Curr Sex Health Rep
https://doi.org/10.1007/s11930-017-0132-3

Testosterone and Cardiovascular Diseases: Causes or Consequences: The Lesson from the Last 5 Years

Giovanni Corona[1] · **Giulia Rastrelli**[2] · **Mauro Dicuio**[3] · **Alessandra Sforza**[1] · **Mario Maggi**[2]

Abstract
Purpose of the Review The relationship between the age-dependent decline of testosterone (T) and cardiovascular (CV) risk in men is still a matter of intense debate. In particular, over the last 5 years, several scientific reports have shed a new negative light on the association between T treatment (TTh) and forthcoming CV diseases (CVD). Based on this evidence, the US Food and Drug Administration agency has recommended that all T supplementations carry a warning that they may increase the risk of heart attack and stroke. To better clarify the available data on this topic, we scrutinized and summarized, also by using meta-analytic methods, the data generated during the last 5 years, as derived from the analysis of observational (either longitudinal or pharmaco-epidemiological) studies and from randomized controlled trials (RCTs) on TTh and CVD risk.
Recent Findings Our analysis shows that there is a clear association between baseline T deficiency and overall mortality and CVD-related mortality when longitudinal surveys were analyzed, although a specific pathogenetic link cannot be made. When interventional trials were studied, several but not all pharmaco-epidemiological studies reported a possible protective role of TTh on CV risk; however, data from RCTs and their meta-analysis, presented here, do not provide us with sufficient information on this point.
Summary Present data do not indicate an increased risk with TTh, but there is also insufficient definitive evidence that TTh is protective. Therefore, further and more specific trials are advisable to better clarify the possible relationship between low T, TTh, and CVD in aging men.

Keywords Testosterone · Cardiovascular risk · Major adverse cardiovascular events (MACE) · Late-onset hypogonadism · Obesity · Insulin resistance

Introduction

In western societies, cardiovascular (CV) diseases (CVD) are currently the leading killer in both genders, with coronary heart disease (CHD) being the main cause of CV morbidity and mortality. Considering that the age-adjusted death rate for CVD and CHD is at least 30 and 50% higher in men than in women, a pathogenic role for sex steroids has been hypothesized [1]. Historically, estrogens were considered beneficial, whereas androgens were considered detrimental to CV health; however, in our opinion, this view is not only naïve but also erroneous. First, the gender-related difference in CHD is more subtle than that described by the previously reported simple prevalence. For example, although occlusive CHD is more often observed in men, in particular in the youngest age bands, non-obstructive CHD is more prevalent in women and often associated with atypical symptoms. Furthermore, acute mortality for myocardial infarction (MI) is higher in women than in men. These gender-related differences cannot be explained just by variations in sex steroids; other genetic, environmental,

This article is part of the Topical Collection on *Medical Comorbidities*

✉ Mario Maggi
m.maggi@dfc.unifi.it

[1] Endocrinology Unit, Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy

[2] Sexual Medicine and Andrology Unit Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Viale Pieraccini 6, 50139 Florence, Italy

[3] Urology Unit, Surgical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy

Published online: 16 November 2017

and psychological issues should be taken into consideration in the stratification of CVD risk according to gender [2].

The supposed negative effect of androgens on male CV health was historically based on data on anabolic steroid abusers [3] or on transgender men treated with testosterone (T) therapy (TTh) [4]. However, data generated on TTh in randomized placebo-controlled trials (RCTs) involving hypogonadal subjects treated with TTh, and their relative meta-analyses [5–7], were consistently reassuring. During the last 5 years, however, several scientific reports have shed a new negative light on the association between TTh and CVD risk. Based on this, the FDA has recommended that all T supplementations carry a warning that they may increase the risk of heart attack and stroke [8].

The aim of the present review is to scrutinize and to summarize, also by using meta-analytic methods, the data generated during the last 5 years, as derived from the analysis of observational (either longitudinal or pharmaco-epidemiological) studies and from RCTs on TTh and CVD risk.

Methods

The analyses have been conducted based on two separate extensive Medline/Embase and Cochrane searches, the former for the identification of observational studies and the latter for the selection of placebo-controlled RCTs. The Medline and Embase search was conducted including the following keywords ((“testosterone”[MeSH Terms] OR “testosterone”[All Fields]) AND (“cardiovascular system”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “system”[All Fields]) OR “cardiovascular system”[All Fields] OR “cardiovascular”[All Fields]) AND (“risk”[MeSH Terms] OR “risk”[All Fields])) AND (“humans”[MeSH Terms] AND English [lang] AND “male”[MeSH Terms]), aimed at identifying observational studies assessing the relationship between endogenous T levels and CV risk (development of new CV events or mortality) and pharmaco-epidemiological studies evaluating the effect of TTh on CV mortality and morbidity. The Cochrane search was conducted using the words (“testosterone” [MeSHTerms] OR “testosterone” [All Fields]) AND (Clinical Trial [ptyp] AND “humans” [MeSH Terms] AND English [lang] AND “male” [MeSH Terms]) and was aimed at retrieving the placebo-controlled RCTs with the same outcome. Both searches were limited to articles published during the last 5 years, introducing (“2012/01/01” [PDat]: “2017/04/01” [PDat]) as a further search term.

Data from observational and pharmaco-epidemiological studies were extracted as unadjusted and adjusted odds ratios (OR) with their confidence interval, when available. For the adjusted data, we selected those deriving from the fully adjusted model in each study. The confounding factors used in each study are reported in Table 1.

Observational Studies

In 2011, we performed a meta-analysis including the available longitudinal studies comparing endogenous T levels in subjects with or without CV morbidity and mortality at follow-up. The meta-analysis involved 10 observational studies, enrolling 12,375 subjects [9]. T level at study entry was significantly lower among patients with incident overall- and CV-related mortality, in comparison with controls; however, we did not find any significant difference in baseline T levels between cases and controls for incident CVD.

Among observational reports published in the last 5 years, 10 studies [10–19] reported information on overall mortality, five [10–12, 16–18] on CV mortality, and five [14, 17–20] on CV events. In addition, one study reported information on CV mortality only as a composite event including also acute myocardial infarction and CV revascularization ([18]; Table 1). The characteristics of the retrieved studies are reported in Table 1 [10–20]. Retrieved trials included 17,813 subjects with a mean follow-up of 339 weeks and mean age of 66.5 years. The studies differed in the considered T reference levels and baseline characteristics of enrolled individuals (Table 1). Seven studies [10, 12, 13, 16–18, 20] were based on data derived from the general population, whereas three studies [14, 15, 19] were performed on specific cohorts. The 10 surveys reporting information on overall mortality [10–19] included 17,322 subjects with a mean age of 65.7 years. The unadjusted data showed that low endogenous T levels at baseline were associated with a higher risk of overall mortality at follow-up (Fig. 1a). This association was confirmed when fully adjusted data were considered (Fig. 1a). The five surveys [10–12, 16–18] reporting information on CV mortality included 11,229 with a mean age of 66.3 years. Similar to what was observed for overall mortality, low T levels at baseline were associated with a higher risk of CV mortality at follow-up when both unadjusted and fully adjusted models were considered (Fig. 1a).

