

Endocrine Society of Australia position statement on male hypogonadism (part 2): treatment and therapeutic considerations

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The Endocrine Society of Australia commissioned this position statement to update its 2000 guidelines for testosterone prescribing¹ and to inform the recommended management of men with androgen deficiency in light of recent regulatory changes to the Pharmaceutical Benefits Scheme.² Part 1 of this position statement dealt with the assessment of male hypogonadism, including the indications for testosterone therapy.³ This article, Part 2, focuses on treatment and therapeutic considerations for male hypogonadism, particularly considering the ongoing debate about the risk of cardiovascular events related to testosterone treatment.⁴ The methods used to develop the position statement are detailed in Part 1.³

Recommendations

Cardiovascular events

The current evidence regarding testosterone treatment and cardiovascular outcomes is contradictory and inconclusive.⁴ There have been no adequately powered randomised controlled trials (RCTs) of testosterone treatment with cardiovascular events as a pre-specified outcome. One RCT has shown an increase in cardiovascular events with testosterone treatment in older men with mobility limitations, many of whom had diabetes or pre-existing cardiovascular disease.⁵ However, event numbers were small and may have been due to chance. Another RCT in a similar population of frail or intermediate-frail older men has not confirmed this finding.⁶ In the United States, the Testosterone Trials reported no difference in cardiovascular events between treatment and placebo arms of the study over 1 year.⁷ A recently published RCT showed no effect of testosterone treatment over 3 years on two measures of pre-clinical atherosclerosis (carotid intima media thickness and coronary calcification).⁸ One meta-analysis showed an increased risk of broadly defined vascular-related events with testosterone therapy but, due to methodological limitations, these data are not definitive.⁹ Another meta-analysis showed no evidence of any increase in major cardiovascular events relating to testosterone therapy.¹⁰ A recent meta-analysis showed no significant increase in cardiovascular events related to testosterone treatment when all administration routes were grouped.¹¹

Some observational studies in older men have shown increased risk, and some decreased risk, of cardiovascular events, or improved survival with testosterone treatment.⁴ A recent retrospective observational study of US veterans (whose indications for testosterone treatment were not made clear) suggested that men with low baseline testosterone levels who achieved normalisation of circulating testosterone levels after treatment had better outcomes compared with men who did not normalise testosterone

Abstract

Introduction: Part 1 of this position statement dealt with the assessment of male hypogonadism, including the indications for testosterone therapy. This article, Part 2, focuses on treatment and therapeutic considerations for male hypogonadism and identifies key questions for future research.

Main recommendations: Key points and recommendations are:

- Excess cardiovascular events have been reported in some but not all studies of older men without pathological hypogonadism who were given testosterone treatment. Additional studies are needed to clarify whether testosterone therapy influences cardiovascular risk.
- Testosterone is the native hormone that should be replaced in men being treated for pathological hypogonadism. Convenient and cost-effective treatment modalities include depot intramuscular injection and transdermal administration (gel, cream or liquid formulations).
- Monitoring of testosterone therapy is recommended for efficacy and safety, focusing on ameliorating symptoms, restoring virilisation, avoiding polycythaemia and maintaining or improving bone mineral density.
- Treatment aims to relieve an individual's symptoms and signs of androgen deficiency by administering standard doses and maintaining circulating testosterone levels within the reference interval for eugonadal men.
- Evaluation for cardiovascular disease and prostate cancer risks should be undertaken as appropriate for eugonadal men of similar age. Nevertheless, when there is a reasonable possibility of substantive pre-existing prostate disease, digital rectal examination and prostate-specific antigen testing should be performed before commencing testosterone treatment.

