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ORIGINAL RESEARCH

Cardiovascular Disease, Hypogonadism and Erectile Dysfunction: Early Detection, Prevention and the Positive Effects of Long-Term Testosterone Treatment: Prospective Observational, Real-Life Data

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Purpose: Erectile dysfunction (ED) is associated with testosterone deficiency and is a symptom of functional hypogonadism. A correlation between ED and cardiovascular disease (CVD) has been recognized, and ED has been proposed as an early marker of CVD. However, the relationship between ED and CVD risk in hypogonadism requires clarification and whether testosterone therapy (TTh) can be a beneficial treatment strategy, but long-term data are limited. This study investigates long-term TTh in men with hypogonadism and ED with a history of CVD.

Methods: Seventy-seven patients with a history of CVD and diagnosed with functional hypogonadism and erectile dysfunction (erectile function domain score <21 on the International Index of Erectile Function questionnaire (IIEF questions 1–5)) were enrolled and TTh effects on anthropometric and metabolic parameters investigated for a maximum duration of 12 years. All men received long-acting injections of testosterone undecanoate at 3-monthly intervals. Eight-year data were analysed. Data collection registry started in November 2004 till January 2015.

Results: In hypogonadal men receiving TTh, IIEF increased by 5.4 ($p<0.001$). Total weight loss was 23.6 ± 0.6 kg after 8 years. HbA1c had declined by an average of 2.0% ($P<0.0001$). Total cholesterol levels significantly declined following TTh after only 1 year ($P<0.0001$), and HDL increased from 1.6±0.5 at baseline to 2±0.5 mmol/L following 8 years of TTh ($P<0.0001$). SBP decreased from 164±14 at baseline to 133±9 mmHg, signifying a reduction of 33±1 mmHg ($P<0.0001$).

Conclusion: In hypogonadal men with a history of CVD, TTh improves and preserves erectile function over prolonged periods with concurrent sustained improvements in cardiometabolic risk factors. Measuring ED and testosterone status may serve as an important male health indicator predicting subsequent CVD-related events and mortality and TTh may be an effective add-on treatment in secondary prevention of cardiovascular events in hypogonadal men with a history of CVD.

Keywords: functional hypogonadism, testosterone therapy, erectile function, cardiovascular disease

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Introduction

Functional hypogonadism is a common medical condition affecting men, characterized by serum testosterone levels of 12.1 nmol/L (<350 ng/dL) and at least one clinical symptom including sexual dysfunction (difficulty achieving organism,

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decrease in libido, erectile dysfunction, reduced physiologic erections, absent penile sensation, and decreased ejaculate), reduced stamina, changes in cholesterol levels, irritability, depressed mood, difficulty concentrating, anemia, osteoporosis, and hot flushes.[1,2] Ageing males experience a progressive decline in serum testosterone levels leading to increased prevalence of testosterone deficiency and/or hypogonadism.[3] Testosterone deficiency is highly prevalent in men with metabolic syndrome (MetS), type 2 diabetes (T2D) and established cardiovascular disease CVD, which also increases with age.[3] A negative correlation between testosterone and cardiovascular outcomes has been established in epidemiological studies.[4] While these associations do not imply causality, the ablation of testosterone through androgen deprivation therapy (ADT) for the treatment of prostate cancer increases the risk of cardiovascular events, including myocardial infarction (MI), stroke and overall cardiovascular mortality[5] while increasing ED.[6]

ED is considered a vascular impairment that shares many risk factors with CVD, and has been proposed as an early marker of symptomatic CVD.[7] T2D is a CVD risk factor and severity of ED in men with diabetes correlates with glycaemic control and disease duration.[8] Additionally, there is a positive correlation between ED and silent CAD in men with seemingly well-controlled T2D.[9] This has led to the suggestion that ED may be an early indicator of CVD.[7,10,11] Reports have identified ED preceding CAD in about two-thirds of cases, with the time interval from ED to CAD symptoms being 2–3 years and a cardiovascular event 3–5 years.[12,13] Furthermore, the severity of ED correlates with the severity of the CAD.[14] Therefore, with ED commonly preceding CVD, its diagnosis may offer an opportunistic window for CVD risk mitigation and treating risk factors for ED may improve cardiovascular health.

Importantly, low testosterone levels are considered a predisposing risk for ED and both ED and testosterone deficiency are independently correlated with increased risk of CAD.[16] Low testosterone increases the risk of men with erectile dysfunction dying from cardiovascular events.[17] Furthermore, hypertension, hyperlipidaemia, diabetes, obesity, and depression are common conditions and risk factors for CVD that are also independently associated with ED and low testosterone.[18] Testosterone therapy (TTh), the primary treatment for alleviating symptoms of functional hypogonadism, improves vascular dysfunction, reduces inflammation associated with atherosclerosis and improves clinical surrogate markers of atherosclerosis in hypogonadal men.[19–21] Several RCTs have also demonstrated improvements in CVD risk factors following TTh, including insulin resistance, dyslipidemia, central adiposity and glycaemic control in hypogonadal men with T2D and/or MetS[22–25]; and, despite the complex relationship between testosterone and the cardiovascular system, TTh is considered safe once other comorbidities are addressed.[26] Similarly, a number of studies have detailed the benefits and improvement of erectile function in hypogonadal men with ED following TTh.[27–29] Furthermore, our previous study showed that long-term TTh for up to 12 years improved erectile function, anthropometric and cardiometabolic risk factors with the benefits of TTh being more pronounced in patients with moderate/severe ED at baseline than in patients with no/mild ED at baseline.[30]

The role of low testosterone and ED as indicators of CVD still, however, remains unclear as long-term data are lacking. Whether treating functional hypogonadism with long-term TTh improves ED as an indicator of vascular health and subsequently improves CVD risk is not known. Testosterone administration is, however, indicated in the treatment of ED in hypogonadal males[30] and such interventional studies afford an opportunity to investigate the potential therapeutic benefits of TTh on ED and CVD (including cardiovascular risk factors such as MetS and T2D). The aim of this study is to investigate the long-term effectiveness of TTh on improving erectile function as an indicator of cardiometabolic/vascular health in men with functional hypogonadism and a history of CVD, and demonstrating our results as a continuation work of previously published paper,[29,56] in which long TTh treatment may decrease the risk of CVD by improving the cardiometabolic parameters in hypogonadal men.

