Risks and benefits of testosterone therapy in older men

Matthew Spitzer, Grace Huang, Shehzad Basaria, Thomas G. Travison and Shalender Bhasin

Abstract | In young men (defined as age <50 years) with classic hypogonadism caused by known diseases of the hypothalamus, pituitary or testes, testosterone replacement therapy induces a number of beneficial effects, for example, the development of secondary sex characteristics, improvement and maintenance of sexual function, and increases in skeletal muscle mass and BMD. Moreover, testosterone treatment in this patient population is associated with a low frequency of adverse events. Circulating testosterone levels decline progressively with age, starting in the second and third decade of life, owing to defects at all levels of the hypothalamic–pituitary–testicular axis. In cohort studies, testosterone levels are associated weakly but consistently with muscle mass, strength, physical function, anaemia, BMD and bone quality, visceral adiposity, and with the risk of diabetes mellitus, coronary artery disease, falls, fractures and mortality. However, the clinical benefits and long-term risks of testosterone therapy—especially prostate-related and cardiovascular-related adverse events—have not been adequately assessed in large, randomized clinical trials involving older men (defined as age >65 years) with androgen deficiency. Therefore, a general policy of testosterone replacement in all older men with age-related decline in testosterone levels is not justified.

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Introduction

Prescription sales of testosterone in the USA, which barely approached 18 million dollars in 1988, crested the 1.6 billion dollar mark in 2011, in continuation of an ascent that started with the introduction of the nongenital, transdermal testosterone patch in 1993 and which accelerated further after the introduction of the transdermal gel in 2000. The prescription sales of testosterone grew by 25–30% annually between 1993 and 2002. However, despite marked increases in testosterone prescriptions, the prevalence of unequivocal hypogonadism remains unchanged. This finding suggests that a sizeable proportion of testosterone therapy is being prescribed for age-related decline in testosterone levels, an indication for which testosterone therapy is not approved; ironically, a substantial fraction of men with hypogonadism remains undiagnosed or suboptimally treated.

An expert panel of the Endocrine Society defined hypogonadism as “a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic–pituitary–testicular axis.” The debate over the risks and benefits of testosterone therapy is often confounded by the failure to distinguish classic hypogonadism in men, which results from known diseases of the testes, pituitary or the hypothalamus, from the age-related decline in testosterone levels. The risk to benefit ratio of testosterone therapy varies substantially according to the patient population being treated and the condition for which testosterone is being administered.

Even though long-term randomized trials of testosterone use are few, agreement exists—on the basis of about 70 years of clinical experience and open-label trials—that testosterone therapy in men with classic hypogonadism induces a number of beneficial effects: the development of secondary sex characteristics; improved aspects of sexual function, mood and well-being; increased skeletal muscle mass and strength; increased BMD and bone quality; and reduced adipose tissue mass. Furthermore, testosterone replacement in young men (defined as age <50 years unless stated otherwise) with classic hypogonadism is associated with a low frequency of adverse events, including, for example, acne and increase in haematocrit. By contrast, in older men (defined as age >65 years unless stated otherwise) with age-related decline in testosterone the clinical benefits and the long-term risks of testosterone therapy remain unknown. Furthermore, some concern exists about potential detrimental effects of testosterone therapy in frail elderly men, who have a high number of comorbid conditions. Testosterone therapy can be indicated in some elderly men who have known pathologic conditions of the testes, pituitary and the hypothalamus (for example, opiate-induced androgen deficiency or secondary hypogonadism after resection of a pituitary tumour).

Potential risks of any therapeutic agent should be considered in relation to its potential benefits and any health consequences of withholding treatment. This Review discusses the potential benefits and risks of testosterone...
therapy in older men with age-related decline in testosterone levels and presents the authors’ perspective on management of these patients in the context of incomplete evidence on safety and efficacy.

**Age-related decline in testosterone**

Testosterone levels, after peaking in the second and third decade of life, decline gradually with advancing age without a clear inflection point or ‘andropause’. As sex hormone-binding globulin (SHBG) levels increase with age, the rate of decline in free testosterone levels is greater than that in total testosterone levels. The age-related decline in testosterone levels is caused by defects at all levels of the hypothalamic-pituitary-testicular axis, and the trajectory of decline is affected by BMI, weight gain, comorbid conditions, medications and genetic factors. 

