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REVIEW

Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies

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ABSTRACT

Background: The relationship between testosterone (T) and cardiovascular (CV) risk in men is conflicting.

Aim: To verify whether T therapy (TTh) represents a possible risk factor for CV morbidity and mortality.

Methods: We conducted a random effect meta-analysis considering all available data from pharmaco-epidemiological studies as well as randomized placebo-controlled trials (RCTs).

Outcomes: CV mortality and morbidity were investigated.

Results: After screening, 15 pharmaco-epidemiological and 93 RCT studies were considered. The analysis of pharmaco-epidemiological studies documented that TTh reduces overall mortality and CV morbidity. Conversely, in RCTs, TTh had no clear effect, either beneficial or detrimental, on the incidence of CV events. However, a protective role of TTh on CV morbidity was observed when studies enrolling obese (body mass index >30 kg/m^2) patients were scrutinized (Mantel-Haenszel odds ratio 0.51 [95% CI 0.27−0.96]; $P = .04$), although this association disappeared when only high-quality RCTs were considered (Mantel-Haenszel odds ratio 0.64 [95% CI 0.22−1.88]; $P = .42$). Finally, an increased risk of CV diseases was observed in RCTs when T preparations were prescribed at dosages above those normally recommended, or when frail men were considered.

Clinical Implications: Pharmaco-epidemiological studies showed that TTh might reduce CV risk, but this effect was not confirmed when RCTs were considered.

Strengths & Limitations: Meta-analysis of pharmaco-epidemiological studies indicates that TTh reduces overall mortality and CV morbidity. In addition, even in RCTs, a protective role of TTh on CV morbidity was envisaged when studies enrolling obese (body mass index >30 kg/m^2) patients were considered. Pharmaco-epidemiological studies should be considered with caution due to the lack of completeness of follow-up and of the management of missing data. In addition, properly powered placebo-controlled RCTs with a primary CV end point, in men with late-onset hypo-gonadism, are not yet available. Finally, the duration of all studies evaluated in the present meta-analysis is relatively short, reaching a maximum of 3 years.

Conclusions: Data from RCTs suggest that treatment with T is not effective in reducing CV risk, however, when TTh is correctly applied, it is not associated with an increase in CV risk and it may have a beneficial effect in some sub-populations. **Corona G, Rastrelli G, Di Pasquale G, et al. Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies. J Sex Med 2018;15:820−838.**

Key Words: Testosterone; Cardiovascular Risk; Obesity; Late-Onset Hypogonadism

INTRODUCTION

Several population-based studies have documented an age-dependent, modest reduction of circulating testosterone (T) levels in men. "Late-onset hypogonadism" (LOH) is the most frequently used term to describe this phenomenon.[1−3] This condition has been associated with several symptoms and signs, including sexual dysfunction, reduced vitality and cognition, depressive symptoms, as well as visceral obesity, and metabolic syndrome.[3,4] In the past 2 decades, the introduction and use of newer user-friendly T preparations has dramatically expanded the

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T market.[5,6] The opportunity to release drug- and disease-related specific advertisements has clearly influenced T sales, especially in the United States. A recent ecologic study, conducted in designated market areas in the United States, has demonstrated that between 2009 and 2013 exposure to televised direct-to-consumer advertising was associated with greater T testing, new initiation of therapy and, especially, initiation of therapy without prior T testing.[7] These data appear even more surprising considering that the clinical significance of LOH is still debated. In fact, it is not thoroughly known whether the reduced T levels observed in elderly men contribute to age-related morbidities and symptoms, or whether low T and associated morbidities are concomitant conditions, both associated with the aging process.[8] To better clarify this point, in 2004 the Institution of Medicine recommended conducting clinical trials to evaluate the efficacy and safety ratio of T therapy (TTh) in older men.[9] The data published in the last 20 years have not definitively clarified this issue. In particular, the debate about LOH has been further complicated by the data published in the last 5 years, emphasizing a possible increase in cardiovascular (CV) risk. In its final 2015 release, the U.S. Food and Drug Administration (FDA) cautioned that the benefits and safety of treatment with T products have not been clearly established for the treatment of low T levels due to aging.[10] In particular, the FDA stated that TTh should be considered only for men with "classical hypogonadism," ie, due to primary or secondary T deficiency resulting from known problems within the testis, pituitary, or hypothalamus.[10] This position has been endorsed by Health Canada[11] and more recently by the Australian Society of Endocrinology.[12] In addition, supporting these views, the concept of *functional hypogonadism* has been introduced.[13] The latter includes all LOH conditions associated with potentially modifiable morbidities impairing hypothalamus-pituitary-testis axis function.[13] In other words, functional hypo-gonadism represents a diagnosis of exclusion when and no identifiable organic problem is detected.[13] These positions have not been supported by the European Medicine Agency, which, after a specific review of the available data, did not find sufficient evidence for declaring a TTh-associated CV risk.[14]

The aim of the present study is to verify, using meta-analytic methods, whether TTh represents a possible risk factor for CV morbidity and mortality, considering all available data from intervention studies, including randomized placebo-controlled trials (RCTs) and pharmaco-epidemiological studies.

METHODS

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary file 1). The protocol of this study (CRD42017054353) was published on the website of the University of York (Center for Reviews and Dissemination): http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054353.

Search Strategy

An extensive MEDLINE, Embase, and Cochrane search was performed including the following words ((“testosterone”[MeSH Terms] OR “testosterone”[All Fields]) AND (“cardiovascular system”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “system”[All Fields]) OR “cardiovascular system”[All Fields] OR “cardiovascular”[All Fields]) AND (“risk”[MeSH Terms] OR “risk”[All Fields])) AND (“humans”[MeSH Terms] AND English[lang] AND “male”[MeSH Terms]) for the selection of interventional pharmaco-epidemiological studies evaluating the effect of TTh on CV mortality and morbidity. In addition, a second separate 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]) for the selection of all placebo-controlled RCTs for the analysis of the same end points.

The search, which accrued data from January 1, 1969, up to March 31, 2017, was restricted to English-language articles and studies of human participants. The identification of relevant studies was performed independently by 2 of the authors (G.R., G.C.), and conflicts resolved by the third investigator (M.M.). We did not employ search software. We hand-searched bibliographies of retrieved studies for additional references. The principal source of information was derived from published articles. If data were missing from a publication, an attempt at retrieval was made through clinicaltrials.gov website.

Study Selection

We included all pharmaco-epidemiological studies or placebo-controlled RCTs evaluating the effects of TTh vs placebo on different end points. All studies without any arbitrary restriction, even if CV events were not the principal end points, were included[15−121] (Supplementary Figure 1A and B; Tables 1 and 2; and Supplementary Tables 1−3). Studies not specifically stating the occurrence or absence of CV-related events were excluded from the analysis. Studies using androgens other than T, as well as studies with simultaneous treatment with other hormones and drugs, were excluded, unless there was a clearly defined treatment arm that received only T treatment. In addition, to reduce possible bias in the statistical analysis, the open-label phase of RCTs was not considered in the analysis of pharmaco-epidemiological trials. Finally, since phosphodiesterase type 5 inhibitors (PDE5is) have been reported to play a possible positive influence on CV outcomes, RCTs evaluating the effect of TTh as an add-on to PDE5i were excluded from the analysis.

Outcome

The principal outcome of this analysis was to evaluate the effect of TTh on CV morbidity and mortality as derived from pharmaco-epidemiological and RCTs studies. In particular, in RCTs, the effect of TTh, as compared to placebo, on the incidence of new major adverse CV events (MACE) was evaluated.

Table 1. Characteristics of the randomized, placebo-controlled clinical studies included in the meta-analysis

Study	No. of patients, T/placebo	Trial duration, wk	Age, y	Comorbidities	Baseline TT, nmol/L	T levels	Dose	Drug company funded
Copenhagen Study Group,[30] 1986	134/87	112	53.0	Alcoholic cirrhosis*	—	Mixed	Micronized T 600 mg/d	No
Drinka et al,[31] 1995	8/10	26	—	Institutionalized men*	—	TT <12 nmol/L	TE 150 mg/70 kg/2 wk	No
Aydin et al,[32] 1996	20/18	8	38.9	Elderly men	—	Eugonadal	TU 120 mg/d	No
Hall et al,[33] 1996	17/18	39	60.8	Rheumatoid arthritis	15.9	Mixed	TE 250 mg/mo	Yes
Coodley and Coodley,[34] 1997	17/18	13	—	HIV	—	Mixed	TC 200 mg/2 wk	Yes
Sih et al,[35] 1997	17/15	26	66.4	Elderly men	9.1	TT <12 nmol/L	TC 200 mg/2 wk	No
Bhasin et al,[36] 1998	20/21	12	—	HIV	8.0	TT <12 nmol/L	T patch 5 mg/d	Yes
Grinspoon et al,[37] 1998	26/25	26	42.0	HIV	10.7	Mixed	TE 300 mg/3 wk	Yes
Clague et al,[38] 1999	7/7	12	66.7	Elderly men	11.5	Mixed	TE 200 mg/2 wk	Yes
Giorgi et al,[39] 1999	11/10	12	27.0	Healthy men in training	—	Eugonadal	TE 3.5 mg/kg/2 wk	No
Snyder et al,[40] 1999	54/54	156	73.1	Elderly men	12.6	Mixed	T patch 6 mg/d	No
Bhasin et al,[41] 2000	17/14	16	41.3	HIV	6.7	TT <12 nmol/L	TE 100 mg/wk	No
English et al,[42] 2000	25/25	12	62.0	Chronic stable angina	12.9	Mixed	T patch 5 mg/d	No
Grinspoon et al,[43] 2000	27/27	12	41.9	HIV	22.8	Eugonadal	TE 200 mg/wk	No
Rabkin et al,[44] 2000	39/35	6	39.0	HIV	13.2	Mixed	TC 200 mg/2 wk	Yes
Münzer et al,[45] 2001	21/17	26	70.0	Elderly men	13.8	Eugonadal	TE 100 mg/2 wk	No
Howell et al,[46] 2001	16/19	26	40.9	Cytotoxic chemotherapy*	13.3	Mixed	T patch 2.5–5 mg/d	Yes
Seidman et al,[47] 2001	13/17	6	51.4	Major depressive disorder	9.1	TT <12 nmol/L	TE 200 mg/wk	No
Simon et al,[48] 2001	6/6	12	53.1	LOH	8.7	TT <12 nmol/L	TG 125 mg/d	No
Amory et al,[49] 2002	12/13	4	70.4	Elderly men	12.8	Mixed	TE 600 mg/wk	No
Blackman et al,[50] 2002	21/17	26	70.0	Elderly men	14.0	Mixed	TE 100 mg/2 wk	No
Ferrando et al,[51] 2002	7/5	26	—	Elderly men	11.3	Mixed	TE 100 mg/wk	No
Liu et al,[52] 2003	17/17	4	67.0	Elderly men	9.6	Mixed	Combination of T propionate T phenylpropionate, T isocaproate, and T decanoate 500–250–250 mg	No
Park et al,[53] 2003	33/6	12	—	Elderly men	8.9	Mixed	TU 160 mg/d	No
Pope et al,[54] 2003	12/10	8	49.2	Refractory depression	9.6	TT <12 nmol/L	TG 100 mg/d	Yes
Steidle et al,[55] 2003	307/99	12	56.8	Sexual dysfunction	8.0	TT <12 nmol/L	TG 100 mg/d	Yes
Tan and Pu,[56] 2003	5/5	52	70.7	Alzheimer disease	—	TT <8 nmol/L	TE 200 mg/2 wk	No