The five surveys reporting information on CV events [14, 17–20] included 4943 subjects with a mean age of 66.7 years. The definition of CV events differed among the studies (Table 1). Only one study reported unadjusted data [19], showing no difference in CV risk when subjects with reduced T levels were compared to those with higher T levels. Similar data were observed when the five trials reporting the fully adjusted data were considered (Mantel-Haenszel-odds ratio (MH-OR) 1.11 [0.89; 1.40]; $p = 0.36$).

Hence, data from the last 5 years are essentially in line with those reported in previous meta-analyses [9, 21, 22] showing a clear association between low T and CV-related or CV-unrelated mortality, but only CV events show a trend toward significance.

Hypogonadism (HG) is a condition characterized by the accumulation of visceral adiposity and by an impaired

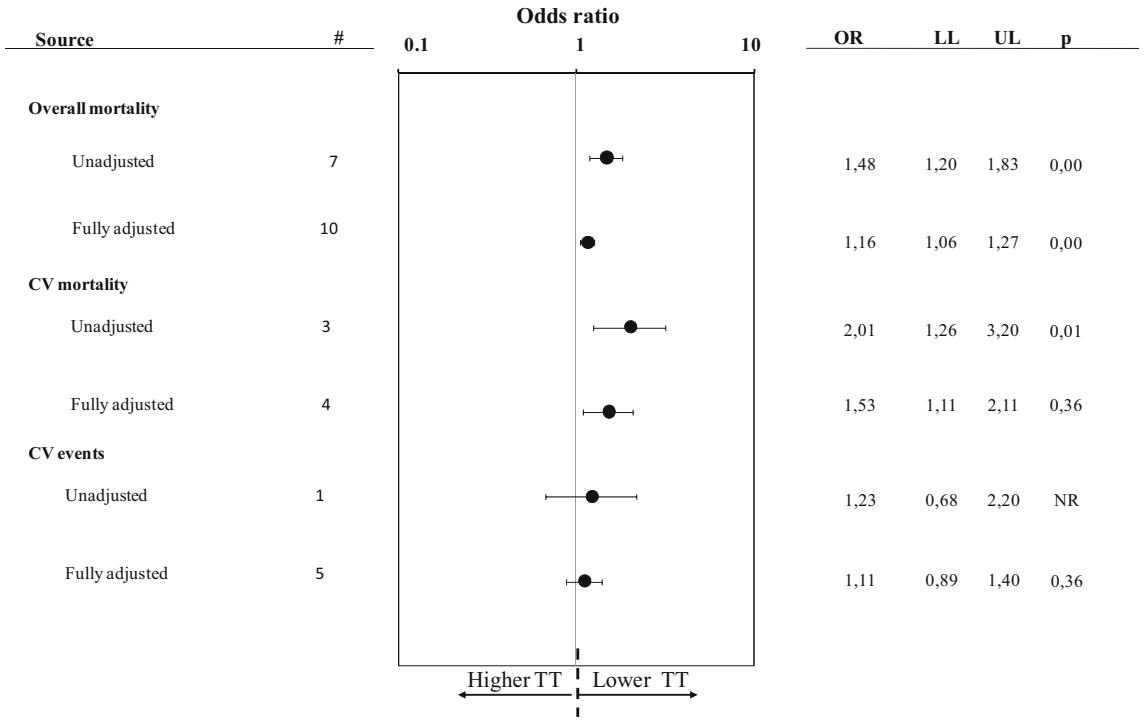
Table 1 Characteristics of the observational studies included in the meta-analysis

Study	No. of patients	Population	Follow-up (weeks)	Risk category	Age (years)	Lower limit of TT (nmol/L)	Type of CV events considered	Confounders used in the fully adjusted model
Hyde et al. [10]	3637	General population	264	Lowest quintile of TT	77.0	5.0	Overall and CV mortality	• Age • Waist-hip ratio • Hypertension • Dyslipidemia diabetes • Smoking status • Charlson comorbidity index • Prevalent CVD • Cancer diagnoses
Lerchbau et al. [11]	2069	Men with CVD	392	Lowest quartile of TT	62.8	11.3	Overall and CV mortality	• Age • Body mass index • Smoking status • Physical activity • Diabetes • C-reactive protein, • Prevalent CHD • Serum calcium • Parathyroid hormone
Schneder et al. [12]	1892	General population	520	TT below the lower limit of normal range	50.0	10.4	Overall and CV mortality	• Age • Systolic blood pressure • High-density lipoprotein cholesterol • Total cholesterol • Antihypertensive medication • Diabetes • Smoking status
Haring et al. [13]	254	General population	520	Each decrease in one quartile of TT	75.5	NR	Overall mortality	• Age • Body mass index • Smoking status • Total cholesterol • High-density lipoprotein cholesterol • Diabetes • Systolic blood pressure • Antihypertensive medication
Soisson et al. [20]	491	General population	208	Lowest vs. second quartile	73.8	13.5	Fatal and non-fatal CHD and stroke	• Study center • Body mass index • Diabetes • Hypertension • Hypercholesterolemia • Smoking status
Bello et al. [14]	623	Men upon hemodialysis	84	TT below the lower limit of normal range	60.7	8.0	Overall mortality, CHD, stroke, PVD	• Age • Smoking status • Body mass index • Sex hormone binding globulin • Cancer • Diabetes
Khurana et al. [15]	2419	Men with ESRD	352	TT below the lower limit of normal range	67.3	12.0	Overall mortality	• Age • Race

Table 1 (continued)

Study	No. of patients	Population	Follow-up (weeks)	Risk category	Age (years)	Lower limit of TT (nmol/L)	Type of CV events considered	Confounders used in the fully adjusted model
								• Estimated glomerular filtrate • Diabetes • Hypertension • CED • CHD • Congestive heart failure • Hyperlipidemia • Cancer • Body mass index • Smoking status • Albumin • T medication
Pye et al. [16]	2599	General population	208	TT below the lower limit of normal range	64.9	8.0	Overall and CV mortality	• Age • Study center • Body mass index • Smoking status • Poor general health
Shores et al. [17]	1032	General population	452	TT below the lower limit of normal range	77.0	9.5	Overall and CV mortality, AMI and stroke	• Age • Race • Study center • Smoking status • Alcohol consumption • Systolic blood pressure • Antihypertensive medication • High-density lipoprotein cholesterol • Body mass index • Waist circumference • Sex hormone binding globulin
Srinath et al. [18]	1558	General population	520	Lowest vs. highest quartile of TT	63.1	9.9	Overall mortality, AMI, CV death, CV revascularization	• Age • Race • Study center • Body mass index • Waist circumference • Smoking status • Diabetes • Hypertension • High-density lipoprotein cholesterol • Low-density lipoprotein cholesterol
Cheung et al. [19]	1239	Men with T2DM	216	TT below 9 nM	59.0	6.9	Overall mortality, AMI, IHD, stroke, HF, PVD	• Metabolic syndrome • Albumin-creatinine ratio • Estimated glomerular filtrate

