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An update on heart disease risk associated with testosterone boosting medications

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Abstract

Introduction: The cardiovascular (CV) safety of testosterone replacement therapy (TRT) remains a crucial issue in the management of subjects with late onset hypogonadism. The authors systematically reviewed and discussed the available evidence focusing our analysis on heart related issues.

Areas covered: All the available data from prospective observational studies evaluating the role endogenous T levels on the risk of acute myocardial infarction (AMI) were collected and analyzed. In addition, the impact of TRT on heart related diseases, as derived from pharmaco-epidemiological studies as well as from randomized placebo-controlled trials (RCTs), was also investigated.

Expert opinion: Available evidence indicates that endogenous low T represents a risk factor of AMI incidence and its related mortality. TRT in hypogonadal patients is able to improve angina symptoms in subjects with ischemic heart diseases and exercise ability in patients with heart failure (HF). In addition, when prescribed according to the recommended dosage, TRT does not increase the risk of heart-related events.

Key words: testosterone, cardiovascular diseases, heart failure, ischemic heart diseases

Article highlights
• Low endogenous testosterone (T) is associated with an increased risk of acute myocardial infarction (AMI)-related mortality and AMI incidence.
• Testosterone replacement therapy (TRT) in hypogonadal patients is able to improve angina symptoms in subjects with ischemic heart diseases and exercise ability in patients with heart failure.
• In 2014, the European Medical Agency (EMA) did not share the FDA's opinion of an increased CV risk linked to T medication, because of the lack of convincing evidence.
• The analysis of all randomized placebo controlled controlled trials showed that when prescribed according to the recommended dosage, TRT does not increase the risk of heart-related events.

1.0 Introduction

Ischemic heart disease or coronary artery disease (CAD) is a medical condition encompassing several etiologies all having as a common factor an imbalance between oxygen supply to the heart and oxygen demand. CAD - including angina pectoris, acute myocardial infarction (AMI) and silent myocardial ischemia - is essentially due to an atherosclerosis-induced inadequate perfusion of the heart from the epicardial coronary arteries and represents the most common of the cardiovascular diseases (CVD) (1).

CAD mortality rates have declined worldwide over the past five decades; however, CAD remains responsible for one out of three deaths in midlife individuals. Data from the National Health and Nutrition Examination Surveys (NHANES) -a cross-sectional, nationally representative survey, conducted between1988 to 1994 and 1999 to 2004– indicate that midlife men had an age-adjusted higher prevalence of CAD than midlife women did; however, the gap narrows as a function of survey time (2). In another US survey, CAD prevalence was confirmed greater among men (7.8%) than women (4.6%), with a decline from 2006 to 2010 of 8.2% and 11.5% in men and women, respectively (3). According to a UK database (4), three times as many men have had a AMI compared with women. All this evidence suggests a possible role for male hormones in the pathogenesis of CAD.

Considering that testosterone (T) is the main male androgen, it is obvious that the suspicion that this hormone could be deleterious for the male cardiovascular (CV) system has been present for a long time, although with mixed evidence (5-7). One randomized controlled trial (RCT) published in 2010 (8) and two large observational studies published in 2013 (9) and 2014 (10) generated great acclaim in the scientific community, suggesting an increased CV risk related to testosterone replacement treatment (TRT). The Testosterone in Older Men with Mobility Limitations (TOM) trial was a double blind placebo-controlled RTC including more than 200 hypogonadal (total T 3.5-12.1 nmol/L or free T <173 pmol/L) men aged 65 years or older with limitations in mobility. The study was prematurely interrupted due to higher CV related events in the active arm. Several flaws have been attributed to this trial. In particular, subjects were treated with supra-physiological dose of T gel (100 mg daily) for six months, CV events were not adjudicated and several minor problems were including self-reported syncope and peripheral edema were considered (6). In 2013, Vigen et al., (9) reported the retrospective analysis of a cohort of 8,709 American Veterans (VA) with reduced T levels (T<10.4 nmol/L), who

underwent coronary angiography between 2005 and 2011. The showed that those who were treated with T during the follow-up period had an increased risk of major adverse cardiovascular events (MACE) or death from any cause when compared to those who did not use T (9). The main problems related to this study were the lack of information concerning T dosing and measurements during the follow up (6). Finally, in 2014 Finkle et al., (10) further published data related the analysis of a large Medicare insurance database including 55,593 subjects. They concluded that TRT doubled the risk of heart attack among men aged 65 years and older, particularly in younger men with a preexisting history of heart disease. Interestingly, the selected control group was based on 167,000 individuals who were prescribed a phosphodiesterase type 5 inhibitor (PDE5i). The latter choice is inevitably questionable, since PDE5i have been reported to have distinct cardio-protective effects (11).The debate reached a turning point in 2015 when the Food and Drug Administration (FDA) issued a safety notification regarding the misuse of T-containing products due to a potential risk of CV harm (12). In particular, the FDA did not support the use of T supplementation in men with a hormone deficiency not due to organic causes, but instead due to age or comorbidities (12). One of the main reasons for such an alert resides in the impressive rise of T sales, even without appropriate diagnosis and corresponding medical prescription (13). In fact, an analysis of the T market in 41 countries reports that T product sales increased 12-fold globally from 2000 through 2011, rising from $150 million in 2000 to $1.8 billion in 2011 (13-15). The sharpest increases in T sales were seen in North America, where off-label, direct-to-consumer product T advertising was permitted (14). In contrast, in southern Europe - including Italy, where the prescription of T was allowed only through specialists and direct-to-consumer product advertising is prohibited - such a dramatic increase in T sales was not observed. In addition, the European Medical Agency (EMA) did not share the FDA's opinion of an increased CV risk linked to T medication, because of the lack of convincing evidence (16). Interestingly, the FDA alert, and its related label change, did not stop the US market of T sales which only showed thereafter a small decrease (17). Interestingly, when a projection of the US data were categorized according to the proportion of use in men with or without CAD, T use was higher for men with CAD, demonstrating a nonselective response to the possible CV risk alert from the FDA (17).

