DOI: 10.1111/nyas.15211

REVIEW

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Cardiovascular disease and testosterone therapy in male hypogonadism

Nipun Lakshitha de Silva[1,2] | Bonnie Grant[1] | Suks Minhas[3] | Channa N. Jayasena[1]

[1]Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK

[2]Faculty of Medicine, General Sir John Kotelawala Defence University, Colombo, Sri Lanka

[3]Department of Urology, Imperial College Healthcare NHS Trust, London, UK

Correspondence
Channa N. Jayasena, Faculty of Medicine, Hammersmith Hospital, Imperial College London, 6th Floor Commonwealth Building, London W12 0NN, UK.
Email: c.jayasena@imperial.ac.uk

Funding information
NIHR Imperial Biomedical Research Centre; National Institute for Health and Care Research; Medical Research Council

Abstract

This review assesses the evidence of the physiological effects of testosterone on cardiovascular health, the association between male hypogonadism and cardiovascular health, and the effects of testosterone therapy on cardiovascular health in male hypogonadism. Preclinical studies suggest complex effects of testosterone on cardiovascular risk by acting on skeletal muscle, cardiomyocytes, vasculature, adipocytes, insulin action, and erythropoiesis. Furthermore, low testosterone has a bi-directional association with cardiometabolic risk. Observational studies have reported worse metabolic profiles in men with organic hypogonadism. However, a consistent association between major cardiovascular events and male hypogonadism has not been established. Hematocrit increases with testosterone therapy; however, most studies do not report an increase in venous thromboembolism risk. Although some observational studies and a small randomized controlled study reported an increased risk of cardiovascular disease, recent data confirm the medium-term cardiovascular safety of testosterone therapy in middle-aged and older men with low testosterone.

KEYWORDS
androgens, cardiovascular risks, hypogonadism, metabolic disorders, testosterone

INTRODUCTION

Rates of testosterone prescriptions have risen exponentially over the last few decades without a substantial increase in the prevalence of organic male hypogonadism.[1,2] This is predominantly due to the treatment of middle-aged or older men with low serum testosterone concentration.[3] In parallel, a small randomized controlled trial (RCT) of older men with low serum testosterone concentration[4] and two observational studies[5,6] reported increased cardiovascular events in men treated with testosterone. This triggered the United States Food and Drug Administration (US FDA) to raise concerns over increased cardiovascular risk with testosterone in older men with low testosterone and required manufacturers to update labeling on this potential risk.[7] However, the European Medicines Agency concluded that there was no need to update their existing guidance due to insufficient evidence for adverse cardiovascular effects of testosterone therapy.[8] Guidelines by professional organizations have acknowledged the lack of conclusive evidence on cardiovascular safety and recommended further studies.[9,10] A subsequent individual participant data (IPD) meta-analysis[11] and a dedicated cardiovascular outcome trial[12] have improved our understanding of the cardiovascular effects of testosterone in men with hypogonadism.

This review will explore the physiological effects of testosterone on cardiovascular health and the association between male hypogonadism and cardiovascular health. Subsequently, we critically appraise evidence from RCTs on the effects of testosterone therapy on

cardiovascular risk factors, major adverse cardiovascular events (death from a cardiovascular cause/non-fatal myocardial infarction/non-fatal stroke), and other cardiovascular outcomes. We identified original studies, systematic reviews, and meta-analyses on cardiovascular risk factors and outcomes in male hypogonadism using PubMed and Google Scholar for this narrative review.

PHYSIOLOGICAL EFFECTS OF TESTOSTERONE ON THE CARDIOVASCULAR SYSTEM AND CARDIOVASCULAR RISK FACTORS

Testosterone has a complex bi-directional relationship with cardiovascular health. Preclinical studies exploring the roles of androgens on cardiovascular physiology have helped in understanding the effects of hypogonadism and testosterone therapy on cardiovascular health. Androgen receptors (ARs) are expressed in many cells throughout the cardiovascular system, including cardiac myocytes, vascular endothelial cells, vascular smooth muscle cells, and platelets.[13]

Several animal studies have reported antiarrhythmic properties of testosterone through its actions on cardiomyocytes.[14–16] Testosterone was observed to protect the myocardium from ischemic injury in several rodent models, although the exact mechanism has not been elucidated.[17,18] Activation of the ATP-sensitive K^+ channels in the cardiac mitochondrial inner membrane is one potential mechanism.[19] Testosterone was also shown to promote the expression of adrenergic receptors in the cardiac myocytes, providing a positive inotropic effect.[20] However, studies using rat models have observed hypertrophic cardiac response to testosterone,[21] with a potential risk of heart failure in the long term.[20] A study comparing AR gene (*Ar*) knockout mice to wild-type mice reported that *Ar* knockout mice had less cardiac hypertrophy in response to angiotensin-II, implicating the importance of androgen action on cardiac muscle growth.[22]

Endothelial cells and endothelial progenitor cells express ARs and estrogen receptors and respond to these hormones, affecting endothelial function, cell proliferation, and migration.[23] The effects of testosterone on vasculature are complex and dependent on multiple factors. A study of male and female rabbits observed endothelium-independent vasodilator properties of testosterone in coronary arteries and the aorta.[24] Similarly, studies using rat models[25,26] and swine models[27] have also confirmed the vasodilatory properties of testosterone. Endothelium-independent vasodilatory effects might be through the inhibition of the voltage-gated calcium channels.[28] However, some animal studies have reported contradictory findings suggesting vasoconstrictor effects of testosterone.[29,30] A study using a hybrid rat model reported lower blood pressures in rats with deficient functional ARs and in castrated rats.[31] Overall, testosterone has vasodilator properties, particularly within the short term, predominantly through its non-genomic actions.[13] However, genomic actions of testosterone seem to promote vasoconstrictor response by potentiating adrenergic effects on vascular smooth muscles.[20] Preclinical studies have reported the potential of androgens to promote vascular calcification, the release of reactive oxygen species, and hypertrophy.[13]

Platelet action is another important factor affecting thrombotic diseases. In orchidectomized rats, testosterone deficiency was associated with platelet aggregation and hypercoagulability, which was reversed with testosterone therapy.[32,33] This could partly be related to the effects of androgen on endothelial nitric oxide release.[34] In contrast, treating eugonadal male rats with testosterone resulted in increased thromboxane A2 receptor density in platelets.[35]

Studies in rabbits using a standard diet[36] or a high-cholesterol diet[37–39] have suggested anti-atherosclerotic effects of androgens on the endothelium. Physiological testosterone replacement inhibited fatty streak deposition in testicular-feminized mice.[40] In contrast, studies using human white blood cells and umbilical vein endothelial cells[41] and human macrophages[42] reported pro-atherosclerotic effects of androgens.

Adiposity and insulin resistance are other cardiovascular risk factors closely linked to androgen action. Testosterone was found to inhibit adipocyte differentiation in animal models.[43–45] Preclinical studies have suggested that androgens impact adipocyte functions, such as insulin signaling, lipid metabolism, and adipokine production.[46] Testosterone is also known to increase insulin sensitivity by increasing GLUT-4–dependent glucose uptake in muscle and adipose tissue and glycolytic activity in cells.[47] Preclinical data suggest that testosterone potentiates glucagon-like peptide-1 action on pancreatic beta cells and promotes insulin secretion in males.[48] Similar findings were obtained using human islet cells, where the conversion of testosterone to dihydrotestosterone within the pancreas enhanced glucose-stimulated insulin secretion.[49,50] Finally, testosterone is known to increase hematocrit by stimulating erythropoietin synthesis and suppressing hepcidin synthesis.[51]

Evidence from the above preclinical studies suggests a complex interrelationship between endogenous testosterone and cardiovascular health, which are likely to be disturbed in male hypogonadism. The following section explores current evidence on the association between male hypogonadism and cardiovascular health. Most of the evidence comes from studies of middle-aged and older men with low testosterone without an intrinsic pathology of the hypothalamic–pituitary–testicular axis (i.e., functional hypogonadism). Evidence from this patient population cannot be extrapolated to men with organic hypogonadism. Where available, literature for these distinct patient groups has been discussed separately. An additional complexity arises due to the challenges faced in diagnosing hypogonadism in men. Intra-individual biological variation in testosterone concentrations as well as variations in testosterone assays confound the biochemical confirmation of male hypogonadism.[52] Male hypogonadism should only be diagnosed in the presence of suggestive clinical features using a standardized assay with repeated measurements of morning-fasted, fasted samples.[52] Not following these prerequisites in some studies can affect the validity of the diagnosis of male hypogonadism in some participants.

