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INVITED REVIEW / DAVETLİ DERLEME

Testosterone replacement therapy and cardiovascular events

Testosteron yerine koyma tedavisi ve kardiyovasküler olaylar

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Summary– A low testosterone level and hypogonadism are associated with cardiovascular disease. Aging, chronic health problems, and obesity are all associated with a low testosterone level as well as the presence and severity of cardiovascular disease. Testosterone is increasingly prescribed for patients with clinical hypogonadism and a low testosterone level. The information we have is still contradictory regarding testosterone replacement therapy (TRT) and its association with adverse cardiovascular events. Older patients and patients who are susceptible to cardiovascular diseases could be at risk with a testosterone prescription. This is a review of the literature to discuss the cardiovascular safety of TRT.

Özet– Düşük testosteron seviyeleri ve hipogonadizm kalp-damar hastalıkları ile ilişkilidir. Yaşlanma, kronik sağlık sorunları ve obezite hem düşük testosteron seviyeleri hem de kalp damar hastalıklarının ciddiyeti ile bağlantılıdır. Klinik hipogonadizmi ve düşük testosteron seviyesi olan hastalara testosteron sıklıkla reçete edilmektedir. Testosteron yerine koyma tedavisi ile olumsuz kardiyovasküler olaylar arasındaki ilişki hakkındaki bilgiler tartışmalıdır. Yaşlı ve kardiyovasküler olaylara yatkın olan hastalar, testosteron tedavisi sonrasında risk altında olabilirler. Bu nedenle testosteron yerine koyma tedavisinin kalp damar hastalıkları yönünden güvenilirliğini tartışmak için literatürü derledik.

Testosterone replacement therapy (TRT) is widely promoted globally, despite unclear cardiovascular effects. Although some observational data suggest that testosterone deficiency might have an impact on cardiovascular diseases, a high level of androgens has also been suggested to increase the incidence of cardiovascular events.[1,2] The use of testosterone has been increasing during the last decade, secondary to its anti-aging effects like muscle gain, fat loss, and increased endurance during exercise. As a low testosterone level is a treatable condition, utilization as self-medication could raise some susceptibility issues for patients with known cardiovascular diseases. This is a review of the data regarding TRT and its influence on adverse cardiovascular events, with a discussion of the physiology of testosterone and the definition of methods to measure the serum testosterone level.

Abbreviations:

DHT	*Dihydrotestosterone*
CABG	*Coronary artery bypass graft*
CAD	*Coronary artery disease*
CI	*Confidence interval*
FSH	*Follicle-stimulating hormone*
GnRH	*Gonadotropin-releasing hormone*
HR	*Hazard ratio*
ICD	*International Classification of Disease*
LDL	*Low-density lipoprotein*
HDL	*High-density lipoprotein*
LH	*Luteinizing hormone*
MACE	*Major adverse cardiovascular event*
MI	*Myocardial infarction*
OR	*Odds ratio*
SHBG	*Sex hormone-binding globulin*
TRT	*Testosterone replacement therapy*

Testosterone Physiology

Testosterone, which is the principal male sex hormone, is a cholesterol-based steroid hormone. The pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus causes both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) to be released from the anterior pituitary. The release of LH signals Leydig cells to produce testosterone and FSH stimulates Sertoli cells to initiate spermatogenesis. Testosterone is primarily secreted by the testes and, to a lesser extent, by the adrenal glands. The hypothalamic-pituitary-testicular axis is controlled by a negative feedback loop. As the testosterone level rises in the blood, GnRH and LH/FSH secretion decline.

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Testosterone in the circulation can be free, weakly bound to albumin, or tightly bound to sex hormone-binding globulin (SHBG). Free and albumin-bound testosterone is available for use by the body, whereas SHBG-bound testosterone, which is the largest percentage, is unavailable for use in the body. Any condition that increases SHBG will decrease the amount of available testosterone. Aging, elevated thyroid hormones, and conditions that elevate estrogen increase the ratio of SHBG-bound testosterone to the biologically available forms, regardless of an unchanged total testosterone level.