The term ‘late-onset hypogonadism’ has been proposed to reflect the view that in some middle-aged (<50–65 years) and older men (>65 years), the age-related decline in testosterone concentration is associated with a cluster of symptoms and signs that resemble those observed in men with classic androgen deficiency. In an analysis of the European Male Ageing Study (EMAS), sexual symptoms—poor morning erection, low sexual desire and erectile dysfunction—were associated with testosterone levels <11 nmol/l or free testosterone levels <220 pmol/l. Men defined as having late-onset hypogonadism by these criteria tended to be older and have a higher BMI, lower muscle mass, BMD and haemoglobin levels and slower gait speed than those deemed eugonadal, which suggests that men with late-onset hypogonadism have end-organ deficits similar to those observed in patients with androgen deficiency. Although 10–15% of men aged ≥65 years have low total testosterone levels, the prevalence of late-onset hypogonadism defined by symptoms and a total testosterone level <8 nmol/l in the EMAS was 3.2% for men aged 60–69 years and 5.1% for those aged 70–79 years. 

In further analyses of the EMAS data, Tajer et al. found that men with late-onset hypogonadism could be further classified into those with primary (serum total testosterone <10.5 nmol/l and luteinizing hormone [LH] >9.4 U/l), secondary (serum total testosterone <10.5 nmol/l and LH ≤9.4 U/l) or compensated hypogonadism (serum total testosterone >10.5 nmol/l and LH >9.4 U/l). Secondary hypogonadism in older men was associated predominantly with obesity, and primary hypogonadism with age. The investigators suggest that combined consideration of symptoms, total testosterone and LH levels might help improve the diagnosis and management of late-onset hypogonadism.

In cohort and experimental studies, the age-related decline in testosterone levels has been associated with reductions in muscle mass, strength, physical function, libido, BMD, bone geometry and quality, haematocrit levels, and frailty. Low testosterone levels are also associated with increased risk of frailty, mobility limitation, falls, fractures, diabetes mellitus, the metabolic syndrome, coronary artery disease, cardiovascular events, anaemia and overall mortality (Table 1). Testosterone levels are not significantly associated with lower urinary tract symptoms, ageing-related psychological symptoms and erectile function. The association of testosterone with measures of depression and cognition has been inconsistent.

**Benefits of testosterone therapy**

The effects of testosterone therapy on health outcomes in men with clinical conditions, such as sexual dysfunction and frailty, remain uncertain.

**Sexual function**

Testosterone therapy in young men with hypogonadism improves many aspects of sexual function, including overall sexual activity, sexual desire, intensity of sexual feelings, sexual fantasies, attentiveness to erotic cues, and the number and duration of night-time and spontaneous erections. However, testosterone therapy does not improve erectile response to visual erotic stimuli.

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**Table 1 | Epidemiologic studies on the association of high testosterone levels with adverse events**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>Serum total testosterone comparison</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>0.94 (0.82–1.07)</td>
<td>Top quintile versus bottom quintile</td>
<td>Roddam et al.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.58 (0.39–0.87)</td>
<td>Top dichotomy versus bottom dichotomy</td>
<td>Ding et al.</td>
</tr>
<tr>
<td>Major cardiovascular-related events</td>
<td>0.71 (0.54–0.93)</td>
<td>Top quartile versus bottom quartile</td>
<td>Ohlsson et al.</td>
</tr>
<tr>
<td>Cardiovascular-related mortality</td>
<td>0.80 (0.63–1.03)</td>
<td>Top tertile versus bottom tertile</td>
<td>Araujo et al.</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.74 (0.62–0.88)</td>
<td>Top tertile versus bottom tertile</td>
<td>Araujo et al.</td>
</tr>
</tbody>
</table>

**Abbreviation:** RR, relative risk.
Even though sexual symptoms are the most consistent factor associated with low testosterone levels in older men, intervention trials have reported inconsistent effects of testosterone on sexual function in these individuals. Many trials included healthy men aged >65 years with low normal or normal testosterone levels, and few studies have investigated the effects of testosterone therapy in this population with symptomatic sexual dysfunction and unequivocally low testosterone levels. Furthermore, the participants were not enrolled on the basis of rigorously defined categories of sexual dysfunction (hypoactive sexual desire disorder, erectile dysfunction, ejaculatory dysfunction or orgasmic disorder); therefore, it is difficult to determine which categories of sexual dysfunction are improved by testosterone therapy. Many trials preceded the development of psychometrically robust modern instruments for the assessment of libido, erectile and ejaculatory function.