In the FDA alert, a dichotomy between hypogonadism due to "certain medical conditions" and an aging-associated T decline was introduced for the first time. Thereafter, the concept of a non-organic or "functional" HG was more clearly defined as a condition with

no recognizable structural intrinsic hypothalamus-pituitary testis axis (HPT) pathology but frequently associated with morbidities impairing HPT axis function (18). According to this view, functional HG is essentially a diagnosis of exclusion. It was also postulated that in functional HG testosterone replacing therapy (TRT) should be avoided, since it is a potentially reversible condition with the improvement of the associated morbidities, including obesity (18). Concerning the risks of CVD, Grossmann & Matsumoto (18) considered them as “unknown” in functional HG, while they were estimated as being “low relative to the benefits” in organic HG. This statement is not evidence-based, because we are not aware of any trial enrolling subjects with organic HG and examining the risk over the benefits of TRT. Conversely, the majority of available trials with TRT enrolled subjects with functional HG, as was the case in the recently published TTrials (19). In the real world, the large majority (85%) of subjects visiting an outpatient clinic for sexual dysfunction – which represents the most specific complex of symptoms associated with adult-onset HG (the so previously called LOH; 20) – are classified as functional HG, as demonstrated by an analysis of more than 4000 individuals (21). Hence, to know whether there is a possible risk for CVD - or even CAD - in subjects with functional HG undergoing TRT is of crucial relevance. If this is the case, only treating the symptom and/or removing or treating the underlying condition are the correct choices. However, our recent meta-analyses on the effect of TRT on several HG-related outcomes clearly show that TRT can improve sexual items (22-24) and have some interesting advantages in body composition and glucose metabolism (25-27).

Is the FDA or the EMA position on a possible risk of T-related CAD correct? This review summarizes our opinion on this hot topic, based on the available evidence.

2.0 Endogenous testosterone and CVD

All the available meta-analyses, including our recent one (7, 28-30), indicate that low endogenous T predicts a higher risk of overall and CV mortality. Conversely, the relationship between reduced T levels and CV morbidity is more conflicting. Previous meta-analyses, performed in a limited number of trials, have failed to document any relationship between reduced T levels and higher incidence of CV events (28-29). Conversely, Ruigue et al., (30) in a further meta-analysis documented a possible higher CV risk for low T, when only subjects younger than 70 years were considered. However, the latter analysis was based on a combined outcome, including both CV mortality and

morbidity (30). Interestingly, we recently performed the largest meta-analysis on this topic. The study included 37 trials with 43,041 subjects and a mean follow-up of 333 weeks (7). Among them, nine surveys reported information on CV events, including 10,479 subjects with a mean age of 60.2 years. The overall analysis showed that low T at enrollment predicted a higher risk of CV events when the fully adjusted model was considered (7). However, it is important to recognize that the CV events considered differ among the trials considered.

2.1 Endogenous testosterone and heart problems

Only few studies evaluated a possible association between low T and the incidence of heart problems.We previously investigated the relationship between the incidence of CV mortality and morbidity in a large series of subjects seeking medical care at our Unit for sexual dysfunction. As stated before, sexual dysfunction represents the most genuine cohort of symptoms characterizing HG during adulthood (24, 31-32). In addition, sexual dysfunctions, and in particular erectile dysfunction, represent a well-recognized harbinger of forthcoming CV events (33), as demonstrated also in our series (34-36). Hence, research on this cohort, although not representative of the general population is important in bridging information between CVD, including AMI, and HG. In our series, information on mortality and morbidity was obtained from our City Registry Office, which contains complete and updated records of all persons living within city boundaries, as previously described (34-35). For those who had moved away, queries were sent to the Registry Office of the new city of residence. Following the International Classification of Diseases (ICD), fatal and non-fatal major cardiovascular events (MACE) were coded as 410–414 (ischemic heart disease), 420–429 (other heart diseases), or 798–799 (sudden death) from cardiac diseases, as 430–434 or 436–438 for cerebrovascular disease, and 440 for peripheral arterial disease. The study included 1687 subjects with a mean age of 52.9 years. After a mean follow up of 4.3±2.6 years, in line with what was reported in the aforementioned meta-analyses, we observed a possible relationship between hypogonadism (total T < 10.4 nM) and overall and CV mortality but not with overall CV events (37).

During the same period, we observed 68 acute myocardial infarction (AMI), 7 of which were fatal. When only AMI events were considered, we here report results in keeping with the previous observation (37). In fact, low T (Total T < 10.4 nM) was associated with an increased risk of AMI mortality but not with AMI incidence (Figure 1, panel A and B). The

latter finding was confirmed in a Cox regression model after adjustment for age and Chronic Diseases Score, which represents an index of concomitant morbidities (38) (Figure 1, inset). Interestingly, a trend toward significance was only observed when a milder form of hypogonadism (total T < 12 nM) was considered, whereas a stronger association was detected in the case of more severe hypogonadism (total T < 8 nM) (Figure 1, inset).

Two other large studies have investigated a possible association between low T and AMI. In the first study, Yeap et al., (39) evaluated the relationship between total T, as measured by liquid chromatography mass spectrometry, and incidence of AMI or stroke in 3046 community-dwelling men aged 70–89 years. They failed to report any association between reduced T levels and AMI when both age-adjusted and fully-adjusted models were considered (39). In a more recent study, Daka et al., (40) evaluated the possible association between low T and AMI in 1109 subjects ≥40 years of age (mean age 62 ± 12 years) with type 2 diabetes mellitus. During a mean follow-up time of 14.1 ± 5.3 years, 74 AMI events occurred. In this study, low T at baseline was associated with an increased risk of AMI when both an age-adjusted and fully-adjusted models were considered (40).

Overall, the latter studies and our survey included 5,842 subjects with a mean age of 58 years and mean follow up of 432 weeks. By meta-analyzing the data deriving from all these studies we here confirm a higher risk of AMI in subjects with reduced T levels at the study entry when both an age-adjusted and fully-adjusted models were considered (Figure 2, panel A and B).

In conclusion, observational data indicate that there is a positive relationship between having low T and AMI mortality, as previously described for CV mortality, and suggest a weak association between low T and incident AMI. However, these studies do not clarify the direction of the relationship, i.e. i) subjects with low T are less healthy than the eugonadal counterpart or ii) low T is somehow causing CV events, including AMI. Only interventional studies with TRT in hypogonadal subjects could clarify this important point.

3.0 Interventional trials with TRT having heart problems as an outcome

3.1 Meta-analysis of pharmaco-epidemiological trials

Pharmaco-epidemiology is a branch of epidemiology that collects information from databases that are observational in nature with the advantage of shedding light on the ‘real-life’ clinical environment of therapies. Eleven studies, published so far, have investigated the possible relationship between TRT and AMI (41-51). The characteristics

of the retrieved trials are reported in Table 1. Retrieved trials included 1,796,747 subjects with a mean follow-up of 199.5 weeks. The mean age of the enrolled cohorts was 63.5 years. Among the studies included, seven studies compared the effect of TRT in treated vs. untreated hypogonadal subjects, whereas in four studies the effect of TRT was compared to a healthy population of untreated subjects (Table 1). By meta-analyzing these studies, we found that TRT in hypogonadal subjects protects from AMI in an unadjusted model and we documented a trend toward a significant effect in a fully-adjusted model (Figure 3, panel A and B).