Changes in management as result of the position statement:

Treatment aims to relieve symptoms and signs of androgen deficiency, using convenient and effective formulations of testosterone. Therapy should be monitored for efficacy and safety.

levels or did not receive treatment.¹² Comparable Australian studies are lacking. However, no firm conclusion can be drawn from these non-randomised retrospective studies — which did not account for the reasons some men were treated and others not, and often used prescription or insurance databases with limited population coverage and clinical information — due to the potential for multiple sources of bias and confounding. A review of the existing data commissioned by the US Food and Drug Administration (FDA) found no convincing increase of major adverse cardiac events in men treated with testosterone and highlighted the deficiencies of available retrospective studies.¹³ Nevertheless, the

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FDA mandated labelling of US testosterone products to warn about a possible increased risk of venous thromboembolism, heart attack and stroke, and recommended a new prospective study of sufficient power to evaluate safety.¹⁴ Overall, until better evidence is available, it seems prudent to use testosterone treatment with a degree of caution in older men with known cardiovascular disease, especially in men without pathological hypogonadism.

Testosterone formulations and side effects

The effects of testosterone in different tissues vary as a result of the metabolism of testosterone into its active metabolites by the enzymes 5 α -reductase (an amplification pathway that converts testosterone to 5 α -dihydrotestosterone [DHT], an androgen with enhanced potency acting on the androgen receptor) and aromatase

(a diversification pathway that converts testosterone to oestradiol, which acts on the oestrogen receptor).¹⁵ Each of these hormones is increasingly recognised as being critical for male health. DHT drives genital differentiation in the male fetus (acting on the urogenital sinus derivatives that form the prostate and external genitalia), while oestradiol is a major determinant of male bone density and has additional roles in the brain, metabolism and possibly sexual function.^{16,17} In many ways, testosterone is “three hormones in one” — an important physiological consideration when using testosterone rather than other androgens for replacement therapy regimens.

Testosterone preparations available in Australia, with their route of administration, dosing and side effects, are shown in [Box 1](#). The more common adverse effects include polycythaemia, elevation of

1 Testosterone formulations currently available in Australia

Preparation	Advantages	Disadvantages and adverse effects	Testosterone level monitoring
Testosterone gel 1% (Testogel, Besins Healthcare) <ul style="list-style-type: none"> • 50 mg sachets (or pump pack) • Daily 	<ul style="list-style-type: none"> • Can be self-administered • Pump applicator option available 	<ul style="list-style-type: none"> • Chance for inadvertent transfer to close contacts (spouse, children, nurses) • Must cover application site • Variation in blood testosterone levels 	<ul style="list-style-type: none"> • Morning, before application, after use for 7 days
Testosterone undecanoate (Reandron 1000, Bayer) <ul style="list-style-type: none"> • 1g intramuscular injection • 3-monthly 	<ul style="list-style-type: none"> • Convenience • Compliance 	<ul style="list-style-type: none"> • Slow to reach steady-state blood testosterone levels • Cannot be self-administered • Injection site pain • Post-injection cough due to pulmonary oil microembolism • Deep intramuscular injection unsuitable for men with coagulopathies or thrombocytopenia 	<ul style="list-style-type: none"> • Morning, before fourth injection; aim for trough level of 10–15 nmol/L • Allow a further 2–3 injections after dose adjustment before rechecking
Testosterone transdermal solution (Axiron, Eli Lilly) <ul style="list-style-type: none"> • 60 mg (2 × 30 mg applications) • Daily 	<ul style="list-style-type: none"> • Can be self-administered 	<ul style="list-style-type: none"> • Chance for inadvertent transfer to close contacts (spouse, children, nurses) • Pump applicator required • Must be administered in the axilla and cover application site • May not wash, shower or swim within 2 hours of application 	<ul style="list-style-type: none"> • After 2 weeks, trough level taken 2–8 hours after application
Testosterone cream 5% (Androforte, Lawley) <ul style="list-style-type: none"> • 2 mL • Daily 	<ul style="list-style-type: none"> • Can be self-administered 	<ul style="list-style-type: none"> • Chance for inadvertent transfer to close contacts (spouse, children, nurses) • Must cover application site • Variation in blood testosterone levels 	<ul style="list-style-type: none"> • Morning, before application, on the 15th day after starting treatment
Testosterone esters (Sustanon, Aspen; or Primoteston, Bayer) <ul style="list-style-type: none"> • 250 mg intramuscular injection • Fortnightly 	<ul style="list-style-type: none"> • Fewer treatment episodes may improve compliance 	<ul style="list-style-type: none"> • Frequency of injections • Fluctuation in blood testosterone levels • Injection site pain • Fluctuation in mood or libido • Excessive erythrocytosis 	<ul style="list-style-type: none"> • Baseline and at intervals during treatment
Testosterone patch (Androderm, Allergan) <ul style="list-style-type: none"> • 2.5 mg or 5.0 mg • Daily 	<ul style="list-style-type: none"> • Can be self-administered 	<ul style="list-style-type: none"> • Skin irritation • Limited scope for dose variation 	<ul style="list-style-type: none"> • Morning, after evening application
Testosterone undecanoate oral (Andriol, Merck Sharp & Dohme) <ul style="list-style-type: none"> • 40 mg capsule • 2–3 times per day 	<ul style="list-style-type: none"> • Can be self-administered 	<ul style="list-style-type: none"> • Frequent dosing required (2–3/day) • Marked variation in blood testosterone levels • Gastrointestinal intolerance 	<ul style="list-style-type: none"> • After 2 weeks

