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Testosterone treatment in older men: clinical implications and unresolved questions from the Testosterone Trials

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A decrease in the concentration of circulating testosterone in many older men is a biomarker and possibly a rectifiable contributing factor to ill health. Low circulating testosterone concentration has been associated with cardiovascular disease, reduced cognition, fracture risk, and anaemia. However, randomised placebo-controlled trials are essential to clarify the benefits and possible risks of testosterone treatment in men without hypothalamic, pituitary, or testicular disease. The Testosterone Trials (T-Trials) were a coordinated set of trials that, following a screening-to-enrolment ratio of 65:1, randomly assigned 790 men aged 65 years or older who had a baseline testosterone concentration of less than 9·54 nmol/L and symptoms consistent with hypogonadism, but no recognisable hypothalamic–pituitary–testicular axis pathology, to daily transdermal testosterone or placebo for 12 months. In the main trial, testosterone treatment resulted in a modest benefit for sexual function, whereas the other primary outcomes of vitality and physical function were not met. Data from concomitant substudies raised a possible concern over changes in coronary plaque volume, showed a neutral effect on memory and other cognitive functions, and revealed improvements in volumetric bone mineral density and anaemia. Although insufficient to alter the existing clinical equipoise, the T-Trials provided substantial new data on organ-specific outcomes for testosterone treatment in older men. Further clinical trials are necessary to determine whether testosterone treatment will translate into patient-valued health outcomes and to clarify effects on the cardiovascular system.

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Introduction

Testosterone replacement is routine for men with androgen deficiency due to underlying hypothalamic, pituitary, or testicular disease.[1] Data from predominantly white populations show that the concentration of circulating testosterone in men decreases with age,[2–4] even in the absence of hypothalamic-pituitary-testicular axis pathology, in parallel with an accumulation of age-related comorbidities. Geographical and racial variation might exist; in the USA, circulating testosterone concentrations are higher in African-American men than in white men, and Asian men living in Hong Kong and Japan have higher circulating testosterone concentrations than Asian men living in the USA. Longitudinal trajectories are less well characterised in men of other ethnic backgrounds.[5,6] Prescription of testosterone therapy to middle-aged and older men has increased markedly in recent decades,[7,8] especially in North America, probably in part because of direct consumer advertising.[9] This trend occurred despite a relatively stable prevalence of pathological hypogonadism and despite the absence of definitive evidence from randomised controlled clinical trials. The Institute of Medicine has recommended short-term trials to determine testosterone efficacy in middle-aged and older men with low testosterone concentrations relative to the normal range for healthy young men and with androgen deficiency-like symptoms, with initiation of subsequent long-term trials dependent on initial findings from these short-term trials.[10] The National Institutes of Health subsequently funded the Testosterone Trials (T-Trials) to address this need. The T-Trials[11,12] were a coordinated set of trials in 12 academic centres in the USA that involved 790 men aged 65 years or more who were randomly assigned to transdermal testosterone or placebo for 12 months. Eligible participants had a baseline testosterone concentration less than 9·54 nmol/L (<275 ng/dL, averaged from at least two measurements) and at least one symptom or sign consistent with hypogonadism (decreased libido, difficulty walking, or low vitality). The telephone screening-to-enrolment ratio was 65:1, equating to a recruitment yield of 1·5%.[11] Dosing was adjusted to ensure that participants in the treatment group maintained a serum testosterone concentration within, but not in excess of, the normal range for healthy young men.[12] Men with pathological hypogonadism were excluded. Most men enrolled into the T-Trials had cardiovascular risk factors such as obesity (63%) and hypertension (72%), and 15% of men had a history of myocardial infarction. Men could be included in one or more of seven trials depending on meeting specific eligibility criteria (table 1). In the European Male Ageing Study,[17] sexual symptoms were most specific to the age-related decrease in testosterone concentrations. It is therefore noteworthy that the T-Trials results published in 2016[12] showed a modest improvement in sexual function with testosterone treatment, whereas the primary outcomes for vitality and physical function were not met (table 1). Here we review the background to and the results of the four remaining substudies, with outcomes related to cardiovascular disease,[13] cognition,[14] bone,[15] and anaemia,[16] and we discuss their clinical implications in the context of the existing evidence.

	Additional eligibility criteria	Testosterone	Placebo	Primary outcome (study-specific)	Whole of cohort analysis
Sexual Function Trial[12]	Self-reported decrease in libido, reduced desire (DISF-M-II ≤20/33), and partner willing to have intercourse twice a month	230/387	229/384	Modest benefit of testosterone on sexual function (increase in PDQ-Q4 by 0·58 from a baseline score of 1·4; p<0·001)*	Modest benefit of testosterone on sexual function (increase in PDQ-Q4 by 0·62 from baseline 1·5, p<0·001)
Physical Function Trial[12]	Self-reported difficulty walking or climbing stairs and gait speed <1·2 m/s on 6 min walk test; exclusion criteria: non-ambulatory men and men with disabling neuromuscular or arthritic conditions	191/392	196/389	Negative result (no significant difference in proportions of men with increase in walking distance ≥50 m in 6 min walk test; p=0·20)†	Increase in walking distance (20·5% *vs* 12·6% increased walking distance ≥50 m in 6 minute walk test at 12 months, p=0·003)
Vitality Trial[12]	Self-reported low vitality and score of <40/56 on FACIT-Fatigue <40/52)	236/394	238/394	Negative result (no difference in proportions of men with increase ≥4 points in FACIT-Fatigue score; p=0·30)‡	Negative result (no difference in proportions of men with increase ≥4 points in FACIT-Fatigue score, p=0·22)§
Cardiovascular Trial[13]	Exclusion criteria: conditions increasing risk or practicality of coronary CT angiography, estimated glomerular filtration rate <60 mL/min per 1·73 m^2, allergy to iodinated contrast medium, weight >136 kg, inability to hold breath for 10 s, tachycardia or irregular heart rhythm, or history of coronary bypass grafting	73	65	Increase in non-calcified plaque volume (from median 204 mm^3 to 232 mm^3 in testosterone group, and from 317 mm^3 to 325 mm^3 in placebo group; p=0·003)¶	NA
Cognition Trial[14]	Age-associated memory impairment: subjective memory complaints (score of 4–5 on ≥1 item of Memory Assessment Clinics Questionnaire) and objective memory impairment (score >1 SD less than performance for young men but not >2 SD less than score for age-matched men on delayed paragraph recall or visual memory); exclusion criteria: cognitive impairment (Mini Mental State Examination score <24/30).	246/394	247/394	Negative result (no improvement in delayed paragraph recall; p=0·88)	Negative result (no improvement in delayed paragraph recall; p=0·80)‖
Bone Trial[15]	Exclusion criteria: medication known to affect bone (except for calcium and vitamin D), no assessable lumbar vertebrae, dual energy absorptiometry T-score at any site less than –3·0	110	101	Increased volumetric BMD of lumbar spine trabecular bone (6·8%; p<0·001)**	NA
Anaemia Trial[16]	Baseline haemoglobin concentration ≤12·7 g/dL; excluded if baseline haemoglobin concentration <10·0 g/dL	56/336	70/321	Improvement in haemoglobin concentration (of those with unexplained anaemia, 54% in the testosterone group *vs* 15% in the placebo group had an increase in haemoglobin concentration ≥1·0 g/dL; p=0·002)††	Improvement in haemoglobin concentration (of those without anaemia, 38% in the testosterone group *vs* 4% in the placebo group had an increase in haemoglobin concentration ≥1·0 g/dL; p<0·001)‡‡