Patients and Methods

Patients

This study represents two prospective, cumulative observational registry studies of 622 hypogonadal men presenting to two urological centers at the Institute of Urology and Andrology, Segeberger Kliniken, Norderstedt-Hamburg, Germany, and Men's Health Department, Hamad Medical Corporation, Doha, Qatar. Study participants were diagnosed with functional hypogonadism by fulfilling the criteria of having total testosterone <12.1 nmol/L (mean 9.78 ± 1.56 nmol/L) in the presence of hypogonadal symptoms

measured by the Aging Males' Symptoms scale (AMS)) and presenting with ED, having an IIEF-EF of <21 (maximum score: 30). Seventy-seven men with a history of CVD (12.4% of the whole patient cohort), indicated by a previous diagnosis of coronary artery disease (CAD) (n=48) and/or myocardial infarction (MI) (n=40) and/or stroke (n=7), were identified and included in the analysis. Forty-one patients (53%) had T2D (Figure 1). Additionally, 72 patients (94%) were on anti-hypertensives, 58 (75%) on statins, and 37 (48%) on antidiabetic medications. Patients received continuous testosterone undecanoate (TU) injections (Nebido®; Bayer AG, Leverkusen, Germany) in 3-monthly intervals, following an initial interval of 6 weeks, for up to 8 years. Mean age at baseline of the 77 patients with a history of CVD was 60.65 ± 4.98 years and mean follow-up time was 7.29 ± 1.20 years. Exclusion criteria for TU administration included previous treatment with androgens, prostate cancer, breast cancer, recent angina, or severe untreated sleep apnea. Data collection registry started in November 2004 till January 2015. Ethical considerations were conducted in accordance with declaration of Helsinki, Institutional Review Board (IRB) approval were given from the ethics committee in the German medical association (Ärztekammer) (EK/CH/AU/1/6/2015) for observational studies in patients receiving standard treatment were followed. After receiving an explanation regarding the nature and the purpose of the study, all subjects provided written consent to be included in the registry and have their data analyzed.

Assessment and Follow-Up

Assessments and measurements were taken at each or every second urology visit (between two and four times per year) and the annual average was calculated for each parameter. Erectile function was evaluated by the erectile function domain of the International Index of Erectile Function (IIEF-EF).[31] IIEF is a validated, multidimensional, 15-item self-administered questionnaire commonly employed to assess erectile function and therapeutic efficacy thereof.[32] Erectile function is specifically addressed by six questions from the "erectile function domain" of the questionnaire. Patients' height and weight were recorded and body mass index (BMI) was calculated (BMI = weight (kg)/height^2 (m^2)). Waist circumference (WC) was measured midway between the iliac crest and the costal margin. Systolic blood pressure (SBP), diastolic blood pressure (DPB) and pulse pressure (SBP-DPB) were also measured. Laboratory tests included glycated hemoglobin (HbA_{1c}) measured by high performance liquid chromatography (HPLC), and serum lipid profile including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs) and non-HDL-C measured enzymatically with Alinity c-Module (Abbott).

Statistical Analysis

Statistical values were reported at each time point such as mean, median, standard deviation (SD), range, and sample size. Linear mixed-effects model was used in change of the outcome scores across the study period. To indicate follow-up

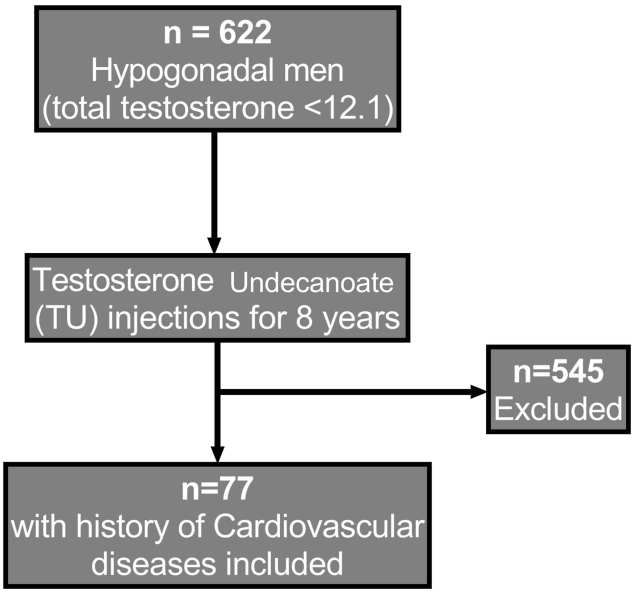

Figure 1 Flow chart for patient's selection.

sessions, time was included as a fixed effect in the model. For the intercept, a random effect was included in the model. Computing the differences in least square means at baseline versus the score at each follow-up visit was used to determine the estimation and test of change in scores.

Results

Effects of Long-Term TTh on Erectile Function

Over the course of TTh, a significant and sustained improvement in erectile function domain score occurred: 19.6±6.34 at baseline, 21.4±5.36 after 1 year, 22.8±4.97 after 2 years, 23.8±4.52 after 3 years, 24.3±4.34 after 4 years, 24.4±4.53 after 5 years, 24.4±4.57 after 6 years, 24.2±4.76 after 7 years and 24.5±4.4 after 8 years (Figure 2). By the end of the follow-up period, the erectile function domain score had improved by 5.4 (P<0.0001) after model adjustment.