3.2 Meta-analysis of placebo-controlled RCTs having heart disease as a primary end-point

Overall, 13 RCTs evaluating the effect of TRT in subjects with heart problems, as a primary end-point were available (Table 2; 52-63). Eight RCTs evaluated the effect of TRT in patients with chronic stable angina having angina-free exercise tolerance, as evaluated by ECG parameters, as a primary end-point. In particular, seven trials assessed the effects of TRT on ECG parameters during a treadmill test; whereas one (59) investigated the role of TRT in reducing the number of ECG documented angina attack/seek (Table 2). These trials enrolled 360 patients with CAD, with a mean age of 53.8 years and a mean follow-up of 11 weeks. Four RCTs evaluated the effect of TRT on patients with heart failure (HF). These studies enrolled 208 patients with a mean age of 65.8 years and mean follow-up of 15 weeks. Trials differ in basal TT levels; in addition, TRT was administered in different formulations and doses (Table 2-3). Combining the results of those trials, TRT was positively associated with a significant improvement in ECG signs of ischemia (Figure 4, panel A) and with a significant increase in exercise capacity (Figure 4, panel B).

3.3 Meta-analysis of placebo-controlled RCTs not having heart disease as a primary end-point

Seven meta-analyses, published so far, have evaluated the possible association between TRT and heart problems, evaluated as secondary end-points (64-70; Table 4). The number of included trials ranged from 15 to 93 including from 1,084 to 8,479 subjects. Six meta-analyses reported outcomes on acute myocardial infarction, and four on coronary by-pass surgery and arrhythmias (Table 4). In addition, three studies investigated the risk of acute coronary syndrome and two the relationship with heart failure (Table 4). Forest plots of estimated odds ratio (95% confidence intervals) for all of the investigated heart events,

as derived from available meta-analyses, are reported in Figure 5. The combined analysis showed no risk related to TRT independent of the heart problem considered. (Figure 5, panels A-B).

4.0 Conclusions

The studies critically scrutinized here clearly show that low T is a marker of poor CV outcomes, including CAD. Meta-analysis of retrospective observational studies suggest that correcting T deficiency marginally improves cardiac outcomes. However, many of the weaknesses linked to pharmaco-epidemiological studies, here discussed, hamper confidence in this conclusion. Meta-analysis of interventional studies having cardiac outcomes as a primary end-point suggest an acute and chronic positive effect of TRT on increasing time to ST-segment depression and in some measures of HF. However, all these studies were of short duration and enrolling a limited number of subjects and therefore they are underpowered. In addition, they may have overlooked early positive transient effects. Nevertheless, prospective studies of longer duration enrolling hypogonadal subjects having cardiac safety as a primary end-point are difficult to realize, due to ethical reasons. For all these reasons, we here summarize in Forest plots results from different meta-analyses of available RCTs not having cardiac outcomes as an end-point, but reporting information on them. Overall, included trials were of low-to-medium quality, enrolling subjects with variable characteristics, using different TRT protocols for various duration and, again, not powered to evaluate cardiac events. Meta-analysis is particularly useful when there are a variety of reports with low statistical power; thus, pooling data can improve power and provide a convincing result. All the different meta-analyses indicate that there is no significant risk for TRT in several cardiac outcomes, including AMI and acute coronary syndrome. It is important to recognize that all the available trials included in the meta-analyses have a relatively short duration, lasting at maximum three years. Therefore, although there is no clear sign of risk in the short term, no information is available on possible long-term effects. Considering that TRT is meant to be a lifelong treatment in the majority of cases the last issue is a relevant point. In conclusion, five years later, we fully endorse the EMA statement concerning TRT saying: “evidence regarding the risk of heart problems was inconsistent” (12). A new trial (TRAVERSE; clinicaltrials.gov, NCT03518034) to evaluate the effect of TRT on the incidence of MACE and efficacy measures in men with hypogonadism is ongoing. This is

the first TRT trial with adequate power to assess CV events in hypogonadal population and it will give important information on this topic in the near future.

5.0 Expert opinion

Present data document that low endogenous T can represent a risk factor for AMI-related mortality and AMI incidence. In the few trials available having heart problems as a primary end-point, TRT in hypogonadal patients was able to improve angina symptoms in subjects with ischemic heart diseases and exercise ability in patients with HF. Analysis of other interventional studies suggest that, when prescribed according to the recommended dosage, TRT does not increase the risk of heart-related events.

The relationship between endogenous T and CV risk has been a matter of intense debate, although a negative association between T and a safer health profile is well-documented (71-74). In the largest meta-analysis published so far considering this issue, we recently reported that reduced T levels increased the risk for CV mortality and morbidity (7). By meta-analyzing available data, we here extend this concept showing that low T is a risk factor also for AMI evens when the fully adjusted model was considered.

Both clinical and animal evidence shows that T exerts a favorable effect upon vascular reactivity, inflammation, cytokine production, and adhesion molecule expressions, as well as on serum lipid concentration and haemostatic factors (71-74). Available data show that T enhances myocardial function through a direct effect on myocardiocytes (71-74). Data derived from available meta-analyses of RCTs indicated that TRT is able to improve CV profile, body composition and metabolic control (25-27). It can be speculated that hypogonadism could lead to a greater severity of atherosclerotic lesions due to a less favorable risk factor profile, which could explain, at least partially, the documented increased risk of AMI mortality and incidence. However, it should be recognized that available epidemiological data does not allow for any inferenceregarding causality on pathological mechanisms between low T and heart mortality and morbidity. In fact, low T could represent only a biomarker of an overall poorer health status associated with morbidities or with unhealthy lifestyle (18, 72). Analysis of interventional trials could shed light on the question of whether low T concentrations are causes or consequences of heart problems. Interventional trials can be divided into observational ones (pharmaco-epidemiological) and RCTs.

Pharmaco-epidemiological studies have the advantage of allowing the collection of a large number of subjects with a long-term follow-up. In line with what has been reported by our groups on overall CV events (70), the meta-analysis of the available data, here presented, indicates that TRT protects from AMI when an unadjusted model was considered. Conversely, only a trend toward a significant effect was found in the fully-adjusted analysis. This is not surprising since a higher prevalence of associated morbidities can reduce the contribution of low T in the stratification of CV risk in aging men (72). Five studies previously investigated the effect of TRT on overall mortality after the adjustment for confounders (46,49, 75-77). These studies included 70,186 subjects hypogonadal subjects treated with T and 57,939 untreated hypogonadal patients. The meta-analysis of the aforementioned studies already showed TRT resulted in a significant reduction of overall mortality (up to 59%; 70) In particular the two of the largest available studies have clearly shown that normalization of T levels is able to reduce overall mortality in American veterans (75) and diabetic subjects (76).