ASSOCIATIONS OF MALE HYPOGONADISM WITH CARDIOVASCULAR DISEASE AND RISK FACTORS

Cardiovascular risk factors

Studies have observed low testosterone concentration among men with metabolic syndrome and diabetes, partly explained by low sex hormone–binding globulin (SHBG).[53] However, even after correcting for low SHBG, testosterone concentrations are lower among men with diabetes and obesity.[54] Functional hypogonadism due to the suppression of the hypothalamic–pituitary axis is the likely mechanism.[55] On the other hand, due to the possible favorable effects of testosterone on body composition, hypogonadism can be causally linked to obesity, diabetes, and metabolic syndrome.[56] In a study assessing the association among obesity, testosterone, and insulin resistance in men, low-serum testosterone was associated with obesity and insulin resistance measured using hyperinsulinemic–euglycemic clamp testing.[57] Prospective studies have reported an increased risk of a future diagnosis of diabetes and metabolic syndrome in men with low testosterone.[58] Metabolic syndrome[59] and diabetes[60] were reported to be more prevalent among men with low testosterone in two different meta-analyses of observational studies. Overall, male hypogonadism is likely to have a bi-directional association with diabetes and metabolic syndrome, with visceral adiposity being a mediator.[56]

The association of male hypogonadism with lipid parameters does not show a consistent pattern. A retrospective study of older Chinese men reported a negative correlation of total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol and a positive correlation of high-density lipoprotein (HDL) cholesterol with total testosterone.[61] In a study of Taiwanese men over 40 years old, testosterone quartiles were positively correlated with both HDL and LDL cholesterol.[62] A recent cross-sectional study from China reported higher triglycerides and lower LDL cholesterol concentration in men with late-onset hypogonadism.[63]

A possible association between hypertension and low testosterone in men had been observed several decades ago with observational studies reporting low testosterone among men with hypertension.[64,65] In a cross-sectional study, men with late-onset hypogonadism were found to have slightly higher systolic blood pressures.[63] In a cohort study of men aged 20–79 years, incident hypertension was higher among men with low testosterone, and men with hypertension were noted to have low testosterone concentration.[66] Another cross-sectional study of middle-aged and elderly men also reported an inverse association between testosterone and the prevalence of hypertension.[67] According to a population-based, cross-sectional study, lower testosterone was associated with higher blood pressure and left ventricular mass, which reduced after adjusting for the body mass index (BMI).[68]

Inflammation is an important mediator of cardiovascular disease. A study of over 10,000 men revealed increased high-sensitivity C-reactive protein (CRP), IL-6, IL-17A, and tumor necrosis factor–α in men with total testosterone <250 ng/dL.[69] Another population-based cross-sectional study also reported an inverse association between high-sensitivity CRP and free and total testosterone.[70]

There are a few studies assessing cardiovascular risk factors in men with organic hypogonadism. The prevalence of metabolic syndrome and insulin resistance was reported to be greater in Klinefelter syndrome compared with healthy controls in some observational studies.[71,72] Atherogenic lipid profiles have also been reported in this population compared to healthy controls.[71] There is no consistent evidence of hypertension within this population.[73] In a retrospective study of 332 men with congenital hypogonadotropic hypogonadism (CHH) and 395 controls, the prevalence of metabolic syndrome was higher, with higher arterial blood pressure, waist circumference (WC), triglyceride, fasting glucose, and lower HDL cholesterol in men with CHH.[74] A higher triglyceride–glucose index (a marker of insulin resistance) has been observed in men with CHH compared with healthy men.[75] One of the oldest studies comparing normogonadal men to men with normoprolactinemic and hyperprolactinemic hypogonadism reported higher LDL-cholesterol and triglycerides in both groups of hypogonadal men.[76]

Data from studies of men with prostate cancer receiving androgen deprivation therapy (ADT) can also provide insight into the effects of hypogonadism on cardiovascular health as this provides a group of men who develop severe, new-onset hypogonadism. ADT for prostate cancer was associated with increased insulin resistance[77] and new-onset diabetes[78] in men without diabetes and poor diabetes control in men with diabetes,[79] suggesting a causal effect of male hypogonadism on insulin resistance and diabetes. This could be related to increased visceral and subcutaneous fat mass observed with ADT.[77,80] Elevated total cholesterol has also been observed with ADT, although the effects on individual lipoproteins are variable.[81,82] Studies have suggested increased arterial stiffness with ADT;[83,84] however, a clear association with hypertension has not been confirmed.[85]

Overall, there is a suggestion of poor metabolic health among middle-aged and older men with low testosterone, though the causality cannot be established. However, worse metabolic profiles seen in men with organic hypogonadism likely suggest a causal link in this population. These associations are summarized in Table 1.

Cardiovascular disease and mortality

A meta-analysis of 37 observational studies published until 2017 with over 40,000 participants observed an increased incidence of cardiovascular morbidity (1.17, 95% CI: [1.01, 1.36]) and mortality (1.54, 95% CI: [1.25, 1.89]) among men with low endogenous testosterone concentration at baseline after adjusting for confounders.[86] There is also evidence of increased carotid intima-media thickness (CIMT), a marker of subclinical atherosclerosis, in middle-aged or older men with symptomatic low testosterone.[87–89] Some studies report long QT interval in men with hypogonadism,[90] which can be a risk factor for torsades de pointes ventricular tachycardias.[91,92]

TABLE 1 Association of cardiovascular risk factors and outcomes with male hypogonadism and effects of testosterone treatment.

Cardiovascular risk factor/outcome	Association with hypogonadism from observational studies	Effects of testosterone treatment from interventional studies of middle-aged and older men
Obesity/visceral adiposity	Positive association[59]	No effect on body mass index and waist circumference;[99,101,108] decrease in fat mass and increase in lean mass[106,110,111]
Insulin resistance	Positive association with insulin resistance and risk of diabetes[57,58]	Inconsistent results on insulin sensitivity; no effect[99,107] or slight improvement[101,106] Inconsistent results on diabetes; no effect[99,100,103] or reduced risk[104,105]
Dyslipidemia	Possible association with atherogenic lipid profile, inconsistent findings for individual lipoproteins[61–63]	Inconsistent results; no effects[113,114] or reduced LDL, HDL, and total cholesterol levels[11,100,101,108]
Hypertension	Positive association[64–66]	Inconsistent results; no effect[11] or slight increase[12,115,116]
Hematocrit	Associated with anemia[139,140]	Risk of polycythemia[104,119]
Major adverse cardiovascular events	Inconsistent results; positive[86] or no association[93–95]	No increased risk in the medium term[11,12]
Venous thromboembolism	No association[95,141,142] (apart from Klinefelter syndrome, where the risk is increased[96,97])	Inconsistent results; no effect[11,136] or slight increase[12]
Arrhythmias	Possible association with long QT interval[90] and ventricular tachycardia[91,92]	Inconsistent results; no effect[11,137] or slight increase[12]

In contrast, a subsequent prospective study of community-dwelling elderly men without an incident of cardiovascular disease failed to demonstrate any association between testosterone and cardiovascular outcomes.[93] Similarly, a recently published UK Biobank prospective cohort study of middle-aged men reported no association between cardiovascular mortality and low total or corrected free testosterone.[94] Another cohort study from Denmark suggested that men with low testosterone levels had a higher 5-year risk of myocardial infarction, stroke, venous thromboembolism, and all-cause mortality in an unadjusted model compared to men with normal testosterone levels; however, after adjusting for age and co-morbidities, there was only an association with all-cause mortality.[95]

Men with Klinefelter syndrome are at increased risk of venous and arterial thromboembolism and thrombotic deaths,[96] which is distinct from other men with hypogonadism due to a presumed relationship to excess X-linked gene dosage.[97] Increased thrombin generation in Klinefelter syndrome possibly related to increased factor VIII levels might be contributory.[98] Evidence from the effects of ADT on cardiovascular events and mortality is mixed, with most observational studies indicating increased cardiovascular risk, whereas RCTs report no association.[85]

In summary, there is no strong evidence of an association between cardiovascular disease and hypogonadism from observational studies (Table 1). The observed association between cardiovascular disease and mortality in men with low testosterone in some studies may be related to associated co-morbidities without having a causal link. Hence, it is difficult to explore which of the cardiovascular risk factors discussed earlier are strongly associated with cardiovascular outcomes in men with hypogonadism.

EFFECTS OF TESTOSTERONE THERAPY ON CARDIOVASCULAR DISEASE AND CARDIOVASCULAR RISK FACTORS

Cardiovascular risk factors

Several placebo-controlled RCTs and a meta-analysis have failed to show a significant improvement in HbA1c or fasting glucose concentration in older men with low serum total testosterone concentration given testosterone therapy.[99–102] Many of the participants in these studies had pre-existing Type 2 diabetes (T2D). The TRAVERSE substudy found no difference between testosterone therapy or placebo groups in progression from prediabetes to diabetes or in diabetes remission.[103]

These findings contrast with the T4DM study, where older overweight men were randomized to receive a placebo or testosterone undecanoate.[104] After 2 years of intervention, men given testosterone therapy had improved 2-h glucose concentration on oral glucose tolerance tests, with a mean glucose change from baseline of −1.7 mmol/L, although there was no difference in HbA1c concentration. These differences may be explained by the differences in the study participants' characteristics. The T4DM trial used a higher serum total testosterone concentration cut-off for inclusion compared with many other RCTs and included men with impaired glucose tolerance or newly diagnosed T2D. It may be that any beneficial effect of testosterone is observed in the early stages of diabetes development rather than well-established diabetes; however, further studies need to be performed. Similarly, another small RCT of men with hypogonadism and newly diagnosed T2D or metabolic syndrome reported beneficial effects on glycemic

outcomes.[105] The effects of testosterone therapy on insulin sensitivity are also inconclusive, with some showing modest improvements[101,106] in fasting insulin levels and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values, whereas others do not report any significant difference.[99,107]

The effect of testosterone therapy on body composition is also important due to the bi-directional relationship between obesity and diabetes. Multiple RCTs have failed to consistently show any improvement in BMI or WC with testosterone,[99,101,108] though a recent observational study reported improvement in weight, BMI, and WC in men treated with testosterone.[109] However, studies have reported a change in body composition, with an increase in lean mass and a decrease in fat mass in men given testosterone therapy.[106,110,111]

Some interventional studies have reported reductions in total cholesterol, LDL-cholesterol, and HDL-cholesterol in men given testosterone therapy compared with placebo.[11,100,101,112] Others have shown no significant change in lipid parameters.[113,114] A recently published double-blind placebo RCT in older men suggested that testosterone therapy may blunt the HDL-cholesterol rise seen with intensive lifestyle intervention.[99] Testosterone therapy does not appear to have a significant effect on triglyceride concentration. These mixed observations are likely a result of significant heterogeneity in the studies with different formulations and durations of testosterone therapy often used.

