



**Ronald S. Swerdloff, MD**  
Chief, Division of Endocrinology  
LABioMedical Research Institute  
Harbor-UCLA Medical Center  
David Geffen School of Medicine at UCLA  
Torrance, California

Dear Colleague:

Recognition that the incidence of cardiovascular disease (CVD) is greater in men than in women has led to tremendous interest in gaining a clearer understanding of the association between testosterone levels and cardiovascular risk factors.

Recent attention focused on the need to clarify the relationship between testosterone and CVD was prompted by a report in *New England Journal of Medicine*. A clinical trial was designed to examine the effect of testosterone therapy on strength and physical function in men aged 65 years or older with mobility limitations. After a review by the data and safety monitoring board for the study, it was deemed necessary to suspend trial enrollment and testosterone therapy administration because of reports of cardiovascular adverse events.

Consequently, perennial questions were raised: What do we know about the relationship between testosterone and CVD? What are the implications of this research in the context of the clinical setting and in future research?

In this issue of *TU Times*, we evaluate the research exploring this association. The feature article examines the current epidemiologic studies of endogenous testosterone and CVD, meta-analyses, and testosterone therapy studies that further our understanding of this relationship.

In the interview, my distinguished colleague Adrian S. Dobs, MD, MHS, offers insight gained from her clinical expertise and research in this area and provides perspective on the implications of these studies.

We hope that you find the information in this newsletter useful in your clinical practice. To this end, please provide us with feedback by submitting the [evaluation and posttest](#).

Sincerely,

## Feature Article

### Ronald S. Swerdloff, MD

It has been demonstrated in cross-sectional and longitudinal studies that serum concentrations of total and free testosterone decline gradually with increasing age in men, beginning after the age of 30 years.<sup>1-3</sup> Age-related declines in serum testosterone levels vary among individuals and are affected by many factors, including adiposity, medications, and chronic disease.<sup>2,4,5</sup>

To date, epidemiologic studies have shown that low endogenous testosterone is an independent risk factor for all-cause and cardiovascular mortality.<sup>3,6,7</sup>

Shores et al evaluated whether low testosterone levels are a risk factor for mortality in male veterans.<sup>3</sup> After adjusting for age, medical morbidity, and other clinical covariates, low

testosterone levels were associated with increased mortality (hazard ratio, 1.88; 95% confidence interval [CI], 1.34-2.63;  $P < .001$ ), whereas equivocal testosterone levels were not significantly different from normal testosterone levels (hazard ratio, 1.38; 95% CI, 0.99-1.92;  $P = .06$ ). When men who died within the first year ( $n = 50$  [5.8%]) were excluded to minimize the effect of acute illness, low testosterone levels continued to be associated with elevated mortality. The authors concluded that increased mortality in male veterans was associated with low testosterone levels and recommended further prospective studies to examine the association between low testosterone levels and mortality.

The landmark prospective, population-based Rancho-Bernardo study investigated whether testosterone insufficiency in older

men is associated with increased risk of death.<sup>7</sup> During follow-up (mean, 11.8 y), 538 deaths occurred. Men with total testosterone levels in the lowest quartile (<241 ng/dL) were 44% more likely to die than those with higher levels of testosterone, independent of age, adiposity, and lifestyle. In cause-specific analyses, low testosterone predicted increased risk of CVD-related death (hazard ratio, 1.38; 95% CI, 1.02-1.85), independent of metabolic syndrome, diabetes, and prevalent CVD. Further adjustment for lipids, blood pressure, inflammatory markers, and estradiol (E<sub>2</sub>) did not attenuate this relationship. The authors concluded that, in older men, hypogonadism is associated with increased risk of death independent of multiple risk factors and several preexisting conditions.

Khaw et al investigated the relationship between endogenous testosterone levels and mortality due to all causes, CVD, and cancer in middle-aged and older men using data from the European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk), a large prospective, population-based study.<sup>6</sup> Analyzing data for 825 men who had died of any cause and comparing that with men who were alive, the investigators found that increasing quartiles of testosterone were protective, such that men in the highest quartile had a 30% lower risk of death compared with those in the lowest quartile. Even after excluding deaths during the first 2 years of follow-up and adjusting for cardiovascular risk factors and sex hormone-binding globulin level, this inverse relationship was maintained.