However, it should alsobe recognized that pharmaco-epidemiological trials present important limitations and the risk of selection bias due to the non-random assignment of T exposure. Accordingly, physicians often prefer to treat healthier individuals, and healthier individuals more often request treatment for their hypogonadism-related problems. In addition, other limitations rely on the lack of information regarding the level of T before and during TRT, as well as on the limited data regarding the type of T preparation used and the follow-up performed during treatment.

RCTs are usually referred to as the best clinical method for investigating the effect of a specific treatment. We previously reported that TRT was *effectiv*e in men with chronic stable angina, as they had greater angina-free exercise tolerance than placebo-treated controls (29). We now confirmed this finding in a larger number of subjects. The mechanism(s) though which TRT can improve angina symptoms has not been completely clarified. Webb et al., (78) previously reported that short-term intracoronary administration of T, at physiological concentrations, leads to a coronary artery dilatation and increases coronary blood flow in men with established CAD. Accordingly, it has been reported that T and its active metabolite, dihydrotestosterone (DHT), are able to stimulate nitric oxide release in human arterial cells in a dose-dependent manner through the activation of PI3k/Akt and ERK 1/2 pathways (79). In addition, T acts as both an L-calcium channel blocker and potassium channel opener in vascular smooth muscle cells at the Nifedpine binding site (80-83).

Data coming from TTrials, a set of seven placebo controlled RCTs, designed to better investigate the role of TRT in elderly men, were in apparent contrast with the positive effects of TRT on men with ischemic heart diseases (15). In particular, the CV trial showed that men enrolled in the active arm had coronary artery plaque progression, as detected by coronary CT angiography, during 12 months of treatment (84). Several limitations should be recognized for the interpretation of the latter results. Men in the placebo group had larger non-calcified plaque volume at baseline when compared to the T arm (317 vs. 204 mm^3). In addition, although the plaque volume showed a greater increase in the active arm, men treated with T sill presented lower volume at the endpoint (232 vs. 325 mm^3). Furthermore, no difference was observed in coronary calcium score, another marker of CV risk as well as in the incidence of CV events between groups. Finally, the prognostic importance in the observed changes in plaque volume is unclear (84).

Similar to what was reported for the angina symptoms, we observed that TRT was able to improve exercise capacity in men with HF. Our data are in line with the meta-analysis reported by Toma et al., (85). However, in the latter meta-analysis, data derived from male and female patients were combined. In a larger number of patients, when only male subjects were selected, we here confirmed a positive effect of TRT in patients with HF. The underlying mechanisms are probably complex and not completely understood. An anabolic/catabolic imbalance, with a final catabolism increase, represents a key feature of patients with advanced HF. An improvement of muscle mass associated with TRT in healthy and hypogonadal individuals might result in an increased endurance and decreased muscle fatiguability in HF subjects (86). Other possible positive effects of TRT include peripheral vasodilatation as well as a rise in hemoglobin levels and an improved baroreceptor sensitivity (87).

It should be recognized that the number of subjects enrolled in the aforementioned RCTs related to angina symptoms or HF is relatively small and the period of treatment quite short to draw final conclusions. In addition, as reported above, concerns related to CV safety of TRT have been raised over the last few years (87-89).

Several meta-analyses have investigated a possible relationship between CV risk and TRT (64-70, 90-92).When aggregated CV events were considered, only Xu et al. (90) documented an increased CV risk, whereas all the other meta-analyses did not support an overall increase of CV risk related to TRT. The limitations of Xu et al. (90) analysis are well known and reviewed elsewhere (87-89). Essentially, the main limitation of the latter study

deals with the consideration of a very broad definition of CV events, leading to an artificial increase in the overall number (89). Only few meta-analyses investigated the relationship between TRT and disaggregate CV events or, in particular, heart-related problems. Data summarized herein showed that TRT was not associated with any increased risk in all heart-related problems considered, including AMI, coronary by-pass surgery, arrhythmias, acute coronary syndrome and HF. Interestingly, the largest meta-analysis produced by our group on this topic showed that an increased CV risk related to TRT was observed when T was incorrectly prescribed at dosages higher than those routinely recommended (70). This information is particularly relevant since recent data indicate that in the US, up to 30% of men who were prescribed T did not have their T levels tested prior to receiving TRT (9).

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*** of considerable interest*

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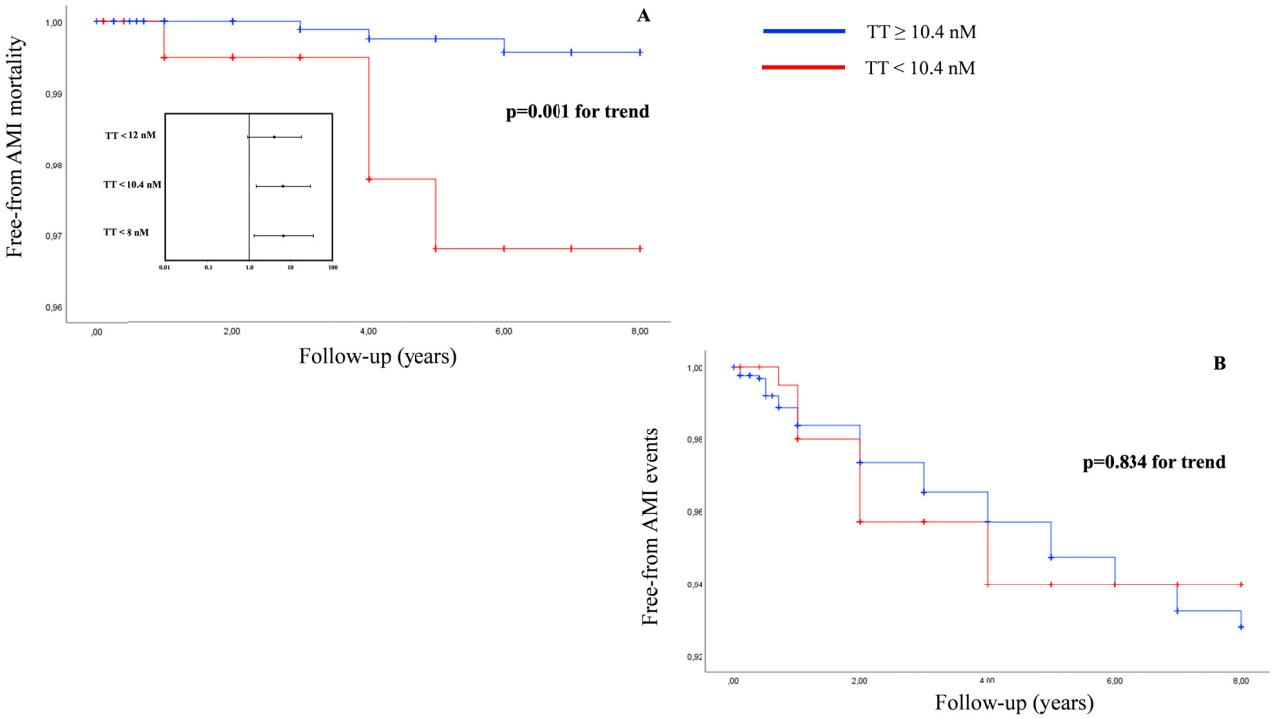
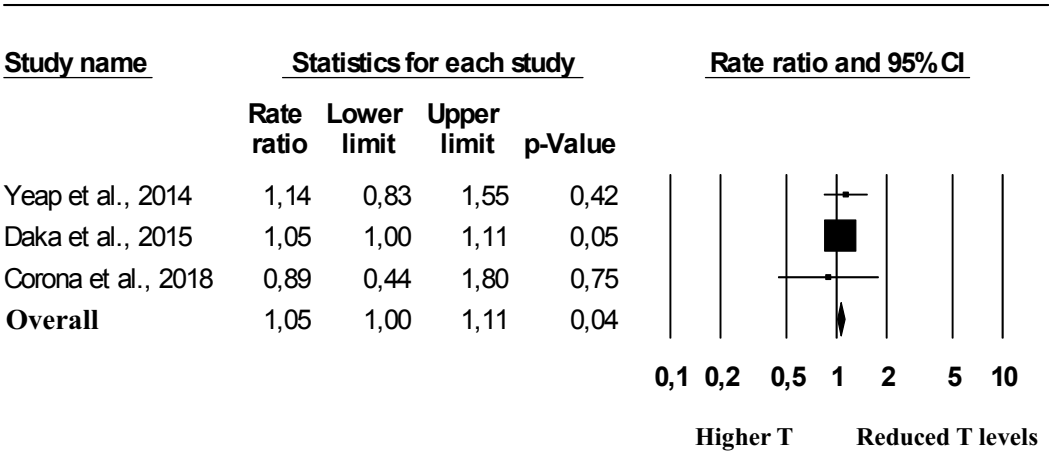


