April 23, 2014  
Margaret A. Hamburg, M.D.  
Commissioner Food and Drug Administration  
Department of Health and Human Services  
WO 2200 10903  
New Hampshire Avenue  
Silver Spring, MD 20993-0002

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

Dear Dr. Hamburg,

It is the position of The Androgen Study Group that the Food and Drug Administration (FDA) should deny the petition by Public Citizen to add a black box warning to product labels for testosterone (T)-containing drugs regarding an increased risk of heart attacks and other cardiovascular (CV) dangers, or any other restrictive warnings on this topic.

That petition was prompted by the publication of two recently published retrospective studies alleging increased CV risks, one by Vigen et al.\(^1\), and the other by Finkle et al.\(^2\) Neither provides serious indication of increased CV risk, for reasons described below. A spokesperson for Public Citizen has already publicly acknowledged serious weaknesses in the study by Vigen et al.\(^3\) The second study by Finkle et al lacks basic clinical information (eg, serum testosterone concentrations, smoking history) and has no control group, rendering its observations impossible to interpret.

The Androgen Study Group is a multidisciplinary group with extensive clinical and research experience with T deficiency (hypogonadism) and its treatment, representing the disciplines of urology, endocrinology, family medicine, and basic science research. Our mission is to promote accurate reporting of results of testosterone research. Our members teach medical students,

\(^{1}\) R. Vigen et al., "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels," JAMA 310, no. 17 (2013).


residents, and fellows at the medical schools of Harvard, Tufts, Brown, Boston University, and Baylor College of Medicine; participate at more than two dozen CME events annually; and have contributed to national and international clinical guidelines and recommendations regarding T therapy. The Androgen Study Group receives no funding from any organization, and no member has any stock ownership or other direct financial stake in these companies. We are wholly dedicated to the science of testosterone in men, and to the wellbeing of our patients.

Public Citizen cites only four studies to support its petition (Vigen 4, Finkle 5, Xu 6, Bhasaria 7) and completely ignores an extensive body of research literature spanning more than thirty years, that demonstrates a strong relationship between CV risks and T deficiency, as well as improvements in CV risk factors and outcomes with T therapy.8 Not one of the studies cited in Public Citizen’s petition provides any serious indication of increased CV risk, including the two recent publications that prompted the FDA to announce its intention to review this topic. One of these studies 9 has already been corrected twice since its original publication, most recently with such major errors in reported data that 29 medical societies and more than 150 distinguished medical scholars from around the world have called for its retraction. The second study 10 lacks a control group and is therefore unable to provide any indication whether observed rates of CV events were higher, lower, or unchanged due to T therapy.

The Androgen Study Group finds baseless the newly voiced concerns that T therapy is associated with increased CV risk. On the contrary, the weight of evidence strongly suggests a beneficial effect of T therapy in men who are T-deficient. Testosterone deficiency causes considerable personal suffering and imposes a substantial public health burden on the U.S. health care system.

**Background**

Testosterone therapy has been in use for more than 70 years for the treatment of testosterone deficiency, historically called hypogonadism.11 For more than 30 years there has been a growing body of scientific research demonstrating that T deficiency is associated with increased risks of

---

4 Vigen et al., "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels."
5 Finkle et al., "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men."
8 See Appendix 1 and Appendix 2.
9 Vigen et al., "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels."
10 Finkle et al., "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men."
atherosclerosis, CV risk factors, and mortality, and that T therapy has beneficial effects on multiple risk factors and risk biomarkers related to these clinical conditions.

Notably, T deficiency has been projected to be involved in the development of approximately 1.3 million new cases of cardiovascular disease, 1.1 million new cases of diabetes, and over 600,000 osteoporosis-related fractures. Over a 20-year period, T deficiency has been estimated to be directly responsible for approximately $190–$525 billion in inflation-adjusted U.S. health care expenditures. In line with this, longitudinal models predict increased outpatient visits and costs from low baseline serum testosterone levels independent of socio-economic and lifestyle factors; even when controlling for age, men aged 20–79 years at baseline with low serum testosterone levels had 29% higher number of outpatient visits and 38% higher outpatient costs at 5-year follow up.

