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INVITED EDITORIAL

Male Endocrinology

Why is understanding the relationship of testosterone to cardiovascular risk so important?

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Epidemiological studies hint at a beneficial influence of endogenous circulating testosterone (T), or its metabolite dihydrotestosterone (DHT), such that men with lower concentrations of T or DHT appear to have poorer health outcomes including frailty, diabetes, cardiovascular disease, and mortality.¹ Small interventional studies of T have shown favorable effects on surrogate outcome measures, but a large randomized controlled trial (RCT) with the prespecified outcome of cardiovascular events has not been performed and would be logistically demanding.² In the absence of such a definitive RCT, there is a controversy about the cardiovascular risks of T-therapy fuelled by contradictory findings from retrospective analyses of insurance databases of men prescribed T.^{3–5} The US Testosterone Trials (T-Trials) are the largest published RCTs of T-therapy in older men with symptoms or signs of hypogonadism and circulating T <9.54 nmol l⁻¹ at baseline.⁶ The T-Trials showed a modest benefit of T-therapy over a 12-month period on sexual function, a significant benefit in bone density and for anemia and neutral effect on cognition.^{7–9} The T-Trials cardiovascular sub-study was designed to determine the effects of T in these older men, and there was a statistically significant difference in the

increase in noncalcified plaque volume in the T-treated group compared to placebo, but it is difficult to interpret these results due to differences in baseline coronary plaque burden (>50% difference) between the treatment and placebo arms of the subset involved.¹⁰ Therefore, there continues to be ongoing uncertainty over the effect of T-therapy on the cardiovascular system in men.

Resolution of the uncertainty of the effects of T-therapy on the male cardiovascular system is important from two perspectives. First, men who are androgen deficient due to diseases of the hypothalamus, pituitary, and testes should be considered for T-replacement therapy.¹¹ In these men who have hypogonadism due to pathology of the gonadal axis, it is essential to inform and advise them of potential benefits and possible risks of treatment.¹² Second, there has been a marked increase in T prescribing worldwide over the past decades, despite the prevalence of pathological hypogonadism remaining relatively stable.^{13,14} In men who do not have hypothalamic, pituitary, or testicular disease, who are typically older with other medical comorbidities and circulating T that would be regarded as low in younger men, the question arises as to the justification for T treatment and whether potential harms might outweigh anticipated benefits.¹⁵ Understanding the extent and the limitations of the existing evidence base would help health practitioners counsel men receiving T treatment for medical indications, may discourage its misuse in men where a medical indication is not clear, and will provide a foundation for future research.

In this Special Issue of the *Asian Journal of Andrology*, authors from around the world provide reviews of the available evidence of the cardiovascular effects of T on men. These reviews cover epidemiological studies of T

and the incidence of cardiovascular events¹⁶ and mortality risk,¹⁷ RCTs representing mechanistic studies of T and the cardiovascular system,¹⁸ T RCTs reporting cardiovascular adverse events,¹⁹ and retrospective reviews of T prescription databases.²⁰ These are accompanied by commentaries on the implications for Andrology in the regional context²¹ and globally for studies of male hormonal contraception.²² Taken together, the content of this Special Issue addresses a pressing debate that affects the care we provide to men with androgen deficiency and future research to preserve health in the expanding population of older men in our communities.

REFERENCES

- 1 Yeap BB, Araujo AB, Wittert GA. Do low testosterone levels contribute to ill-health during male ageing? *Crit Rev Clin Lab Sci* 2012; 49: 168–82.
- 2 Onasanya O, Iyer G, Lucas E, Lin D, Singh S, *et al.* Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol* 2016; 4: 943–56.
- 3 Vigen R, O'Donnell CI, Baron AE, Grunwald GK, Maddox TM, *et al.* Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 2013; 310: 1829–36. Erratum published in *JAMA* 2014; 311: 967.
- 4 Sharma R, Oni OA, Gupta K, Chen G, Sharma M, *et al.* Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J* 2015; 36: 2706–15.
- 5 Cheetham TC, An JJ, Jacobsen SJ, Niu F, Sidney S, *et al.* Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. *JAMA Intern Med* 2017; 177: 491–9.
- 6 Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, *et al.* Effects of testosterone treatment in older men. *N Engl J Med* 2016; 374: 611–24.
- 7 Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, *et al.* Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA* 2017; 317: 717–27.
- 8 Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, Ellenberg SS, Cauley JA, *et al.* Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical

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- trial. *JAMA Intern Med* 2017; 177: 471–9.
- 9 Roy CN, Snyder PJ, Stephens-Shields AJ, Artz AS, Bhasin S, *et al.* Association of testosterone levels with anemia in older men: a controlled clinical trial. *JAMA Intern Med* 2017; 177: 480–90.
 - 10 Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, Wenger NK, *et al.* Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA* 2017; 317: 708–16.
 - 11 Yeap BB, Grossmann M, McLachlan RI, Handelsman DJ, Wittert GA, *et al.* Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. *Med J Aust* 2016; 205: 173–8.
 - 12 Yeap BB, Grossmann M, McLachlan RI, Handelsman DJ, Wittert GA, *et al.* Endocrine Society of Australia position statement on male hypogonadism (part 2): treatment and therapeutic considerations. *Med J Aust* 2016; 205: 228–31.
 - 13 Handelsman DJ. Global trends in testosterone prescribing, 2000–2011: expanding the spectrum of prescription drug misuse. *Med J Aust* 2013; 199: 548–51.
 - 14 Layton JB, Li D, Meier CR, Sharpless JL, Stumer T, *et al.* Testosterone lab testing and initiation in the United Kingdom and the United States 2000–2011. *J Clin Endocrinol Metab* 2014; 99: 835–42.
 - 15 Swerdloff R, Anawalt BD. Clinical decisions: testosterone-replacement therapy. *New Engl J Med* 2014; 371: 2032–4.
 - 16 Yeap BB. Testosterone and its metabolites: differential associations with cardiovascular and cerebrovascular events in men. *Asian J Androl* 2018; 20: 109–14.
 - 17 Meyer EJ, Wittert G. Endogenous testosterone and mortality risk. *Asian J Androl* 2018; 20: 115–9.
 - 18 Jones TH, Kelly DM. Randomized controlled trials – mechanistic studies of testosterone and the cardiovascular system. *Asian J Androl* 2018; 20: 120–30.
 - 19 Gagliano-Juca T, Basaria S. Trials of testosterone replacement reporting cardiovascular adverse events. *Asian J Androl* 2018; 20: 131–7.
 - 20 Shores MM. Testosterone treatment and cardiovascular events in analyses of prescription databases. *Asian J Androl* 2018; 20: 138–44.
 - 21 An Q, Gu YQ. Testosterone replacement therapy: dilemmas and challenges in China and Asia. *Asian J Androl* 2018; 20: 149–51.
 - 22 Zitzmann M. Would male hormonal contraceptives affect cardiovascular risk? *Asian J Androl* 2018; 20: 145–8.

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