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Testosterone Therapy Reduces Cardiovascular Risk Among Hypogonadal Men: A Prospective Cohort Study in Germany

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Abstract

Background: Low testosterone level has been associated with predictors of cardiovascular disease (CVD); however, controversies exist regarding the role of testosterone therapy, a treatment to improve testosterone levels, in preventing cardiovascular risk. Longitudinal studies with a large sample size and long follow-up duration are limited.

Materials and Methods: We conducted a prospective cohort study using data from 602 hypogonadism men free of CVDs at study baseline from a registry study in Germany who were eligible for testosterone therapy, with an age range of 31–74 years and a follow-up duration of up to 12 years. Receiving testosterone therapy or not was based on the patient's own choice at study entry. Patients who decided to take testosterone therapy were classified as treatment group ($n = 325$), and the rest were classified as the control group ($n = 277$). We compared the Framingham Global CVD Risk Score between the treatment and control groups over time and cardiovascular incidence during the follow-up period. We adjusted for baseline characteristics between the treatment and control groups in the mixed-effect model examining the longitudinal effect of testosterone treatment on the risk score, and we applied propensity score matching to control for confounders.

Results: We found that the control group had an overall increasing risk score and decreasing testosterone level over time. For the treatment group with improved testosterone level and lipid and glucose profiles, the risk score decreased before 24 months, and it became stable later on. After propensity score matching, there were 0 cardiovascular events in the treatment group and 45 in the control group.

Conclusions: Low testosterone level is associated with higher cardiovascular risk. Long-term testosterone therapy reduces cardiovascular events among hypogonadal men. Clinicians should be informed of this association when assessing a male patient's cardiovascular risk and ensure timely treatment if needed.

Keywords: hypogonadism; testosterone; Framingham Risk Score; cardiovascular risk

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and the leading cause of death globally.[1] Smoking, increased blood glucose, low-density lipoprotein (LDL) cholesterol, and blood pressure are major risk factors for CVD.[2] Multivariate risk prediction algorithms incorporating these risk factors has been developed to conveniently evaluate an individual's risk of developing future CVD events, including the widely used Framingham Global CVD Risk Score calculated

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based on age, gender, total cholesterol, smoking status, high-density lipoprotein (HDL) cholesterol, and systolic blood pressure.[3,4]

Studies have recently been focused on the role of testosterone in cardiovascular risk among men, as it is the most abundant male hormone that is critical in maintaining normal glucose and lipid metabolism in men. It has been suggested that testosterone may limit vascular inflammation and cytokine activity underpinning the atherosclerosis process, and the morphological changes in the walls of the arteries might be due to metabolic syndrome resulting from testosterone deficiency.[5,6] Studies have shown that low testosterone levels were associated with higher carotid intima media thickness,[7–9] which is a surrogate marker of atherosclerosis that is closely related to abnormal glucose metabolism and lipid profile as well as a strong predictor of future clinical ischemic cardiac and cerebrovascular events.[10–12]

Although low testosterone level has been closely associated with predictors of CVD, controversies exist regarding the role of exogenous testosterone therapy, a treatment to improve testosterone levels, in preventing cardiovascular risk. One of the earliest randomized controlled trials, the testosterone in older men trial, was terminated because of the higher number of cardiovascular events in the intervention group compared with the placebo group.[13] However, study subjects in this trial were elderly men aged 65 years or older with a high prevalence of preexisting heart disease, obesity, diabetes, and hypertension, and "with no standard indication for testosterone therapy".[14] In addition, these elderly men had limitations in mobility, who were more likely to have clinical or subclinical cardiovascular conditions than those who did not have these limitations.

A recent study reviewed seven systematic reviews that included a total of 94 randomized controlled trials and investigated the association between exogenous testosterone and cardiovascular events.[15] Six of them showed no association, and one showed a significant increased risk for CVD associated with exogenous testosterone. The authors pointed out that because of limited sample sizes and short follow-up periods, these trials were underpowered to detect a true difference in cardiovascular risk between treatment and control groups. More evidence from well-designed studies with eligible participants, large sample sizes, and sufficient follow-up time are needed before a determination on the safety of testosterone therapy can be made.

