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The cardiovascular trial of the testosterone trials: rationale, design, and baseline data of a clinical trial using computed tomographic imaging to assess the progression of coronary atherosclerosis

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\textbf{Background} Data from prior studies have yielded inconsistent results on the association of serum testosterone levels with the risk for cardiovascular disease. There are no clinical trial data on the effects of testosterone replacement therapy on plaque progression.

\textbf{Objective} We designed a study to investigate the effect of testosterone therapy on coronary artery plaque progression using serial coronary computed tomographic angiography (CCTA). In this paper, we describe the study design, methods, and characteristics of the study population.

\textbf{Methods} The Cardiovascular Trial of The Testosterone Trials (TTrials; NCT00799617) is a double-blind, placebo-controlled trial of 1 year of testosterone therapy in men 65 years or older with clinical manifestations of androgen deficiency and unequivocally low serum testosterone concentrations (< 275 ng/dl). CCTA performed at baseline and after 12 months of therapy will determine the effects of testosterone on the progression of the total volume of noncalcified plaques. All scans are evaluated at a central reading center by an investigator blinded to treatment assignment.

\textbf{Results} A total of 165 men were enrolled. The average age is 71.1 years, and the average BMI is 30.7. About 9% of men had a history of myocardial infarction, 6% angina, and 10% coronary artery revascularization. A majority reported hypertension and/or high cholesterol; 31.8% reported diabetes. Total noncalcified plaque at baseline showed a slight but nonsignificant trend toward lower plaque volume with higher serum testosterone concentrations ($P = 0.12$).

\textbf{Conclusion} The Cardiovascular Trial will test the hypothesis that testosterone therapy inhibits coronary plaque progression, as assessed by serial CCTA. \textit{Coron Artery Dis} 00:000–000 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Keywords: cardiovascular disease, coronary artery plaque progression, coronary computed tomographic angiography, randomized controlled trial, testosterone

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\textbf{Introduction} As demonstrated by both cross-sectional [1] and longitudinal studies [2,3], men’s serum testosterone concentration falls gradually, beginning at age 20 years. Although the reported prevalence rates vary in different studies, one widely quoted sentinel study reported that by the eighth decade, \textasciitilde{} 30% of US men have concentrations of total testosterone lower than normal for younger men and 70% have a free testosterone concentration lower than normal for younger men [3]. Whether age-related decline in testosterone concentrations contributes to, or is independent of, atherosclerosis progression with age is currently unknown. Although testosterone was once considered to be a risk factor for cardiovascular disease (CVD), the data are mixed. Several recent studies in men have shown an inverse association between serum testosterone concentration and CVD, metabolic syndrome, and diabetes [4–6], an association independent of traditional CVD risk factors. A recent randomized trial, however, has demonstrated increased CV risk in participants receiving testosterone replacement [7], and recent meta-analyses have shown conflicting results.
The Cardiovascular Trial, a component of The Testosterone Trials (TTrials), was designed to assess the effects of testosterone treatment on several markers of CVD in men 65 years or older with symptoms and signs consistent with androgen deficiency and low serum testosterone concentrations [8]. These include progression of coronary atherosclerosis, as assessed by serial coronary computed tomographic angiography (CCTA); cardiovascular risk factors such as blood pressure, and lipid and lipoprotein levels; and markers of glucose metabolism, inflammation, coagulation and platelet function, endothelial function, and myocardial damage, as assessed by high-sensitivity troponin levels.

Materials and methods

Design

The TTrials are a coordinated group of multicenter, double-blind, placebo-controlled trials [8] to evaluate the effects of testosterone treatment in older men with low testosterone levels for no apparent reason other than age on clinical endpoints that have been shown to improve with testosterone therapy in men with disease-induced hypogonadism. The TTrials are registered at clinicaltrials.gov (NCT00799617).