Data are number of men randomly assigned to each trial group in each substudy/total number of men in the whole cohort with available data. Only the men in the Cardiovascular and Bone substudies had those specific outcomes of interest assessed. The Testosterone Trials were a coordinated set of seven double-blind, placebo-controlled trials of transdermal testosterone gel 50 mg daily versus placebo for 12 months in 790 men. Dose adjustments were made to maintain serum testosterone concentrations within the normal range for healthy young men. Participants were 65 years or older, with average baseline testosterone concentration less than 9·54 nmol/L. General exclusion criteria were history of prostate cancer, more than a 35% risk of prostate cancer or more than a 7% risk of high-grade prostate cancer, International Prostate Symptom Score of more than 19 out of 35, conditions known to cause hypogonadism, medications affecting testosterone concentrations, high cardiovascular risk (previous myocardial infarction or stroke within past 3 months, unstable angina, New York Heart Association class III or IV congestive heart failure, systolic blood pressure >160 mm Hg, or diastolic blood pressure >100 mm Hg), and severe depression (Patient Health Questionnaire 9 score ≥20 out of 27). DISF-M-II=Derogatis Interview for Sexual Functioning in Men-II. IIEF=International Index of Erectile Function. PDQ-Q4=Psychosexual Daily Questionnaire question 4. FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue scale. SF-36=Medical Outcomes Study 36-Item Short-Form Health Survey. PHQ-9=Patient Health Questionnaire 9. NA=non-applicable. BMD=bone mineral density. *Secondary outcomes: improvement in DISF-M-II sexual desire and IIEF erectile function scores. †Secondary outcomes: improvement in Physical Function Scale score. ‡Secondary outcomes: improvement in SF-36 vitality, Positive and Negative Affect Schedule, and PHQ-9 scores. §Secondary outcome: improvement in FACIT-Fatigue score (treatment effect 1·27; p=0·006). ¶Secondary outcomes: increase in total plaque volume and no difference in coronary calcium score. ‖Secondary outcomes: improvement in executive function (Trail Making Test), and no differences in visual memory, spatial ability, subjective memory, global cognitive function, or immediate paragraph recall. **Secondary outcomes: increase in spine whole bone (4·2%; p<0·001) and hip whole bone (1·3%; p<0·001) volumetric BMD; increase in spine bone strength (7·1%; p<0·001) and hip bone strength (1·8%; p<0·001), as assessed by finite element analysis; and increase in lumbar spine (1·2%; p=0·01) but not hip or femoral neck areal BMD. ††Secondary outcomes: increase in haemoglobin concentration (0·83 g/dL; p<0·001) in participants with unexplained anaemia and consistent results in participants with anaemia of known cause. ‡‡Secondary outcome: increase in circulating haemoglobin concentration in participants without anaemia (0·90 g/dL; p<0·001).

Table 1: **The Testosterone Trials**

Testosterone and cardiovascular disease

Findings from epidemiological studies have shown that reduced endogenous androgens in middle-aged and older men are associated with adverse cardiovascular outcomes, including a higher incidence of cardiovascular events such as stroke[18–20] and increased cardiovascular and all-cause mortality.[21–24] These associations have been confirmed in several large meta-analyses.[25–27] However, observational studies do not prove causality, and in the case of menopausal hormone therapy in women, large interventional studies did not have the outcomes predicted from observational findings.[28] Ill health is associated with low testosterone concentrations, so in observational studies low testosterone might be a risk marker rather than a cause of the outcome.[29] Ultimately, the question of whether low testosterone concentrations are cause or consequence of cardiovascular disease can only be answered by adequately designed randomised controlled trials of testosterone treatment. A crucial knowledge gap remains as to the effect of testosterone treatment on cardiovascular disease risk. To date, no such trial has had sufficient power to assess clinical cardiovascular events as a prespecified endpoint.[30] A definitive conclusion as to whether exogenous testosterone reduces the incidence of cardiovascular events in middle-aged and older men, or otherwise, can therefore not be drawn.

Some insight has been gained from analyses of cardiovascular adverse events in retrospective

	Eligibility criteria	Formulation of androgen	Active drug (baseline testosterone concentration)	Placebo (baseline testosterone concentration)	Duration, months	Result
Basaria et al (2010)[44]	Aged ≥65 years; testosterone concentration 3·5–12·1 nmol/L or free testosterone concentration <173 pmol/L; mobility limitation	Transdermal testosterone gel 100 mg daily	n=106 (8·7 nmo/L)	n=103 (8·2 nmol/L)	6	Trial stopped prematurely because of excess cardiovascular adverse events in testosterone group
Srinivas-Shankar et al (2010)[45]	Aged ≥65 years; testosterone concentration ≤12 nmol/L or free testosterone concentration ≤250 pmol/L; frail or intermediate frail	Transdermal testosterone gel 50 mg daily	n=130 (11·0 nmol/L)	n=132 (10·9 nmol/L)	6	Improved muscle strength and physical function; no signal for cardiovascular adverse events
Idan et al (2010)[46]	Aged >50 years without prostate disease	Transdermal dihydrotestosterone gel 70 mg daily	n=56 (17·1 nmol/L)	n=58 (17·5 nmol/L)	24	No difference in rates of change in carotid intima-media thickness; no signal for cardiovascular adverse events
Basaria et al (2015)[47]	Aged ≥60 years; testosterone concentration 3·5–13·9 nmol/L or free testosterone concentration <173 pmol/L	Transdermal testosterone gel 75 mg daily	n=155 (10·7 nmol/L)	n=151 (10·7 nmol/L)	36	No difference in rates of change in carotid intima-media thickness or coronary artery calcium; no signal for cardiovascular adverse events
Snyder et al (2016)[12]	Aged ≥65 years; testosterone concentration <9·5 nmol/L; symptoms to include at least one of sexual dysfunction, difficulty walking, or low vitality	Transdermal testosterone gel 50 mg daily	n=395 (8·2 nmol/L)	n=395 (8·1 nmol/L)	12	Modest benefit of testosterone on sexual function; no signal for cardiovascular adverse events