In this study, we conducted a prospective cohort study by using data from 602 hypogonadism men of a registry study conducted in Germany who were eligible for testosterone therapy, with an age range of 31–74 years and a follow-up duration of up to 12 years. Receiving testosterone therapy or not was based on the patient's own choice at study entry. Patients who decided to take testosterone therapy were classified as the treatment group ($n = 325$), and the rest were classified as the control group ($n = 277$).

We investigated the association between testosterone therapy and cardiovascular risk by comparing the Framingham Global CVD Risk Score[3] between the treatment and control groups over time and cardiovascular incidence during the follow-up period. We controlled for baseline health condition and medication use between the treatment and control groups in the mixed-effect model examining the longitudinal effect of testosterone treatment on the Framingham Global CVD Risk Score, and we applied propensity score matching to control for confounders when comparing the incidence between the two groups. We hypothesize that treatment groups are more likely to have improvement in Framingham Global CVD Risk Score and fewer cardiovascular events as compared with the control group.

Materials and Methods

Study population

We used de-identifiable data from a registry study in Germany. Eight hundred five men were recruited from one urology center in Bremerhaven, Germany from 2004, where they had sought medical consultation for various urological complaints, including sexual dysfunction. Hypogonadism diagnosis was confirmed if they had total testosterone level ≤12.1 nmol/L (∼350 ng/dL) and symptoms as assessed by the Aging Males' Symptoms scale. We have chosen the threshold of 12.1 nmol/L, which is ∼350 ng/dL based on our own clinical experience and that was confirmed by Bhasin et al.[16] After excluding patients who had prior cardiovascular events, a total of 602 patients were included in the study. Among prostate cancer patients, measurements after cancer diagnosis have also been removed for the analysis. Ethical guidelines formulated by the German Ärztekammer (German Medical Association) for observational studies in patients receiving standard treatment were followed.

After receiving an explanation about the nature and the purpose of the study, all patients provided written consent to be included in the registry and had their

data analyzed. Participants were followed up annually or semi-annually for updates in serum testosterone level, prostate-specific antigen (PSA) levels, height, weight, body mass index (BMI), waist circumference, blood pressure, lipid profile, glucose, and several other physical, laboratory, and imaging test results. Details on lab measurements have been described elsewhere.[17]

Treatment assignment

Patients with PSA <4 ng/mL were given the option of testosterone therapy. Hematocrit and other parameters were measured, and the laboratory cut-off was used as an inclusion criterion. Receiving testosterone therapy or not was based on the patient's own choice at the beginning of the study. Patients who decided to take testosterone therapy were classified as treatment group ($n = 325$), and the rest were classified as control group (277). As previously described,[18,19] patients on testosterone therapy received injections of 1000 mg of testosterone undecanoate with the second injection 6 weeks after the first injection, followed by 12-week intervals throughout the observation time. Since every injection was administered and documented in the urology office, the adherence to testosterone was 100%.

Cardiovascular outcome ascertainment

Cardiovascular events, including myocardial infarction and stroke occurring during follow-up, were recorded. Cardiovascular events were partly reported in the form of "physician letters" from the hospital or the cardiologist/neurologist/family physician, partly by patients themselves or relatives. The latter usually occurs when already scheduled patient visits have to be postponed due to an event. The Framingham Global CVD Risk Score was calculated for each patient at each visit. Details on score calculation have been described elsewhere.[3] Higher score indicates higher 10-year risk/probability of developing future cardiovascular events.

Statistical analysis

In the descriptive analysis, baseline characteristics, follow-up, comorbidity condition, and medication use between the treatment and control groups were compared by using *t*-test or chi-square test. Line charts were used to compare the mean risk score, lipid profile, glucose, circumference, and BMI changes over time between the two groups.

A mixed-effect model with a random intercept as the random effect, and follow-up time, treatment and their interaction as fixed effects were fitted to assess the testosterone therapy effect on longitudinal changes of the Framingham Global CVD Risk Score, adjusting for baseline risk score, age at study entry, family history of CVD, smoking, alcohol consumption, baseline total cholesterol, baseline HDL, type 2 diabetes (yes/no), and hypertension (yes/no), after considering collinearity.