DM diabetes mellitus, *CVD* cardiovascular diseases, *CHD* coronary heart diseases, *AMI* acute myocardial infarction, *T2DM* type 2 DM, *ESRD* end-stage renal diseases, *BMI* body mass index, *TT* total testosterone, *NR* not reported, *CHD* coronary heart diseases, *CED* cerebrovascular diseases, *PVD* peripheral vascular diseases, *HF* heart failure, *MACE* major adverse cardiovascular diseases (CV death, non-fatal acute myocardial infarction (AMI) and stroke, and acute coronary syndromes and/or HF), *IHD* ischemic heart diseases



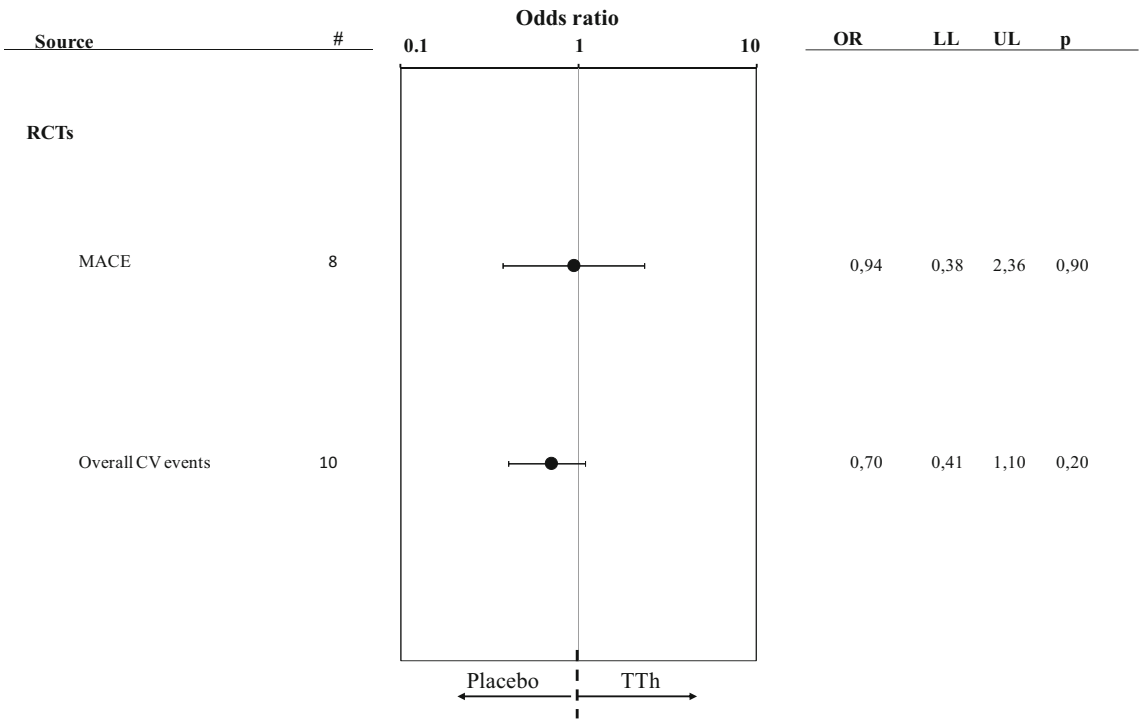


Fig. 1 **a** Odds ratio for unadjusted and fully adjusted overall mortality, cardiovascular (CV) mortality, and CV events in subjects with lower endogenous total testosterone (TT) in comparison to those with higher TT levels at enrolment. **b** MH-odds ratio for major adverse cardiovascular events (MACE) in subjects treated with testosterone substitution (TTh) or placebo as derived from randomized controlled trials (RCTs). Among MACE, the authors considered cardiovascular death, non-fatal myocardial infarction and stroke, and acute coronary syndromes and/or heart failure. LL, lower limit; MH-OR, Mantel-Haenszel-odds ratio; UL, upper limit

metabolic profile with insulin resistance and dyslipidemia [23–26]. TTh reverts this phenotype, as demonstrated by meta-analyses of RCTs [27••] and interventional trials [28, 29], and so one would obviously speculate that, in HG, any potentially lethal event leads more often to overall and CV mortality. However, it is also possible that the reverse is true.

In fact, unfavorable medical conditions, including diabetes and CVD, are associated with reduced T levels [30]. From this point of view, low T is not a causal condition, but it is instead a consequence of chronic illnesses. The non-specificity of the association of low T with all-cause mortality, as well as CV mortality or other disease-related mortality (i.e., cancer-related mortality; [16]), and the lack of an association with the development of CVDs support the latter hypothesis, according to which low T represents a marker of poor health. Whether the decline in T has a biological meaning remains an issue. From a mechanical point of view, it could be a mere consequence of a pro-inflammatory state, common in several chronic diseases, which leads to a multileveled disruption of the gonadal axis [31–33], without any pathogenic meaning. Conversely, in a more finalistic conception, we have formulated another hypothesis [34, 35]. The decline in T occurring in ailing conditions, such as chronic diseases, could be a protective mechanism intended to abolish unnecessary functions in frail subjects (such as fertility and fatherhood, sexual behavior, muscle strength and endurance), aimed at sparing energy for basic functions. Although this hypothesis is not evidence-based, it fits well with the low T3 syndrome, which represents a similar adaptive mechanism which blunts thyroid function during critical illnesses [36].

Data from observational studies cannot provide an answer on the possible hypothesized pathophysiologic mechanisms; however, shedding light on this topic could be of particular importance, because if low T is a risk factor for increased mortality, TTh could be beneficial. Conversely, if low T is a biomarker of frailty or a protective mechanism, TTh might result in a null or even deleterious effect. In this regard, pharmaco-epidemiological studies are more informative.

Pharmaco-epidemiological Studies

Pharmaco-epidemiology is the study of the utilization and effects of treatments in large numbers of people, often based on the use of computerized healthcare datasets, and is useful to quantify positive or adverse events over a long period of observation. In the last 5 years, two pharmaco-epidemiological studies published in 2013 and 2014 [37•, 38•] have raised great debate in the international scientific community, suggesting an increased risk of CV events related to TTh. In the first study, Vigen et al. [37•] retrospectively assessed a cohort of 8709 veterans (VA) with low T levels (T total < 10.4 nmol) that underwent an angiogram between 2005 and 2011. Within the population studied, the risk of major adverse cardiovascular events (MACE) or general mortality was significantly higher among those who were treated with TTh vs. those who did not receive any treatment (25.7 vs. 19.9%; OR = 1.29 [1.04; 1.58]; $p = 0.02$). A few months after the publication of this report, Finkle and coll [38•] published similar results in another pharmaco-epidemiological study. The authors analyzed a large American insurance database (55,593 subjects) by comparing the rate of MI in the 90 days after the TTh began to the rate in the year before the prescription. The final data analysis showed that TTh doubled the risk of MI among men over the age of 65 years, and, in the younger age bands, the risk increased in those who reported a history of CV disease [38•]. In addition, the data were compared with a group of 167,000 individuals who had been prescribed at the same time a type 5 phosphodiesterase inhibitor (PDE5i) demonstrating once again an increased risk of CV in the T-group. Both studies, showing an association of adverse CV events with TTh, have been greatly criticized [39–45]. In addition, in the same time span, another series of pharmaco-epidemiological studies [26, 27••, 28–30, 36] reported just the opposite: TTh was associated with a more favorable outcome.