Figure 1. Risk of acute myocardial infarction (AMI) mortality (A) and incidence (B) as derived from Kaplan Mayer curves, according to total testosterone (TT) levels. Panel A inset: Odds ratio of AMI mortality according to baseline TT levels, as derived from Cox regression model after adjustment for age and Chronic Diseases Score, which represents an index of concomitant morbidities. Data are derived from a consecutive series of 1687 subjects attending our Unit seeking medical care for sexual dysfunction with a mean follow up of 4.3±2.6 years.


Study name
Statistics for each study
Rate ratio and 95% CI
Rate ratio
Lower limit
Upper limit
p-Value
Yeap et al., 2014 1,14 0,83 1,55 0,42
Daka et al., 2015 1,05 1,00 1,11 0,05
Corona et al., 2018 0,89 0,44 1,80 0,75
Overall 1,05 1,00 1,11 0,04
0,1 0,2 0,5 1 2 5 10
Higher T
Reduced T levels

A

B

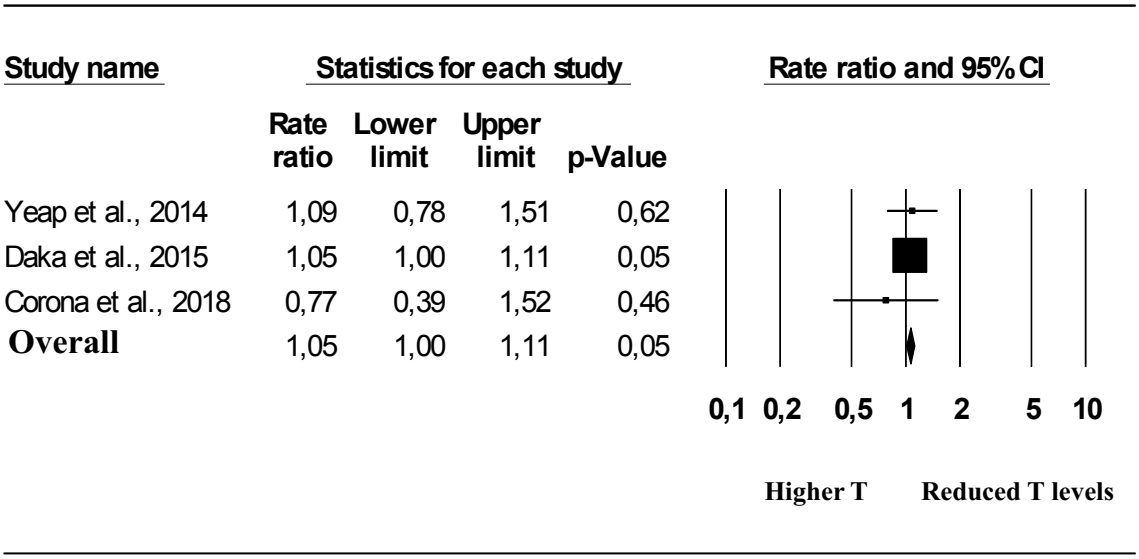
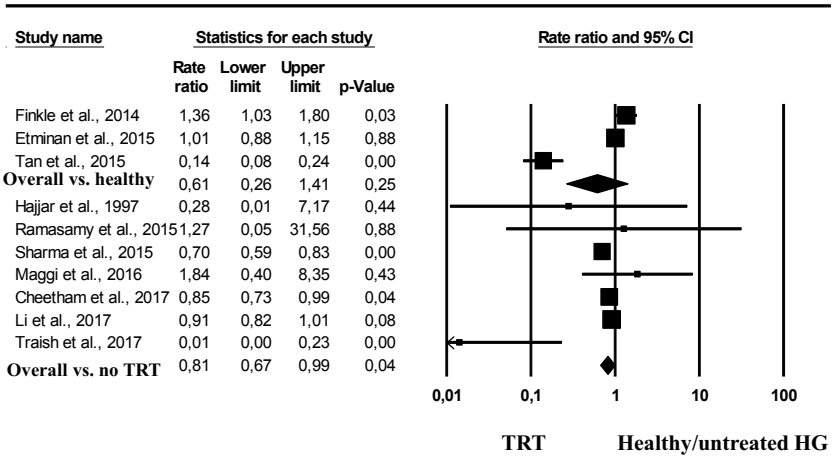


Figure 2. Odds ratio for overall unadjusted (A) and fully adjusted (B) acute myocardial infarction mortality (A) in subjects with lower endogenous total testosterone (T) in comparisons to those with higher T levels at enrolment.

