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Review

Cardiovascular impact of testosterone therapy for hypogonadism

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Abstract

Introduction. Since 2010 some evidence supporting the possible increased cardiovascular (CV) risk related to testosterone treatment (TTh) has created much debate in the scientific community. Based on these results, the US Food and Drug Administration agency has questioned TTh for aging men recognizing its value only for classical hypogonadism due to genetic or organic causes. To better clarify this topic, we scrutinized and summarized, also by using meta-analytic methods, the data generated during the last seven years, as derived from the analysis of randomized controlled trials (RCTs) on TTh and CV risk.

Areas covered. Analysis included 31 RCTs published between 2010 and 2018. Retrieved trials included 2675 and 2308 patients in TTh and placebo groups, respectively. The analysis documented that TTh was not associated with an increased CV mortality or morbidity either when overall or major adverse CV events were considered.

Expert commentary. Despite present evidence it is important to recognize that the duration of the available trials is short (lower that 3 years) limiting final conclusions on this topic. In particular, the available information on possible long-term effects of TTh on CV risk is limited. Long-term safety studies are advisable to better clarify these points.

Keywords: Testosterone, cardiovascular risk, major adverse cardiovascular events (MACE), late-onset hypogonadism, testosterone treatment

1.0 Introduction

Over the last 200 years life expectancy has dramatically increased worldwide (1). Before 1800 no country had a life expectancy above 40 years. After that period a progressive improvement of life expectancy has been observed in each region of the world, although the "health transition" - the period in which life expectancy began to increase - has differed according to different countries. In particular, Europe, North America and Oceania began to see increases in life expectancy around 1870, whereas Africa did not begin to see increases until around 1920 (1). Knowledge, science and technology were, and still are, the key elements underlying this phenomenon. During the course of modernization and industrialization, the health of the population improved, allowing better levels of living, better nutrition, better housing and better sanitation. Most recently, the major life-saving scientific innovations in medical procedures and the introduction of new drugs - including statins, and antihypertensives acting on the renin system - have had a major effect, particularly on reduced mortality from cardiovascular (CV) disease (CVD). Similar progress has been observed in the field of endocrinology and of hormonal substitution, in particular (1). Insulin was successfully used in 1922 for the first time by Banting and Best to treat a 14 year old, severely diabetic boy: Leonard Thompson (2). Some years earlier, in 1914, thyroxin was isolated although it took a long time before it was synthesized on a commercial basis, i.e. 1949, as tablets of desiccated thyroid extract (3). In 1950, Dennis Douda was awarded a Nobel Prize for his contributions to isolating and identifying cortisone (4). Sex steroids were isolated in the early 30s. In 1935, 17α-methyl-testosterone (T) was synthesized for oral use (5-6) whereasestradiol benzoate was introduced for medical use via intramuscular injection in 1936 (7). No concerns have ever been raised for the use of insulin, thyroxin or cortisol in the presence of hormonal deficiency. The use of sex steroids in the case of hypogonadism has been approved for a long time for men and women. In women, the use of hormone replacement therapy (HRT) in postmenopause has been suggested to prevent vasomotor symptoms and bone loss, improving sexual function, mood, well-being and CVD. However, data from the Women's Health Initiative (WHI) study published in the early 2000s dramatically changed this view (8). The WHI was a double blind placebo-controlled trial in which 16608 postmenopausal women aged 50-79 years received conjugated equine estrogens, plus medroxyprogesterone acetate (if not hysterectomized) or placebo for a planned duration of 8.5 years.

However, the study was prematurely interrupted after a mean of 5.2 years of follow-up due to higher risk of CVD observed in the active arm (8). The limitations of this study have been thereafter recognized (9). However, the impact of this study in the scientific community and lay press was tremendous and the number of women taking HRT dropped precipitously. This approach resulted in an increase in osteoporosis and bone fractures with their related medical and economic consequences (10). The world-wide estimated prevalence of osteoporotic fractures in 2000 was of 9 million, accounting for 5.8 million DALYs lost, which integrates the years of life lost due to a fracture and the disability in those people that survive (10). The burden of osteoporosis indicates a possible increase by 41 % in women in 2015 (10). Accordingly, more recently the Endocrine Society stated that when taken during perimenopause, or the initial years of menopause, in selected cases, HRT carries significantly fewer risks than previously published, and prevents bone loss, reducing all cause mortality in most patient scenarios (9).