A number of cross-sectional studies have shown an association between low testosterone level and CVD but have not fully supported a causal relationship.<sup>8-10</sup> Akishita et al recently published in *Atherosclerosis* results of a study in middle-aged Japanese men (N=171; age range, 30-69 y; mean [SD], 48 [13] y) who had any coronary risk factors (eg, hypertension, diabetes, dyslipidemia, smoking, and obesity) without a history of CVD.<sup>10</sup> During the mean follow-up period of 77 (46) months, cardiovascular adverse events included: coronary artery disease, 11; myocardial infarction, 3; percutaneous coronary intervention, 4; medically treated angina pectoris, 3; and coronary artery bypass, 1. Men in the lowest tertile of testosterone (<14.2 nmol/L) had a nearly 4-fold higher risk of a cardiovascular adverse event compared with men in the higher testosterone tertiles. After adjustment, low plasma testosterone level was associated with cardiovascular adverse events independent of coronary risk factors and endothelial function.

Many individual testosterone trials have shown that the administration of exogenous testosterone improves muscle mass and strength, bone density, and body composition.<sup>11-14</sup> However, none of the studies were powered sufficiently (ie, of

sufficient size or duration) to adequately address potential risk, and cardiovascular risk was not a primary endpoint.<sup>13</sup>

To date, the safety and efficacy of testosterone therapy in improving muscle performance and physical function have not been thoroughly evaluated in older men with mobility limitations. A placebo-controlled, randomized study, the Testosterone in Older Men With Mobility Limitations (TOM) trial, was designed to ascertain the effects of testosterone therapy on lower extremity strength and physical function in a population of older men with hypogonadism and limitations in mobility.<sup>15</sup>

Men aged 65 years or older (mean age, 74 y) with a serum total testosterone level of 100 to 350 ng/dL or free testosterone level of <5 pg/mL were eligible, and participants were randomized to receive testosterone gel (100 mg 1% Testim®) or placebo for 6 months.<sup>16</sup> Based on serum testosterone evaluation, patients received 150 or 50 mg of testosterone. After dose adjustment, 16 men received 150 mg testosterone, 61 received 100 mg,

and 29 received 50 mg. Mean serum testosterone levels achieved were 574 (403) ng/dL versus 292 (160) ng/dL in the placebo group.

The primary efficacy endpoint was change from baseline in maximal voluntary muscle strength in a leg-press exercise; secondary endpoints included chest-press strength, 50-m walking speed, and stair-climbing speed and power.<sup>16</sup> The testosterone-treated group had significantly greater improvements, compared with placebo, in leg-press and chest-press strength and stair-climbing while carrying a load. In the treatment arm, hematocrit and hemoglobin levels increased

significantly, whereas high-density lipoprotein and low-density lipoprotein levels decreased. Provoking further concern, a significantly greater number of cardiovascular adverse events were reported in patients receiving testosterone therapy (23 receiving testosterone vs 5 receiving placebo).

Based on the significantly increased incidence of cardiovascular adverse events in the treatment arm of the TOM trial, a National Institute on Aging data and safety monitoring board recommended cessation of study enrollment and administration of testosterone therapy, leading to the subsequent early termination of the study in December 2009.<sup>16</sup>

The TOM trial investigators noted that caution is warranted in extrapolating from these findings to other doses and formulations of testosterone or to other populations, particularly men with hypogonadism without CVD or mobility limitations.<sup>16</sup> Cardiovascular adverse events were not projected primary or secondary outcomes and, therefore, were not formally evaluated. Furthermore, characteristics of this study population

**Caution is warranted in extrapolating findings of the TOM trial to other doses and formulations of testosterone or to other populations because...**<sup>16</sup>

- Cardiovascular adverse events were not projected primary or secondary outcomes and, therefore, were not formally evaluated
- Prematurely discontinued trials are susceptible to overestimated differences in treatment effect
- Characteristics of this study population deviate from most clinical or study populations administered testosterone therapy
- Variable clinical importance may be assigned to the cardiovascular adverse events, which lacked any pattern and were few in number, raising the prospect that the differences observed between the trial groups may be attributable solely to chance

deviate from most clinical or study populations administered testosterone therapy. Also, prematurely discontinued trials are susceptible to overestimated differences in treatment effect. Finally, variable clinical importance may be assigned to the cardiovascular adverse events, which lacked any pattern and were few in number, raising the prospect that the differences observed between the trial groups may be attributable solely to chance.