(continued)

Table 1. Continued

Study	No. of patients, T/placebo	Trial duration, wk	Age, y	Comorbidities	Baseline TT, nmol/L	T levels	Dose	Drug company funded
Amory et al,[57] 2004	24/24	156	71.0	Elderly men	10.2	TT <12 nmol/L	TE 200 mg/2 wk	No
Cavallini et al,[58] 2004	40/45	52	66.0	Elderly men	10.2	TT <12 nmol/L	TU 160 mg/d	No
Kenny et al,[59] 2004	6/5	12	79.6	Mild cognitive loss	13.8	Mixed	TE 200 mg/3 wk	No
Malkin et al,[60] 2004	5/5	4	60.8	Ischemic heart disease	4.2	Eugonadal	Combination of T propionate, T phenylpropionate, T isocaproate, and T decanoate 100 mg/2 wk	No
Malkin et al,[61] 2004	29/29	4	61.6	Elderly men	4.4	TT <8 nmol/L	Combination of T propionate, T phenylpropionate, T isocaproate, and T decanoate 100 mg/2 wk	No
Rabkin et al,[62] 2004	38/39	8	41.0	HIV	20.4	Mixed	TC 400 mg/2 wk	Yes
Svartberg et al,[63] 2004	15/14	26	66.5	COPD	21.1	Eugonadal	TE 250 mg/mo	No
Seidman et al,[64] 2005	13/13	6	46.4	Refractory depression	14.7	TT <12 nmol/L	TE 200 mg/wk	No
Sullivan et al,[65] 2005	37/34	12	78.2	Elderly frail men*	10.7	Mixed	TE 100 mg/wk	No
Brockenbrough et al,[66] 2006	19/21	26	55.8	Dialysis subjects*	7.2	TT <12 nmol/L	TG 100 mg/d	Yes
Giannoulis et al,[67] 2006	23/20	26	69.9	Elderly men	16	Mixed	T patch 5 mg/d	No
Gold et al,[68] 2006	66/80	12	39.9	HIV	25.7	Eugonadal	Combination of T propionate, T phenylpropionate, T isocaproate, and T decanoate 250 mg/2 wk	Yes
Kapoor et al,[69] 2006	27/27	26	63.2	T2DM	8.6	TT <8 nmol/L	Combination of T propionate, T phenylpropionate, T isocaproate, and T decanoate 200 mg/2 wk	No
Katznelson et al,[70] 2006	17/17	12	72.0	Elderly men	14.1	TT <12 nmol/L	T patch 5 mg/d	Yes
Lu et al,[71] 2006†	9/9	24	69.8	Mild Alzheimer disease	12.2	Mixed	TG 75 mg/d	Yes
Lu et al,[71] 2006	14/15	24	62.3	Elderly men	13.0	Mixed	TG 75 mg/d	Yes
Malkin et al,[72] 2006	37/39	52	64.0	Heart failure	13.0	Mixed	T patch 5 mg/d	No
Marks et al,[73] 2006	22/22	26	69.0	Elderly men	8.1	TT <12 nmol/L	TE 150 mg/2 wk	Yes
Merza et al,[74] 2006	20/19	26	61.4	Elderly men	8.0	TT <12 nmol/L	T patch 5 mg/d	Yes
Nair et al,[75] 2006	30/32	104	66.7	Elderly men	13	Mixed	T patch 5 mg/d	No
Okun et al,[75] 2006	15/15	26	68.3	Parkinson disease	11.1	Mixed	TE 200 mg/wk	No

(continued)

Table 1. Continued

Study	No. of patients, T/placebo	Trial duration, wk	Age, y	Comorbidities	Baseline TT, nmol/L	T levels	Dose	Drug company funded
Bhasin et al,[77] 2007	44/44	24	45.5	HIV	13.9	Mixed	TG 100 mg/d	No
Chiang et al,[78] 2007	20/18	12	—	Elderly men	8.1	TT <12 nmol/L	TG 50 mg/d	Yes
Agledahl et al,[79] 2008	13/13	52	69.1	Elderly men	8.4	TT <12 nmol/L	TU 1,000 mg/12 wk	Yes
Allan et al,[80] 2008	31/31	52	63.3	Elderly men	14.1	Mixed	T patch 5 mg/d	Yes
Basurto et al,[81] 2008	25/23	52	63.2	Elderly men	10.5	TT <12 nmol/L	TE 250 mg/3 wk	No
Emmelot-Vonk et al,[82] 2008	120/117	26	67.3	Elderly men	10.7	Mixed	TU 160 mg/d	No
Knapp et al,[83] 2008	30/31	17	43.2	HIV	14.6	Mixed	TE 300 mg/wk	No
Svartberg et al,[84] 2008	19/19	52	69.0	Elderly men	8.3	TT <12 nmol/L	TU 1,000 mg/12 wk	Yes
Caminiti et al,[85] 2009	35/35	12	70.0	Heart failure	7.5	Mixed	TU 1,000 mg/12 wk	Yes
Chiang et al,[86] 2009	20/20	13	—	Erectile dysfunction	6.2	Mixed	TG 50 mg/d	No
Chapman et al,[87] 2009	6/6	52	76.0	Elderly frail men*	20.3	Mixed	TU 160 mg/d	Yes
Legros et al,[88] 2009	237/79	52	58.7	Elderly men	12.8	Mixed	TU 80–240 mg/d	Yes
Mathur et al,[89] 2009	7/6	52	64.8	Stable chronic angina	9.9	TT <12 nmol/L	TU 1,000 mg/12 wk	Yes
Seidman et al,[90] 2009	13/10	6	50.6	Dysthymia	11.6	Mixed	TC 200 mg/10 days	No
Shores et al,[91] 2009	17/16	12	59.3	Dysthymia	10.1	Mixed	TG 75 mg/d	Yes
Aversa et al,[92] 2010	40/10	104	57.8	MetS and/or T2DM	8.5	TT <12 nmol/L	TU 1,000 mg/12 wk	No
Aversa et al,[93] 2010	42/10	52	57.2	MetS and/or T2DM	7.4	TT <12 nmol/L	TU 160 mg/d TU 1,000 mg/12 wk	No
Basaria et al,[94] 2010	106/103	26	74	Elderly frail men*	8.3	TT <12 nmol/L	TG 100 mg/d	Yes
Cornoldi et al,[95] 2010	43/44	12	68.7	Chronic stable angina	—	Mixed	TU 120 mg/d	No
Gopal et al,[96] 2010	11/11	26	44.2	T2DM	10.1	TT <12 nmol/L	TC 200 mg/2 wk	No
Kalinchenko et al,[97] 2010	113/71	30	52.1	MetS	7	TT <12 nmol/L	TU 1,000 mg/12 wk	Yes
Srinivas-Shankar et al,[98] 2010	136/138	26	73.8	Elderly frail men*	11	Mixed	TG 50 mg/d	Yes
Amiaz et al,[99] 2011	50/50	6	51.1	Major depressive disorder	11.8	Mixed	TG 50–100 mg/d	No
Ho et al,[100] 2012	60/60	48	53.2	Elderly men	9	Mixed	TU 1,000 mg/12 wk	Yes
Jones et al,[101] 2011	108/112	52	59.9	MetS and/or T2DM	9.5	Mixed	TG 60 mg/d	Yes
Kaufman et al,[102] 2011	234/40	26	53.9	Elderly men	9.7	TT <12 nmol/L	TG 12.5–50 mg/d	Yes
Hoyos et al,[103] 2012	33/34	18	48.5	Obese with OSA	13.3	Mixed	TU 1,000 mg/12 wk	Yes
Behre et al,[104] 2012	183/179	48	62.0	Elderly men	10.5	Mixed	TG 50–75 mg/d	Yes
Hackett et al,[105] 2013	92/98	30	61.5	T2DM	9.0	TT <12 nmol/L	TU 1,000 mg/12wk	Yes
Hildreth et al,[106] 2013	96/47	52	66.5	Elderly men	10.2	TT <12 nmol/L	TG 100mg/d	Yes
Maggio et al,[107] 2013	43/24	156	71.8	Elderly men	13.4	Mixed	T patch 6 mg/d	No