In addition, CVD incidence rates of the two groups were compared after propensity score matching on baseline risk score, LDL, hypertension, HbA1c, family history of CVD, and alcohol consumption to balance the baseline health condition between treatment and groups.

All analyses were performed with R version 3.3.3. Tests results were considered statistically significant at $\alpha = 0.05$.

Results

After excluding patients with prior CVD events, a total of 602 patients were included in the study, of whom 277 received testosterone therapy. The mean age of total participants is 60 years, and the median follow-up is 8 years. Baseline characteristics, health condition, and medication use between the treatment and control groups are presented in Table 1. Age at study entry, follow-up period, lipid panel, glucose profile, alcohol consumption, smoking status, comorbidity condition, medication use, and family history of CVD were statistically significantly different between the two groups.

Results from the mixed-effect model are shown in Table 2. Overall, after adjusting for confounders, in the control group, for a 1-month increase in time, the Framingham Global CVD Risk Score increased by 0.02; in the treatment group, for a 1-month increase in time, the risk score increased by 0.02–0.01 = 0.01. Before 24 months, for a 1-month increase, risk score in the control group increased by 0.03 and decreased by 0.03 (0.03 = 0.028–0.057) in the treatment group; after 24 months, for a 1-month increase, risk score in the control group increased by 0.03 and increased by 0.01 (0.01 = 0.027–0.014) in the treatment group.

As shown in Figures 1 and 2, testosterone level in the control group was decreasing over time, together with increased Framingham Global CVD Risk Score; whereas in the treatment group, testosterone level was increasing over time, along with decreased Framingham Global CVD Risk Score and improved lipid profile, glucose, BMI, and waist circumference. In a *post hoc* analysis among patients with metabolic syndrome, we noticed improved lipid profile and glucose

Table 1. Baseline Characteristics and Mean Follow-Up of Patients, by Treatment Group

	Control ($n=277$)		Treatment ($n=325$)		
Characteristics	**Mean ± SE**	**Range**	**Mean ± SE**	**Range**	***p***
Age at study entry (years)	63.63 ± 4.78	45–74	56.69 ± 7.73	31–71	<0.001
Testosterone (nmol/L)	9.68 ± 1.11	5.9–11.79	9.69 ± 1.42	0.8–12.13	<0.855
PSA (ng/mL)	2.45 ± 1.35	0.2–7.9	1.65 ± 0.93	0.08–3.87	<0.001
Total cholesterol (mg/dL)	249.49 ± 46.09	173–388	297.88 ± 38.09	202–423	<0.001
LDL (mg/dL)	131.56 ± 49.97	55–246	159.21 ± 30.96	82–229	<0.001
HDL (mg/dL)	47.49 ± 19.15	16–93	38.31 ± 11.78	15–88	<0.001
Glucose (mmol/L)	5.74 ± 0.56	5.11 ± 9.32	6.14 ± 1.15	4.88–9.99	<0.001
HbA1c (%)	6.11 ± 1.29	4.3–9.3	7.04 ± 1.79	4.1–13.4	<0.001
Systolic blood pressure (mmHg)	135.57 ± 9.76	115–181	147.63 ± 16.29	120–188	<0.001
Diastolic blood pressure (mmHg)	77.94 ± 7.17	66–121	87.51 ± 10.58	68–121	<0.001
BMI (kg/m2)	29.72 ± 3.88	22.2–44.1	32.15 ± 5.22	21.91–46.51	<0.001
Follow-up (years)	8.08 ± 1.93	1–12	7.60 ± 2.86	1.25-11.75	0.016
	n	%	*n*	%	
Alcohol consumption	129	46.60	111	34.20	0.003
Smoker	82	29.60	135	41.50	0.003
Type 2 diabetes	105	37.90	92	28.30	0.016
Hypertension	186	67.10	289	88.95	<0.001
Anti-diabetic use	105	37.90	101	31.10	0.094
Anti-hypertensive use	31	11.20	117	36.00	<0.001
Statin use	149	53.80	97	29.80	<0.001
Family history of CVD	31	11.20	73	22.50	<0.001

BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSA, prostate specific antigen; SE, standard error.

panel among those who received testosterone therapy and an opposite situation in the control group (data not shown).