To date, meta-analyses have not clearly demonstrated the cardiovascular benefit or significant risk of testosterone therapy, suggesting that other factors, some age-related, may play an important role.<sup>17-20</sup>

In 2007, Haddad et al published a systematic review and meta-analysis of 30 randomized, placebo-controlled trials to assess the effect of testosterone therapy on cardiovascular adverse events and risk factors in men with varying degrees of hypogonadism.<sup>19</sup> Of the 1642 men included in the study, 808 received testosterone therapy. Confounders included limited patient enrollment and reporting of methodology that prevents biased results and brief study length (eg, <1 y). Furthermore, several trials failed to report data on measured outcomes. Overall, testosterone therapy did not effect significant changes in blood pressure, glycemia, and lipid fractions. The odds ratio between testosterone use and any cardiovascular adverse event pooled across trials that reported these events (N=6) was 1.82 (95% CI, 0.78-4.23). The authors concluded that available evidence weakly supports the position that testosterone therapy is not associated with important cardiovascular adverse events.

In a recent meta-analysis of 51 studies with follow-up duration ranging from 3 months to 3 years, testosterone therapy was associated with significant increases in hemoglobin and hematocrit and a small decrease in high-density lipoprotein, potentially considered adverse effects of treatment.<sup>20</sup> However, there were no significant effects on mortality, prostate, and cardiovascular outcomes. The authors resolved that these findings are of unknown clinical significance.

Preliminary findings suggest that testosterone therapy may provide symptomatic benefit for hypogonadal men with angina or chronic heart failure (CHF).<sup>21-23</sup> Caminiti et al investigated the effect of long-acting testosterone undecanoate therapy in men with moderately severe CHF.<sup>21</sup> This randomized, placebo-controlled trial demonstrated positive effects on maximal exercise capacity, ventilatory efficiency, muscle strength, insulin resistance, and baroreflex sensitivity (BRS) in older patients (median age, 70 y) with CHF who received treatment, suggesting that long-acting testosterone therapy improves exercise capacity, muscle strength, glucose metabolism, and BRS. Additional preliminary studies support the assertion that testosterone therapy is safe and well-tolerated and may impart the beneficial effects of improving physical capacity and symptoms and reducing morbidity in patients with CHF.<sup>24,25</sup>

Large-scale randomized trials are needed to thoroughly establish the effect of testosterone therapy on cardiovascular risk or all-cause mortality.<sup>19</sup> Future trials may confirm the safety and potential benefit of testosterone therapy in these patient populations. Though compelling, epidemiologic studies do not indicate a causal relationship between hypogonadism and CVD. To date, individual studies provide limited data to reinforce or contradict the findings of the TOM trial. Further, meta-analyses have shown no discernable effect of testosterone therapy on CVD risk and have been limited by inadequate methods of ascertaining adverse events, small study size, and few older participants.<sup>13,16</sup>

The Endocrine Society's recently updated clinical practice guideline highlights the challenges in evaluating and diagnosing hypogonadism in men, particularly older men, who present with vague signs and symptoms of hypogonadism.<sup>2</sup> At this time, it is still necessary to evaluate the net benefit of the restoration of eugonadal testosterone levels. Acknowledging that serum testosterone may be an indicator of comorbidities, the guideline does not support population screening but does reinforce the need to apply a standardized plan to carefully monitor patients receiving therapy.

## An Interview With Dr Dobs



**Adrian S. Dobs, MD, MHS**  
Professor of Medicine and Oncology  
Johns Hopkins University  
Baltimore, Maryland



**Age-related declines in serum testosterone levels begin in middle age, and these changes parallel physical and behavioral changes, such as decreased bone mass, sexual function, and muscle mass and strength and increased body fat, depressive symptoms, and fatigue. Are these changes caused by decreasing testosterone levels? Is there evidence that testosterone therapy improves these physical and behavioral changes associated with aging?**



Just because two events are happening simultaneously does not mean the factors interact, are caused by, or are even related to each other. Though the testosterone receptor is fairly ubiquitous, not all the signs and symptoms of aging are due to declines in the circulating hormone. For example, osteoarthritis incidence increases with age, but there is no proof that an age-related decline in testosterone level is directly related to this condition.

We need to think in terms of primary effect. Because testosterone is a strong regulator of muscle mass and bone mineral density, it might make sense that at least some of these end-organ declines are a result of low testosterone levels. Therefore, based on the evidence demonstrating that bone density is low in hypogonadal men, testosterone therapy may be indicated to achieve eugonadal serum concentrations and thereby improve bone mineral density.

Serum testosterone concentrations likely tell just one part of the story and perhaps need to be addressed in concert with other interventions. For example, men with type 2 diabetes may have low serum testosterone levels and may benefit from testosterone therapy, but certainly it is imperative to treat diabetes with exercise, medical nutrition therapy, and weight loss, along with a glucose-lowering medication as indicated.