(continued)

Table 1. Continued

Study	No. of patients, T/placebo	Trial duration, wk	Age, y	Comorbidities	Baseline TT, nmol/L	T levels	Dose	Drug company funded
NCT00957528	9/8	20	69.6	Elderly men	–	Mixed	TE 100 mg/wk	Yes
Borst et al,[108] 2014	14/16	52	70.5	Elderly men	8.8	TT <10.4 nmol/L	TE 125 mg/wk	Yes
Gianatti et al,[109] 2014	45/43	40	62.0	T2DM	8.6	<12 nmol/L	TU 1,000 mg/12 wk	Yes
Janjgava et al,[110] 2014	43/42	24	49.7	T2DM	–	Mixed	TE 250/12 wk	No
Asih et al,[111] 2015	25/25	24	–	Elderly men	17.2	Mixed	T cream 5% 50 mg/d	Yes
Basaria et al,[112] 2015	155/151	156	67.6	Elderly men	10.5	Mixed	TG 75 mg/d	Yes
Basaria et al,[113] 2015	36/29	14	48.9	Treated with opioids	8.5	TT <12 nmol/L	TG 50 mg/d	Yes
Cherrier et al,[114] 2015	10/12	24	70.5	Elderly men	10.6	TT <10.4 nmol/L	TG 50–100 mg/d	No
Glintborg et al,[115] 2015	23/23	24	67.5	Elderly men	–	BT <7.3 nmol/L	TG 50–100 mg/d	Yes
Paduch et al,[116] 2015	40/36	16	50.7	Ejaculatory dysfunction	7.5	TT <10.4 nmol/L	T solution 60 mg/d	Yes
Brock et al,[117] 2016	358/357	12	55.3	Elderly men	6.9	TT <10.4 nmol/L	T solution 60–120 mg/d	Yes
Chillarón et al,[118] 2016	6/7	22	46.3	T1DM	10.9	TT <10 nmol/L	TU 1,000 mg/12 wk	Yes
Dhindsa et al,[119] 2016	22/22	23	54.7	T2DM	8.6	FT <225 pmol/L	TC 200 mg/2 wk	No
Snyder et al,[120] 2016*	395/395	52	72.2	Elderly men	8.0	TT <9.5 nmol/L	TG 50–100 mg/d	Yes
Budoff et al,[121] 2017	88/82	52	71.2	Elderly men	8.2	TT <9.5 nmol/L	TG 50 mg/d	Yes

BT = bioavailable testosterone; COPD = chronic obstructive pulmonary diseases; FT = free testosterone; LOH = late-onset hypo-gonadism; MetS = metabolic syndrome; OSA = obstructive sleep apnea; T = testosterone; TC = testosterone cypionate; TE = testosterone enanthate; TG = testosterone gel; TT = total testosterone; TU = testosterone undecanoate; T2DM = type 2 diabetes mellitus.
*Considered as frail men.
†Subjects with Alzheimer disease.

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 reported as serious adverse events. Secondary outcomes included all CV-related events defined as anything reported as such by the authors, that is, events reported as cardiac disorders, CV symptoms, CV events, vascular disorders, cardiac or CV, or when the event description fell within the *International Statistical Classification of Diseases, 10th Revision* chapter IX (I00–I99). Recommended starting T preparation dosages were derived from available guidelines[3] (Supplementary Table 4).

Quality Assessment

The quality of RCTs was assessed using the Cochrane suggestions.[122] In addition, we also employed the ROBINS-I approach to rate the quality of evidence proposed by Sterne et al[123] (Supplementary Tables 1 and 3).

In particular, in pharmaco-epidemiological studies, we evaluated the risk of bias due to the following[123]: confounding factors, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. In RCTs, the following risks of bias were evaluated[122,123]: arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. For each interventional study, we also assessed how the population was selected, the duration and route of TTh, the adequacy of study follow-up, and the funding source.

Statistical Analysis

Heterogeneity was assessed by using Cochran Q and I^2 statistics. Even when a low heterogeneity was detected, a random-effects model was applied, because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication or disclosure bias we used funnel plots and the Begg adjusted rank correlation test.[124,125] However, because these tests have low statistical power when the number of trials is small, undetected bias may still be present. In RCTs, Mantel-Haenszel (MH) odds ratio

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

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,[108] 1997	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
Shores et al,[109] 2012	398/633	Veterans	81	T treatment vs no treatment	T cypionate or T enanthate	HG vs HG	TT<8.7 nmol/L	62.1	32.0	38.0	-	-	8.7
Muraleedharan et al,[110] 2013	64/174	Men with T2DM	166	T treatment vs no treatment	Mixed	HG vs HG	TT<10.4 nmol/L	60.3	33.6	100	48.1	9.3	7.5
Vigen et al,[111] 2013	1,223/7,486	Veterans with CVD	110	T treatment vs no treatment	Mixed	HG vs HG	TT<10.4 nmol/L	63.4	-	55.3	92.5	-	6.9
Baillargeon et al,[112] 2014	6,355/19,065	Elderly from general population	182	TTh prescription vs no TTh prescription	Mixed	-	-	-	-	16.3	-	-	-
Finkle et al,[113] 2013	55,593/141,031	General population	140	TTh prescription vs PDE5i prescription	Mixed	-	-	54.3	-	19.0	26.6	-	-
Eisenberg et al,[114] 2015	284/225	Men with sexual dysfunction or infertility	520	TTh prescription vs no TTh prescription	Mixed	HG vs HG	-	54.4	-	-	-	-	11.6
Etminan et al,[115] 2015	30,066/120,264	Elderly from general population	145	TTh prescription vs no TTh prescription	Mixed	-	-	70.4	-	0.7	-	14.0	-
Ramasamy et al,[116] 2015	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,[117] 2015	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,[118] 2015	19,968/821,725	General population	72	TTh prescription vs no TTh prescription	Mixed	HG vs HG	TT<12.0 nmol/L	-	-	-	-	-	-
Maggi et al,[119] 2016	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
Wallis et al,[120] 2016	10,311/28,029	Elderly men from general population	260	TTh prescription vs no TTh prescription	Mixed	HG vs HG	-	-	-	34.2	-	-	-

(continued)

Table 2. Continued

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)
Cheetham et al,[121] 2017	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,[122] 2017	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

BMI= body mass index; BT= bioavailable testosterone; CVD= cardiovascular diseases; DM= diabetes mellitus; HG= hypogonadism; HT = hypertension; T= testosterone; TT= total testosterone; T2DM= type 2 DM; - = not reported.

(OR) with 95% CI was calculated for all the adverse events defined above, on an intention-to-treat basis, excluding trials with 0 events. A sensitivity analysis was performed with continuity corrections for trials with 0 events. In addition, sub-analysis considering the incidence of MACE according to baseline population characteristics was also performed. In particular, meta-regression analyses were performed to test the effect of different parameters, whenever indicated. All analyses were performed using software (Comprehensive Meta-analysis, Version 2; Biostat, Englewood, NJ). Multivariate analyses were performed on software (SPSS for Windows 22.0; IBM Corp, Armonk, NY).

RESULTS

During the first search, out of 896 retrieved articles, 15 pharmaco-epidemiological studies were included in the study (Supplementary Figure 1A). In addition, after the second separate search including only RCTs, out of 2,940 retrieved articles, 92 were included in the study (Supplementary Figure 1B). Furthermore, 1 completed but still unpublished study was also identified (NCT00957528) (Supplementary Figure 1B).

Randomized Controlled Trials

Among the 93 studies included in the analysis, 91, 88, 89, and 92 reported information on MACE, AMI, stroke, and CV mortality, respectively. In addition, 88 studies also reported information on acute coronary syndrome, 88 on arrhythmias, 87 on by-pass coronary surgery, and 88 on hospitalization for heart failure. The characteristics of the retrieved trials (including parameters on trial quality) and the number of events recorded are reported in Table 1 and Supplementary Tables 1 and 2. Retrieved trials included 4,653 and 3,826 patients in TTh and placebo groups, respectively, with a mean trial duration of 33.5 weeks.

Clinical Characteristics of the Studies

The mean age, body mass index (BMI), and baseline T of enrolled patients were 60.1 years, 29.1 kg/m^2, and 11.1 nmol/L, respectively. TTh was administered in different doses, formulations, and cohorts. In particular, 52 RCTs evaluated the effect of TTh in a mixed population of hypo-gonadal/eugonadal subjects, and 42 in hypo-gonadal patients (T below 12 nmol/L). In addition, 8 trials used oral T formulations, whereas 48 and 37 studies employed intra-muscular and trans-dermal T preparation. Finally, in 1 RCT, both intra-muscular and trans-dermal T preparations were used.

