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INVITED EDITORIAL

Male Endocrinology

# Conclusions about testosterone therapy and cardiovascular risk

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**In this issue of *Asian Journal of Andrology* (AJA), several experts have reviewed the latest data on the potential and known effects of endogenous and exogenous testosterone (T) on cardiovascular risk. In the review by Meyer and Wittert, low endogenous serum T appears to be associated with higher risk of cardiovascular disease and overall mortality in certain populations such as Klinefelter syndrome and older men, but not in men with congenital hypogonadotropic hypogonadism.[1] Whether this association is causal or whether low serum testosterone is a marker of other risk factors for cardiovascular disease such as obesity, diabetes mellitus, or other systemic disease is unknown. In Yeap's review of the relationship between circulating endogenous testosterone and its major metabolites, dihydrotestosterone, and estradiol, he raises the provocative hypotheses that there might be differential effects on cardiovascular and cerebrovascular risk related to endogenous testosterone and dihydrotestosterone concentrations.[2] Based on the same epidemiological studies, Yeap postulates that there might be a U-shaped curve for circulating endogenous androgen concentrations such that lower and higher concentrations might confer greater risk of cardiovascular events and all-cause mortality than midrange concentrations. Shores demonstrates in a carefully done review of studies of large prescription databases (including >200 000 men) that testosterone therapy is not associated with overall mortality, myocardial infarction, stroke, or deep venous thrombosis events.[3]**

These reviews of epidemiological data on the relationship between cardiovascular risk and endogenous or exogenous testosterone do not provide definitive answers to the controversy surrounding the risks and benefits of testosterone therapy with respect to myocardial infarction, stroke, venothrombotic disease, or mortality. Jones and Kelly review the data from randomized controlled studies of the effects of testosterone therapy on the underlying mechanisms of ischemic heart disease and heart failure.[4] They conclude that testosterone has favorable direct vasodilatory effects on coronary vasculature and peripheral system vascular resistance and positive effects on cardiac and skeletal muscle function that might also be favorable. Jones and Kelly also provide some data that testosterone might provide metabolic benefits including improved insulin sensitivity and favorable changes in body composition. However, Gagliano-Juca and Basaria present a more cautionary note in their review of randomized trials of testosterone therapy that reported cardiovascular adverse events.[4] As they note, some randomized controlled trials have reported increased cardiovascular events in older men with prevalent cardiovascular disease.[5] Although the United States Testosterone Trial, the largest placebo-controlled trial of testosterone therapy in older men to date, did not demonstrate increased cardiovascular events after one year of testosterone replacement therapy compared to placebo, there was an increased risk of progression of non-calcified coronary plaque.[6,7]

Because testosterone replacement therapy is commonly prescribed to men around the world, it is essential to continue to study the potential cardiovascular risks and benefits of testosterone administration. In addition, testosterone and other androgens are being developed as potential novel therapies. For example, Zitzmann reviews some of the data on the potential cardiovascular effects of male hormonal contraceptive regimens that are under development.[8] Finally, An and Gu remind us in their commentary that more studies on the safety of testosterone therapy must be done in Asia, the site of the largest population of men in the world.[9]

It is common to conclude reviews with a clarion call for more research, but it is particularly important to have carefully designed research on the effects of androgen therapy on men's health. Low serum testosterone concentrations are common in middle-aged and older men, and testosterone therapy is commonly prescribed to men with low serum testosterone concentrations and no defined pathology of the hypothalamic-pituitary-testicular axis. Yet, the evidence of safety and benefit for such practice is minimal. There are no large, long term (>1 year) randomized controlled studies of testosterone therapy that include cardiovascular outcomes, and there is no requirement for systematic post-marketing data collection of safety outcomes in men treated with testosterone.

However, data from such studies will not be available for many years, and clinicians must practice based on current scientific knowledge. Based on the reviews in this issue of AJA, it appears likely that testosterone replacement therapy does not cause marked increases in risk of cardiovascular events. On the other hand, clinicians must exercise

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prudence in the use of testosterone in men with prevalent atherosclerotic coronary and cerebrovascular disease. At a minimum, we clinicians should inform middle aged and older men and men with ischemic heart disease or a history of cerebrovascular events that there is a controversy about the cardiovascular risk of testosterone therapy, and we should discuss and weigh the potential benefits against the potential risks before initiating testosterone therapy in any man.

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