**Q Please provide a brief overview of your understanding of the relationship between testosterone and CVD.**

**A** Eugonadal testosterone levels could have multiple effects on CVD risk, direct and indirect. Testosterone may have a direct effect on the myocardium or skeletal muscle to increase protein synthesis and body cell mass, thus affecting functional status. It may act on the endothelial surface and alter vascular reactivity or lipid composition. In addition, testosterone may lower CVD risk indirectly by reducing visceral adiposity and increasing lean body mass, factors involved in metabolic syndrome.

Based on epidemiologic studies, we know that a growing body of evidence suggests that low endogenous testosterone levels are associated with all-cause and cardiovascular mortality; however, we cannot assume that testosterone therapy will ameliorate the increased risk. Placebo-controlled, longitudinal, randomized trials of testosterone therapy in hypogonadal patients are necessary to fully evaluate the effect of testosterone therapy on CVD and cardiovascular and all-cause mortality.

Studies have associated long-term androgen deprivation therapy (ADT) with increased cardiovascular risk caused by profound hypogonadism. Recognizing the relationship between ADT and cardiovascular adverse events, the American Urological Association, the American Heart Association, and the American Cancer Society issued a science advisory recommending that patients receiving ADT be monitored for CVD.<sup>26</sup> To fully elucidate this relationship, large-scale, prospective studies are necessary.

**Q Where do we stand regarding the use of testosterone therapy in truly hypogonadal men: Is it positive, neutral, or detrimental?**

**A** I think there is little doubt that, in the classic cases of hypogonadism, when there is a clear etiology, testosterone therapy needs to be offered to the men for its benefit to sexual function, quality of life, bone density, and body composition. These men, particularly younger patients, will generally note an improvement in sexual function and quality of life within weeks of hormone therapy initiation. Of course, “truly hypogonadal” is difficult to define: The descriptor could relate to a serum level or an etiologic diagnosis. Thus, every man, regardless of age, needs to be evaluated individually. Given that diagnosing hypogonadism can be challenging—particularly because signs and symptoms are nonspecific and affected by age, comorbidities, and illness—in the clinical setting, we generally consider it to be characterized by a combination of signs and symptoms and serum testosterone levels below 300 ng/dL.

The new [Endocrine Society clinical practice guideline](#) is an excellent resource for clinicians interested in the evaluation and treatment of hypogonadism in adult men.

**Q Please summarize epidemiologic data and studies that deviate: Why are there aberrant studies, and how do we explain the differences in those data?**

**A** The type of clinical study performed can affect the findings. The epidemiologic studies are informative, because they were based on large sample sizes, but suffer from the facts that they typically assayed only one serum sample, the specimens were frozen for varying lengths of time, and the outcomes differed according to follow-up periods. The Rancho-Bernardo cohort, EPIC-Norfolk, and the VA (Veterans Affairs) population are excellent examples of population-based samples of men in whom low testosterone preceded illness or death. Most interestingly, this association persisted even after adjustment for obesity, type 2 diabetes, and other classic cardiovascular risk factors, which themselves may be modulated by low testosterone. This suggests that low testosterone may have a direct effect on CVD.

We are still at a point of uncertainty. To date, there is no clinical trial proving that testosterone therapy will reduce the risk of CVD mortality. In fact, it may require a study similar in scope to the Women’s Health Initiative. The expected results of such a study are unknown. It might show a detrimental effect of testosterone, perhaps via an increase in thromboembolic events. After all, testosterone will be aromatized to  $E_2$ . Conversely, it could have a very different result from that of the hormone therapy studies in women. Perhaps the direct effect of testosterone on its receptor or the improvement in body composition would result in a major beneficial effect.

Unfortunately, at this point, I can neither recommend universal screening of men nor recommend treating an asymptomatic man for purposes of preventing CVD. In fact, Basaria et al's study reinforces that we need to be extremely careful when considering treating an older, frail patient with multiple comorbidities, cautiously evaluating the appropriateness of treatment and monitoring.

**Q Please describe the study design of the TOM trial?**

**A** Basaria et al performed a randomized, placebo-controlled, parallel-armed clinical trial in which men 65 years of age or older with total testosterone levels between 100 and 350 ng/dL or free testosterone levels of <50 pg/mL were enrolled for 6 months. The primary outcome was leg-press strength and secondary outcomes were chest-press strength, timed walk, and stair-climbing speed and power. The design did not include evaluating cardiovascular adverse events, whether as a primary or secondary outcome.