Despite what has been observed for estrogen in women, in men T slightly and progressively declines as a function of age. Late onset hypogonadism (LOH) is the most frequently used term to indicate this phenomenon (11-12). Much evidence has documented that, in aging men, low T is associated with worse metabolic profile and higher CV risk suggesting that T replacement therapy (TTh) might improve metabolic profile preventing CVD (13-15). This possibility was particularly emphasized in the US and North America where the T market - supported by the possibility to release drug and disease-related specific advertisements - increased 12-fold in the last 15 years (16). However, 10 years after the publication of WHI, a similar scenario observed for HRT occurred for TTh. In particular, in 2010 the results of the Testosterone in Older Men with Mobility (TOM) study - a double-blind placebo-controlled randomized trial (RCT) aimed at the evaluation of the improvement of frailty in older men with limited mobility (17) – created much debate. In fact, the study was prematurely interrupted due to an imbalance in respiratory, dermatological and, more importantly, CV events between the two arms (CV events: T = 23 vs. placebo=5). Similar to WHI, the Testosterone in Older Men with Mobility Limitation (TOM) study presents important limitations (18-19). First of all the study was not powered to detect differences in CV events, but it was stopped early due to 23 cardiovascular-related events (two deaths) in the 106 men in the testosterone group versus five in the placebo group, despite positive results in study endpoints. In addition, the study involved treatment

initiation with 100 mg of topical T gel (twice the recommended starting dose), rapid escalation up to 150 mg per day (above the manufacturer's recommended dose), and many of the events were reported with inadequate validation and mainly occurred in those subjects receiving the higher doses (17).

However, some years later two other pharmaco-epidemiological surveys further supported a possible increased CV risk related to TTh. Vigen et al. (20) retrospectively evaluated a cohort of more than 8,000 American Veterans who had undergone coronary angiography between 2005 and 2011 showing that those who were prescribed TTh had an increased risk of major adverse CV events (MACE), or died from any cause. Some months later this publication, Finkel et al., (21) published data from another retrospective study, funded by the National Institutes of Health, based on a large health-care database in the US showing that TTh is associated with a higher rate of nonfatal myocardial infarction. These data, along with other limited evidence (22), had the same impact on the scientific community and lay press as that observed for WHI. Based on this, the US Food and Drug Administration (FDA) in its final release cautioned that the use of TTh for aging men should be considered only for men with "classical hypogonadism", i.e. due to primary or secondary T deficiency resulting from known problems within the testis, pituitary, or hypothalamus (e.g. genetic problems, or damage from surgery, chemotherapy, or infection; 23). This position was thereafter endorsed by Health Canada (24) and more recently by the Endocrine Society of Australia (25). Of note, the European Medicine Agency (EMA), after conducting a similar review of the data as had the FDA, did not find sufficient evidence for declaring TTh to be associated with an increased CV risk (26).

The aim of the present review is to scrutinize and to summarize, also by using meta-analytic methods, the data generated since the TOM study's publication, as derived from the analysis of interventional studies on TTh and CVD risk.

2.0 Methods

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. The search was limited to articles published during the last 7 years, introducing ("2010/01/01"[PDat] : "2018/01/31"[PDat]). A

Mantel-Haenszel odds ratio with 95% Confidence Interval (MH-OR) was calculated for all the adverse CV events, on an intention-to-treat basis, excluding trials with zero events. A random-effect model was applied, because the validity of tests of heterogeneity can be limited with a small number of component studies. In addition, sub-analysis considering the incidence of MACE according to baseline population characteristics was also performed. MACE were defined as the composite of CV death, non-fatal acute myocardial infarction (AMI) and stroke, and acute coronary syndromes and/or heart failure (HF) were reported as serious adverse events.

