Testosterone treatment and cardiovascular and venous thromboembolism risk: what is 'new'?

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ABSTRACT

In men, testosterone (T) production declines as a function of ageing. Late-onset hypogonadism (LOH) is the most commonly used term to indicate this age-related condition. In LOH, the relative clinical significance and the potential benefit of testosterone treatment (TTh) are still the subject of strong criticisms in the scientific community. The debate is further complicated by the recent position statement of the US Food and Drug Administration (FDA) emphasizing that, in LOH, the benefits and safety of TTh have not been fully established. Hence, the FDA required a labeling change to inform patients about a possible increased cardiovascular (CV) risk of TTh. Similar considerations were previously released by the FDA and by Health Canada concerning a TTh-related venous thromboembolism (VTE) risk. In this review, we will summarize the available evidence concerning a possible link among TTh and CV and VTE risks. For this purpose, data derived from epidemiological studies analyzing relationships between the aforementioned risks and endogenous T levels will be analyzed. In addition, evidence deriving from interventional studies including pharmacoepidemiological and placebo-controlled randomized controlled trials (RCTs) will be examined. Our analysis shows that available data do not support an increased CV risk related to TTh. Similar considerations can be drawn for the relationship between TTh and VTE. The previously reported cases of TTh-related VTE were frequently related to a previously undiagnosed thrombophilia-hypofibrinolysis status. Hence, an anamnestic screening for thrombophilia before starting TTh is recommended, just as it is for the use of oral contraceptives.

INTRODUCTION

Testosterone (T) is the main androgen secreted by the male gonadal gland and its biological actions and effects depend on the different life stages. During the fetal stage, T is mainly involved in the differentiation of internal genitalia and in the testis descent, whereas its 5α reduced dihydrotestosterone is essential for prostate and external genital differentiation. During puberty, under T regulation, secondary sexual characteristics appear, fertility is achieved and the adolescent growth spurt occurs.[1–3] In adulthood, T modulates penile erection—as well as other sexual behaviors and attitudes[4]—and is also involved in the regulation of body composition, including glycometabolic homeostasis.[5–7] Furthermore, T and, in particular, its aromatized metabolite, oestradiol, contributes to bone metabolism.[8] Finally, a possible role for T in mood regulation and well-being has also been suggested.[8]

Epidemiological data indicate that T production declines progressively as a function of age and that a significant percentage of men over the age of 60 have serum T levels below the lower limits of young adult men.[1] Late-onset hypogonadism (LOH) is the most commonly used term to indicate this condition.[1] However, the clinical significance of LOH is still the subject of strong criticisms in the scientific community. In particular, it is not clear whether reduced T levels observed in ageing males play a direct contribution to ageing-related morbidities and symptoms or whether low T and associated morbidities are concomitant conditions, both associated with the ageing process per se.[1 9 10]

The debate about LOH was further complicated by a recent position statement of the US Food and Drug Administration (FDA). In fact, in its final 2015 release, the FDA cautioned prescribing T products, stating that they should be only considered for men with 'classical hypogonadism', that is, due to primary or secondary T deficiency resulting from known problems within the testis, pituitary, or hypothalamus (eg, genetic problems, or damage from surgery, chemotherapy, or infection). In addition, the FDA stressed the lack of conclusive data on the benefits and safety of T medications in ageing men.[11] Similar considerations were released in 2014 for the risk of venous thromboembolism (VTE) by the FDA and Health Canada.[12 13] Recently, this position has been essentially endorsed by the Australian Society of Endocrinology.[14]

The aim of this review is to summarize the available evidence supporting a possible link among LOH, cardiovascular (CV) and VTE risks. In particular, for this purpose, three different types of information will be scrutinized concerning LOH and CV or VTE risk: (1) data derived from epidemiological studies analyzing relationships between the aforementioned risks and endogenous T levels; (2) data derived from pharmacoepidemiological studies investigating the effect of T treatment (TTh); and (3) data derived from the use of TTh in placebo-controlled randomized controlled trials (RCTs). Results from

already published meta-analyses will be discussed and analyzed and, in addition, some new meta-analytic analyses will be provided.