Effects of Long-Term TTh on Weight Loss, WC, and BMI

Weight declined progressively from year to year, reducing from 114.5 ± 13.41 to 90.42 ± 8.77 after 8 years of continuous TTh in 77 hypogonadal men (Figure 3A) (P<0.0001) and significant weight loss (WL) totalled 23.6 ± 0.6 kg (19.62 ± 5.71%) after 8 years. The percentage of change in weight was progressive and increased with continuous treatment (model adjusted 2.6% after 1 year, 7.1% after 2 years, 10.4% after 3 years, 13.2% after 4 years, 15.4% after 5 years, 17.4% after 6 years, 19.0% after 7 years, and 20.2% after 8 years) (Figure 3B). WL was complemented by a significant gradual decrease in WC. WC reduction in response to TTh was significant from year to year decreasing from 111.8±8.2 at baseline to 99.2 ± 6.5 cm after 8 years of TTh (Figure 3C). WC reduction totalled to 12.5 ± 0.4 cm at the end of the 8-year follow-up period (model adjusted 1.7% after 1 year, 4.4% after 2 years, 6.3% after 3 years, 7.7% after 4 years, 8.8% after 5 years, 9.6% after 6 years, 10.4% after 7 years, and 11.1% after 8 years). BMI also reduced considerably over the entire follow-up period with a mean reduction of 8 kg/m^2 (Figure 3D).

Effects of Long-Term TTh on CVD Risk Factors

Effects on HbA_{1c}

HbA_{1c} levels were significantly reduced year to year following TTh: 7.6% at baseline, 7.2% after 1 year, 6.8%

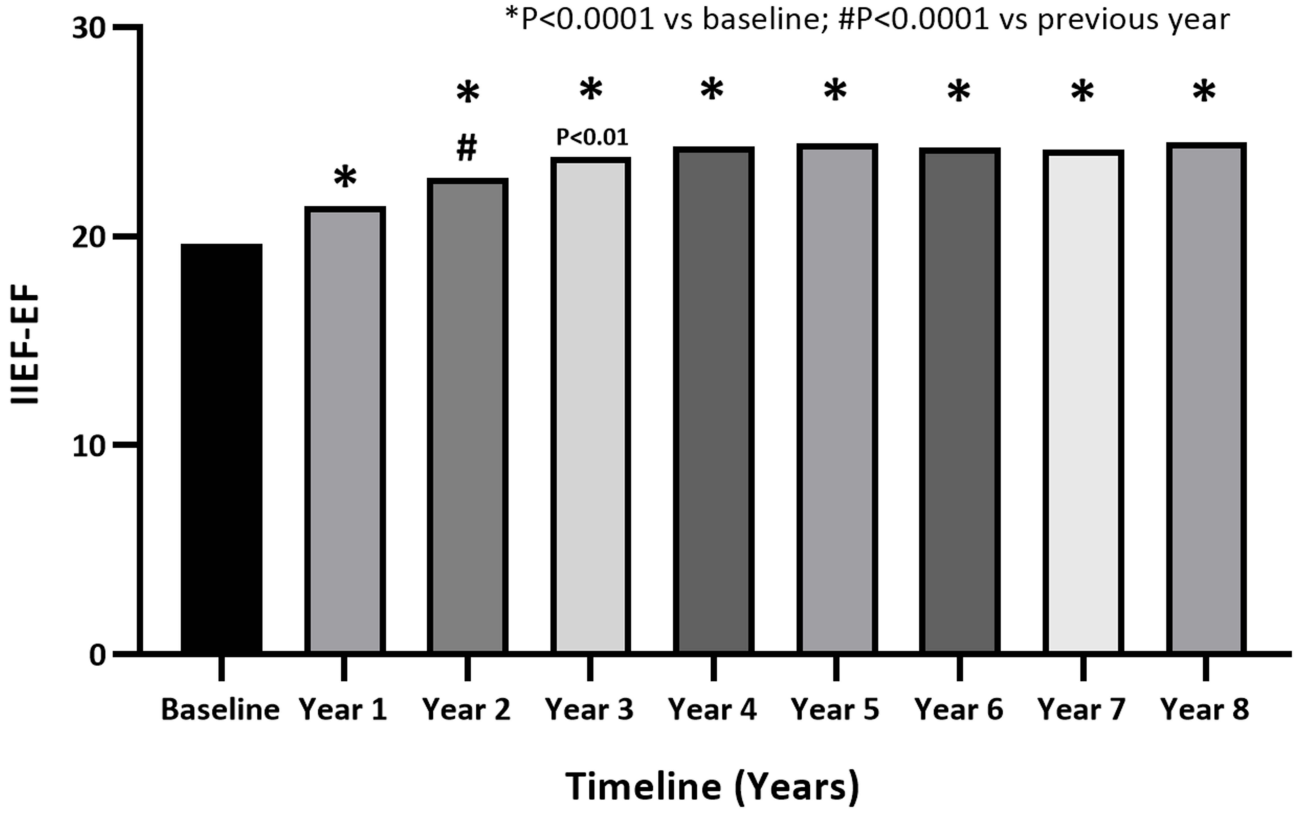

Figure 2 International index of erectile function – erectile function domain (IIEF-EF) in 77 hypogonadal men with a CVD history receiving continuous treatment with testosterone undecanoate. Data are shown as mean. *p<0.0001 vs baseline. #p<0.0001 vs previous year.