Table 2: **Pivotal randomised controlled trials of testosterone treatment in middle-aged and older men in whom cardiovascular adverse events were reported**

case-control studies, small clinical trials examining surrogate outcomes for cardiovascular risk, and randomised controlled trials reporting adverse events. Retrospective studies have major methodological limitations, and data from such studies show conflicting results associating testosterone treatment with either increased risk of myocardial infarction,[31,32] neutral or reduced risk of myocardial infarction,[33,34] reduced risk of major cardiovascular events,[35,36] or reduced mortality.[34,37–39] However, these studies are open to biases from confounding by indication and time-related biases.[40,41] Protective effects of exogenous testosterone on the myocardium have been reported from small intervention studies. Transdermal testosterone improved angina threshold in men with chronic stable angina[42] and exerted protective effects on exercise-induced ischaemia that were maintained for up to 12 months.[43] However, one randomised controlled trial of testosterone in older men with mobility limitations was prematurely halted because of an excess of cardiovascular adverse events in the testosterone group.[44] Limitations of this study include the fact that cardiovascular events were not a planned primary or secondary outcome of the trial so no structured evaluation of cardiovascular events was done, and the actual number of events was small.[44] No such signal for cardiovascular adverse events was seen in a very similar trial with intermediate-frail or frail older men[45] or in the main T-Trials study, in which seven men in each group were adjudicated to have had a major cardiovascular event (table 2).[12] The results of the T-Trials cardiovascular disease study are therefore timely.[13]

T-Trials Cardiovascular Trial

170 of the men enrolled in the T-Trials had coronary artery plaque progression quantified by coronary CT angiography (CCTA) during the 12-month treatment period.[13] 66% of participants had hypertension, 30% diabetes, and 9% a prior myocardial infarction—a similar cardiovascular burden to the entire T-Trial population.[12] 51% of participants had a coronary artery calcification score greater than 300 Agatston units at baseline, suggesting severe atherosclerosis. 138 of the 170 men who were enrolled completed the study.[13] Compared with placebo, treatment with testosterone was associated with a greater increase in the primary endpoint, non-calcified coronary plaque volume, during the 12-month intervention period (table 1).[13] Total plaque volume also increased more in the testosterone group than in the placebo group. No major cardiovascular events were reported in either group. The authors concluded that larger studies were needed to understand the clinical implications of this finding.[13]

A number of issues limit the interpretation that testosterone treatment increases coronary plaque burden. According to the original Cardiovascular Trial protocol,[13] the estimated requirement to enrol 400 men was reduced to 140 men when the primary outcome was changed from total plaque volume to non-calcified plaque volume. Importantly, groups were unbalanced, with men in the placebo group having much more plaque at baseline. Non-calcified plaque volume increased from 204 mm³ to 232 mm³ in the testosterone group, and from 317 mm³ to 325 mm³ in the placebo group. Despite a greater increase in plaque volume, men in the testosterone group still had less plaque at study end than men in the placebo group. Conversely, men in the placebo group had a smaller increase in plaque volume but still more plaque at the end of the study, but the difference between the two groups appeared to have slightly narrowed. Although analyses were adjusted for baseline plaque volume, this might not fully correct for the marked baseline imbalance. Changes in plaque volume could have been

	Key finding	Clinical implications	Strengths	Limitations
Cardiovascular Trial[13]	Testosterone treatment was associated with a 41 mm³ difference in non-calcified coronary plaque, but the prognostic significance of this finding remains uncertain	Testosterone therapy is indicated in men with androgen deficiency due to diseases of the hypothalamus, pituitary, or testes in whom cardiovascular risk should be optimally managed; further studies are needed to clarify the effect of testosterone on cardiovascular risk in older men; practitioners should inform patients that the effect of testosterone therapy on cardiovascular disease is unknown	Examination of coronary atheroma using coronary CT angiography; consistent findings for non-calcified and total plaque volume	Small subset of main Testosterone Trials; groups unbalanced, with men in the placebo group having substantially more non-calcified and total plaque at baseline and end of study; uncertain prognostic significance of the observed magnitude of change in plaque volume; non-concordant result for coronary calcification; does not inform with respect to men without pre-existing severe atherosclerosis (as defined by baseline plaque volume); not powered for cardiovascular events
Cognitive Function Trial[14]	Testosterone treatment did not improve memory, but there was a weak signal for an effect on executive function	Older men commencing testosterone replacement therapy can expect some improvement in sexual function and indices of wellbeing but should not expect an improvement in memory or cognitive function	Selection of men with age-associated memory impairment; large subset of main T-Trials; detailed battery of cognitive assessments; data available for whole cohort enabling exploratory analysis	Baseline cognitive deficits were minimal to mild; multiple exploratory outcomes; negative result does not exclude possible modest effect
Bone Trial[15]	Testosterone treatment increased bone density and estimated bone strength	Measurement of circulating testosterone concentration is an important part of the diagnostic workup of men with osteoporosis; testosterone treatment should not be used for the sole purpose of improving skeletal health; an increase in bone density could be a collateral benefit for men receiving testosterone therapy for treatment of established androgen deficiency; testosterone treatment has not been shown to reduce fracture rates, so men with low testosterone concentrations and high fracture risk should be considered for antiresorptive therapy, irrespective whether they receive testosterone treatment or not	Groups balanced for baseline areal BMD; detailed assessment of volumetric BMD and bone strength at spine and hip; consistent findings for primary and range of secondary outcomes	Not designed to analyse independent effects of testosterone and oestradiol; men had normal baseline BMD; effect of observed changes in bone strength on clinical endpoints not fully established; not powered for incident fracture
Anaemia Trial[16]	Testosterone increased haemoglobin concentrations in men with and without mild anaemia	Measurement of circulating testosterone concentration should be considered in men with unexplained anaemia; testosterone treatment in older men with low testosterone concentration is likely to improve their anaemia; an increase in haemoglobin concentration could be a collateral benefit for men receiving testosterone therapy for treatment of established androgen deficiency; additional studies are needed to determine whether or not testosterone treatment of men with anaemia leads to clinically important health benefits	Selection of men with anaemia (haemoglobin concentration <12·7 g/dL); assessment of causes of anaemia; data available for whole cohort enabling exploratory analysis; consistent findings in men with explained and unexplained anaemia, and in men without anaemia	Small subset of main Testosterone Trials; unable to determine effect of changes in haemoglobin concentration on health status; diagnosis of anaemia based on single laboratory values

BMD=bone mineral density.

