

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS  
AND AMERICAN COLLEGE OF ENDOCRINOLOGY  
POSITION STATEMENT ON THE ASSOCIATION OF  
TESTOSTERONE AND CARDIOVASCULAR RISK**

*Neil Goodman, MD, FACE<sup>1</sup>; Andre Guay, MD, FACE<sup>2,\*</sup>; Paresh Dandona, MD, PhD, FACE<sup>3</sup>;  
Sandeep Dhindsa, MD<sup>4</sup>; Charles Faiman, MD, MACE<sup>5</sup>; Glenn R. Cunningham, MD<sup>6</sup>;  
for the AACE Reproductive Endocrinology Scientific Committee*

*This document represents the official position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no randomized controlled trials or specific U.S. FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Position statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician.*

---

From the <sup>1</sup>University of Miami Miller School of Medicine, Miami, Florida, <sup>2</sup>Lahey Clinic Northshore, Peabody, Massachusetts and Tufts School of Medicine, Boston, Massachusetts, <sup>3</sup>Division of Endocrinology, State University of New York at Buffalo, Buffalo, New York, <sup>4</sup>Division of Endocrinology and Metabolism, Texas Tech University Health Sciences Center- Permian Basin Campus, Odessa, Texas, <sup>5</sup>Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, Ohio, and <sup>6</sup>Molecular & Cellular Biology, Baylor College of Medicine Diabetes & Endocrinology, Baylor St. Luke's Medical Center, Houston, Texas.

Address correspondence to American Association of Clinical Endocrinologists, 245 Riverside Ave., Suite 200, Jacksonville, FL 32202.  
E-mail: publications@aace.com. DOI:10.4158/EP14434.PS  
To purchase reprints of this article, please visit: [www.aace.com/reprints](http://www.aace.com/reprints).  
Copyright © 2015 AACE

**This material is protected by US copyright law. To purchase commercial reprints of this article, visit [www.aace.com/reprints](http://www.aace.com/reprints). For permission to reuse material, please access [www.copyright.com](http://www.copyright.com) or contact the Copyright Clearance Center, Inc. (CCC).**

## EXECUTIVE SUMMARY

Several recent publications have raised concern that testosterone replacement therapy (TRT) in men increases cardiovascular risk (1,2). This resulted in the U.S. Food and Drug Administration (FDA) holding a hearing and issuing the following statement on March 3, 2015:

*“Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests. Health care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy. Patients using testosterone should seek medical attention immediately if symptoms of a heart attack or stroke are present, such as chest pain, shortness of breath or trouble breathing, weakness in one part or one side of the body, or slurred speech. Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program.”*

It is the purpose of this document to state briefly the position of American Association of Clinical Endocrinologists on the association of TRT with cardiovascular risk. A detailed document presenting the scientific evidence for the association of low testosterone concentrations with and the effects of testosterone therapy upon cardiovascular risk follows this statement.

The **key points** described in the document are:

1. Epidemiologic studies strongly support the association of low testosterone concentrations and hypogonadism with cardiovascular events and all-cause mortality, especially in elderly men (3,4). However, low testosterone could be a marker of illness and not a causal factor.
2. TRT favorably changes many cardiovascular risk factors. It decreases fat mass, increases muscle mass, decreases insulin resistance and can reverse metabolic syndrome in some men (5).
3. Randomized controlled trials have not been powered to evaluate the effect of testosterone replacement in men on cardiovascular events or mortality. However, 2 retrospective reports have raised concern that testosterone therapy increases cardiovascular risk (1,2). As reviewed in the accompanying document and in the March 3, 2015 FDA report (available online at: <http://www.fda.gov/drugs/drugsafety/ucm436259.htm>), these studies have major flaws precluding meaningful conclusions to be drawn. A more recent retrospective cohort study using enrollment and claims data

for Medicare beneficiaries showed no effect of TRT on myocardial infarctions (6). However, this study suffered from the same limitations as those mentioned above.

4. Following a formal in-depth review, the FDA released a new warning and updated labeling on TRT to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. The Committee concurs in the FDA conclusion that the signal for cardiovascular risk is weak and that we need definitive studies.
5. The FDA also recommended that: “Testosterone is an FDA-approved replacement therapy only for men with disorders of the testicles, pituitary gland or brain that cause hypogonadism” and that “it should not be used to relieve symptoms in men who have low testosterone for no reasons other than aging.”