Many intervention studies have consistently demonstrated improvements in CV risk factors such as fat mass, obesity, waist circumference, blood pressure, and glycemic control. These important findings provide a reasonable biological mechanism to explain the frequent outcome of increased mortality among men with the lowest quartiles of serum T or frank testosterone deficiency. Importantly, T deficiency in older men is associated with increased risk of death over the following 20 yr, independent of multiple traditional risk factors and several preexisting health conditions.

---

12 Appendix 1: Investigations of serum testosterone concentrations and cardiovascular disease and mortality.
13 Appendix 2: Effects of testosterone therapy (TTh) on cardiovascular risk factors in placebo-controlled studies.
15 Ibid.
17 See appendix 2 "Beneficial effects of testosterone therapy on cardiovascular risk factors and obesity".
18 K. T. Khaw 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 116, no. 23 (2007).
20 B. B. Yeap et al., "In Older Men an Optimal Plasma Testosterone Is Associated with Reduced All-Cause Mortality and Higher Dihydrotestosterone with Reduced Ischemic Heart Disease Mortality, While Estradiol Levels Do Not Predict Mortality," ibid.99 (2014).
25 Laughlin, Barrett-Connor, and Bergstrom, "Low Serum Testosterone and Mortality in Older Men."
26 Haring et al., "Low Serum Testosterone Levels Are Associated with Increased Risk of Mortality in a Population-Based Cohort of Men Aged 20-79."
Small randomized placebo-controlled T trials have even shown reduction in carotid intima-medial thickness with T therapy 27, raising the possibility that normalizing serum T may actually cause reversal of atherosclerosis in critical vascular beds. Moreover, two studies published within the last 2 years demonstrated reduced mortality, by half, in T-deficient men who received T prescriptions compared with similar men who did not, one in a VA population 28 and the other in diabetic men.29

It was therefore astounding to those of us with experience in this field when study results published in JAMA November 2013 reported an increased risk of heart attack, stroke, and death in T-deficient men compared with untreated men.30 This study received widespread media attention, and created a new concern regarding CV risks with T prescriptions, with little attention paid to the substantial contradictory literature, nor the critical methodological flaws in that study (outlined below). A separate study published in PLoS One in January 2014, appeared to confirm these concerns regarding CV risks by reporting an association noted between T prescriptions and increased rate of non-fatal myocardial infarction.31 This latter study lacked the most basic level of information required to assess increased risk associated with testosterone therapy (see below). Nonetheless, responding to highly publicized concerns in the media regarding these two studies, the FDA announced on January 31, 2014 its intention to review cardiovascular risks of T therapy.32

Analysis

In contrast to many dozens of studies demonstrating beneficial CV effect of T therapy in humans, there appear to be only four articles that suggest increased CV risk, all cited by Public Citizen as if these four studies constituted the entirety of evidence regarding T and CV outcomes. Careful analysis reveals that none of these four studies provide any compelling evidence of increased risks. It is also important to note that the two recent articles that prompted concern are retrospective analyses of datasets obtained for other purposes. As the Agency well knows, these types of studies lack the fundamental feature of a good experiment, namely the ability to isolate the response to a single variable, such as risks related to a specific treatment. These studies are therefore susceptible to inherent bias and substantial errors, and it is widely accepted that results of such study should be regarded as hypothesis-generating, rather than conclusive. Experience has shown that results of this type are irreproducible in the majority of cases.33

27 Appendix 2: Effects of testosterone therapy (TTh) on cardiovascular risk factors in placebo-controlled studies.

28 M. M. Shores et al., "Testosterone Treatment and Mortality in Men with Low Testosterone Levels," J Clin Endocrinol Metab 97, no. 6 (2012).


30 Vigen et al., "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels."

31 Finkle et al., "Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men."


1. Vigen et al JAMA 2013 34

This was a retrospective analysis of men who had undergone coronary angiography within the VA healthcare system. The study reported that the overall rate of MI, stroke, and death in men with serum T <300ng/dl was higher in men who received a T prescription compared with untreated men. Although no statistically significant differences were noted at years 1, 2, or 3, the overall rate of events over the course of the study was reported to be significantly higher in T-treated men by 29%.