3.0 CV safety from RCTs

Characteristics of the retrieved trials are summarized in Table 1. Among the 31 studies included in the analysis, 30 reported information on MACE, 28 on AMI, 29 on stroke and 31 on CV mortality, respectively (Table 2). In addition, 29 studies also reported information on overall CV events, 29 on acute coronary syndrome and 28 on hospitalization for HF. Finally, 27 studies also described data on arrhythmias and 27 on by-pass coronary surgery (Table 2). Retrieved trials included 2675 and 2308 patients in TTh and placebo groups, respectively, with a mean trial duration of 41.0 weeks. TTh was administered in different doses, formulations and on subjects with different baseline characteristics in the cohorts (Table 1).

Of the 30 trials reporting information on MACE, 14 detected no events; therefore, the main analysis was performed on 16 trials. The use of TTh was not associated with any significant difference in the incidence of MACE with respect to placebo (MH-OR: 0.81[0.42; 1.59]; p=0.54) (Figure 1, panel A). In addition, similar results were confirmed when the individual MACE was analyzed separately and when other CV events (including arrhythmias or aorto-coronary by-pass surgery) or overall CV-related events were considered (Figure 1, panel A). Furthermore, no difference were observed when only studies published in the last 5 years were considered (MH-OR: 0.94[0.38;2.37]; p=0,89 and 0.70[0.38;1.28]; p=0.24 for MACE and overall CV events, respectively).Similarly no differences were observed when data derived from the use of transdermal T preparation were compared to those obtained with injectable T medication (MH-OR: 0.56[0.12; 2.65] vs. 0.96[0.41;2.24]; Q=0.35; p=0.55). Interestingly, when MACE events were considered and only those studies enrolling subjects with a mean BMI > 30 were selected, TTh resulted in a protective

role when compared to placebo (Figure 1, panel B and C). Similar results were observed when overall CV events were observed.

4.0 Conclusion

Despite this analysis of the available evidence it is important to recognize that the duration of the available trials is short (lower that 3 years) and the studies differ in the T thresholds considered. Hence, limited information on possible long-term effects of TTh on CV risk are available. Accordingly, the FDA has recommended performing long-term safety studies in order to better clarify these points although the Euroepan.

5.0 Expert commentary

Present data essentially confirm what has been reported by previous studies (58) suggesting that when MACE are considered no CV risk related to TTh is observed. In 2013, a meta-analysis of the available placebo controlled RCTs reported a 54% increased CV risk related to TTh contributing to the uncertainness related to CV safety of T medications. However, it is important to recognize that the latter meta-analysis presents important limitations (22). First of all, the authors used in their analysis a fixed effect model, which presents important limitations (60). In addition, Xu et al., (22) decided to use a broader definition of CV events, including all the events reported as CV according to the investigator's perception. This resulted in the inclusion of minor CV events, such as self-reported syncope and peripheral edema, leading to an artificial increase of the overall event number. Conversely, the evaluation of the incident MACE is what was requested by all the regulatory agencies involved in the assessment of the drug safety. Quite unexpectedly, the latter outcome was never investigated in available meta-analyses before the publication of our study in 2014. (58). At that time we included 75 placebo-controlled RCTs concluding that no CV risk related to TTh was observed when either MACE or any CV were considered. Similar conclusions were previously (61-63) and thereafter (64-66) drawn by other authors when disaggregate or aggregate CV were analyzed (see for review 59, 67-68). In 2017, however, new concerns related to TTh were reported. In the last year a double-blind placebo controlled trial involving 138 men (73 receiving TTh and 65 placebo) aged 65 years or older

from 9 academic medical centers in the US concluded that TTh resulted in a significantly greater increase in non-calcified plaque volume from baseline when compared to placebo (57). Interestingly, this study is a CV component of the Testosterone Trials (TTrials), which were designed to assess the effects of TTh treatment on several outcomes in men ≥65 years old with symptoms and signs consistent with androgen deficiency and low serum T concentrations (69). Our analysis showed that the inclusion of this RCTs as well as of all other trials published since 2010 did not result in any increased CV risk when MACE and overall CV events were considered.