This recommendation is not clear. It is our opinion that any patient being considered for TRT must undergo a thorough diagnostic work-up (7-9). The decision to replace testosterone should be guided by the signs/symptoms and testosterone concentrations rather than the underlying cause. These men should be told that we do not have definitive studies demonstrating efficacy or risk for treating men with these conditions. The committee agrees that the risk/benefit ratio of TRT is not well established in aging-associated hypogonadism. Our recommendations follow:

- a) We recommend that symptomatic men who have unequivocally low total and/or free testosterone levels that are assayed on at least 2 samples drawn before 10 AM should be considered for TRT.
- b) We advise the practicing clinician to be extra cautious in the symptomatic elderly with demonstrably low testosterone levels prior to embarking on replacement therapy and to avoid treatment of the frail elderly until better outcome data are available.

**Conclusion:** Recent reports related testosterone treatment to increased cardiovascular events. However, there is no compelling evidence that testosterone therapy either increases or decreases cardiovascular risk. Large-scale prospective randomized controlled trials on testosterone therapy, focusing on cardiovascular benefits and risks, are clearly needed. As with therapeutics in general, common sense, experience, and an individualized approach are recommended. (**Endocr Pract.** 2015;21:1066-1073)

### Abbreviations:

**CI** = confidence interval; **FDA** = Food and Drug Administration; **LH** = luteinizing hormone; **MI** = myocardial infarction; **TRT** = testosterone replacement therapy

## INTRODUCTION

Several recent publications have raised concern that testosterone therapy in men increases cardiovascular risks. Media reports declared that testosterone therapy is dangerous, without addressing the scientific validity of these studies. It is the purpose of this position statement to assess critically the scientific evidence for the association of low testosterone concentrations and testosterone therapy with cardiovascular risk.

## HYPOGONADISM AND INCREASED CARDIOVASCULAR RISK

A large body of scientific evidence has substantiated that low levels of testosterone in men are associated with obesity, type 2 diabetes, and the metabolic syndrome, known risk factors for cardiovascular morbidity and mortality (10-13). Consistent with this association, prospective observational studies have shown that low testosterone concentrations are associated with an increase in the incidence of cardiovascular events (3,14,15). Low testosterone concentrations are also predictive of an increase in all-cause mortality, especially in men >70 years of age (4,16). A recent meta-analysis of 11 trials concluded that low total testosterone is likely associated with higher risk of all-cause and cardiovascular mortality. However, substantial between-study heterogeneity limited the ability to provide valid summary estimates (17). These authors caution that low testosterone levels could be markers of illness and not causal factors.

## DOES TREATMENT OF HYPOGONADISM WITH TESTOSTERONE REDUCE CARDIOVASCULAR RISK FACTORS?

An increasing body of evidence shows that testosterone replacement therapy (TRT) in men with hypogonadism can favorably modulate cardiovascular risk factors, including a decrease in insulin resistance, waist circumference, and fat mass (5,18). Several studies have also shown that men with the metabolic syndrome experience reversal of the features of the syndrome after testosterone replacement (19-21). The more dramatic effects of testosterone treatment on obesity and components of the metabolic syndrome have only been observed with injectable testosterone undecanoate. A randomized, placebo-controlled trial in men with hypogonadism and metabolic syndrome showed a significant decrease in carotid intima media thickness after 12 months of testosterone replacement (20). Testosterone therapy, however, may not improve glyce-mic control in men with type 2 diabetes (22). This finding prompted these authors not to recommend its use, at present, in men with type 2 diabetes and/or the metabolic

syndrome for improvement in cardiovascular risk factors or hyperglycemia.

## DOES TESTOSTERONE THERAPY MODIFY CARDIOVASCULAR RISK?

A meta-analysis with a database spanning 1981-2008 evaluated men with low or low-normal testosterone treated with testosterone for at least 90 days (23). The aim was to evaluate the adverse effects of testosterone therapy in men. Fifty-one testosterone therapy trials, ranging in duration from 3 months to 3 years, were included. There was no increase in the rates of death, myocardial infarction (MI), revascularization procedures, or cardiac arrhythmias as compared with the placebo-nonintervention groups. None of these trials, however, was powered to show a difference in these end points.

