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REVIEW

Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study

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Abstract

Objective: To verify whether hypogonadism represents a risk factor for cardiovascular (CV) morbidity and mortality and to verify whether testosterone replacement therapy (TRT) improves CV parameters in subjects with known CV diseases (CVDs).

Design: Meta-analysis.

Methods: An extensive Medline search was performed using the following words 'testosterone, CVD, and males'. The search was restricted to data from January 1, 1969, up to January 1, 2011.

Results: Of the 1178 retrieved articles, 70 were included in the study. Among cross-sectional studies, patients with CVD have significantly lower testosterone and higher 17-β estradiol (E_2) levels. Conversely, no difference was observed for DHEAS. The association between low testosterone and high E_2 levels with CVD was confirmed in a logistic regression model, after adjusting for age and body mass index (hazard ratio (HR)=0.763 (0.744–0.783) and HR=1.015 (1.014–1.017), respectively, for each increment of total testosterone and E_2 levels; both $P<0.0001$). Longitudinal studies showed that baseline testosterone level was significantly lower among patients with incident overall- and CV-related mortality, in comparison with controls. Conversely, we did not observe any difference in the baseline testosterone and E_2 levels between case and controls for incident CVD. Finally, TRT was positively associated with a significant increase in treadmill test duration and time to 1 mm ST segment depression.

Conclusions: Lower testosterone and higher E_2 levels correlate with increased risk of CVD and CV mortality. TRT in hypogonadism moderates metabolic components associated with CV risk. Whether low testosterone is just an association with CV risk, or an actual cause–effect relationship, awaits further studies.

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Introduction

Cardiovascular disease (CVD) is the world's leading killer disease, and over 80% of deaths due to CVD occur in low- and middle-income countries (1). However, in all populations studied, CVD is more frequent and has a greater mortality risk in men than in women (2). In Europe, one in four men dies before the age of 75 years due to CVD, while the figure for women is only one in six. This gender-related difference is even more evident for deaths before the age of 65 years (12 vs 5% in men and women, respectively, see also www.heartstats.org/temp/ESspweb08spchapter.1.pdf). For coronary heart disease (CHD), women trail men in increased incidence by 10 years, although the gap closes with advancing age (3). The reasons for such gender difference have not been completely understood (4–10). However, sex hormones have been considered as a possible factor. Premenopausal women have been thought to have decreased risk of CVD because of their estrogen dominance, and it was presumed that men had an increased risk due to their androgens, although this has never been proven scientifically. The universal excess risk of CHD in men observed above, coupled with the apparent loss of the female advantage in women who had an early menopause and to the higher CV risk profile in women with hyperandrogenism, led to the hypothesis that the effects of endogenous estrogens and androgens are beneficial or harmful respectively. Data on the role of estrogens and DHEAS in the pathogenesis of male CVD are limited. Studies on the role of testosterone as a predictor of CV risk in men are

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controversial. Recent evidence suggests that reduction, rather than increase, of testosterone level could be associated with higher CV risk (1, 11, 12). However, a meta-analysis of epidemiological studies displayed no association between endogenous testosterone and risk for CVD in middle-aged men (13). This meta-analysis (which did not provide data on 17β estradiol (E_2) and DHEAS) was limited to longitudinal (cohort) studies in middle-aged men, excluding older individuals. Clinical trials were, in fact, not considered (13). Several meta-analyses on testosterone replacement therapy (TRT) safety derived from randomized clinical trial (RCT) studies are presently available (see for review references (1, 12)); however, they are not focused on TRT efficacy on CV risk in patients with documented ischemic cardiac diseases.

The aim of our meta-analysis was

i) to verify whether hypogonadism represents a risk factor for CV morbidity and mortality and
ii) to verify whether TRT improves CV parameters in subjects with known CVD.

We therefore performed a systematic review and meta-analysis of available cross-sectional (14–68) and prospective studies on sex steroids and CVD (34, 38, 58, 69–75). In addition, we also performed a specific meta-analysis on the potentially beneficial CV effects of TRT, as derived from the available RCTs (76–81).

Methods

A meta-analysis was performed including all prospective and cross-sectional studies, comparing testosterone levels in subjects with or without CVD. In addition, RCTs – either with a cross-over or a parallel series design – enrolling patients with CVD and comparing TRT with placebo were also included, provided that they reported data on treadmill test in TRT and placebo groups. Meta-analysis on the effect of TRT on CV outcomes was limited to those trials designed to test the effect of TRT on treadmill test parameters in men with chronic stable angina. In addition, to make the results more comparable, studies not reporting hormonal parameters as continuous variables, expressed as mean ± S.D. (or S.E.M.), were excluded.

An extensive Medline search was performed using the following words: 'testosterone, CVD, and males'. The search, which accrued data from January 1, 1969 up to January 1, 2011 was restricted to English-language articles and studies of human participants. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (G Corona and G Rastrelli) and conflicts were resolved by the third investigator (M Monami). The quality of RCTs was assessed using the parameters proposed by Jadad *et al.* (82).

Completed but still unpublished trials were identified through a search of www.clinicaltrials.gov website and the results, when not already available on the website, were obtained through a formal request to the authors.

Statistical analysis

Heterogeneity for cross-sectional studies was assessed using the I^2 test for total testosterone (TT). Considering that heterogeneity could not be excluded ($I^2 = 93.50\%$), standardized mean differences in TT, sex hormone-binding globulin (SHBG), E_2, and DHEAS between subjects with or without CVD were calculated using a random effect model. Meta-regression analysis was performed to test the effect of age and body mass index (BMI), diabetes, and hypertension on TT and E_2 levels. In addition, linear regression analysis model, weighing each study for the number of subjects enrolled, was performed to verify the independent effect of age, BMI, and CVD on TT and E_2 levels.

In longitudinal studies, after verifying heterogeneity ($I^2 = 98.7\%$), standardized mean differences for TT between incident cases of CVD and controls were calculated using a random effect model.

In RCTs, the lack of homogeneity ($I^2 = 56.3\%$) suggested the use of a random effect model to calculate the standardized difference in mean values of time to 1 mm ST segment depression and other treadmill test parameters.

All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA) and SPSS 17.0 (Chicago, IL, USA).

Results

Of the 1178 retrieved articles, 70 were included in the study. In particular, 54, 10, and six were cross-sectional, longitudinal, and interventional studies

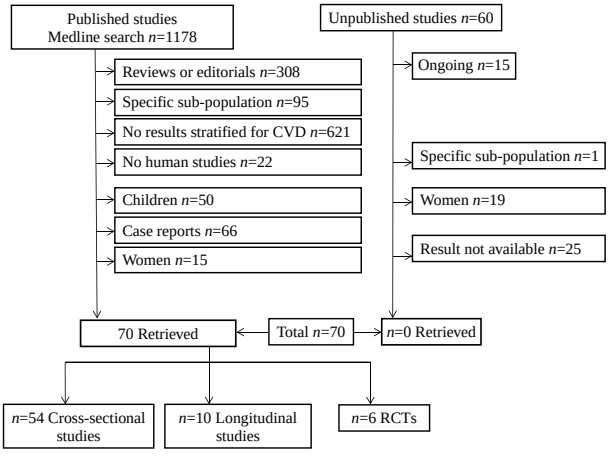

Figure 1 Trial flow diagram. CVD, cardiovascular diseases; RCTs, randomized clinical trials.