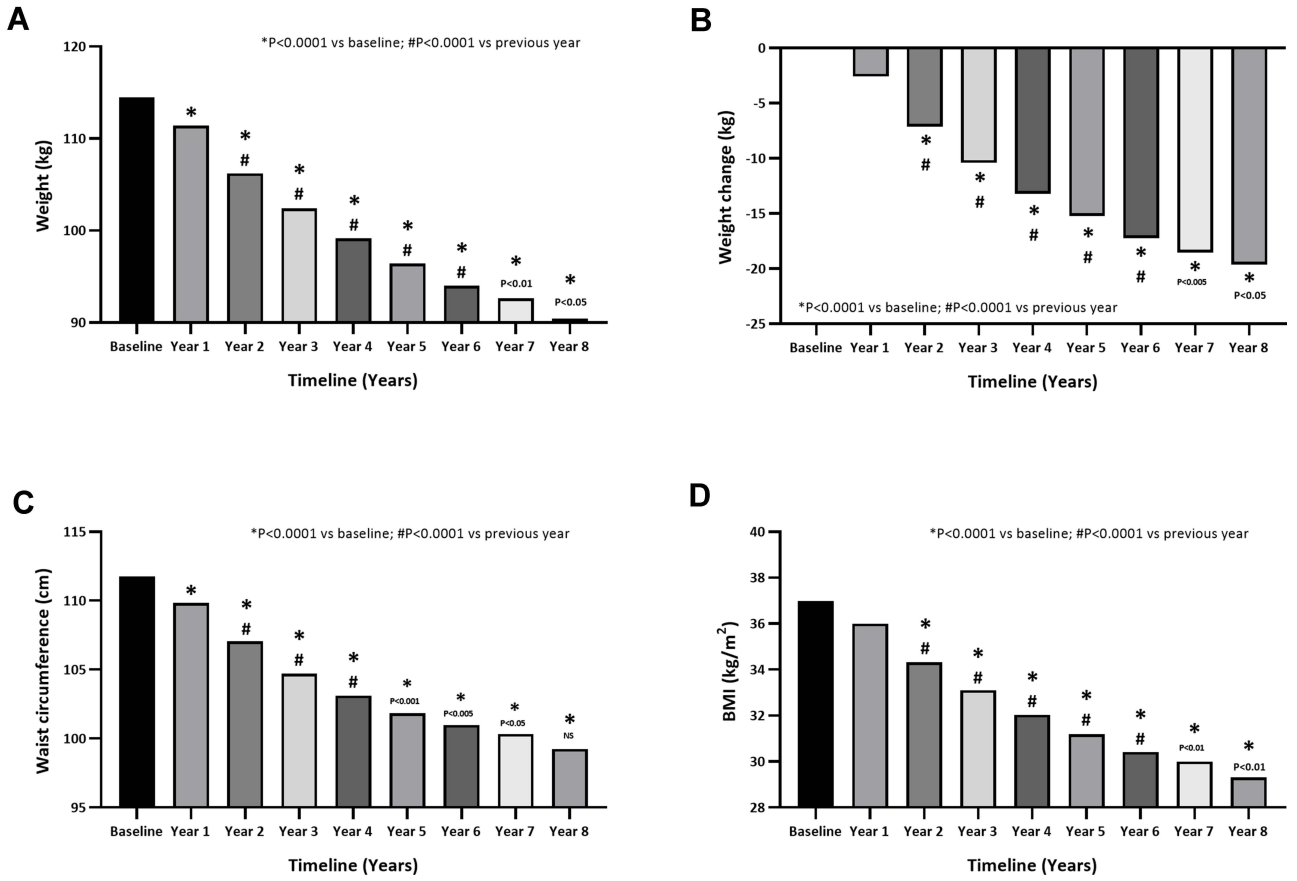

Figure 3 Anthropometric parameters in hypogonadal men with a history of cardiovascular disease receiving long-term testosterone therapy.
Notes: (**A**) Body weight (kg), (**B**) weight loss (%), (**C**) waist circumference (cm), and (**D**) BMI (kg/m^2). Data are shown as mean. *p<0.0001 vs baseline. #p<0.0001 vs previousyear.
Abbreviation: BMI, body mass index.

after 2 years, 6.6% after 3 years, 6.4% after 4 years, 6.2% after 5 years, 6.0% after 6 years, 5.9% after 7 years, and 5.7% after 8 years (Figure 4). HbA_{1c} had declined by an average of 2.0% (P<0.0001) at the end of the follow-up period. The TGs:HDL-C ratio was used as a surrogate marker of insulin resistance and decreased from 5.4±2 to 2.5±0.6 (P<0.0001).

Effects on Lipid Profiles

TC levels significantly declined following TTh after only 1 year (P<0.0001) and continued to gradually decline over the 8-year follow-up period (Figure 5A). TC decreased from 7.8±0.9 mmol/L at baseline to 4.8±0.2 mmol/L after 8 years (P<0.0001). Similarly, following 8 years of TTh, LDL-C was reduced from 4.7±0.9 to 3.0±0.7 mmol/L (Figure 5B), and TGs from 3.4±0.7 to 2.1±0.1 mmol/L (Figure 5C) (P<0.0001). Furthermore, HDL increased from 1.6±0.5 at baseline to 2±0.5 mmol/L following 8 years of TTh (P<0.0001) (Figure 6D). The TC:HDL ratio declined from 5.5±2.0 at baseline to 2.6±0.7 at 8 years (P<0.0001). Non-HDL cholesterol decreased from 6.2±0.8 at baseline to 2.8±0.5 mmol/L at 8 years) (P<0.0001).