A meta-analysis of randomized trials in men (weighted mean age 57.5 years) with testosterone levels <10 nmol/l found overall improvements in sexual thoughts, erectile function, intercourse, morning erections and sexual satisfaction with testosterone therapy; the treatment effects were small to moderate (Figure 1). Randomized trials using oral testosterone formulations in elderly men with low or low normal testosterone levels have reported inconsistent effects on sexual function.

Androgen deficiency and erectile dysfunction are two distinct syndromes that are independently distributed in men. A substantial fraction of older men with erectile dysfunction would be expected to have low testosterone levels simply by virtue of their age. Selective phosphodiesterase type 5 inhibitors (PDE5Is) have emerged as an effective first-line therapy for erectile dysfunction, although about one-third of men with erectile dysfunction will not respond to PDE5Is; some men with erectile dysfunction who do not respond to PDE5Is have low testosterone levels. These observations have led some experts to recommend measurement of testosterone levels in men with erectile dysfunction and have raised speculation that testosterone therapy might improve erectile response to PDE5Is.

In a randomized, placebo-controlled trial, our group determined whether addition of testosterone to the PDE5I sildenafil improves erectile response in men with erectile dysfunction and low testosterone levels. After optimization of the sildenafil dose, study participants were randomly allocated to 14 weeks of daily transdermal gel that contained either 10 g testosterone or placebo. Sildenafil plus testosterone was not superior to sildenafil plus placebo in improving erectile function in men with erectile dysfunction and low testosterone levels. Given that serum testosterone levels increased with administration of sildenafil alone, it is possible that sildenafil administration raised testosterone levels above some threshold above which no further benefit can be expected. In another placebo-controlled trial of men with erectile dysfunction who were refractory to treatment with the PDE5I tadalafil, the primary analysis of all randomized individuals did not show a greater improvement in erectile function in the testosterone arm than in the placebo arm. However, in post hoc analysis, erectile function improved with the addition of testosterone in a subset of men with baseline testosterone levels ≤10 nmol/l. Thus, randomized trials have failed to support the hypothesis that addition of testosterone to PDE5Is improves erectile function in men with erectile dysfunction.

Physical function, mobility and frailty
In epidemiological studies, a low bioavailable testosterone concentration is associated with decreased lean body mass and muscle strength. Men with low testosterone levels are also more prone to have worse physical performance than those with normal testosterone levels. Low free testosterone levels have been associated with increased risk of mobility limitation, frailty and falls.

Pharmacologically induced androgen deficiency is associated with loss of muscle mass and strength; conversely, testosterone replacement of men with hypogonadism increases muscle mass, maximal voluntary strength and muscle protein synthesis. Randomized trials of testosterone administration in older men have reported consistent increases in whole-body and
appendicular lean mass and in maximal voluntary strength, as well as decreases in body adipose tissue mass (Figure 1).79–87 The effects of testosterone on muscle mass and strength and on adipose tissue mass are dose-related.88–90

Testosterone induces hypertrophy of type I and type II skeletal muscle fibres and increases the number of satellite cells, thereby enhancing skeletal muscle mass.91–94 Moreover, testosterone promotes the differentiation of muscle progenitor cells into the myogenic lineage and inhibits their differentiation into the adipogenic lineage by activating the Wnt–β catenin pathway and increasing expression of a number of Wnt target genes, including follistatin, which blocks signalling through the TGF-β pathway.95–98 Testosterone has also been reported to increase muscle protein synthesis and reduce protein degradation.99–101

Testosterone administration has been associated with improvements in self-reported physical function and in stair-climbing power,82,90 however, improvements in other performance-based measures of physical function have been modest and less consistent. Several reasons are possible for the failure of first-generation trials to demonstrate meaningful improvements in some performance-based measures of physical function. The measures of physical function used in some trials had a low ‘ceiling’ (that is, individuals exhibited near maximal performance on the test, so that any improvement as a result of anabolic intervention would not be expected to further increase performance on the test). Furthermore, the men recruited in these studies were healthy men who had low normal testosterone levels and no physical dysfunction.