On the other hand, a number of recent studies have reported increased cardiovascular events and mortality in testosterone-treated men. In the Testosterone in Older Men with Mobility Limitations trial, 209 elderly frail men, mean age 74 years, with limitations in mobility and low total serum testosterone levels, were randomly assigned a placebo gel or testosterone gel, to be applied daily for 6 months (24). There was a high prevalence of comorbidities, including hypertension, diabetes, congestive heart failure, and renal insufficiency. A total of 23 subjects in the testosterone group, as compared with 5 in the placebo group, had cardiovascular-related adverse events, including 1 death in the treatment group. The study was halted because of these adverse effects. It should be noted, however, that the study was not designed to investigate cardiovascular events and no criteria for defining cardiovascular events were set out in advance. The majority of events would not be included as an "event" in any cardiovascular study due to questionable clinical significance, including peripheral edema, hypertension, and tachycardia, as well as nonspecific electrocardiogram changes. With a low number of serious events and the absence of any predetermined cardiovascular end points or specific cardiovascular investigations, this study does not demonstrate a clear increased cardiovascular disease risk. However, it raises concerns that testosterone treatment could increase cardiovascular events in men with pre-existing cardiovascular disease. Other studies in elderly populations also have not shown an increase in cardiac events after testosterone replacement (25-29). A prospective, randomized, double-blind multicenter trial of transdermal testosterone therapy for 1 year in 220 hypogonadal men with type 2 diabetes or metabolic syndrome reported that cardiovascular events were less common with testosterone therapy than with placebo (4.6% versus 10.7%), but this difference was not statistically significant ( $P = .095$ ) (18). A recent 6-month randomized, placebo-controlled trial of intramuscular testosterone therapy in 88

men with type 2 diabetes did not show a difference in rates of cardiovascular events amongst testosterone or placebo groups (30).

Five meta-analyses have evaluated the effect of testosterone therapy on cardiovascular events (23,31-34). Of these, only one reported increased cardiovascular events with testosterone therapy versus placebo (33). This study, by Xu et al (33), evaluated 27 randomized controlled trials, each at least 3 months in duration. The authors concluded that testosterone therapy increased the risk of "cardiovascular related events" by 54%. However, "events" again included clinically questionably anecdotal items, including peripheral edema and hypertension. On the contrary, a recent meta-analysis that included 75 randomized, placebo-controlled trials of testosterone treatment and evaluated the incidence of major adverse cardiovascular events did not find any association of testosterone therapy with actual cardiovascular events. (34).

It should be emphasized that none of these trials was designed to assess cardiovascular events. Randomized controlled trials designed to evaluate the effect of testosterone replacement in men on cardiovascular events or mortality have not yet been carried out. At this time, there is clearly a paucity of long-term studies to carry out a meta-analysis of the relationship of testosterone therapy with actual cardiovascular events.

Two retrospective studies have shown a benefit of testosterone treatment on cardiovascular events. An observational cohort study examined total mortality rates in 398 hypogonadal men (total testosterone <250 ng/dL) treated with testosterone therapy at 7 Veteran Affairs hospitals in the northwest United States (35). A total of 633 untreated hypogonadal men served as the comparison group. The mean age was 62 years, and the mean follow-up period was 40 months. Mortality rates in treated and untreated men were 10 and 21% ( $P < .001$ ), respectively. After multifactorial adjustment, testosterone-treated men had a 39% reduction in mortality risk ( $P = .008$ ). A retrospective cohort study in an endocrine clinic investigated the effect of TRT in 238 hypogonadal men with type 2 diabetes on all-cause mortality (36). Sixty-four men received testosterone (mean duration,  $42 \pm 21$  months). A total of 60 patients received TRT for 12 months or more and 51 had treatment for 2 years or more. A total of 174 men were not treated. The mortality rate in the untreated group was 20%, whereas the group treated with testosterone had a mortality rate of 9.4% ( $P = .002$ ). After multivariable adjustment, the hazard ratio for decreased survival in the untreated group was 2.3 (95% confidence interval [CI], 1.3 to 3.9;  $P = .004$ ). By comparison, the mortality rate in a cohort of 343 men with type 2 diabetes and normal testosterone concentrations was 9% (36). Although this study showed a reduction in cardiovascular risk after testosterone, this study was retrospective. While of interest, retrospective studies should serve as hypothesis generating for randomized clinical trials and

cannot serve as the basis for drawing firm conclusions regarding therapy.