Effects on SBP and DBP

Long-term TTh in hypogonadal patients with a history of CVD resulted in marked and significant reduction in blood pressure. SBP decreased from 164±14 at baseline to 133±9 mmHg following 8 years of TTh, signifying a reduction of 33±1 mmHg (P<0.0001) (Figure 6A). The decrease in SBP was gradual but significant over the first 6 years compared to the previous year and gradually declined up to the end of the 8-year follow-up period. Similarly, 8 years of TTh reduced DBP by 24±1 mmHg from 99±11 mmHg at baseline to 77±5 mmHg (P<0.0001) (Figure 6B). Again, a significant decrease of DBP occurred over the first 6 years of treatment compared to the previous year and then remained low for the remainder of the 8-year follow-up period.

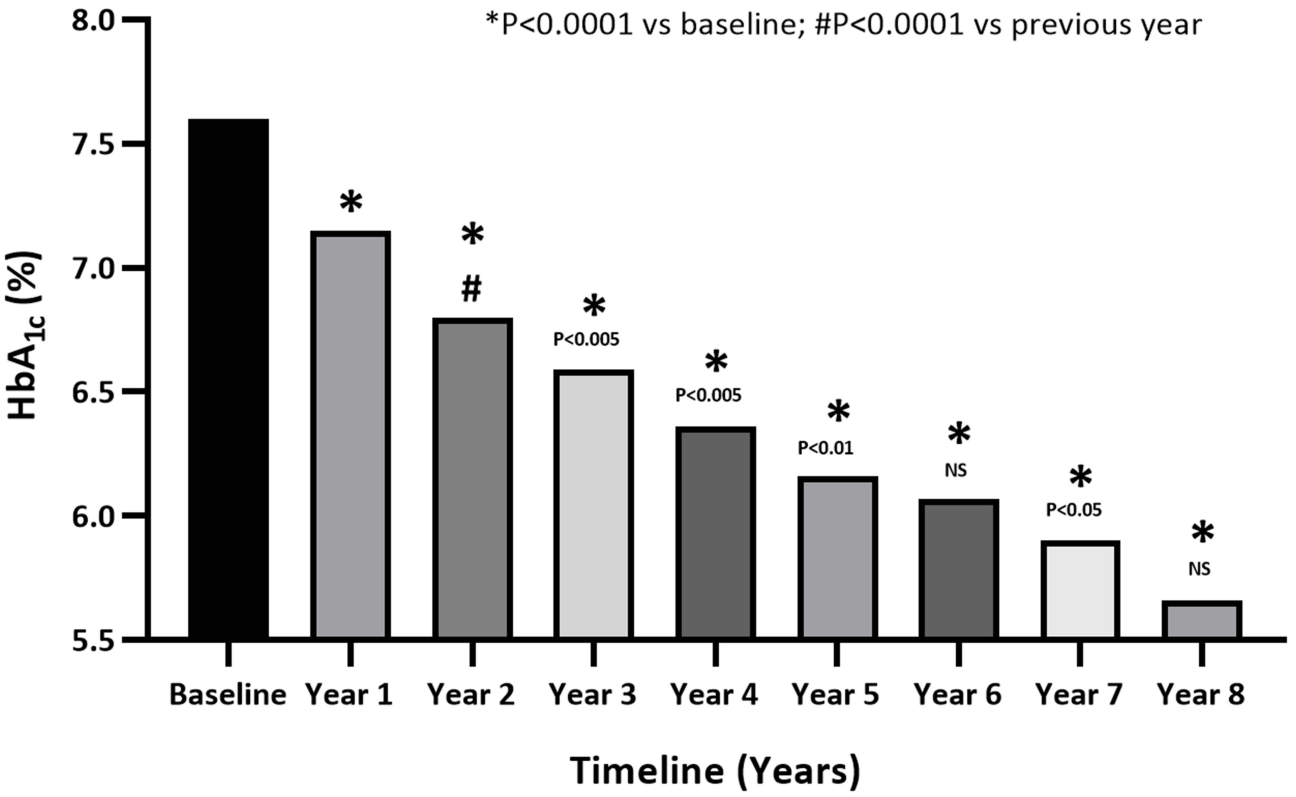

Figure 4 HbA_{1c} (%) in hypogonadal men with a history of cardiovascular disease receiving long-term testosterone therapy.
Notes: Data are shown as mean. *p<0.0001 vs baseline. #p<0.0001 vs previousyear.
Abbreviation: HbA_{1c}, glycated hemoglobin.

Effects on Pulse Pressure

Long-term TTh resulted significant reduction in pulse pressure from 65±6 to 57±8 in hypogonadal patients with a history of CVD. Pulse pressure was gradually and significantly reduced over the course of treatment compared to baseline with a mean change of 9±1 at the end of the follow-up period. Pulse pressure finally dropped to within the normal range after 5 years of TTh (Figure 6C).

Safety and Compliance

There were no major adverse CV events recorded for any patient. No patient had a urological event (prostate cancer or voiding dysfunction). No patient missed a single TU injection. No patient dropped out.

Discussion

This observational registry assessing 77 hypogonadal men with a history of CVD on continuous TTh for up to 8 years demonstrated significant and progressive improvements in IIEF sexual function scores following long-term TU administration accompanied by decreased cardiovascular events compared to non-treated age and health status–matched controls. Furthermore, a gradual yet significant reduction in blood pressure following TTh was maintained over the entire 8-year treatment period. Importantly, 94% of the patients included in this study were on anti-hypertensives to control their blood pressure, although with limited success as baseline blood pressure was elevated prior to TTh. Pulse pressure, indicated as a surrogate marker for arterial stiffness, was also significantly reduced following TTh demonstrating further vascular improvements.