The effect of testosterone therapy on blood pressure also shows some conflicting results. In many studies administering testosterone, blood pressure did not significantly change.[4,100] Others, however, have reported increases in systolic and diastolic blood pressure during testosterone replacement therapy, particularly with oral testosterone undecanoate.[115,116] Although a small increase in mean systolic blood pressure was reported in the TRAVERSE study, this was only 0.3 mmHg (95% CI: [−0.3, 0.9]).[12] The clinical significance of this slight increase is likely to be minimal.

Testosterone stimulates erythropoiesis, and one of the biggest treatment-limiting factors in testosterone therapy is increased hematocrit.[117,118] Erythrocytosis is a commonly reported adverse event in trials administering testosterone.[104,119] Although testosterone therapy in Klinefelter syndrome was not associated with changes in cardiovascular risk factors in some observational studies,[72,120] an RCT reported improved total and abdominal fat with testosterone therapy.[121] Testosterone therapy was associated with a reduction in fibrinogen levels in men with Klinefelter syndrome in an observational study.[122] Interestingly, an observational study followed testosterone-treated men with CHH and reported an increase in BMI, systolic blood pressure, and triglycerides and a decrease in HDL cholesterol after 5.63 ± 2.6 months of treatment.[74]

In summary, current published literature fails to show a consistent benefit, or risk, of testosterone therapy on cardiovascular risk factors (Table 1).

Cardiovascular disease and mortality

Data from pharmacovigilance studies and retrospective analyses have played an important role in the initial discussions on testosterone safety. A retrospective study of men who underwent coronary angiography with low testosterone reported increased mortality, myocardial infarctions, and strokes in men receiving testosterone therapy.[5] Major flaws in the data analysis and contamination of the sample with females resulted in questioning of the validity of these results.[123] Another prospective cohort study also found increased myocardial infarction rates with testosterone prescription in older men and younger men with pre-existing heart disease.[6] However, the study methodology comparing pre- and post-treatment cardiovascular events was considered unsound.[123]

Some other observational studies have reported no increase in cardiovascular risk in men treated with testosterone.[124] Interestingly, another study following up on men with T2D whose testosterone was measured reported increased survival in men whose low testosterone was treated.[125] A large retrospective study of male veterans reported reduced myocardial infarctions, strokes, and all-cause mortality in those whose low testosterone was corrected with testosterone replacement.[126] Caution should be exercised in interpreting these results because these observational studies introduce a high risk of bias. Patients treated with testosterone may have different characteristics compared with those who were not treated with testosterone.

Data from multiple RCTs of testosterone therapy in middle-aged and older men have provided insight into the cardiovascular effects of testosterone, although none of them were primarily designed to assess the cardiovascular safety of testosterone. The Testosterone Efficacy and Safety (TestES) consortium analyzed individual patient data (IPD) from RCTs that reported cardiovascular outcomes of testosterone and placebo experimental groups.[11] IPD of 3431 participants from 17 countries were analyzed, with a mean treatment duration of 9.5 months. Cardiovascular events occurred in 120 men (7.5%) receiving testosterone and 110 (7.2%) men receiving placebo (OR 0.17, 95% CI: [0.81, 1.42]). Overall mortality was not significantly lower in the testosterone group (6 deaths, 0.4%) compared with the placebo group (12 deaths, 0.8%) (OR 0.46, 95% CI: [0.17, 1.42]). Men in the analysis had high cardiovascular risk, with a mean age of 65 years, mean BMI of 30 kg/m^2, and diabetes in 27%. The robust methodology used in the study selection, data extraction, and data analysis, and the use of IPD strengthen the validity of the reported results. Furthermore, this study design has enabled the use of previously unpublished cardiovascular outcome data. However, shorter follow-up duration and cardiovascular outcomes not being primary outcomes in the studies need to be considered when interpreting these results.

Out of the studies included in the above-mentioned IPD analysis, a few studies warrant further attention. The Testosterone in Older Men with Mobility Limitations (TOM) trial enrolled men over the age of 65

years with total testosterone between 100 and 350 ng/dL. The study was terminated prematurely because the data and safety monitoring board observed excess cardiovascular events in men treated with testosterone.[4] However, these events were not pre-specified primary or secondary outcomes and were of questionable clinical significance, such as pedal edema and electrocardiography changes. Testosterone Trials (TTrials) were a set of seven coordinated RCTs recruiting men over 65 years of age with total testosterone <275 ng/dL who were treated with testosterone or placebo for 12 months. Out of a total of 394 men, there was no difference in major cardiovascular events, with 7 men in each group developing myocardial infarction, stroke, or death from a cardiovascular event.[127] However, the cardiovascular trial of this study observed an increase in non-calcified plaque volume with testosterone therapy.[128] The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial randomized 308 men older than 60 years of age and total testosterone concentrations between 100 and 400 ng/dL or free testosterone <50 pg/mL and administered testosterone gel or placebo for 3 years. Only a few cardiovascular events occurred during the study period, and there was no statistically significant difference among the groups.[129] The study also did not observe any difference in the CIMT test or coronary calcium scores.

Two small RCTs have assessed the effects of testosterone on subclinical atherosclerosis, with contradictory findings to the above. A small RCT of 13 men randomized to receive testosterone undecanoate injections or placebo for 12 months found significant beneficial effects of testosterone on CIMT.[130] Another RCT of 50 men with metabolic syndrome and late-onset hypogonadism observed improved CIMT and high-sensitivity CRP with testosterone undecanoate injections.[114]

None of the above individual studies were long enough or large enough to ascertain the cardiovascular safety of testosterone. Due to the requirement of the FDA, the TRAVERSE trial was conducted to assess the cardiovascular safety of testosterone replacement in middle-aged and older men with low testosterone.[12] This trial enrolled 5246 men with symptoms of hypogonadism, testosterone concentration <300 ng/dL, and high cardiovascular risk and randomized them to receive testosterone gel or placebo. After a mean follow-up of 33 months, the first adjudicated major adverse cardiovascular event occurred in 182 (7%) in the testosterone group and 190 (7.3%) in the placebo group. The hazard ratio for death from cardiovascular disease was 0.84 (0.63–1.12). This being the largest study to date, with a longer follow-up duration and having cardiovascular outcomes as the primary outcome, it provides good-quality evidence on the medium-term cardiovascular safety of testosterone in the given population. There are, however, several limitations of this study. Mean testosterone concentration in the treatment group was consistently below 16 nmol/L (460 ng/dL), which is considered relatively low. Over 60% of the participants discontinued treatment.

Population and case-crossover studies have reported an association between testosterone therapy and venous thromboembolism.[131,132] Polycythemia during testosterone therapy has been independently associated with venous thromboembolism.[133] Though TRAVERSE reported an increased incidence of pulmonary embolism in the testosterone group compared to placebo (24; 0.9% vs. 12; 0.5%), statistical significance was not tested. The reported increased incidence of venous thromboembolism also did not reach statistical significance.[12] Previous meta-analyses of aggregate data[134–136] and the recent TestES IPD meta-analysis[11] also did not observe any increased risk of venous thromboembolism with testosterone, irrespective of the route of administration.

TRAVERSE reported an increased incidence of non-fatal arrhythmias warranting interventions, including atrial fibrillations. However, a recent updated meta-analysis did not observe an increased risk of non-fatal arrhythmias with testosterone in RCTs (excluding TRAVERSE).[137] Interestingly, a database study has found a reduced incidence of atrial fibrillation with testosterone therapy in men with low testosterone.[138]

CONCLUSIONS

Testosterone has multiple physiological effects on the cardiovascular system. Although male hypogonadism seems to be associated with an adverse metabolic profile, there is no consistent evidence for increased cardiovascular risk in men with low testosterone. Similarly, testosterone therapy has not consistently improved cardiovascular risk factors or outcomes in men with hypogonadism. On the other hand, recent data suggest medium-term cardiovascular safety of testosterone therapy in middle-aged and older men with low testosterone; long-term cardiovascular safety is yet to be established.