Table 1 Moderators and outcome variables in individual cross-sectional studies included in the meta-analysis. All data are reported as mean±S.D.

References	Type of CVD	AG (Y/N)	CVD (Y/N)	Age (years)	BMI (kg/m^2)	DM (%)	HT (%)	CVD/no CVD			
								TT (nmol/l)	**E_2** (nmol/l)	**DHEAS** (μmol/l)	**SHBG** (nmol/l)
(14)	CHD	No	23/23	NA	NA	NA	NA	15.1±9.7/23.9±8.1	NA	NA	NA
(15)	CHD	N	48/48	51.4	25.2	0.0	0.0	17.5±6.2/17.5±8.3	NA	NA	NA
(16)	CHD	N	35/35	40.9	NA	NA	NA	23.0±5.5/20.7±5.8	249.0±56.9/140.0±25.0	NA	NA
(17)	Other CVD	–	25/27	56.5	NA	0.0	NA	11.1±5.0/11.0±3.1	96.0±47.0/96.0±41.6	NA	NA
(18)	Other CVD	–	43/15	46.1	NA	NA	NA	11.7±5.7/17.2±4.0	NA	NA	NA
(19)[a]	CHD	N	29/28	43.9	NA	NA	NA	NA	303.0±274.2/112.5±34.2	NA	NA
(19)	CHD	N	17/28	43.1	NA	NA	NA	NA	240.1±110.3/112.5±34.2	NA	NA
(20)	CHD	N	11/12	48.8	NA	NA	NA	17.7±9.3/16.4±1.9	191.2±33.1/139.7±33.1	NA	NA
(20)	CHD	Y	21/12	48.2	NA	NA	NA	19.3±5.8/16.4±1.9	169.1±40.4/139.7±33.1	NA	NA
(21)[a]	CHD	N	30/34	51.9	NA	NA	18.8	24.8±5.7/21.8±5.4	250.0±50.0/120.0±40.0	NA	NA
(21)	CHD	N	50/34	51.2	NA	NA	15.5	23.6±4.7/21.8±5.4	240.0±60.0/120.0±40.0	NA	NA
(22)	CHD	N	13/35	45.1	NA	0.0	0.0	16.1±6.5/14.6±3.6	106.6±29.4/106.6±22.1	NA	NA
(22)	CHD	Y	13/35	45.5	NA	0.0	0.0	16.6±6.4/18.5±6.2	95.6±36.8/117.7±51.5	NA	NA
(23)	CHD	Y	11/9	44.6	NA	0.0	0.0	17.0±3.2/22.7±5.1	128.0±39.0/156.0±43.0	NA	NA
(24)	CHD	N	61/61	70.0	27.1	NA	NA	14.3±5.0/13.5±4.3	120.4±27.4/134.3±36.7	NA	NA
(25)	CHD	Y	35/32	NA	NA	0.0	NA	17.0±7.6/24.2±7.6	NA	NA	NA
(26)[a]	CHD	N	13/15	43.1	NA	NA	NA	12.8±3.7/19.2±2.3	177.8±53.3/116.7±24.2	NA	NA
(26)	CHD	N	13/15	39.2	NA	NA	NA	12.1±5.1/19.2±2.3	280.1±184.8/116.7±24.2	NA	NA
(27)[b]	CHD	N	39/32	56.5	25.3	NA	22.6	19.0±6.0/16.0±4.0	147.0±44.0/147.0±35.0	NA	NA
(27)	CHD	N	21/32	56.2	25.8	NA	37.8	18.0±5.0/16.0±4.0	136.0±44.0/147.0±35.0	NA	NA
(28)	CHD	Y	28/28	34.1	23.7	NA	NA	14.9±3.7/19.9±5.8	114.1±30.7/107.8±27.5	NA	43.5±14.8/46.7±14.8
(29)	CHD	Y	64/81	57.4	26.8	NA	36.6	20.1±9.2/24.8±9.7	114.9±55.8/117.1±52.8	NA	NA
(30)	CHD	Y	17/20	45.2	26.5	NA	0.0	21.6±5.6/22.3±5.7	NA	NA	29.5±13.6/36.9±9.7
(31)	CHD	N	572/1754	NA	NA	2.0	NA	20.9±7.4/22.0±7.5	237.7±58.7/242.0±63.5	NA	NA
(32)	CHD	N	15/28	56.2	26.4	65.1	NA	12.4±5.7/15.7±6.3	99.0±58.0/108.0±38.2	NA	NA
(33)	CHD	N	137/872	NA	NA	NA	NA	18.6±6.4/18.6±6.3	139.7±47.8/136.0±40.4	NA	34.4±24.2/32.1±18.4
(34)	CHD	N	96/96	60.8	24.0	NA	NA	15.6±5.9/16.3±7.3	91.2±29.4/94.9±31.3	NA	NA
(35)	CHD	Y	10/10	35.9	25.4	NA	NA	12.7±4.3/16.5±2.5	120.7±27.9/94.1±26.0	NA	45.4±5.5/43.8±9.1
(36)	CHD	Y	32/26	36.3	NA	0.0	NA	19.2±8.2/22.2±8.3	NA	5.9±2.8/7.6±2.7	26.4±9.1/27.6±9.2
(37)	Other CVD	–	35/48	55.1	NA	NA	NA	16.2±8.8/17.0±8.6	199.9±117.3/121.9±127.2	NA	NA
(38)	CVD	N	117/107	47.0	24.6	20.1	NA	15.1±4.0/16.6±4.7	136.2±40.7/117.4±36.8	NA	49.8±10.5/52.4±12.5
(39)	Other CVD	–	9/10	55.4	NA	NA	NA	10.2±6.9/16.8±5.7	NA	NA	NA
(40)	CHD	N	200/74	55.5	26.3	NA	NA	17.9±5.5/19.3±5.3	119.9±63.2/108.5±44.5	5.3±3.1/5.4±5.3	34.7±14.9/33.5±14.8
(41)	CHD	N	119/229	49.4	NA	NA	NA	14.8±5.8/16.9±6.5	NA	NA	NA
(42)	CHD	N	62/97	48.0	NA	NA	NA	19.6±7.3/19.1±6.7	NA	7.7±4.8/6.6±3.1	50.2±21.6/46.6±20.3
(43)	CHD	N	42/74	50.4	26.5	NA	24.1	13.8±3.9/14.2±4.2	84.9±26.6/89.3±22.4	NA	34.9±12.3/38.6±16.3
(44)	Other CVD	–	138/47	70.1	NA	NA	NA	13.8±5.9/16.5±4.8	134.0±46.8/133.0±41.1	NA	NA
(45)	CHD	N	50/18	62.5	27.3	NA	NA	22.7±9.3/20.0±6.1	141.5±32.4/117.3±26.1	2.9±1.7/2.9±2.0	41.2±19.3/40.1±14.4
(46)	Other CVD	–	40/41	71.6	25.8	0.0	NA	13.6±5.1/14.9±5.1	97.9±30.4/106.1±28.8	NA	34.6±14.5/39.5±13.4
(47)	CHD	N	33/33	54.0	26.1	0.0	0.0	12.9±4.3/26.8±3.2	129.0±6.3/66.7±12.1	NA	NA
(48)	CHD	Y	102/99	62.7	23.4	NA	NA	8.7±4.4/14.3±10.7	162.6±106.8/172.1±118.5	NA	NA
(49)	CHD	Y	213/124	53.3	24.6	11.9	37.7	13.9±10.8/12.2±5.2	125.4±50.4/119.5±44.5	NA	NA
(50)	CHD	N	99/39	63.5	23.4	NA	NA	11.1±5.3/16.9±6.6	150.5±83.4/146.8±52.9	NA	NA
(51)	CHD	Y	60/30	59.9	27.7	6.7	37.8	13.3±4.1/15.3±5.9	71.8±33.3/98.4±41.6	NA	36.4±11.9/34.4±13.9
(52)	CHD	Y	76/20	53.3	27.6	12.5	62.5	11.9±4.8/21.2±7.4	109.4±56.7/146.4±66.5	NA	34.4±10.2/31.4±13.3
(53)	CHD	Y	105/23	53.8	26.1	0.0	66.1	NA	NA	NA	NA
(54)	CHD	Y	48/19	49.2	26.5	NA	NA	17.2±6.7/20.8±7.3	79.6±21.1/68.7±20.5	5.2±2.1/5.9±2.7	29.1±11.4/25.4±12.6
(55)	CHD	Y	56/30	50.4	26.7	0.0	NA	17.0±6.4/19.4±6.6	73.8±27.8/78.6±22.0	5.8±2.4/5.1±2.3	29.7±11.8/25.0±10.9
(56)	CHD	Y	95/92	47.4	26.2	NA	NA	16.6±4.9/17.2±5.4	NA	4.4±3.5/5.1±3.4	31.6±13.2/33.3±13.4
(57)	CHD	Y	236/143	63.0	23.8	14.2	22.9	NA	NA	2.8±1.6/2.6±1.5	NA
(58)	CHD	N	221/294	61.5	26.5	NA	NA	18.4±5.7/18.1±6.5	139.3±90.3/143.3±71.4	NA	63.7±35.8/66.4±36.3
(59)	Other CVD	–	10/32	55.0	25.0	0.0	0.0	11.3±4.0/19.3±5.5	NA	NA	NA
(60)	CHD	Y	388/114	56.1	28.2	20.4	28.7	16.6±6.7/15.8±7.3	NA	NA	NA
(61)	CHD	Y	258/156	61.4	24.6	NA	NA	25.4±10.3/25.7±6.7	314.7±160.7/340.8±129.4	NA	NA
(62)[a]	CHD	Y	30/28	51.7	25.8	NA	NA	12.4±3.1/16.9±4.5	194.5±36.8/144.1±24.6	NA	23.6±4.8/28.3±10.5
(62)	CHD	Y	21/28	52.7	25.4	NA	NA	15.5±3.7/16.9±4.5	166.2±31.3/144.1±24.6	NA	31.7±4.6/28.3±10.5
(63)	CHD	Y	69/56	41.1	25.9	12.8	27.2	10.7±5.9/14.2±7.1	96.7±44.5/93.0±26.8	NA	NA
(64)	Other CVD	–	124/124	74.6	26.5	25.5	63.5	NA	NA	NA	39.8±17.2/54.3±34.3
(65)	CHD	N	51/55	63.8	NA	0.0	NA	NA	NA	NA	NA
(66)	Other CVD	–	209/1452	55.2	27.3	8.0	30.0	16.7±5.8/18.1±6.1	NA	3.0±1.9/3.1±1.3	33.6±16.9/32.1±16.2
(67)	CHD	Y	388/114	56.1	28.2	20.4	28.7	16.6±6.7/15.8±7.3	NA	3.1±1.9/2.9±1.9	NA
(68)	CHD	N	139/400	72.4	24.9	NA	NA	17.0±7.1/21.1±6.2	116.6±49.9/95.9±49.7	1.0±2.1/2.2±1.6	107.5±87.2/186.0±89.5