After propensity score matching, there were 232 participants in the treatment group and 212 participants in the control group. Forty-five CVD events were in the control group, and 0 events were in the treatment group. The incidence in the control group is 0.00219 whereas that in the treatment group is 0 (Table 3). The difference is statistically significant (Fisher's exact, $p<0.0001$). In the *post hoc* analysis, we also examined all-cause mortality in the two groups (Table 4), and we found that the control group has a significantly higher mortality rate as compared with the treatment group.

Discussion

This prospective cohort study using data from a registry study conducted in Germany demonstrated that hypogonadal men who did not receive testosterone therapy were more likely to experience an increase in

Table 2. Coefficients from Random-Effect Model Investigating the Effect of Testosterone Therapy on the Longitudinal Changes of the Framingham Global Cardiovascular Disease Risk Score

	Overall		Before 24 months		After 24 months	
Variable	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**	**Coefficient**	**95% CI**
Month	0.024	(0.02, 0.03)	0.028	(0.02, 0.03)	0.027	(0.026, 0.028)
Treatment	1.795	(1.61, 1.98)	1.544	(1.33, 1.75)	1.881	(1.64, 2.12)
Month*treatment	−0.011	(−0.013, −0.010)	−0.057	(−0.07, −0.05)	−0.014	(−0.02, −0.01)
Baseline risk score	0.077	(0.05, 0.10)	0.247	(0.22, 0.28)	0.055	(0.03, 0.08)
Age at study entry	0.289	(0.28, 0.30)	0.245	(0.23, 0.26)	0.290	(0.27, 0.30)
BMI	0.066	(0.05, 0.08)	0.046	(0.03, 0.06)	0.069	(0.05, 0.09)
Smoker	4.000	(3.92, 4.08)	3.515	(3.39, 3.63)	4.082	(3.92, 4.25)
Alcohol	−0.175	(−0.28, −0.07)	−0.366	(−0.49, −0.24)	−0.082	(−0.12, 0.03)
Type 2 diabetes	2.599	(2.44, 2.76)	2.221	(2.04, 2.40)	2.726	(2.56, 2.89)
Hypertension	0.371	(0.22, 0.52)	0.475	(0.31, 0.64)	0.173	(0.01, 0.33)
Total cholesterol	0.025	(0.02, 0.03)	0.018	(0.016, 0.020)	0.022	(0.020, 0.023)
HDL	−0.080	(−0.082, −0.077)	−0.065	(−0.07, −0.06)	−0.078	(−0.080, −0.075)
Family history of CVD	0.043	(−0.12, 0.21)	0.131	(−0.04, 0.30)	0.005	(−0.17, 0.18)

CI, confidence interval.

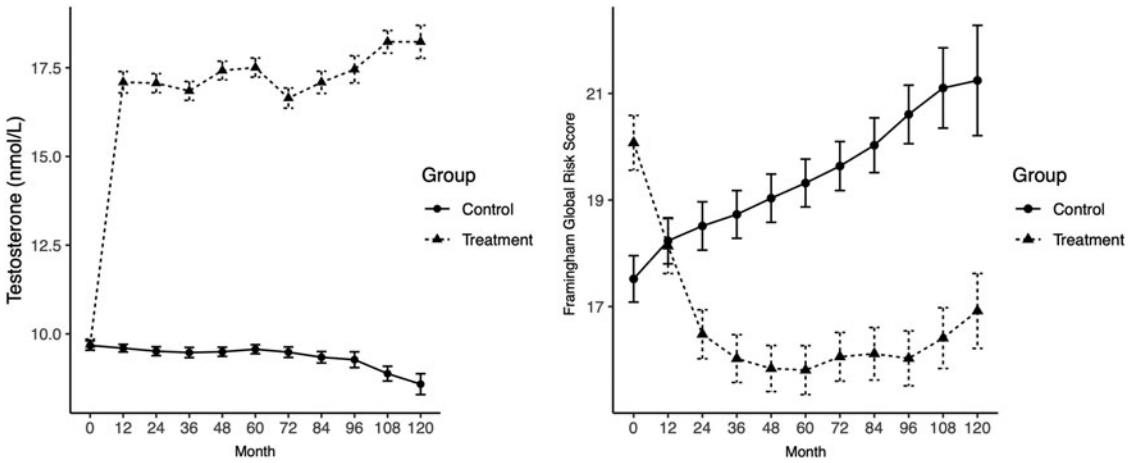

FIG. 1. Framingham global cardiovascular disease risk score and testosterone level changes over time, by treatment group.