The TTrials include 12 clinical sites geographically distributed across the USA and are sponsored by the National Institute on Aging, National Institute of Neurological Disorders and Stroke, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Heart, Lung, and Blood Institute, and AbbVie Inc. Men who were 65 years or older, with a mean serum testosterone concentration less than 275 ng/dl on two morning measures, with subjective complaints and objective evidence of sexual dysfunction, physical dysfunction, and/or reduced vitality (clinical conditions thought to be potentially improved by testosterone supplementation), and who were not at an elevated risk for prostate, cardiovascular, or hematologic problems associated with high levels of testosterone were recruited; those eligible and consenting were assigned to 1 year of treatment with testosterone therapy or placebo [8,9]. The Cardiovascular Trial, designed to determine the effect of testosterone on the progression of coronary atherosclerosis, was conducted at nine of the 12 TTrials sites. All the sites have CCTA scanners with 64 slices or more and staff with sufficient experience using them, as determined by a questionnaire completed at each site.

The protocols of TTrials and the Cardiovascular Trial were approved by the Institutional Review Boards of the participating sites. All participants provided written informed consent before the trial-related procedures were conducted. Participant safety and the trial conduct were overseen by an Independent Data and Safety Monitoring Board appointed by the National Institute on Aging.

Treatment

Participants received AndroGel, testosterone in an alcohol–water gel, or a matched placebo gel, administered transdermally daily, for 1 year. Treatment allocation used a minimization algorithm with a random component [8,10]. The testosterone dose was adjusted by the (unblinded) data coordinating center as needed to maintain testosterone concentration levels between 500 and 800 ng/ml; similar adjustments were performed on matched placebo participants to maintain blinding. Regular monitoring of participants for potential adverse effects of testosterone was performed.

Eligibility criteria

Inclusion and exclusion criteria for the TTrials have been published [8]. Age, serum testosterone concentration, biochemical and clinical conditions that could affect the interpretation of the results, and conditions that could be worsened or exacerbated by testosterone therapy were the major factors used in assessing eligibility. In addition to the testosterone concentration and symptom requirements mentioned earlier, participants in TTrials had to have a normal baseline renal function [estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m²] to be eligible for the Cardiovascular Trial (Table 1). Men were excluded if their weights were greater than 300 pounds, they had known allergy to iodinated contrast medium, they were unable to breath-hold for 10 s, they had a prior diagnosis of tachycardia or irregular heart rhythm (e.g. atrial fibrillation), or they had undergone coronary artery bypass graft surgery according to patient report or medical records.

Follow-up

Men enrolled in The Cardiovascular Trial underwent CCTA scanning without and with contrast to allow calculation of noncalcified plaque volume, total plaque volume, subcutaneous fat, and coronary artery calcium (CAC) score. The month 12 visit involved re-evaluation of medical history for the development of allergy to iodinated contrast medium and review of renal function based on month 12 eGFR calculation (> 60 ml/min/1.73 m²). All participants still enrolled at 12 months, with an eGFR greater than 60 ml/min/1.73 m² and no new contraindication, underwent a second CCTA scan for the same measures obtained at the baseline visit.

Primary endpoint

The primary trial endpoint was percent change in noncalcified coronary plaque volume over the 12-month treatment period. The rationale behind using noncalcified plaque volume is that prior trials have shown significant reductions in the noncalcified plaque volume among statin users; calcified plaques are generally not considered amenable to reversal, and may even be increased by statins [11]. Experienced readers in the CCTA core lab who were blinded to the assigned
Table 1: Inclusion and exclusion criteria for the Cardiovascular Trial of the Testosterone Trials

<table>
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<th>Inclusion criterion</th>
<th>Exclusion criteria</th>
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<td>Normal baseline renal function, as assessed by estimated glomerular filtration rate &gt; 60 ml/min/1.73 m^2 at baseline and month 12 visits</td>
<td>Weight &gt; 300 lb</td>
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<td></td>
<td>Known allergy to contrast medium</td>
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<td></td>
<td>Inability to hold breath for 10 s</td>
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<td></td>
<td>Known diagnosis of tachycardia or irregular heart rhythm (e.g., atrial fibrillation)</td>
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<td></td>
<td>Prior coronary artery bypass grafting by patient report or medical records</td>
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</table>