AG, angiography; HT, hypertension; TT, total testosterone; CVD, cardiovascular disease; CHD, coronary artery disease; Y/N, yes/no; DM, diabetes mellitus; BMI, body mass index; E_2, estradiol; SHBG, sex hormone-binding globulin; NA, not available; y, years.

[a]Acute myocardial infarction.

[b]Normotensive group.

respectively (Fig. 1). The characteristics of the trials included in the meta-analysis are summarized in Tables 1–4.

Cross-sectional studies

Among the cross-sectional studies (including 5153 CVD patients and 7513 non-CVD patients), information on TT and SHBG was available in 49 and 14 respectively. In addition, among studies evaluating TT, 25, 20, and eight studies evaluated men with non-angiographically and angiographically documented CHD or other CVD respectively. Finally, data on E_2 and DHEAS were available in 36 and 11 studies respectively.

The Begg adjusted rank correlation test (Kendall $\tau = -0.170$; $P = 0.06$), calculated on the basis of TT in cross-sectional studies, suggested no major publication bias.

When considering data on TT, patients with any CVD showed significantly ($P < 0.0001$) lower TT plasma levels in comparison with individuals without CVD (-2.55 (-3.39, -1.71) nmol/l). Similar results were obtained when analyzing separately subjects with ($P < 0.0001$) and without ($P < 0.01$) angiographically documented CHD or other CVD ($P < 0.0001$, see also Fig. 2A–C). Conversely, no significant difference between patients with or without CVD was observed for SHBG and DHEAS (Table 5). No sub-group analyses for the type of CVD were performed for SHBG due to insufficient available data.

Meta-regression analysis on cross-sectional studies showed that differences in TT between patients with and without any CVD did not differ as a function of age, while they were significantly higher in obese, diabetic, and hypertensive patients, i.e. in patients with chronic diseases (Fig. 3A–D). In a logistic regression model, adjusting for age and BMI, the presence of any CVD was still associated with lower TT levels (HR = 0.837 (0.823–0.852) for each nmol/l increment of testosterone; $P < 0.0001$). The same results were observed when diabetes and hypertension prevalence were introduced in the model, as covariates (HR = 0.536 (0.447–0.606) for each nmol/l increment of testosterone; $P < 0.0001$).

When considering data on E_2, patients with any CVD showed significantly ($P < 0.0001$) higher E_2 plasma levels in comparison with subjects without CVD (25.11 (10.59–39.63) pmol/l; Fig. 4A). Similar results were obtained when only patients with CHD were considered (Fig. 4B). No sub-group analyses for the type of CHD were performed for E_2, due to insufficient data.