The benefits of TTh have been observed in men with congestive heart failure and cardiac ischemia/angina, including a reduction in carotid intima-media thickness (CIMT), a clinical surrogate marker of atherosclerosis.[33] In the present study, we report that there were no CV deaths or major adverse CV events (MACE) recorded for any patient receiving TTh. The lack of MACE in patients with moderate/severe ED is particularly remarkable considering their worse baseline health status and higher mortality risk. Studies have previously shown that mortality in men with low testosterone levels was reduced following

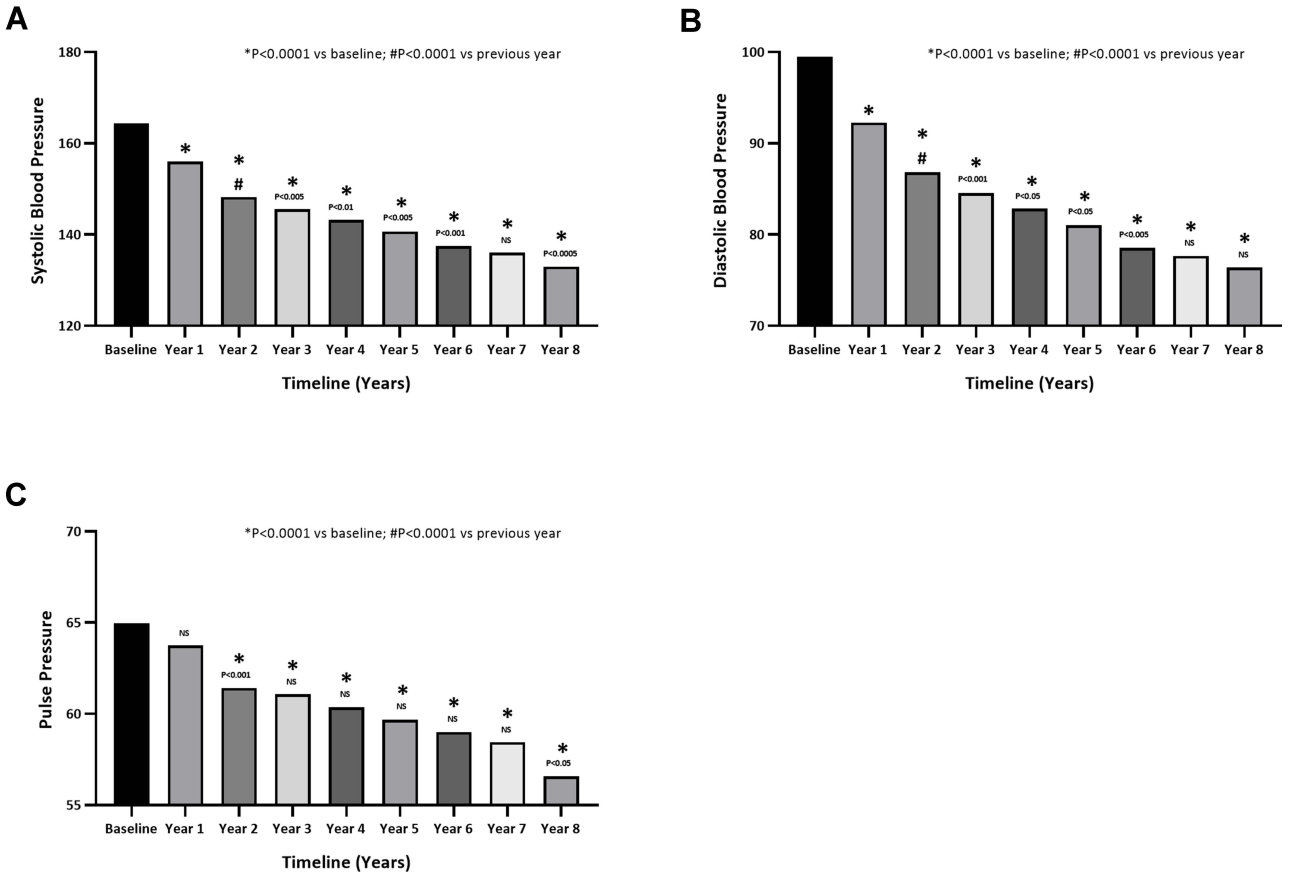

Figure 5 (**A**) Systolic and (**B**) diastolic blood pressure (mmHg) in hypogonadal men with a history of cardiovascular disease receiving long-term testosterone therapy. (**C**) Pulse pressure in hypogonadal men with a history of cardiovascular disease receiving long-term testosterone therapy.
Notes: (**A**) Systolic blood pressure and (**B**) diastolic blood pressure. Data are shown as mean. *p<0.0001 vs baseline. #p<0.0001 vs previousyear.
Abbreviation: NS, nonsignificant.

TTh.[34,35] Shores et al[34] observed that men receiving TTh had a lower mortality rate (10.3%) compared with untreated hypogonadal men (20.7%). Muraleedharan et al[35] also observed that TTh in hypogonadal men with T2D reduced mortality to 8.4% compared with 19.2% in untreated men. Most importantly, following the 8-years of continuous TTh in the present study, we did not observe any increase in CVD risk in this subset of patients.

A negative correlation between testosterone and hypertension has been demonstrated in men.[36] It is suggested that testosterone modulates arterial blood pressure via various mechanisms.[37] Testosterone levels have reported being negatively associated with SBP.[36] In a study of 206 men from the Baltimore Longitudinal Study of Ageing, serum testosterone levels were an independent negative predictor for developing arterial stiffness.[38] This association persisted after adjusting for risk factors such as age, pulse pressure, fasting plasma glucose, BMI and TC, suggesting that hypogonadism contributes to elevated blood pressure and TTh decreases blood pressure.[39,40] In the current study, we report that TTh gradually, yet significantly decreases blood pressure, which was maintained over the 8-year follow-up period. Furthermore, pulse pressure (PP) is an indicator for arterial stiffness, which is related to endothelial dysfunction, and increased PP is related to increase risk of cardiovascular events, hence increase mortality.[41,42] An association between ED and PP was revealed by the present study. In TTh group, a reduction in PP was noticed to be associated with a significant improvement in ED, whereas no improvement and a progressive deterioration was experienced in PP and ED in the other group. The present study therefore supports beneficial effects of TTh on vascular function reported in previous observational studies[43] and placebo-controlled trials[44] whereby a reduction in arterial stiffness was reported following TTh.