In men with hypogonadism, baseline assessments for pre-existing cardiovascular disease and risk factors (e.g., obesity, diabetes, dyslipidemia, hypertension, and smoking) and optimization of these risk factors are vital and independent of testosterone therapy to improve overall cardiovascular outcomes. In middle-aged and older men with low testosterone, lifestyle modifications (weight loss, exercise, and smoking cessation) and optimization of risk factors would take precedence over testosterone therapy for improved cardiovascular outcomes. Apart from hematocrit, any additional monitoring for cardiovascular risk reduction would not be routinely required during testosterone therapy.

AUTHOR CONTRIBUTIONS

N.L.d.S. and B.G. reviewed the literature and drafted the initial manuscript. C.N.J. and S.M. revised the manuscript. All authors read and agreed on the final manuscript.

ACKNOWLEDGMENTS

The Section of Endocrinology and Investigative Medicine is funded by grants from the MRC, NIHR and is supported by the NIHR Biomedical Research Centre Funding Scheme and the NIHR/Imperial Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. C.N.J. was also funded by the NIHR post-doctoral fellowship.

CONFLICT OF INTEREST STATEMENT

C.N.J. received investigator-led grants from Logixx Pharma Ltd.

ORCID

Channa N. Jayasena https://orcid.org/0000-0002-2578-8223

PEER REVIEW

The peer review history for this article is available at: https://publons.com/publon/10.1111/nyas.15211.

REFERENCES

1. Layton, J. B., Li, D., Meier, C. R., Sharpless, J. L., Stürmer, T., Jick, S. S., & Brookhart, M. A. (2014). Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *The Journal of Clinical Endocrinology & Metabolism*, *99*(3), 835–842.
2. Gan, E. H., Pattman, S., Pearce, H. S., & Quinton, R. (2013). A UK epidemic of testosterone prescribing, 2001–2010. *Clinical Endocrinology*, *79*(4), 564–570.
3. Nguyen, C. P., Hirsch, M. S., Moeny, D., Kaul, S., Mohamoud, M., & Joffe, H. V. (2015). Testosterone and "age-related hypogonadism"—FDA concerns. *New England Journal of Medicine*, *373*(8), 689–691.
4. Basaria, S., Coviello, A. D., Travison, T. G., Storer, T. W., Farwell, W. R., Jette, A. M., Eder, R., Tennstedt, S., Ulloor, J., Zhang, A., Choong, K., Lakshman, K. M., Mazer, N. A., Miciek, R., Krasnoff, J., Elmi, A., Knapp, P. E., Brooks, B., Appleman, E., …, Bhasin, S. (2010). Adverse events associated with testosterone administration. *New England Journal of Medicine*, *363*(2), 109–122.
5. Vigen, R. (2013). Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*, *310*(17), 1829–1836.
6. Finkle, W. D., Greenland, S., Ridgeway, G. K., Adams, J. L., Frasco, M. A., Cook, M. B., Fraumeni, J. F., & Hoover, R. N. (2014). Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE*, *9*(1), e85805.
7. U.S. Food and Drug Administration. (2015). *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.* U.S. Food and Drug Administration.
8. European Medicines Agency. (2014). *No consistent evidence of an increased risk of heart problems with testosterone medicines.* European Medicines Agency.
9. Bhasin, S., Brito, J. P., Cunningham, G. R., Hayes, F. J., Hodis, H. N., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., Wu, F. C., & Yialamas, M. A. (2018). Testosterone therapy in men with hypogonadism: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *103*(5), 1715–1744.
10. Jayasena, C. N., Anderson, R. A., Llahana, S., Barth, J. H., Mackenzie, F., Wilkes, S., Smith, N., Sooriakumaran, P., Minhas, S., Wu, F. C. W., Tomlinson, J., & Quinton, R. (2022). Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism. *Clinical Endocrinology*, *96*(2), 200–219.
11. Hudson, J., Cruickshank, M., Quinton, R., Aucott, L., Aceves-Martins, M., Gillies, K., Bhasin, S., Snyder, P. J., Ellenberg, S. S., Grossmann, M., Travison, T. G., Gianatti, E. J., van der Schouw, Y. T., Emmelot-Vonk, M. H., Giltay, E. J., Hackett, G., Ramachandran, S., Svartberg, J., Hildreth, K. L., … Jayasena, C. N. (2022). Adverse cardiovascular events and mortality in men during testosterone treatment: An individual patient and aggregate data meta-analysis. *The Lancet Healthy Longevity*, *3*(6), e381–e393.
12. Lincoff, A. M., Bhasin, S., Flevaris, P., Mitchell, L. M., Basaria, S., Boden, W. E., Cunningham, G. R., Granger, C. B., Khera, M., Thompson, I. M., Wang, Q., Wolski, K., Davey, D., Kalahasti, V., Khan, N., Miller, M. G., Snabes, M. C., Chan, A., Dubcenco, E., … Nissen, S. E. (2023). Cardiovascular safety of testosterone-replacement therapy. *New England Journal of Medicine*, *389*(2), 107–117.
13. Lucas-Herald, A. K., Alves-Lopes, R., Montezano, A. C., Ahmed, S. F., & Touyz, R. M. (2017). Genomic and non-genomic effects of androgens in the cardiovascular system: Clinical implications. *Clinical Science*, *131*(13), 1405–1418.
14. Bai, C.-X., Kurokawa, J., Tamagawa, M., Nakaya, H., & Furukawa, T. (2005). Nontranscriptional regulation of cardiac repolarization currents by testosterone. *Circulation*, *112*(12), 1701–1710.
15. Pham, T. V., Sosunov, E. A., Anyukhovsky, E. P., Danilo, P., & Rosen, M. R. (2002). Testosterone diminishes the proarrhythmic effects of dofetilide in normal female rabbits. *Circulation*, *106*(16), 2132–2136.
16. Brouillette, J., Rivard, K., Lizotte, E., & Fiset, C. (2005). Sex and strain differences in adult mouse cardiac repolarization: Importance of androgens. *Cardiovascular Research*, *65*(1), 148–157.
17. Liu, J., Tsang, S., & Wong, T. M. (2006). Testosterone is required for delayed cardioprotection and enhanced heat shock protein 70 expression induced by preconditioning. *Endocrinology*, *147*(10), 4569–4577.
18. Tsang, S., Wu, S., Liu, J., & Wong, T. M. (2008). Testosterone protects rat hearts against ischaemic insults by enhancing the effects of α1-adrenoceptor stimulation. *British Journal of Pharmacology*, *153*(4), 693–709.
19. Er, F., Michels, G., Gassanov, N., Rivero, F., & Hoppe, U. C. (2004). Testosterone induces cytoprotection by activating ATP-sensitive K^+ channels in the cardiac mitochondrial inner membrane. *Circulation*, *110*(19), 3100–3107.
20. Carbajal-García, A., Reyes-García, J., & Montaño, L. M. (2020). Androgen effects on the adrenergic system of the vascular, airway, and cardiac myocytes and their relevance in pathological processes. *International Journal of Endocrinology*, *2020*, 1–25.
21. Marsh, J. D., Lehmann, M. H., Ritchie, R. H., Gwathmey, J. K., Green, G. E., & Schiebinger, R. J. (1998). Androgen receptors mediate hypertrophy in cardiac myocytes. *Circulation*, *98*(3), 256–261.
22. Ikeda, Y., Aihara, K.-I., Sato, T., Akaike, M., Yoshizumi, M., Suzaki, Y., Izawa, Y., Fujimura, M., Hashizume, S., Kato, M., Yagi, S., Tamaki, T., Kawano, H., Matsumoto, T., Azuma, H., Kato, S., & Matsumoto, T. (2005). Androgen receptor gene knockout male mice exhibit impaired cardiac growth and exacerbation of angiotensin II-induced cardiac fibrosis. *Journal of Biological Chemistry*, *280*(33), 29661–29666.
23. Cai, J.-J., Wen, J., Jiang, W. H., Lin, J., Hong, Y., & Zhu, Y. S. (2016). Androgen actions on endothelium functions and cardiovascular diseases. *Journal of Geriatric Cardiology: JGC*, *13*(2), 183.
24. Yue, P., Chatterjee, K., Beale, C., Poole-Wilson, P. A., & Collins, P. (1995). Testosterone relaxes rabbit coronary arteries and aorta. *Circulation*, *91*(4), 1154–1160.
25. Jones, R. D., English, K. M., Jones, T. H., & Channer, K. S. (2004). Testosterone-induced coronary vasodilatation occurs via a non-genomic mechanism: Evidence of a direct calcium antagonism action. *Clinical Science*, *107*(2), 149–158.
26. Tep-Areenan, P., Kendall, D. A., & Randall, M. D. (2002). Testosterone-induced vasorelaxation in the rat mesenteric arterial bed is mediated predominantly via potassium channels. *British Journal of Pharmacology*, *135*(3), 735–740.
27. O'connor, E. K., Ivey, J. R., & Bowles, D. K. (2012). Differential effects of androgens on coronary blood flow regulation and arteriolar diameter in intact and castrated swine. *Biology of Sex Differences*, *3*, 1–11.
28. Scragg, J. L., Jones, R. D., Channer, K. S., Jones, T. H., & Peers, C. (2004). Testosterone is a potent inhibitor of L-type Ca^{2+} channels. *Biochemical and Biophysical Research Communications*, *318*(2), 503–506.
29. Ceballos, G., Figueroa, L., Rubio, I., Gallo, G., Garcia, A., Martinez, A., Yañez, R., Perez, J., Morato, T., & Chamorro, G. (1999). Acute and nongenomic effects of testosterone on isolated and perfused rat heart. *Journal of Cardiovascular Pharmacology*, *33*(5), 691–697.