Meta-regression analysis on cross-sectional studies showed that differences in E_2 between patients with CVD and controls were significantly lower in younger, obese, diabetic, and hypertensive patients (Fig. 5A–D). In a logistic regression model, after adjusting for age

Table 2 Moderators and outcome variables in individual longitudinal studies included in the meta-analysis. All data are reported as mean ± S.D

References	Type of CVD	Follow up	CVD (Y/N)	Age (years)	BMI (kg/m^2)	DM (%)	HT (%)	CVD/no CVD			
								TT (nmol/l)	E_2 (nmol/l)	DHEAS (μmol/l)	SHBG (nmol/l)
(69)	Any CVD	Up to 8 y	163/163	NA	NA	NA	NA	27.4 ± 10.2/26.9 ± 8.9	97.8 ± 35.3/95.2 ± 30.9	NA	NA
(38)	Any CVD	12 y	114/758	NA	NA	NA	NA	18.1 ± 5.9/18.7 ± 6.4	136.0 ± 36.8/136.0 ± 40.4	NA	35.3 ± 21.6/31.5 ± 17.8
(34)	CHD	Mean 3.5 y	56/96	60.8	24.0	NA	NA	15.3 ± 5.6/15.9 ± 6.9	95.9 ± 29.0/98.2 ± 34.2	NA	NA
(70)	CHD	Mean 9.5 y	46/124	58.8	25.2	NA	NA	21.2 ± 9.4/20.8 ± 4.7	161.8 ± 44.1/165.4 ± 80.9	NA	NA
(71)	CHD	5 y	134/2192	NA	NA	NA	NA	23.0 ± 7.6/22.9 ± 7.4	257.0 ± 69.0/250.0 ± 61.0	NA	NA
(72)	Overall death	10 y	68/119	NA	NA	NA	NA	20.2 ± 6.6/23.1 ± 9.2	NA	NA	NA
(58)	CHD	20 y	154/384	61.5	NA	NA	NA	11.1 ± 2.5/21.2 ± 3.9	122.8 ± 40.9/123.5 ± 57.6	NA	39.7 ± 12.4/41.1 ± 9.8
(73)	Overall death	Mean 7 y	825/1489	67.3	26.7	4.7	20.0	15.8 ± 5.7/16.7 ± 5.7	NA	2.8 ± 1.9/2.9 ± 1.8	45.4 ± 18.3/45.0 ± 16.2
(73)	CVD death	Mean 7 y	369/1489	67.3	26.7	9.5	31.5	15.7 ± 6.1/16.7 ± 5.7	NA	2.7 ± 1.8/2.9 ± 1.8	45.2 ± 18.2/45.0 ± 16.2
(74)	Stroke/TIA	3.5 y	119/3324	76.2	NA	15.0	76.0	14.5 ± 5.1/15.5 ± 5.6	NA	NA	NA
(75)	Overall death	4.3 y	49/1326	NA	NA	NA	NA	14.5 ± 6.4/16.6 ± 6.2	NA	NA	NA
(75)	CVD death	4.3 y	12/1463	NA	NA	NA	NA	13.5 ± 8.7/16.5 ± 6.2	NA	NA	NA
(75)	Any CVD	4.3 y	120/1355	51.8	26.3	NA	NA	15.9 ± 5.6/16.6 ± 6.2	NA	NA	NA

HT, hypertension; TT, total testosterone; CVD, cardiovascular disease; CHD, coronary artery disease; DM, diabetes mellitus; BMI, body mass index; E_2, estradiol; SHBG, sex hormone-binding globulin; NA, not available; y, years.

Table 3 Characteristics of the randomized clinical studies included in the meta-analysis.

	Studies (references)					
Characteristics	(76)	(77)	(78)	(79)	(80)	(81)
Drug	Test. (i.v.)	Test. (i.v.)	Test. patch	Test. (i.v.)	Sustanon (i.m.)	TU (i.m.)
Dose	2.5 mg once	2.3 μg once	5 mg daily	*	100 mg twice/week	1.000 mg/12 weeks
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Randomization	A	A	A	A	A	A
Blinding	A	A	A	A	A	A
Drop-out	A	A	A	A	A	A
Intention to treat	Yes	Yes	Yes	Yes	Yes	Yes

Test., testosterone; TU, testosterone undecanoate in castor oil; A, adequate; NA, not adequate.*Testosterone doses were individualized to produce physiologic (defined as double the baseline testosterone level) or supra-physiologic (6× baseline) serum testosterone level.

and BMI, the presence of any CVD was still associated with higher E_2 levels (HR = 1.002 (1.003–1.004) for each pmol/l increment of E_2; $P<0.0001$). Similar results were observed when TT level was introduced in the same regression model (HR = 0.763 (0.744–0.783), $P<0.0001$, and HR = 1.015 (1.014–1.017), respectively, for each increment of TT and E_2 levels; both $P<0.0001$).

Longitudinal studies

In longitudinal studies ($n=10$), enrolling 12 375 subjects, baseline TT level was significantly lower among patients with incident overall- and CV-related mortality, in comparison with controls (Fig. 6A and B). Conversely, we did not observe any difference in baseline TT levels between case and controls for incident CVD (Fig. 6C). Similarly, baseline E_2 levels were not different in patients who have found to have CVD at follow-up (Fig. 6D). No analyses for the overall and CV mortality were performed for E_2, due to insufficient data.

Clinical trials

The six RCTs available enrolled 258 patients with CHD, with a mean follow-up of 23 weeks. Although all of these trials enrolled only CHD patients, they differ in basal TT levels (Tables 3 and 4). In addition, TRT was administered in different formulations and doses (Table 3). Combining the results of those trials, TRT was positively associated with a significant increase in treadmill test duration and time to 1 mm ST segment depression (Fig. 7A and B). Similar results were observed when studies evaluating an acute testosterone effect (with i.v. testosterone or placebo administration) were excluded from the analysis (mean difference in reaching 1 mm ST depression = 98.592 (20.027–177.157) s; $P<0.014$).

Discussion

This is the first study that systematically and comprehensively explores available data on the association between testosterone (and related sex steroids) and CVD in men. Our results show that both low testosterone and high E_2 levels are independently associated with overall CV and CHD in cross-sectional surveys. In addition, in longitudinal observational studies, while low testosterone predicts overall and CV mortality, no association between both testosterone and E_2 and CV incidence has been found. Finally, no relationship between DHEAS and CVD has been observed.

The role of androgens in the pathogenesis of CVD is also a matter of debate. Phillips *et al.* (24) first reported an inverse relationship between free testosterone (FT) levels and the degree of CAD in a group of subjects undergoing coronary angiography. Similar results were confirmed thereafter by Zhao *et al.* (48).

Table 4 Outcome variables in individual randomized controlled studies included in the meta-analysis. All data are reported as mean ± S.D.

References	**No. of patients** (ID/C)	**Trial duration** (weeks)	**Age** (years)	**TT baseline** (nmol/l)	**DM baseline** (%)	**MI baseline** (%)	**Exercise duration endpoint** (s ID/C)	**Time to 1 mm ST depression endpoint** (s ID/C)
(76)	7/7	–	58.0	NA	7.1	35.7	631.0 ± 180.0/541.0 ± 204.0	579.0 ± 204.0/471.0 ± 210.0
(77)	14/14	–	57.0	5.3	21.4	50.0	NA	364.0 ± 149.7/298.0 ± 127.2
(78)	22/24	14	62.0	12.9	15.3	10.9	NA	361.0 ± 103.2/292.0 ± 117.6
(79)	34/34	–	69.1	NA	NA	32.0	NA	294.0 ± 132.0/288.0 ± 132.0
(79)[a]	34/34	–	69.1	NA	NA	32.0	NA	288.0 ± 138.0/288.0 ± 132.0
(80)	10/10	4	60.8	4.2	50.0	30.0	NA	399.0 ± 84.0/352.0 ± 150.0
(81)	7/6	52	64.8	9.9	23.1	30.8	463.6 ± 46.2/363.3 ± 143.5	449.0 ± 67.5/262.7 ± 110.3

ID/C, investigational drug/comparator; TT, total testosterone; DM, diabetes mellitus; MI, myocardial infarction; NA, not available; s, second.
[a]Supra-physiologic (6× baseline) serum testosterone level.