Three trials conducted in men aged >50 years with functional limitations are noteworthy.100–104 In a trial of pre-frail men (those who met one or two criteria of frailty according to Fried et al.105) or frail men (those who met three or more criteria), 50 mg testosterone gel daily for 6 months induced greater improvements in lean mass, knee extension peak torque and sexual symptoms than did placebo gel.104 Performance-based measures of physical function did not differ significantly between groups, but they improved in a subgroup of frail elderly men.104 Basaria et al. randomly allocated men with mobility limitation to either placebo or 10 g testosterone gel daily for 6 months in the Testosterone in Older Men (TOM) trial.102 The testosterone dose was adjusted to achieve testosterone levels between 17.4 nmol/l and 34.7 nmol/l. Leg-press and chest-press strength and chest-press power, as well as loaded stair-climbing speed and power improved more in men assigned to testosterone than in those receiving placebo. A greater proportion of men in the testosterone arm improved more than the minimal clinically important difference for leg-press and chest-press strength and stair-climbing speed than that in the placebo arm (Figure 2). Because of a higher frequency of cardiovascular-related events in the testosterone arm compared with the placebo arm, the trial’s data and safety monitoring board stopped further administration of study medication.102

Thus, although evidence for gains in muscle mass and strength exists with testosterone therapy, the benefits on clinically important health outcomes (physical function, falls, fractures and disability) in men with clinical conditions have not been demonstrated. Strategies to translate gains in muscle mass and strength induced by testosterone into functional improvements are needed. Adjunctive exercise training might be required to induce the neuromuscular and behavioural adaptations that are necessary to translate the gains in muscle mass and strength into functional improvements. The findings of the TOM trial have heightened concern that frail elderly men with a high burden of chronic comorbidities are at an increased risk of adverse events;104 hence, strategies to achieve increased selectivity and a more favourable risk to benefit ratio in this vulnerable population are needed.

**Mood**

The association between testosterone levels and depression in older men has been inconsistent.105 Testosterone levels are lower in men with dysthyemic disorder (which is characterized by chronic depression, with less severe but longer-lasting symptoms than clinical depression) than in those without depressive symptoms. Testosterone levels have been associated more consistently with subsyndromic depression and dysthymia than with clinical depression.46–49

Testosterone trials in men with clinical depression have yielded inconsistent results.107–111 Randomized trials in men whose depression was suboptimally responsive or resistant to antidepressant therapy have failed to show marked improvements in depression indices with testosterone therapy.112 A systematic review found no evidence of additional improvements in depressive symptoms with testosterone augmentation in patients with depression treated with antidepressants.113 The studies included were limited by small sample sizes, short treatment duration, heterogeneity of patient population and testosterone doses and regimens, and large placebo effects.

**Cognition**

Cohort studies have reported weak associations of testosterone levels with measures of visuospatial cognition and verbal memory. Clinical trials on the effects of testosterone on cognitive function have revealed inconclusive results. Several studies investigating the effects of testosterone replacement in older men have shown no clinically significant changes in cognition.114–116 One small study conducted in men with Alzheimer disease reported greater improvements in spatial memory, constructional abilities and verbal memory in men treated with testosterone compared with those treated with placebo.117 However, another small placebo-controlled study performed in men with Alzheimer disease found no effect on cognition.118 One study, in which eugonadal elderly men were randomly allocated to either testosterone or placebo for 90 days, reported declines in verbal memory and decreased activity in medial-temporal and prefrontal regions on PET scan in testosterone-treated men.119 By contrast, Azad and colleagues reported
increased cerebral perfusion on PET scan in men with hypogonadism treated with testosterone, which hints at an association between testosterone and cognitive function. Overall, most studies were limited by small numbers, short duration and inclusion of surrogate measures; few trials have included men with cognitive impairments. Thus, the current evidence is insufficient to conclude that testosterone therapy is beneficial or harmful to cognitive function.

**BMD and fracture risk**

Bioavailable testosterone levels have been associated with areal as well as volumetric BMD, bone geometry and bone quality. Men aged >65 years with low testosterone levels are at an increased risk of falls, osteoporosis and fractures. A meta-analysis reported a significant increase in lumbar BMD in trials that used intramuscular testosterone injections but not in trials that used transdermal testosterone (Figure 1). The changes in femoral BMD did not differ between placebo and testosterone arms. A controlled trial evaluated the effect of 36 months of testosterone undecanoate on bone health in men with late-onset hypogonadism; this study found substantial increases in both lumbar and femoral neck BMD. A randomized, placebo-controlled trial assessing the effects of testosterone enanthate injections on bone health demonstrated improvements in lumbar spine but not femoral neck BMD. No clinical trials have evaluated the effects of testosterone on falls or fractures.