The bulk of secreted testosterone is inactivated by liver metabolism, and a small proportion in circulation is converted into other hormones, such as dihydrotestosterone (DHT), by 5-alpha reductase, and estradiol, by aromatase, which is present in many cardiovascular cell types and in fatty tissue. DHT has 3 to 10 times more potent affinity for androgen receptors compared with testosterone. Estradiol, DHT, and the DHT product, 3-alpha androstanediol, have established roles in reproductive, cardiovascular, bone, hepatic, renal, dermatological, prostatic, penile, and central nervous system functions. In obese men, the increased amount of fat leads to increased aromatase activity, resulting in increased levels of estradiol. A high circulating level of estradiol down-regulates the hypothalamic-pituitary axis and decreases the amount of circulating testosterone.

Free testosterone and DHT bind to the androgen receptor present in the cytosol of most tissues.[3] The testosterone-androgen receptor complex is translocated to the nucleus, where it stimulates transcription of numerous genes, which subsequently act on target tissues. These transcriptional processes have multiple co-regulators, which are not fully understood yet. Androgen receptor size and function is also suggested to have role in the response rate to testosterone supplementation.[4]

Testosterone has anabolic effects that cause overt physical changes in the male. Body musculature and fat distribution are affected, leading to virilization. Bone growth and epiphyseal closure are promoted. There is laryngeal enlargement and subsequent vocal cord thickening, as well as testicular growth and the initiation of spermatogenesis.

After physical maturity, testosterone has a more homeostatic function. It sustains spermatogenesis, maintains muscle bulk, maintains secondary sex characteristics, and aids in erectile function. It also has an effect on erythropoietin secretion, which increases red blood cell production. Testosterone maintains bone density, bone growth, and bone marrow production of red blood cells. Testosterone is also responsible for the sex drive, and aids cognition, memory, and mood.

Factors Affecting Testosterone Levels

There are numerous factors that can affect testosterone level and its variability, including aging, the presence of acute or chronic illness, geography, ethnicity, genetics, lifestyle factors, diurnal, and intraindividual variations.

Aging has been demonstrated to have an indirect effect on both total and free testosterone levels. A longitudinal cohort study reported a 0.8% yearly decrease in total, and a 2% yearly decrease in free testosterone secondary to SHBG increase in men.[5] Despite this observation, there is still controversy about this interaction as an independent risk factor. In a study evaluating 1588 men over a 5-year period, age was not reported as an independent risk factor in decreasing testosterone level; however, smoking, obesity, chronic illness, marital status, depression, and lifestyle factors were independently related.[6] On the contrary, the European Male Aging Study reported age-related symptomatic hypogonadism at a rate of 0.1% in men aged 40 to 49 years, and increasing gradually to present in 5.1% of men 70 to 79 years of age.[7]

Several lifestyle factors have been shown to be independently related to variations in testosterone level. Obesity was reported to be inversely correlated with gonadotropins and testosterone.[8] A meta-analysis demonstrated that weight loss with diet alone increased testosterone 83 ng/dL, and bariatric surgery, which achieved greater weight loss, led to an increase of 252 ng/dL.[9] Exercise, smoking, and alcohol consumption are other lifestyle factors that may have an impact on testosterone levels.[10–12]

Endogenous Testosterone and Coronary Artery Disease

There are conflicting data regarding the relationship between the endogenous testosterone level and coronary artery disease (CAD). Numerous studies suggest

Table 1. The relationship between testosterone and cardiovascular risk factors

	Low endogenous testosterone is associated with	Exogenous testosterone replacement causes
Obesity	Adiponectin ↑	Lean body mass ↑
	Adipogenesis ↑	Body fat ↓
	Lipolysis ↓	Waist circumference ↓
Dyslipidemia	Total cholesterol ↑	Total cholesterol ↓
	LDL-cholesterol ↑	LDL-cholesterol ↓
	HDL-cholesterol ↓	HDL-cholesterol ↑
Glucose metabolism	Insulin concentration ↑	Insulin sensitivity ↑
	Insulin resistance ↑	Blood glucose ↓
	Type 2 diabetes ↑	HbA1C ↓
Hypertension	Systolic BP ↑	Systolic BP ↓
	Diastolic BP ↑	Diastolic BP ↓
Inflammation	Intrleukin-1β ↑	Intrleukin-1β ↓
	Interleukin 6 ↑	Interleukin 6 ↓
	CRP ↑	CRP →
	TNF-α ↓	TNF-α ↑

BP: Blood pressure; CRP: C-reactive protein; HbA1C: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TNF-α: Tumor necrosis factor alpha.

that lower levels of testosterone have a significant relationship, whereas others did not demonstrate a direct association.[13–16] This discrepancy could be due to the testosterone subfraction used as a measure in the studies. A biologically inactive form of testosterone makes up approximately 68% of total testosterone, and the remaining 30% is loosely bound to albumin; only 1% to 3% of total testosterone is circulating freely in the serum.[17] Currently, we do not have convincing data regarding whether free testosterone is superior to bioavailable testosterone in terms of the presence and progression of CAD.