CARDIOVASCULAR SAFETY

Acute or chronic illnesses might interfere with the hypothalamic–pituitary–testis axis activity, leading to the development of primary or, more frequently, secondary hypogonadism. It can be speculated that the reduction of T in unfavorable situations—such as in acute or chronic illnesses—might represent a protective mechanism, turning off T-dependent functions (such as reproduction and/or physical and sexual activity) that are not desirable when the physical condition is ailing.[9] Similar adaptive mechanisms have been previously described for other hormonal axes.[15] In line with this possibility, we previously reported in a series of more than 1600 subjects with sexual dysfunction —followed longitudinally for a mean follow-up of 4.3 years—that hypogonadism (total T <12 nmol/L or 350 ng/dL) was associated with a lower (and not higher) incidence of new CV events in those men who had already suffered from CV diseases (CVD) or obesity at enrollment.[16 17] Similar results have been reported in subjects with HIV-related hypogonadism.[18] In line with these data, reports in the scientific and lay press significantly halted the enthusiasm on androgen boosting, suggesting that TTh does increase CV risk. Accordingly, the FDA[11] and the Australian Endocrinology Society[14] stressed the lack of conclusive data on the benefits and safety of T medications in ageing men. In addition, the FDA has mandated pharmaceutical companies that market patented T delivery systems to conduct a placebo-controlled trial that is powered to address potential CV events.[19] It is likely that the trial will involve 5000–6000 hypogonadal men and treatment will last up to 6 years.

Available evidence regarding the possible relationship between TTh and CV risk will be analyzed in more detail in the following sections.

Relationship between endogenous T levels and CV risk

By meta-analyzing available population-based data, three independent meta-analyses have failed to show an association between baseline low T and incident CVD.[20–22] Conversely, a significant increase in the risk of incident CV mortality for subjects with low T has been reported in one meta-analysis,[22] while in others a non-significant trend toward an increase was observed.[20 21] In addition, heterogeneity in the primary data was also observed. Hence, a possible alternative conclusion is that low T could be reflective of an overall poorer health status and not causally related to increased CV mortality.[20–23]

Pharmacoepidemiological studies

Pharmacoepidemiology is a science dealing with the analysis of efficacy and safety of drugs in specific populations.[24] The advantage of pharmacoepidemiology when compared to RCTs is the possibility to assess the incidence of adverse events during long periods of follow-up. Two large observational register studies published in 2013 and 2014 generated great acclaim in the scientific community, suggesting an increased CV risk related to TTh. The first study was based on a retrospective analysis of a cohort of 8709 American Veterans (VA) with reduced T levels (T<10.4 nmol/L), who underwent coronary angiography between 2005 and 2011.[25] Among the VA cohort, those that received TTh during the follow-up period had an increased risk of major adverse cardiovascular events (MACE) or death from any cause when compared with those who were untreated with T.[25] The main criticisms related to this study deal with the lack of T measurements during the follow-up and with the treatment inadequacy in many of the included cases.[10 26]

Some months later the publication of Vigen *et al*,[25] a subsequent study of Finkle *et al*,[27] further supported a TTh-related CV risk. The latter study reports the analysis of a large Medicare insurance database (55 593 subjects) comparing the rate of heart events in the 90 days after starting TTh with the rate in the prior year. The authors concluded that TTh doubled the risk of heart attack among men aged 65 years and older, and particularly in younger men with a pre-existing history of heart disease. The data were compared to 167 000 individuals who were prescribed a phosphodiesterase type 5 inhibitor (PDE5i) without any increase in CV events. However, it is important to recognize that comparison of TTh with PDE5i is questionable, because PDE5i has distinct cardioprotective effects.[27] Besides these two studies, several other reports were previously and thereafter published (table 1[26 28–36]).

Overall, 12 studies have been published so far, including 185 801 cases and 1 160 325 controls (table 1). Among them, six studies compared the effect of TTh in hypogonadal men versus untreated hypogonadal men. In the other six studies, the effect of T prescription was compared with subjects who were not prescribed T. In the latter cases, limited information regarding the T levels was available (table 1). Overall, an increased CV risk was reported only in the Vigen *et al*[25] and Finkle *et al*[27] studies. Conversely, in all other reports a neutral or beneficial effect of TTh was found either when overall mortality or myocardial infarction risks were analyzed (table 1). It is important to recognize that, despite their strengths, observational clinical research presents remarkable limitations, which include selection, information, and confounding biases. Hence, results from observational studies showing small differences should be evaluated with caution. In particular, one of the most important limitations of the observational trials is the presence of limited information regarding the level of T before and during TTh, the number of the controls performed, the dosages used, and the levels of hematocrit. This issue is particularly relevant because a recent report showed that in the USA, among a sample of nearly 250 000 men, only 72% had a claim submitted for T level testing prior to receiving a TTh prescription; 21% never had any claim; and only 6% had claims submitted after receiving their initial TTh prescription.[37] In addition, a general healthcare population survey including more than 4700 hypogonadal men (total T <212 ng/dL; 7.3 nmol/L) treated with T documented that the normalization of T during the treatment was associated with a reduced MACE and death risk over 3 years of follow-up.[37]