Table 2 summarizes the characteristics of the 14 pharmaco-epidemiological studies published in the last 5 years [37•, 38•, 46–57]. Nine studies [37•, 46, 47, 49, 51, 52•, 54, 56, 57] compared the effect of TTh in treated vs. untreated hypogonadal subjects, whereas in five studies [38•, 48, 50, 52•, 55], the effect of TTh in HG was compared to a healthy population of untreated subjects. The published trials included 1,382,232 subjects with a mean follow-up of 232 weeks, and the mean age of the enrolled cohorts was 63.4 years. Information on overall mortality was available in nine studies [46, 47, 49, 51, 52•, 54–57], seven of which [46, 47, 51, 52•, 55–57] showed a positive, and two [49, 54] a lack of association between TTh and survival. Information on acute myocardial infarction (AMI) was available in eight studies [38•, 48, 50, 52•–54, 56, 57]. Only one [38•] study reported an increased risk of MI along with TTh, whereas four reported a lower risk [51, 55–57]and three no association [48, 50, 54]. Four studies reported an association between TTh and cerebrovascular events [52•, 54, 56, 57]. Among these, three studies [52•, 56, 57] indicated a protective effect of TTh and one study [54] found no association at all. Finally, one study [37•] reported only information related to a composite risk including overall mortality, MI, and stroke, showing that TTh was associated with increased CV risk.

Overall, the large majority of retrospective intervention studies show a negative association between T use and CVD, although a few studies have claimed the reverse. As stated before, the studies showing a negative effect of TTh on CV health have received more attention, including media attention, than the positive studies.

All the pharmaco-epidemiological studies had several flaws, which limit the conclusions that can be drawn about the relationship between CVD and TTh in these populations. In fact, although the results are often adjusted, residual confounding factors may still be a source of selection bias due to the non-random assignment of T exposure. In fact, physicians often prefer to treat healthier and/or younger individuals, and

Table 2 Descriptive characteristics of the available pharmaco-epidemiological studies evaluating the impact of testosterone (T) treatment (TTh) on forthcoming overall and cardiovascular mortality and morbidity

Study	No. of patients (cases/controls)	Population	Follow-up (weeks)	Study design	Medication used	Treated vs. untreated	Diagnosis of hypogonadism	Age (years), mean/range	Overall mortality	AMI	CE
Shores et al. [46]	398/633	Veterans	81	T treatment vs. no treatment	T cypionate or T enanthate	HG vs. HG	TT < 8.7 nmol/L	62.1	↓	NA	NA
Muraleedharan et al. [47]	64/174	Men with T2DM	166	T treatment vs. no treatment	Mixed	HG vs. HG	TT < 10.4 nmol/L	60.3	↓	NA	NA
Vigen et al. [37•]	1223/7486	Veterans with CVD	110	T treatment vs. no treatment	Mixed	HG vs. HG	TT < 10.4 nmol/L	63.4	↑[a]	↑[a]	↑[a]
Baillargeon et al. [48]	6355/19,065	Elderly from general population	182	TTh prescription vs. no TTh prescription	Mixed	NA	NA	NA	NA	↔	NA
Finkle et al. [38•]	55,593/141,031	General population	140	TTh prescription vs. PDE5i prescription	Mixed	NA	NA	54.3	NA	↑	NA
Eisenberg et al. [49]	284/225	Men with sexual dysfunction or infertility	520	TTh prescription vs. no treatment	Mixed	HG vs. HG	NA	54.4	↔	NA	NA
Etminan et al. [50]	30,066/120,264	Elderly from general population	145	TTh prescription vs. no TTh prescription	Mixed	NA	NA	70.4	NA	↔	NA
Ramasamy et al. [51]	153/64	Men attending a tertiary urology clinic	191	T treatment vs. no treatment	Mixed	HG vs. HG	TT < 10.4 nmol/L	74.3	↓	NA	NA
Sharma et al. [52•]	60,632/21,380	Veterans	304	T treatment vs. no treatment	Mixed	HG vs. HG	TT lower than the local laboratory reference range	66.2	↓[b]	↓[b]	↓[b]
Tan et al. [53]	19,968/821,725	General population	72	TTh prescription vs. no TTh prescription	Mixed	HG vs. mixed	TT < 12.0 nmol/L	NA	NA	↓	NA
Maggi et al. [54]	759/249	Men with sexual dysfunction or infertility	156	T treatment vs. no treatment	Mixed	HG vs. HG	TT lower than the local laboratory reference range	59.1	↔	↔	↔
Wallis et al. [55]	10,311/28,029	Elderly men from general population	260	TTh prescription vs. no TTh prescription	Mixed	HG vs. No HG	NA	NA	↓	NA	NA
Cheetham et al. [56]	8808/ 35,527	General population	224	T treatment vs. no treatment	Mixed	HG vs. HG	Mixed hypogonadal and eugonadal subjects	NA	↓	↓	↓
Traish et al. [57]	360/296	Men with urological complaints	364	T treatment vs. no treatment	T undecanoate, 1000 mg every/12 weeks	HG vs. HG	TT < 12.1 nmol/L	60.7	↓	↓	↓

TT total testosterone, *BT* bioavailable testosterone, *HG* hypogonadism, *T* testosterone, *NA* not available, *BMI* body mass index, *DM* diabetes mellitus, *HT* hypertension, *T2DM* type 2 DM, *CVD* cardiovascular diseases, ↓ reduced risk, ↑ increased risk, ↔ unchanged risk

[a] Composite of all-cause mortality, MI, and ischemic stroke

[b] Normalized treated vs. untreated

healthier and/or younger individuals more often request treatment for their hypogonadism-related problems thus accounting for mortality and morbidity being lowest in this group. In fact, in a cross-sectional study involving a large sample of veterans [58], it was shown that TTh was more often prescribed to younger men and those free from previous CV events. The propensity of physicians to prescribe TTh in younger men was also found in an Italian prospective study involving more than 400 men referred to Endocrinology Clinics [59]. In pharmaco-epidemiological studies, in addition, diagnostic indications for using TTh and pre- and post-treatment drug levels of T were often not available. It is unknown whether the patient, after having received a prescription, actually had it filled, used it, or obtained and used refills. Finally, some studies used only all-cause mortality as the outcome, making it impossible to capture the extent of CV-related mortality. Because of the large variability in the inclusion and exclusion criteria, the different definitions of the hypogonadal state at the study entry, the variability in the type of T preparation employed, and the lack of follow-up during treatment (see Table 2), all the results obtained with retrospective pharmaco-epidemiological studies must be interpreted with caution.