The most common cause of ED is an underlying vascular disease caused mainly by atherosclerosis within the

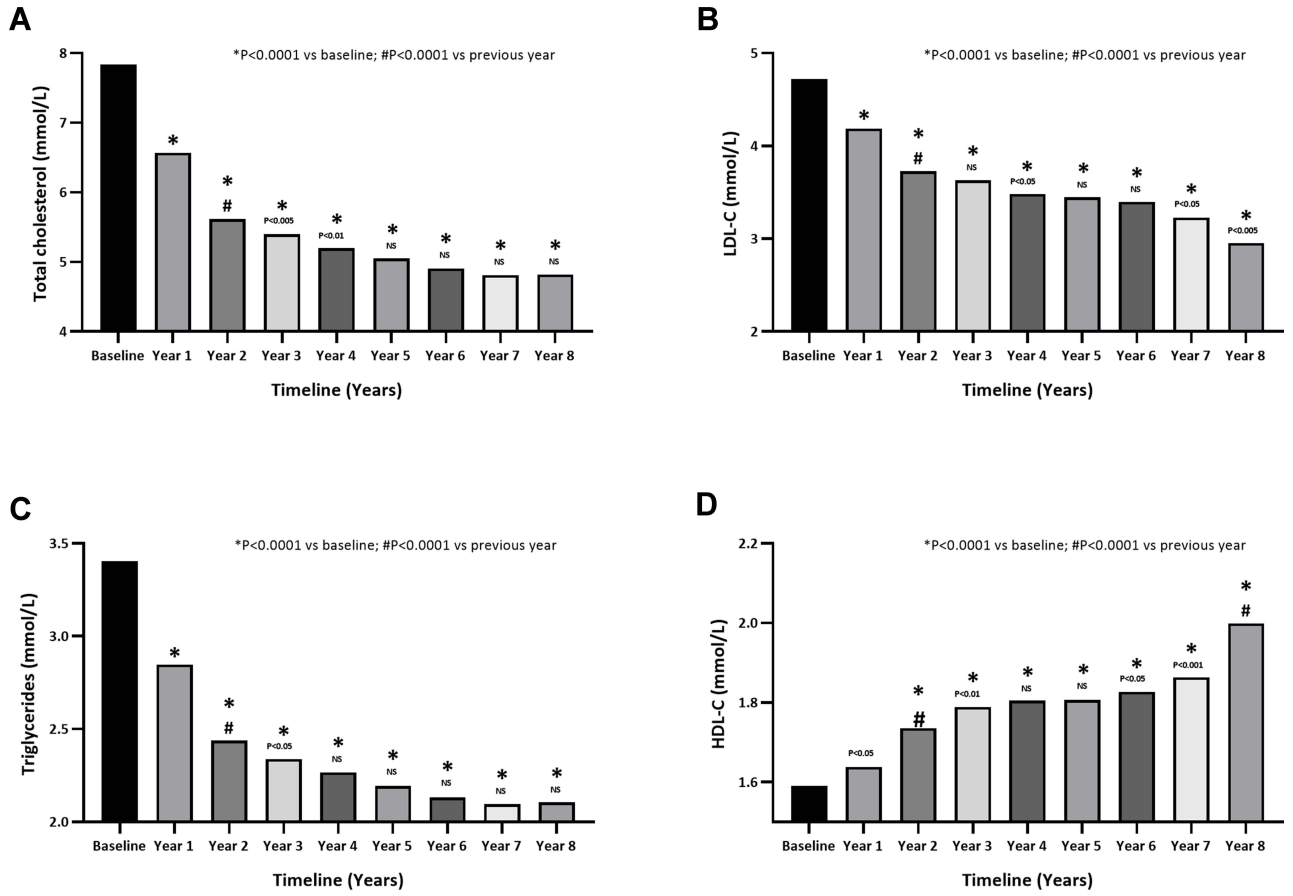

Figure 6 Serum lipids in hypogonadal men with a history of cardiovascular disease receiving long-term testosterone therapy (**A**) total cholesterol, (**B**) LDL-cholesterol, (**C**) triglycerides and (**D**) HDL-cholesterol. **Note:** Data are shown as mean. *p<0.0001 vs baseline. #p<0.0001 vs previous year.
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, nonsignificant.

penile arteries, and the prevalence of ED is higher in patients with CVD.[45] The severity of ED has been reported to directly correlate with the severity of the CAD[14] and suggested as a potential indicator of silent CAD in men with uncomplicated T2D and relatively low CAD risk.[9] Therefore, ED is considered a manifestation of a generalized vascular disease and has been suggested as an indicator for future cardiovascular events. The artery size hypothesis indicates that vascular disease may be comparative in arteries independent of location and vessel size yet the same level of endothelial dysfunction and atherosclerosis may lead to a more significant reduction of blood flow in erectile tissues compared with that in coronary arteries suggesting ED would precede CAD.[11] Several studies show that ED manifests prior to CAD in approximately two-thirds of cases,[12–14,46] with the time interval from ED to CAD symptoms being 2–3 years and ED to a cardiovascular event 3–5 years.[41] Due to the increased risk of CAD among men with functional hypogonadism and ED[16] findings from our previous study[42] and the present study, a role for routinely assessing ED to identify individuals at increased risk of CAD is supported. Indeed, hypogonadism is prevalent in patients with ED, and low testosterone levels are reported in around 23–36% of the patients presenting with ED.[15] Low testosterone levels are considered to be a predisposing risk for ED, and both ED and testosterone deficiency are both independently associated with increased risk of CAD.[16] Therefore, identifying men at risk of CAD via diagnosis of ED and underlying.