**Q Based on this research, what parameters must we consider carefully, both in the clinical setting and in future research (eg, comorbid conditions, close evaluation of serum lipid and hematocrit levels)?**

**A** Many new research questions need to be examined. For example, men with comorbidities often have diminished serum testosterone. An example of this is men with CHF, cancer, or HIV (human immunodeficiency virus). Many of these men might benefit from testosterone treatment, and more research is needed to document testosterone's effect on quality of life and mobility. However, the concern generated by Basaria et al's recent publication is that men with multiple comorbidities may be exactly who is at the most risk. We need to identify the phenotype of the man at risk for complications of treatment. There may be factors, such as erythrocytosis, that put a man at particular risk for premature mortality.

**Q What do you do in the clinical setting to ensure that testosterone therapy is administered safely and monitored appropriately?**

**A** All men should have a thorough evaluation for etiology of hypogonadism before initiating any therapy. Safety should be evaluated with a complete blood count (CBC; particularly, hematocrit levels), prostate-specific antigen (PSA) levels, and a digital rectal examination (DRE) for prostate nodules. Men with significant cardiovascular conditions or a history of thromboembolic disease should be educated about the risk:benefit ratio. Patients should be monitored for signs of CVD to prompt secondary preventive measures as needed, including lipid- and glucose-lowering therapy or antihypertensive or antithrombotic agents. CBC, PSA levels, DRE results, and serum testosterone levels should be monitored during treatment to ensure adequate serum testosterone levels are achieved while supraphysiologic levels are avoided. These blood tests are typically done at baseline; at 3, 6, and 12 months; and then annually.

## References

1. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab.* 2002;87(2):589-598.
2. Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95(6):2536-2559.
3. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med.* 2006;166(15):1660-1665.
4. Wu FC, Tajar A, Pye SR, et al; European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab.* 2008;93(7):2737-2745.
5. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab.* 2006;91(11):4335-4343.
6. Khaw KT, Dowsett M, Folkard E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) prospective population study. *Circulation.* 2007;116(23):2694-2701.
7. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab.* 2008;93(1):68-75.
8. Jeppesen LL, Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS, Winther K. Decreased serum testosterone in men with acute ischemic stroke. *Arterioscler Thromb Vasc Biol.* 1996;16(6):749-754.
9. Feldman HA, Johannes CB, McKinlay JB, Longcope C. Low dehydroepiandrosterone sulfate and heart disease in middle-aged men: cross-sectional results from the Massachusetts Male Aging Study. *Ann Epidemiol.* 1998;8(4):217-228.
10. Akishita M, Hashimoto M, Ohike Y, et al. Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. *Atherosclerosis.* 2010;210(1):232-236.
11. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab.* 2010;95(2):639-650.
12. Page ST, Amory JK, Bowman ED, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab.* 2005;90(3):1502-1510.

13. Bremner WJ. Testosterone deficiency and replacement in older men. *N Engl J Med.* 2010;363(2):189-191.
14. Wang C, Swerdloff RS, Iranmanesh A, et al; Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. *J Clin Endocrinol Metab.* 2000;85(8):2839-2853.
15. LeBrasseur NK, Lajevardi N, Miciek R, Mazer N, Storer TW, Bhasin S. Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (the TOM trial): design and methods. *Contemp Clin Trials.* 2009;30(2):133-140.
16. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med.* 2010;363(2):109-122.
17. Buvat J, Maggi M, Gooren L, et al. Endocrine aspects of male sexual dysfunctions. *J Sex Med.* 2010;7(4 Pt 2):1627-1656.
18. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis [review]. *JAMA.* 2006;295(11):1288-1299.
19. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc.* 2007;82(1):29-39.
20. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2010;95(6):2560-2575.
21. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol.* 2009;54(10):919-927.
22. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation.* 2000;102(16):1906-1911.
23. Mathur A, Malkin C, Saeed B, Muthusamy R, Jones TH, Channer K. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. *Eur J Endocrinol.* 2009;161(3):443-449.
24. Pugh PJ, Jones RD, West JN, Jones TH, Channer KS. Testosterone treatment for men with chronic heart failure. *Heart.* 2004;90(4):446-447.
25. Malkin CJ, Channer KS, Jones TH. Testosterone and heart failure. *Curr Opin Endocrinol Diabetes Obes.* 2010;17(3):262-268.
26. Levine GN, D'Amico AV, Berger P, et al; American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, American Cancer Society, American Urological Association. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation.* 2010;121(6):833-840.