The type of T preparation has been considered a possible confounding factor in the analysis of CV risk related to TTh. Accordingly, Borst et al., (64) suggested an increased CV risk related to the use of oral T formulations whereas Albert et al., (65) emphasized a possible increased risk CV risk when transdermal preparations and shorter trials (lasting < 12 months) were considered. The analysis of CV risk related to oral T preparations presents important bias. The Copenhagen study published in the early 80s represents a crucial point. This is a phase 3 study resulting in a significantly higher CV risk in the active treatment. However, it is important to recognize that this study was performed in frail men with alcoholic cirrhosis using an oral T formulation which never entered the market, causing supra-physiological blood T levels during the study (70). In addition, in their study Borst et al (64) considered also RCTs including a combination of TTh with other medications. When these limitations were adequately considered, no risk related to oral T preparation has been reported (59). The analysis of Albert et al (65) presents major methodological problems. In fact, in their analysis the authors used a fixed effect model which, as reported above, presents important limitations. Accordingly, the present data documented that when random effect was applied no difference in CV risk between transdermal and injectable T preparations was observed. Unfortunately, insufficient data were available to compare long-acting injectable TU with other preparations. However, by meta-analyzing all the available evidence we previously reported that the latter T formulation presents a good benefit/safety profile (71).

The increase of hematocrit has been considered for a long time one of the possible factors underlying TTh-related CV risk. Accordingly, the effects of T in stimulating the secretion of endogenous erythropoietin and bone marrow erythroid progenitor cells are well known (72-74). In addition, the role of T in the suppression

of hepcidin, involved in the iron pathway and, the contribution of genetic factors (androgen receptor CAG repeats) might represent further mechanisms supporting the TTh-dependent increase of erythropoiesis (73). Much evidence, mainly derived from uncontrolled studies, has documented that short-acting T formulations have the highest incidence of erythrocytosis (73). Accordingly, data derived from our previous analysis of RCTs demonstrated that transdermal T preparations had the lowest risk of polycythemia, when only those studies including hypogonadal patients at baseline were considered. Similar outcomes have been reported for long acting injectable TU (72).

Interestingly, our study documented that when the data were limited to those trials enrolling obese subjects at the study entry, TTh appeared to have a protective role against CV events, even when MACE were considered. It is possible that the improvement of body composition and glycometabolic profile, related to TTh, might explain, at least partially, the protective role of TTh and CV risk documented in this analysis (75-78).

Data deriving from observational studies essentially confirm the safety of TTh when used according to the current guidelines (79). In fact, the two aforementioned studies suggesting an increased CV risk related to TTh present important limitations. Vigen et al., (20) incorrectly excluded from the analysis 1132 patients who experienced CV events before TTh, when they should have been included in the untreated group, increasing the event number by 70%. When challenged, the authors revised the number to 132, but admitted that 104 women had been mistakenly included in the results (18-19, 80). In addition, in this study there were also no data confirming a correct diagnosis of reduced T levels at baseline and none on compliance with therapy (18-19, 80). Finkle et al. (21), in their study, did not report crucial data on fatal CV events and all-cause mortality. In addition, the study design was not prospective, which casts doubts on the validity of retrospective assessment for the 12 month pre-treatment period. While this study has been widely quoted in public media, it is discredited by several design flaws and statistical analyses (18-19, 80). Several other observational studies have documented positive TTh CV outcomes. In a retrospective study involving 1031 hypogonadal men, 372 of whom were under TTh, Shores et al., (80) reported a cumulative mortality of 21% in the untreated group versus 10% in the treated group. A prospective study involving 581 men with type 2 diabetes mellitus (T2DM) followed up for a mean of 5.81 years showed that the mortality

rate was lowest in men with normal T levels during TTh (81). Similarly, results were reported by Sharma et al, (82) who retrospectively evaluated 83,010 male veterans with recorded low serum T levels. A real-life observational registry study assessed the long-term effectiveness and safety of long-acting injectable T undecanoate (TU) used for up to 10 years in 656 men with a mean age of 60.7 years (83). The authors concluded that the mortality related to CVD was significantly reduced in the TTh versus the untreated group (83). Similar results were more recently reported by Hacket et al., (84) in an open-label extension of a placebo-controlled RCT involving 857 men with T2DM followed up for 4 years after baseline T measurement. A study comparing AMI rates in 6355 men receiving at least one T injection, compared with a matched placebo group over 8 years, found no overall increase in events. In those at greatest risk, there was a significant reduction in events and mortality (85). Similarly, Andersen et al., (86) have more recently shown significant reduction in CV events in a cohort of hypogonadal men with angiographically diagnosed coronary artery disease. In a study of 10,311T-treated men compared with 28,029 controls, Wallis et al, (87) demonstrated a reduction in all-cause and CV mortality with TTh achieved and maintained in the normal range. Finally, Cheetham et al, (88) retrospectively reported on 8,808 T-treated and 35,527 untreated men with low T levels and found a 33% reduction in cardiac events associated with TTh.