Conversely, conflicting results have been reported in cross-sectional studies, comparing subjects with CHD to healthy controls (1, 51, 83). Our meta-analysis shows that patients with CVD have, on average, lower testosterone level than healthy controls. Furthermore,

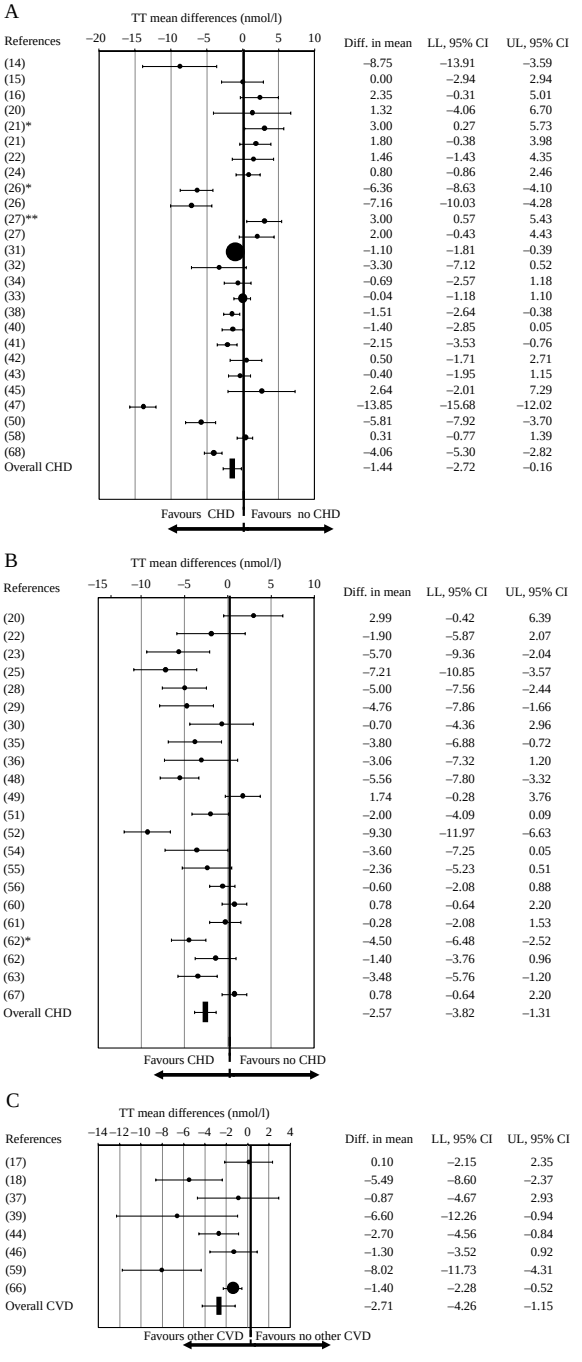

Figure 2 Weighted differences (with 95% CI) of mean total testosterone (TT) between non-angiographically documented (A), angiographically documented (B) coronary heart diseases (CHD) or other types of cardiovascular diseases (CVD; C) and controls from cross-sectional studies. *Acute myocardial infarction. **Normotensive group.

Table 5 Weighted differences (with 95% CI) of mean SHBG and DHEAS between patients with cardiovascular diseases and controls from cross-sectional studies.

	SHBG (nmol/l)				**DHEAS** (μmol/l)			
References	Differences in means	LL (95% CI)	UL (95% CI)	***P***	Differences in means	LL (95% CI)	UL (95% CI)	***P***
(28)	−3.20	−10.96	4.56	0.42	–	–	–	–
(30)	2.60	−4.93	10.13	0.50	–	–	–	–
(33)	2.30	−1.17	5.77	0.19	–	–	–	–
(35)	1.62	−4.96	8.20	0.63	–	–	–	–
(36)	−1.20	−5.93	3.53	0.62	−1.74	−3.16	−0.32	0.02
(38)	−2.58	−5.60	0.44	0.09	–	–	–	–
(40)	1.20	−2.77	5.17	0.55	−0.10	−1.12	0.92	0.85
(42)	3.60	−3.03	10.23	0.29	1.10	−0.13	2.33	0.08
(43)	−3.70	−9.39	1.99	0.20	–	–	–	–
(45)	1.10	−8.69	10.89	0.83	–	–	–	–
(46)	−4.90	−10.98	1.18	0.11	−1.40	−2.28	−0.52	0.00
(51)	2.05	−3.47	7.57	0.47	0.00	−0.96	0.96	1.00
(52)	3.00	−2.37	8.37	0.27	–	–	–	–
(54)	3.70	−2.54	9.94	0.25	−0.62	−1.84	0.61	0.32
(55)	4.70	−0.40	9.80	0.07	0.66	−0.39	1.72	0.22
(56)	−1.71	−5.52	2.10	0.38	−0.70	−1.68	0.28	0.16
(57)	–	–	–	–	0.11	−0.22	0.44	0.52
(58)	−2.74	−9.04	3.56	0.39	–	–	–	–
(62)[a]	−4.70	−8.86	−0.54	0.03	–	–	–	–
(62)	3.40	−1.41	8.21	0.17	–	–	–	–
(64)	−14.50	−21.25	−7.75	0.00	−0.14	−0.65	0.38	0.61
(66)	1.50	−0.86	3.86	0.21	1.50	−0.86	3.86	0.21
(67)	–	–	–	–	0.12	−0.29	0.53	0.57
(68)	−78.52	−95.68	−61.36	0.00	−1.22	−1.56	−0.88	0.00
Overall	−1.67	−4.29	0.95	0.21	−0.32	−0.76	0.13	0.16

LL, lower limit; UL, upper limit.
[a]Normotensive group.

the presence of several associated morbidities, such as diabetes, obesity, and hypertension, are associated with increased testosterone differences between cases and controls, confirming numerous clinical observations. All of these morbidities were previously found to be associated with male hypogonadism (1, 84–86). It has been shown in previous meta-analyses (87, 88) that diabetes, in particular type 2 diabetes mellitus (T2DM), is a clinical condition which is often comorbid with a reduction in circulating testosterone in males, most probably from mixed (central and peripheral) hypogonadism. Accordingly, the recently updated Endocrine Society Guidelines suggests a systematic investigation for possible hypogonadism in diabetic patients (89). The association between obesity and hypogonadism is also well documented (84–86). The European Male Aging study, a large population-based study involving more than 3000 subjects enrolled in eight different European centers, confirms a stepwise reduction in testosterone levels as a function of obesity class and number of associated morbidities, without a concomitant LH rise (90). Conversely, the relationship between testosterone levels and hypertension is more controversial (91). In particular, while some studies have shown reduced androgen levels in subjects with essential hypertension (92, 93), others did not confirm these results (21). We previously demonstrated that only pulse pressure (i.e. the arithmetic difference