MACE-Related CV Risk

Of the 91 trials reporting information on MACE, 59 detected no events; therefore, the main analysis was performed on 32 trials. Q and I^2 were 27.8 and 0.0, respectively ($P = .63$). Funnel plot and Begg adjusted rank correlation test (Kendall

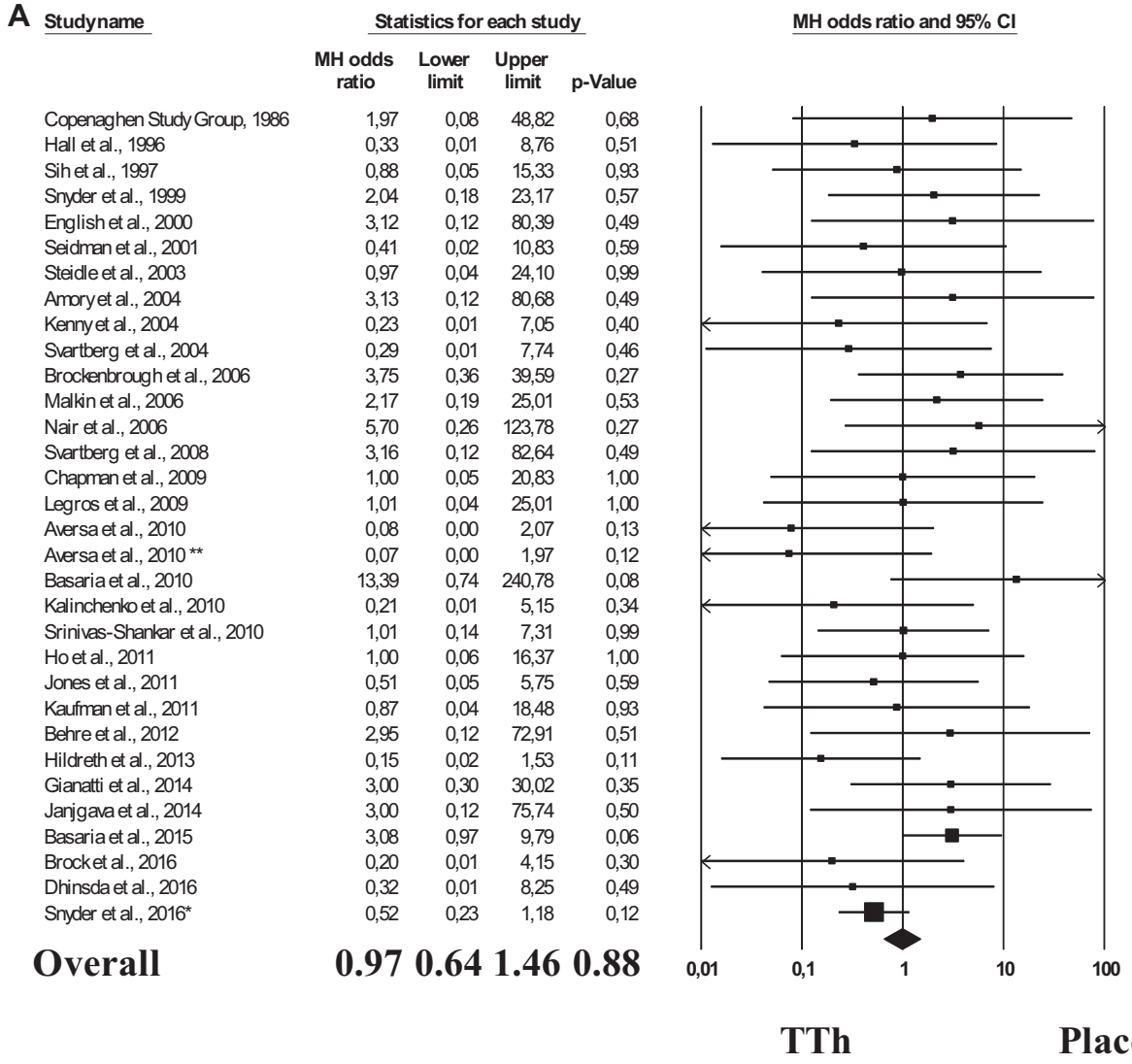
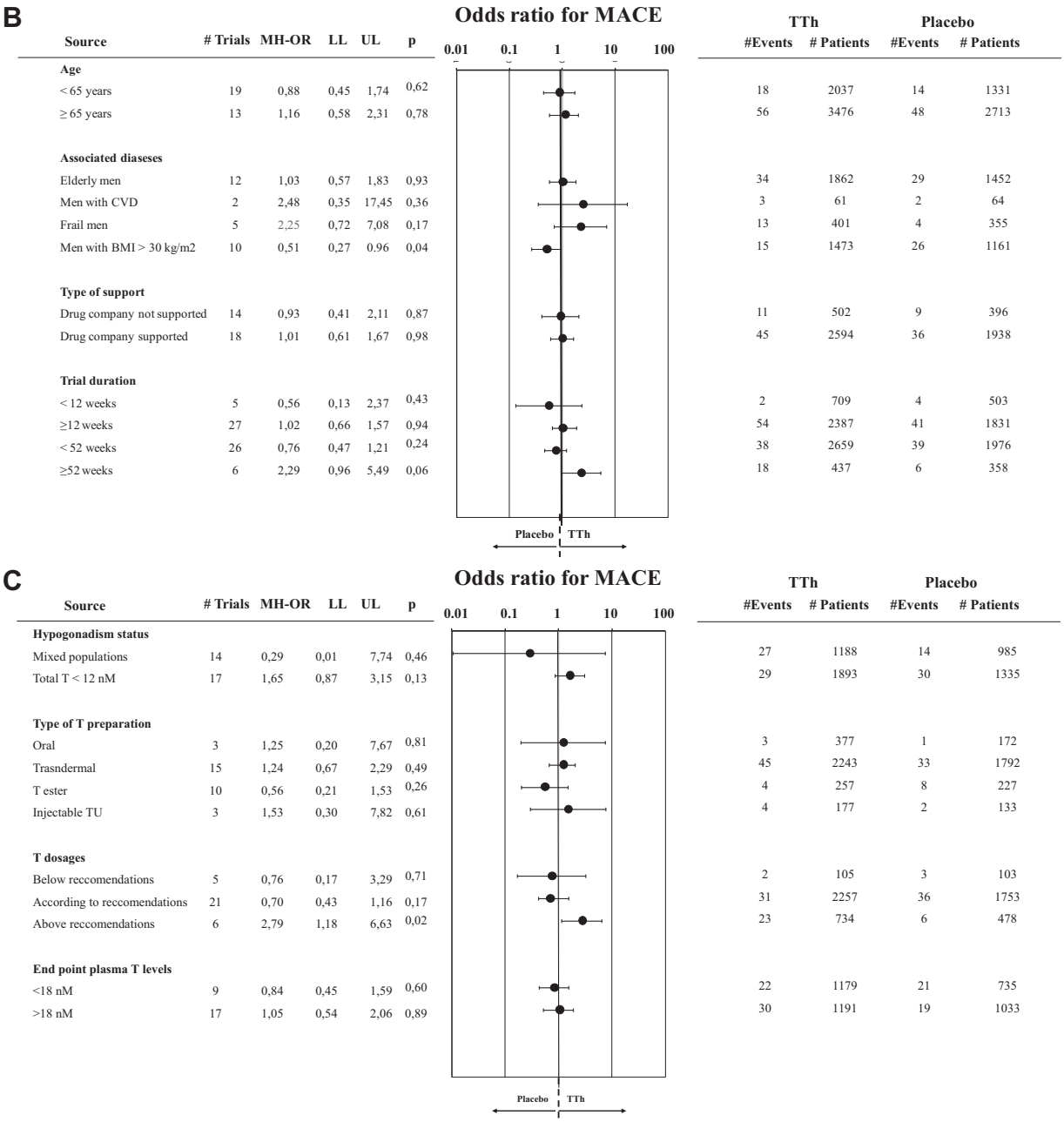


Figure 1. Panel A. Odds ratio for major adverse cardiovascular events (MACE) in subjects treated with testosterone substitution (TTh) or placebo. Panel B-C. Odds ratio for MACE according to baseline characteristics in subjects treated with TTh or placebo. Among MACE, the authors considered cardiovascular death, non-fatal myocardial infarction and stroke, and acute coronary syndromes and/or heart failure. CVD: Cardiovascular diseases; BMI: body mass index; T: T testosterone; TU; T undecanoate; LL: Lower limit; MH-OR: Mantel-Haenszel odds ratio; UL: Upper limit.

τ: −0.17; $P = .18$) suggested no major publication bias. The use of TTh was not associated with any significant difference in the incidence of MACE with respect to placebo (MH-OR 0.97 [95% CI 0.64−1.46]; $P = .88$) (Figure 1A). These data were confirmed, even when the heterogeneity was decreased (Q = 18.42), excluding from the general meta-analysis the outlier studies, defined as the ones with estimates beyond the overall measured effect[97,105] or with a very wide 95% CI[77] (MH-OR 0.90 [95% CI 0.53−1.54]; $P = .71$). Meta-regression analysis showed no difference in the incidence of MACE according to baseline age (years), BMI (kg/m^2), or T level (nmol/L) (slope [S] = 0.01 [−0.05; 0.06]; $P = .77$, S = −0.11 [−0.25; 0.04]; $P = .15$; and S = 0.05 [−0.10; 1.20]; $P = .52$). A sensitivity analysis was performed with continuity correction, confirming the results of the main analysis (MH-OR 0.94 [95% CI 0.73−1.22]; $P = .66$). Similar results were confirmed in a further sensitivity analysis when only high-quality (low overall risk of bias) RCTs were considered (MH-OR 1.27 [95% CI 0.62−2.61]; $P = .52$). In addition, similar results were confirmed when the individual MACE was analyzed separately (Supplementary Figure 2) or when arrhythmias or by-pass coronary surgery were considered (not shown). When separate analyses were performed according to the baseline population characteristics of the subjects enrolled, TTh showed a protective effect in obese patients (BMI ≥30 kg/m^2) and an increased risk of MACE in subjects treated with a T dosage above the current recommendations (Figure 1B and C). However, the former association was not confirmed when only



Source	# Trials	MH-OR	LL	UL	p	TTh #Events	TTh # Patients	Placebo #Events	Placebo # Patients
Age									
< 65 years	19	0,88	0,45	1,74	0,62	18	2037	14	1331
≥ 65 years	13	1,16	0,58	2,31	0,78	56	3476	48	2713
Associated diaseses									
Elderly men	12	1,03	0,57	1,83	0,93	34	1862	29	1452
Men with CVD	2	2,48	0,35	17,45	0,36	3	61	2	64
Frail men	5	2,25	0,72	7,08	0,17	13	401	4	355
Men with BMI > 30 kg/m2	10	0,51	0,27	0.96	0,04	15	1473	26	1161
Type of support									
Drug company not supported	14	0,93	0,41	2,11	0,87	11	502	9	396
Drug company supported	18	1,01	0,61	1,67	0,98	45	2594	36	1938
Trial duration									
< 12 weeks	5	0,56	0,13	2,37	0,43	2	709	4	503
≥12 weeks	27	1,02	0,66	1,57	0,94	54	2387	41	1831
< 52 weeks	26	0,76	0,47	1,21	0,24	38	2659	39	1976
≥52 weeks	6	2,29	0,96	5,49	0,06	18	437	6	358

