*7th Annual Women's Heart & Vascular Symposium*

# The Rise and Fall of Estrogen Therapy:

## Is Testosterone for "Manopause" Next?

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Deaths caused by cardiovascular disease (CVD) have declined more than 40% since 2000. This reduction has been attributed to primary prevention efforts (hyperlipidemia therapy, blood pressure control, and aspirin use) and to improved treatment of patients with established disease.[1] Age is the chief risk factor for the development of CVD. Aging is associated with many physiologic changes, including reduced levels of estrogen in women and testosterone in men. The U.S. Food and Drug Administration (FDA) approved estrogen decades ago as short-term therapy for women in the perimenopausal period, and, later, testosterone was approved for a small, select group of men with premature gonadal failure. Prescriptions for both hormones were few until marketing campaigns established aging as a target for treatment. After the effects of estrogen-replacement therapy on postmenopausal women were studied and reported, the number of clinical prescriptions declined precipitously. This might herald a warning for men who pursue testosterone therapy to treat their age-related low testosterone levels (widely called "low T").[2]

### Hormone Replacement Therapy and Cardiovascular Risk in Postmenopausal Women

Cardiovascular (CV) risk increases 2 to 4 times in women after menopause, which might explain the typically delayed onset of CVD events in women. Before menopause, women are thought to be naturally protected from adverse cardiac events by their internal hormonal milieu. Menopause is associated with high low-density-lipoprotein cholesterol levels, blood pressure, insulin resistance, and body weight, which in turn elevate CVD risk. Practice patterns in the 1980s and 1990s encouraged women to use postmenopausal hormone-replacement therapy (HRT) to decrease the vasomotor symptoms of menopause, to maintain youthfulness, and to stay "feminine forever."[3]

*Epidemiologic Data.* Data from cohort studies further served to encourage women that HRT benefited their overall and CV health. In the Nurses' Health Study—a prospective epidemiologic study of 28,263 healthy postmenopausal women—HRT users experienced relative risk reductions of 40% in CVD incidence and 50% in all-cause death. However, after conducting a 20-year follow-up study, investigators reported a somewhat elevated stroke risk from HRT use in postmenopausal women.[4]

*Controlled Trials.* The first randomized controlled trial of HRT enrolled older women (average age, 67 yr) who had CVD (secondary prevention), and the results cast a long shadow over the efficacy of HRT in postmenopausal women. The Heart and Estrogen/Progestin Replacement Study (HERS) trial was stopped within 4 years because of excessive early deaths and myocardial infarctions in this high-risk older cohort.[5,6] A larger follow-up study, the Women's Health Initiative, was the first randomized controlled trial conducted to evaluate the effect of HRT on the primary prevention of a combination of health outcomes—breast and colon cancers, hip fracture, and venous thromboembolism (VTE), along with the CV risk factors of stroke, myocardial infarction, and CV death—in healthy postmenopausal women (average age, 63 yr). In women who used HRT, stroke risk rose by 41%, and that of coronary death and myocardial infarction rose by 29%. The risk of VTE increased twofold,[7] and the global health index rose by 15%, suggesting an overall hazard to women's health from HRT.

These study results highlighted discrepancies in the epidemiologic data, revealed the need for controlled treatment trials, and led to 70% fewer clinical prescriptions of

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HRT for postmenopausal women during the 10 years after the results were released. Hormone replacement remains the best therapy for vasomotor symptoms associated with menopause; however, its use—at the lowest possible dose and for the shortest feasible duration—is now recommended only in women at low risk of heart disease.

### Men and Declining Testosterone Levels

A similar situation seems to be evolving for men, who have natural, continuous reductions in androgen levels after the age of 30 years. Obesity is most influential in reducing testosterone levels: an increase in body mass index to >25 kg/m$^2$ lowers testosterone levels in equivalence to aging 15 years.[8] Symptoms of low energy, fatigue, diminished libido, and psychological depression have been attributed to male menopause (popularly called "manopause"). Marketers of testosterone products have instilled artificial alarm about these symptoms: the number of testosterone prescriptions written for U.S. men has tripled since 2001, and 3 million prescriptions were written in 2012 for the market leader, AndroGel® (AbbVie Inc.; N. Chicago, Ill). Cumulative sales of testosterone-boosting drugs, an estimated $2 billion in 2012,[9] were projected to rise to $5 billion by 2017.