Finally, it should be recognized that some evidence has documented that differences in the degree to which serum dihydrotestosterone (DHT) is elevated during TTh may represent an important confounding factor (64). In fact it has been proposed that serum DHT may increase the risk of CVD through mechanisms involving inflammation, coagulation and vasoreactivity although the results of studies investigating this association have been conflicting (64).

6.0 Five-year view

The evidence derived from the last 5-years is essentially in line to what reported above. Accordingly, the overall CV and MACE risk related to TTh were not different when data derived from the last 7 years were compared to those obtained in the last 5 years. The latter finding is particular important and further supports the lack of CV risk related to TTh. In fact, as reported above, the TOM trial (29), published in 2010, used a very broad definition for CV events resulting in an inappropriate increase of the events eventually

considered. Accordingly, in our analysis it represents an outlier study with estimates beyond the overall measured effect.

Key issues

- The use of testosterone therapy (TTh) for late onset hypogonadism has been questioned due to possible increased cardiovascular risk.
- Food and Drug Administration Drug Administration (FDA) in its final release approved TTh only for men with "classical hypogonadism", i.e. due to primary or secondary T deficiency resulting from known problems within the testis, pituitary, or hypothalamus (e.g. genetic problems, or damage from surgery, chemotherapy, or infection).
- Available data on TTh derived from randomized clinical trials published in the last 7 years suggest that CV risk is not a major issue.
- Possible advantages in CV prevention can be detected in specific subpopulations (i.e obese men without major comorbidities).
- Duration of the available trials is short (lower that 3 years). Hence, limited information on possible long-term effects of TTh on CV risk are available.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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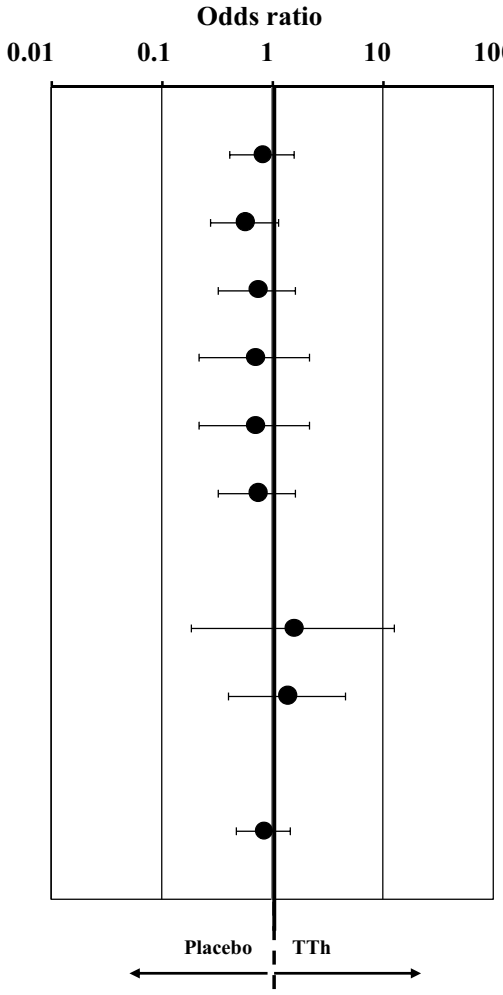
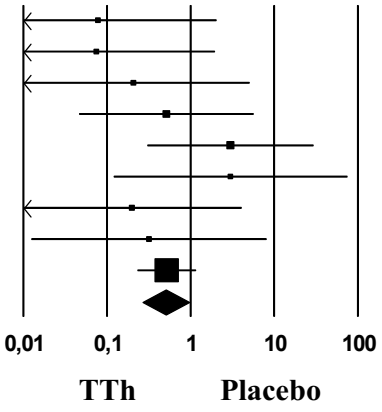