Source	# Trials	MH-OR	LL	UL	p	TTh #Events	TTh # Patients	Placebo #Events	Placebo # Patients
Hypogonadism status									
Mixed populations	14	0,29	0,01	7,74	0,46	27	1188	14	985
Total T < 12 nM	17	1,65	0,87	3,15	0,13	29	1893	30	1335
Type of T preparation									
Oral	3	1,25	0,20	7,67	0,81	3	377	1	172
Trasndermal	15	1,24	0,67	2,29	0,49	45	2243	33	1792
T ester	10	0,56	0,21	1,53	0,26	4	257	8	227
Injectable TU	3	1,53	0,30	7,82	0,61	4	177	2	133
T dosages									
Below reccomendations	5	0,76	0,17	3,29	0,71	2	105	3	103
According to reccomendations	21	0,70	0,43	1,16	0,17	31	2257	36	1753
Above reccomendations	6	2,79	1,18	6,63	0,02	23	734	6	478
End point plasma T levels									
<18 nM	9	0,84	0,45	1,59	0,60	22	1179	21	735
>18 nM	17	1,05	0,54	2,06	0,89	30	1191	19	1033

Figure 1. (*continued*).

high-quality RCTs (low overall risk of bias) were considered (MH-OR 0.64 [95% CI 0.22−1.88]; $P = .42$). In addition, a higher risk of MACE was detected in leaner patients with BMI <30 kg/m^2 (MH-OR 2.05 [95% CI 1.12−3.77]; $P = .021$), however, this association was no longer statistically significant when studies using T dosages above the recommendation were excluded from the analyses (MH-OR 1.51 [95% CI 0.71−3.24]; $P = .28$). No other difference between TTh and placebo was detected for age, other patient clinical characteristics, reported pharmaceutical industry support, trial duration >12 weeks, type of T preparation used, and T levels at enrollment or at end point (Figure 1B−C).

Any CV-Related Event Risk

Similar results were obtained when any CV-related events were considered (Supplementary Figure 3A−C). In addition, in the latter case, a higher risk of CV events in the TTh arm was observed when frail patients were considered (Supplementary Figure 3B). However, the latter result was not confirmed when the Basaria et al[94] study was removed from the analysis (MH-OR 1.68 [95% CI 0.88−3.26]; $P = .12$).

Finally, similar to what was observed for MACE, the protective role of TTh in obesity was not confirmed when only high-quality RCTs (low overall risk of bias) were considered (MH-OR 0.76 [95% CI 0.47−1.23]; $P = .26$).

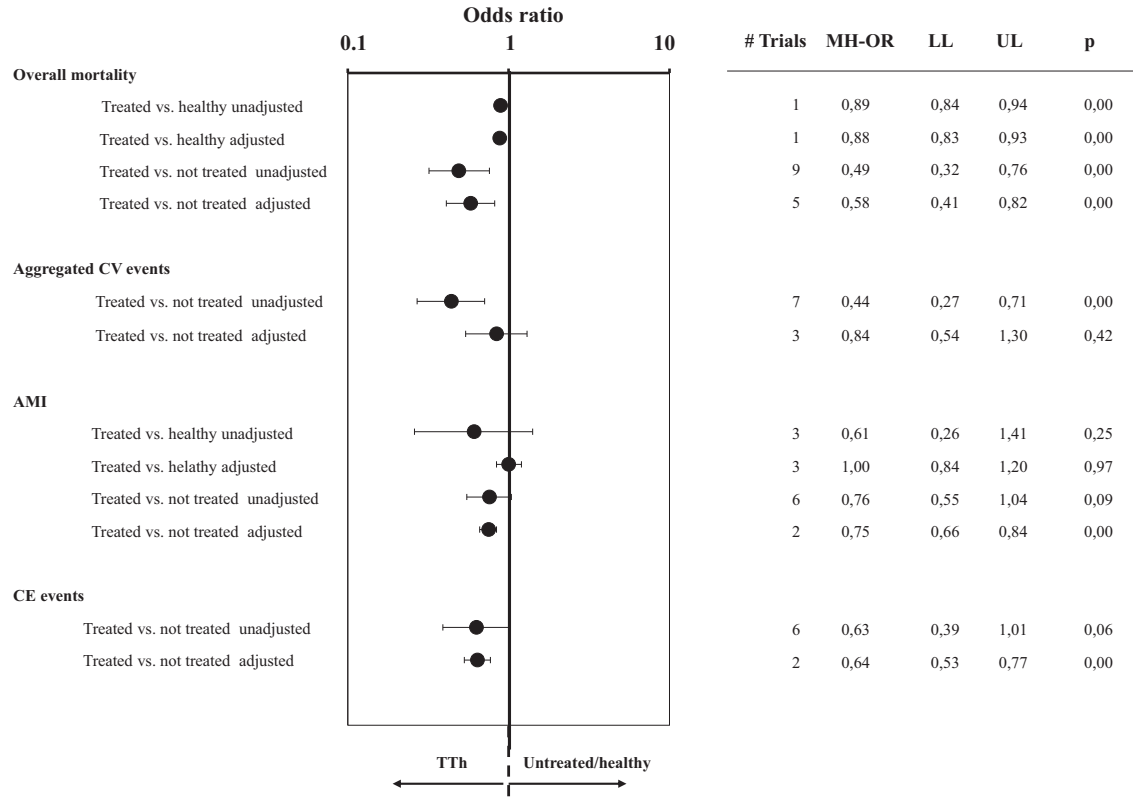


Figure 2. Unadjusted and adjusted odds ratio for overall mortality, aggregate cardiovascular (CV) events (overall mortality, acute myocardial infarction, AMI, and cerebrovascular events, CE), AMI and CE events in subjects treated with testosterone (TTh) in comparisons to those not treated or healthy. Data are derived from pharmaco-epidemilogical studies. Overall= treated hypogonadal subjects with TTh; no TTh = untreated hypogonadal subjects; healthy = healthy eugonadal populations.

Pharmaco-Epidemiological Studies

Among the included studies, information on overall mortality, AMI, and stroke was available in 10, 10, and 6 cases, respectively. In addition, 1 study reported only information related to a composite risk including overall mortality, AMI, and stroke. The characteristics of the retrieved trials (including parameters on trial quality) are reported in Table 2 and Supplementary Table 3. Retrieved trials included 1,382,395 subjects with mean follow-up of 223 weeks and the mean age of the enrolled cohorts was 64.2 years. Finally, 10 studies compared the effect of TTh in treated vs untreated hypo-gonadal subjects, whereas in 5 studies the effect of TTh was compared to a healthy population of untreated subjects. Q and I^2 performed on the fully adjusted model considering overall mortality were 381.4 and 98.7 ($P < .0001$). Funnel plot and Begg adjusted rank correlation test (Kendall τ: 0.00; $P = 1.00$) suggested no major publication bias. By meta-analyzing these studies we found that the absence of TTh in hypo-gonadal subjects increased their risk of mortality by up to 68% in unadjusted analyses and up to 59% when the fully adjusted models were considered (Figure 2, and Supplementary Figure 4A and B). Only 1 trial compared the effect of TTh in hypo-gonadal individuals vs healthy controls, confirming a positive effect of TTh. Additionally, even when the high heterogeneity was decreased (Q and I^2 = 4.22 and 28.88, respectively; $P = .24$), excluding from the general meta-analysis the outlier studies defined as the ones with estimates beyond the overall measured effect,[116,119] the meta-analysis again indicated a protective role of TTh (MH-OR 0.71 [95% CI 0.67−0.76]; $P < .0001$), thus confirming the analysis.

When aggregated events including overall mortality, AMI and cerebrovascular events were considered, TTh was associated with a reduced risk when unadjusted models were considered (Figure 2 and Supplementary Figure 4C), but the results were not confirmed when a fully adjusted model was applied (Figure 2 and Supplementary Figure 4D). Finally, when individual CV events were considered, the protective effect of TTh was confirmed when adjusted models and TTh vs non-TTh groups were analyzed (Figure 2 and Supplementary Figure 4E−H).

DISCUSSION

Meta-analysis of pharmaco-epidemiological studies indicates that TTh reduces overall mortality and CV morbidity. Conversely, in RCTs, TTh had no clear effect, either beneficial or detrimental, on the incidence of MACE or on their individual components. However, even in RCTs, a protective role of TTh on CV morbidity was envisaged when studies enrolling obese (BMI ≥30 kg/m^2) patients were scrutinized, whereas the opposite effect was observed in leaner (BMI <30 kg/m^2) patients. Finally, an increased risk of MACE and overall CV

diseases was observed in RCTs when T preparations were prescribed at dosages above those normally recommended, or when frail men were considered. Hence, TTh, when correctly applied, does not appear to be associated with an increase of CV risk and it may have a beneficial effect in some sub-populations.