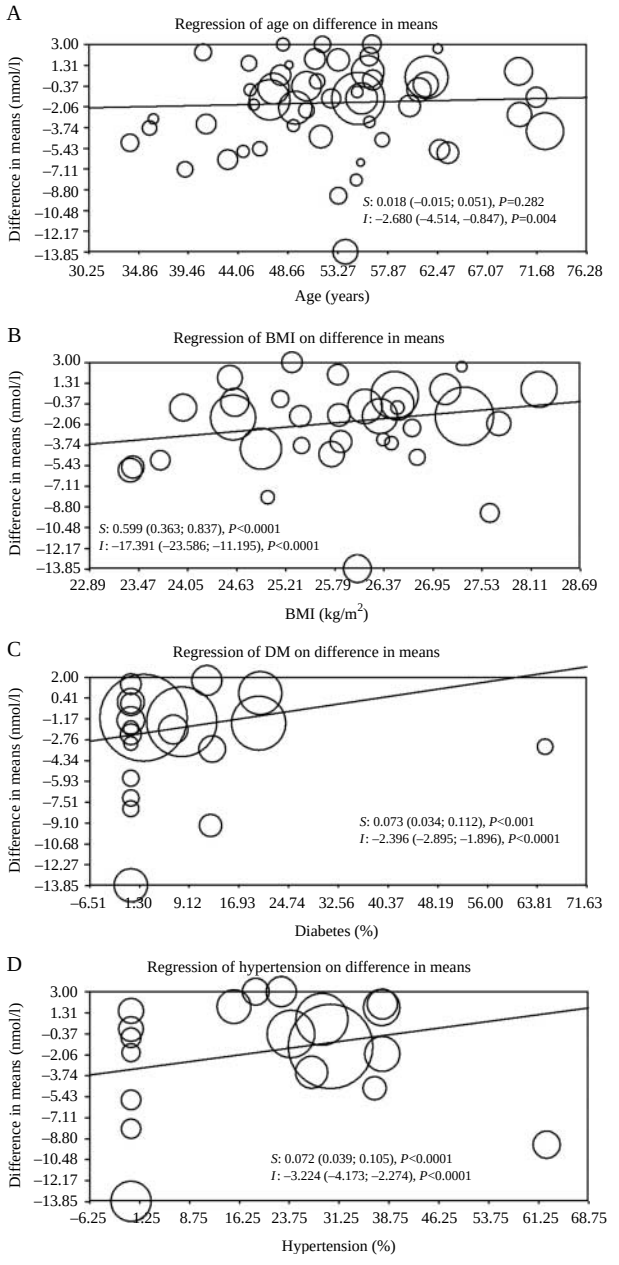

Figure 3 Influence of age (A) and body mass index (BMI; B), diabetes mellitus (DM; C), and hypertension (D) on total testosterone weighted mean differences between patients with cardiovascular diseases and controls.

between systolic and diastolic blood pressure), but not systolic or diastolic blood pressure, is androgen dependent (94). No information on pulse pressure was available in the studies included in this study. It is important to note that when testosterone levels were introduced as a covariate in a logistic model, together with the aforementioned morbidities, they retain an independent, negative association with CVD. In longitudinal studies, baseline low testosterone predicts overall and CV-related mortality but not incident CVD. Taken together, these results suggest that low testosterone may be considered as a marker of poor general health status, negatively affecting prognosis, rather than a specific CV risk factor (11, 84–86, 95). Low testosterone level has also been associated with an increased mortality in patients affected by non-CVD, such as hypopituitarism (96), Klinefelter's syndrome (97), and mental retardation (98), as well as in specific populations, such as Veterans (99).

Conversely, longitudinal observational studies in prostate cancer patients show that androgen ablation is associated with an increased incidence of CVD (100–104). Although this suggests that suppressed testosterone might have a causal role in CV frailty, the castrate testosterone levels resulting from testosterone ablation may not really be compared to the slightly decreased testosterone levels observed in men with CVD. In addition, the association between low testosterone and forthcoming CVD was obtained in a rather selective population sample, such as those with prostate cancer. Studies performed in community-dwelling males have provided conflicting results (see for review reference (1)). Some authors did not report any association between testosterone levels and CV morbidity, after adjusting for confounders (33, 70, 71, 105–108). Conversely, data from the Health In Men Study (74) suggested a strong relationship between low to normal levels of TT and incidence of cerebrovascular events, whereas overt low testosterone levels (TT $<$ 8 nmol/l) were not significantly related to incidence of transitory ischemic attack (TIA) and stroke in elderly men.

Available data show that testosterone enhances myocardial function through direct and indirect effect on myocardiocytes (109, 110); it is therefore possible that hypogonadism leads to an increased functional damage following the onset of coronary artery disease.

In order to verify the causal relationship between hypogonadism and CVD, data from interventional studies (i.e. RCTs) are helpful. Isidori *et al.* (111) reported that TRT in middle-aged men is able to reduce fat mass and total cholesterol. Similarly, Whitsel *et al.* (112), in a meta-analysis on the effects of i.m. TRT in hypogonadal men, showed a small dose-dependent decrease in total cholesterol and LDL- and HDL-cholesterol. Very few RCTs have evaluated the impact of TRT in patients with metabolic syndrome (MetS) and T2DM. In patients with MetS, TRT was associated with a significant reduction in fasting plasma glucose, HOMA index, triglycerides, and waist circumference as well as with an increase in HDL-cholesterol (113). Similar results were observed when T2DM was considered. In particular, TRT was associated with a significant reduction in fasting plasma glucose, HbA1c, fat mass, and triglycerides (88).

A previous meta-analysis on 30 placebo-controlled studies, evaluating the effect of TRT on CV events, showed TRT safety, because it was not associated with an increased risk of CVD (114). Similar results were