**Testosterone in diabetes mellitus**

In cohort studies, low total testosterone levels are associated with increased risk of type 2 diabetes mellitus in men. Nearly one-third of men with diabetes mellitus have low testosterone levels. In longitudinal analysis, SHBG levels, but not total or free testosterone levels, are independently associated with incident diabetes mellitus and the metabolic syndrome after adjusting for age, BMI and comorbid conditions. Acute withdrawal of testosterone therapy in healthy men with idiopathic hypogonadotropic hypogonadism and in men with prostate cancer who receive androgen deprivation therapy is associated with the development of insulin resistance.

Several randomized, placebo-controlled trials of testosterone have been conducted in men with diabetes mellitus, although only the results of one such trial have been published. The TIMES2 study was a randomized trial in which men with type 2 diabetes mellitus and/or the metabolic syndrome were randomly allocated to receive either 2% testosterone gel or placebo gel for 6 months. The dose of testosterone was adjusted to achieve target testosterone levels between 17.4 nmol/l and 34.7 nmol/l. The mean (SE) change was determined from baseline to either the end of the intervention period or to the last measurement performed in study participants who dropped out before study completion. The MCID for each outcome was determined using an anchor-based method within the trial. The proportion of men (percentage) whose change from baseline either equaled or exceeded the MCID is shown below the figure along with the P value for the comparison of placebo and testosterone groups. Abbreviation: MCID, minimal clinically important difference.

**Risks of testosterone therapy**

Open-label studies in young men with hypogonadism have found a low frequency of adverse events with testosterone therapy. Common drug-related adverse events include increase in haematocrit, acne, oiliness of skin and breast tenderness. The frequency of cardiovascular
As haematocrit levels increase from low to normal levels, plasma viscosity and tissue blood flow increase along with an increase in tissue oxygen delivery. However, as haematocrit levels rise further, plasma viscosity increases disproportionately, and at some level of haematocrit, tissue blood flow and oxygen delivery begin to decline. The haematocrit level at which tissue oxygen delivery is compromised is not known and might be lower in men with coronary artery disease than in healthy men.

The Endocrine Society’s expert panel recommends that testosterone administration should be withheld in men whose haematocrit rises above 54% during testosterone therapy. When the haematocrit has fallen into the normal range, testosterone therapy can be re instituted at a lower dose. The frequency of neuro-occlusive events (that is, stroke) in association with increased haematocrit in testosterone trials has been extremely low.

The mechanisms by which testosterone increases red cell mass are poorly understood. Testosterone increases erythropoietin levels, but the erythropoietin levels return towards baseline with continued testosterone therapy. However, erythropoietin levels are elevated in relation to the increased haemoglobin levels in testosterone-treated men. Testosterone might potentially increase the sensitivity of erythroid progenitor cells to erythropoietin. Our group has shown that testosterone suppresses the iron-regulatory protein hepcidin by regulating its transcription, and increases iron bioavailability for erythropoiesis.

**Prostate-related adverse events**

A great deal of controversy has shrouded the relationship between testosterone administration and the risk of prostate cancer. No evidence exists to suggest that testosterone causes prostate cancer or worsens lower urinary tract symptoms. An analysis of prospective epidemiologic studies found no significant association between testosterone levels and the risk of prostate cancer. However, androgen receptor signalling plays a central part in the biology of prostate cancer, and testosterone administration promotes the growth of metastatic prostate cancer.

Testosterone therapy increases the risk of detection of subclinical prostate disease because of increased surveillance and testosterone-induced increase in prostate-specific antigen (PSA) levels, which might lead to increased risk of prostate biopsy. In a meta-analysis of randomized studies, men aged ≥45 years receiving testosterone had 1.8 times the odds of experiencing a prostate-related adverse event compared with men receiving placebo. Men assigned to testosterone had numerically greater number of prostate biopsies, PSA level >4 ng/ml and prostate cancer diagnoses than those assigned to placebo.

