PERSPECTIVE

Testosterone therapy and risk of CVD in older men

BU B. YEAP MB BS, FRACP, PhD

Circulating testosterone levels decline in ageing men, and low testosterone levels are associated with an increased risk of cardiovascular disease (CVD). There is controversy over the use of testosterone therapy and risk of adverse cardiovascular events in older men. Testosterone therapy should only be considered in men who are androgen deficient, and a cautious approach employed in older men with comorbidities including pre-existing CVD.

Testosterone is the primary male sex hormone (androgen) responsible for sexual development, virilisation and body composition in adult men. Testosterone is produced by testicular Leydig cells under the influence of pituitary luteinising hormone and is metabolised to dihydrotestosterone, which is a more potent androgen, and also to oestradiol, a ligand for the oestrogen receptor. Older men have lower testosterone concentrations compared with younger men and an increased burden of ill health. The key question is, do lower testosterone concentrations in older men contribute to disease, or do they reflect the presence of obesity or pre-existing ill health?

Defining low testosterone levels in younger and older men

When measured accurately using mass spectrometry, young reproductively normal men aged 21 to 35 years are expected to have plasma testosterone levels in the range of 10.4 to 30.1 nmol/L,[1] and healthy older men aged 70 to 89 years are expected to have plasma testosterone levels in the range of 6.4 to 25.7 nmol/L.[2] Mass spectrometry is the preferred method for assay of testosterone as automated immunoassays are less accurate.[1] Therefore, the lower limit of the reference range for testosterone is 10.4 nmol/L in men up to the age of 35 years and 6.4 nmol/L at 70 years and above. The threshold

Key points

- **Older men have lower testosterone concentrations compared with younger men, and lower circulating testosterone is a biomarker for poorer health outcomes.**
- **Whether testosterone supplementation in older men is associated with increased risk of cardiovascular events remains controversial, with contrasting reports and no evidence of excess events in a recent meta-analysis.**
- **The diagnosis of androgen deficiency should be made following careful clinical assessment and measurement of early morning testosterone concentrations using an accurate assay and age-appropriate reference intervals.**
- **Testosterone therapy in older men who are androgen deficient should aim for a testosterone concentration in the middle rather than the high end of the reference range.**

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Professor Yeap is Professor at the School of Medicine and Pharmacology, University of Western Australia, Perth, and Consultant Endocrinologist at the Department of Endocrinology and Diabetes, Fremantle and Fiona Stanley Hospitals, Perth, WA.

for low testosterone levels in middle-aged men between 35 and 70 years of age can be interpolated from these results.

Low testosterone levels, CVD and mortality

Obesity is associated with lower testosterone concentrations, and conversely lower circulating testosterone predisposes to loss of lean mass and gain in fat. Lower testosterone concentrations in older men are associated with poorer health outcomes, for example, a higher risk of stroke or transient ischaemic attack.[3] Lower testosterone concentrations are also associated with increased risk of mortality.[4] However, optimal rather than higher testosterone concentrations are associated with longevity in older men. In the Western Australian Health In Men Study (HIMS), men aged 70 years and over with plasma testosterone levels in the middle of the range had the lowest rate of death from any cause.[5] Higher dihydrotestosterone levels were also associated with reduced mortality from ischaemic heart disease, suggesting a cardioprotective role for androgen exposure. Therefore, epidemiological studies indicate lower circulating androgens are biomarkers for, or contributors to, increased risk of cardiovascular disease (CVD) events or mortality in ageing men.

Randomised trials of testosterone therapy in older men

Although observational data suggest a beneficial influence of androgens on cardiovascular risk, randomised controlled trials of testosterone therapy have not been powered for the outcomes of cardiovascular events or mortality. Controversy arose when the trial of Testosterone in Older Men (≥65 years) with Mobility Limitations (TOM) in the USA was stopped prematurely due to an excess of cardiovascular adverse events in men receiving testosterone.[6] Many men enrolled in this study had prior CVD and a relatively high dose of transdermal testosterone was given. However, a similarly sized randomised controlled trial of testosterone in frail older men (≥65 years) in the UK did not report any such adverse signal.[7] In both of these studies, testosterone therapy improved measures of strength or physical performance. It is possible that in the US trial, testosterone therapy might have unmasked pre-existing CVD in older men by precipitating symptoms or events. A recent meta-analysis that included both these studies did not find any definite evidence of excess cardiovascular adverse events associated with testosterone therapy.[8] Therefore, additional studies are needed, pending which a conservative approach should be adopted for older men (aged ≥65 years) with major comorbidities who require androgen therapy.