	# Trials	MH-OR	LL	UL	p
MACE	16	0,81	0,42	1,59	0,54
Acute coronary syndrome	13	0,56	0,28	1,14	0,11
Acute myocardial infarction	11	0,74	0,33	1,65	0,46
Stroke	4	0,70	0,22	2,21	0,66
Heart Failure	4	0,70	0,22	2,21	0,54
CV mortality	8	0,74	0,33	1,65	0,80
By-pass surgery	2	1,55	0,19	12,84	0,68
Arrhythmias	5	1,36	0,40	4,60	0,62
Overall CV events	18	0,83	0,48	1,46	0,53

Study name	MH odds ratio	Lower limit	Upper limit	p-Value
Aversa et al., 2010	0,08	0,00	2,07	0,13
Aversa et al., 2010 **	0,07	0,00	1,97	0,12
Kalinchenko et al., 2010	0,21	0,01	5,15	0,34
Jones et al., 2011	0,51	0,05	5,75	0,59
Gianatti et al., 2014	3,00	0,30	30,02	0,35
Janjgava et al., 2014	3,00	0,12	75,74	0,50
Brock et al., 2016	0,20	0,01	4,15	0,30
Dhinsda et al., 2016	0,32	0,01	8,25	0,49
Snyder et al., 2016	0,52	0,23	1,18	0,12
Overall	0,50	0,26	0,95	0,03



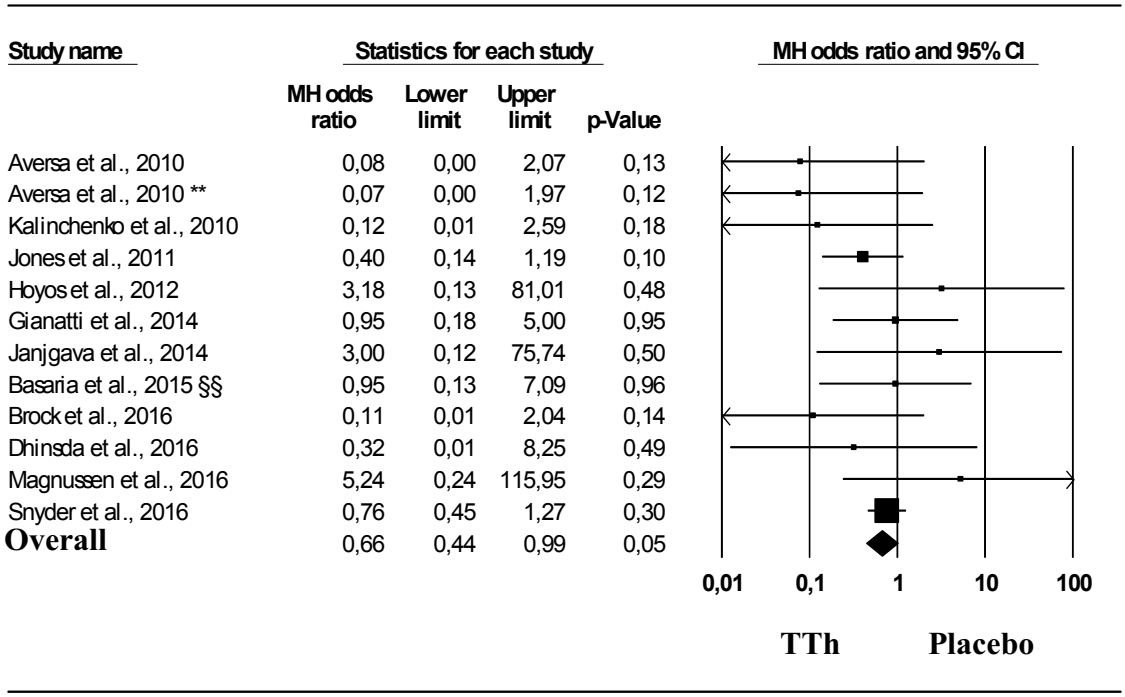


Figure 1. Panel A. Odds ratio for major adverse cardiovascular (CV) events (MACE) and overall CV events in subjects treated with testosterone substitution (TTh) or placebo. Among MACE, the authors considered cardiovascular death, non-fatal myocardial infarction and stroke, and acute coronary syndromes and/or heart failure. **Panel B-C**. Odds ratio for MACE and overall CV events considering only those studies with a mean body mass index > 30 kg/m^2. LL: Lower limit; MH-OR: Mantel-Haenszel odds ratio;; UL: Upper limit.