Two recent publications have raised concern that testosterone therapy increases cardiovascular risk (1,2). These studies were retrospective observational analyses and have been criticized, based on detailed epidemiologic and statistical analyses (37,38). One study examined mortality, MI, and stroke rates in men with low testosterone levels (<300 ng/mL) who had undergone coronary angiography (1). The published critiques have focused on many flaws in this study, among which are:

1. Actual reported rate of events was 10.1% for the testosterone-treated group and 21.2% in controls, showing a reduced event rate in the treated group by more than 50% (38,39). The Kaplan-Meier calculation based on statistical adjustment for more than 50 variables converted this into an event rate of 19.9% in the untreated group and 25.7% in the testosterone-therapy group at 3 years, thus reversing the results of raw data. The risk differences were 1.3% (95% CI, -7.1 to 9.7%) at 1 year, 3.1% (95% CI, -4.9 to 11.0%) at 2 years, and 5.8% (95% CI, -1.4 to 13.1%) at 3 years. While these were not statistically significant, the reported overall Kaplan-Meier survival curve based on these estimates over 3 years suggested a hazard ratio of 1.29 (95% CI, 1.04 to 1.58;  $P = .02$ ).
2. Statistical adjustments were done for over 50 variables, but not were done for baseline testosterone concentrations. This is an important lapse, since the patients in the testosterone-therapy group had lower baseline testosterone concentrations than the untreated group (175.5 ng/dL versus 206.5 ng/dL;  $P < .001$ ) and since testosterone concentrations are inversely related to mortality in elderly men (3).
3. The mean duration of therapy was only 1 year. Men receiving testosterone therapy had limited follow-up. There was no information about whether subjects in the testosterone arm of the study actually took testosterone. Moreover, 40% did not have follow-up testosterone measurements during testosterone therapy. Of the 60% who had posttreatment testosterone concentration measured, the mean concentration increased from 175.5 ng/dL to only 332.2 ng/dL, evidently due to inadequate replacement (7,40,41). The fact that complex statistical adjustments reversed the conclusions of the raw data likely point to the importance of comorbidities in predicting cardiovascular events, rather than that of testosterone therapy.
4. This study has undergone 2 published corrections. The first was for misreporting their results as "absolute risk" when in fact the results were based on highly statistical, derived estimates and,



as noted above, were not supported by the raw data. A second correction was published 4 months after publication, when the authors admitted to a series of data errors. To date, 29 medical societies have called for retraction of this article based on the conclusion that the reported results represent “misinformation” (42).

The second study, by Finkle et al (2), examined 55,593 insurance claims with the information based on diagnosis codes, procedure codes, and prescription data. No data were available on indications for testosterone therapy prescription, race, laboratory findings, occupational, environmental, or lifestyle factors. They reported an increased rate of nonfatal MIs (from 0.35 to 0.48%; rate ratio, 1.36; 95% CI, 1.03 to 1.81) within the first 90 days of filling the testosterone prescription compared with the previous 12 months. However, since this was a retrospective study and not a prospective one, it is critical to understand that the population was preselected based on potentially requiring testosterone and thus being hypogonadal and having a relatively higher cardiovascular risk. There was no control group of untreated hypogonadal patients. Furthermore, there were no data on testosterone concentrations prior to or following testosterone treatment. Nor were any data available on the diagnosis, blood pressure, smoking, or body mass index. The “lead-in” period of 12 months prior to the prescription of testosterone does not represent an adequate control, especially in view of an increase of 36% within 90 days of testosterone use, which seems highly improbable in view of other studies with testosterone replacement.

In contrast, another retrospective claims-based analysis did not find an association of testosterone treatment with MI (6). This recently published retrospective cohort study used enrollment and claims data for a 5% national sample of Medicare beneficiaries. The authors compared 6,355 men aged 66 years or older who received intramuscular testosterone treatment to 19,065 controls. The primary outcome was MI based on discharge diagnosis ICD-9 code. After adjusting for demographic and clinical characteristics, testosterone therapy was not associated with an increased risk of MI (hazard ratio, 0.84; 95% CI, 0.69 to 1.02). Furthermore, testosterone therapy seemed to be protective in men at highest risk of MI (hazard ratio, 0.69; 95% CI, 0.53 to 0.92). However, being a retrospective claims-based analysis, this study also has the limitations mentioned above.