30. Masuda, A., Mathur, R., & Halushka, P. V. (1991). Testosterone increases thromboxane A2 receptors in cultured rat aortic smooth muscle cells. *Circulation Research*, *69*(3), 638–643.
31. Ely, D. L., Salisbury, R., Hadi, D., Turner, M., & Johnson, M. L. (1991). Androgen receptor and the testes influence hypertension in a hybrid rat model. *Hypertension*, *17*(6 Part 2), 1104–1110.
32. Alqahtani, S. A., & Alhawiti, N. M. (2019). Administration of testosterone improves the prothrombotic and antifibrinolytic parameters associated with its deficiency in an orchidectiomized rat model. *Platelets*, *30*(5), 624–630.
33. Li, S., Li, X., Li, J., Deng, X., Li, Y., & Cong, Y. (2007). Experimental arterial thrombosis regulated by androgen and its receptor via modulation of platelet activation. *Thrombosis Research*, *121*(1), 127–134.
34. Campelo, A. E., Cutini, P. H., & Massheimer, V. L. (2012). Testosterone modulates platelet aggregation and endothelial cell growth through nitric oxide pathway. *Journal of Endocrinology*, *213*(1), 77–87.
35. Matsuda, K., Ruff, A., Morinelli, T. A., Mathur, R. S., & Halushka, P. V. (1994). Testosterone increases thromboxane A2 receptor density and responsiveness in rat aortas and platelets. *American Journal of Physiology-Heart and Circulatory Physiology*, *267*(3), H887–H893.
36. Hanke, H., Lenz, C., Hess, B., Spindler, K.-D., & Weidemann, W. (2001). Effect of testosterone on plaque development and androgen receptor expression in the arterial vessel wall. *Circulation*, *103*(10), 1382–1385.
37. Alexandersen, P., Haarbo, J., Byrjalsen, I., Lawaetz, H., & Christiansen, C. (1999). Natural androgens inhibit male atherosclerosis: A study in castrated, cholesterol-fed rabbits. *Circulation Research*, *84*(7), 813–819.
38. Arad, Y., Badimon, J. J., Badimon, L., Hembree, W. C., & Ginsberg, H. N. (1989). Dehydroepiandrosterone feeding prevents aortic fatty streak formation and cholesterol accumulation in cholesterol-fed rabbit. *Arteriosclerosis: An Official Journal of the American Heart Association, Inc*, *9*(2), 159–166.
39. Gordon, G. B., Bush, D. E., & Weisman, H. F. (1988). Reduction of atherosclerosis by administration of dehydroepiandrosterone. A study in the hypercholesterolemic New Zealand white rabbit with aortic intimal injury. *The Journal of Clinical Investigation*, *82*(2), 712–720.
40. Nettleship, J. E., Jones, T. H., Channer, K. S., & Jones, R. D. (2007). Physiological testosterone replacement therapy attenuates fatty streak formation and improves high-density lipoprotein cholesterol in the Tfm mouse: An effect that is independent of the classic androgen receptor. *Circulation*, *116*(21), 2427–2434.
41. Mccrohon, J. A., Jessup, W., Handelsman, D. J., & Celermajer, D. S. (1999). Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation*, *99*(17), 2317–2322.
42. Ng, M. K. C., Quinn, C. M., Mccrohon, J. A., Nakhla, S., Jessup, W., Handelsman, D. J., Celermajer, D. S., & Death, A. K. (2003). Androgens up-regulate atherosclerosis-related genes in macrophages from males but not females: Molecular insights into gender differences in atherosclerosis. *Journal of the American College of Cardiology*, *42*(7), 1306–1313.
43. Dieudonne, M. N., Pecquery, R., Leneveu, M. C., & Giudicelli, Y. (2000). Opposite effects of androgens and estrogens on adipogenesis in rat preadipocytes: Evidence for sex and site-related specificities and possible involvement of insulin-like growth factor 1 receptor and peroxisome proliferator-activated receptorγ 2. *Endocrinology*, *141*(2), 649–656.
44. Lacasa, D., Agli, B., Moynard, D., & Giudicelli, Y. (1995). Evidence for a regional-specific control of rat preadipocyte proliferation and differentiation by the androgenic status. *Endocrine*, *3*, 789–793.
45. Singh, R., Artaza, J. N., Taylor, W. E., Gonzalez-Cadavid, N. F., & Bhasin, S. (2003). Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology*, *144*(11), 5081–5088.
46. O'reilly, M. W., House, P. J., & Tomlinson, J. W. (2014). Understanding androgen action in adipose tissue. *The Journal of Steroid Biochemistry and Molecular Biology*, *143*, 277–284.
47. Kelly, D. M., Akhtar, S., Sellers, D. J., Muraleedharan, V., Channer, K. S., & Jones, T. H. (2016). Testosterone differentially regulates targets of lipid and glucose metabolism in liver, muscle and adipose tissues of the testicular feminised mouse. *Endocrine*, *54*, 504–515.
48. Xu, W., Morford, J., & Mauvais-Jarvis, F. (2019). Emerging role of testosterone in pancreatic β cell function and insulin secretion. *Journal of Endocrinology*, *240*(3), R97–R105.
49. Xu, W., Schiffer, L., Qadir, M. M. F., Zhang, Y., Hawley, J., Mota De Sa, P., Keevil, B. G., Wu, H., Arlt, W., & Mauvais-Jarvis, F. (2020). Intracrine testosterone activation in human pancreatic β-cells stimulates insulin secretion. *Diabetes*, *69*(11), 2392–2399.
50. Mitsuhashi, K., Senmaru, T., Fukuda, T., Yamazaki, M., Shinomiya, K., Ueno, M., Kinoshita, S., Kitawaki, J., Katsuyama, M., Tsujikawa, M., Obayashi, H., Nakamura, N., & Fukui, M. (2016). Testosterone stimulates glucose uptake and GLUT4 translocation through LKB1/AMPK signaling in 3T3-L1 adipocytes. *Endocrine*, *51*, 174–184.
51. Dandona, P., Dhindsa, S., Ghanim, H., & Saad, F. (2021). Mechanisms underlying the metabolic actions of testosterone in humans: A narrative review. *Diabetes, Obesity and Metabolism*, *23*(1), 18–28.
52. Jayasena, C. N., de Silva, N. L., O'reilly, M. W., Mackenzie, F., Marrington, R., Jones, H., Livingston, M., Downie, P., Hackett, G., Ramachandran, S., Tomlinson, J., David, J., Boot, C., Patel, M., Tarling, J., Wu, F., & Quinton, R. (2023). Standardising the biochemical confirmation of adult male hypogonadism; a joint position statement by the Society for Endocrinology and Association of Clinical Biochemistry and Laboratory Medicine. *Annals of Clinical Biochemistry*, *60*(4), 223–227.
53. Wu, F. C., Tajar, A., Pye, S. R., Silman, A. J., Finn, J. D., O'Neill, T. W., Bartfai, G., Casanueva, F., Forti, G., Giwercman, A., Huhtaniemi, I. T., Kula, K., Punab, M., Boonen, S., Vanderschueren, D., & European Male Aging Study Group. (2008). Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: The European Male Aging Study. *The Journal of Clinical Endocrinology & Metabolism*, *93*(7), 2737–2745.
54. Dhindsa, S., Miller, M. G., Mcwhirter, C. L., Mager, D. E., Ghanim, H., Chaudhuri, A., & Dandona, P. (2010). Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care*, *33*(6), 1186–1192.
55. Huhtaniemi, I. T., & Wu, F. C. (2022). Ageing male (part I): Pathophysiology and diagnosis of functional hypogonadism. *Best Practice & Research Clinical Endocrinology & Metabolism*, *36*(4), 101622.
56. Gianatti, E. J., & Grossmann, M. (2020). Testosterone deficiency in men with type 2 diabetes: Pathophysiology and treatment. *Diabetic Medicine*, *37*(2), 174–186.
57. Pitteloud, N., Mootha, V. K., Dwyer, A. A., Hardin, M., Lee, H., Eriksson, K.-F., Tripathy, D., Yialamas, M., Groop, L., Elahi, D., & Hayes, F. J. (2005). Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care*, *28*(7), 1636–1642.
58. Haffner, S. M., Shaten, J., Stem, M. P., Smith, G. D., & Kuller, L. (1996). Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. *American Journal of Epidemiology*, *143*(9), 889–897.
59. Brand, J. S., Rovers, M. M., Yeap, B. B., Schneider, H. J., Tuomainen, T.-P., Haring, R., Corona, G., Onat, A., Maggio, M., Bouchard, C., Tong, P. C. Y., Chen, R. Y. T., Akishita, M., Gietema, J. A., Gannagé-Yared, M.-H., Undén, A.-L., Hautanen, A., Goncharov, N. P., Kumanov, P., … van der Schouw, Y. T. (2014). Testosterone, sex hormone-binding globulin