Table 3: **Key findings, clinical implications, strengths, and limitations of the Cardiovascular, Cognition, Bone, and Anaemia Trials within the Testosterone Trials**

affected by this baseline difference, with an element of regression to the mean whereby smaller plaques progressed most and larger plaques progressed least. Thus if smaller plaques increased in volume more rapidly than larger plaques, with growth slowing as plaques enlarged, this could account for the differences seen in the two groups even without an effect of testosterone. This highlights the difficulty in interpreting the findings when randomisation does not result in comparable baseline characteristics in such a substudy. Similar inconclusive results were seen with total plaque volume. Furthermore, there was no difference in coronary calcium score, an alternative marker of cardiovascular risk, between groups.[13]

These results differ from previous randomised controlled trial outcomes related to cardiovascular risk (table 2). In a study by Idan and colleagues,[46] treatment of healthy men older than 50 years with dihydrotestosterone, the potent downstream metabolite of testosterone, for 2 years did not result in a difference in carotid intimamedia thickness.[46] Basaria and colleagues[47] found that among men of similar age, but at lower cardiovascular risk than T-Trial participants, testosterone treatment for 3 years did not result in a difference in carotid intima-media thickness or coronary calcium score compared with placebo. Although higher grades of stenosis or obstruction, or presence of plaque versus no plaque on CCTA, are associated with increased risk of cardiovascular disease events,[48,49] the predictive value of subtle changes in plaque volume or features of vulnerability remain to be determined. The extent to which a 41 mm³ difference in non-calcified coronary plaque (95% CI 14–67; p=0·003) or a 47 mm³ difference in total plaque volume (13–80; 0·006), as reported by Budoff and colleagues,[13] would translate into risk of future cardiovascular events remains uncertain.[50] Major strengths and limitations of the Cardiovascular Trial are summarised in table 3. Although coronary atheroma was examined using CCTA and findings were consistent for non-calcified and total plaque volume, this was a small

subset of the main T-Trials, groups were unbalanced for baseline plaque volumes, and the prognostic importance of the observed change in plaque volume is unclear. Neither the Cardiovascular Trial nor the main T-Trials were powered for cardiovascular events as an outcome. In the overall T-Trials, the actual number of men who had cardiovascular adverse events defined as myocardial infarction, stroke, or death from cardiovascular causes was small and was identical in both trial arms (n=7).[12]

In general, meta-analyses of testosterone randomised controlled trials have not associated testosterone treatment with adverse cardiovascular events, except possibly in men aged 65 years or older in the first year of treatment.[51] This is in keeping with an observational study by Wallis and colleagues,[39] in which testosterone treatment in men aged 66 years or older was associated with reduced mortality, but the risk of adverse outcomes was higher in men treated for a short time (median of 2 months) than in untreated controls. However, even in meta-analyses the number of randomised controlled trials and cardiovascular events reported are limited, making it difficult to draw firm conclusions. Furthermore, reports of major adverse events from trials might not be comprehensive, leading to unintentional under-reporting.[52] The US Food and Drug Administration[53] had previously recommended against the use of testosterone in men with low testosterone concentrations due to ageing and required labelling changes to warn of a possible increase in the risk of heart attack and stroke. Abuse of anabolic androgenic steroids, for example by taking supraphysiological doses of different formulations to gain muscle mass, has been associated with harms including reduced left ventricular ejection fraction and increased coronary plaque volume.[54] However, that scenario is very different to administration of testosterone under medical supervision to achieve physiological concentrations.

Additional perspectives can be gained by mendelian randomisation. If a functional genetic polymorphism alters exposure to a risk factor, this exposure is determined randomly at birth and is independent of subsequent lifestyle factors and should be unaffected by reverse causality.[55] In men, aromatase polymorphisms that reduce circulating oestradiol concentrations are associated with shortened leucocyte telomere length, associating this bioactive metabolite of testosterone with slower biological ageing.[56] By contrast, genetic markers of testosterone exposure tend to be indirectly related, involving polymorphisms in the sex hormone-binding globulin gene or other genes not within the testosterone biosynthetic pathway.[57] In a mendelian randomisation study[58] using two such polymorphisms, no evidence of a causal association with cardiometabolic risk factors or mortality was found. However, results of another analysis[59] using markers associated with follicle-stimulating hormone, anti-Mullerian hormone, and testicular dysgenesis syndrome suggested a possible relationship between reduced androgen exposure and ischaemic heart disease. Larger studies involving collaborative analyses of multiple cohorts might be required to provide more definitive answers using this approach.[60]

In the context of the study by Budoff and colleagues,[13] can we draw these disparate strands together? The epidemiological data indicate that reduced endogenous testosterone concentrations are independent predictors for cardiovascular events and mortality risk. Therefore, there might be an opportunity to intervene to preserve health in the expanding demographic of older men. However, in older men with multiple cardiovascular risk factors or prevalent cardiovascular disease, there might be a risk of cardiovascular adverse events, especially shortly after initiation or within the first year of treatment. Whether this is mediated by changes to the volume, composition, or stability of existing coronary plaque or simply reflects an increase in sexual or physical activity, unmasking latent disease by precipitating exertional symptoms or events, remains unclear.

Despite being a well conducted study, the T-Trials Cardiovascular Trial adds little to answer these questions, limited primarily by the substantial difference in the randomised groups at baseline and the unclear translation of the noted changes in non-calcified plaque volume into altered risk. The results reinforce the existing clinical equipoise where the benefits of testosterone therapy in men with androgen deficiency due to diseases of the hypothalamus, pituitary, or testes[1] probably outweigh theoretical cardiac risks, especially with concomitant careful management of cardiovascular disease risk factors.[61] There is persisting uncertainty over the cardiovascular benefits versus risks of testosterone treatment for older men in the absence of pathological hypogonadism and a pressing need for further data in view of the millions of older men using testosterone therapies. Further mechanistic studies are warranted to explore the relationship between exogenous testosterone and cardiovascular risk, but clinicians need the information only a large-scale, long-term randomised controlled trial designed and powered for the endpoint of cardiovascular events can provide.