In view of these recent reports, on January 31, 2014, the U.S. Food and Drug Administration (FDA) announced that it was investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. On March 3, 2015, the FDA released a drug safety communication on this issue (43): “FDA is requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses

of these medications. FDA is also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone.” In addition, the FDA cautioned that “prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man’s symptoms seem related to low testosterone.” The FDA expressed concern that a large number of patients appear to be started on TRT without appropriate diagnostic work-up (44,45). However, the recommendation issued was too vague to be clinically meaningful. The Committee considered these points:

- a) Since there is no meaningful definition of aging, will restrictions apply to middle-aged individuals as well? It has been well-documented that the decline in testosterone concentrations is continuous across the life span of men beyond the age of 30 years (46).
- b) The decrease in testosterone concentrations is sometimes accompanied by increases in luteinizing hormone (LH) concentrations. The FDA statement implies that there is no pathophysiological basis for the lowering of testosterone concentrations with aging. In fact, studies have delineated that the accompanying LH hypersecretion with aging results from both decreased androgen-mediated feedback inhibition as well as decreased testicular sensitivity to LH (45,46).
- c) A large portion of the aging-related testosterone decline is attributed to comorbidities, such as obesity, type 2 diabetes, chronic kidney disease, and other chronic illnesses (10,47,48). However, these comorbidities are associated with lowering of testosterone concentrations at all ages, including adolescents and young men (49,50).
- d) How will “older” patients who are currently on long-term therapy and have experienced demonstrable improvement of quality of life be persuaded to discontinue therapy?

It is our opinion that any patient being considered for TRT undergo a thorough diagnostic work-up (7-9). The decision to replace testosterone therapy should be guided by the signs/symptoms and testosterone concentrations rather than the underlying cause. However, the committee agrees that the risk/benefit ratio of TRT is not well established, particularly in aging-associated hypogonadism. Our recommendations follow:

- a) We recommend that symptomatic men, who have unequivocally low total and/or free testosterone levels that are assayed on at least 2 samples drawn before 10 AM should be considered for TRT. The decision to replace testosterone therapy should be

guided by the signs/symptoms and testosterone concentrations rather than the underlying cause. These men should be told that we do not have definitive studies demonstrating efficacy or risk for treating men with these conditions.

- b) Since the risk/benefit ratio of TRT is not well established in aging-associated hypogonadism, we advise the practicing clinician to be extra cautious in the symptomatic elderly with demonstrably low testosterone levels prior to embarking on replacement therapy and to avoid treatment of the frail elderly altogether.

In general, the benefits of TRT are more consistent in men with very low testosterone concentrations than in those with concentrations just below the normal range. Health care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy. TRT should not be provided to men who have untreated or metastatic prostate cancer or breast cancer. Relative contra-indications include untreated severe sleep apnea, a hematocrit >50%, severe lower urinary tract symptoms with an International Prostate Symptom Score above 19, uncontrolled or poorly controlled heart failure, a MI or cerebrovascular accident within the past 6 months, a personal or family history of a procoagulant state, or a personal history of thromboembolism (7,51).

## CONCLUSION

Testosterone therapy can provide significant benefits for hypogonadal men. As recently concluded in an extensive review of literature, there is no compelling evidence that testosterone therapy increases cardiovascular risk (37). Indeed, the FDA concluded that the “signal of cardiovascular risk is weak.” We agree with their recommendation that large-scale prospective, randomized controlled trials on testosterone therapy, focusing on cardiovascular benefits and risks, are clearly needed. The Institute of Medicine also recommended that studies be done to determine if TRT is efficacious and safe in older men. The National Institute of Aging is funding a relatively large trial to address this issue, and results should be available later in 2015. While safety issues are being addressed, the study is not powered to determine if TRT will increase the risk of prostate cancer or cardiovascular events. If the ongoing studies determine that there is a benefit in treating symptomatic older men, a much larger trial will need to be funded and conducted to assess potential risk. In the interim, clinical decisions on TRT, based on appropriate clinical and laboratory assessment, will need to be individualized and discussed with each and every patient. It needs to be emphasized that low testosterone is often a marker for chronic disease, and the underlying cardiovascular disease risk factors should

be addressed. In patients with vascular disease and minor symptoms of hypogonadism, a more cautious approach towards testosterone therapy is prudent. Physicians should have a detailed discussion with such patients about the above-mentioned reports before embarking on testosterone replacement.