and the metabolic syndrome in men: An individual participant data meta-analysis of observational studies. *PLoS ONE*, *9*(7), e100409.
60. Ding, E. L., Song, Y., Malik, V. S., & Liu, S. (2006). Sex differences of endogenous sex hormones and risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA*, *295*(11), 1288–1299.
61. Zhang, N., Zhang, H., Zhang, X., Zhang, B., Wang, F., Wang, C., Zhao, M., Yu, C., Gao, L., Zhao, J., & Guan, Q. (2014). The relationship between endogenous testosterone and lipid profile in middle-aged and elderly Chinese men. *European Journal of Endocrinology*, *170*(4), 487–494.
62. Jiann, B.-P., Hsieh, J.-T., Liu, S.-P., Hsu, S. H.-J., & Wu, H.-C. (2011). Associations of endogenous testosterone and lipid profiles in middle-aged to older Taiwanese men. *International Journal of Impotence Research*, *23*(2), 62–69.
63. Sun, K., Wang, C., Lao, G., Lin, D., Huang, C., Li, N., Li, L., Li, F., Xiao, H., & Yan, L. (2020). Lipid accumulation product and late-onset hypogonadism in middle-aged and elderly men: Results from a cross-sectional study in China. *BMJ Open*, *10*(2), e033991.
64. Khaw, K.-T., & Barrett-Connor, E. (1988). Blood pressure and endogenous testosterone in men: An inverse relationship. *Journal of Hypertension*, *6*(4), 328–332.
65. Fogari, R., Preti, P., Zoppi, A., Fogari, E., Rinaldi, A., Corradi, L., & Mugellini, A. (2005). Serum testosterone levels and arterial blood pressure in the elderly. *Hypertension Research*, *28*(8), 625–630.
66. Torkler, S., Wallaschofski, H., Baumeister, S. E., Völzke, H., Dörr, M., Felix, S., Rettig, R., Nauck, M., & Haring, R. (2011). Inverse association between total testosterone concentrations, incident hypertension and blood pressure. *The Aging Male*, *14*(3), 176–182.
67. Chasland, L. C., Green, D. J., Schlaich, M. P., Maiorana, A. J., Cooke, B. R., Cox, K. L., Naylor, L. H., & Yeap, B. B. (2021). Effects of testosterone treatment, with and without exercise training, on ambulatory blood pressure in middle-aged and older men. *Clinical Endocrinology*, *95*(1), 176–186.
68. Svartberg, J., Von Muhlen, D., Schirmer, H., Barrett-Connor, E., Sundfjord, J., & Jorde, R. (2004). Association of endogenous testosterone with blood pressure and left ventricular mass in men. The Tromso Study. *European Journal of Endocrinology*, *150*(1), 65–71.
69. Pastuszak, A. W., Kohn, T. P., Estis, J., & Lipshultz, L. I. (2017). Low plasma testosterone is associated with elevated cardiovascular disease biomarkers. *The Journal of Sexual Medicine*, *14*(9), 1095–1103.
70. Kupelian, V., Chiu, G. R., Araujo, A. B., Williams, R. E., Clark, R. V., & Mckinlay, J. B. (2010). Association of sex hormones and C-reactive protein levels in men. *Clinical Endocrinology*, *72*(4), 527–533.
71. Bojesen, A., Kristensen, K., Birkebaek, N. H., Fedder, J., Mosekilde, L., Bennett, P., Laurberg, P., Frystyk, J., Flyvbjerg, A., Christiansen, J. S., & Gravholt, C. H. (2006). The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care*, *29*(7), 1591–1598.
72. Pasquali, D., Arcopinto, M., Renzullo, A., Rotondi, M., Accardo, G., Salzano, A., Esposito, D., Saldamarco, L., Isidori, A. M., Marra, A. M., Ruvolo, A., Napoli, R., Bossone, E., Lenzi, A., Baliga, R. R., Saccà, L., & Cittadini, A. (2013). Cardiovascular abnormalities in Klinefelter syndrome. *International Journal of Cardiology*, *168*(2), 754–759.
73. Salzano, A., Arcopinto, M., Marra, A. M., Bobbio, E., Esposito, D., Accardo, G., Giallauria, F., Bossone, E., Vigorito, C., Lenzi, A., Pasquali, D., Isidori, A. M., & Cittadini, A. (2016). Klinefelter syndrome, cardiovascular system, and thromboembolic disease: Review of literature and clinical perspectives. *European Journal of Endocrinology*, *175*(1), R27–R40.
74. Sonmez, A., Haymana, C., Bolu, E., Aydogdu, A., Tapan, S., Serdar, M., Altun, B., Barcin, C., Taslipinar, A., Meric, C., Uckaya, G., & Kutlu, M. (2011). Metabolic syndrome and the effect of testosterone treatment in young men with congenital hypogonadotropic hypogonadism. *European Journal of Endocrinology*, *164*(5), 759–764.
75. Demirci, I., Haymana, C., Candemir, B., Meric, C., Yuksel, B., Eser, M., Akın, O., Akın, S., Ersoz Gulcelik, N., & Sonmez, A. (2021). Triglyceride-glucose index levels in patients with congenital hypogonadotropic hypogonadism and the relationship with endothelial dysfunction and insulin resistance. *Endokrynologia Polska*, *72*(3), 232–237.
76. Oppenheim, D. S. (1989). Elevated serum lipids in hypogonadal men with and without hyperprolactinemia. *Annals of Internal Medicine*, *111*(4), 288–292.
77. Smith, M. R., Lee, H., & Nathan, D. M. (2006). Insulin sensitivity during combined androgen blockade for prostate cancer. *The Journal of Clinical Endocrinology & Metabolism*, *91*(4), 1305–1308.
78. Keating, N. L., O'malley, A. J., & Smith, M. R. (2006). Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *Journal of Clinical Oncology*, *24*(27), 4448–4456.
79. Keating, N. L., Liu, P.-H., O'malley, A. J., Freedland, S. J., & Smith, M. R. (2014). Androgen-deprivation therapy and diabetes control among diabetic men with prostate cancer. *European Urology*, *65*(4), 816–824.
80. Hamilton, E. J., Gianatti, E., Strauss, B. J., Wentworth, J., Lim-Joon, D., Bolton, D., Zajac, J. D., & Grossmann, M. (2011). Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. *Clinical Endocrinology*, *74*(3), 377–383.
81. Braga-Basaria, M., Muller, D. C., Carducci, M. A., Dobs, A. S., & Basaria, S. (2006). Lipoprotein profile in men with prostate cancer undergoing androgen deprivation therapy. *International Journal of Impotence Research*, *18*(5), 494–498.
82. Yannucci, J., Manola, J., Garnick, M. B., Bhat, G., & Bubley, G. J. (2006). The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. *The Journal of Urology*, *176*(2), 520–525.
83. Smith, J., Bennett, S., Evans, L. M., Kynaston, H. G., Parmar, M., Mason, M. D., Cockcroft, J. R., Scanlon, M. F., & Davies, J. S. (2001). The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *The Journal of Clinical Endocrinology & Metabolism*, *86*(9), 4261–4267.
84. Dockery, F., Bulpitt, C. J., Agarwal, S., Donaldson, M., & Rajkumar, C. (2003). Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. *Clinical Science*, *104*(2), 195–201.
85. Hu, J.-R., Duncan, M. S., Morgans, A. K., Brown, J. D., Meijers, W. C., Freiberg, M. S., Salem, J.-E., Beckman, J. A., & Moslehi, J. J. (2020). Cardiovascular effects of androgen deprivation therapy in prostate cancer: Contemporary meta-analyses. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *40*(3), e55–e64.
86. Corona, G., Rastrelli, G., Di Pasquale, G., Sforza, A., Mannucci, E., & Maggi, M. (2018). Endogenous testosterone levels and cardiovascular risk: Meta-analysis of observational studies. *The Journal of Sexual Medicine*, *15*(9), 1260–1271.
87. Mäkinen, J., Järvisalo, M. J., Pöllänen, P., Perheentupa, A., Irjala, K., Koskenvuo, M., Mäkinen, J., Huhtaniemi, I., & Raitakari, O. T. (2005). Increased carotid atherosclerosis in andropausal middle-aged men. *Journal of the American College of Cardiology*, *45*(10), 1603–1608.
88. Svartberg, J., von Mühlen, D., Mathiesen, E., Joakimsen, O., Bønaa, K. H., & Stensland-Bugge, E. (2006). Low testosterone levels are associated with carotid atherosclerosis in men. *Journal of Internal Medicine*, *259*(6), 576–582.
89. Muller, M., van den Beld, A. W., Bots, M. L., Grobbee, D. E., Lamberts, S. W. J., & van der Schouw, Y. T. (2004). Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation*, *109*(17), 2074–2079.
90. Pecori Giraldi, F., Toja, P. M., Filippini, B., Michailidis, J., Scacchi, M., Stramba Badiale, M., & Cavagnini, F. (2010). Increased prevalence of prolonged QT interval in males with primary or secondary hypogonadism: A pilot study. *International Journal of Andrology*, *33*(1), e132–e138.