Strangely, the actual rate of adverse events was only half as great in the T group (123 events in 1223 men at risk=10.1%) as in the untreated group (1587 events in 7486 men= 21.2%). The authors failed to acknowledge this fact, and came to an opposite interpretation of the data based on complex statistics that included adjustment for more than 50 variables.

This article has already undergone two official corrections. The first, published January 15 2014, was for misreporting of primary results as “absolute risk,” suggesting results were based on raw data.35 In response to criticism following publication, the article was corrected to replace “absolute risk” with “Kaplan-Meier estimated cumulative percentages with events,” a term that more accurately reflects the highly statistical nature of the results.

On March 5, 2014, JAMA published a second correction.36 In response to a letter challenging the exclusion of 1132 men who had suffered adverse events in the non-T group, the authors revealed they had made a series of errors. The numbers of men in this excluded group was changed from 1132 to 128 men, a difference of greater than 1000 men. The value for a second group was found to be incorrect by more than 900 men. Most astonishingly, the all-male study group was found to include nearly 10% women.

In response to these revelations, 29 medical societies with expertise in testosterone therapy, combined with a remarkably distinguished group of more than 150 physician-scientists from 32 countries have petitioned JAMA to retract this article.37 The retraction letter, written by the Androgen Study Group and signed by these experts and medical societies, cites “gross data mismanagement and contamination” that rendered the study “no longer credible.” The letter further argues for retraction because of the harm done to the field by the promotion of this study’s misinformation. The letter, and its list of signers, is attached as an appendix.

The medical societies urging retraction are:

American Society for Men’s Health (ASMH)
Brazilian Society of Endocrinology and Metabolism
Canadian Men’s Sexual Health Council, an affiliate of the CUA

37 http://www.androgenstudygroup.org/initiatives/letter-to-jama-asking-for-retraction-of-misleading-article-on-testosterone-therapy
Canadian Society for the Study of Men’s Health (CSSAM)
European Society for the Study of the Aging Male (ESSAM)
European Society for Sexual Medicine (ESSM)
Indonesian Andrologist Association
International Society for Men’s Health (ISMH)
International Society for Sexual Medicine (ISSM)
International Society for the Study of the Aging Male (ISSAM)
Irish Association of Sexual Medicine
Italian Society of Andrology
Italian Society of Andrology and Sexual Medicine
Japan ASEAN Council for Men’s Health and Aging
Japanese Society for Men’s Health
Korean Society for Sexual Medicine and Andrology
Malaysian Men’s Health Initiative
Malaysian Society of Andrology and the Study of the Aging Male
Mens Health Initiative of British Columbia (Canada)
Mexican Association of Bone and Mineral Metabolism
Middle East Society for Sexual Medicine
Russian Society for Men’s Health
South Asian Society for Sexual Medicine
Sexual Medicine Society of North America
Sociedade Latinoamericana de Medicina Sexual (Latin American Society for Sexual Medicine)
The Society for Men’s Health, Singapore
Society for the Study of Androgen Deficiency

In short, the worldwide community of experts in the field of testosterone therapy has repudiated this study, called for its retraction, and finds the results “not credible.” The actual percentage of men exposed to testosterone therapy who experienced an adverse event over the course of the study was lower by half compared with untreated men. This result is consistent with the two published studies that investigated effect of T therapy in men with documented T deficiency on mortality. 38 39


The study by Finkle et al is a retrospective study of a health insurance database that reported rates of non-fatal myocardial infarction in up to 90 days following a testosterone prescription, and compared this to MI rates in the prior12 months. The authors reported the rate ratio of MI post-prescription to pre-prescription was 1.36, and the rate in men older than 65 years was 2.19. In comparison, no increase in MI rate was noted for men who received a prescription for a phosphodiesterase type 5 inhibitor (PDE5i).