Treatment visually evaluated the CTA scans for the presence, extent, and severity of coronary artery plaques. CCTA imaging and measurement of coronary plaques were conducted using standardized procedures and technology for longitudinal measurements of change in atherosclerosis. The baseline and follow-up scans were compared side by side [with blinding to both the treatment arm and the date of the study (baseline vs. 12 month)] to ensure that like segments were compared and measured. The area of each coronary plaque visualized in at least two adjacent slices (reconstructed slice thickness 0.6 mm) was determined on all affected slices [12]. The total plaques per segment was summed over all segments with plaques. The degree of coronary artery stenosis was assessed using axial images, multiplanar reconstructions, and curved multiplanar images to assess the degree of luminal narrowing in all assessable coronary segments. The coronary artery stenosis severity was classified into four groups (0, 1–29, 30–69, and ≥70% stenosis). The most narrowed diameter in each segment was determined, even if the plaque was eccentric. A segment stenosis score was generated on the basis of the degree of underlying stenotic disease in each segment (0: no plaque, 1: 1–29% stenosis, 2: 30–49% stenosis, 3: 50–69% stenosis, 4: ≥70% stenosis). The extent scores of all 17 individual segments were summed to yield a total stenosis score ranging from 0 to 68 [12]. In addition, each coronary territory (right coronary, left main, left anterior descending, and left circumflex arteries) was also scored according to the presence of the most significant lesion.

The composition of the coronary atherosclerotic plaques was evaluated from both axial source images and multiplanar reconstruction images of the long axis at each site of the coronary arteries. Each coronary segment was classified as either normal (no plaque), containing noncalcified plaques, or containing partially calcified plaques with either predominantly noncalcified plaques (<50% of the plaque area occupied by calcium) or predominantly calcified plaques (>50% of the plaque area occupied by calcium) [13]. A calcified atherosclerotic plaque was defined as any discernible structure that: (i) had a computed tomography density greater than that of the contrast-enhanced lumen, (ii) was clearly assignable to the coronary artery wall, and (iii) was identified in at least two independent planes [13]. Details of the CCTA methods have been described elsewhere [11–16].

Secondary outcomes
Secondary CCTA measures include changes in total plaque volume, CAC score, and subcutaneous fat levels. HgA1C and HOMA-IR will also be assessed as secondary endpoints in participants without diabetes at baseline. CAC measures will include the presence of any CAC (dichotomous variable) and the CAC score, as well as changes in left ventricular mass between the testosterone and placebo groups.

Scanning methodology
Noncalcified plaque volume
Plaque volume in all affected coronary segments was assessed at baseline and follow-up visits by experienced readers at the CCTA core lab by CCTA using semi-automated software (QAngio CT Research Edition 2.1.2; Medis Medical Imaging Systems b.v., the Netherlands; Fig. 1) [17]. First, an automatic tree-extraction algorithm was used to obtain all the three-dimensional centerlines of the coronary tree [18]. On the basis of these centerlines, straightened multiplanar reformatted volumes were created for all vessels. Next, the lumen border contours and vessel wall borders were assessed using spatial first-derivative and second-derivative gradient filters in longitudinal cross-sections, in combination with knowledge of the expected CCTA intensity values in the arteries [17–19].