Testosterone administration increases PSA levels in men with hypogonadism. The average increase
in PSA levels in healthy men with hypogonadism is 0.30 ng/ml in young and 0.43 ng/ml in older men. Incremental >1.4 ng/ml above baseline are unusual in any 3–6-month period in older men without prostate cancer and warrant urologic evaluation if confirmed. The Endocrine Society recommends against testosterone supplementation in men with prostate cancer and advocates individualized consideration of prostate cancer risk prior to treatment initiation.4

**Adverse cardiovascular-related events**

Long-term effects of testosterone therapy on cardiovascular risk in older men remain unknown. Although many cross-sectional cohort studies have reported an association of low testosterone levels with increased risk of diabetes mellitus, the metabolic syndrome, proatherogenic dyslipidaemia and cardiovascular disease, the data from longitudinal studies have not demonstrated an association between testosterone levels and incident cardiovascular disease. In the MrOS Sweden cohort, the men in the highest quartile of testosterone levels (≥19 nmol/l) had lower cardiovascular-related event rates than those in the lowest quartile (≤12 nmol/l; Table 1).4 Some, but not all, studies have also reported a negative association between testosterone levels and overall mortality, especially cardiovascular-related mortality. A meta-analysis of observational studies noted a nonsignificant increased risk of cardiovascular-related mortality among men with lower testosterone levels (Table 1).8 Testosterone might be a marker of health, and low testosterone levels could be a consequence of obesity, diabetes mellitus and other comorbid conditions that increase the risk of death. Epidemiological studies have found a negative relationship between testosterone levels and cardiovascular risk markers, such as BMI, waist circumference, visceral adiposity and carotid intima–media thickness.

Testosterone replacement is associated with a modest reduction in levels of HDL cholesterol and total cholesterol but does not notably affect LDL cholesterol or triglyceride levels. Orally administered androgens, especially nonaromatizable androgens, are associated with substantially greater reductions in plasma HDL cholesterol levels than aromatizable parenterally administered testosterone.159 Testosterone infusion improves coronary blood flow and has been investigated for the treatment of angina pectoris in men with coronary heart disease. The vasodilatory effects of testosterone are mediated through L-type calcium channels. The effects of testosterone therapy on vascular reactivity have been inconsistent. Clinical trials data on the effects of testosterone on cardiovascular-related events are limited. The number of cardiovascular-related events reported in randomized testosterone trials has been strikingly low—even lower than that expected for the age and comorbid conditions of the participants. A higher frequency of cardiovascular-related events in men assigned to testosterone than in those assigned to placebo in the TOM trial has heightened concern about the cardiovascular safety of testosterone in frail elderly men. Meta-analyses of randomized trials have not demonstrated a statistically increased risk of cardiovascular-related events in men randomly allocated to receive testosterone compared with those assigned to placebo (Figure 3). However, these meta-analyses are limited by the small size of most trials, heterogeneity of study populations, poor quality of adverse-event reporting and short treatment duration in many trials. Many participants were healthy older men aged ≥65 years.

Participants in the TOM trial had a high prevalence of chronic conditions, such as heart disease, diabetes mellitus, obesity, hypertension and hyperlipidaemia. Men aged ≥75 years and men with higher on-treatment testosterone levels seem to be at the greatest risk of cardiovascular-related events. The dose of testosterone used in the TOM trial was higher than that used in some previous trials, but not dissimilar from or lower than that used in some other trials. In the TOM trial, 27%, 58% and 15% of participants treated with testosterone received a daily topical dose of 5 g, 10 g and 15 g testosterone 1% gel, respectively. For comparison, doses of daily topical testosterone 1% gel have ranged from 2.5 g to 10 g daily in other randomized, placebo-controlled clinical trials. The average on-treatment testosterone concentrations in the TOM trial (~20 nmol/l) were well within the target range and not dissimilar from levels reached in other trials.

None of the testosterone trials to date was sufficiently powered to adequately assess safety outcomes. The rigour of adverse-event reporting varied greatly among studies. The frequency of study participants reporting at least one cardiovascular-related adverse event while receiving testosterone displays considerable heterogeneity across trials. The HORMA (Hormonal Regulators of Muscle and Metabolism in Aging) trial reported a statistically significant increase in blood pressure in men treated with testosterone. Testosterone administration causes salt and water retention, which can induce oedema and worsen pre-existing heart failure. A retrospective analysis reported reduced overall mortality in men receiving testosterone. Thus, large prospective randomized trials are needed to determine the effects of testosterone therapy on cardiovascular health.

**Obstructive sleep apnoea**

Testosterone therapy has been reported to exacerbate sleep apnoea, in a randomized trial in men with obesity and obstructive sleep apnoea, testosterone administration worsened sleep–disordered breathing. Nevertheless, testosterone therapy can improve body composition (loss of adipose tissue mass) and insulin sensitivity in men with sleep apnoea, which could ultimately have beneficial effects on sleep apnoea. Testosterone administration depresses hypercapnoic ventilator drive and induces apnoea in primates. Short-term administration of high doses of testosterone shortens sleep duration and worsens sleep apnoea in men aged >60 years; however, the frequency of sleep apnoea in randomized testosterone trials
in older men has been very low. Obstructive sleep apnoea is often associated with low testosterone levels.