Randomized controlled trials

RCTs are often considered the gold standard for testing a specific treatment. The people participating in trials are

Table 1 Descriptive characteristics of the available pharmacoepidemiological studies evaluating the impact of testosterone treatment on forthcoming overall mortality or myocardial infarction

Study	Age (years) mean/ range	n (cases/ controls)	Follow-up (weeks)	Diabetes (%)	Diagnosis of hypogonadism	Study design	Adjusted overall mortality	Adjusted acute myocardial infarction
Shores *et al*,[28] 2012	62.1	398/633	81	38	TT <250 ng/dL (8.7 nmol/L)	T treatment vs no treatment	↓	NA
Finkle *et al*,[27] 2013	54.3	55 593/ 141 031	140	18.9	NA	TTh prescription vs PDE5i prescription	NA	↑
Muraleedharan *et al*,[29] 2013	45–59	64/174	16.5	100	TT <300 ng/dL (10.4 nmol/L)	T treatment vs no treatment	↓	NA
Vigen *et al*,[25] 2013	63.4	1223/7486	110	55.3	TT <300 ng/dL (10.4 nmol/L)	T treatment vs no treatment	↑*	↑*
Baillargeon *et al*,[30] 2014	66 or older	6355/ 19 065	182	16.3	NA	TTh prescription vs no TTh prescription	NA	↔
Eisenberg *et al*,[31] 2015	54.4	284/225	520	NA	NA	TTh prescription vs no TTh prescription	↔	NA
Etminan *et al*,[32] 2015	70.4	30 066/ 120 264	145	0.3	NA	TTh prescription vs no TTh prescription	NA	↔
Ramasamy *et al*,[26] 2015	74.3	153/64	191	NA	TT <300 ng/dL (10.4 nmol/L)	T treatment vs no treatment	↔	NA
Sharma *et al*,[33] 2015	66.2	60 632/ 21 380	304	30.6	TT lower than the local laboratory reference range	T treatment vs no treatment	↓§	↓§
Tan *et al*,[34] 2015	20–86	19 968/ 821 725	72	31.3	TT <350 ng/dL (12.0 nmol/L)	TTh prescription vs no TTh prescription	NA	↓
Maggi *et al*,[35] 2016	59.1	759/249	156	28.7	TT lower than the local laboratory reference range	T treatment vs no treatment	↔	↔
Wallis *et al*,[36] 2016	65 or older	10 311/ 28 029	260	34.3	NA	TTh prescription vs no TTh prescription	↓	NA

*Composite of all-cause mortality, myocardial infarction, and ischemic stroke.
†Normalized treated versus untreated.
↓ reduced risk; ↑ increased risk; ↔ unchanged risk.
NA, not available; T, testosterone; TT, total testosterone.

randomly allocated to either the group receiving the treatment under investigation or to a group receiving a standard treatment (or placebo), as the control. Randomization reduces selection bias and the different comparison groups allow the researchers to determine any clinical or safety effects of the treatment, when compared with the control group. Several RCTs evaluating the effects of TTh on different outcomes have been published so far. However, properly powered placebo-controlled RCTs with a primary CV end point, in men with LOH, are not available yet. The available individual trials have had different eligibility criteria, relatively small numbers of participants, different entry T levels, different T formulations, different target T levels, limited durations of treatment, failure to prespecify CV outcomes, and failure to adjudicate CV outcomes. The Testosterone in Older Men with Mobility Limitations (TOM) trial represents the best example of the aforementioned limitations. The authors enrolled 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 to placebo or supraphysiological dose of T gel (100 mg daily) for 6 months, to evaluate the effect of TTh on exercise tolerance.[38] Although improved physical function was noted, the trial was ended early on due to increased risk of respiratory, dermatological, and, more importantly, CV (T=23 vs placebo=5) events in T-treated men. Interestingly, CV events were not adjudicated and several were of minor importance including self-reported syncope and peripheral edema. In addition, the type of population enrolled (frail men) and the use of double of T recommended dosages further limit the study's evaluation.[38] More recently, a double-blind, placebo-controlled trial including 170 men aged 65 years or older with an average of two serum T levels lower than 275 ng/dL showed that T gel for 1 year compared with placebo was associated with a significantly greater increase in coronary artery non-calcified plaque volume, as measured by coronary CT angiography.[39] However, no difference in the incidence of CV events was observed when T-treated subjects were compared with placebo.[39]