Thereafter, lumen and vessel contours were detected in the individual transverse cross-sections perpendicular to the centerlines, whereby the locations from the longitudinal analyses were taken into account. This method is insensitive to differences in attenuation values between datasets and independent of window and level settings. As previously described [19], 740 and 220 HU were used as window and width levels to identify luminal and vessel outlines. Once automated software completed the vessel trace, expert readers manually corrected areas if additionally needed. The plaque area of each coronary plaque visualized in at least two adjacent slices (slice thickness 0.6 mm) was determined on all slices and plaque volumes assessed by multiplying the area and slice thickness. The plaque volume was measured in any coronary artery segment 1.5 mm or higher diameter. For each lesion, the
minimal lumen diameter was summed and reported as noncalcified plaque including fibrous plaque, fibrous fatty plaque, low-attenuation plaque, and dense calcified plaque, all variables of which have been widely used for quantitative plaque assessment in numerous previous studies [14,20–22]. Plaque composition is based on predefined fixed-intensity cutoff values in HU. These thresholds are based on studies in our lab and others comparing CCTA with virtual histology by intravascular ultrasound or histological examination [23–27]. The fixed HU cutoff values for classification are as follows: −30 to 30 HU for low-attenuation plaques, 31–130 HU for fibrous fatty plaques, 131–350 HU for fibrous plaques, and greater than 350 HU for dense calcified plaques. These values were initially based on a previous report by Brodoefel et al. [28] and empirically optimized using three representative training sets [17,29,30]. The excellent interobserver and intraobserver variabilities for lumen and vessel segmentation have been described previously [27,29]. On a per-patient basis, the total plaque volume is calculated as the sum of all plaques measured in available segments at baseline and follow-up. As previously described [19], the total plaque volume, the total plaque burden [(total plaque volume/total vessel volume) × 100], and the normalized total plaque volume (TPVNorm) [(total plaque volume/total segment length) × (mean total segment length in the whole population)] were assessed at baseline and follow-up. The changes in these variables between serial CCTAs were also assessed (Fig. 2).

Coronary artery calcium scanning

For CAC scanning, each scan extended from 1 cm below the carina to the bottom of the heart to include the entire coronary tree. Scanning parameters were obtained as follows: prospective electrocardiogram triggering (typically 65–80%), 35 cm field-of-view, 512 × 512 matrix size, and peak tube voltage 120 kVp. Slice thickness was 3 mm. The acquired images were then transferred to the CCTA core lab for analysis. All coronary calcium score measurements were performed on a GE AW system (AW Volume Share; GE Medical Systems, Milwaukee, Wisconsin, USA) to quantify coronary artery calcification using the Agatston method [31]. Coronary calcium was identified in three contiguous voxels using a cutoff point of 130 HU, resulting in a minimum calcified lesion area of 1.02 mm². The area density method was used to compute the lesion score, in which the lesion area was multiplied by an attenuation factor. This attenuation factor is derived from the maximal HU within the area, as described by Agatston and colleagues, ranging from 1 to 4. The total CAC score was obtained by aggregating...
individual lesion scores from each of the four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries).

**Coronary computed tomographic angiography quality assurance/control**

Experienced readers in the CCTA core lab read all the CCTA scans, blinded to all demographics, testosterone randomization, and risk factors, in near real-time (within 1 week of acquisition) during enrollment and during the scanning period for stenosis evaluation and assessability. Three level 3 experienced cardiac CT readers evaluated all studies in the trial. The prevalence of slab, blurring, and partial volume averaging artifacts on all scans were also evaluated in the CCTA core lab. The contrast-to-noise ratio of the distal left anterior descending artery is calculated for each scan as a quantitative metric of image quality.

**Sample size**

We reviewed data on 63 older men from an observational study using CT angiography techniques similar to those used in this trial. Of these men, 35 were taking statins and 28 were not. Scans were performed at two time points ~1 year apart. In this cohort, the SDs of the changes from the first to the second scan were similar in the two groups; we used the larger of the two values (an SD of 26) for our calculations, which indicated that 140 participants would provide 80% power to detect a difference of 12 mm³ in noncalcified plaque volume, somewhat less than the difference of 14 mm³ between statin users and nonusers seen in the prior study. As it was difficult to know the number of men who would enroll, as this was dependent on the proportion of men to be enrolled in the TTrials who would be eligible for and would consent to participate in this trial, we also calculated power for a total sample size of 120, 60/arm; this number would provide 80% power to detect a 13 mm³ difference between treatment arms after 1 year of treatment.