the Framingham Global CVD Risk Score later on, whereas patients who received testosterone therapy were more likely to experience a significant decrease in risk score at an early phase of treatment and became relatively stable afterward. After propensity score matching, the treatment group had 0 cardiovascular events as compared with 45 incident cases in the control group. The adjusted incidence rate in the control group is 0.00219, which is statistically significantly higher than the treatment group.

It has been suggested that testosterone is closely associated with surrogate markers of CVD (e.g., cholesterol level, waist circumference, fasting glucose, blood pressure).[20,21] Monroe and Dobs reviewed articles regarding the relationship between endogenous testosterone and lipid profile and found endogenous testosterone to be inversely associated with LDL cholesterol, triglyceride, and total cholesterol, but positively associated with HDL cholesterol in cross-sectional and prospective observational studies.[22] Corona et al. conducted a systematic review and found that men with metabolic syndrome were likely to benefit from testosterone therapy.[23] This is consistent with our findings that patients with metabolic syndrome in the treatment group experienced elevated testosterone level as well as improved lipid and glucose profile during the study period.

Low testosterone level among hypogonadal men may affect lipid metabolism by upregulating the genes involved in HDL cholesterol clearance and decreasing triglyceride uptake,[22,24] resulting in central obesity and adverse lipid profiles. The excess lipid accumulation due to abnormal lipid metabolism then forms the plaque in the walls of the arteries, the first step of atherosclerosis that may eventually lead to cardiovascular or cerebrovascular events if no action is taken. Recent evidence shows that oxidative stress and inflammation induced by elevated cholesterol level, high glucose, and hypertension may also contribute to the progression of atherosclerosis.[25,26]

In addition, as a predictor for atherosclerosis related to testosterone and future cardiovascular or cerebrovascular events, carotid intima-media thickness is also found to be associated with endogenous testosterone levels. This is because carotid intima–media thickening is a complex process, depending on a variety of factors including blood pressure, glycemic control, and lipid metabolism,[2,27] which are closely related to testosterone levels. Vikan et al., Soisson et al., Koskenvuo et al., and Kwon et al. reported an inverse association between testosterone and carotid intima–media thickness.[7–9,28] Our previous studies also suggested the beneficial effect of testosterone therapy on cardiometabolic function in aging men.[18,29]

Testosterone therapy that maintains normal testosterone level may improve lipid profile and glucose management and, therefore, reduce cardiovascular risk and mortality. Though the beneficial effect of testosterone therapy on cardiovascular health and potential underlying mechanisms have been reported in previous studies,[30–32] findings in clinical trials have been inconsistent.