91. Salem, J.-E., Waintraub, X., Courtillot, C., Shaffer, C. M., Gandjbakhch, E., Maupain, C., Moslehi, J. J., Badilini, F., Haroche, J., Gougis, P., Fressart, V., Glazer, A. M., Hidden-Lucet, F., Touraine, P., Lebrun-Vignes, B., Roden, D. M., Bachelot, A., & Funck-Brentano, C. (2018). Hypogonadism as a reversible cause of torsades de pointes in men. *Circulation*, *138*(1), 110–113.
92. Salem, J.-E., Bretagne, M., Lebrun-Vignes, B., Waintraub, X., Gandjbakhch, E., Hidden-Lucet, F., Gougis, P., Bachelot, A., & Funck-Brentano, C. (2019). Clinical characterization of men with long QT syndrome and torsades de pointes associated with hypogonadism: A review and pharmacovigilance study. *Archives of Cardiovascular Diseases*, *112*(11), 699–712.
93. Collet, T.-H., Ewing, S. K., Ensrud, K. E., Laughlin, G. A., Hoffman, A. R., Varosy, P. D., Stefanick, M. L., Stone, K. L., Orwoll, E., & Bauer, D. C. (2020). Endogenous testosterone levels and the risk of incident cardiovascular events in elderly men: The MrOS prospective study. *Journal of the Endocrine Society*, *4*(5), bvaa038.
94. Yeap, B. B., Marriott, R. J., Antonio, L., Chan, Y. X., Raj, S., Dwivedi, G., Reid, C. M., Anawalt, B. D., Bhasin, S., Dobs, A. S., Hankey, G. J., Matsumoto, A. M., Norman, P. E., O'Neill, T. W., Ohlsson, C., Orwoll, E. S., Vanderschueren, D., Wittert, G. A., Wu, F. C. W., & Murray, K. (2021). Serum testosterone is inversely and sex hormone-binding globulin is directly associated with all-cause mortality in men. *The Journal of Clinical Endocrinology & Metabolism*, *106*(2), e625–e637.
95. Adelborg, K., Rasmussen, T. B., Nørrelund, H., Layton, J. B., Sørensen, H. T., & Christiansen, C. F. (2019). Cardiovascular outcomes and all-cause mortality following measurement of endogenous testosterone levels. *The American Journal of Cardiology*, *123*(11), 1757–1764.
96. Chang, S., Christiansen, C. F., Bojesen, A., Juul, S., Münster, A.-M. B., & Gravholt, C. H. (2020). Klinefelter syndrome and testosterone treatment: A national cohort study on thrombosis risk. *Endocrine Connections*, *9*(1), 34–43.
97. Zöller, B., Ji, J., Sundquist, J., & Sundquist, K. (2016). High risk of venous thromboembolism in Klinefelter syndrome. *Journal of the American Heart Association*, *5*(5), e003567.
98. Indirli, R., Ferrante, E., Scalambrino, E., Profka, E., Clerici, M., Lettera, T., Serban, A. L., Vena, W., Pizzocaro, A., Bonomi, M., Cangiano, B., Carosi, G., Mazziotti, G., Persani, L., Lania, A., Arosio, M., Peyvandi, F., Mantovani, G., & Tripodi, A. (2021). Procoagulant imbalance in Klinefelter syndrome assessed by thrombin generation assay and whole-blood thromboelastometry. *Journal of Clinical Endocrinology and Metabolism*, *106*(4), e1660–e1672.
99. Gonzalez-Gil, A. M., Barnouin, Y., Celli, A., Viola, V., Villarreal, M. D., Duremdes Nava, M. L., Sciuk, A., Qualls, C., Armamento-Villareal, R., & Villareal, D. T. (2024). Metabolic effects of testosterone added to intensive lifestyle intervention in older men with obesity and hypogonadism. *The Journal of Clinical Endocrinology & Metabolism*, dgae249. https://doi.org/10.1210/clinem/dgae249
100. Jones, T. H., Arver, S., Behre, H. M., Buvat, J., Meuleman, E., Moncada, I., Morales, A. M., Volterrani, M., Yellowlees, A., Howell, J. D., & Channer, K. S. (2011). Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care*, *34*(4), 828–837.
101. Mohler, E. R., Ellenberg, S. S. III, Lewis, C. E., Wenger, N. K., Budoff, M. J., Lewis, M. R., Barrett-Connor, E., Swerdloff, R. S., Stephens-Shields, A., Bhasin, S., Cauley, J. A., Crandall, J. P., Cunningham, G. R., Ensrud, K. E., Gill, T. M., Matsumoto, A. M., Molitch, M. E., … Snyder, P. J. (2018). The effect of testosterone on cardiovascular biomarkers in the testosterone trials. *The Journal of Clinical Endocrinology & Metabolism*, *103*(2), 681–688.
102. Grossmann, M., Hoermann, R., Wittert, G., & Yeap, B. B. (2015). Effects of testosterone treatment on glucose metabolism and symptoms in men with type 2 diabetes and the metabolic syndrome: A systematic review and meta-analysis of randomized controlled clinical trials. *Clinical Endocrinology*, *83*(3), 344–351.
103. Bhasin, S., Lincoff, A. M., Nissen, S. E., Wannemuehler, K., McDonnell, M. E., Peters, A. L., Khan, N., Snabes, M. C., Li, X., Li, G., Buhr, K., Pencina, K. M., & Travison, T. G. (2024). Effect of testosterone on progression from prediabetes to diabetes in men with hypogonadism: A substudy of the TRAVERSE randomized clinical trial. *JAMA Internal Medicine*, *184*(4), 353–362.
104. Wittert, G., Bracken, K., Robledo, K. P., Grossmann, M., Yeap, B. B., Handelsman, D. J., Stuckey, B., Conway, A., Inder, W., McLachlan, R., Allan, C., Jesudason, D., Fui, M. N. T., Hague, W., Jenkins, A., Daniel, M., Gebski, V., & Keech, A. (2021). Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): A randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *The Lancet Diabetes & Endocrinology*, *9*(1), 32–45.
105. Heufelder, A. E., Saad, F., Bunck, M. C., & Gooren, L. (2009). Fifty-two—Week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *Journal of Andrology*, *30*(6), 726–733.
106. Dhindsa, S., Ghanim, H., Batra, M., Kuhadiya, N. D., Abuaysheh, S., Sandhu, S., Green, K., Makdissi, A., Hejna, J., Chaudhuri, A., Punyanitya, M., & Dandona, P. (2016). Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. *Diabetes Care*, *39*(1), 82–91.
107. Huang, G., Pencina, K. M., Li, Z., Basaria, S., Bhasin, S., Travison, T. G., Storer, T. W., Harman, S. M., & Tsitouras, P. (2018). Long-term testosterone administration on insulin sensitivity in older men with low or low-normal testosterone levels. *The Journal of Clinical Endocrinology & Metabolism*, *103*(4), 1678–1685.
108. Isidori, A. M., Giannetta, E., Greco, E. A., Gianfrilli, D., Bonifacio, V., Isidori, A., Lenzi, A., & Fabbri, A. (2005). Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: A meta-analysis. *Clinical Endocrinology*, *63*(3), 280–293.
109. Saad, F., Doros, G., Haider, K. S., & Haider, A. (2020). Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: Real-world data from a controlled registry study. *International Journal of Obesity*, *44*(6), 1264–1278.
110. Wang, C., Cunningham, G., Dobs, A., Iranmanesh, A., Matsumoto, A. M., Snyder, P. J., Weber, T., Berman, N., Hull, L., & Swerdloff, R. S. (2004). Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism*, *89*(5), 2085–2098.
111. Frederiksen, L., Højlund, K., Hougaard, D. M., Brixen, K., & Andersen, M. (2012). Testosterone therapy increased muscle mass and lipid oxidation in aging men. *Age*, *34*, 145–156.
112. Gianatti, E. J., Hoermann, R., Lam, Q., Dupuis, P., Zajac, J. D., & Grossmann, M. (2016). Effect of testosterone treatment on cardiac biomarkers in a randomized controlled trial of men with type 2 diabetes. *Clinical Endocrinology*, *84*(1), 55–62.
113. Groti, K., Žuran, I., Antonič, B., Foršnarič, L., & Pfeifer, M. (2018). The impact of testosterone replacement therapy on glycemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes. *The Aging Male*, *21*(3), 158–169.
114. Aversa, A., Bruzziches, R., Francomano, D., Rosano, G., Isidori, A. M., Lenzi, A., & Spera, G. (2010). Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 24-month, randomized, double-blind, placebo-controlled study. *The Journal of Sexual Medicine*, *7*(10), 3495–3503.