**Statistical analysis**

The primary hypothesis was that testosterone treatment would decrease progression of noncalcified coronary artery plaque volume, as assessed by CCTA. Efficacy was measured using a multivariate linear model that adjusts for baseline noncalcified plaque volume and all balancing variables used in the minimization procedure: study site, indicator variables of participation in each primary efficacy trial, baseline testosterone concentration (≤ or > 200 ng/dl), age (≤ or > 75), use of antidepressants, and use of PDE inhibitors. All participants with baseline and 12-month plaque volume measurements were included in the analysis. Significance was assessed using the two-sided Wald test and confidence interval for the treatment effect.

**Safety analysis and evaluation of adverse events**

Safety measures related to CT angiography include the amount of radiation absorbed by the body tissues and the exposure to iodinated contrast agents. β-Blockers were used to control the heart rate and thus maintain the radiation dose as low as reasonably achievable. Other radiation reduction methods included prospective triggering, limited field of view, limited scan length, iterative reconstruction, and reduced tube voltage whenever possible based on body habitus [32–35].

**Results and discussion**

**Recruitment**

A total of 199 men consented to be screened for the trial. Of these, 170 were eligible, and 165 underwent baseline scanning. Five men could not be scanned because of high heart rates or lack of venous access.

**Demographics**

A total of 165 men were enrolled in the Cardiovascular Trial and underwent baseline CCTA. Baseline information for these men is listed in Table 2. The average age of the participants was 71 years. Most men were overweight or obese; 61% had a BMI of 30 or higher. Hypertension and/or hyperlipidemia were present in around two to three participants, and approximately one-third of the participants were diabetic. A prior MI was reported by 9% of participants; 10% had had a prior revascularization and 6% had a history of angina. The mean volume of noncalcified plaques was 91.0 mm³, with an SD of 95.9 mm³.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD or N (%)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>71.1 ± 5.7</td>
</tr>
<tr>
<td>65–74</td>
<td>135 (79.4)</td>
</tr>
<tr>
<td>75–84</td>
<td>26 (14.7)</td>
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<tr>
<td>≥ 85</td>
<td>10 (5.9)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>≥ 30</td>
<td>104 (61.2)</td>
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<tr>
<td>&lt; 30</td>
<td>66 (38.8)</td>
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<tr>
<td>Prior MI</td>
<td>18 (8.9)</td>
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<tr>
<td>Angina</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (0.6)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>17 (10.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>TIA</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2 (1.2)</td>
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<tr>
<td>Leg pain/cramping</td>
<td>13 (7.7)</td>
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<tr>
<td>Angioplasty/stent</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>112 (65.9)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>111 (65.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>54 (31.8)</td>
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<tr>
<td>Taking antidiabetics</td>
<td>47 (27.7)</td>
</tr>
<tr>
<td>Ever smoker: cigarettes</td>
<td>108 (63.5)</td>
</tr>
<tr>
<td>Current smoker: cigarettes</td>
<td>11 (6.5)</td>
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<tr>
<td>Current smoker: cigars</td>
<td>6 (3.5)</td>
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<tr>
<td>COPD</td>
<td>12 (7.1)</td>
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<tr>
<td>Serum total testosterone (ng/dl)</td>
<td>2373 ± 59.5</td>
</tr>
<tr>
<td>Noncalcified plaque volume (mm³)</td>
<td>91.0 ± 95.9</td>
</tr>
</tbody>
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COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIA, transient ischemic attack.

*By self-report.
Association of coronary plaque volume with serum testosterone concentration

We assessed whether there was any notable association between serum testosterone levels and noncalcified coronary plaque volume at baseline. These data are shown in Fig. 2. There was a trend toward higher values of testosterone associated with lower plaque volumes, but this association was found not to be statistically significant on using a linear regression model ($P = 0.12$).