2 Pharmaco-epidemiological studies, published between the end of 2013 and the beginning of 2014, created a great clamor in the scientific community, emphasizing a possible increased CV risk related to TTh.[110,112] Limitations and methodological biases of these studies have been previously reported.[126,127] Several other pharmaco-epidemiological studies have been published.[107–109,111,113–121] In a qualitative analysis of 10 available pharmaco-epidemiological reports, Alexander et al,[128] concluded that all studies showed a marked clinical and methodological heterogeneity and very low quality, due to the high risk of bias, imprecision, and inconsistency. By using meta-analytic methods and including a larger number of studies, we here confirmed the overall heterogeneity of these type of studies, but we were unable to confirm a risk of publication bias. Interestingly, when overall mortality and CV mortality and morbidity were considered, TTh showed an overall protective effect. In line with this finding, the 4-year follow-up from the BLAST study, including 869 men with type 2 diabetes mellitus, documented that TTh was independently associated with reduced mortality.[129] However, it is important to recognize that in these kinds of studies only limited information is available on CV mortality and morbidity. In addition, residual confounding factors may still be a source 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 hypo-gonadism-related problems, thus accounting for mortality being lowest in this group. In addition, data derived from pharmaco-epidemiology present other important limitations including the lack of information regarding the level of T before and during TTh, the number of the blood samples drawn during treatment, the type of T preparations used, the dropout, and the level of hematocrit. This issue is particularly relevant because a recent report showed that, in the United States, up to 30% of men who were prescribed T did not have their T levels tested prior to receiving a TTh or had it done only after the prescription.[7] Finally, the lack of information on the possible use of PDE5i might represent a further limitation.

RCTs are considered the gold standard for testing the effect of a specific treatment. Several RCTs evaluating the effects of TTh on different outcomes have been published so far and 8 systematic meta-analyses of them are available on the association between TTh and CV risk.[128,130–136] A discussion on the specific limitations and strengths of these meta-analyses is beyond the aim of this article and the topic was recently covered elsewhere by our[126,137] and other[138] groups. Only the meta-analysis of Xu et al[133] found an increased CV risk related to TTh. However, Xu et al[133] in their meta-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. In addition, when specific T preparations were considered, Borst et al[135] found, in their meta-analysis, an increased CV risk due to the use of oral T formulations. It is important to recognize that CV risk related to oral T preparations presents important bias. In fact, the analysis of this issue is included in the Copenhagen study, a phase III trial performed in men with alcoholic cirrhosis using an oral T formulation that never entered the market, and causing supra-physiological blood T levels during the study.[30] The present meta-analysis—which includes the largest number of RCTs considered so far—is in line with the latter observations: TTh is not associated with increased CV risk, when either aggregate or disaggregate CV events are considered. Although the meta-analyses are usually performed on a much smaller number of studies, we observed that TTh was associated with an increased risk of overall CV diseases and MACE only when T preparations were used at dosages higher that those recommend. We also found an increased risk of overall CV diseases when studies on frail men were selected and a similar association trend was observed for leaner (BMI <30 kg/m^2) individuals. In contrast, TTh was protective against CV risk in trials enrolling subjects with a mean baseline BMI >30 kg/m^2. It is possible that the benefits of TTh on CV risk in obese individuals suggested by the present analysis of RCTs are mediated, at least partially, by weight loss and improvement of other metabolic risk factors. In leaner individuals, such benefits could be less relevant. Accordingly, in a previous meta-analysis performed by our group, we reported a protective CV role of TTh in subjects with metabolic diseases.[132] In line with this finding, a recent guideline—issued on the behalf of the American Association of Clinical Endocrinologists and the American College of Endocrinology—recognizes that all men who have an increased waist circumference or who have obesity should be assessed for hypogonadism (HG). The same guideline recognizes that men with true HG and obesity, and not seeking fertility, should be considered for TTh, in addition to lifestyle intervention, because TTh in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters.[139] This position is in apparent contrast with the recommendation of the FDA, which, in its final release, emphasized that TTh should be considered only for men with "classic hypo-gonadism." When these strict FDA criteria are applied to a population of symptomatic hypo-gonadal patients—seeking medical care for ED with total testosterone <10.4 nmol/L—TTh could be offered only to a minority of patients (ie, 10% and 50% for secondary and primary HG, respectively) whereas all the others would be unsuitable for treatment.[140] However, a recent meta-analysis clearly demonstrated that in hypo-gonadal subjects TTh is able to improve ED, irrespective of the nature of HG.[141] The same study[138] also documented that almost three fourths of cases of the unknown causes of HG could be attributed to obesity or other metabolic diseases. In addition, data derived from an animal model of metabolic syndrome (obtained by

feeding rabbits with a high-fat diet for 12 weeks) showed that the condition is associated with a chronic inflammation within the hypo-thalamus, impairing gonadotropin-releasing hormone secretion and leading to the development of secondary HG.[142] Hence, these data suggest that obesity and its associated metabolic complication causes an "organic" central damage. In addition, quite interestingly, in apparent contrast to FDA recommendations, no trials, among those considered in the present analysis, deal with subjects with "classical" hypo-gonadism. Hence, in the latter condition the CV risk related to TTh is unknown. Longer studies can result in better outcomes. Accordingly, by meta-analyzing available data on the effect of TTh on several metabolic outcomes as derived from observational studies, we observed a positive effect of TTh in reducing body weight only after 2 years of treatment.[143] Whether or not TTh in obese subjects protects from CV risk needs to be confirmed by specific studies. In fact, only a limited number of trials were available and our results were not confirmed when only high-quality RCTs were analyzed. In addition, properly powered placebo-controlled RCTs with a primary CV end point, in men with LOH, are not yet available. Finally, the duration of all studies evaluated in the meta-analyses is relatively short, reaching a maximum of 3 years. This is probably the reason why benefits were only seen in high-risk groups where the absolute numbers of events were higher. Therefore, although there is no clear sign of risk in the short term, no information is available on possible long-term effects.

The increased CV risk related to the use of high-dose T is not surprising, and it is in line with what has been observed for the abuse of anabolic steroids.[144] In particular, recently Baggish et al[145] reported that androgen abuse is associated with impaired cardiac function. In addition, Rasmussen et al[146] showed that androgen abuse is associated with hypertension and aortic stiffness which can, at least partially, explain the observed CV risk related to TTh used above the recommended dosages.

The increased overall CV risk observed in frail men suggests that caution is necessary before prescribing TTh in older men with several associated morbidities. Accordingly, the results were no longer confirmed when the Basaria et al[79] study, performed in men with high prevalence of associated morbidities and using a supra-physiological T dosage (100 mg of T gel), was excluded from the analysis. In fact, in these cases, low T can be considered an epi-phenomenon caused by the underlying disease burden or even a resilient mechanism to save energy and to prevent reproduction, not needed when the body is ailing.[147–149] However, it should be recognized that several definitions of frailty are available and our selection of studies including frail men can be considered too arbitrary.

CONCLUSION

In conclusion, low T is a marker of CV risk. Available data from RCTs suggest that treatment with T is not effective in reducing such risk. Hence, it is important to clarify that TTh should not be considered cardio-prevention therapy. At the same time, those same RCTs show that TTh is safe with respect to CV morbidity and mortality. However, longer-term, specifically designed trials are needed to confirm the profile of action of T on CV risk. Additionally, it is possible that TTh has either beneficial or detrimental CV effects in specific sub-populations of subjects. In any case, over-dosage of T should be carefully avoided.

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REFERENCES

1. Corona G, Rastrelli G, Vignozzi L, et al. Emerging medication for the treatment of male hypogonadism. **Expert Opin Emerg Drugs 2012;17:239-259.**
2. Corona G, Rastrelli G, Maggi M. The pharmacotherapy of male hypogonadism besides androgens. **Expert Opin Pharmacother 2015;16:369-387.**
3. Khera M, Adaikan G, Buvat J, et al. Diagnosis and treatment of testosterone deficiency: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). **J Sex Med 2016;13:1787-1804.**
4. Corona G, Vignozzi L, Sforza A, et al. Obesity and late-onset hypogonadism. **Mol Cell Endocrinol 2015;418:120-133.**
5. Baillargeon J, Urban RJ, Ottenbacher KJ, et al. Trends in androgen prescribing in the United States, 2001 to 2011. **JAMA Intern Med 2013;173:1465-1466.**