38 Shores et al., “Testosterone Treatment and Mortality in Men with Low Testosterone Levels.”
39 Muraleedharan et al., “Testosterone Deficiency Is Associated with Increased Risk of Mortality and Testosterone Replacement Improves Survival in Men with Type 2 Diabetes.”
40 Finkle et al., “Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men.”
As an insurance database, available information was limited to diagnosis codes, procedure codes, and prescriptions. There was no information available regarding any standard CV risk factors, such as blood pressure, smoking history, or obesity, and no information for any blood test result, such as serum testosterone, or lipid profiles. The weakness of the dataset as an investigative tool for assessment of CV risk is underscored by the fact that the endpoint in the study, non-fatal MI, was determined solely by the use of an insurance diagnosis code, and was unverified. Although the authors claim that this diagnosis code correlates strongly with true MI rates, the single study they cite to support this claim used an algorithm specifically designed to increase accuracy by excluding individuals hospitalized for less than three days. No such algorithm was used in this study. A separate study reported an accuracy rate of only 88% for MI diagnosis codes when medical records were examined for verification that an MI occurred. This means that as many as 12% of MI’s in this study never occurred.

Methodologically, it is inappropriate to compare post-treatment rates of MI to pre-treatment rates, as these rates measure different things. Since this was not an experimental study, the 12 months prior to receiving a prescription should not be confused with a run-in period to determine the natural history of untreated T deficiency. Rather, it measures what physicians actually did, i.e., to whom they felt it was appropriate to treat. In comparison, MI rates following a prescription reflect “what happened.” As a ratio, it should be clear that any reluctance of physicians to prescribe T therapy within 12 months of an MI will produce a reduced MI rate pre-treatment, and will cause the ratio of post-treatment to pre-treatment to appear increased.

However, the greatest weakness of this study is the absence of a control group. In the absence of a control group it is impossible to determine whether the reported rates of MI following a T prescription were higher, lower, or unchanged compared to a group of similar men who did not receive a prescription. Moreover, it is critical to appreciate that the reported rates of MI before (3.48 per 1000 person-years) and after (4.75 per 1000 person-years) a T prescription were substantially lower than would be predicted based on the NIH risk calculator for similar-aged US men using favorable parameters (13 per 1000 person-year), specifically age 54y (same as mean age of study participants), non-smoker, total cholesterol 230 mg/dl, HDL 40 mg/dl, systolic BP 140 mm/Hg. Finally, the comparison with men who received a PDE5i prescription was inappropriate. These were two dissimilar groups treated with dissimilar medications for dissimilar indications. This is a classic case of apples and oranges that provides no useful information. It is impossible to conclude from this study that a testosterone prescription is associated with increased risk of MI.

3. Basaria et al, NEJM 2010

This was a prospective randomized trial designed to investigate whether testosterone gel provided greater muscular and functional benefits over placebo in an elderly, frail population of men. The study was terminated early due to an observation of increased adverse events.

---

44 Basaria et al., "Adverse Events Associated with Testosterone Administration."
categorized as “cardiovascular” in the testosterone arm. There were 23 of these events in the testosterone arm and 5 in the placebo arm.

However it is critical to understand that this study was not designed to investigate CV events, and none of the reported events were primary or secondary endpoints. A large majority of reported “events” were subjective or noted incidentally, and were of questionable clinical importance, such as palpitations, pedal edema, and premature ventricular contractions noted incidentally on electrocardiogram. None of these reported events were defined prior to study enrollment, and there was no attempt made to systematically determine rates of these events in both groups.

Although there were 5 major adverse cardiac events (1 death, 2 MI’s, one coronary revascularization, one stroke), all in the T group, one must be extremely cautious in drawing conclusions from rare events. In a similar study in frail elderly men performed in the UK, there were two major CV events (1 death, 1 MI), both occurring in the placebo group. As the authors themselves stated:

“The lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone.”

We concur. It is impossible to conclude from this study that T prescription confer an increased risk of CV events.

4. Xu et al, BMC 2013

This meta-analysis of CV events in 27 placebo-controlled T studies of 12 weeks duration or longer reported that CV events were greater in men who received T compared with placebo.