Systematic reviews and meta-analyses are often considered as the highest level of evidence, particularly when available data are conflicting. Since 2005, eight systematic meta-analyses on the association between TTh and CV risk are available (table 2[40–47]). The number of trials considered ranged from 19 to 75 including from 1084 to 5464 subjects. Seven meta-analyses[40 41 43–47] reported outcomes on aggregate CV events, whereas Fernández-Balsells *et al*[42] assessed only disaggregate events. The latter were analyzed by four further meta-analyses;[40 41 44 47] however, only our work[44] included data on MACE. Finally three meta-analyses[43 45 46] included only composite events. In particular, two[43 45] included all CV events considered as CV by the investigators, Albert *et al*[46] used a broader definition of events including MACE as well as percutaneous coronary intervention, coronary bypass, syncope and arrhythmias (table 2). Use of composite outcomes increases the number of expected events and could reduce the required sample size and duration of a trial, often improving statistical power. However, major pitfalls are that pooled outcomes vary substantially in their importance to patients, clinicians, and trial investigators. Hence, the magnitude or direction of reported treatment effects can vary across component end points, limiting the scientific value of their use. Figure 1 shows forest plots of estimated OR (95% CIs) for aggregate or disaggregate CV events as derived from available meta-analyses derived from RCTs on the effect of testosterone therapy (TTh) versus placebo. As shown in the forest plot of figure 1A, only the meta-analysis of Xu *et al*[43] found an increased CV risk related to TTh. As mentioned above, it is important to recognize that Xu *et al*[43] in their analysis used a broader definition of CV events, which included all the events reported as CV by the investigator report, leading to an artificial increase of the overall number of events.[48] In all the other meta-analyses no significant risk was associated with the use of TTh, when both aggregate and disaggregate events were considered (figure 1A–C). However, two systematic reviews showed a significantly increased CV risk in their subgroup analyses of orally administered T.[45 46] In addition, a possible increased CV risk in older individuals (> 65 years old) in shorter trials (<12 months) has been emphasized by Albert *et al*.[47] However, all the latter studies used a composite CV definition in their analysis. Conversely, when the effect of TTh on MACE was considered, no difference in comparison to placebo was reported.[44] Interestingly, the evaluation of MACE is what it is required by the regulatory agencies assessing the safety of any drugs. Finally, it is important to recognize that the duration of all studies evaluated in meta-analyses is relatively short, reaching a maximum of 3 years. Therefore, although there is no clear sign of risk in the short term, no information is available on possible long-term effects.

VENOUS THROMBOEMBOLISM RISK

VTE is a common multifactorial disease with serious complications and potentially fatal outcomes. In the USA alone, VTE causes 600 000 hospitalizations and 60 000 deaths each year.[49] Similar results have been reported in Europe.[50] Major factors underlying VTE include recent surgery or trauma, active cancer, and prolonged immobilization for severe medical diseases. Sex hormones, and in particular estrogens,[49 50] have been considered as a further pathogenetic factor.

Relationship between endogenous T levels and VTE risk

The contribution of T as a risk factor for VTE in men is controversial. Two large population-based studies failed to find an association between endogenous T and VTE (table 3).[51 52]

In particular, data from the fourth survey of the Tromsø study (1994–1995)—which included 1350 community-dwelling men aged 50–84 years—showed a lack of association between endogenous total and free T and risk of VTE.[51] Similar results were reported by Holmegard *et al*[52] in the Copenhagen City Heart Study, including 4673 men representative for the adult Danish population. In line with these data, Mumoli *et al*[53] were unable to detect any difference in T and oestradiol levels between 63 patients with unprovoked deep venous thrombosis (DVT) and matched controls (table 3).

Pharmacoepidemiological studies

Several case series have documented VTE in patients who received TTh (see for review ref. 56). Possible advocated pathogenetic mechanisms include: (1) hematocrit increase with associated increased blood viscosity, (2) platelet aggregation, and (3) increased thromboxane A2 concentrations in platelets.[56] In addition, considering that TTh also increases circulating estrogens, it is plausible that the latter may play a role in thrombotic events.[56] In line with these data, in June 2014 the US FDA[12] and Health Canada[13] added a warning regarding the risk of VTE to the label of all T products, based on postmarketing surveillance reports. However, the vast majority (39 over 40 subjects) of the previously reported cases of TTh-related VTE with measured thrombophilia-hypofibrinolysis was found to have a previously undiagnosed thrombophilia-hypofibrinolysis.[56] Accordingly, when compared with 105 healthy eugonadal controls and with 42 hypogonadal subjects on TTh but without thrombotic events, the 40 cases with thrombotic events were more likely to have Factor V Leiden heterozygosity, higher Factor VIII, and high Factor XI.[56] More recently, the same authors reported similar results in a study including 347 patients hospitalized for pulmonary embolism (PE).[57] Hence, by summarizing current evidence deriving from available observational studies, it is important to emphasize as a major limitation the lack of a control group including non-TTh users with a comparable rate of underlying thrombophilia.