A


Study name
Statistics for each study
Rate ratio
Lower limit
Upper limit
p-Value
Rate ratio and 95% CI
Finkle et al., 2014 1,36 1,03 1,80 0,03
Etminan et al., 2015 1,01 0,88 1,15 0,88
Tan et al., 2015 0,14 0,08 0,24 0,00
Overall vs. healthy 0,61 0,26 1,41 0,25
Hajjar et al., 1997 0,28 0,01 7,17 0,44
Ramasamy et al., 2015 1,27 0,05 31,56 0,88
Sharma et al., 2015 0,70 0,59 0,83 0,00
Maggi et al., 2016 1,84 0,40 8,35 0,43
Cheetham et al., 2017 0,85 0,73 0,99 0,04
Li et al., 2017 0,91 0,82 1,01 0,08
Traish et al., 2017 0,01 0,00 0,23 0,00
Overall vs. no TRT 0,81 0,67 0,99 0,04
0,01
0,1
1
10
100
TRT
Healthy/untreated HG

B

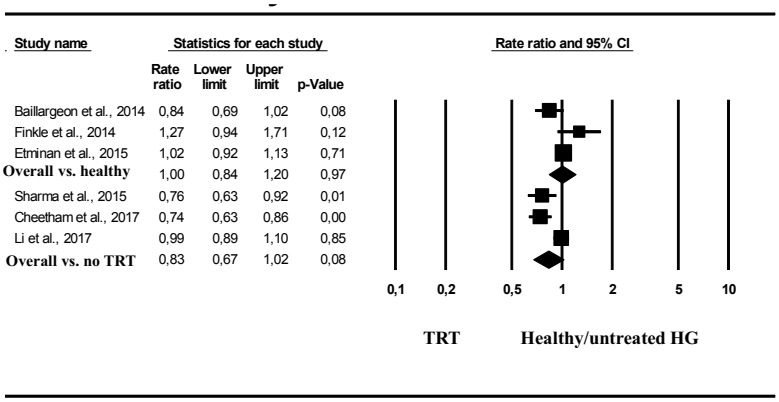
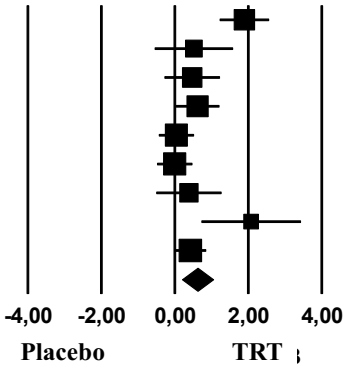


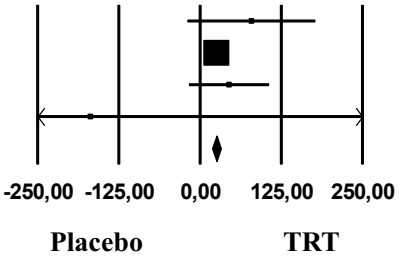
Figure 3. Odds ratio for unadjusted (A) and fully adjusted (B) acute myocardial ischemia in subjects treated with testosterone (TRT) in comparisons to those not treated or healthy.

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Jaffe et al., 1977	1,90	1,23	2,56	0,00
Rosano et al., 1999	0,52	-0,54	1,59	0,34
Webb et al., 1999	0,48	-0,28	1,23	0,22
English et al., 2000	0,62	0,03	1,21	0,04
Thompson et al., 2002	0,05	-0,43	0,52	0,85
Thompson et al., 2002*	0,00	-0,48	0,48	1,00
Malkin et al., 2004	0,39	-0,50	1,27	0,39
Mathur et al., 2009**	2,08	0,73	3,43	0,00
Coronoldi et al., 2010	0,43	0,00	0,85	0,05
Overall	0,62	0,20	1,05	0,00



A

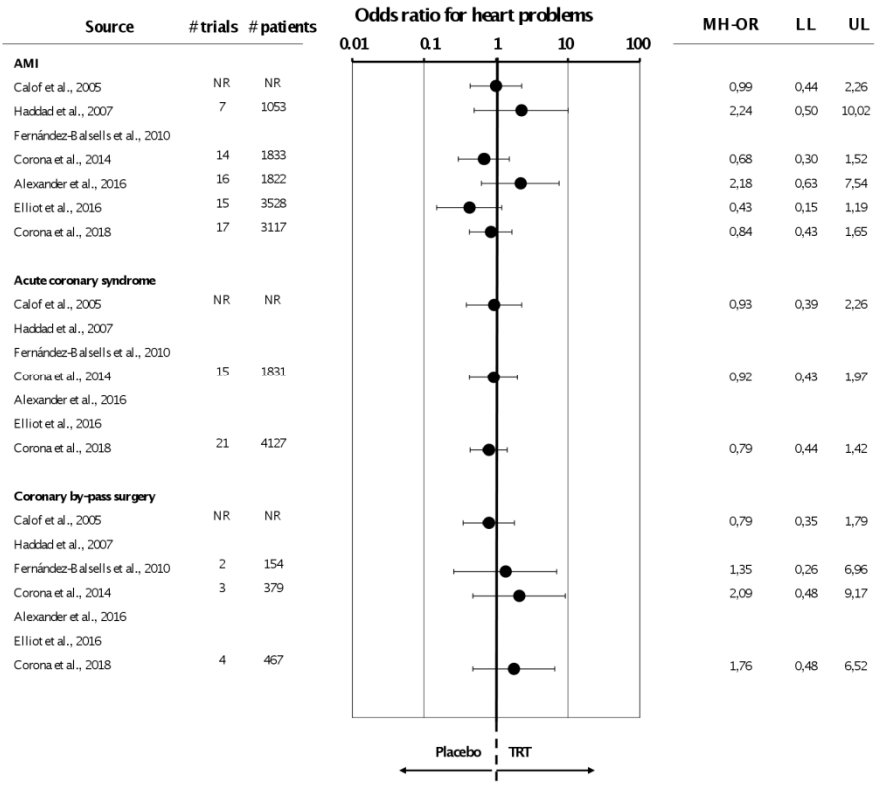
Study name	Difference in means	Lower limit	Upper limit	p-Value
Pugh et al., 2004	79,000	-19,195	177,195	0,115
Malkin et al., 2006	25,000	18,253	31,747	0,000
Caminiti et al., 2009	44,600	-16,909	106,109	0,155
Stotut et al., 2012	-168,900	-962,489	624,689	0,677
Overall	25,469	18,778	32,160	0,000



B

Figure 4. A) Standardized weighted differences (with 95%CI) in ECG parameters in subjects treated with testosterone (TRT) or placebo with chronic stable angina at endpoint across randomized controlled trials. * supra-physiologic (6 X baseline) serum testosterone level. B) Weighted mean differences (with 95%CI) in exercise capacity (meters of walking) as derived from incremental shuttle walk test or 6-minute walk test in subjects with heart failure in subjects treated with testosterone (TRT) or placebo at endpoint across randomized controlled trials.