It should be noted that this is the only one of several prior meta-analyses and systematic reviews to suggest any increased risk with T therapy. As with all meta-analyses, the results are influenced greatly by the definitions of endpoints of interest, and the selection of studies. The authors specifically included only studies in which CV events were reported, meaning that studies without any CV events were excluded. This selection process exaggerates the apparent rate of events, and distorts absolute differences in event rates between groups. In addition, just two of the 27 studies contributed 35% of all CV events in the T arm. The disproportionate influence of these two studies on the outcome of the meta-analysis merits closer scrutiny. One is the study by Basaria et al (2010), discussed above, in which 18 of 23 events (incorrectly reported as 25 events by Xu et al) would not normally be included in reporting of CV events. The other is a 1986 Copenhagen study in which a non-approved oral formulation of micronized testosterone was administered at a remarkably high dose of 600 mg daily to men with cirrhosis of the liver,

---

46 Basaria et al., "Adverse Events Associated with Testosterone Administration."
47 Xu et al., "Testosterone Therapy and Cardiovascular Events among Men: A Systematic Review and Meta-Analysis of Placebo-Controlled Randomized Trials."
resulting in serum testosterone concentrations exceeding 4000 ng/dl (approximately 140 nmol/L) in a quarter of the testosterone group, and with levels reaching as high as 21,000 ng/dl (745 nmol/L), a value approximately 20 times the upper limit of the normal range. Since these oral forms of testosterone are known to cause liver toxicity via a first-pass effect, it should be no surprise that markedly supraphysiologic T doses in a hepatically compromised population would prove harmful. This study has no place in a meta-analysis that purports to assess CV risks related to clinically relevant use of testosterone.

Without the contributions of the Copenhagen study and the non-major cardiovascular events in the study by Basaria et al, the rates of adverse CV events in the testosterone and placebo groups are similar, with a slightly lower rate in the T group (78 events in 1599 men; 4.88% vs 60 events in 1174 men; 5.1%, respectively). It should be underscored that this is the only one of several prior meta-analyses and systematic reviews to demonstrate increased risk with T treatment.\textsuperscript{48} \textsuperscript{49} \textsuperscript{50} Notable findings in three large meta-analyses that specifically focused on identifying potential adverse effects of testosterone treatment, are as follows:

* The frequency of cardiovascular events, sleep apnea or death was not significantly different between the two groups.\textsuperscript{51}

* Currently available evidence weakly supports the inference that testosterone use in men is not associated with important cardiovascular effects.\textsuperscript{52}

* There was no significant effect on mortality, prostate, or cardiovascular outcomes.\textsuperscript{53}

**Conclusions and Summary**

Any objective assessment of the literature regarding testosterone and CV effects must recognize a broad, rich literature in which numerous studies demonstrate increased CV concerns with T deficiency, and improvement in a variety of CV risk factors and some CV outcomes with T therapy. New concerns regarding CV risks stem almost exclusively from two retrospective analyses of large databases, neither of which provides credible evidence of increased risk. Indeed, both studies more easily could be interpreted to show protective benefits of T therapy. The study by Vigen et al, if the data are to be trusted, revealed that the actual percentage of individuals who suffered an adverse event was lower by half among men who received T

\textsuperscript{49} A. M. Isidori et al., "Effects of Testosterone on Body Composition, Bone Metabolism and Serum Lipid Profile in Middle-Aged Men: A Meta-Analysis," *Clin Endocrinol (Oxf)* 63, no. 3 (2005).
compared with men who did not. That result is consistent with two prior retrospective studies that investigated mortality in T-deficient men.\textsuperscript{54} \textsuperscript{55}

And in the study by Finkle et al, observed MI rates following receipt of a T prescription were substantially lower than would be expected based on the NIH risk calculator for heart attacks.

In summary, we find no scientific basis for the suggestion that T therapy increases CV risk. In fact, as of this date, we are unaware of any compelling evidence that T therapy is associated with increased CV risk. On the contrary, the weight of evidence accumulated by researchers around the world over several decades clearly indicates that higher levels of testosterone are associated with amelioration of CV risk factors, and reduced risk of mortality.\textsuperscript{56} \textsuperscript{57} \textsuperscript{58}

Specifically, we have attached a series of tables that provide some perspective on the wealth of studies regarding T and CV issues. For example, we note there are six studies demonstrating an association between low T and incident coronary artery disease (CAD), 4 that show no relationship, yet none demonstrating any association with high T concentrations. For many other items, the relative numbers of studies in favor of low T as a predictor of CV disease, or T therapy as beneficial, is even more glaring. This includes studies regarding severity of CAD (4 studies demonstrating increased severity with low T, 0 for higher T); carotid intima-media thickness (associated with low T in 8, none with higher T); effect of T therapy vs placebo on obesity or fat mass (decrease with T therapy in >20, none showing increase with T therapy); effect of T therapy vs placebo on glycemic control (T therapy associated with improvement in 6 studies, none for worsening); and effect of T therapy on inflammatory markers associated with CAD (improvement in 8 studies, none demonstrating worsening).