Studies investigating CAD severity have reported an inverse relationship between testosterone level and Gensini score or coronary artery score.[18,19] Low levels of endogenous testosterone may influence the progression of CAD by increasing the inflammatory response and adversely affecting inflammatory response mediators like interleukin-6, tumor necrosis factor alpha, and C-reactive protein. Also, low levels of testosterone have been shown to be related to obesity, diabetes mellitus, metabolic syndrome, dyslipidemia, and hypertension, which are risk factors for CAD.[20–23]

Many studies have shown a clear relationship between a low testosterone level and all-cause or cardiovascular mortality. Studies considering total testosterone are contradictory. While some were able to demonstrate a significant indirect relationship, some could not confirm a statistical significance regarding cardiovascular mortality.[24–27] In a large, community-based meta-analysis, it was reported that a low total testosterone level was associated with increased all-cause mortality with a hazard ratio (HR) of 1.35 (95% confidence interval [CI], 1.13–1.62; p<0.001), and an increased trend of cardiovascular mortality that did not reach statistical significance with an HR of 1.25 (95% CI, 0.97–1.60; p=0.06).[1] The authors of this meta-analysis emphasized the heterogeneity of the studies included in the analysis regarding age, length of follow-up, assays used, and baseline testosterone levels.

Testosterone Replacement Therapy and Cardiovascular Events

TRT must be lifelong in young, hypogonadal males. In addition, age-related hypogonadism is a common problem. Guidelines recommend TRT in patients who have low sex hormone levels that were measured at least twice, and which are correlated with clinical symptoms and signs. However, clinical practice shows that there is a large number of patients receiv-

Table 2. Meta-analyses about the effect of testosterone replacement therapy on cardiovascular events

Authors	Number of studies	Enrollment criteria	End-points	Main results
Calof et al.[28]	19 RCTs enrolled. 651 TRT and 433 placebo patients	Medically stable men aged ≥45 years with low or low-normal testosterone on TRT ≥90 days	18 events (2.8%) in TRT group (No deaths, 5 cases of arrhythmia, 4 MI, 4 angina, 2 coronary procedure, 3 vascular events); 16 events (3.7%) in placebo group (1 arrhythmia, 3 MI, 3 angina, 5 coronary procedures, 4 vascular events)	Combined end-points were similar between groups. OR: 1.14 (95% CI, 0.59–2.20)
Haddad et al.[20]	30 RCTs enrolled. 808 TRT and 834 placebo patients	All published RCTs with any baseline testosterone level or any formulation	14 events (8.7%) in the TRT group (5 MI, 1 cardiovascular death, 8 soft end-points); 7 events (4.8%) in placebo group (2 MI, 1 death, 4 soft end-points)	Combined cardiovascular end-points were similar between groups. OR: 1.82 (95% CI, 0.78–4.23)
Fernández-Balsells et al.[29]	51 studies (both RCTs and non-RCTs) enrolled (Patient numbers varied for each end-point analysis)	Adult men with low or low-normal baseline testosterone treated with any formulation for ≥3 months	36 deaths (13.8%), 3 arrhythmias (5.6%), 3 CABG (3.8%), 5 MI (0.8%) in TRT group; 23 deaths (10.7%), 1 arrhythmias (1.9%), 2 CABG (2.5%), 4 MI (1%) in control group	TRT did not increase all-cause death, MI, CABG or arrhythmia. OR for all-cause mortality: 1.12 (95% CI, 0.70–1.81); OR for arrhythmia: 3 (95% CI, 0.32–27.94); OR: for CAGB: 1.35 (95% CI, 0.26–6.96); OR: for MI: 0.91 (95% CI, 0.29–2.82)
Xu et al.[30]	27 RCTs enrolled. 1733 TRT and 1261 placebo patients.	Placebo-controlled trials, reporting cardiovascular events and ≥12 weeks follow-up	115 events (6.6%) in the TRT group; 65 events (5.2%) in the placebo group	Combined cardiovascular events were higher in the TRT group. OR: 1.54 (95% CI, 1.09–2.18)
Corona et al.[31]	75 RCTs enrolled. 3016 TRT and 2448 placebo patients.	Any placebo-controlled TRT trial that was reporting cardiovascular events	31 events (1.6%) in the TRT group; 20 events (1.5%) in the placebo group	Major adverse cardiovascular events were similar between groups. OR: 1.01 (95% CI, 0.57–1.77)