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Study (ref.)	# patients (T/placebo)	Trial duration (weeks)	Age (years)	Baseline total T (nmol/l)	T levels	Route of administration	Dose
Aversa et al., 2010 (27)	40/10	104	57,8	8,5	TT< 12 nM	Parental	TU 1000mg/12week
Aversa et al., 2010 (28)	42/10	52	57,2	7,4	TT< 12 nM	Oral	TU 160 mg/day/ TU 1000mg/12week
Basaria et al., 2010 (29)	106/103	26	74	8,3	TT< 12 nM	Transdermal	TG 100 mg/day
Cornoldi et al., 2010 (30)	43/44	12	68,7	-	Mixed	Oral	TU 120 mg/day
Gopal et al., 2010 (31)	11/11	26	44,2	10,1	TT< 12 nM	Parental	TC 200 mg/2 week
Kalinchenko et al., 2010 (32)	113/71	30	52,1	7	TT< 12 nM	Parental	TU 1000mg/12week
Srinivas-Shankar et al., 2010 (33)	136/138	26	73,8	11	Mixed	Transdermal	TG 50 mg/day
Amiaz et al., 2011 (34)	50/50	6	51.1	11.8	Mixed	Transdermal	TG 50-100 mg/day
Ho et al., 2011 (35)	60/60	48	53,2	9	Mixed	Parental	TU 1000mg/12week
Jones et al., 2011 (36)	108/112	52	59,9	9,5	Mixed	Transdermal	TG 60 mg/day
Kaufman et al., 2011 (37)	234/40	26	53,9	9,7	TT< 12 nM	Transdermal	TG 12.5-50mg/day
Hoyos et al., 2012 (38)	33/34	18	48,5	13,3	Mixed	Parental	TU 1000mg/12week
Behre et al., 2012 (39)	183/179	48	62,0	10,5	Mixed	Transdermal	TG 50-75 mg/day
Hackett et al., 2013 (40)	92/98	30	61,5	9,0	TT< 12 nM	Parental	TU 1000mg/12wk
Hildreth et al., 2013 (41)	96/47	52	66,5	10,2	TT< 12 nM	Transdermal	TG 100mg/day
Maggio et al., 2013 (42)	43/24	156	71,8	13,4	Mixed	Transdermal	T patch 6 mg/day
Borst et al., 2014 (43)	14/16	52	70,5	8,8	TT< 10,4 nM	Parental	TE 125 mg/week
Gianatti et al., 2014 (44)	45/43	40	62,0	8,6	< 12 nM	Parental	TU 1000 mg/12 week
Janjgava et al., 2014 (45)	43/42	24	49,7	-	Mixed	Parental	TE 250/12 week
Asih et al., 2015 (46)	25/25	24	-	17,2	Mixed	Transdermal	T cream 5% 50 mg/day
Basaria et al., 2015 (47)	155/151	156	67,6	10,5	Mixed	Transdermal	TG 75 mg/day
Basaria et al., 2015 (48)	36/29	14	48,9	8,5	TT< 12 nM	Transdermal	TG 50 mg/day
Cherrier et al., 2015 (49)	10/12	24	70,5	10,6	TT< 10,4 nM	Transdermal	TG 50-100 mg/day
Glintborg et al., 2015 (50)	23/23	24	67.5	-	BT < 7.3 nM	Transdermal	TG 50-100 mg/day
Paduch et al., 2015 (51)	40/36	16	50,7	7,5	TT< 10,4 nM	Transdermal	T solution 60 mg/day
Brock et al., 2016 (52)	358/357	12	55,3	6,9	TT< 10,4 nM	Transdermal	T solution 60-120 mg/day
Chillarón et al., 2016 (53)	6/7	22	46,3	10,9	TT< 10 nM	Parental	TU 1000 mg/12 week
Dhinsda et al., 2016 (54)	22/22	23	54,7	8,6	FT <225 pM	Parental	TC 200 mg/2 week
Magnussen et al., 2016 (55)	22/21	24	60.0	8,2	BT < 7.3 nM	Transdermal	TG 50 mg/day
Snyder et al., 2016 (56)	395/395	52	72,2	8,0	TT< 9.5 nM	Transdermal	TG 50-100 mg/day
Budoff et al., 2017 (57)	88/82	52	71,2	8,2	TT< 9.5 nM	Transdermal	TG 50 mg/day