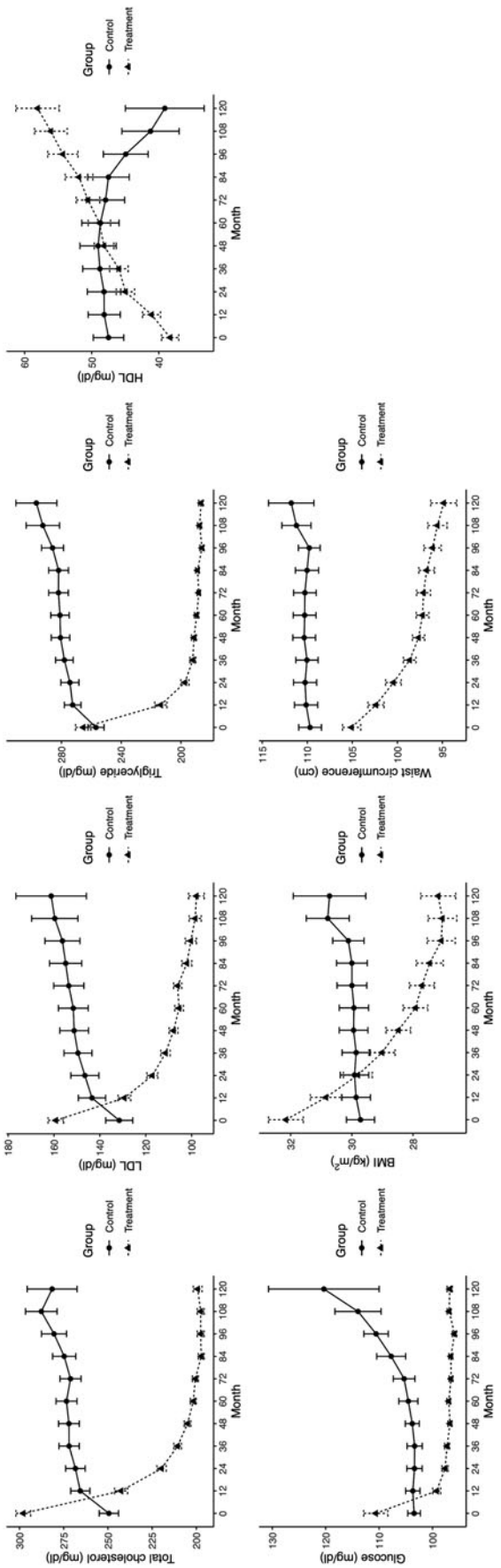

FIG. 2. Lipid profile, glucose, body mass index (BMI), waist circumference changes over time, by treatment group.

Table 3. Cardiovascular Incidence, by Treatment Group

	CVD events	Total participants	Total person month	Incidence rate*
Before matching				
Treatment	0	325	29,631	0
Control	52[a]	277	26,874	0.00193
After matching				
Treatment	0	232	18,645	0
Control	45[b]	212	20,520	0.00219

*Incidence rate difference between the treatment and control group is statistically significant different from 0 ($p < 0.0001$, Fisher's exact test).
[a]Thirty cases of myocardial infarctions, 21 cases of strokes, and 1 case of both myocardial infarction and stroke.
[b]Twenty-five cases of myocardial infarctions, 19 cases of strokes, and 1 case of both myocardial infarction and stroke.

Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) ($n = 308$, 3-year follow-up)[33] and the Testosterone Trials (TTrials) ($n = 138$, 1-year follow-up)[34] are two randomized clinical trials (RCTs) that investigated the effect of exogenous testosterone administration on cardiovascular function in older men with low testosterone levels. TTrials found among hypogonadal men that 1-year testosterone treatment was associated with a greater increase of coronary artery noncalcified plaque volume as compared with the placebo group. TEAAM found among older men with low or low-normal testosterone levels, after 3 years' treatment, that no significance difference in either common carotid artery intima–media thickness or coronary artery calcium changes was observed in the testosterone treatment group versus placebo group.

Though considered as the gold standard for causal inference, due to the highly restrictive inclusion and exclusion criteria, findings from RCTs cannot be easily generalized to the real-world scenarios. In addition, with a relatively shorter follow-up period and small–moderate sample sizes, these RCTs might be underpowered to detect the true effect of testosterone therapy on cardiovascular risk. This was also mentioned in Gagliano-Jucá and Basaria's recent review study on the evidence from epidemiologic studies regarding the cardiovascular safety of testosterone therapy.[35] They believe no trials of testosterone replacement therapy published to date were designed or adequately powered to assess cardiovascular events.

Table 4. All-Cause Mortality, by Treatment Group

	Death	Total participants	Total person month	Mortality rate*
Before matching				
Treatment	8	325	29,634	0.00003
Control	35	277	27,432	0.00128
After matching				
Treatment	5	232	18,666	0.00027
Control	30	212	20,874	0.00144

*Mortality rate difference between the treatment and control group is statistically significant different from 0 ($p < 0.0001$, Fisher's exact test).