CABG: Coronary artery bypass graft surgery; CI: Confidence interval; MI: Myocardial infarction; OR: Odds ratio; RCT: Randomized clinical trial; TRT: Testosterone replacement therapy.

ing off-label TRT. The main target of TRT is to replace testosterone to physiological ranges and to reverse hypogonadal symptoms and signs. Because a significant number of male patients who receive TRT are also at a risk for CAD, the concern about developing an adverse cardiovascular event should be clarified. We reviewed the literature to understand the potential benefit or harm of exogenous TRT with respect to cardiovascular events. As there are numerous studies, we reviewed the meta-analyses published and some more recent studies. There were 5 meta-analyses published between 2005 and 2014.[20,28–31]

The first meta-analysis of 19 randomized placebo-controlled studies was performed by Calof et al.[28] They included 651 men who received TRT and 433 men who received a placebo. The inclusion criteria were men ≥45 years old with a low or low-normal testosterone level who had been on TRT for at least 90 days and who were medically stable. They did not find any significant difference in cardiovascular events between the TRT and placebo groups. There were no deaths in the TRT group and 2 deaths in the placebo group with an unknown etiology. The 18 cardiovascular events (2.8%) observed in the 651 testosterone-treated men included atrial fibrillation or arrhythmia in 5 men; myocardial infarction (MI) in 4; chest pain or ischemia in 4; coronary procedure, including coronary artery bypass graft (CABG), in 2; and vascular events, including cerebrovascular accidents, in 3. The 16 cardiovascular events (3.7%) in the 433 placebo-treated men included atrial fibrillation or arrhythmia in 1 man; MI in 3; chest pain or ischemia in 3; coronary procedures, including CABG, in 5; and vascular events, including cerebrovascular accidents, in 4. The combined end-points were also similar between the 2 groups with an odds ratio (OR) of 1.14 (95% CI, 0.59–2.20). This meta-analysis included heterogeneous studies with different testosterone formulations (patch, gel, oral, injectable), age range, initial testosterone level, and study duration. Cardiovascular events included both soft and hard end-points. Combined major cardiovascular end-points, such as MI, cerebrovascular events, coronary procedure, and death, were observed in 9 of 651 men (1.3%) in the TRT group and 12 of 433 men (2.8%) in the placebo group.

A meta-analysis conducted by Haddad et al. of 30 randomized, placebo-controlled trials included 808 men who received TRT and 834 men who received a placebo.[20] Blood pressure and lipid subfractions were compared between these 2 groups and no significant change in systolic or diastolic blood pressure after TRT was observed. Lipid subfractions were not significantly affected after TRT in the low baseline testosterone group. In the low-normal and normal baseline testosterone groups, total cholesterol levels were significantly reduced in the TRT group (OR:-0.47; 95% CI, -0.77 to -0.17), whereas low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were decreased and triglycerides were increased without statistical significance. Cardiovascular events were analyzed as a subanalysis of 6 studies that reported consistent cardiovascular events, which included 161 men in the TRT group and 147 men in the placebo group. Cardiovascular events were defined as cardiovascular death, nonfatal MI, angina or claudication, revascularization, and stroke. A total of 14 events (8.7%), including 5 MIs and 1 cardiovascular death in the TRT group, and 7 events (4.8%), including 2 MIs and 1 death in the placebo group, were observed. The pooled OR for cardiovascular events was 1.82 (95% CI, 0.78–4.23), which was not statistically significant.