A


Source
#trials
#patients
Odds ratio for heart problems
0.01
0.1
1
10
100
MH-OR
LL
UL
AMI
Calof et al., 2005 NR NR 0,99 0,44 2,26
Haddad et al., 2007 7 1053 2,24 0,50 10,02
Fernández-Balsells et al., 2010
Corona et al., 2014 14 1833 0,68 0,30 1,52
Alexander et al., 2016 16 1822 2,18 0,63 7,54
Elliot et al., 2016 15 3528 0,43 0,15 1,19
Corona et al., 2018 17 3117 0,84 0,43 1,65
Acute coronary syndrome
Calof et al., 2005 NR NR 0,93 0,39 2,26
Haddad et al., 2007
Fernández-Balsells et al., 2010
Corona et al., 2014 15 1831 0,92 0,43 1,97
Alexander et al., 2016
Elliot et al., 2016
Corona et al., 2018 21 4127 0,79 0,44 1,42
Coronary by-pass surgery
Calof et al., 2005 NR NR 0,79 0,35 1,79
Haddad et al., 2007
Fernández-Balsells et al., 2010 2 154 1,35 0,26 6,96
Corona et al., 2014 3 379 2,09 0,48 9,17
Alexander et al., 2016
Elliot et al., 2016
Corona et al., 2018 4 467 1,76 0,48 6,52
Placebo
TRT

B

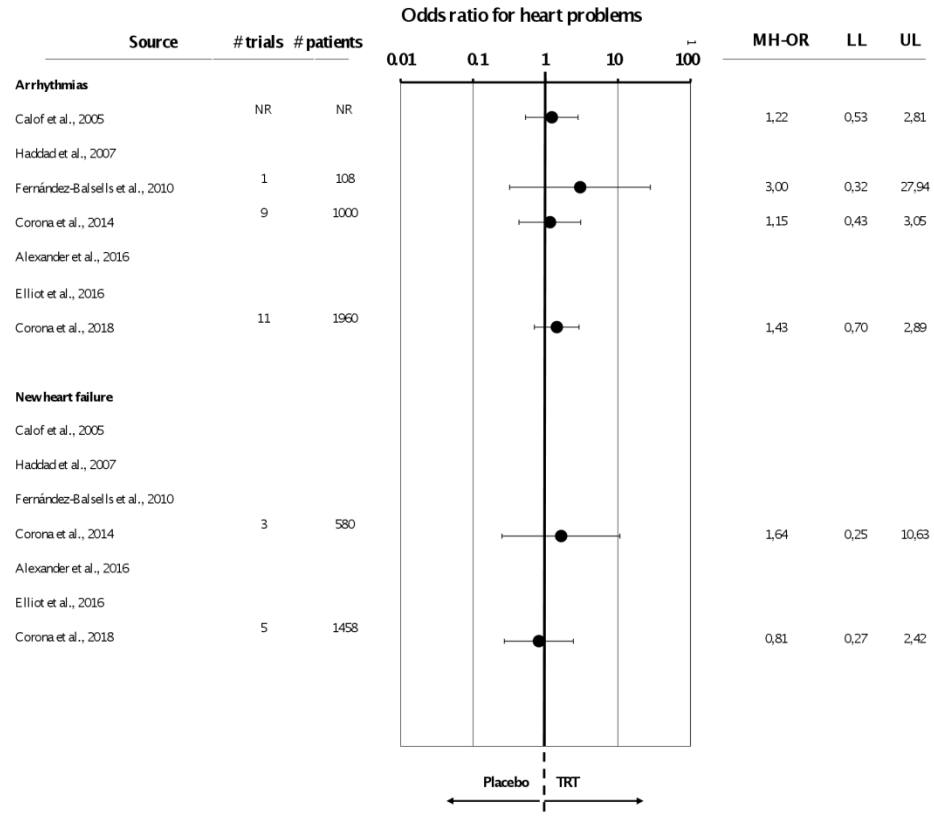

Source
#trials
#patients
Odds ratio for heart problems
0.01
0.1
1
10
100
MH-OR
LL
UL
Arrhythmias
Calof et al., 2005 NR NR 1,22 0,53 2,81
Haddad et al., 2007
Fernández-Balsells et al., 2010 1 108 3,00 0,32 27,94
Corona et al., 2014 9 1000 1,15 0,43 3,05
Alexander et al., 2016
Elliot et al., 2016
Corona et al., 2018 11 1960 1,43 0,70 2,89
New heart failure
Calof et al., 2005
Haddad et al., 2007
Fernández-Balsells et al., 2010
Corona et al., 2014 3 580 1,64 0,25 10,63
Alexander et al., 2016
Elliot et al., 2016
Corona et al., 2018 5 1458 0,81 0,27 2,42
Placebo
TRT

Figure 5. Forest plot of estimated odds ratio (95% confidence intervals) for aggregate heart related events as derived from available meta-analyses of randomized controlled trials on the effect of testosterone therapy (TRT) versus placebo. AMI= acute myocardial infarction. LL=lower limits; UP= upper limits.

Study	# patients (cases/controls)	Population	Follow-up (weeks)	Study design	Medication used	Treated vs. untreated	Diagnosis of hypogonadism	Age (years) Mean/ range	BMI (kg/m^2)	DM (%)	HT (%)	Smokers (%)	TT (nmol/L)
Hajjar et al., 1997 (41)	45/27	Men with sexual dysfunction	104	T treatment vs. no treatment	T cypionate or T enanthate 200 mg/2 wk	HG vs. HG	BT<2.5 nmol/L	70.9	-	-	-	-	10.2
Baillargeon et al., 2014 (42)	6,355/19,065	Elderly from general population	182	TTh prescription vs. no TRT prescription	Mixed	-	-	-	-	16.3	-	-	-
Finkle et al., 2013 (43)	55,593/141,031	General population	140	TRT prescription vs. PDE5i prescription	Mixed	-	-	54.3	-	19.0	26.6	-	-
Etminan et al., 2015 (44)	30,066/120,264	Elderly from general population	145	TRT prescription vs. no TRT prescription	Mixed	-	-	70.4	-	0.7	-	14.0	-
Ramasamy et al., 2015 (45)	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	-	-	-	-	-
Sharma et al., 2015 (46)	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	33.0	30.6	17.1	-	-

