ANDROLOGY

Testosterone and cardiovascular risk—deciphering the statistics

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A recent retrospective study reporting increased risk of cardiovascular events and death with testosterone therapy has received extensive media attention. However, the authors' conclusions are highly questionable given the extensive data manipulation and serious methodological errors. Indeed, a rich body of literature strongly suggests that testosterone therapy offers cardiovascular benefits.

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The rapid increase in the use of testosterone therapy over the past decade has led to heightened scrutiny regarding the potential risks. Curiously, as concerns regarding an increased risk of prostate cancer have eased,[1,2] new concerns regarding the relationship between testosterone therapy and cardiovascular disease have surfaced. Although considerable evidence indicates that normal serum testosterone levels are associated with a reduced risk of mortality and cardiovascular disease compared with low serum testosterone levels,[3,4] two highly publicized reports[5,6]—one of which was published recently in *The Journal of the American Medical Association* (*JAMA*)[6]—have spawned concerns regarding testosterone therapy and cardiovascular risk. Here we analyse these two poorly understood studies and provide additional context.

> "...the reliability of a result decreases the further it is removed from the raw data"

In 2010, a 6-month placebo-controlled trial of testosterone therapy was terminated early owing to a high rate of adverse cardiovascular events among men who received testosterone gel versus placebo (23 events and five events, respectively).[5] Despite this concerning result, it is important to remember that the trial was not designed to investigate cardiovascular events. Rather, it was designed to investigate the impact of testosterone gel on muscle strength and functionality in men aged 65 years or older with limited mobility. Reported adverse events consisted of subjective symptoms reported by patients, medical notes from outside physicians, or findings observed by study investigators. A wide variety of minor adverse events were reported, many of uncertain clinical significance, such as palpitations or incidental pedal oedema, but only four major cardiac adverse events (one death of indeterminate cause, two myocardial infarctions, and one stroke) occurred over 6 months in 209 men with substantial comorbidities, including hypertension, hyperlipidaemia, diabetes, and obesity. Although all four events occurred in the testosterone group, one must be extremely cautious when drawing conclusions from such low event rates, particularly as a similarly designed study in the UK involving 274 frail men, also using testosterone gel versus placebo, reported very different findings, with just two major cardiovascular events, both occurring in the placebo group.[6] Given the very low number of serious events and the absence of any predetermined cardiovascular end points or specific cardiovascular investigations, it is difficult to conclude from the study by Basaria *et al.*[5] that testosterone therapy is associated with increased cardiovascular risk.

Now, a new study has reported that rates of death, myocardial infarction, and stroke are increased in men who receive testosterone therapy.[7] The *JAMA* study was a retrospective analysis of a large cohort of men who underwent coronary angiography in the Veterans Affairs hospital system and had a documented serum testosterone level of <300 ng/dl. According to the authors, the absolute rate of events was 19.9% in the group who did not receive testosterone therapy versus 25.7% in the testosterone therapy group at 3 years following angiography. However, this conclusion is inaccurate and misleading. Among the 1,223 men who received testosterone therapy, there were 67 deaths, 23 myocardial infarctions, and 33 strokes, amounting to an overall event rate of 10.1% (123 events in 1,223 men). By comparison, of the 7,486 men who did not receive testosterone therapy, there were 681 deaths, 420 myocardial infarctions, and 486 strokes, meaning an overall major event rate of 21.2% (1,587 events in 7,486 men)—roughly twice the rate of events for men on testosterone therapy.

The authors have since been obligated to revise their article, removing the term 'absolute risk', which falsely indicated that the raw data supported their conclusion, and replacing this term with 'Kaplan-Meier estimated cumulative percentages with events'. This wording more accurately reflects the highly statistical methodology, with adjustments made for over 50 variables, from standard items such as age and race to unusual items such as prior cardiac MRI. Upon extensive

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multivariate analysis, the estimated event rate was approximately 30% for the testosterone group, which is threefold greater than the actual event rate. Although sophisticated statistical analysis has a vital role in biomedical research, it should be understood that the reliability of a result decreases the further it is removed from the raw data. In this case, it is particularly concerning that an actual event rate that was twofold lower in the testosterone group was reported to be greater after statistical manipulation.

> “...a rich body of literature suggests that normal testosterone levels have an important role in maintaining cardiovascular health...”

Moreover, the study design created a remarkably messy data set. Unlike most studies that compare results from two or more distinct groups, all men in this study began in the no-testosterone group until some filled a prescription for testosterone, at which point they were assigned to the testosterone group. Thus, all men in the testosterone group also contributed data to the no-testosterone group. A myocardial infarction was attributed to the testosterone group if a man had filled his testosterone prescription that same day, but to the no-testosterone group if he hadn't yet filled it. Multiple statistical assumptions are required to create two groups under these conditions, with questionable reliability.

Finally, the study is fatally flawed by a serious methodological error. The authors excluded 1,132 men who received testosterone therapy after myocardial infarction or stroke. As these men had completed their contribution to the study once an event occurred, it was irrelevant whether they were subsequently treated with testosterone. All these events should have been attributed to the no-testosterone group, raising the rate of events for that group by 71%, which would almost certainly have resulted in a greater risk for the no-testosterone group compared with men who received testosterone.

Indeed, two prior retrospective analyses revealed reduced mortality among men with low testosterone levels who received testosterone therapy. Shores *et al.*[8] also investigated the use of testosterone therapy in men with testosterone levels of <250 ng/dl (or 8.7 nmol/l), who were also included within the Veterans Affairs hospital population. In that study, the rate of mortality in testosterone-treated men was 10.3%, compared with 20.7% in untreated men ($P<0.0001$). Muraleedharan *et al.*[9] assessed mortality in diabetic men and found that men with low serum testosterone levels (<300 ng/dl or 10.4 nmol/l) demonstrated a mortality rate of 17.2% compared with 9.0% for men with normal testosterone levels (>300 ng/dl; $P=0.003$). Among men with low testosterone who received testosterone therapy, mortality was 8.4% compared with 19.2% in men who did not receive testosterone therapy ($P=0.002$). Treated men with low testosterone thus demonstrated a reduced mortality comparable to men with normal testosterone concentrations.

Definitive assessment of the effects of testosterone therapy on risk of cardiovascular events and mortality will ultimately require a large prospective randomized trial. In the meantime, clinicians should be aware that a rich body of literature suggests that normal testosterone levels have an important role in maintaining cardiovascular health, including an association between higher serum testosterone concentrations and reduced mortality, benefits of testosterone therapy for men with angina and congestive heart failure, and improvements in cardiac risk factors such as diabetes, obesity, and the metabolic syndrome.[4,10] At present, there are no compelling data to show that testosterone therapy increases the risk of cardiovascular events or mortality.

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Competing interests
A.M. has acted as a consultant for AbbVie, Auxilium, and Merck & Co., has received honoraria from Auxilium, Bayer AG, and Merck & Co., and has received research support from Antares Pharma, Auxilium, and Eli Lilly and Company. R.K. declares no competing interests.

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SEXUAL DYSFUNCTION

First EAU priapism treatment guidelines published

Maarten Albersen and Trinity J. Bivalacqua

The EAU has issued the first clinical practice guidelines on priapism, which have been published in short form in *European Urology*. Put together by the EAU panel on male sexual dysfunction, these guidelines provide an accessible, structured guide for the diagnosis and treatment of this rare clinical disorder.

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The first clinical practice guidelines on the diagnosis and treatment of priapism—put together by the EAU panel on male sexual dysfunction—have recently been published.[1] The guidelines provide, for the first time, a view of how priapism is best diagnosed and