To date, only two large pharmacoepidemiological studies have compared the rate of TTh-related VTE with a control group. The first large case–control study included 30 572 men 40 years and older who were enrolled in one of the USA's largest commercial insurance programs between January 1, 2007 and December 31, 2012.[54] Cases were defined as men who had a primary diagnosis of VTE based on International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) codes as primary diagnosis position and received an anticoagulant drug in the 60 days after their diagnoses. Cases were matched with controls who were not diagnosed with DVT or PE at any time during the study period. After the adjustment for confounders, TTh was not associated with an increased risk of VTE (adjusted ratio, 0.90 (0.73 to 1.12)).[54] In contrast to

Table 2 Comparisons of the available meta-analyses evaluating the relationship between testosterone therapy (TTh) and cardiovascular (CV) risk

Inclusion criteria	Calof *et al*,[40] 2005		Haddad *et al*,[41] 2007		Fernández-Balsells *et al*,[42] 2010		Xu *et al*,[43] 2013		Corona *et al*,[44] 2014		Borst *et al*,[45] 2014		Albert *et al*,[46] 2016		Alexander *et al*,[47] 2016	
Number of trials included	19		30		51		27		74		35		45		39	
Number of patients analyzed	1084		1642		2679		2944		5464		3703		5328		5441	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Primary end point MACE incidence		X		X		X		X	X			*X*		*X*		
Primary end point AMI and stroke		X		X		X		X		X		*X*		*X*	*X*	
Primary end point all CV-event incidence	X		X				X			X	X					X
Primary end point all TTh adverse events		X		X		X		X		X		X				X
Primary end point MACE+ percutaneous coronary intervention, coronary bypass, syncope, arrhythmia		X		X		X		X		X		X	X			X
Time restriction (>12 weeks)	X			X			X			X		X		X		X
Age restriction (≥45 years old)	X			X				X		X		X		X		X
Not considered HIV, schizophrenia, end stage renal disease or primary hypogonadism		X		X		X		X		X		X		X	X	
All available RCTs reporting CV adverse events		X	X		X	X		X	X			X		X		X
Cardiovascular event analysis																
All CV events	X		X			X	X		X		X		X			X
Serious adverse events (including MACE)		X		X		X	X			X		X		X		X
MACE		X		X		X		X	X			X		X		X
AMI	X		X		X			X	X			X		X	X	
Acute coronary syndrome	X			X		X		X	X			X		X		X
Coronary bypass surgery	X			X	X			X	X			X		X		X
Stroke	X			X		X		X	X			X		X	X	
New heart failure		X		X		X		X	X			X		X		X
Arrhythmias	X			X	X			X	X			X		X		X
CV mortality		X		X		X	X		X			X		X		
Overall mortality		X		X		X		X		X		X		X	X	

AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; RCTs, randomized controlled trials.