Testosterone and cognition

Findings from epidemiological studies have associated reduced circulating testosterone concentration with poorer cognitive performance, but the data are not wholly consistent.[62] In cross-sectional studies of middle-aged and older men, positive associations of testosterone with measures of general cognition have been reported,[63–66] as have neutral[67] or inverse associations.[68] In longitudinal studies, an increased ratio of testosterone to sex hormone-binding globulin was associated with reduced rates of decline in visual memory[69] and with decreased risk of developing Alzheimer's disease.[70] However, other longitudinal studies have not found low

	Eligibility criteria	Formulation of androgen	Study population	Duration, months	Result
Janowsky et al (1994)[74]	Aged 60–75 years	Transdermal testosterone 15 mg scrotal patch daily	n=56 (27 in active drug group; 29 in placebo group)	3	Enhanced spatial cognition; no effect on verbal memory, dexterity, or cognitive flexibility
Sih et al (1997)[75]	Aged ≥50 years; non-SHBG-bound testosterone concentration ≤2·1 nmol/L	Intramuscular testosterone 200 mg fortnightly	n=32 (17 in active drug group; 15 in placebo group)	12	No effect on memory, recall, or verbal fluency
Cherrier et al (2001)[76]	Aged 50–80 years	Intramuscular testosterone 100 mg weekly	n=28 (15 in active drug group; 13 in placebo group)	1·5	Improved spatial memory and ability, and verbal memory; no effect on attention or verbal fluency
Cherrier et al (2002)[77]	Aged 21–46 years	Intramuscular testosterone 100 mg weekly with or without oral levonorgestrel 125 µg daily	n=32	2	Decreased performance in tests of verbal memory in levonorgestrel-treated group; improved selective attention in testosterone plus levonorgestrel group
Kenny et al (2002)[78]	Aged ≥65 years, non-SHBG-bound testosterone concentration ≤4·4 nmol/L	Transdermal testosterone 5 mg patch daily	n=64 (24 in active drug group; 40 in placebo group)	12	No difference in cognitive test results between groups
Kenny et al (2004)[79]	Aged ≥65 years, non-SHBG-bound testosterone concentration ≤4·4 nmol/L	Intramuscular testosterone 200 mg every 3 weeks	n=11 (6 in active drug group; 5 in placebo group)	3	No difference in cognitive test results between groups
Haren et al (2005)[80]	Aged ≥60 years, SHBG-bound testosterone concentration 0·3–0·5; testosterone concentration >8 nmol/L	Oral testosterone 80 mg twice a day	n=76 (39 in active drug group; 37 in placebo group)	12	No difference in visuomotor tracking and visuospatial ability
Gray et al (2005)[81]	Aged 60–75 years	Gonadotropin-releasing hormone plus intramuscular testosterone 25 mg, 50 mg, 125 mg, 300 mg, or 600 mg weekly	n=60	5	Differences in visuospatial cognition across treatment groups, with highest scores in men on highest dose (600 mg per week)
Cherrier et al (2005)[82]	Aged 50–90 years	Intramuscular testosterone 100 mg weekly with or without oral anastrazole 1 mg daily	n=60	1·5	Improved spatial memory in testosterone and testosterone plus anastrazole groups, improved verbal memory in testosterone group only
Maki et al (2007)[83]	Aged 66–86 years	Intramuscular testosterone 200 mg every 2 weeks	n=15	9*	Decreased verbal memory
Vaughan et al (2007)[84]	Aged 65–83 years; testosterone concentration <12·1 nmol/L	Intramuscular testosterone 200 mg fortnightly with or without oral finasteride 5 mg daily	n=69	36	No differences in multiple cognitive tests except for improved verbal memory with testosterone plus finasteride; improved attention with testosterone only
Cherrier et al (2007)[85]	Aged 50–90 years	Intramuscular testosterone 50 mg, 100 mg, or 200 mg weekly	n=57	1·5	Improved verbal and spatial memory associated with moderate increases in testosterone, but not with smaller or larger increases
Emmelot-Vonk et al (2008)[86]	Aged 60–80 years; testosterone concentration <13·7 nmol/L	Oral testosterone 80 mg twice a day	n=223 (113 in active drug group; 110 in placebo group)	6	No differences in verbal memory, perceptual speed, attention, or visuospatial performance
Young et al (2010)[87]	Aged 25–35 years; 60–80 years	Gonadotropin-releasing hormone plus transdermal testosterone gel 100 mg or 75 mg with or without oral anastrazole 1 mg daily	n=26 (aged 25–35 years); n=62 (aged 60–80 years)	1·5	No effect on measures of executive function, memory, and spatial cognition
Huang et al (2016)[88]	Aged ≥60 years; testosterone concentration 3·5–13·9 nmol/L or free testosterone concentration <173 pmol/L	Transdermal testosterone gel 75 mg daily	n=280 (140 in active drug group; 140 in placebo group)	36	No differences in visuospatial ability, verbal fluency, verbal memory, manual dexterity, attention, or executive function

SHBG=sex hormone-binding globulin. *Cross-over design.

Table 4: **Randomised placebo-controlled studies of testosterone in men with outcomes related to memory and other measures of cognitive performance**

testosterone to be associated with decline in cognitive function or increased risk of dementia.[71,72] In a meta-analysis[73] of seven prospective cohort studies with a total of 5721 older men, reduced endogenous testosterone was associated with increased risk of being diagnosed with Alzheimer's disease.

Findings from randomised controlled trials of testosterone treatment in generally healthy men with cognition-related outcomes are summarised in table 4. Inconsistent results from these trials reflect the limited sample sizes and different testosterone formulations, intervention durations, and outcome measures. In different studies, beneficial effects of testosterone on some but not other measures of cognitive performance were reported.[74,76,77,82,84] A dose-dependent effect[81] or an optimal dose phenomenon[85] have been suggested. However, in other studies, no effects of testosterone treatment were found across a range of cognitive

	Eligibility criteria	Formulation of androgen	Active drug	Placebo	Duration, months	Results
Tan et al (2003)[89]	Aged 68–80 years; newly diagnosed Alzheimer's disease; testosterone concentration <7 nmol/L	Intramuscular testosterone 200 mg fortnightly	n=5	n=5	12	Improved general cognition and visuospatial ability
Cherrier et al (2005)[90]	Aged 63–85 years; Alzheimer's disease or mild cognitive impairment	Intramuscular testosterone 100 mg weekly	n=9 with Alzheimer's disease; n=10 with mild cognitive impairment	n=6 with Alzheimer's disease; n=7 with mild cognitive impairment	1·5	Improved spatial memory and ability and verbal memory; no differences in verbal fluency or attention
Lu et al (2006)[91]	Men with Alzheimer's disease and healthy controls	Transdermal testosterone gel 75 mg daily	n=9 with Alzheimer's disease; n=14 controls	n=9 with Alzheimer's disease; 15 controls	6	Trend to improvement in visuospatial function in men with Alzheimer's disease; no difference in verbal memory

Table 5: **Randomised placebo-controlled studies of testosterone in men with mild cognitive impairment or Alzheimer's disease with outcomes of cognitive performance**

outcome measures,[75,78–80,86–88] and a decrease in verbal memory was reported in one study.[83] No difference in cognitive outcomes were found in two of the largest randomised controlled trials.[86,88]

The effect of exogenous testosterone on cognition can vary depending on the degree of cognitive impairment, if any, at baseline. Relatively few randomised controlled trials have recruited men with impaired cognition or Alzheimer's disease (table 5). These trials have tended to be small in scale, suggesting either possible beneficial effects of testosterone on general cognition,[89] spatial memory, and ability[90] or no benefit with testosterone.[91]

Declines in memory have been observed in small studies of androgen deprivation therapy.[92] The results of a meta-analysis[93] of 14 studies with 417 men with prostate cancer showed that treatment with androgen deprivation therapy was associated with worse performance on visuomotor tasks compared with groups of men without cancer. Although consistent with a role for sex steroids in maintaining aspects of cognition,[73,93] the findings might also represent the preferential use of androgen deprivation therapy in men with a higher comorbid burden (ie, confounding by indication). Moreover, data from a mendelian randomisation study[94] using two aromatase and one oestrogen receptor polymorphism as predictive markers of reduced testosterone concentrations showed no evidence for an association with cognition. In view of the inconsistency in the existing data, the T-Trials Cognitive Function Study[14] represents a welcome addition to the literature.