**Perspective on management**

The Endocrine Society’s guidance—that clinicians consider testosterone therapy on an individualized basis in older men with consistently low testosterone levels and clinically significant symptoms of androgen deficiency, after explicit discussion of the uncertainty about the risks and benefits of testosterone therapy—seems reasonable, although, admittedly, this recommendation is not supported by strong evidence. The panel shied away from taking a strong position on the level of testosterone at which therapy should be offered, reflecting the disagreement among the members of the panel, but expressed that given the uncertainty about the risks and benefits, a lower testosterone cut-off level might be reasonable in elderly men with age-related decline of testosterone levels who do not have a known disease of the hypothalamus, pituitary or the testes.

Age-related decline in testosterone levels can be due to physiologic or functional effects on the hypothalamic–pituitary–gonadal axis. However, how to distinguish physiologic from pathologic decline or how to determine when or whom to treat remains undetermined. The uncertainty about risks and benefits of testosterone therapy further clouds our thinking about this issue. If physicians choose to use testosterone therapy, several steps should be instituted to mitigate risk, including using a lowered target range for on-treatment testosterone levels (13.9–24.3 nmol/l); adherence to a standardized monitoring plan as recommended by the Endocrine Society; exclusion of patients with uncompensated heart failure or those who have had a myocardial infarction, an acute coronary event, a revascularization procedure or a stroke in the preceding 6 months. Moreover, as on-treatment testosterone levels vary substantially among individuals and on different days in the same individual, especially in men being treated with transdermal testosterone, testosterone levels should be measured on multiple occasions to ensure that they are within the target range. Long-term randomized trials are needed to definitively determine the risks and benefits of testosterone therapy in men aged ≥65 years with age-related decline and associated clinical conditions.

**Conclusions**

The contentious debate over the risks and benefits of testosterone therapy has been confounded by the failure to distinguish the effects of testosterone in the context of the various conditions for which testosterone therapy can be prescribed. Testosterone therapy in young men with hypogonadism, with known diseases of the testes, pituitary or the hypothalamus, is generally safe and beneficial. By contrast, the benefits of testosterone therapy on health outcomes—sexual function, physical function, falls, fractures, depression, dementia or disability—have not been demonstrated in older men with clinical conditions associated with age-related decline in testosterone levels. Moreover, the long-term risks of testosterone therapy in this population are unknown. Finally, a small number of randomized trials in the frail elderly or in critically ill persons have suggested that administration of anabolic therapy in these settings can be harmful. Therefore, testosterone therapy is indicated for men with symptomatic androgen deficiency due to known diseases of the testes, pituitary and the hypothalamus. However, the available evidence does not support a general policy of offering testosterone therapy to all older men with low testosterone levels.

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**Review criteria**

A search for original articles published until January 2013 and focusing on testosterone was performed in MEDLINE and PubMed. The search terms used were “testosterone deficiency”, “androgen deficiency”, “age-related decline in testosterone”, “late-onset hypogonadism”, and “testosterone in combination with prostate cancer”, “diabetes”, “cardiovascular disease”, “metabolic syndrome”, “cardiovascular disease”, “physical function”, “muscle performance”, “effects in older men”, “muscle performance”, “randomized trials” and “older men”, “hemoglobin”, “adverse effects” and “men”, “erythropoiesis” “sexual function”, “erectile function”, “bone” and “muscle”. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further papers.


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Basaria, S., Muller, D. C., Carducci, M. A., Lakshman, K. M., Bhasin, S. & Araujo, A. B.
Haren, M. T., Wittert, G. A., Chapman, I. M., supplementation on functional mobility, cognition, mobility limitation: results from a randomized administration on liver fat in older men with metabolic syndrome (the TIMES2 study).
men with idiopathic hypogonadotropic hyponagonadism and metabolic syndrome: results from a 36 months controlled study.


Author contributions
M. Spitzer, G. Huang, T. G. Travison and S. Bhasin researched the data for the article. All authors provided a substantial contribution to discussions of the content, contributed to writing the article, and reviewed and/or edited the manuscript before submission.