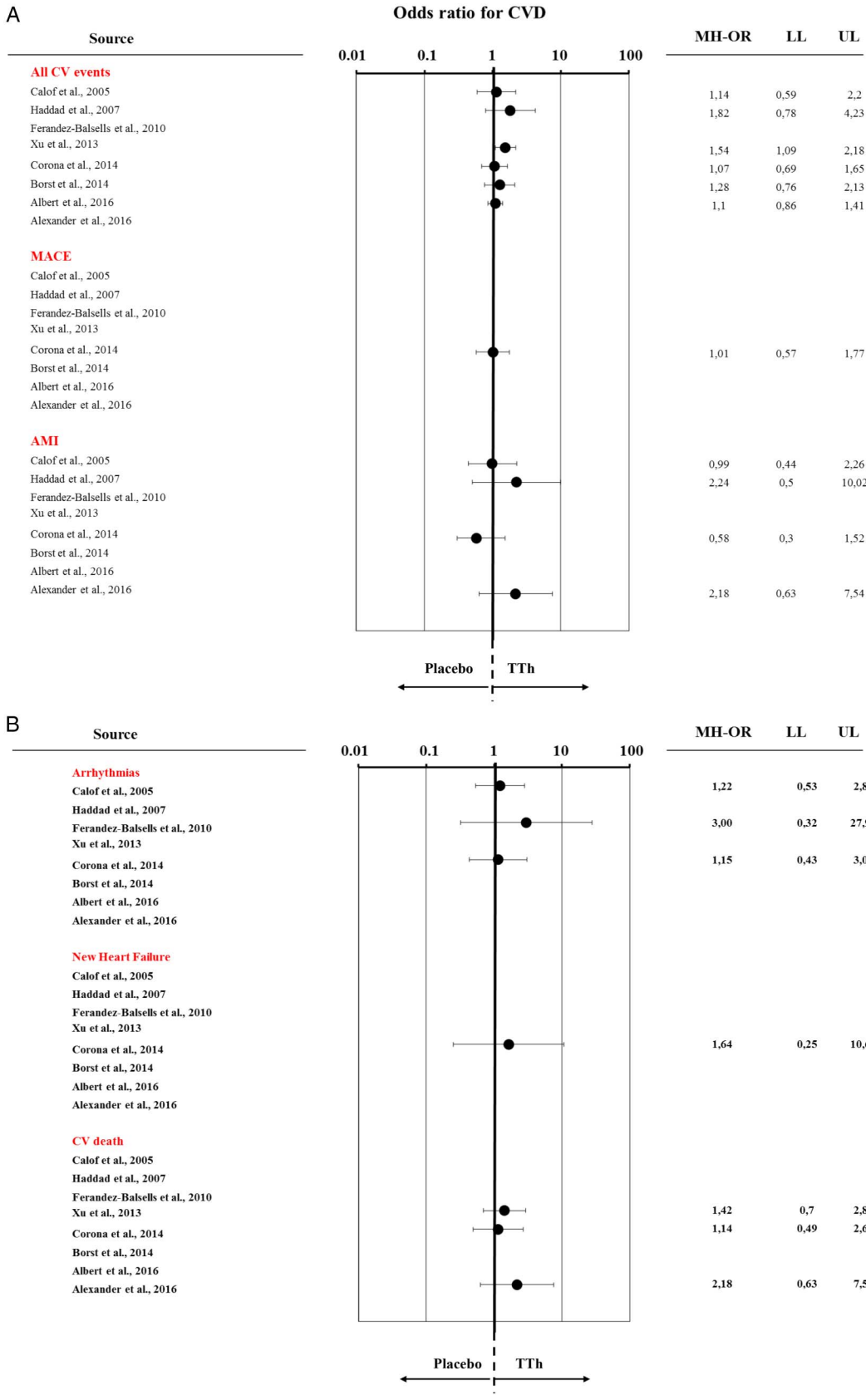

Figure 1 Forest plot of estimated OR (95% CIs) for aggregate or disaggregate cardiovascular (CV) disease (CVD) events as derived from available meta-analyses derived from randomized controlled trials on the effect of testosterone therapy (TTh) versus placebo. AMI, acute myocardial infarction; LL, lower limits; MACE, major adverse cardiovascular events; UP, upper limits.