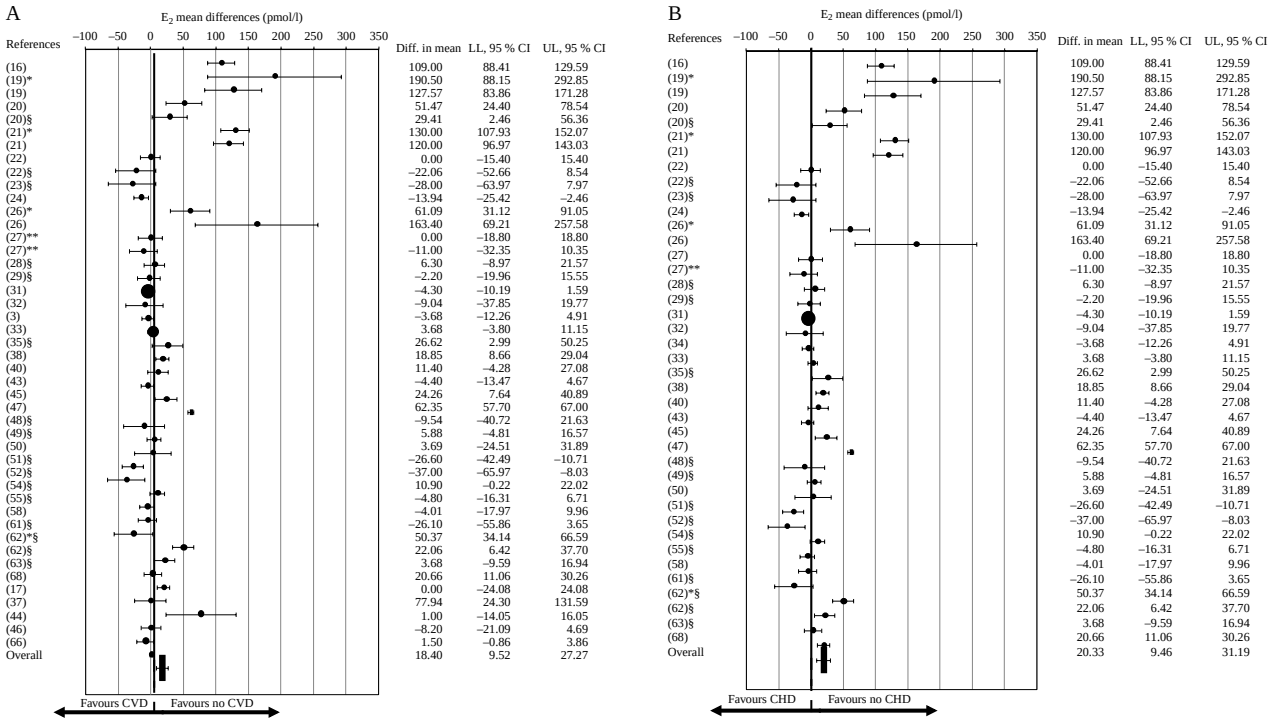

Figure 4 Weighted differences (with 95% CI) of mean total 17-β estradiol (E_2) between cardiovascular disease (CVD; A) or coronary heart disease (CHD; B) and controls from cross-sectional studies. *Acute myocardial infarction. **Normotensive group. §CHD angiographically documented.

more recently reported by Fernández-Balsells *et al.* (115) who meta-analyzed 51 placebo-controlled studies with follow-up ranging from 3 months up to 3 years. Interestingly, we now report that TRT is effective in men with chronic stable angina, as they had greater angina-free exercise tolerance than placebo-treated controls. The possible beneficial effect of chronic TRT on CV risk needs to be better elucidated through large-scale, long-term, placebo-controlled studies.

Data from the Health in Men Study, a population-based study of 3616 men aged 70–88 years, have documented that low free testosterone independently predicted frailty (HR 1.22 (1.05–1.42)) (116). Recent RCT studies on the effect of transdermal testosterone on two groups of more than 200 hypogonadal (TT below 12 nmol/l) elderly men with frailty indicated that TRT prevents age-associated loss of lower limb muscle strength, while improving body composition, quality of life, and physical function (117, 118). These two RCTs were not included in the present meta-analysis because they did not fulfill our inclusion criteria. In the Testosterone in Older Men with Mobility Limitation trial (117), employing in some patients a high testosterone dose (100 mg of a 1% gel) in order to obtain a serum testosterone level in the target range, the treated frail elderly men reported a high rate of CV adverse events, which induced a premature termination of the study. The same authors recognized that the generalizability of these data about the safety of TRT are limited by several factors, including that CV events were i) observed in a population characterized by a high prevalence of chronic disease, ii) not a planned primary or secondary outcome, and iii) the number of adverse events was relatively small (23 vs 5%, respectively, for treatment and placebo arms).

While low testosterone level could contribute to the pathogenesis of CVD, the reverse is also possible. It can be speculated that CVD-associated hypogonadism is an adaptive mechanism. In fact, we cannot exclude the possibility that low testosterone, as observed in several chronic diseases, has a protective role by turning off testosterone-dependent functions (such as reproduction and physical labor) that are not desirable when the physical condition is ailing. A recent longitudinal observational study confirms that hypogonadism is a CV risk marker in lean subjects. However, in those with higher BMI, hypogonadism is associated with a lower CV risk, suggesting that testosterone reduction induced by adiposity could have a beneficial effect (95). Hence, the suppression of testosterone in obesity could represent a protective mechanism.

In our meta-analysis, higher E_2 level was associated with prevalent CVD in cross-sectional studies, but it was not a predictor of incident CVD in longitudinal studies. This apparent discrepancy could be accounted for by several factors. If high E_2 is an indicator of poor health

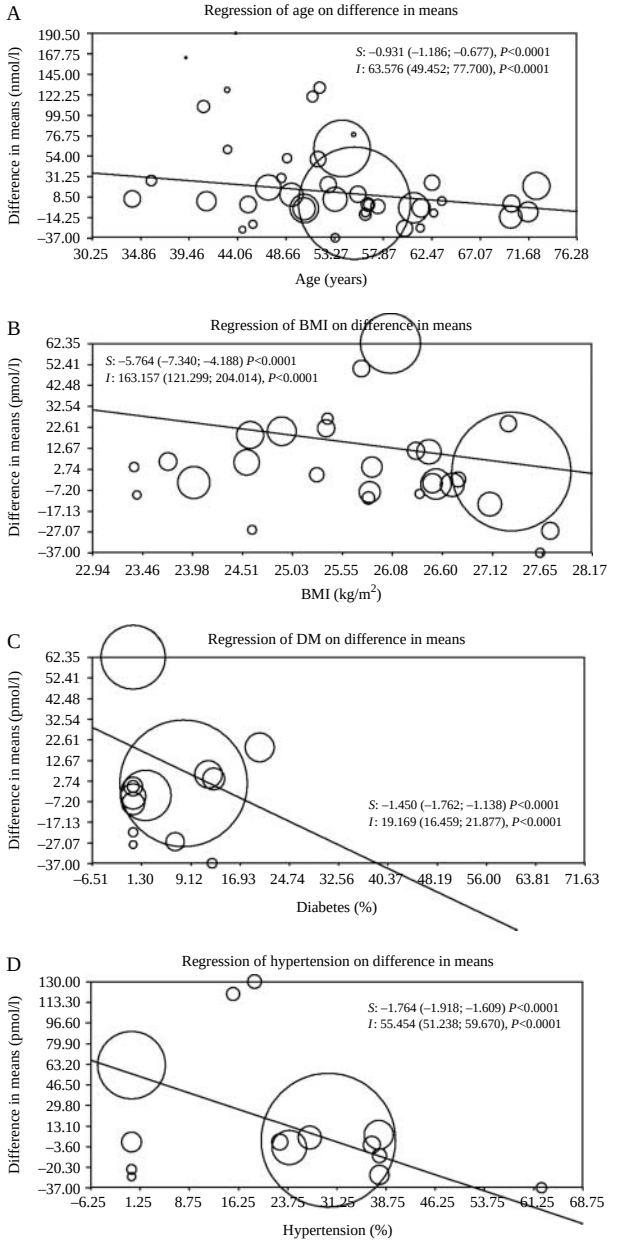

Figure 5 Influence of age (A) and body mass index (BMI; B), diabetes mellitus (DM; C), and hypertension (D) on total 17-β estradiol weighted mean differences between patients with cardiovascular disease and controls.

status (33, 106, 107, 119–124) or obesity (84–86, 125, 126), its higher level could be the consequence, rather than the cause, of CVD. However, it is also possible that the limited size and number of longitudinal cohort studies prevented the detection of the effect of E_2 on incident CVD.