Randomized Controlled Trials

Randomized placebo-controlled trials (RCTs) are often considered as the gold standard for assessing the efficacy and safety of a specific treatment because of reduced selection bias through randomization and rigorous assessment of the variable(s) tested by using the comparison with a control group. Up to now, RCTs specifically designed to test the effect of TTh on CV outcomes have been scanty and dated. In 2003, an Institute of Medicine panel [60] recommended a series of clinical trials to critically evaluate the usefulness of TTh for several clinical indications. Under this auspice, the T-Trials—a group of seven coordinated, placebo-controlled, rigorously designed and well-executed trials—were performed at 12 sites across the USA. They enrolled 790 men to address the efficacy of TTh in men aged 65 years or older with low T (< 9.5 nmol/L) for any apparent reason other than age. Results from some of these trials have recently been published and one addressed whether there is a change in CV risk factors upon TTh, as compared to placebo [61•]. The primary outcome was the change from baseline in non-calcified plaque volume, as measured by computed tomography angiography. Non-calcified plaque volume was used as an estimate of the increased risk of MI and other CV events. The unexpected result was that the non-calcified plaque volume increased significantly more in the T-treated group, as compared to placebo. In addition, a significantly greater—although weaker—increase was noticed for one of the secondary outcomes, fibrous plaque, in TTh men as compared with the placebo arm. These results suggest that TTh is associated with a worsening in the atherosclerotic process, particularly with regard to the most unstable type of plaque, the non-calcified one. However, it should be noticed that prevalence of atherosclerosis, as well as plaque volume, was greater at baseline in placebo-treated than TTh group, thus introducing a bias in the interpretation of the results. In fact, the greater increase in non-calcified plaque volume observed in the TTh group could be considered particularly severe because it occurred in relatively healthier men. However, an alternative interpretation is that the limited increase in plaque volume found in the placebo treated arm could be the expression of an advanced atherosclerotic disease, which had already achieved a plateau, thus preventing it from worsening any further. Besides being not homogenously distributed in the study arms, men with useful information on the topic of artery disease were relatively few, as only 170 enrolled men participated for a total length of 1 year. Based on the small sample size, also the authors recognized that larger studies are needed to establish a real link between TTh and MACE. Results of the T-trial were in contrast with those from another RCT recently performed in the USA, the TEAAM study [62]. TEAAM was a placebo-controlled, double-blind, parallel-group randomized trial involving 308 men 60 years or older with a broad range of low or low-normal testosterone levels (2.5–14 nmol/L), recruited at three US sites. After 3 years of observation, no difference in the progression of subclinical atherosclerosis between the men assigned to receive TTh or placebo was found, as measured by the joint primary endpoints of intima-media thickness for the carotid artery and coronary artery calcium, as surrogate markers of atherosclerotic progression [62]. It is important to note that both T-Trials and TEAAM do not have actual CV events as their primary endpoint but utilize alleged markers of them instead. As stated before, there are no recent, large, long-term RCTs to provide definitive conclusions about TTh and CV risk. Hence, information can be derived from RCTs conducted for other purposes, where CVD represented a secondary endpoint, and from their meta-analyses. It is important to note that no RCTs scrutinized by these meta-analyses were powerful enough for the assessment of safety outcomes. Onasanya et al. [63••] and Corona et al. [64] have provided an overview of the available meta-analyses. In the last 5 years, five distinct meta-analyses were released [65–69]. The conclusion they reached was in apparent contrast. Whereas Xu et al. [65] found a T-associated increase in CV risk, the other four did not, although with some caveats. In fact, in the meta-analyses by Borst et al. [67] and by Albert et al. [68], an increase in risk associated with the use of TTh via oral route was reported. In addition, in that of Albert et al. [68], an increased risk associated also with transdermal preparation was found, but only in men older than 65 years.

Among the 19 RCTs published in the last 5 years [61•, 62, 70–86], some of them [70–73] were not taken into consideration in the aforementioned meta-analyses, because they were

published later. In addition, one completed but still unpublished study was also identified through the clinicaltrials.gov website (NCT00957528) and considered only in one previous analysis [66]. We, therefore, decided to perform a new meta-analysis of recent (last 5 years) trials, including the most recent RCTs ([61•, 62, 70–86]; NCT00957528). Characteristics of the retrieved trials are summarized in Table 3, whereas Fig. 1b reports the main conclusions. Among the 20 RCTs included in the analysis ([61•, 62, 70–86]; NCT00957528), 19, 16, 17, and 19 studies reported information on MACE ([61•, 62, 70–73, 75–86]; NCT00957528), MI [61•, 62, 70–73, 76–84, 86], stroke [61•, 62, 70–73, 76–86], and CV mortality [61•, 62, 70–86], respectively. In addition, 17 studies also reported information on acute coronary syndrome [61•, 62, 70–73, 76–86] and 16 on hospitalization for heart failure (HF; [61•, 70–73, 75–86]). Retrieved trials included 1710 and 1623 patients in TTh and placebo groups, respectively, with a mean trial duration of 42.9 weeks. Note that TTh was administered in different doses, formulations, and cohorts (Table 3).

Of the 19 trials reporting information on MACE ([61•, 62, 70–73, 75–86]; NCT00957528), 11 detected no events ([61•, 72, 73, 76, 78, 79, 82–84]; NCT00957528); therefore, the main analysis was performed on eight trials [62, 71, 75, 77, 80, 81, 85, 86]. The use of TTh was not associated with any significant difference in the incidence of MACE with respect to placebo (MH-OR 0.94 [0.38; 2.36]; $p = 0.90$) (Fig. 1b). In addition, similar results were confirmed when the individual MACE was analyzed separately (not shown) and when any CV-related events were considered (Fig. 1b). Hence, information derived from the last 5 years of RCTs are not divergent from the previous studies: TTh was not associated with forthcoming CV events, even though a protective role of the therapy could not be demonstrated.

Overall, the results from RCTs are reassuring, as they do not demonstrate a harmful effect of TTh on CV health. However, their results should be considered with caution. In fact, although evidence deriving from RCTs is regarded as having the highest level of quality, RCTs also have a number of drawbacks. Firstly, results from RCTs are often of limited generalizability, because subjects are usually enrolled according to a number of strict inclusion and exclusion criteria. In addition, RCTs typically have relatively short-term follow-ups and those on the topic of TTh-related CV risk are no exception, as their duration was no longer than 3 years. This time frame could be insufficient for capturing CV risk associated with a long-lastingexposure to TTh. In fact, it is conceivable that TTh is associated with subtle pathophysiologic changes, which may take years before developing into an adverse CV event. In addition, none of the RCTs evaluated the occurrence of CV events as the primary outcome and only intermediate endpoints have been considered by some RCTs, providing conflicting results. Pending further, longer lasting, specifically designed and powered RCTs, present evidence shows that TTh is not associated with an increased short-term CV risk, even though it does not support the contrary hypothesis of a protective role of TTh on CV health either.