Observational studies of men receiving testosterone

Unfortunately, recent observational studies of men receiving androgen therapy have clouded rather than clarified the issue of whether testosterone therapy is associated with decreased or increased risk of cardiovascular adverse events. A retrospective study of US veterans reported that men found to have low testosterone levels who were treated with testosterone had a better survival rate than those with low testosterone levels who did not receive treatment.[9] However, this was an observational study lacking randomisation and thus vulnerable to potential confounders (for example, physicians might have prescribed testosterone to healthier men and not to men who were less well), therefore, it should not be regarded as demonstrating an effect of improved survival with use of testosterone.

By contrast, another retrospective study in US veterans who had undergone coronary angiography and had a total testosterone level below 10.4 nmol/L claimed that those men prescribed testosterone had a 29% higher risk of subsequent death, myocardial infarction or stroke.[10] This study sparked controversy and attracted considerable criticism, as the actual raw data showed that only 10.1% of men prescribed testosterone experienced an event compared with 21.2% of men not prescribed testosterone. A complex statistical model reversed this trend. Additionally, a large number of men who were prescribed testosterone after an outcome event were excluded, instead of being included as not receiving testosterone before the event. Their inclusion would have increased the rate of events in the 'no testosterone' group to 31.5%, making it even harder to conclude an increased risk of cardiovascular events with use of testosterone. The published correction suggested many of those men had not been classified correctly, and showed more men being excluded for incomplete data and some for being women (see: *JAMA* 2014; 311: 967). This paper remains somewhat contentious.

Following this, an analysis of prescription data suggested that men prescribed testosterone had an increased rate of nonfatal myocardial infarction in the 90 days following the prescription, compared with the 12 months prior.[11] The increased risk was shown in men aged below 65 years with existing CVD and in men aged 65 years or over without CVD. There are several limitations to this analysis including the comparison of event rates pre- and post-prescription, lack of matched controls, absence of information on fatal myocardial infarction or outcomes beyond 90 days, and the relatively small number of events occurring in men aged 65 years or above.

The latest study used Medicare prescription data in American men aged 66 years or over to examine outcomes in those who were prescribed testosterone compared with matched controls who were not prescribed testosterone.[12] After adjusting for potential confounders, testosterone therapy was not associated with hospitalisation for myocardial infarction. In the 25% of men with the highest myocardial infarction prognostic risk (most likely to experience a myocardial infarction) testosterone therapy was associated with a 31% reduced

risk of myocardial infarction.[12] Therefore, these observational studies of men prescribed testosterone possess inherent limitations, exhibit conflicting results and cannot substitute for prospective randomised controlled trials that explore the effect of testosterone on CVD risk and events.

What are the implications for clinical practice?

Randomised controlled trials of testosterone with the prespecified endpoint of CVD events will be challenging to design and difficult to conduct because they require very large numbers of men to be randomised and treated for an extended duration. There is still a need for observational studies based on large population-based cohorts with prospective follow up to better understand the role of sex hormones to stratify CVD risk, and also for carefully targeted proof of concept interventional studies to provide a robust justification for larger trials. Pending further studies, clinicians should consider testosterone therapy in androgen-deficient men to relieve the symptoms and signs of hypogonadism[13] (see also www.nytimes.com/2014/09/18/health/testosterone-drugs-fda.html). The diagnosis of androgen deficiency should be based on a thorough clinical assessment, and accurate measurement of early morning testosterone concentrations using appropriate reference intervals. Although measurement of testosterone using mass spectrometry is preferred, a carefully validated immunoassay for testosterone can be informative.

A conservative approach to testosterone therapy is appropriate in men with substantial comorbidities, including CVD, particularly in older men. The finding that optimal rather than high testosterone concentrations predicted survival in men aged 70 years and above suggests that treatment for androgen deficiency should increase testosterone concentrations towards the middle rather than top of the reference range in older men.[5] **CT**

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