T-Trials Cognitive Function Trial

The Cognitive Function Trial reported by Resnick and colleagues[14] included 493 men with age-associated memory impairment, defined as the presence of both subjective memory complaints and objective memory impairment (table 1). Baseline Mini Mental State Examination score was 28 (of a maximum score of 30). Testosterone and placebo groups were balanced in terms of baseline covariates and baseline cognitive function test scores. The trial result was clearly negative, and testosterone treatment did not improve the primary endpoint of delayed paragraph recall score (adjusted mean difference –0·07 (95% CI –0·92 to 0·79; p=0·88). Visual memory, spatial ability, executive function, subjective memory, global cognitive function, or immediate paragraph recall also did not differ between treatment groups (table 1).[14] Cognitive assessments in all T-Trials participants enabled an exploratory analysis of the entire cohort, including men ineligible for the cognition trial because memory impairment was absent at baseline. When all T-Trials participants were analysed, men in the testosterone group had a modest improvement in executive function, as assessed by the Trail Making Test. The relevance of this result is difficult to interpret, and at best hypothesis generating, given a between-group imbalance in test performance at baseline (a problem similar to the differences at baseline complicating the interpretation of the cardiovascular study data) and that the test was one of seven exploratory outcome measures.[14] The investigators found no differences in any of the other measures of cognition between the two groups.

The Cognitive Function Trial is the largest randomised controlled trial to date of testosterone with cognition as a prespecified outcome. The negative findings are quite robust, making it unlikely that testosterone treatment meaningfully improves memory or other cognitive function in men with age-associated memory impairment. Key findings, strengths and limitations, and clinical implications of the cognition study are summarised in table 3. Strengths include the selection of men with age-associated memory impairment and the use of a detailed battery of cognitive assessments in a large subset of the main T-Trials cohort. Limitations were that the baseline cognitive deficits were slight, there were multiple exploratory outcomes, and the negative result does not exclude a possible modest effect. Whether testosterone might improve cognition in men with more severe cognitive impairment or slow the progression of dementia remains unknown, but the available data do not support treatment decisions regarding testosterone therapy based on expectations of improvement in cognitive outcomes.

	Eligibility criteria	Formulation	Active drug (baseline testosterone concentration)	Placebo (baseline testosterone concentration)	Duration, months	Result
Snyder et al (1999)[115]	Aged >65 years; testosterone concentration <1 SD less than 16·5 nmol/L; lumbar spine BMD less than the mean in healthy young men (<1·26 g/cm²)	Testosterone scrotal patch 6 mg daily	n=54 (12·7 nmol/L)	n=54 (12·8 nmol/L)	36	No difference in lumbar spine or femoral neck BMD*
Kenny et al (2001)[116]	Aged >65 years; low bioavailable testosterone concentration (<4·44 nmol/L)	Testosterone patch 5 mg daily	n=34 (13·5 nmol/L)	n=33 (13·5 nmol/L)	12	Increase in femoral neck BMD (1·9%; p<0·05); no difference in lumbar spine BMD
Christmas et al (2002)[117]	Aged >65 years; testosterone concentration >1 SD less than 16·3 nmol/L	Testosterone enanthate 100 mg intramuscular every 2 weeks	n=19 (14·2 nmol/L)	n=17 (13.6 nmol/L)	6	No difference in lumbar spine or femoral neck BMD
Amory et al (2004)[118]	Aged ≥65 years; testosterone concentration <12·1 nmol/L	Testosterone enanthate 200 mg intramuscular every 2 weeks	n=24 (9·9 nmol/L)	n=24 (10·5 nmol/L)	36	Increase in lumbar spine (8·9%; p<0·01) and femoral neck (2·9%; p<0·05) BMD†
Basurto et al (2008)[119]	Aged ≥60 years; testosterone concentration <11·1 nmol/L	Testosterone enanthate 250 mg intramuscular every 3 weeks	n=25 (10·4 nmol/L)	n=23 (10·8 nmol/L)	12	Increase in lumbar spine BMD (3·5%; p<0·01); no difference in femoral neck BMD
Kenny et al (2010)[120]	Aged ≥60 years; testosterone concentration <12·1 nmol/L or bioavailable testosterone concentration <1·5 SD less than the mean testosterone concentration in young adult mean; hip BMD T-score <–2·0 or non-traumatic fracture within preceding 5 years	Testosterone gel 50 mg daily	n=69 (13·2 nmol/L)	n=62 (14·5 nmol/L)	12	Increase in lumbar spine BMD (2·9%; p<0·01); no difference in femoral neck BMD (decrease in radius BMD [–1·1%; p<0·01])

BMD=bone mineral density. *Post-hoc analysis: increase in lumbar spine BMD according to baseline total testosterone concentration: >13·9 nmol/L testosterone, non-significant change in BMD; <10·4 nmol/L testosterone, 3·4% increase in lumbar spine BMD (p<0·01); <6·9 nmol/L testosterone, 5·9% increase in lumbar spine BMD (p<0·01). †Increases in lumbar spine BMD were positively correlated with the magnitude of increase in serum total testosterone and oestradiol concentrations but not related to baseline serum total testosterone concentration, oestradiol concentration, or BMD.