Discussion

In longitudinal observational studies, there is a clear association between baseline T deficiency and overall mortality and CVD-related mortality, even when scrutinizing surveys from the last 5 years. Concerning the question whether testosterone deficiency is the cause or the consequence of these CV diseases, this systematic analysis of the most recent reports does not help substantially in profiling the direction of this association. In fact, there are at least three possible open scenarios for interpreting the relationship: (i) CVD and hypogonadism are concomitant conditions; (ii) low T favors CVD; and (iii) CVD induces a hypogonadal state. Concerning the third possibility, only studies having T levels as a primary outcome and designed to treat CVD will provide information; however, such studies are not available yet. It is possible that CVD could induce a decline in T through the effect of pro-inflammatory cytokines, which commonly characterize CVD and other chronic illnesses [31–33], acting at several levels of the gonadal axis. We have hypothesized that this mechanism occurring in CVD, as well as other morbidities, and aging itself, could induce a hypogonadal state as a resilient mechanism to save energy and to decrease fertility, protecting the species from inefficient fathers and the subjects from spending excessive energy. Accordingly, we observed that CVD-associated HG could have a protective effect against forthcoming MACE [34, 35]. In fact, in a population at high CV risk, such as that of patients consulting an Andrology clinic for erectile dysfunction, having low T at study entry is associated with a significant decrease in the occurrence of adverse CV events, in particular when cohorts at high risk were selected, such as those with obesity [34]or those with a previous CV event [35]. Concerning subjects at high CV risk because of a previous MACE, total $T < 12$ nmol/L was associated with a lower incidence of new CV events. Similarly, patients with a lower testis volume (TV) have a lower incidence of CV events, even after adjusting for lifestyle factors and comorbidities. When the two factors were combined (low T + low TV), those with a history of CVD and fulfilling the two criteria (low T + low TV) were entirely free of further incident CV events. Hence, careful consideration of the mechanisms involved is always necessary prior to translating observational data into therapeutic decisions. In fact, many epidemiological associations are determined by adaptive mechanisms and not by pathogenic factors; the treatment of a compensatory alteration can easily produce a detrimental effect.

Concerning the possibility that low T favors CV events, treating the hypogonadal condition should offer a protection

Table 3 Characteristics of the randomized, placebo controlled clinical studies included in the meta-analysis

Study (ref.)	No. of patients (T/placebo)	Trial duration (weeks)	Age (years)	Comorbidities	Baseline total T (nmol/L)	T levels	Dose
Hoyos et al. [74]	33/34	18	48.5	Obese with OSA	13.3	Mixed	TU 1000 mg/12-weeks
Behre et al. [75]	183/179	48	62.0	Elderly men	10.5	Mixed	TG 50–75 mg/day
Hackett et al. [76]	92/98	30	61.5	T2DM	9.0	TT < 12 nM	TU 1000 mg/12-weeks
Hildreth et al. [77]	96/47	52	66.5	Elderly men	10.2	TT < 12 nM	TG 100 mg/day
Maggio et al. [78]	43/24	156	71.8	Elderly men	13.4	Mixed	T patch 6 mg/day
NCT00957528	9/8	20	69.6	Elderly men	NR	Mixed	TE 100 mg/week
Borst et al. [79]	14/16	52	70.5	Elderly men	8.8	TT < 10.4 nM	TE 125 mg/week
Gianatti et al. [80]	45/43	40	62.0	T2DM	8.6	< 12 nM	TU 1000 mg/12-weeks
Janjgava et al. [81]	43/42	24	49.7	T2DM	NR	Mixed	TE 250/12 weeks
Asih et al. [82]	25/25	24	NR	Elderly men	17.2	Mixed	T cream 5% 50 mg/day
Basaria et al. [62]	155/151	156	67.6	Elderly men	10.5	Mixed	TG 75 mg/day
Basaria et al. [83]	36/29	14	48.9	Treated with opioids	8.5	TT < 12 nM	TG 50 mg/day
Cherrier et al. [73]	10/12	24	70.5	Elderly men	10.6	TT < 10.4 nM	TG 50–100 mg/day
Glintborg et al. [72]	23/23	24	67.5	Elderly men	NR	BT < 7.3 nM	TG 50–100 mg/day
Paduch et al. [84]	40/36	16	50.7	Ejaculatory dysfunction	7.5	TT < 10.4 nM	T solution 60 mg/day
Brock et al. [71]	358/357	12	55.3	Elderly men	6.9	TT < 10.4 nM	T solution 60–120 mg/day
Chillarón et al. [70]	6/7	22	46.3	T1DM	10.9	TT < 10 nM	TU 1000 mg/12-weeks
Dhinsda et al. [85]	22/22	23	54.7	T2DM	8.6	FT <225 pM	TC 200 mg/2 weeks
Snyder et al. [86]	395/395	52	72.2	Elderly men	8.0	TT < 9.5 nM	TG 50–100 mg/day
Budoff et al. [61•]	88/82	52	71.2	Elderly men	8.2	TT < 9.5 nM	TG 50 mg/day

TT total testosterone, *FT* free testosterone, *BT* bioavailable testosterone, *TE* testosterone enanthate, *TU* testosterone undecanoate, *TC* testosterone cypionate, *TG* testosterone gel, *NR* not reported, *T2DM* type 2 diabetes mellitus, *T1DM* type 1 diabetes mellitus, *OSA* obstructive sleep apnea

against forthcoming adverse events. This is apparently the lesson from several [46–57], but not all [37•, 38•], pharmaco-epidemiological studies recently published. However, as extensively discussed before, such studies suffer from several pitfalls: the most important is a selection bias due to the non-random allocation of the intervention arm. Usually, the healthier subjects are treated, whereas those with underlying conditions are not. Hence, only analysis of RCTs with a rigorous design can tell us whether TTh might increase or decrease the risk of CV events. RCTs published in the last 5 years and their meta-analysis presented here do not provide us with clear information on this point. While there is no clear sign of increased risk, there is also no sign of protection. The first possibility seems to be the most reasonable—low T and CV disease are concomitant conditions, and higher T represents a useful biomarker of general and CV health.

Conclusions

The interconnections between T and CV health are complex and far from having been fully clarified. During the last few years, several scientific reports have pointed out a CV risk associated with TTh, thus shedding a new negative light on the safety of TTh. This led the US Food and Drug Administration agency to release an alert requiring that labels of medicines containing T report a warning that they may increase the risk of heart attack and stroke.