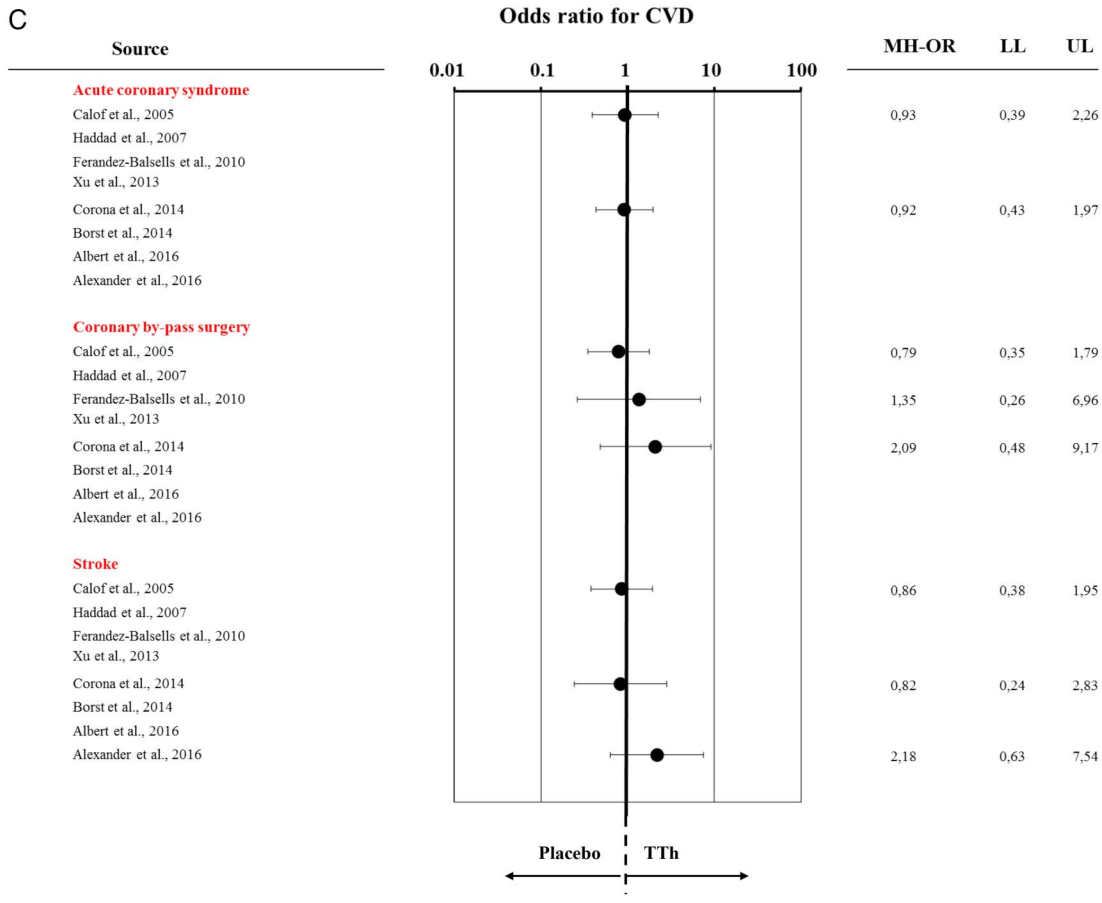

Figure 1 Continued

this study, a more recent report reached opposite findings.[55] In this study, data were derived from 370 general practitioners in UK primary care, including all men aged 20–89 years registered in the Clinical Practice Research Datalink. Cases comprised 19 215 patients with confirmed VTE evaluated between January 2001 and May 2013. Matched controls included 909 530 subjects from the same database not exposed to TTh. The overall adjusted rate ratio of VTE for current versus no TTh was 1.25 (0.94 to 1.66), and, therefore, not statistically significant. However, when the data were limited to the first 6 months of TTh, the rate ratio of VTE was significant, 1.63 (1.12 to 2.37),

Table 3 Characteristics of the longitudinal studies evaluating difference in testosterone (T) levels between subjects with or without venous thromboembolism (VTE) (upper panels) and risk for VTE as derived from available pharmacoepidemiological studies (lower panels)

Study (ref.)	No. of patients	Follow-up duration (years)	Age (years)	Body mass index	DM	Smoking	Unadjusted risk of VTE	Adjusted risk of VTE
Risk of VTE based on baseline T levels								
Svartberg *et al*,[51] 2009	1350	8	63±7	26.1±3.5	3.8	32.1	–	1.21 (0.62;2.44)*
Holmegard *et al*,[52] 2014	4673	21	57 (48–65)	26 (23–28)	13	64	–	1.30 (0.62;2.73)*
Mumoli *et al*,[53] 2015	126	2	64.6±14.2	26.7±2.8	–	–	–	No difference
Risk of VTE based on TTh exposition in case–control studies								
Baillargeon *et al*,[54] 2015	Cases 7643 Controls 22 929	–	≥ 40	–	–	–	0.92 (0.75;1.13)†	0.90 (0.73;1.12)†
Martinez *et al*,[55] 2016	Cases 19 215 Controls 909 530	–	64.8±15.2	26.0±4.6	–	19.8	1.84 (1.42;2.38)†	1.25 (0.94;1.66)†

*Highest versus lowest T quartile.
†Exposed versus unexposed to testosterone treatment (TTh).
DM, diabetes mellitus.

Table 4 Characteristics of the randomized, placebo-controlled clinical studies included in the meta-analysis on venous thromboembolism risk

Study (ref.)	No. of patients (T/placebo)	Trial duration (weeks)	Age (years)	Comorbidities	Baseline total T (nmol/L)	T levels	Dose
Copenhagen Study Group,[59] 1986	134/87	112	53.0	Alcoholic cirrhosis	NR	Mixed	Micronized T 600 mg/day
Marin *et al*,[60] 1993	11/10	32	57.2	Overweight/ obese	14.8	Mixed	TG 100 mg/day
Srinivas-Shankar *et al*,[61] 2010	136/138	26	73.8	Elderly frail men	11	Mixed	TG 50 mg/day
Behre *et al*,[62] 2012	183/179	48	62.0	Elderly men	10,5	Mixed	TG 50–75 mg/day
Brock *et al*,[63] 2016	358/357	12	55.3	Elderly men	6,9	<12 nM	T solution 2% 30–60 mg/day
Snyder *et al*,[64] 2016	395/395	52	72.2	Elderly men	8.2	<12 nM	TG 50–100 mg/day

T, testosterone; TG, testosterone gel.