DHEA and its sulfate (DHEAS) are steroids abundantly present in peripheral circulation, without a clear physiological role, apart from being precursors of bioactive androgens. However, they have been implicated in a broad range of biological abnormalities including obesity, diabetes, osteoporosis, cancer, and mental disorders (127). In addition, there is a widespread, non-supervised use of DHEA as a dietary supplement for elderly people in the hope of a fountain of youth. However, the results of several small DHEA supplementation studies are rather inconclusive, if not negative (128, 129). Epidemiological studies demonstrate that the association between low DHEAS and all-cause or CVD mortality is, at least, conflicting

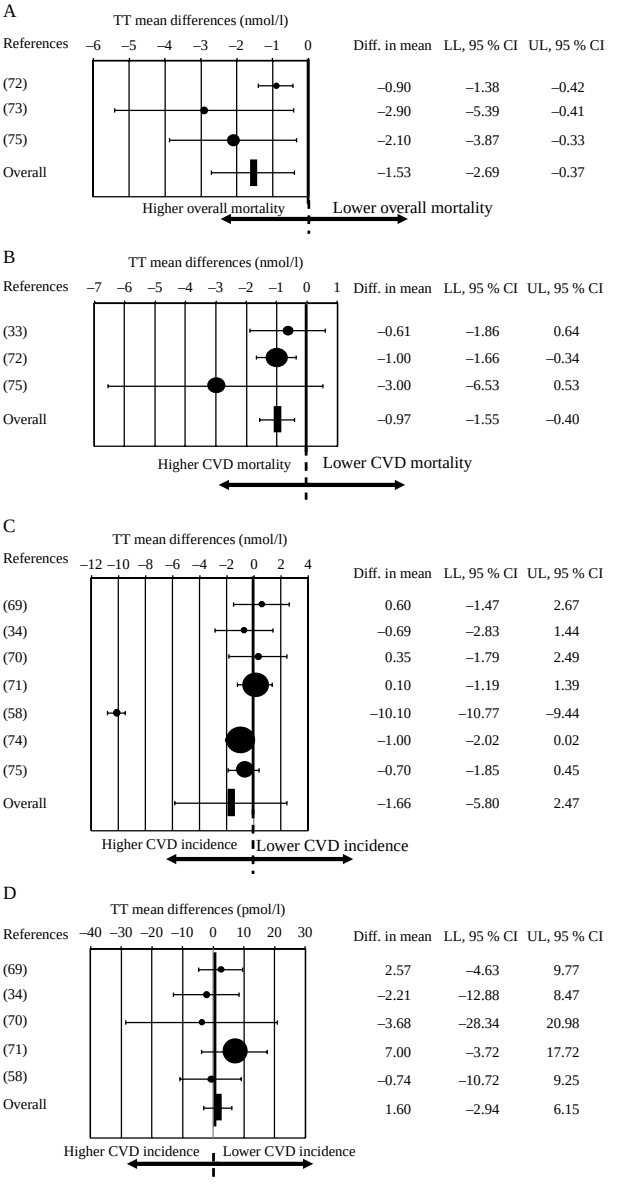

Figure 6 Baseline weighted differences (with 95% CI) of mean total testosterone (TT) between patients with incident overall (A) and cardiovascular disease (CVD) mortality (B) or incident CVD (C) and controls from longitudinal studies. D) Baseline weighted differences (with 95% CI) of mean 17-β estradiol (E_2) between patients with incident CVD and controls from longitudinal studies.

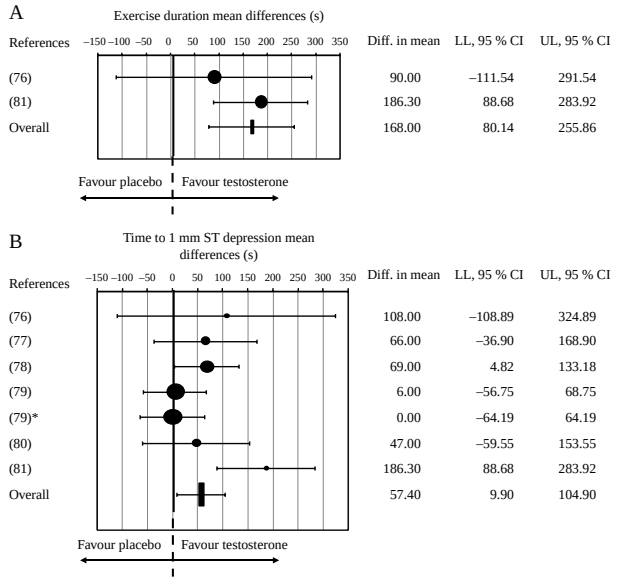

Figure 7 Weighted differences (with 95% CI) of mean treadmill test duration (A) and time to 1 mm ST segment depression (B) during treadmill test at endpoint across randomized controlled trials. *Supra-physiologic (6× baseline) serum testosterone level.

(130–135). Our study found no significant relationship between DHEAS levels and CVD.

Several limitations should be recognized. Potential selection bias and confounding factors may exist. Several longitudinal studies evaluating the incidence of CVD or CVD mortality were not included in the present meta-analysis, since they do not report continuous hormone values. Data on E_2 should be considered with caution since the assays used in these publications is missing. The number and the duration of RCTs as well as the number of the patients enrolled are very limited. However, it should be important to emphasize that we considered only studies evaluating the effect of TRT on CV parameters derived from treadmill test in men with chronic stable angina. Further prospective investigations on TRT in CVD and CHD patients are advisable.

Conclusions

This meta-analysis of the relationship between testosterone and CVD, risks and consequences, reinforces many other studies but unifies several of the concepts previously published separately. Low testosterone levels have been shown to correlate significantly with CV risk factors but also with the incidence of CHD events, and indeed, with the incidence of CVD events in general. This also correlates with the ultimate risk of mortality itself. This is very important as the review began by reminding us that death due to CVD is the most common cause of mortality in men. One interesting finding was that the increase in CVD was associated with medical co-factors, especially obesity, diabetes, and hypertension, and not a function of age *per se*. These findings were also accompanied by a higher E_2 level, which may be more a result of the medical conditions and risks, rather than a cause. It is therefore very important that clinicians look for hypogonadism in men with CV risk factors and disease and conversely look for CV comorbidities when hypogonadism is found. The encouraging news is that early studies have shown that treatment of low testosterone states may moderate many of the medical co-factors and thus may decrease CV risks (136). This has to be proven with much larger numbers followed over a longer period of time so that we can see whether treatment of hypogonadism may actually decrease CV events, data that we do not have at this point in time. This conclusion leads to an unsolved dilemma: is low testosterone level in CVD a positive consequence of the body trying to decrease unnecessary energy by reducing reproductive expenditure in order to survive, or does it represent a pathophysiologic factor in the same illness? In the first scenario, testosterone supplementation may not be advisable, whereas in the second scenario it would be recommended. Present available data are not sufficient to sort out the beneficial or harmful effects of TRT on CV morbidity and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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