Severe ED additionally functions as a prognostic indicator of cardiovascular risk comorbidities in men with functional hypogonadism.[42] Indeed, our previous study suggested that the severity of ED within patients with functional hypogonadism correlated with comorbidities including increased waist circumference, hyperglycemia, hypertriglyceridemia, hyperlipidemia and a history of diabetes mellitus.[47] ED was found to be present in 33% of

men with uncomplicated T2D and silent CAD, compared to the 5% in T2D men without myocardial ischemia suggesting ED as an indicator of CAD in T2D men.[9] Furthermore, obesity and increased adiposity are common clinical features of functional hypogonadism frequently associated with ED.[48] In the current study, TTh reduced weight, WC and mean BMI (which was within the obese range at baseline) in a gradual yet sustained manner. Additionally, despite being treated with statins to control their dyslipidemia, most patients exhibited elevated serum lipid profiles at baseline which were significantly improved (reduced TC, LDL-C, TGs and increased HDL-C) following long-term TTh. It worth to mention, that 25% of the patients did not undergone statin treatment, at which they are more susceptible to CAD. HbA_{1c} was also improved by TTh. The shared aetiology between metabolic dysfunction, vascular dysfunction and ED suggests that the improvements in ED and CVD following TTh in this study may be due to the overall improvement in metabolic parameters.

TTh to treat functional hypogonadism in the present investigation and other studies has resulted in improvement of components of MetS and T2D that are considered CVD risk factors, thus improving cardiometabolic function[49] and reducing the risk of CVD.[50,51] It is noted that continuous treatment with TTh is required to maintain the long-term benefits of testosterone.[52,53] These well-recognized benefits of TTh on metabolic parameters also extend to the improvement of erectile function and quality of life.[51,54] Therefore, the IIEF-5 questionnaire may be regarded not only as a clinical indicator to screen for ED but also as a potential diagnostic tool to assess the global CAD risk profile of men with functional hypogonadism allowing early intervention with TTh to improve ED and CVD risk. However, in a cohort of men with erectile dysfunction it was suggested that hypogonadism-associated CV risk was dependent upon the characteristics of subjects, being more evident in normal weight than in obese patients.[55] Conversely, in patients with a previous history of CV events, hypogonadism was associated with a reduced risk of new CV events, even after adjusting for confounders, whereas no relationship was observed in subjects free of previous CV events.[56]

This observational study is not without inherent limitations. As this was not a randomized placebo-controlled trial, it does not allow direct comparison of TTh versus non-treatment, limiting the scope of interpretation. However, we consider that the cardiovascular health benefits of TTh are time dependent, particularly when related to metabolic improvements, and therefore this real-world evidence study provides valuable data about the true clinical significance of TTh, which cannot be derived from RCTs due to their short-term nature. Long-term treatment is also more reflective of the therapeutic application of TTh for the responding patient, as we have previously demonstrated that treatment interruption can lead to regression of clinical benefits including parameters of cardiovascular health.[52,57] Moreover, during long-term clinical trials, there are important ethical considerations of not treating hypogonadal men who presented at our clinic wishing to undergo TTh. Reported cardiovascular disease was the clinical outcome indicating vascular health, but assessing subclinical measures, such as carotid intima media thickness (CIMT) or vascular composition via CT scan, may give a more detailed analysis of disease progression, remission or regression.

Conclusions

The triad of aetiological disparities of low T, ED and CVD, correlate and interact to indicate an underlying negative health status in men and suggests that both ED and testosterone levels could have a predictive capacity for worse cardiovascular outcomes. This study indicates that ED may be an early predictor of CVD and low testosterone may be an early indicator of vascular dysfunction associated with ED and CVD, particularly in the presence of cardiometabolic risk factors. Due to the increased risk of CVD among men with functional hypogonadism,[15] findings from our previous study[42] and the present study, we support a role for routinely assessing ED to identify individuals at increased risk of CVD. Furthermore, a diagnosis of ED should prompt a clinical investigation of serum testosterone levels and consequently correlated CVD comorbidities, and TTh considered. Correcting testosterone levels in men via TTh may therefore confer a vascular benefit that leads to improvements in both CVD and ED. Indeed, the beneficial effect of long-term TTh on CVD-related major adverse events was clearly confirmed in the present study with no MI and no stroke reported in the TTh group. We demonstrate that long-term TTh for up to 8 years in men with functional hypogonadism and a history of CVD significantly improves erectile function and protects against CVD events. The present study highlights the importance for patients to remain on TTh consistently for an extended period of time compared to published randomized controlled studies in order to achieve the maximum benefits of TTh in clinical practice. Therefore, ED and testosterone status warrant thorough clinical assessment to identify "at-risk" males for the consideration of long-term TTh with the goal of correcting the

biochemical hormonal defect to improve both sexual function and cardiovascular health.

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Disclosure

Prof. Dr Aksam Yassin reports grants from Bayer AG, during the conduct of the study; personal fees from honoraria, generally, outside the submitted work. Prof. Dr Farid Saad reports personal fees from Bayer AG, during the conduct of the study and outside the submitted work; and owns shares of Bayer AG, Berlin, Germany. The authors report no other potential conflicts of interest for this work.

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