The meta-analysis of the available evidence on this topic helped to depict a comprehensive scenario. Low endogenous T levels are associated with overall mortality and CVD-related mortality. This finding appears to be a robust one since it keeps on confirming previous results; however, it does not provide definitive information on the pathogenetic relationship between these two conditions. In fact, T deficiency could represent either a marker of frailty, which develops concomitantly with a chronic illness, or it is the cause of health deterioration, finally leading to death. In the latter case, it could be expected that TTh improves CV health and decreases mortality. However, such a conclusion cannot be drawn from a meta-analysis of RCTs, apart from a subgroup analysis concerning few studies enrolling subjects with metabolic disturbances [66]. Conversely, in the last few years, concerns about the CV safety of TTh have arisen, but it should be recognized that, at present, there is no consistent evidence of a detrimental effect of TTh. Data from most pharmaco-epidemiological studies suggest an unchanged or decreased CV risk associated with TTh, whereas only very few have demonstrated an increased mortality or CV risk, although the latter received much more editorial and medical attention in scientific journals and the lay press. The meta-analysis of the available RCTs did not find any CV risk associated with TTh. Keeping in mind all the drawbacks of both the observational pharmaco-epidemiological and the RCT designs, available evidence is reassuring in terms of the safety of TTh and a short-term CV risk. On the other hand, there is no proof of a protective role. There is still a need for further longer and adequately powered studies to shed light on this complicated and highly debated matter.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124:2145–54.
2. Humphries SE. Common variants for cardiovascular disease. Circulation. 2017;135:2102–5.
3. Pope HG, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. Endocr Rev. 2014;35:341–75.
4. Velho I, Fighera TM, Ziegelmann PK, Spritzer PM. Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. Andrology. 2017; https://doi.org/10.1111/andr.12382.
5. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, 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;60:1451–7.
6. Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Boloña ER, Sideras K, 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.
7. Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, et al. Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010;95:2560–75.
8. FDA Drug Safety Communication: FDA cautions about using T products for low T due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. US Food and Drug Administration website. http://www.fda.gov/Drugs/DrugSafety/ucm436259.htmforHumanMedicalProducts/ucm402054.htm. Published March 3, 2015 (Accessed August 3, 2017).
9. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol. 2011;165:687–701.
10. Hyde Z, Norman PE, Flicker L, et al. Low free testosterone predicts mortality from cardiovascular disease but not other causes: the Health in Men Study. J Clin Endocrinol Metab. 2012;97:179–89.
11. Lerchbaum E, Pilz S, Boehm BO, et al. Combination of low free testosterone and low vitamin D predicts mortality in older men referred for coronary angiography. Clin Endocrinol (Oxf). 2012;77:475–83.
12. Schneider HJ, Wallaschofski H, Völzke H, et al. Incremental effects of endocrine and metabolic biomarkers and abdominal obesity on cardiovascular mortality prediction. PLoS One. 2012;7:e33084.
13. Haring R, Teng Z, Xanthakis V, et al. Association of sex steroids, gonadotrophins, and their trajectories with clinical cardiovascular disease and all-cause mortality in elderly men from the Framingham Heart Study. Clin Endocrinol (Oxf). 2013;78:629–34.
14. Bello AK, Stenvinkel P, Lin M, et al. Serum testosterone levels and clinical outcomes in male hemodialysis patients. Am J Kidney Dis. 2014;63:268–75.
15. Khurana KK, Navaneethan SD, Arrigain S, Schold JD, Nally JV Jr, Shoskes DA. Serum testosterone levels and mortality in men with CKD stages 3-4. Am J Kidney Dis. 2014;64:367–74.

16. Pye SR, Huhtaniemi IT, Finn JD, et al. Late-onset hypogonadism and mortality in aging men. J Clin Endocrinol Metab. 2014;99: 1357–66.
17. Shores MM, Biggs ML, Arnold AM, et al. Testosterone, dihydrotestosterone, and incident cardiovascular disease and mortality in the cardiovascular health study. J Clin Endocrinol Metab. 2014;99: 2061–8.
18. Srinath R, Hill Golden S, Carson KA, Dobs A. Endogenous testosterone and its relationship to preclinical and clinical measures of cardiovascular disease in the atherosclerosis risk in communities study. J Clin Endocrinol Metab. 2015;100:1602–8.
19. Cheung KK-T, Lau ES-H, So W-Y, Ma RC-W, Ozaki R, Kong AP-S, et al. Low testosterone and clinical outcomes in Chinese men with type 2 diabetes mellitus—Hong Kong Diabetes Registry. Diabetes Res Clin Pract. 2017;123:97–105.
20. Soisson V, Brailly-Tabard S, Helmer C, et al. A J-shaped association between plasma testosterone and risk of ischemic arterial event in elderly men: the French 3C cohort study. Maturitas. 2013;75: 282–8.
21. Ruige JB, Mahmoud AM, De Bacquer D, Kaufman JM. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. Heart. 2011;97:870–5.
22. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;96:3007–19.
23. Dhindsa S, Ghanim H, Batra M, Kuhadiya ND, Abuaysheh S, Sandhu S, et al. Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. Diabetes Care. 2016;39:82–91.
24. Corona G, Cipriani S, Rastrelli G, Sforza A, Mannucci E, Maggi M. High triglycerides predicts arteriogenic erectile dysfunction and major adverse cardiovascular events in subjects with sexual dysfunction. J Sex Med. 2016;13:1347–58.
25. Corona G, Vignozzi L, Sforza A, Mannucci E, Maggi M. Obesity and late-onset hypogonadism. Mol Cell Endocrinol. 2015;418: 120–33.
26. Brand JS, Rovers MM, Yeap BB, Schneider HJ, Tuomainen TP, Haring R, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. PLoS One. 2014;9:e100409.
27.•• Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, et al. Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol. 2016;174:R99–116. **Important meta-analysis summarizing the effect of testosterone treatment on body composition and metabolic profile.**
28. Corona G, Maseroli E, Maggi M. Injectable testosterone undecanoate for the treatment of hypogonadism. Expert Opin Pharmacother. 2014;15:1903–26.
29. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. J Endocrinol Investig. 2016;39:967–81.
30. Corona G, Maseroli E, Rastrelli G, Francomano D, Aversa A, Hackett GI, et al. Is late-onset hypogonadotropic hypogonadism a specific age-dependent disease, or merely an epiphenomenon caused by accumulating disease-burden? Minerva Endocrinol. 2016;41:196–210.
31. Traish AM, Feeley RJ, Guay A. Mechanisms of obesity and related pathologies: androgen deficiency and endothelial dysfunction may be the link between obesity and erectile dysfunction. FEBS J. 2009;276:5755–67.
32. Morelli A, Sarchielli E, Comeglio P, Filippi S, Vignozzi L, Marini M, et al. Metabolic syndrome induces inflammation and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits. Mol Cell Endocrinol. 2014;382:107–19.
33. Veldhuis J, Yang R, Roelfsema F, Takahashi P. Proinflammatory cytokine infusion attenuates LH's feedforward on testosterone secretion: modulation by age. J Clin Endocrinol Metab. 2016;101: 539–49.
34. Corona G, Rastrelli G, Monami M, Melani C, Balzi D, Sforza A, et al. Body mass index regulates hypogonadism-associated CV risk: results from a cohort of subjects with erectile dysfunction. J Sex Med. 2011;8:2098–105.
35. Corona G, Rastrelli G, Maseroli E, Fralassi N, Sforza A, Forti G, et al. Low testosterone syndrome protects subjects with high cardiovascular risk burden from major adverse cardiovascular events. Andrology. 2014;2:741–7.
36. Bartalena L, Bogazzi F, Brogioni S, Grasso L, Martino E. Role of cytokines in the pathogenesis of the euthyroid sick syndrome. Eur J Endocrinol. 1998;138:603–14.
37.• Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA. 2013;310:1829–36. **Pharmaco-epidemiological study empathizing possible increased cardiovascular risk related to testosterone treatment.**
38.• Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. Gong Y., editor PLoS One 2014; 9:e85805. **Pharmaco-epidemiological study empathizing possible increased cardiovascular risk related to testosterone treatment.**
39. Corona G, Maggi M. Testosterone supplementation and cardiovascular risk. Trends Cardiovasc Med. 2015;25:258–60.
40. Katz J, Nadelberg R. Deaths and cardiovascular events in men receiving testosterone. JAMA. 2014;311:963.
41. Riche DM, Baker WL, Koch CA. Deaths and cardiovascular events in men receiving testosterone. JAMA. 2014;311:963.
42. Irwin G. Knowledge is power. J Sex Med. 2014;11:613–5.
43. Page ST. Testosterone, cardiovascular disease, and mortality in men: living in the dark. Lancet Diabetes Endocrinol. 2014;2:609–11.
44. Morgentaler A. Testosterone, cardiovascular risk, and hormonophobia. J Sex Med. 2014;11:1362–6.
45. Corona G, Dicuio M, Rastrelli G, Maseroli E, Lotti F, Sforza A, et al. Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'? J Investig Med. 2017;65:964–73.
46. 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;97:2050–8.
47. 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;169:725–33.
48. Baillargeon J, Urban RJ, Kuo YF, et al. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother. 2014;48:1138–44.
49. Eisenberg ML, Li S, Herder D, Lamb DJ, Lipshultz LI. Testosterone therapy and mortality risk. Int J Impot Res. 2015;27:46–8.
50. Etminan M, Skeldon SC, Goldenberg SL, Carleton B, Brophy JM. Testosterone therapy and risk of myocardial infarction: a pharmacoepidemiologic study. Pharmacotherapy. 2015;35:72–8.
51. Ramasamy R, Scovell J, Mederos M, Ren R, Jain L, Lipshultz L. Association between testosterone supplementation therapy and thrombotic events in elderly men. Urology. 2015;86:283–5.
52.• Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J. 2015;36:2706–15. **Pharmaco-epidemiological study empathizing possible reduced cardiovascular risk related to testosterone treatment.**