## ACKNOWLEDGMENT

The 2014-2015 AACE Reproductive Medicine Committee is comprised of the following AACE members: Paresh Dandona, MD, PhD, FACE, Chair; Sandeep Dhindsa, MD, Vice-Chair; Sandra L. Weber, MD, FACE, Board Liaison; Rhoda H. Cobin, MD, MACE; Glenn R. Cunningham, MD; Charles Faiman, MD, MACE; Walter Futterweit, MD, FACP, FACE; Jennifer S. Glueck, MD; Neil F. Goodman, MD, FACE; Andre Guay\*, MD, FACE; Rachel Pessah-Pollack, MD, FACE; Ronald Tamler, MD; and Kathleen Wyne, MD, PhD, FNLA, FACE. \*Deceased.

## DISCLOSURE

Dr. Cunningham has received research support from Abbvie; has served on advisory panels for Abbvie, Apricus, Clarus Therapeutics, Endo Pharma, and Lilly; and has served as a consultant for Clarus Therapeutics, Endo Pharma, Ferring, Purdue Pharma, and Repros Therapeutics. Dr. Dhindsa has served on a speaker panel for Abbvie. Dr. Dandona has received research support from GlaxoSmithKline, Novo Nordisk, Bristol Meyer Squibb, Takeda Pharmaceuticals, Allergan, Sanofi-Aventis, Conjuchem, Dannipon Pharmaceuticals, Proctor and Gamble Pharma, Mitsubishi, Quigley Pharma Inc, Solvay Pharmaceuticals, Transition Therapeutics, and ToleRx; has received honoraria from Eli Lilly, Novartis, GlaxoSmithKline, Merck, Novo Nordisk, Takeda, and Sanofi-Aventis; and has received grants from the National Institutes of Health, GlaxoSmithKline, the U.S. Centers for Disease Control, Bristol Meyers Squibb, Novartis Pharmaceuticals, Abbott Labs, Takeda Pharmaceuticals, Sankyo Pharmaceuticals North America, the Oishei Foundation, the Citrus Industry of Florida, Solvay Pharmaceuticals, the William G. McGowan Charitable Fund, and the Millard Fillmore Foundation. Dr. Goodman is on the AbbVie speaker bureau for AndroGel. The other authors have no multiplicity of interest to disclose.

## REFERENCES

1. **Vigen R, O'Donnell CI, Barón AE, et al.** Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA.* 2013;310:1829-1836.
2. **Finkle WD, Greenland S, Ridgeway GK, et al.** Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One.* 2014;9:e85805.

3. **Laughlin GA, Barrett-Connor E, Bergstrom J.** Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab.* 2008;93:68-75.
4. **Tivesten A, Vandenput L, Labrie F, et al.** Low serum testosterone and estradiol predict mortality in elderly men. *J Clin Endocrinol Metab.* 2009;94:2482-2488.
5. **Haider A, Yassin A, Doros G, Saad F.** Effects of long-term testosterone therapy on patients with "diabesity": results of observational studies of pooled analyses in obese hypogonadal men with type 2 diabetes. *Int J Endocrinol.* 2014;2014:683515.
6. **Baillargeon J, Urban RJ, Kuo YF, et al.** Risk of myocardial infarction in older men receiving testosterone therapy. *Ann Pharmacother.* 2014;48:1138-1144.
7. **Bhasin S, Cunningham GR, Hayes FJ, et al.** Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95:2536-2559.
8. **Wang C, Nieschlag E, Swerdloff RS, et al.** ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male.* 2009;12:5-12.
9. **Petack SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau LJ.** American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients--2002 update. *Endocr Pract.* 2002;8:440-456.
10. **Dandona P, Dhindsa S.** Update: hypogonadotropic hypogonadism in type 2 diabetes and obesity. *J Clin Endocrinol Metab.* 2011;96:2643-2651.
11. **Grossmann M.** Low testosterone in men with type 2 diabetes: significance and treatment. *J Clin Endocrinol Metab.* 2011;96:2341-2353.
12. **Laaksonen DE, Niskanen L, Punnonen K, et al.** Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care.* 2004;27:1036-1041.
13. **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. *JAMA.* 2006;295:1288-1299.
14. **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;116:2694-2701.
15. **Corona G, Rastrelli G, Monami M, et al.** Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol.* 2011;165:687-701.
16. **Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR.** Low serum testosterone and mortality in male veterans. *Arch Intern Med.* 2006;166:1660-1665.
17. **Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA.** Clinical review: endogenous testosterone and mortality in men: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2011;96:3007-3019.
18. **Jones TH, Arver S, Behre HM, et al.** Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care.* 2011;34:828-837.
19. **Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F.** Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. *Clin Endocrinol (Oxf).* 2010;73:602-612.
20. **Aversa A, Bruzziches R, Francomano D, et al.** Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med.* 2010;7:3495-3503.
21. **Francomano D, Lenzi A, Aversa A.** Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol.* 2014;2014:527470.
22. **Grossmann M, Hoermann R, Wittert G, Yeap BB.** Effects of testosterone treatment on glucose metabolism and symptoms in men with type 2 diabetes and the metabolic syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. *Clin Endocrinol (Oxf).* 2014 Dec 29 [Epub ahead of print].
23. **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;95:2560-2575.
24. **Basaria S, Coviello AD, Travison TG, et al.** Adverse events associated with testosterone administration. *N Engl J Med.* 2010;363:109-122.
25. **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;95:639-650.
26. **Nair KS, Rizza RA, O'Brien P, et al.** DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med.* 2006;355:1647-1659.
27. **Borst SE, Yarrow JF, Conover CF, et al.** Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol Metab.* 2014;306:E433-E442.
28. **Amory JK, Watts NB, Easley KA, et al.** Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab.* 2004;89:503-510.
29. **Snyder PJ, Peachey H, Hannoush P, et al.** Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab.* 1999;84:2647-2653.
30. **Gianatti EJ, Dupuis P, Hoermann R, et al.** Effect of testosterone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial. *Diabetes Care.* 2014;37:2098-2107.
31. **Calof OM, Singh AB, Lee ML, et al.** Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci.* 2005;60:1451-1457.
32. **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;82:29-39.
33. **Xu L, Freeman G, Cowling BJ, Schooling CM.** Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med.* 2013;11:108.
34. **Corona G, Maseroli E, Rastrelli G, et al.** Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. *Expert Opin Drug Saf.* 2014;13:1327-1351.