prostate-specific antigen (PSA) levels (which includes an expected effect of testosterone replacement at the start of treatment, but may also detect subclinical or latent prostate cancer), acne and oily skin, reduced sperm production and impaired fertility. Less common adverse effects include gynaecomastia, male pattern balding (which can be familial) and weight gain, as well as fluctuations in mood, libido or hot flushes, which reflect stop–start treatment or excessive fluctuations in serum testosterone levels. Other reported side effects include difficulty passing urine, muscle pain, priapism and increased blood pressure. Refer to prescribing information for further details of formulation-specific side effects.

Monitoring of testosterone therapy

Efficacy. The best clinical measure of adequate restoration of androgen status is identification and monitoring of the man's leading symptom. These clinical features are highly variable between men but highly reproducible within any man and distinctive to that individual.¹⁸ Timing of hormone sampling relative to the most recent dose is important in monitoring the adequacy of testosterone replacement therapy, with the goal being to evaluate steady-state blood levels. This is feasible with injectable and transdermal products, using the trough (ie, pre-next dose sampling), but not with oral testosterone, due to its capricious pharmacokinetics. Random blood sampling without regard to the timing of the most recent dose is uninformative and not recommended. In patients using injectable or transdermal testosterone products, trough testosterone levels should be within the lower part of the reference interval for eugonadal men. In patients with testicular failure (primary or hypergonadotropic hypogonadism), persistent elevation of serum luteinising hormone levels during treatment may indicate inadequate testosterone dosage, frequency or compliance. Periodic monitoring of bone density (at intervals of 1–2 years) may assist in evaluating extent and chronicity of pre-treatment androgen deficiency, as well as adequacy of replacement therapy.¹⁹

Safety. There is no convincing evidence that men with pathological hypogonadism treated with testosterone have any increased risk of benign or malignant prostate disease, although men with lifelong androgen deficiency due to Klinefelter syndrome are relatively protected against prostate cancer.²⁰ A recent meta-analysis of 22 RCTs involving 2351 participants treated for up to 36 months found no association of testosterone treatment with prostate cancer.²¹ Similarly, an analysis from a population-based linked cancer registry did not find any association of testosterone therapy with high-grade prostate cancer.²² Given that population screening for prostate cancer by measuring serum PSA levels is not recommended, as it is not sufficiently safe and cost-effective,²³ monitoring for prostate disease during testosterone treatment should be undertaken as appropriate for eugonadal men of similar age (ie, based on individualised clinical assessment and judgement). However, when there is a reasonable possibility of substantive pre-existing prostate disease, digital rectal examination and PSA testing are required before testosterone treatment is commenced, so that pre-existing prostate cancer is not missed. Although PSA monitoring during testosterone therapy has become widely used,²⁴ it is possible that routine PSA testing could essentially constitute PSA screening for prostate cancer and may lead to overdiagnosis and harm from interventions for clinically insignificant organ-confined prostate cancers.