Any objective assessment of the literature clearly reveals a strong relationship between higher serum T concentrations, endogenous or via T therapy, as beneficial for CV disease and CV risk factors. Public health may be harmed not only by inadequate appreciation of an actual risk, but also by the failure to offer beneficial treatment for a medical condition due to claims of false risk concerns. Based on the current state of evidence, placing restrictions on the appropriate use of T therapy for T-deficient men is likely to result in compromise of public health and a substantially increased future financial burden on the US health care system.\textsuperscript{59}

We have faith that the FDA will rigorously evaluate the quality of the scientific evidence regarding T and CV risk, and will dismiss studies that are poorly executed, and with substantial flaws in methodology and data collection that lead to unwarranted conclusions. We are confident the FDA will agree the evidence does not support any increased risk of CV risk, and will deny the petition to add a black box warning to T products. We hope this decision will be announced

\textsuperscript{54} M. M. Shores et al., "Testosterone Treatment and Mortality in Men with Low Testosterone Levels," ibid.97 (2012).
\textsuperscript{55} Muraleedharan et al., "Testosterone Deficiency Is Associated with Increased Risk of Mortality and Testosterone Replacement Improves Survival in Men with Type 2 Diabetes."
\textsuperscript{56} Appendix 1: Investigations of serum testosterone concentrations and cardiovascular disease and mortality.
\textsuperscript{57} Appendix 2: Effects of testosterone therapy (TTh) on cardiovascular risk factors in placebo-controlled studies.
\textsuperscript{58} C. Ohlsson et al., "High Serum Testosterone Is Associated with Reduced Risk of Cardiovascular Events in Elderly Men. The MrOs (Osteoporotic Fractures in Men) Study in Sweden," J Am Coll Cardiol 58, no. 16 (2011).
\textsuperscript{59} Moskovic et al., "The 20-Year Public Health Impact and Direct Cost of Testosterone Deficiency in U.S. Men."
in a public manner such that the average consumer will be reassured that allegations of increased CV risk with T therapy are false, as accurate information is critical for public health.

Finally, as an organization representing the views of 29 medical societies and more than 150 distinguished scholars in the field, we respectfully request the opportunity to share our research and analysis with the FDA on this topic if and when it convenes a formal review.

Sincerely,

The Androgen Study Group

Abraham Morgentaler, MD, Chairman
Abdul Traish, PhD
Andre Guay, MD
Mohit Khera, MD
Martin Miner, MD

References


Appendix Table of Contents

Tables 1-3 and 6-9 are from Oskui et al.\textsuperscript{60}

Table 5 is from.\textsuperscript{61}

APPENDIX 1

Investigations of serum testosterone concentrations and cardiovascular disease and mortality.

Table 1. Association Between Levels of Endogenous Testosterone and Mortality.
Table 2. Association Between Testosterone Level and Incidence of Coronary Artery Disease.
Table 3. Association Between Testosterone Level and Severity of Coronary Artery Disease.
Table 4. Association Between Endogenous Testosterone Level and Carotid Intima-Media Thickness.

APPENDIX 2

Effects of testosterone therapy (TTh) on cardiovascular risk factors in placebo-controlled studies.

Table 5. Changes in Parameters of Obesity with Testosterone (T) Treatment Versus Placebo (Plc).
Table 6. Effects of Testosterone Replacement Therapy on Cholesterol Levels - Meta-analyses.
Table 7. Effects of Testosterone Replacement Therapy on Indices of Glycemic Control.
Table 8. Effects of Testosterone Replacement Therapy on Markers of Inflammation.

\textsuperscript{60} P. M. Oskui et al., "Testosterone and the Cardiovascular System: A Comprehensive Review of the Clinical Literature," \textit{J Am Heart Assoc} 2, no. 6 (2013).