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. 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. 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. 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. 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 anaemia and neutral effect on cognition. 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. 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. 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. Second, there has been a marked increase in T prescribing worldwide over the past decades, despite the prevalence of pathological hypogonadism remaining relatively stable. 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.

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 events and mortality risk, RCTs representing mechanistic studies of T and the cardiovascular system, T RCTs reporting cardiovascular adverse events, and retrospective reviews of T prescription databases. These are accompanied by commentaries on the implications for Andrology in the regional context and globally for studies of male hormonal contraception. 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.
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