wake-up call

Prospective randomized studies on the effects of testosterone therapy on cardiovascular-related events have been scarce [30,31]. In 2010, the publication of the Testosterone in Older Men with Mobility Limitations trial [32] drew attention to the possibility that testosterone therapy might negatively impact cardiovascular health. This trial was stopped prematurely after 209 of the planned 252 men were enrolled because of the observation of higher rates of cardiovascular-related events among men assigned to testosterone compared with those assigned to placebo (23 vs. 5), raising concerns about the cardiovascular safety of testosterone therapy in frail elderly men [32]. However, the participants in this trial had high rates of chronic comorbid conditions such as heart disease, DM, obesity, hypertension, and hyperlipidemia, and men aged 75 years or older and men with higher on-treatment testosterone levels appear to be at the highest risk for cardiovascular-related events [32]. Further, the lack of structured ascertainment of cardiovascular events and the utilization of higher testosterone dosages limit the generalizability of the study. Conversely, meta-analyses of randomized trials did not demonstrate any increased risk for cardiovascular-related events in men randomly allocated to receive testosterone compared with those receiving placebo [30,31,33]. However, these meta-analyses were somewhat limited by the small sample size of most trials, heterogeneity of study populations, poor quality of adverse-event reporting, and short treatment duration. Further, many participants were healthy older men aged 65 years or older [34].

The exposure of testosterone in the media has gathered further momentum recently following the publication of three studies within the past 12 months that have raised further concerns about the possible adverse cardiovascular outcomes associated with testosterone therapy. The first was a meta-analysis by Xu *et al.* [35] of 27 small studies involving 2994 predominantly older men that demonstrated that testosterone therapy increased the risk for cardiovascular-related events, and that the effect of testosterone therapy was more dependent on the source of funding of the reported trials than on underlying baseline testosterone levels. The second was a study by Vigen *et al.* [12], who presented a retrospective analyses from the Veteran's Administration healthcare system of 8709 men who had undergone coronary angiography with testosterone levels less than 300 ng/dl. Through linkage with pharmacy data, 1223 men aged 60.6 years who initiated testosterone therapy were compared with 7486 men aged 63.8 years who did not. The testosterone users were found to have an increased risk for the composite endpoints: 67 died, 23 had myocardial infarctions, and 33 had strokes, whereas among those who did not receive testosterone therapy 681 died, 420 had myocardial infarctions, and 482 had strokes, revealing an absolute 3-year event rate of 25.7 versus 19.9% (hazard ratio, 1.29; 95% confidence interval, 1.04–1.58). Notably, this estimate did not differ between the men with and those without coronary artery disease, which was ascertained in all men by coronary angiography, and was similar when revascularization was included in the outcome. The third and most recent study was by Finkle *et al.* [11], who analyzed the data from 55 593 men derived from a large healthcare database from 2006 to 2010 and compared the incidence rate of myocardial infarction in the 90 days after starting testosterone therapy with the rate in the 1 year before testosterone therapy. In this study, the investigators found a two-fold rise in the postprescription/prepreprescription testosterone rate ratio for men older than 65 years and a two-fold to three-fold increase for men younger than 65 years with a previous history of heart disease to nonfatal myocardial infarctions.

Although the study by Finkle *et al.* [11] provided the springboard that triggered the media to report its findings and raised public health concerns [9,36], several important questions remain. In the studies by Xu *et al.* [35] and Vigen *et al.* [12], combined cardiovascular disease endpoints were used, as individual outcomes, particularly severe events, were too few to evaluate. Perhaps because of this, or because of other factors, the point estimates of risks were also divergent among the studies, with hazard ratios ranging from less than 1.3 to greater than 5.0. All of these studies also recognized the importance of evaluating risk among men with and those without pre-existing

cardiovascular disease; however, they did not have sufficient numbers of participants to adequately assess this issue. In the study by Vigen *et al.* [12], the follow-up of patients on testosterone therapy was short (an average of 27.5 months), the patients were somewhat undertreated, with the majority of patients receiving testosterone patches (63.3 vs. 35.7% injections vs. 1.1% gel), and the factors of pretreatment testosterone levels and concomitant medications were not included in the analysis of covariates. In addition, the studies by Xu *et al.* [35] and Vigen *et al.* [12] predominantly evaluated older men, and the risks in younger men were not addressed, among whom the recent increases in prescriptions have been the most significant, and patient compliance was assumed once therapy was initiated until an outcome event occurred or until the end of follow-up. In contrast, in the study by Finkle *et al.* [11], the investigators included some younger men (defined as age less than 65 years) and used the treated group as their own control, comparing risk before versus after starting testosterone therapy over a short-time frame. Importantly, and frustratingly perhaps, the studies by Vigen *et al.* [12] and Finkle *et al.* [11] do not report the testosterone doses used, nor do they report the timing and levels of testosterone achieved at the point at which the cardiovascular events occurred. In these studies [11,12,35], the method of testosterone administration (gel, injection, or patches) at the time at which the cardiovascular events occurred is also not known, which is clinically relevant. This is because of the following reasons: for gel, patient compliance has been reported to be only 35% after 6 months and 15% after 12 months [37]; for patches, skin irritation was found to occur in more than 50% of patients [38]; and for injections (for which the injection intervals were also unknown), fluctuations in testosterone levels can occur, resulting in levels being out of the therapeutic range [39].