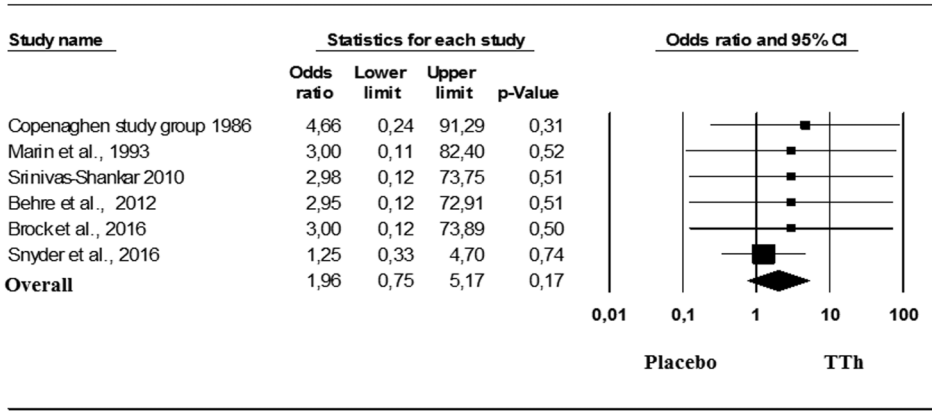

Figure 2 Forest plot of estimated OR (95% CIs) for venous thromboembolism (VTE) of testosterone treatment (TTh) versus placebo, as derived from available placebo-controlled available trials.

corresponding to 10.0 (1.9 to 21.6) additional VTE above the base rate of 15.8 per10 000 person years.[55] By meta-analyzing the two aforementioned studies we here report that TTh is not associated with an increased risk of VTE either when unadjusted (OR=1.3 (0.66 to 2.55); p=0.46) or fully adjusted (OR=1.05 (0.76 to 1.44); p=0.78) data were considered (see table 3 and see online supplementary figure 1A,B). Interestingly, the data were confirmed in a sensitivity analysis when events derived from the first 6 months of TTh in the Martinez *et al*[55] study were considered (OR=1.19 (0.66 to 2.12); p=0.56; see online supplementary figure 1C).

Randomized controlled trial

The interpretation of epidemiological data is complex because of the effect of confounders. Accordingly, observational studies cannot be used to infer causal relationships, which can be more properly derived from the analysis of RCTs. However, it should be recognized that, no long-term, prospective, intervention RCTs on TTh with VTE or CV as the primary end point are available. Only results from short-term studies, or obtained from RCTs designed for other purposes, are available. By meta-analyzing the few available data, Xu *et al*[58] previously reported that TTh was associated with a fivefold increased risk of VTE. However, at that time, the data were only based on three RCTs, including 516 men. In addition, the authors used a fixed model for their statistical analysis. It is important to recognize that, when a low heterogeneity is detected, a random-effect model should be applied, because the validity of tests of heterogeneity is rather limited, due to the small number of component studies. Hence, in our opinion, results from this meta-analysis are questionable. In order to overcome some of the limitations of the analysis of Xu *et al*,[58] we here performed an updated systematic review and meta-analysis of RCTs on TTh, including only studies reporting VTE events in T or placebo arms. An extensive Medline search was performed including the following words ("testosterone"[MeSH Terms] OR "testosterone"[All Fields]) AND (Clinical Trial [ptyp] AND "humans"[MeSH Terms] AND English [lang] AND "male"[MeSH Terms]). The search, which accrued data from January 1, 1969 up to December 1, 2016, was restricted to TTh placebo-controlled RCTs on different outcomes, English-language articles, and studies of human participants.

Out of 2904 retrieved articles, six were included in the study.[59–64] The characteristics of the retrieved trials and the number of events recorded are reported in table 4.

Retrieved trials included 1217 and 1166 patients in TTh and placebo groups, respectively; mean trial duration was 42.0 weeks and mean age 47 years. TTh was administered

in different cohorts, doses, and formulations (table 4). I^2 was 0.0 (p=0.96). Funnel plot and Begg adjusted rank correlation test (Kendall's τ=0.0; p=1.0) suggested no major publication bias. By applying a random-effect model, our data indicated that the use of TTh was not associated with any significant difference in the incidence of VTE in comparison to placebo (MH-OR=1.96 (0.75 to 5.17); p=0.17) (figure 2).

CONCLUSIONS

Men with underlying chronic illnesses, including CV diseases, often have low T, which can be symptomatic (LOH). Although some uncontrolled claims suggest potential risks in treating LOH, data available from controlled trials so far do not suggest any documentable risk, as demonstrated by the Forest plots reported here, summarizing OR results from different meta-analyses. In addition, meta-analysis of RCTs and of the few pharmacoepidemiological studies available does not suggest any relationships between TTh and VTE risk. Hence, TTh, when applied to the right patient (documented LOH), should be considered safe and appropriate.

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