Elevation of haemoglobin (or haematocrit [packed cell volume]) levels above the normal reference interval may occur with testosterone treatment, particularly in smokers. Haematology profile

should be assessed 3 months after initiation of testosterone treatment and then monitored on an annual basis. Secondary polycythaemia induced by testosterone treatment should prompt evaluation of other aggravating hypoxic conditions, such as smoking, sleep apnoea and respiratory failure. It can usually be managed by reduction of the testosterone dose (and/or frequency), but may rarely require venesection. In men with obstructive sleep apnoea, low testosterone levels are related primarily to obesity and will improve with weight loss. Treatment with continuous positive airway pressure improved testosterone levels in one study, but not in another study or a meta-analysis.^{25–27} Testosterone treatment only transiently worsens the severity of obstructive sleep apnoea,²⁸ which, unless severe and untreated, need not be considered an absolute contraindication to its use (see Part 1, Box 4).³

Product-specific safety issues (Box 1). Injectable testosterone preparations are relatively contraindicated in patients who have bleeding disorders or who are taking anticoagulants, where deep intramuscular injection carries a risk (although low) of haematoma formation.²⁹ Transdermal preparations are preferable in this setting. In all patients, injectable preparations carry a risk of pain, bruising and pulmonary oil microembolism, which results in cough at the time of injection.^{29,30}

All transdermal preparations remain on the skin for some hours after application. These should be applied after morning showering, then covered with clothing to avoid direct skin transfer and risk of virilisation among children or women in intimate contact with the patient.

Conclusions

Different formulations of testosterone are available for replacement therapy to relieve symptoms and signs of androgen deficiency in men with pathological hypogonadism, and can be personalised to individual men. There is no evidence that appropriate use of

2 Key research questions for well controlled clinical trials

- Does testosterone therapy provide meaningful health benefits in older men without pathological hypogonadism?
- Does testosterone treatment improve weight loss, in addition to lifestyle measures?
- Is testosterone an effective and safe treatment for preventing progression of pre-diabetes to type 2 diabetes in men?
- Does testosterone therapy among men without pathological hypogonadism influence the risk of heart attacks or strokes?
- What is the role of testosterone therapy in men with suppression of the hypothalamic–pituitary–testicular (HPT) axis from opioids?
- What is the optimal management of men with prolonged suppression of the HPT axis as a result of recreational misuse of androgens?
- What is the effect of depression and treatment of depression on function of the HPT axis?
- Is there a therapeutic role for partial oestrogen blockade (eg, using clomiphene) and aromatase inhibition (eg, using anastrozole, letrozole) to improve suppressed HPT axis function in men?
- Is there a role for pharmacological androgen therapy with 5 α -dihydrotestosterone in men with specific diseases, to increase muscle or bone mass, aid wound healing or treat other systemic illness? ♦

testosterone therapy increases the risk of prostate cancer. Testosterone replacement may be safely used among men with pathological hypogonadism at any age. A cautious approach to testosterone replacement is warranted in older, frail men, particularly in those with a history of cardiovascular disease. In complex cases, evaluation by an endocrinologist is recommended.

The recommendations given in this position statement are based on data from a limited number of RCTs, as well as non-randomised

clinical studies and observational studies. As such, further research is warranted, which may have an impact on the recommendations. Key research questions for future well controlled clinical trials are presented in [Box 2](#).

Competing interests: Author disclosures are listed in the [Appendix](#).

