EDITORIAL

Testosterone and Male Aging
Faltering Hope for Rejuvenation

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Hopes for hormonal rejuvenation appear periodically throughout history—with the most prominent attempt occurring around the turn of the 20th century only to vanish in the 1930s following the discovery of testosterone, which discredited testis extracts and manipulations. In recent decades, there has been a renewed attempt for hormonal rejuvenation with testosterone in men.

Today, 8 decades since the first clinical use of testosterone,[1] the sole unequivocal indication for testosterone treatment is as replacement therapy for men with pathological hypogonadism (ie, organic disorders of the reproductive system).[2] Yet despite no proven new indications, global testosterone sales increased 100-fold over the last 3 decades, including increases of 40-fold in Canada and 10-fold in the United States from 2000-2011.[3] This was achieved by marketing strategies that circumvented the need for efficacy and safety testing of testosterone for male aging by stretching the definition of the term *hypogonadism* to encompass virtually any condition associated with low circulating testosterone levels. Promoted under the rubric "low T" (also referred to as andropause or late-onset hypogonadism), this process was facilitated by individual physicians and professional societies that minimized the fundamental distinction between pathological hypogonadism and functional states (including aging) associated with low circulating testosterone levels.[4]

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This issue of *JAMA* includes the findings from 2 studies that report outcomes from the Testosterone Trials (TTrials), a set of 7 integrated, placebo-controlled randomized clinical trials with overlapping outcomes that tested whether testosterone treatment could ameliorate various aspects of male aging.[5] These studies originated from an authoritative 2004 US Institute of Medicine (now National Academy of Medicine) review[6] that concluded the paucity of efficacy evidence for testosterone treatment to ameliorate male aging precluded justifying a large-scale, prospective study comparable in scope with the Women's Health Initiative for estrogen therapy in menopause.[7] Responding to the mandate of that review, the National Institutes of Health funded the multicenter TTrials to test the short-term efficacy of testosterone on 7 clinical end points (sexual function, physical function, vitality, cognition, anemia, bone health, and cardiovascular health).[5]

The article reporting the primary TTrials outcomes[8] was based on 790 men (recruited from millions of invitation letters and resulting in >50 000 telephone interviews) who were 65 years or older with low circulating testosterone levels for no apparent reason other than age (ie, excluding pathological hypogonadism) who were randomized to receive daily testosterone transdermal gel or placebo gel for 12 months. Compared with placebo, testosterone produced a modest increase in sexual function (a 42% relative increase compared with baseline) early in the study before waning by the end of the study, but there was no objective benefit for physical function or vitality. The authors concluded that the benefits for sexual function were less robust than those associated with phosphodiesterase 5 inhibitors. An accompanying editorial suggested that the findings were insufficient clinically to justify initiating testosterone use.[9]

In a report in this issue of *JAMA*, Resnick and colleagues[10] present findings from the TTrials study examining cognitive function based on 493 men with a low testosterone level and age-associated memory impairment at baseline who completed a battery of cognitive function tests at baseline, 6 months, and 12 months, including 247 men in the testosterone group and 246 in the placebo group. The Cognitive Function Trial aimed to detect testosterone-induced enhancement in verbal or other cognitive functions in men with age-associated memory impairment. However, other than some practice (indistinguishable from placebo) effects, the authors found that testosterone produced no benefit in the primary outcome measured on the delayed paragraph recall test or in the secondary outcomes involving visual memory, spatial memory, or executive functions. An exploratory analysis extended to all men in the TTrials (ie, regardless of baseline memory) produced the same findings of no statistical or clinically significant differences between groups.

This is the largest well-controlled study of cognitive effects of testosterone in male aging to my knowledge, but the findings are not surprising because, among placebo-controlled studies, only a single small study ever indicated otherwise[11] and a longer (3 years) but smaller study also had negative findings.[12] These convincing, unequivocal findings affirm that testosterone treatment does not improve cognitive function in older men. Nevertheless, this does not preclude other possible psychological (eg, mood-elevating) effects of testosterone.

In another report in this issue of *JAMA*, Budoff and colleagues[13] present findings of the TTrials cardiovascular trial involving a subset of 138 men with low testosterone who completed computed tomographic (CT) evaluation of coronary artery plaque volume before and after 12 months of testosterone

treatment (73 men) or placebo treatment (65 men).[7] Participants in this cardiovascular substudy had high atherosclerotic risk because most were obese, hypertensive, and current or former smokers with a high prevalence of type 2 diabetes. Compared with placebo, testosterone treatment was associated with a significantly greater increase in noncalcified and total plaque volume, but not in calcified plaque. No major cardiovascular events occurred in either treatment group, although the study was not designed to detect such events.