Table 6: **Previous randomised controlled trials of testosterone treatment in middle-aged or older men with low-normal baseline serum testosterone concentrations with dedicated bone endpoints**

Testosterone, bone structure, and fracture risk

Pathological hypogonadism due to hypothalamic, pituitary, or testicular disease is an important risk factor for osteoporosis in adult men.[95] The prevalence of hypogonadism in older men with osteoporosis is not well described. In uncontrolled case series of men older than 60 years referred to metabolic bone clinics with previous minimal trauma fractures, 7–8% had evidence of hypogonadism.[96,97] Although randomised controlled trials have not been done, testosterone replacement therapy increases bone density in men with androgen deficiency and known gonadal axis pathology.[98] Testosterone is important for skeletal health in older men: androgen deprivation therapy for prostate cancer, commonly given to men older than 70 years, accelerates the age-related bone loss by 5–10-fold[99] and increases fracture risk by 30%.[100] Although men with pathological hypogonadism, particularly those receiving androgen deprivation therapy, have low testosterone concentrations, the age-related reductions in circulating testosterone concentrations are comparatively modest.[2–4]

The effect of reduced testosterone concentration on bone might primarily be an effect of reduced substrate availability for aromatisation to oestradiol. Findings from large epidemiological studies with older men have consistently shown that compared with circulating testosterone, low circulating oestradiol concentration is more strongly associated with loss of bone mineral density (BMD) at trabecular and cortical sites and with reduced estimated bone strength.[101–104] In a large prospective study,[105,106] low circulating oestradiol concentration but not low testosterone concentration independently predicted fracture risk in older white and Chinese men. However, the highest rates of bone loss and fractures occur in men with reductions in concentrations of both oestradiol and testosterone, suggesting additional contributions of low testosterone concentration.[106–108] Associations between circulating sex steroid concentrations and fracture risk are attenuated but persist after adjustment for BMD, indicating that low sex steroid concentrations could increase fracture risk by mechanisms other than reduced bone density.[105,106] Testosterone is an important determinant of skeletal muscle mass, and increased muscle mass might improve bone strength by increased mechanical loading.[109] Low testosterone concentrations are associated with sarcopenia and frailty in older men,[110] and in the MrOS study,[111] low testosterone concentration, but not low oestradiol concentration, independently predicted fall risk, an important fracture precipitant. Overall, these observational findings suggest that although the effects of testosterone on bone architecture are predominantly mediated via aromatisation to oestradiol, testosterone might contribute to reduced fracture risk via extraskeletal mechanisms, including increased muscle mass and reduced fall risk.[104,112] No formal mendelian randomisation studies have been reported, but data from observational studies have shown associations of polymorphisms in the aromatase

gene[113] and the promoter of the *SHBG* gene[114] with BMD in community-dwelling men. This finding suggests that, at least in part, effects of sex steroids on bone health might be genetically determined.

Even large prospective studies can be limited by their observational design, reliance on single hormone measures, low proportions of men with frankly low testosterone concentrations, and incomplete adjustment for confounders. Evidence for a causal role therefore requires adequately designed and powered randomised controlled trials. Randomised controlled trials of testosterone treatment with dedicated bone endpoints are summarised in table 6.[115–120] Participants in these trials were generally healthy, community-dwelling, older men without known pituitary or testicular disease. Studies were heterogeneous and limited by small size and assessment of BMD solely by dual-energy x-ray absorptiometry (DXA) that, at the spine, is prone to interference by osteophytes and vascular calcifications, which are common in older men. No study to date (including the T-Trials) has been designed to determine fracture rates. Men had normal to modestly reduced baseline testosterone concentrations, and reduced BMD was an inclusion criterion in only one study.[120] Although the results were not wholly consistent, the data from these trials suggested that testosterone treatment increases BMD predominantly at the lumbar spine (table 6). Likewise, in a meta-analysis[121] of 29 testosterone treatment randomised controlled trials (most of which were not designed with BMD as a primary endpoint), enrolling a total of 1083 middle-aged men, BMD improved at the lumbar spine (3·7%), but no changes were observed in femoral neck BMD.

T-Trials Bone Trial

The Bone Trial[15] is the largest randomised controlled trial of the effects of testosterone treatment on BMD in older men (table 1). The study investigators determined the effect of testosterone on bone structure using quantitative CT. Nine of the 12 T-Trial sites in the USA participated and enrolled 211 men, meeting the enrolment target of 200 men. Men had normal BMD at baseline, as quantified by DXA, with T-scores ranging from –0·3 to 1·3 at baseline. After 12 months, compared with placebo, testosterone treatment increased the primary outcome (volumetric BMD of trabecular bone at the lumbar spine) by 6·8% (95% CI 4·8–8·7; p<0·001).[15] Statistically significant treatment effects were also observed for secondary outcome measures, including spine whole bone volumetric BMD (increase of 4·2%) and, to a more modest degree, hip whole bone volumetric BMD (increase of 1·3%). Additionally, testosterone treatment increased estimated bone strength at the spine and hip and, broadly consistent with previous studies,[115–121] modestly increased areal BMD (as quantified by DXA) at the lumbar spine (increase of 1·2%) but not at the total hip or femoral neck.

In summary, the Bone Trial[15] has yielded the most convincing evidence to date that in men with low testosterone concentrations, short-term testosterone treatment improves bone architecture and estimated bone strength. Effects are especially pronounced for trabecular bone, consistent with findings reported in men with frank hypogonadism.[122] Strengths of the study include balanced baseline characteristics in addition to detailed assessment of bone volumetric BMD and bone strength (table 3). However, the study also has limitations: given normal baseline BMD, these findings cannot be extrapolated to men with osteoporosis. Like previous randomised controlled trials (table 6), the Bone Trial was not designed to determine whether testosterone treatment, which increases circulating testosterone and oestradiol concentrations, increases bone density directly or via conversion of testosterone to oestradiol. In men treated with testosterone, increases in volumetric BMD were associated with increases in both circulating testosterone and oestradiol concentration.[15] Finally and importantly, the Bone Trial was not designed or powered for fracture outcomes. During the treatment year, 12 fractures occurred, six in each treatment group.

Clinical implications of the Bone Trial, in the context of the overall available evidence, are summarised in table 3. These recommendations are broadly consistent with the Endocrine Society Clinical Practice Guideline on osteoporosis in men.[123] Unless and until adequately powered and dedicated fracture endpoint trials of testosterone treatment in older men are available, men with high fracture risk should be treated with pharmacological drugs for osteoporosis with evidence for antifracture benefit, irrespective of whether they receive testosterone treatment or not. Indeed, antiresorptive treatment reduces fracture risk irrespective of circulating testosterone concentrations,[124] even in men with castrate testosterone concentrations,[125] which shows that men with low endogenous testosterone are not refractory to the anti-fracture benefits of bisphosphonates[124] or denosumab.[125] However, in men with low testosterone concentration and low BMD who do not meet criteria for antiresorptive therapy, treatment with testosterone will probably improve both these parameters and might be considered in clinical decision making with such patients.

Testosterone and anaemia

In community-dwelling men, the concentration of circulating testosterone correlates with haemoglobin concentrations.[126,127] Moreover, in multiple studies in both older and young men, testosterone treatment was found to increase haemoglobin concentration and haematocrit in a dose-dependent manner.[128–131] Recent findings by Bhasin and colleagues[132,133] suggested that testosterone induces erythropoiesis by decreasing expression of hepcidin, an important regulator of red blood cell production, resulting in increased iron availability for red

cell synthesis and through increased erythropoietin expression in the kidney. Despite these important mechanistic insights, clinical studies to date have focused on increased haematocrit as a potential adverse side-effect of testosterone treatment.[134] Few groups have explored the potential therapeutic benefits of supplemental androgens for older men with hypogonadism and chronic anaemia of unclear aetiology.