Fernández-Balsells et al. performed a meta-analysis that included 51 studies.[29] Randomized and non-randomized studies that enrolled adult men with a low or low-normal testosterone level and who were treated with any testosterone formulation for at least 3 months were eligible for the meta-analysis. This meta-analysis was focused on prostate outcomes, cardiovascular outcomes, and red cell mass. TRT resulted in an increase in hemoglobin and hematocrit levels, whereas there were no significant differences in prostate cancer or prostate-related adverse events. All-cause mortality was reported in 5 studies, arrhythmia was reported in a single study, CABG during follow-up was reported in 2 studies, and MI was reported in 7 studies. These outcomes were analyzed separately, rather than comparing combined adverse event between groups. There were 36 deaths among 261 (13.8%) TRT patients and 23 deaths among 215 (10.7%) control patients (OR: 1.12; 95% CI, 0.70–1.81). Arrhythmias were reported in 3 among 54 patients (5.6%) in the TRT group and in 1 of 54 patients (1.9%) in the control group (OR: 3; 95% CI, 0.32–27.94). CABG was reported in 3 of 79 patients (3.8%) in the TRT group and in 2 among 79 patients (2.5%) in the control group (OR: 1.35; 95% CI, 0.26–6.96). MI was observed in 5 among 657 pa-

tients (0.8%) in the TRT group and in 4 among 396 patients (%) in the control group (OR: 0.91; 95% CI, 0.29–2.82). TRT did not increase MI, CABG, arrhythmia, or all-cause mortality significantly, compared with the control group, according to this meta-analysis. Cardiometabolic parameters were also investigated in this meta-analysis. The testosterone and control groups did not differ significantly in the incidence of diabetes mellitus or in the changes from baseline in cardiometabolic risk factors, such as fasting glucose, total or LDL cholesterol, triglycerides, systolic or diastolic blood pressure levels. HDL cholesterol levels were significantly lower in the TRT group than in the control group (weighted mean difference: 0.49 mg/dL; 95% CI, 0.85–0.13). Significant heterogeneity was reported among studies.

Another recent meta-analysis was performed by Xu et al.[30] Placebo-controlled randomized trials of TRT with a minimum follow-up of 12 weeks of reporting cardiovascular events were eligible. A total of 27 trials with 2994 patients were included. The primary outcome was the composite of cardiovascular related events, which were defined as events reported as cardiac disorders, cardiovascular complaints, cardiovascular events, vascular disorders that may be cardiac or cardiovascular, or where the event description fell within the International Classification of Disease (ICD) 10th revision, chapter IX (I00 to I99). Serious cardiovascular events were defined as cardiovascular-related events described as serious adverse events or where the outcome was death, life-threatening, hospitalization, involved permanent damage, required medical/surgical intervention, or was 1 of the following types of cardiovascular event: MI, unstable angina, coronary revascularization, CAD, arrhythmias, transient ischemic attack, stroke or congestive heart failure, but not deep vein thrombosis. The incidence of adverse cardiovascular events was higher in the TRT group (115 events in 1733 patients) compared with placebo (65 events in 1261 patients) (OR: 1.54; 95% CI, 1.09–2.18). Interestingly, when the studies were stratified as pharmaceutical industry-funded (13 studies) or not (14 studies), fewer cardiovascular events were reported in the funded group. The incidence of adverse cardiovascular events was similar in the TRT group (36 events among 1020 patients) and the placebo group (30 events among 631 patients) in the industry-funded group (OR: 0.89; 95% CI, 0.50–1.60). Whereas, in the non-funded group, the incidence of adverse cardiovascular events was significantly higher in the TRT group (79 events among 713 patients) compared with the placebo group (35 events among 630 patients) (OR: 2.06; 95% CI, 1.34–3.17). The authors suggested that the benefits of testosterone therapy outweighed the potential risk. The age range was observed to be lower in the industry-funded studies, which might have had an impact on favorable outcomes. In addition, the cardiovascular events could not be reported separately in detail; therefore, it is difficult to comment on the etiological value. The trial conducted by Basaria et al., which had the greatest weight in this meta-analysis, dissented from the other enrolled studies.[32] The supraphysiological doses of testosterone in elderly men and the broad and unadjudicated cardiovascular event definitions could have influenced the results. The study was terminated prematurely due to a higher rate of cardiovascular events in the TRT group. However, although some were harder end-points, like MI, observed in 2 members of the TRT group, other end-points were softer, including edema, syncope, ectopy or left ventricular strain pattern on electrocardiogram, carotid bruit, tachycardia with fatigue, or elevated blood pressure. In conclusion, TRT was reported to increase the risk of cardiovascular-related events overall in this meta-analysis.