Discussion

Observational studies have found associations of low testosterone concentrations in older men with adverse cardiovascular outcomes [4–6]. Further, in a study of 40–79-year-old community-dwelling men in Rancho Bernardo, baseline serum testosterone concentrations were found to be inversely correlated with blood pressure [4], prevalence of diabetes, and the risk for future diabetes [5]. In the same cohort, men with a testosterone level less than 250 ng/dl were found to have a significantly increased risk of mortality compared with men with higher levels of testosterone, independent of other covariates. In a larger cohort study from England, testosterone levels in men were found to be inversely associated with cardiovascular risk, with a graded stepwise association throughout the entire range of testosterone [6]. This association was independent of traditional risk factors. Some [35,36], but not other [37,38] retrospective studies of testosterone treatment have raised concerns that exogenous testosterone might increase the risk for CVD events, and results of meta-analysis have been mixed [39–46]. The conclusions of a critical review of 31 placebo-controlled trials of testosterone therapy in older men published in 2004 by the Institute of Medicine were that the effects of testosterone therapy, including effects on coronary atherosclerosis and cardiovascular risk in this population, were uncertain [39]. However, a randomized trial of testosterone in older men with limited mobility [7] was stopped early because of the increased frequency of cardiovascular adverse events in the testosterone arm.

Strengths of the study

The Cardiovascular Trial has many strengths. We selected CCTA as the imaging modality to assess coronary atherosclerosis in this trial. Until recently, estimating plaque progression was only possible using intravascular ultrasound (IVUS), an invasive approach that shows only proximal coronary artery plaque volumes and correlates poorly with the individual total plaque burden [9,40]. It is also invasive and expensive, with well-defined associated morbidity. Therefore, IVUS studies generally recruit patients with acute coronary syndromes, to justify the first invasive angiogram and IVUS. CCTA has emerged as a promising noninvasive tool to directly examine the coronary artery wall, determine the degree of plaque burden, and assess the degree of coronary artery stenosis [41]. In addition, based on tissue-specific radiographic attenuation characteristics, CCTA also provides additional information on atherosclerotic plaque composition. It is able to differentiate calcified from predominantly noncalcified plaques and those that contain a large lipid pool [11,42] and allows volumetric analysis of plaques. Plaque characterization (i.e. determining the vulnerability of plaque rupture by examining its tissue components) is now possible using CCTA. New CCTA technology with 64 slices or more is extremely accurate in detecting lesions obstructing more than 50% of the lumen, with sensitivity, specificity, and positive and negative predictive values all better than 90% in patients without known CAD; it also has an important role in characterizing vulnerable nonobstructive plaques [43]. Tissue density measured by CCTA can be used to characterize atherosclerotic plaque composition.

The Cardiovascular Trial applies strict standardization and quality control measures in assessing the imaging data, with all readings made by the same readers, who were blind to treatment assignment. The equivocal results of prior testosterone trials were once thought to be due to selection of men who did not have sufficiently low testosterone concentrations. This pitfall was avoided in the TTrials, as the eligibility criterion for serum testosterone was set at a level low enough to ensure that men were unequivocally testosterone deficient. In addition, the serum testosterone concentration is measured at months 1, 2, 3, 6, and 9 to allow the assessment of medication compliance, as well as dosage adjustments to maintain the serum testosterone concentration of the men assigned to the testosterone arm within the normal range for young men.

Limitations of the study

The TTrials had a long list of inclusion and exclusion factors [8]; hence, this study will not be representative of all men over the age of 65 years. In particular, men with a recent myocardial infarction, those with serum testosterone within the normal range or less than 100 ng/dl, and those without functional concerns were excluded. In addition, the size of the study and the 1-year duration are insufficient to assess the effect of testosterone on clinical cardiovascular outcomes.

The continuing uncertainty over the benefits of testosterone therapy in elderly men emphasizes the need for initiation of randomized trials such as the TTrials and the associated Cardiovascular Trial to test this treatment rigorously. Larger trials focused on clinical outcomes will be needed to fully assess the impact of testosterone therapy on cardiovascular health.

TTrials research group members

Peter J Snyder MD¹, Susan S Ellenberg, PhD², Glenn R Cunningham MD³, Alvin M Matsumoto MD⁴, Shalender Bhasin MD⁵, Elizabeth Barrett-Connor MD⁶, Thomas M

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Trial to test testosterone effect on progression of coronary atherosclerosis Abd alamir et al.

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References


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