115. Swerdloff, R. S., Wang, C., White, W. B., Kaminetsky, J., Gittelman, M. C., Longstreth, J. A., Dudley, R. E., & Danoff, T. M. (2020). A new oral testosterone undecanoate formulation restores testosterone to normal concentrations in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism*, *105*(8), 2515–2531.
116. White, W. B., Bernstein, J. S., Rittmaster, R., & Dhingra, O. M. (2021). Effects of the oral testosterone undecanoate Kyzatrex™ on ambulatory blood pressure in hypogonadal men. *The Journal of Clinical Hypertension*, *23*(7), 1420–1430.
117. Coviello, A. D., Kaplan, B., Lakshman, K. M., Chen, T., Singh, A. B., & Bhasin, S. (2008). Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *The Journal of Clinical Endocrinology & Metabolism*, *93*(3), 914–919.
118. Snyder, P. J., Peachey, H., Berlin, J. A., Hannoush, P., Haddad, G., Dlewati, A., Santanna, J., Loh, L., Lenrow, D. A., Holmes, J. H., Kapoor, S. C., & Strom, B. L. (2000). Effects of testosterone replacement in hypogonadal men. *The Journal of Clinical Endocrinology & Metabolism*, *85*(8), 2670–2677.
119. Ponce, O. J., Spencer-Bonilla, G., Alvarez-Villalobos, N., Serrano, V., Singh-Ospina, N., Rodriguez-Gutierrez, R., Salcido-Montenegro, A., Benkhadra, R., Prokop, L. J., Bhasin, S., & Brito, J. P. (2018). The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials. *The Journal of Clinical Endocrinology & Metabolism*, *103*(5), 1745–1754.
120. Ehrhart, M. D., Guthrie, I. R., Qeadan, F., & Burge, M. R. (2018). Metabolic effects of androgen-associated body mass in Klinefelter syndrome. *Archives of Medicine (Oviedo)*, *10*(1), 8.
121. Høst, C., Bojesen, A., Erlandsen, M., Groth, K. A., Kristensen, K., Jurik, A. G., Birkebæk, N. H., & Gravholt, C. H. (2019). A placebo-controlled randomized study with testosterone in Klinefelter syndrome: Beneficial effects on body composition. *Endocrine Connections*, *8*(9), 1250–1261.
122. Chang, S., Just, J., Skakkebæk, A., Johannsen, E. B., Fedder, J., Gravholt, C. H., & Münster, A.-M. B. (2024). Testosterone replacement therapy in Klinefelter syndrome-follow-up study associating hemostasis and RNA expression. *Journal of Clinical Endocrinology and Metabolism*, *109*(4), 978–991.
123. Morgentaler, A., Miner, M. M., Caliber, M., Guay, A. T., Khera, M., & Traish, A. M. (2015). Testosterone therapy and cardiovascular risk: Advances and controversies. *Mayo Clinic Proceedings*, *90*(2), 224–251.
124. Baillargeon, J., Urban, R. J., Kuo, Y.-F., Ottenbacher, K. J., Raji, M. A., Du, F., Lin, Y.-L., & Goodwin, J. S. (2014). Risk of myocardial infarction in older men receiving testosterone therapy. *Annals of Pharmacotherapy*, *48*(9), 1138–1144.
125. Muraleedharan, V., Marsh, H., Kapoor, D., Channer, K. S., & Jones, T. H. (2013). Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *European Journal of Endocrinology*, *169*(6), 725–733.
126. Sharma, R., Oni, O. A., Gupta, K., Chen, G., Sharma, M., Dawn, B., Sharma, R., Parashara, D., Savin, V. J., Ambrose, J. A., & Barua, R. S. (2015). Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *European Heart Journal*, *36*(40), 2706–2715.
127. Snyder, P. J., Bhasin, S., Cunningham, G. R., Matsumoto, A. M., Stephens-Shields, A. J., Cauley, J. A., Gill, T. M., Barrett-Connor, E., Swerdloff, R. S., Wang, C., Ensrud, K. E., Lewis, C. E., Farrar, J. T., Cella, D., Rosen, R. C., Pahor, M., Crandall, J. P., Molitch, M. E., Cifelli, D., … Ellenberg, S. S. (2016). Effects of testosterone treatment in older men. *New England Journal of Medicine*, *374*(7), 611–624.
128. Budoff, M. J., Ellenberg, S. S., Lewis, C. E., Mohler, E. R., Wenger, N. K., Bhasin, S., Barrett-Connor, E., Swerdloff, R. S., Stephens-Shields, A., Cauley, J. A., Crandall, J. P., Cunningham, G. R., Ensrud, K. E., Gill, T. M., Matsumoto, A. M., Molitch, M. E., Nakanishi, R., Nezarat, N., Matsumoto, S., … Snyder, P. J. (2017). Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA*, *317*(7), 708–716.
129. Basaria, S., Harman, S. M., Travison, T. G., Hodis, H., Tsitouras, P., Budoff, M., Pencina, K. M., Vita, J., Dzekov, C., Mazer, N. A., Coviello, A. D., Knapp, P. E., Hally, K., Pinjic, E., Yan, M., Storer, T. W., & Bhasin, S. (2015). 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*, *314*(6), 570–581.
130. Mathur, A., Malkin, C., Saeed, B., Muthusamy, R., Jones, T. H., & Channer, K. (2009). Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *European Journal of Endocrinology*, *161*(3), 443–449.
131. Martinez, C., Suissa, S., Rietbrock, S., Katholing, A., Freedman, B., Cohen, A. T., & Handelsman, D. J. (2016). Testosterone treatment and risk of venous thromboembolism: Population based case-control study. *BMJ*, *355*, i5968.
132. Walker, R. F., Zakai, N. A., Maclehose, R. F., Cowan, L. T., Adam, T. J., Alonso, A., & Lutsey, P. L. (2020). Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. *JAMA Internal Medicine*, *180*(2), 190–197.
133. Ory, J., Nackeeran, S., Balaji, N. C., Hare, J. M., & Ramasamy, A. R. (2022). Secondary polycythemia in men receiving testosterone therapy increases risk of major adverse cardiovascular events and venous thromboembolism in the first year of therapy. *Journal of Urology*, *207*(6), 1295–1301.
134. Houghton, D. E., Alsawas, M., Barrioneuvo, P., Tello, M., Farah, W., Beuschel, B., Prokop, L. J., Layton, J. B., Murad, M. H., & Moll, S. (2018). Testosterone therapy and venous thromboembolism: A systematic review and meta-analysis. *Thrombosis Research*, *172*, 94–103.
135. Baillargeon, J., Urban, R. J., Morgentaler, A., Glueck, C. J., Baillargeon, G., Sharma, G., & Kuo, Y. F. (2015). Risk of venous thromboembolism in men receiving testosterone therapy. *Mayo Clinic Proceedings*, *90*, 1038–1045.
136. Ayele, H. T., Brunetti, V. C., Renoux, C., Tagalakis, V., & Filion, K. B. (2021). Testosterone replacement therapy and the risk of venous thromboembolism: A systematic review and meta-analysis of randomized controlled trials. *Thrombosis Research*, *199*, 123–131.
137. Corona, G., Rastrelli, G., Sparano, C., Carinci, V., Casella, G., Vignozzi, L., Sforza, A., & Maggi, M. (2024). Cardiovascular safety of testosterone replacement therapy in men: An updated systematic review and meta-analysis. *Expert Opinion on Drug Safety*, *23*(5), 565–579.
138. Sharma, R., Oni, O. A., Gupta, K., Sharma, M., Sharma, R., Singh, V., Parashara, D., Kamalakar, S., Dawn, B., Chen, G., Ambrose, J. A., & Barua, R. S. (2017). Normalization of testosterone levels after testosterone replacement therapy is associated with decreased incidence of atrial fibrillation. *Journal of the American Heart Association*, *6*(5), e004880.
139. Gagliano-Jucá, T., Pencina, K. M., Ganz, T., Travison, T. G., Kantoff, P. W., Nguyen, P. L., Taplin, M.-E., Kibel, A. S., Li, Z., Huang, G., Edwards, R. R., Nemeth, E., & Basaria, S. (2018). Mechanisms responsible for reduced erythropoiesis during androgen deprivation therapy in men with prostate cancer. *American Journal of Physiology-Endocrinology and Metabolism*, *315*(6), E1185–E1193.
140. Roy, C. N., Snyder, P. J., Stephens-Shields, A. J., Artz, A. S., Bhasin, S., Cohen, H. J., Farrar, J. T., Gill, T. M., Zeldow, B., Cella, D., Barrett-Connor, E., Cauley, J. A., Crandall, J. P., Cunningham, G. R., Ensrud, K. E., Lewis, C. E., Matsumoto, A. M., Molitch, M. E., Pahor, M., … Ellenberg, S. S. (2017). Association of testosterone levels with anemia in older men: A controlled clinical trial. *JAMA Internal Medicine*, *177*(4), 480–490.
141. Holmegard, H. N., Nordestgaard, B. G., Schnohr, P., Tybjærg-Hansen, A., & Benn, M. (2014). Endogenous sex hormones and risk of venous

thromboembolism in women and men. *Journal of Thrombosis and Haemostasis*, *12*(3), 297–305.

142. Roetker, N. S., MacLehose, R. F., Hoogeveen, R. C., Ballantyne, C. M., Basu, S., Cushman, M., & Folsom, A. R. (2018). Prospective study of endogenous hormones and incidence of venous thromboembolism: The atherosclerosis risk in communities study. *Thrombosis and Haemostasis*, *118*(11), 1940–1950.

How to cite this article: de Silva, N. L., Grant, B., Minhas, S., & Jayasena, C. N. (2024). Cardiovascular disease and testosterone therapy in male hypogonadism. *Ann NY Acad Sci.*, 1–12. https://doi.org/10.1111/nyas.15211