6. Garnick MB. Testosterone replacement therapy faces FDA scrutiny. **JAMA 2015;313:563-564**.
7. Layton JB, Kim Y, Alexander GC, et al. Association between direct-to-consumer advertising and testosterone testing and initiation in the United States, 2009–2013. **JAMA 2017; 317:1159-1166**.
8. Corona G, Maseroli E, Rastrelli G, et al. Is late-onset hypogonadotropic hypogonadism a specific age-dependent disease, or merely an epiphenomenon caused by accumulating disease-burden? **Minerva Endocrinol 2016;41:196-210**.
9. Liverman CT, Blazer DG. Testosterone and aging. Available at www.nap.edu/read/10852/chapter/1. Accessed May 8, 2018.
10. US Food and Drug Administration. Drug safety communication: FDA cautions about using T products for low T due to aging requires labeling change to inform of possible increased risk of heart attack and stroke with use. Available at: http//www.fda.gov/Drugs/DrugSafety/ucm436259.htmforHumanMedicalProducts/ucm402054.htm. Accessed October 1, 2017.
11. Health Canada. Summary safety review-testosterone replacement product-cardiovascular risk. Available at: http//www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/testosterone-eng.php. Accessed October 1, 2017.
12. Yeap BB, Grossmann M, McLachlan RI, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1) assessment and indications for testosterone therapy. **Med J Aust 2016;205:173-178**.
13. Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. **J Clin Endocrinol Metab 2017; 102:1067-1075**.
14. Available at: http//www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Testosterone-containing_medicines/human_referral_prac_000037.jsp&mid=WC0b01ac05805c516f. Accessed October 1, 2017.
15. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. **J Clin Endocrinol Metab 1997; 82:3793-3796**.
16. Shores MM, Smith NL, Forsberg CW, et al. Testosterone treatment and mortality in men with low testosterone levels. **J Clin Endocrinol Metab 2012;97:2050-2058**.
17. Muraleedharan V, Marsh H, Kapoor D, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. **Eur J Endocrinol 2013;169:725-733**.
18. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. **JAMA 2013; 310:1829-1836**.
19. Baillargeon J, Urban RJ, Kuo YF, et al. Risk of myocardial infarction in older men receiving testosterone therapy. **Ann Pharmacother 2014;48:1138-1144**.
20. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. **PLoS One 2014;9:e85805**.
21. Eisenberg ML, Li S, Herder D, et al. Testosterone therapy and mortality risk. **Int J Impot Res 2015;27:46-48**.
22. Etminan M, Skeldon SC, Goldenberg SL, et al. Testosterone therapy and risk of myocardial infarction: a pharmacoepidemiologic study. **Pharmacotherapy 2015;35:72-78**.
23. Ramasamy R, Scovell J, Mederos M, et al. Association between testosterone supplementation therapy and thrombotic events in elderly men. **Urology 2015;86:283-285**.
24. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. **Eur Heart J 2015; 36:2706-2715**.
25. Tan RS, Cook KR, Reilly WG. Myocardial infarction and stroke risk in young healthy men treated with injectable testosterone. **Int J Endocrinol 2015;970:750**.
26. Maggi M, Wu FC, Jones TH, et al; RHYME Investigators. Testosterone treatment is not associated with increased risk of adverse cardiovascular events: results from the Registry of Hypogonadism in Men (RHYME). **Int J Clin Pract 2016; 70:843-852**.
27. Wallis CJ, Lo K, Lee Y, et al. Survival and cardiovascular events in men treated with testosterone replacement therapy: an intention-to-treat observational cohort study. **Lancet Diabetes Endocrinol 2016;4:498-506**.
28. Cheetham TC, An J, Jacobsen SJ, et al. Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. **JAMA Intern Med 2017;177:491-499**.
29. Traish AM, Haider A, Haider KS, et al. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism. **J Cardiovasc Pharmacol Ther 2017;22:414-433**.
30. The Copenhagen Study Group for Liver Diseases. Testosterone treatment of men with alcoholic cirrhosis: a double-blind study. **Hepatology 1986;6:807-813**.
31. Drinka PJ, Jochen AL, Cuisinier M, et al. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. **J Am Geriatr Soc 1995;43:899-901**.
32. Aydin S, Odabaş O, Ercan M, et al. Efficacy of testosterone, trazodone and hypnotic suggestion in the treatment of non-organic male sexual dysfunction. **Br J Urol 1996; 77:256-260**.
33. Hall GM, Larbre JP, Spector TD, et al. A randomized trial of testosterone therapy in males with rheumatoid arthritis. **Br J Rheumatol 1996;35:568-573**.
34. Coodley GO, Coodley MK. A trial of testosterone therapy for HIV-associated weight loss. **AIDS 1997;11:1347-1352**.
35. Sih R, Morley JE, Kaiser FE, et al. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. **J Clin Endocrinol Metab 1997;82:1661-1667**.
36. Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. **J Clin Endocrinol Metab 1998; 83:3155-3162**.

37. Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. **Ann Intern Med 1998;129:18-26.**
38. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. **Int J Androl 1999;22:261-265.**
39. Giorgi A, Weatherby RP, Murphy PW. Muscular strength, body composition and health responses to the use of testosterone enanthate: a double-blind study. **J Sci Med Sport 1999; 2:341-355.**
40. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. **J Clin Endocrinol Metab 1999; 84:2647-2653.**
41. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. **JAMA 2000; 283:763-770.**
42. English KM, Mandour O, Steeds RP, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double blind, placebo-controlled study. **Circulation 2000;102:1906-1911.**
43. Grinspoon S, Corcoran C, Parlman K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. A randomized, controlled trial. **Ann Intern Med 2000;133:348-355.**
44. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. **Arch Gen Psychiatry 2000; 57:141-147; discussion 155–156.**
45. Münzer T, Harman SM, Hees P, et al. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. **J Clin Endocrinol Metab 2001;86:3604-3610.**
46. Howell SJ, Radford JA, Adams JE, et al. Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. **Clin Endocrinol (Oxf) 2001;55:315-324.**
47. Seidman SN, Spatz E, Rizzo C, et al. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. **J Clin Psychiatry 2001;62:406-412.**
48. Simon D, Charles MA, Lahlou N, et al. Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. **Diabetes Care 2001;24:2149-2151.**
49. Amory JK, Chansky HA, Chansky KL, et al. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. **J Am Geriatr Soc 2002;50:1698-1701.**
50. Blackman MR, Sorkin JD, Münzer T, et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. **JAMA 2002;288:2282-2292.**
51. Ferrando AA, Sheffield-Moore M, Yeckel CW, et al. Testosterone administration to older men improves muscle function molecular and physiological mechanisms. **Am J Physiol Endocrinol Metab 2002;282:E601-E607.**
52. Liu PY, Yee B, Wishart SM, et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. **J Clin Endocrinol Metab 2003;88:3605-3613.**
53. Park NC, Yan BQ, Chung JM, et al. Oral testosterone undecanoate (Andriol) supplement therapy improves the quality of life for men with testosterone deficiency. **Aging Male 2003; 6:86-93.**
54. Pope HG Jr, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. **Am J Psychiatry 2003; 160:105-111.**
55. Steidle C, Schwartz S, Jacoby K, et al; North American AA2500 T Gel Study Group. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. **J Clin Endocrinol Metab 2003;88:2673-2681.**
56. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. **Aging Male 2003;6:13-17.**
57. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. **J Clin Endocrinol Metab 2004;89:503-510.**
58. Cavallini G, Caracciolo S, Vitali G, et al. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. **Urology 2004;63:641-646.**
59. Kenny AM, Fabregas G, Song C, et al. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. **J Gerontol A Biol Sci Med Sci 2004; 59:75-78.**
60. Malkin CJ, Pugh PJ, Morris PD, et al. Testosterone replacement in hypogonadal men with angina improves ischemic threshold and quality of life. **Heart 2004;90:871-876.**
61. Malkin CJ, Pugh PJ, Jones RD, et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. **J Clin Endocrinol Metab 2004;89:3313-3318.**
62. Rabkin JG, Wagner GJ, McElhiney MC, et al. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. **J Clin Psychopharmacol 2004; 24:379-385.**
63. Svartberg J, Aasebø U, Hjalmarsen A, et al. Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. **Respir Med 2004;98:906-913.**
64. Seidman SN, Miyazaki M, Roose SP. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: randomized placebo-controlled clinical trial. **J Clin Psychopharmacol 2005;25:584-588.**

65. Sullivan DH, Roberson PK, Johnson LE, et al. Effects of muscle strength training and testosterone in frail elderly males. **Med Sci Sports Exerc 2005;37:1664-1672.**
66. Brockenbrough AT, Dittrich MO, Page ST, et al. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. **Am J Kidney Dis 2006; 47:251-262.**
67. Giannoulis MG, Sonksen PH, Umpleby M, et al. The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. **J Clin Endocrinol Metab 2006; 91:477-484.**
68. Gold J, Batterham MJ, Rekers H, et al; E-1696 Study Investigators. Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. **HIV Med 2006;7:146-155.**
69. Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycemic control, visceral adiposity and hypercholesterolemia in hypogonadal men with type 2 diabetes. **Eur J Endocrinol 2006; 154:899-906.**
70. Katznelson L, Robinson MW, Coyle CL, et al. Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. **Eur J Endocrinol 2006;155:867-875.**
71. Lu PH, Masterman DA, Mulnard R, et al. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. **Arch Neurol 2006;63:177-185.**
72. Malkin CJ, Pugh PJ, West JN, et al. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo-controlled trial. **Eur Heart J 2006; 27:57-64.**
73. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. **JAMA 2006;296:2351-2361.**
74. Merza Z, Blumsohn A, Mah PM, et al. Double-blind placebo-controlled study of testosterone patch therapy on bone turnover in men with borderline hypogonadism. **Int J Androl 2006;29:381-391.**
75. Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. **N Engl J Med 2006;355:1647-1659.**
76. Okun MS, Fernandez HH, Rodriguez RL, et al. Testosterone therapy in men with Parkinson disease: results of the TEST-PD study. **Arch Neurol 2006;63:729-735.**
77. Bhasin S, Parker RA, Sattler F, et al; AIDS Clinical Trials Group Protocol A5079 Study Team. Effects of testosterone supplementation on whole body and regional fat mass and distribution in human immunodeficiency virus-infected men with abdominal obesity. **J Clin Endocrinol Metab 2007; 92:1049-1057.**
78. Chiang HS, Hwang TI, Hsui YS, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. **Int J Impot Res 2007;19:411-417.**
79. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. **Scand J Clin Lab Invest 2008;68:641-648.**
80. Allan CA, Strauss BJ, Burger HG, et al. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in non obese aging men. **J Clin Endocrinol Metab 2008;93:139-146.**
81. Basurto L, Zarate A, Gomez R, et al. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. **Aging Male 2008;11:140-145.**
82. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. **JAMA 2008;299:39-52.**
83. Knapp PE, Storer TW, Herbst KL, et al. Effects of a supraphysiological dose of testosterone on physical function, muscle performance, mood, and fatigue in men with HIV-associated weight loss. **Am J Physiol Endocrinol Metab 2008;294:E1135-E1143.**
84. Svartberg J, Agledahl I, Figenschau Y, et al. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. **Int J Impot Res 2008;20:378-387.**
85. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure: a double-blind, placebo-controlled, randomized study. **J Am Coll Cardiol 2009;54:919-927.**
86. Chiang HS, Cho SL, Lin YC, et al. Testosterone gel monotherapy improves sexual function of hypogonadal men mainly through restoring erection evaluation by IIEF score. **Urology 2009;73:762-766.**
87. Chapman IM, Visvanathan R, Hammond AJ, et al. Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. **Am J Clin Nutr 2009;89:880-889.**
88. Legros JJ, Meuleman EJ, Elbers JM, et al; Study 43203 Investigators. Oral testosterone replacement in symptomatic late-onset hypogonadism effects on rating scales and general safety in a randomized, placebo-controlled study. **Eur J Endocrinol 2009;160:821-831.**
89. Mathur A, Malkin C, Saeed B, et al. Long-term benefits of testosterone replacement therapy on angina threshold and atheroma in men. **Eur J Endocrinol 2009;161:443-449.**
90. Seidman SN, Orr G, Raviv G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized, placebo-controlled clinical trial. **J Clin Psychopharmacol 2009;29:216-221.**
91. Shores MM, Kivlahan DR, Sadak TI, et al. A randomized, double-blind, placebo-controlled study of testosterone treatment in hypogonadal older men with sub threshold depression (dysthymia or minor depression). **J Clin Psychiatry 2009;70:1009-1016.**

92. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. **J Sex Med 2010;7:3495-3503.**
93. Aversa A, Bruzziches R, Francomano D, et al. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. **J Endocrinol Invest 2010;33:776-783.**
94. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. **N Engl J Med 2010;363:109-122.**
95. Cornoldi A, Caminiti G, Marazzi G, et al. Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease. **Int J Cardiol 2010;142:50-55.**
96. Gopal RA, Bothra N, Acharya SV, et al. Treatment of hypogonadism with testosterone in patients with type 2 diabetes mellitus. **Endocr Pract 2010;16:570-576.**
97. Kalinchenko SY, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. **Clin Endocrinol (Oxf) 2010;73:602-612.**
98. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. **J Clin Endocrinol Metab 2010;95:639-650.**
99. Amiaz R, Pope HG Jr, Mahne T, et al. Testosterone gel replacement improves sexual function in depressed men taking serotonergic antidepressants: a randomized, placebo-controlled clinical trial. **J Sex Marital Ther 2011;37:243-254.**
100. Ho CC, Tong SF, Low WY, et al. A randomized, double-blind, placebo-controlled trial on the effect of long-acting testosterone treatment as assessed by the Aging Male Symptoms scale. **BJU Int 2012;110:260-265.**
101. Jones TH, Arver S, Behre HM, et al; TIMES2 Investigators. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). **Diabetes Care 2011;34:828-837.**
102. Kaufman JM, Miller MG, Garwin JL, et al. Efficacy and safety study of 1.62% testosterone gel for the treatment of hypogonadal men. **J Sex Med 2011;8:2079-2089.**
103. Hoyos CM, Yee BJ, Phillips CL, et al. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnea: a randomized placebo-controlled trial. **Eur J Endocrinol 2012;167:531-541.**
104. Behre HM, Tammela TL, Arver S, et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. **Aging Male 2012;15:198-207.**
105. Hackett G, Cole N, Bhartia M, et al. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs placebo in a population of men with type 2 diabetes. **J Sex Med 2013;10:1612-1627.**
106. Hildreth KL, Barry DW, Moreau KL, et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. **J Clin Endocrinol Metab 2013;98:1891-1900.**
107. Maggio M, Snyder PJ, Ceda GP, et al. Is the hematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. **Andrology 2013;1:24-28.**
108. Borst SE, Yarrow JF, Conover CF, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. **Am J Physiol Endocrinol Metab 2014;306:E433-E442.**
109. Gianatti EJ, Dupuis P, Hoermann R, et al. Effect of testosterone treatment on glucose metabolism in men with type 2 diabetes: a randomized controlled trial. **Diabetes Care 2014;37:2098-2107.**
110. Janjgava S, Zerekidze T, Uchava L, et al. Influence of testosterone replacement therapy on metabolic disorders in male patients with type 2 diabetes mellitus and androgen deficiency. **Eur J Med Res 2014;19:56.**
111. Asih PR, Wahjoepramono EJ, Aniwiyanti V, et al. Testosterone replacement therapy in older male subjective memory complainers: double-blind randomized crossover placebo-controlled clinical trial of physiological assessment and safety. **CNS Neurol Disord Drug Targets 2015;14:576-586.**
112. Basaria S, Harman SM, Travison TG, et al. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. **JAMA 2015;314:570-581.**
113. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. **Pain 2015;156:280-288.**
114. Cherrier MM, Anderson K, Shofer J, et al. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. **Am J Alzheimers Dis Other Demen 2015;30:421-430.**
115. Glintborg D, Christensen LL, Kvorning T, et al. Differential effects of strength training and testosterone treatment on soluble CD36 in aging men: possible relation to changes in body composition. **Scand J Clin Lab Invest 2015;75:659-666.**
116. Paduch DA, Polzer PK, Ni X, et al. Testosterone replacement in androgen-deficient men with ejaculatory dysfunction a randomized controlled trial. **J Clin Endocrinol Metab 2015;100:2956-2962.**
117. Brock G, Heiselman D, Maggi M, et al. Effect of testosterone solution 2% on testosterone concentration, sex drive and energy in hypogonadal men: results of a placebo controlled study. **J Urol 2016;195:699-705.**

118. Chillarón JJ, Fernández-Miró M, Albareda M, et al. Testosterone undecanoate improves lipid profile in patients with type 1 diabetes and hypogonadotrophic hypogonadism. **Endocr J 2016;63:849-855.**
119. Dhindsa S, Ghanim H, Batra M, et al. Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. **Diabetes Care 2016;39:82-91.**
120. Snyder PJ, Bhasin S, Cunningham GR, et al; Testosterone Trials Investigators. Effects of testosterone treatment in older men. **N Engl J Med 2016;374:611-624.**
121. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. **JAMA 2017;317:708-716.**
122. Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, Welch V, eds. Cochrane methods. Cochrane Database Syst Rev, 10 (Suppl); 2016.
123. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. **BMJ 2016;12:355i4919.**
124. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. **Biometrics 1994;50:1088-1101.**
125. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. **BMJ 1997;315:629-634.**
126. Corona G, Dicuio M, Rastrelli G, et al. Testosterone treatment and cardiovascular and venous thromboembolism risk: what is "new"? **J Investig Med 2017;65:964-973.**
127. Morgentaler A, Zitzmann M, Traish AM, et al. Fundamental concepts regarding testosterone deficiency and treatment: international expert consensus resolutions. **Mayo Clin Proc 2016;91:881-896.**
128. Alexander GC, Iyer G, Lucas E, et al. Cardiovascular risks of exogenous testosterone use among men: a systematic review and meta-analysis. **Am J Med 2017;130:293-305.**
129. Hackett G, Heald AH, Sinclair A, et al. Serum testosterone, testosterone replacement therapy and all-cause mortality in men with type 2 diabetes: retrospective consideration of the impact of PDE5 inhibitors and statins. **Int J Clin Pract 2016;70:244-253.**
130. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo controlled trials. **J Gerontol A Biol Sci Med Sci 2005;60:1451-1457.**
131. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. **Mayo Clin Proc 2007;82:29-39.**
132. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. **J Clin Endocrinol Metab 2010;95:2560-2575.**
133. Xu L, Freeman G, Cowling BJ, et al. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. **BMC Med 2013;11:108.**
134. Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone boosting medications: a systematic review and meta-analysis. **Expert Opin Drug Saf 2014;13:1327-1351.**
135. Borst SE, Shuster JJ, Zou B, et al. Cardiovascular risks and elevation of serum DHT vary by route of testosterone administration: a systematic review and meta-analysis. **BMC Med 2014;12:211.**
136. Albert SG, Morley JE. Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. **Clin Endocrinol (Oxf) 2016;85:436-443.**
137. Corona G, Sforza A, Maggi M. Testosterone replacement therapy long-term safety and efficacy. **World J Mens Health 2017;35:65-76.**
138. Onasanya O, Iyer G, Lucas E, et al. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. **Lancet Diabetes Endocrinol 2016;4:943-956.**
139. Garvey WT, Mechanick JI, Brett EM, et al. Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. **Endocr Pract 2016;22(Suppl):1-203.**
140. Corona G, Maggi M. Perspective: regulatory agencies' changes to testosterone product labeling. **J Sex Med 2015;12:1690-1693.**
141. Corona G, Rastrelli G, Morgentaler A, et al. Meta-analysis of results of testosterone therapy on sexual function based on International Index of Erectile Function Scores. **Eur Urol 2017;72:1000-1011.**
142. Morelli A, Sarchielli E, Comeglio P, et al. Metabolic syndrome induces inflammation and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits. **Mol Cell Endocrinol 2014;382:107-119.**
143. Corona G, Giagulli VA, Maseroli E, et al. Testosterone supplementation and body composition: results from a meta-analysis of observational studies. **J Endocrinol Invest 2016;39:967-981.**
144. Nieschlag E, Vorona E. Mechanisms in endocrinology. Medical consequences of doping with anabolic androgenic steroids effects on reproductive functions. **Eur J Endocrinol 2015;173:R47-58.**
145. Baggish AL, Weiner RB, Kanayama G, et al. Cardiovascular toxicity of illicit anabolic-androgenic steroid use. **Circulation 2017;135:1991-2002.**

146. Rasmussen JJ, Schou M, Madsen PL, et al. Increased blood pressure and aortic stiffness among abusers of anabolic androgenic steroids: potential effect of suppressed natriuretic peptides in plasma? **J Hypertens 2018;36:277-285.**

147. Corona G, Rastrelli G, Monami M, et al. Body mass index regulates hypogonadism-associated CV risk: results from a cohort of subjects with erectile dysfunction. **J Sex Med 2011; 8:2098-2105.**

148. Corona G, Rastrelli G, Maseroli E, et al. Low testosterone syndrome protects subjects with high cardiovascular risk burden from major adverse cardiovascular events. **Andrology 2014;2:741-747.**

149. Rochira V, Diazzi C, Santi D, et al. Low testosterone is associated with poor health status in men with human immunodeficiency virus infection: a retrospective study. **Andrology 2015;3:298-308.**

SUPPLEMENTARY DATA

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