A large RCT (a planned sample of ~6000 men, with 5-year treatment duration) that is currently recruiting will be powered to evaluate the effect of testosterone therapy on the incidence of major adverse cardiovascular events and efficacy measures in hypogonadal men (TRAVERSE study, NCT03518034). However, it still takes time to collect essential data before any analysis. Until then, well-designed observational studies with a sufficient sample size and a longer follow-up period may be able to provide convincing evidence in a more naturalistic setting. A multi-national, prospective study ($n = 999$) that used real-world data from the Registry of Hypogonadism in Men study assessed cardiovascular safety of testosterone therapy.[36] The authors found no increased cardiovascular risk in the treatment group, which is in line with our study findings.

Our study is a prospective cohort study with a relatively large sample size, long follow-up duration, and wide age range. All participants were hypogonadal and, therefore, had indication for testosterone treatment at the time of study. We used the Framingham Global CVD Risk Score, which well predicts the risk of future cardiovascular events.[3,37] As compared with the older versions of Framingham Risk Score,[38,39] this global risk score was derived based on a larger number of events, incorporated multiple risk factors as continuous variables instead of categorical variables, and replaced the disease-specific algorithms with a single general CVD prediction tool, which may increase the prediction precision as well as simplify risk prediction in office-based practices.[3]

In this study, we observed a protective effect of treatment on cardiovascular events, which are consistent with previous observational studies that used Framingham study-based Risk Score as the outcome variable. Lee et al. found a significant negative correlation between total testosterone level and the Framingham Risk Score among 308 patients with sexual dysfunction.[40] Chock and colleagues identified that 1479 veterans had previous total plasma testosterone checked in 2008 and reported a negative association between both total testosterone and free testosterone levels and the Framingham Risk Score.[41] We used repeated measurements of testosterone level and, therefore, were able to examine the effect of treatment on the longitudinal changes of the risk scores over time.

However, limitations of this study should be noted. First, though we have controlled for multiple covariates unevenly distributed in the two treatment groups due to the nature of observational study, there is always a confounding issue. Nevertheless, the effect of residual confounding would be minimal as we adjusted for major confounders in the model.

Second, the potential association between testosterone and cardiovascular risk may be curvilinear,[42] and treatment effect may only work when the individual's testosterone is supplemented and maintained at normal level.[14,21,42,43] We did not differentiate the treatment effects in this study. Besides, our results can only be related to this type of testosterone therapy, given the various treatment patterns available. Future studies may take this into account and compare the treatment effect difference when testosterone has not yet been elevated to normal level, in the normal level, and above normal level, and also consider the effect of other testosterone treatment methods.

Third, the Framingham Risk Score may overestimate cardiovascular risk in the European population.[4] Future studies comparing prediction abilities of different tools among populations with diverse makeup are needed.

Lastly, though low testosterone is a risk factor for CVD because it contributes to abnormal lipid metabolism and is physiologically plausible, it may be also reasonable to suggest that testosterone is a consequence of abnormal lipid metabolism. Low testosterone leads to excess fat accumulation, and overweight and obesity in turn worsen hypogonadism, similar to a vicious cycle.[44] However, the focus of this study is not to find out which comes first. We expected clinicians to be informed of this potential association and break the vicious cycle to prevent future cardiovascular events from happening.

Conclusions

In this longitudinal study, we found that low testosterone level was associated with impaired lipid and glucose profile and higher Framingham Global CVD Risk Score among hypogonadal men. Long-term testosterone therapy may improve lipid and glucose profile and reduce Framingham Global CVD Risk Score. Clinicians should be informed of this association when assessing the male patient's cardiovascular risk and make sure timely treatment if needed.

Authors' Contributions

X.Z.: conceptualization, visualization, writing—original draft preparation, writing—reviewing and editing. K.H.: data curation, methodology, software, formal analysis visualization. F.S.: writing—reviewing and editing. K.S.H.: writing—reviewing and editing. A.H.: writing—reviewing and editing. X.X.: resources, supervision, conceptualization, visualization, writing—reviewing and editing, project administration.

Author Disclosure Statement

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Abbreviations Used

BMI = body mass index
CI = confidence interval
CVD = cardiovascular disease
HbA1c = hemoglobin A1c
HDL = high-density lipoprotein
LDL = low-density lipoprotein
PSA = prostate specific antigen
SE = standard error