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- 1 Conway AJ, Handelsman DJ, Lording DW, et al. Use, misuse and abuse of androgens. The Endocrine Society of Australia consensus guidelines for androgen prescribing. *Med J Aust* 2000; 172: 220-224. Erratum in: *Med J Aust* 2000; 172: 334. <https://www.mja.com.au/journal/2000/172/5/use-misuse-and-abuse-androgens>
- 2 Australian Government Department of Health. Pharmaceutical Benefits Scheme. Testosterone undecanoate. <http://www.pbs.gov.au/medicine/item/10205D> (accessed Nov 2015).
- 3 Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. *Med J Aust* 2016; 205: xxx-xxx.
- 4 Yeap BB. Testosterone and cardiovascular disease risk. *Curr Opin Endocrinol Diabetes Obes* 2015; 22: 193-202.
- 5 Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363: 109-122.
- 6 Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010; 95: 639-650.
- 7 Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med* 2016; 374: 611-624.
- 8 Basaria S, Harman SM, Travison TG, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. *JAMA* 2015; 314: 570-581.
- 9 Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 2013; 11: 108.
- 10 Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2014; 13: 1327-1351.
- 11 Borst SE, Shuster JJ, Zou B, et al. Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. *BMC Medicine* 2014; 12: 211.
- 12 Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J* 2015; 36: 2706-2715.
- 13 US Food and Drug Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. 3 Mar 2015. <http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm> (accessed Mar 2015).
- 14 US Food and Drug Administration. Summary minutes of the Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. September 17, 2014. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM418144.pdf> (accessed Nov 2015).
- 15 Lakshman KM, Kaplan B, Travison TG, et al. The effects of injected testosterone dose and age on the conversion of testosterone to estradiol and dihydrotestosterone in young and older men. *J Clin Endocrinol Metab* 2010; 95: 3955-3964.
- 16 Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med* 2013; 369: 1011-1022.
- 17 Sartorius GA, Ly LP, Handelsman DJ. Male sexual function can be maintained without aromatisation: randomized placebo-controlled trial of dihydrotestosterone (DHT) in healthy, older men for 24 months. *J Sex Med* 2014; 11: 2562-2570.
- 18 Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. *J Clin Endocrinol Metab* 2004; 89: 3813-3817.
- 19 Aminorroaya A, Kelleher S, Conway AJ, et al. Adequacy of androgen replacement influences bone density response to testosterone in androgen-deficient men. *Eur J Endocrinol* 2005; 152: 881-886.
- 20 Swerdlow AJ, Schoemaker MJ, Higgins CD, et al. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. *J Natl Cancer Inst* 2005; 97: 1204-1210.
- 21 Cui Y, Zong H, Yan H, Zhang Y. The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2014; 17: 132-143.
- 22 Baillargeon J, Kuo Y-F, Fang X, Shahinian VB. Long-term exposure to testosterone therapy and the risk of high grade prostate cancer. *J Urol* 2015; 194: 1612-1616.
- 23 Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. *Cochrane Database Syst Rev* 2013; (1): CD004720.
- 24 Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; 95: 2536-2559.
- 25 Grunstein RR, Handelsman DJ, Lawrence SJ, et al. Neuroendocrine dysfunction in sleep apnoea: reversal by continuous positive airways pressure therapy. *J Clin Endocrinol Metab* 1989; 68: 352-358.
- 26 Knapp A, Myhill PC, Davis WA, et al. Effect of continuous positive airway pressure therapy on sexual function and serum testosterone in males with type 2 diabetes and obstructive sleep apnoea. *Clin Endocrinol (Oxf)* 2014; 81: 254-258.
- 27 Zhang XB, Jiang XT, Du YP, et al. Efficacy of continuous positive airway pressure on testosterone in men with obstructive sleep apnea: a meta-analysis. *PLoS One* 2014; 9: e115033.
- 28 Killick R, Wang D, Hoyos CM, et al. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: a randomised, placebo-controlled trial. *J Sleep Res* 2013; 22: 331-336.
- 29 Middleton T, Turner L, Fennell C, et al. Complications of injectable testosterone undecanoate in routine clinical practice. *Eur J Endocrinol* 2015; 172: 511-517.
- 30 Sartorius G, Fennell C, Spasevska S, et al. Factors influencing time course of pain after depot oil intramuscular injection of testosterone undecanoate. *Asian J Androl* 2010; 12: 227-233. ■