Obstacles and limitations to interpreting observational retrospective studies

The secretion of testosterone is controlled by pituitary gonadotropins and shows a diurnal variation, with the highest levels being secreted early in the morning among younger men. Therefore, a source of variability in the interpretation of large observational studies might be the timing of blood sample collections – that is, morning versus evening collections and, in testosterone injection users, when the blood sample was collected in relation to the last testosterone injection, where peak and trough testosterone levels are often observed.

Presentation of the data according to total, free, or bioavailable concentrations may also pose difficulties in interpreting the data. First, there may be questions on the accuracy and comparability of different assay techniques and calculations used to estimate free and bioavailable testosterone fractions [40]. Second, there may be potential conceptual issues. For example, data presenting the relationship between total testosterone and incident DM may differ from data presenting the relationship between free testosterone and incident DM. Data with a statistically significant association between free testosterone and incident DM suggest a direct sex steroid effect [41], whereas data on total testosterone might reflect the relationship between sex hormone-binding globulin and DM, as a low sex hormone-binding globulin level is a predictor of DM [42].

The rate of peripheral aromatization of testosterone to estradiol affects circulating testosterone levels through the negative feedback inhibition of gonadotropins exerted by estradiol [43], and may be enhanced in older men because of increased adiposity [44]. Whether the differences in circulating estradiol levels resulting from variation in aromatization *per se* contribute to cardiovascular disease remains unknown.

As with any observational retrospective study, unmeasured bias and error are unavoidable. Results of most observational studies of men in the general population might also be affected by other confounding factors, such as smoking, concurrent medications, alcohol, obstructive sleep apnea, and physical inactivity that may induce worsening body composition that predisposes these individuals to the development of metabolic syndrome, DM and cardiovascular disease. Whether the abnormal body composition is a cause or consequence of low testosterone is difficult to ascertain from these studies, as this may affect their responsiveness to testosterone therapy.

Discussion

The clinical question about which men, apart from those with severe hypogonadism such as those with hypothalamic–pituitary and genetic diseases, should receive testosterone therapy remains controversial, with data from short-term clinical trials suggesting benefits for improving sexual function, strength, energy, and well-being. What the current literature sorely lacks is adequately powered randomized studies to assess the long-term benefits and risks of testosterone therapy in relatively healthy middle-aged men, who, for example, have gained some weight, lack endurance, are experiencing daytime somnolence, and who have a low–normal or below-normal level of testosterone. The limited evidence from randomized trials documents only small improvements in lean body mass and body fat, libido, and sexual satisfaction, which may or may not be clinically meaningful, with no clear effect on weight, depression, or strength. Whether important cardiovascular risks exist remains unknown. Unfortunately, even the meta-analyses by Xu *et al.* [35] and others [31] cannot provide a clear explanation because of questionable ascertainment of cardiovascular outcomes in so many of the individual trials. However, the two recent trials by Vigen *et al.* [12] and Finkle *et al.* [11] have certainly been a

wake-up call in suggesting that testosterone therapy may be harmful in older men from a cardiovascular standpoint. It is also noteworthy that the men included in these studies represent a real-world population of men with a substantial burden of comorbidities, more than those in the typical men enrolled in most randomized clinical trials. Frustratingly little information is available in these two studies on the type of underlying comorbidities, whether testosterone was appropriately prescribed according to accepted guidelines [13], clinical problems that could be related to testosterone deficiency, and appropriate clinical monitoring of testosterone levels. In addition, the number of men using testosterone injections is unknown, and this is particularly important as testosterone injections have the disadvantage of inducing nonphysiologic testosterone peak and trough levels. Perhaps the most important question is the generalizability of the results of these studies to the broader population of men taking testosterone – that is, men of this age group who are taking testosterone for 'low testosterone symptoms' and for 'anti-aging' purposes, and younger men and athletes taking it for physical enhancement. Does the purported increased risk for myocardial infarction, ischemic stroke, or mortality apply to these groups as well? If so, are the benefits, be it real or perceived for this group of men, worth the associated increase in cardiovascular risk?

In light of the increasing number of prescriptions and aggressive marketing by testosterone manufacturers [9], prescribers and patients are urged to be wary. There is now emerging evidence of potentially a signal of adverse cardiovascular outcomes associated with testosterone therapy that cannot be ignored, and therefore warrant both cautious and responsible testosterone prescription, and vigilant testosterone monitoring for all patients being considered for this therapy. Given the ongoing controversy in this field, it is prudent for now to initiate testosterone therapy in men with symptomatic and biochemical evidence of hypogonadism with coexisting cardiovascular disease in the same way as initiation of levothyroxine therapy for patients with hypothyroidism, which is to start low and go slow with close monitoring to maintain testosterone levels within the therapeutic range, combined with concurrent lifestyle advice. Additional sufficiently powered long-term prospective randomized placebo-controlled studies on testosterone therapy in older men are more urgently needed now than ever before.

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Conflicts of interest

There are no conflicts of interest.

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