Tan et al., 2015 (47)	19,968/821,725	General population	72	TRT prescription vs. no TRT prescription	Mixed	HG vs. HG	TT<12.0 nmol/L	-	-	-	-	-	-
Maggi et al., 2016 (48)	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	30.0	28.7	46.4	13.2	9.5
Cheetham et al., 2017 (49)	8,808/35,527	General population	224	T treatment vs. no treatment	Mixed	HG vs. HG	Mixed hypogonadal and eugonadal subjects	-	-	23.0	44.0	-	-
Traish et al.,2017 (50)	360/296	Men with urological complaints	364	T treatment vs. no treatment	T undecanoate i.m. 1000 mg every/ 12 wk	HG vs. HG	TT<12.1 nmol/L	60.7	31.4	39.4	37.5	-	9.7
Li et al.,2017 (51)	207,176/207,176	General population	312	T treatment vs. no treatment	mixed	HG vs. HG	-	51.8	-	21.1	44.7	5,2	-

Table 1. Descriptive characteristic of the available pharmaco-epidemiological studies evaluating the impact of testosterone (T) treatment (TRT) on acute myocardial infarction (AMI). TT= total testosterone; BT= bioavailable testosterone; HG= hypogonadism; T= testosterone; - = not reported; BMI= body mass index; DM= diabetes mellitus; HT = hypertension; T2DM= type 2 DM.

Study (Ref.)	# patients (ID/C)	Trial duration	Age (years)	TT Baseline	DM Baseline (%)	MI Baseline (%)	ECG	Time to 1-mm ST	ISWT/ 6M
Ischemic heart diseases									
Jaffe et al., 1977 (52)	25/25	8	58.0	NA	10.0	20.0	Treadmill	§	-
Rosano et al., 1999 (53)	7/7	-	58.0	NA	7.1	35.7	Treadmill	X	-
Webb et al., 1999 (54)	14/14	-	57.0	5.3	21.4	50.0	Treadmill	X	-
English et al., 2000 (55)	22/24	14	62.0	12.9	15.3	10.9	Treadmill	X	-
Thompson et al., 2002 (56)	34/34	-	69.1	NA	NA	32.0	Treadmill	X	-
Thompson et al., 2002*(56)	34/34	-	69.1	NA	NA	32.0	Treadmill	X	-
Malkin et al., 2004 (57)	10/10	4	60.8	4.2	50.0	30.0	Treadmill	X	-
Mathur et al., 2009 (58)	7/6	52	64.8	9.9	23.1	30.8	Treadmill	X	-
Coronoldi et al., 2010 (59)	43/44	12	70.0	NA	100	100	IA /week ECG	-	-
Heart failure									
Pugh et al., 2004 (60)	20/20	12	62.0	NA	10.0	20.0	-	-	ISWT
Malkin et al., 2006 (61)	37/39	52	64.0	12,9	17.9	-	-	-	6MWT
Caminiti et al., 2009 (62)	31/33	12	70.0	7.5	28.6	-	-	-	6MWT
Stotut et al., 2012 (63)	15/13	12	67.2	10.8	32.1	64.2	-	-	ISWT

Table 2. Outcome variables in individual randomized controlled studies included in the meta-analysis. ID/C = Investigational Drug/Comparator; TT= total testosterone; DM= diabetes mellitus; MI= myocardial infarction; NA = not available. § =sum (mm) of ST segment depression in leads II, V4, V5, and V6. IA=ischemic attack; ISWT = incremental shuttle walk test; 6MWT= 6-minute walk test.* supra-physiologic (6 X baseline) serum testosterone level

Study (Ref.)	**Drug**	**Dose**	**Randomization**	**Blinding**	**Drop-out**	**Intention-to-treat**
Ishemic heart diseases						
Jaffe et al., 1977 (52)	TC	200 mg/week	A	A	A	Yes
Rosano et al., 1999 (53)	T (iv)	2.5 mg once	A	A	A	Yes
Webb et al., 1999 (54)	T (iv)	2.3 µg once	A	A	A	Yes
English et al., 2000 (55)	T patch	5 mg daily	A	A	A	Yes
Thompson et al., 2000 (56)	T (iv)	*	A	A	A	Yes
Malkin et al., 2004 (57)	Sustanon (im)	100 mg twice/week	A	A	A	Yes
Mathur et al., 2009 (58)	TU (im)	1.000 mg/12 week	A	A	A	Yes
Coronoldi et al., 2010 (59)	TU (oral)	40mg/ 3 times daily	A	A	A	Yes
Heart failure diseases						
Pugh et al., 2004 (60)	Sustanon	100 mg /2 weeks	A	A	NA	Yes
Malkin et al., 2006 (61)	T patch	5 mg daily	A	A	A	Yes
Caminiti et al., 2009 (62)	TU (im)	1.000 mg/12 week	A	A	A	Yes
Stotut et al., 2012 (63)	Sustanon	100 mg /2 weeks	A	A	A	Yes

	Placebo	Placebo
Randomization	A	A
Blinding	A	A
Drop-out	A	A
Intention-to-treat	YES	YES

Table 3. Characteristics of the randomized clinical studies included in the meta-analysis. TC= testosterone cypionate; T= testosterone; TU= testosterone undecanoate in castor oil; im= intramuscular; iv= intravenous; A= adequate; NA= not adequate.*Testosterone doses were individualized to produce physiologic (defined as double the baseline testosterone level) or supra-physiologic (6 X baseline) serum testosterone level.

Inclusion criteria	**Calof et al., 2005 (64)**		**Haddad et al., 2007 (65)**		**Fernández-Balsells et al., 2010 (66)**		**Corona et al., 2014 (67)**		**Alexander et al., 2016 (68)**		**Elliot et al., 2016 (69)**		**Corona et al., 2018 (70)**	
Number of trials included	19		30		51		74		39		15		93	
Number of patients analyzed	1,084		1,642		2,679		5,464		5,441		3,528		8,479	
	Yes	*No*	***Yes***	*No*	***Yes***	***No***	***Yes***	*No*	*Yes*	***No***	*yes*	***no***	*yes*	*No*
Data according to T preparations		X		X						**X**			X	
Cardiovascular event analysis														
AMI	**X**		**X**				**X**		X		X		x	
Acute coronary ɔme	**X**			X		X	**X**			X		**X**	X	
Coronary by-pass y	**X**			X	**X**		**X**			X		**X**	X	
New heart failure		X		X		X	**X**			X		**X**	X	
Arrhythmias	**X**			X	**X**		**X**			X		**X**	X	

Table 4. Comparisons of the available meta-analyses evaluating the relationship between testosterone (T) therapy (TRT) and heart related diseases risk. AMI= acute myocardial infarction.