T-Trials Anaemia Trial

The Anaemia Trial[16] was designed to specifically address whether treating older men with both low testosterone concentration and unexplained anaemia (haemoglobin concentration <12·7 g/dL) would increase haemoglobin concentrations. In so doing, this T-Trials substudy in part addressed the issue raised by the Institute of Medicine with respect to the need to demonstrate a benefit for testosterone therapy in several organ systems before conducting a larger randomised controlled trial powered to explore long-term risks.[10] By contrast with results of previous studies of testosterone supplementation in men with hypogonadism, this study carefully adjudicated the aetiology of the anaemia in each participant, utilising a panel of three haematologists masked to patient treatment allocation. Men were included in the Anaemia Trial if they had baseline haemoglobin concentration of 10·0–12·7 g/dL; further classification of the anaemia was on the basis of clinical history and quantification of creatinine, mean corpuscular volume, neutrophil and platelet counts, ferritin, folate, vitamin B12, transferrin saturation, haptoglobin, and immunoglobulins. The primary endpoint of the study was prespecified as an increase in haemoglobin concentration of 1·0 g/dL, chosen on the basis of evidence from other trials of anaemia suggesting a positive effect of this change on quality of life.[16] 64 of the 126 participants in the Anaemia Trial had anaemia of known cause.[16] The effect of testosterone on haemoglobin in men without anaemia at baseline (n=657) was also examined. Although men with marked anaemia (haemoglobin concentration <10 g/dL) were excluded, the participants with mild anaemia were only informed of this finding retroactively.[135]

As anticipated from previous trials, overall haemoglobin concentrations increased in all men treated with testosterone compared with placebo, irrespective of baseline haemoglobin concentration. About 50% of participants (with either explained or unexplained anaemia at baseline) treated with testosterone had a 1·0 g/dL increase in haemoglobin concentration, whereas 15% of participants receiving placebo had such an effect (adjusted odds ratio [OR] 31·5, 95% CI 3·7–277·8; p=0·002). For participants without anaemia at baseline, the mean increases in haemoglobin concentration were more modest (average increase of 0·5 g/dL), but nearly 40% of men treated with testosterone reached the response threshold of 1·0 g/dL, significantly more than in the placebo group (4%). About 60% of men (with either unexplained or known causes of anaemia) were no longer anaemic after 12 months of testosterone therapy compared with 15–20% in the placebo group. Thus, in the case of anaemia, treatment of hypogonadism with testosterone was sufficient to reverse the underlying anaemia, even in many cases where the anaemia was ascribed to additional underlying causes. Key strengths of the study include the exclusive focus on men with anaemia, an assessment of the underlying cause of anaemia, and consistent findings across subgroups (table 3). Key limitations include the reliance on single laboratory values to diagnose and assess anaemia. Moreover, the trial was not designed to determine the effects of changes in haemoglobin concentration on overall health status. Strengths, limitations, and clinical implications of this study are summarised in table 3.

About 10% of older men have anaemia,[136–138] and many studies report a correlation between anaemia, functional impairment, morbidity, and mortality. Interestingly, in the overall T-Trials, prevalence of anaemia was about 16% and probably enriched because of underlying low baseline testosterone concentrations. Indeed, data from previous cross-sectional studies showed that reduced testosterone was associated with reduced haemoglobin concentrations.[126,127] Yearly costs of anaemia treatment in the USA have been estimated at upwards of US$20 000 per year.[136] An adjunctive, potentially cost-saving benefit of testosterone therapy might therefore be a clinically significant increase in haemoglobin concentration in men with concomitant anaemia, provided their circulating testosterone concentrations are at least as low as in the T-Trial participants. This might be particularly relevant for men in whom the underlying cause of anaemia is not treatable or the anaemia remains refractory to other interventions. Thus, anaemia should be considered when selecting older men who might benefit the most from testosterone treatment. In men without anaemia, an increase in haematocrit above the reference range is one of the most common adverse effects associated with testosterone treatment,[134] and older men receiving injectable testosterone preparations are particularly susceptible.[139] In view of the potential link between erythrocytosis and thrombo-embolic events, men receiving testosterone should undergo regular haematocrit monitoring.[61,140]

Conclusions

Collectively, the T-Trials represent an important step forward and provide the most definitive and systematic evidence to date with respect to the multiorgan effects of testosterone treatment in carefully selected older men without overtly pathological hypogonadism. Testosterone treatment increased bone density and bone strength and improved haemoglobin concentrations, resolving anaemia irrespective of the aetiology in a substantial proportion of men. These results could be expected to translate into

improved health outcomes. Testosterone treatment also provided modest benefits in sexual function and, to a lesser extent, mood and walking distance.[12]

In contrast, testosterone treatment did not improve measures of cognition in men with or without age-associated memory impairment, making it unlikely that testosterone treatment will have clinically meaningful benefits on cognitive function. Although testosterone was associated with increased non-calcified coronary artery plaque in the subset of men in the Cardiovascular Trial, the relevance of this finding is unclear, in part because the baseline plaque burden was not balanced between the testosterone and placebo groups. The effects of testosterone on cardiovascular risk factors, such as blood pressure, coagulation factors, and inflammatory markers, could have been recorded in T-Trials but as yet have not been reported.

The prevalence of comorbidities, including obesity and diabetes, was relatively high in the T-Trials.[12] Existing comorbidities, including obesity, might contribute to both androgen deficiency-like symptoms and reduced testosterone concentrations.[141,142] A holistic approach to the care of older men in which facilitating healthy lifestyle measures and optimising management of comorbidities are central elements is therefore needed.[143]

Taken together, the results from the T-Trials are a major advance in understanding the endocrinology of male ageing and aid in the selection of older men who are most likely to benefit from testosterone therapy. However, the findings should not be extrapolated to men without clinical evidence of androgen deficiency or with less marked reductions in testosterone concentrations, and they should not in any way support the treatment of older men with supraphysiological doses of exogenous testosterone. In line with stipulations from the Institute of Medicine, the T-Trials were not designed to assess long-term risks, and the recruitment rate was low because of rigorous selection criteria. Moreover, treatment of medical comorbidities was not regulated, potentially masking some effects of testosterone treatment. Priority areas for future studies include clarifying potential cardiovascular benefits versus risks of testosterone treatment in men without pathological hypogonadism and determining whether the multiorgan benefits found in the T-Trials will affect important health outcomes such as functional status and fracture incidence.

Contributors

BBY searched the literature and contributed to the writing of the Series paper. STP and MG contributed to the literature search and the writing of the Series paper.

Declaration of interests

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