Androgen deficiency in adult men is defined as symptomatic gonadal failure that leads to a loss of body hair, lower mineral density in bones, gynecomastia, smaller testes, less muscle strength, and higher fat mass. Diagnosis is made on the basis of below-normal bioavailable serum testosterone concentrations collected on separate mornings, combined with psychosomatic symptoms and metabolic factors.[10] However, evidence for exogenous androgen replacement is lacking: as early as 2003, the National Institute on Aging suggested that the rapidly increasing use of testosterone by men who sought to avoid the effects of aging had outpaced the scientific evidence about the hormone's benefits and risks.[11]

### Risks of Testosterone Replacement

Therapy with testosterone ultimately suppresses the pituitary-testicular axis, and withdrawal of therapy provokes even lower testosterone levels. In addition, inhibited spermatogenesis from this therapy leads to smaller testicular size. Testosterone therapy is contraindicated under the following circumstances: prostate or breast cancer, elevated prostate-specific antigen levels (especially in black men), a family history of prostate cancer, hematocrit >50% (because of higher thromboembolism risk), and untreated obstructive sleep apnea.[12]

### Cardiovascular Risk and Testosterone Therapy

More recent warnings have been issued concerning testosterone therapy and CV risk. In March 2015, the FDA warned of a higher risk of heart attack and stroke in men who use testosterone replacements.[13,14] A meta-analysis of 27 small randomized trials that included nearly 3,000 older men who had been treated with testosterone revealed 180 CV events—a 54% increase in testosterone-treated men versus those who had used a placebo.[15] In a larger retrospective cohort of 56,000 men, investigators[16] reported a 36% higher risk for heart attack in the 3 months after testosterone therapy had begun. Men younger than 65 years of age with a history of heart disease were at 3 times greater CV risk than were men without a history, and CV risk was 2.2-fold higher in men older than age 65 than in younger men.[15] These CV risks in men mirror those revealed in the clinical trials of HRT-treated women, suggesting increased coagulability in the presence of atherosclerotic plaque.

Other investigators[17] retrospectively studied 8,709 men with confirmed low testosterone levels who had undergone angiography; 80% of that cohort had substantial coronary artery disease. Those who subsequently underwent testosterone therapy had an absolute risk increase of 1.3% in composite all-cause death, myocardial infarction, and stroke (11.3% vs 10% with no therapy). The authors considered this risk to be small; however, its magnitude was increased by the prevalence of coronary artery disease in men, especially those older than 65 years.

To clarify the benefits and risks associated with testosterone replacement, a urology study group organized a 12-site series of double-blinded, randomized trials: the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial.[18] Patients applied testosterone gel or placebo gel for one year. Enrollees were all older than 65 years and had serum testosterone levels <275 ng/dL in 2 separate tests. Patients with a history of prostate cancer, high-risk cardiac factors, or severe psychological depression were excluded; only 1.6% of those screened for the trial were included. Patients given testosterone therapy experienced improved sexual activity, sexual desire, and erectile function, but showed no improvement in vitality or in results of a 6-minute walk test. Rates of adverse events were similar between the groups, although the risk of CV complications could not be evaluated, given the sample size and short duration of treatment.[18] The CV risks of testosterone therapy in men with established CVD and in those older than 65 years appear to be similar to the risks of HRT in women. However, despite the FDA's warning in 2015, testosterone use in aging men has continued to increase.[19]

It took decades of scientific investigation to discredit and curtail the standard clinical practice of prescribing HRT to postmenopausal women. Meanwhile, testosterone therapy for middle-aged and older men has been broadly accepted, absent definitive evidence of its beneficial effects—and, more important, with incomplete examination of its risks. The marketing of natural aging

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in men as "low T" has created a disease begging for a treatment. Men eager to avoid more difficult lifestyle modifications have seemingly embraced advertisers' promises of readily restorable youth.[19,20] Indiscriminate testosterone therapy for "low T" might indeed share a scientific final chapter with the widespread use of estrogen, and we think that these male consumers deserve more stringent evaluation of the risks associated with this supposed elixir of youth.

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