35. **Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM.** Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab.* 2012;97:2050-2058.
36. **Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH.** Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol.* 2013;169:725-733.
37. **Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM.** Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc.* 2015;90:224-251.
38. **Morgentaler A, Traish A, Kacker R.** Deaths and cardiovascular events in men receiving testosterone. *JAMA.* 2014;311:961-962.
39. **Traish AM, Guay AT, Morgentaler A.** Death by testosterone? We think not! *J Sex Med.* 2014;11:624-629.
40. **Dhindsa S, Batra M, Dandona P.** Deaths and cardiovascular events in men receiving testosterone. *JAMA.* 2014;311:964.
41. **Jones TH, Channer KS.** Deaths and cardiovascular events in men receiving testosterone. *JAMA.* 2014;311:962-963.
42. **Morgentaler A, Lunenfeld B.** Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation. *Aging Male.* 2014;17:63-65.
43. **U.S. Food and Drug Administration.** Testosterone products: drug safety communication - FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm436280.htm>. Accessed March 4, 2015.
44. **Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS.** Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med.* 2013;173:1465-1466.
45. **Garnick MB.** Testosterone replacement therapy faces FDA scrutiny. *JAMA.* 2015;313:563-564.
46. **Bhasin S, Pencina M, Jasuja GK, et al.** Reference ranges for testosterone in men generated using liquid chromatography tandem mass spectrometry in a community-based sample of healthy nonobese young men in the Framingham Heart Study and applied to three geographically distinct cohorts. *J Clin Endocrinol Metab.* 2011;96:2430-2439.
47. **Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB.** The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. *J Clin Endocrinol Metab.* 2007;92:549-555.
48. **Dhindsa S, Miller MG, McWhirter CL, et al.** Testosterone concentrations in diabetic and nondiabetic obese men. *Diabetes Care.* 2010;33:1186-1192.
49. **Chandel A, Dhindsa S, Topiwala S, Chaudhuri A, Dandona P.** Testosterone concentration in young patients with diabetes. *Diabetes Care.* 2008;31:2013-2017.
50. **Mogri M, Dhindsa S, Quattrin T, Ghanim H, Dandona P.** Testosterone concentrations in young pubertal and post-pubertal obese males. *Clin Endocrinol (Oxf).* 2013;78:593-599.
51. **U.S. Food and Drug Administration.** Testosterone products: FDA/CDER statement - risk of venous blood clots. Available at: <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm402054.htm>.