53. Tan RS, Cook KR, Reilly WG. Myocardial infarction and stroke risk in young healthy men treated with injectable testosterone. Int J Endocrinol. 2015;2015:970750.
54. Maggi M, Wu FC, Jones TH, et al. Testosterone treatment is not associated with increased risk of adverse cardiovascular events: results from the Registry of Hypogonadism in Men (RHYME). Int J Clin Pract. 2016;70:843–52.
55. Wallis CJ, Lo K, Lee Y, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. Lancet Diabetes Endocrinol. 2016;4:498–506.
56. Cheetham TC, An J, Jacobsen SJ, et al. Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. JAMA Intern Med. 2017;177:491–9.
57. Traish AM, Haider A, Haider KS, Doros G, Saad F. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism. J Cardiovasc Pharmacol Ther. 2017;22(5):414–33.
58. Jasuja GK, Bhasin S, Reisman JI, Hanlon JT, Miller DR, Morreale AP, et al. Who gets testosterone? Patient characteristics associated with testosterone prescribing in the veteran affairs system: a cross-sectional study. J Gen Intern Med. 2017;32:304–11.
59. Rastrelli G, Giovannini L, Calogero AE, Gianfrilli D, Serra E, Pizzocaro A, et al. Predictors and clinical consequences of starting androgen therapy in men with low testosterone: results from the SIAMO-NOI registry. J Endocrinol Investig. 2016;39:695–708.
60. Testosterone and Aging: Clinical Research Directions. Institute of Medicine (US) Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy; Liverman CT, Blazer DG, editors. Washington (DC): National Academies Press (US); 2004.
61.• Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, Wenger NK, Bhasin S, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. JAMA. 2017;317:708–16. **Important double-blind placebo-controlled trial reporting increased coronary plaque volume related to testosterone treatment.**
62. Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels. JAMA. 2015;314:570.
63.•• Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. Lancet Diabetes Endocrinol. 2016;4:943–56. **Summary of the available meta-analyses summarizing the effect of testosterone treatment of cardiovascular risk.**
64. Corona G, Sforza A, Maggi M. Testosterone replacement therapy: long-term safety and efficacy. World J Mens Health. 2017;35(2):65–76.
65. 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.
66. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, et al. Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf. 2014;13:1327–51.
67. Borst SE, Shuster JJ, Zou B, Ye F, Jia H, Wokhlu A, et al. Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. BMC Med. 2014;12:211.
68. Albert SG, Morley JE. Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. Clin Endocrinol. 2016;85:436–43.
69. Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular risks of exogenous testosterone use among men: a systematic review and meta-analysis. Am J Med. 2017;130:293–305.
70. Chillaron JJ, Fernandez-Mirò M, Albareda M, Sara F, Colom C, Vila L, et al. Testosterone undecanoate improves lipid profile in patients with type 1 diabetes and hypogonadotropic hypogonadism. Endocr J. 2016;63:849–55.
71. Brock G, Heiselman D, Maggi M, Kim SW, Rodríguez Vallejo JM, Behre HM, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. J Urol. 2016;195:699–705.
72. Glintborg D, Christensen LL, Kvorning T, Larsen R, Højlund K, Brixen K, et al. Differential effects of strength training and testosterone treatment on soluble CD36 in aging men: possible relation to changes in body composition. Scand J Clin Lab Invest. 2015;75:659–66.
73. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. Am J Alzheimers Dis Other Demen. 2015;30:421–30.
74. Hoyos CM, Yee BJ, Phillips CL, et al. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial. Eur J Endocrinol. 2012;167:531–41.
75. Behre HM, Tammela TL, Arver S, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. Aging Male. 2012;15:198–207.
76. Hackett G, Cole N, Bhartia M, et al. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. J Sex Med. 2013;10:1612–27.
77. Hildreth KL, Barry DW, Moreau KL, et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J Clin Endocrinol Metab. 2013;98:1891–900.
78. Maggio M, Snyder PJ, Ceda GP, et al. Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. Andrology. 2013;1:24–8.
79. 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:E433–42.
80. 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;37:2098–107.
81. Janjgava S, Zerekidze T, Uchava L, Giorgadze E, Asatiani K. Influence of testosterone replacement therapy on metabolic disorders in male patients with type 2 diabetes mellitus and androgen deficiency. Eur J Med Res. 2014;19:56.
82. Asih PR, Wahjoepramono EJ, Aniwiyanti V, et al. Testosterone replacement therapy in older male subjective memory complainers: double-blind randomized crossover placebo-controlled clinical trial of physiological assessment and safety. CNS Neurol Disord Drug Targets. 2015;14:576–86.
83. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. Pain. 2015;156:280–8.
84. Paduch DA, Polzer PK, Ni X, Basaria S. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction: a randomized controlled trial. J Clin Endocrinol Metab. 2015;100:2956–62.
85. Dhindsa S, Ghanim H, Batra M, et al. Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. Diabetes Care. 2016;39:82–91.
86. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374:611–24.