First author (year)	All CV events (T/P)	MACE (T/P)	AMI (T/P)	ACS (T/P)	CBPS (T/P)	Stroke (T/P)	HF (T/P)	Arrythmias (T/P)	CV mortality (T/P)
Aversa et al., 2010 (27)*	0/1	0/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0
Aversa et al., 2010 (28)*	0/1	0/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0
Basaria et al., 2010 (29)	25/5	6/0	3/0	5/0	1/0	1/0	0/0	5/2	1/0
Cornoldi et al., 2010 (30)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Gopal et al., 2010 (31)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Kalinchenko et al., 2010 (32)*	0/2	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/2
Srinivas-Shankar et al., 2010 (33)	5/2	2/2	0/1	0/0	0/0	0/0	1/0	0/0	1/1
Amiaz et al., 2011 (34)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Ho et al., 2011 (35)	2/2	1/1	1/1	1/1	0/0	0/0	0/0	0/0	1/1
Jones et al., 2011 (36)*	5/12	1/2	1/2	1/2	0/0	0/0	0/0	0/0	0/1
Kaufman et al., 2011 (37)	17/2	2/0	1/0	1/0	0/0	0/0	1/0	0/0	0/0
Hoyos et al., 2012 (38)*	1/0	NR	NR	NR	NR	NR	NR	NR	0/0
Behre et al., 2012 (39)	NR	1/0	NR	NR	NR	NR	NR	NR	1/0
Hackett et al., 2013 (40)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Hildreth et al., 2013 (41)	4/11	1/3	0/0	1/3	0/0	0/0	0/0	0/4	0/0
Maggio et al., 2013 (42)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Borst et al., 2014 (43)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Gianatti et al., 2014 (44)*	3/3	3/1	1/0	1/1	1/1	0/0	2/1	0/0	0/0
Janjgava et al., 2014 (45)*	1/0	1/0	0/0	1/0	0/0	0/0	0/0	0/0	0/0
Asih et al., 2015 (46)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Basaria et al., 2015 (47)*	0/0	12/4	3/2	3/2	NR	3/0	NR	NR	1/0
Basaria et al., 2015 (48)	28/24	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Cherrier et al., 2015 (49)	2/2	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Glintborg et al., 2015 (50)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Paduch et al., 2015 (51)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Brock et al., 2016 (52)*	0/4	0/2	0/0	0/1	0/0	0/1	0/0	0/0	0/0
Dhinsda et al., 2016 (53)*	0/1	0/1	NR	0/1	0/0	0/0	0/0	0/0	0/0
Magnussen et al., 2016 (54)*	2/0	0/0	0/0	0/0	0/0	0/0	0/0	1/0	0/0
Snyder et al., 2016 (55)*	28/36	9/17	2/2	2/6	NR	5/5	2/6	7/4	0/1
Budoff et al., 2017 (56)	NR	0/0	0/0	0/0	0/0	0/0	0/0	1/0	0/0
Chillarón et al., 2017 (57)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

Table 2. Cardiovascular (CV) outcomes of the randomized, placebo controlled clinical studies included in the meta-analysis. § subjects with Alzheimer disease. T= testosterone; P=placebo; MACE= major adverse cardiovascular events; AMI= acute myocardial infarction; ACS= acute coronary syndrome; CBPS=coronary by-pass surgery; HF= heart failure; NR=not reported. * mean body mass index > 30 Kg/m^2

Table 1. Characteristics of the randomized, placebo controlled clinical studies included in the meta-analysis. § Subjects with Alzheimer disease. TT=totaltestosterone, FT= free testosterone; BT= bioavailable testosterone TE= testosterone enanthate, TU= testosterone undecanoate; TC=testosterone cypionate. TG= testosterone gel; NR= not reported.

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** of interest*

*** of considerable interest*

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