In the most recent meta-analysis, performed by Corona et al., 75 randomized and placebo-controlled TRT trials were enrolled, and included 3016 patients on TRT and 2448 placebo-treated men.[31] The mean follow-up period was 34 weeks. The primary outcome of this analysis was the effect of TRT, as compared with placebo, on the incidence of a new major adverse cardiovascular event (MACE). MACE was defined as cardiovascular death, non-fatal MI, stroke, acute coronary syndromes, and/or heart failure. Secondary outcomes included all cardiovascular-related events, defined as anything reported as such by the authors; that is, events reported as cardiac disorders; cardiovascular complaints; cardiovascular events; vascular disorders, cardiac or cardiovascular; or when the event description fell within that of the ICD. In this analysis, 73 trials reported MACE. In 47 of these trials, cardiovascular events were not observed. Therefore, the final analysis was performed using 26 studies. TRT was not associated with any significant difference regarding MACE incidence (OR: 1.01; 95% CI, 0.57–1.77). A total of 31 events

(1.6%) were observed among 1895 TRT patients compared with 20 events (1.5%) among 1341 placebo-treated patients. No difference in MACE was observed when the trials were categorized to baseline testosterone level, age, industry funding, or trial duration >12 weeks. TRT was shown to be protective in patients with known metabolic disease (OR: 0.19; 95% CI, 0.04–0.85). Similar results were observed in the analysis of any cardiovascular event. A total of 126 events (6.3%) occurred in 1994 TRT patients and 83 events (6%) occurred in 1390 placebo-treated patients (OR: 1.07; 95% CI, 0.69–1.65). A study conducted by Vigen et al. that was included in this meta-analysis received some criticism for their reported results.[33] The authors reported a higher Kaplan-Meier-estimated cumulative percentage for the TRT group (25.7%) compared with the placebo group (19.9%) regarding combined end-point of all-cause mortality MI and stroke. However, when raw data of the 7486 control patients were used, 681 died, 420 had MI, and 486 had a stroke, with a total of 1587 MACE (21%), and of the 1223 TRT patients, 67 died, 23 had MI, and 33 had a stroke, with a total of 123 MACE (10%). According to the raw numbers, the TRT group had fewer cardiovascular events compared with the control group. Finkle et al. published another study on testosterone safety in 2014 that was controversial.[34] The authors analyzed 55,953 patients who were on TRT and compared the rate of non-fatal MI in the 90 days after the initial prescription to the rate in the year before TRT. The post-/pretreatment OR was 1.36 (95% CI, 1.03–1.81), which was statistically significant. The patients were not followed up for compliance with the prescription or for testosterone level. Other cardiovascular end-points, such as fatal MI, stroke, or cardiovascular mortality were not reported. The follow-up was 90 days, which is a relatively short duration to draw conclusions about the safety of TRT. However, this study was conducted with a large number of patients, which was the strongest element.

A recent retrospective study by Sharma et al. compared patients who were on TRT and who had achieved a normal testosterone level, patients who were on TRT and who did not achieve a normal testosterone level, and patients who did not receive TRT.[35] Patients who had a normal testosterone level after TRT had lower all-cause mortality, MI, and stroke.

Conclusion

Low testosterone level and hypogonadism are often associated with cardiovascular disease. Numerous studies have shown that low endogenous testosterone is related with obesity, decreased HDL cholesterol, increased LDL cholesterol, high blood pressure, increased incidence of diabetes, and an increase in inflammatory markers, which were also shown to be reversed by exogenous testosterone. Testosterone might be considered a biomarker for poor general health and aging, as well as cardiovascular disease. However, data regarding the effects of testosterone replacement on cardiovascular events are contradictory. Although there are many studies indicating that TRT improves survival in hypogonadal men, there are also studies with unfavorable cardiovascular events in patients receiving exogenous testosterone. However, in the meta-analyses we have mentioned, TRT has been shown to generally be safe without increasing overall cardiovascular events. Older men with hypogonadal symptoms should be asked about existing cardiovascular disease and counseled before prescription of testosterone, as there is still insufficient data about patients who are at high risk for cardiovascular events receiving exogenous testosterone. Randomized-controlled studies are needed with a longer follow-up period in this subgroup of patients to draw a conclusion on the safety of TRT. Until then, TRT should be restricted to symptomatic hypogonadal men without high risk for cardiovascular events.

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