Using CT to measure coronary artery plaque volume, a direct measure of coronary atherosclerosis, provides an important assessment of the safety of testosterone in older men. The coronary luminal narrowing observed over 12 months in this study is an unprecedented drug effect and appears ominous in signifying accelerated atherosclerosis, and is perhaps a harbinger of increased cardiac ischemic events. Early plaque growth may explain previous reports suggesting an association between testosterone use and cardiovascular harm in older men[14] as well as transient cardiovascular harms confined to the first 6 to 12 months after commencing testosterone treatment.[15,16] These findings may provide a possible mechanistic basis of an adolescent "head start" in atherogenesis[17] to explain the earlier onset and greater severity of atherosclerosis in men compared with age-matched women despite parallel age-specific risks of men and women.[18]

Nevertheless, as CT coronary plaque measurement has limited long-term evaluation, its prognostic significance and relationship with plaque remodeling, stabilization, and rupture—the proximate determinants of coronary ischemic events—remain to be better defined. Progressive plaque growth should produce a distinct risk of cardiovascular events, whereas the most recent meta-analysis shows only a nonsignificant increase in odds ratio for the association between testosterone use and cardiovascular risk.[15] However, existing studies have mostly overlooked early transient effects and remain inevitably underpowered[19] because decisive prospective studies with a primary safety end point are neither ethical nor feasible without well-established efficacy. Increase in plaque volume over 1 year is also at variance with placebo-controlled randomized clinical trials of ultrasonic carotid artery intimal media thickness showing no effects of testosterone treatment for 3 years in 308 men[20] or high-dose dihydrotestosterone treatment for 2 years in 114 men[21] despite greater exposure (in patient-years).

So where to from here? Further reports from 2 other substudies of the TTrials were recently published in *JAMA Internal Medicine*. One study demonstrated that testosterone treatment increased hemoglobin levels among men with anemia,[22] and speculated that low testosterone levels could be considered as a possible cause of unexplained mild anemia in older men, whereas the other study showed that testosterone treatment increased bone mineral density and estimated bone strength.[23] Even though these findings may represent useful and beneficial effects, they are not indications to initiate testosterone treatment.

Overall, the findings from subtrials of the TTrials do not materially change the unfavorable balance of safety and efficacy to initiate testosterone treatment for age-related hypogonadism. Rather, low testosterone levels due to obesity and other aging comorbidities are better addressed by lifestyle measures directed at those comorbidities. For physicians prescribing off-label testosterone, these cardiovascular findings make it incumbent to strengthen warnings of adverse cardiovascular risk. Moreover, similar warnings apply for androgen (anabolic steroid) abusers.[24] These findings also support the US Food and Drug Administration (FDA) decision in September 2015, based on sentinel safety signals, to tighten cardiovascular safety warnings about off-label testosterone prescribing.[25]

Testosterone overprescribing has been propelled not only by direct-to-consumer advertising, but also with the complicity of some professional organizations and physicians that have supported redefinition of the term *hypogonadism*[26] through permissive guidelines appearing to minimize the fundamental distinction between pathological hypogonadism and age-related, low circulating testosterone. Testosterone misuse will not simply disappear for lack of logic or evidence as none was needed to get it started—rejuvenation fantasies thrive on hope without needing facts—and educational efforts are essential. Professional societies should revise guidelines that provide tacit, uncritical endorsement, which is too readily used for boosting testosterone as a panacea for male aging. Testosterone and synthetic androgens have valuable medical applications but a key lesson is that such novel indications should be established by efficacy and safety studies and not preceded by wide-scale, off-label adoption.

It is unlikely that the limited efficacy shown by the TTrials meets the mandate of the 2004 Institute of Medicine report to warrant public funding for a powerful, long-term, large randomized clinical trial for evaluating testosterone. In September 2015 the FDA mandated that testosterone manufacturers undertake longer-term safety and efficacy trials for off-label use of testosterone for aging men.[25] If such a study proceeds, it could provide a valuable extension to the short-term safety of the TTrials supported by the manufacturers who have reaped large financial benefit from the boom in testosterone sales. In any case, with the results of the studies by Resnick et al[10] and by Budoff et al[13] in this issue of *JAMA*, the hopes for testosterone-led rejuvenation for older men are dimmed and disappointed if not yet finally dashed.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Handelsman has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. He reports grants from Lawley Pharmaceuticals and Besins Healthcare and serving as a medical expert in testosterone litigation.

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