Effects of Testosterone Replacement on Electrocardiographic Parameters in Men: Findings From Two Randomized Trials

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Context: Endogenous testosterone levels have been negatively associated with QTc interval in small case series; the effects of testosterone therapy on electrocardiographic parameters have not been evaluated in randomized trials.

Objective: To evaluate the effects of testosterone replacement on corrected QT interval (QTcF) in two randomized controlled trials.

Participants: Men with pre- and postrandomization electrocardiograms (ECGs) from the Testosterone and Pain (TAP) and the Testosterone Effects on Atherosclerosis in Aging Men (TEAAM) Trials.

Interventions: Participants were randomized to either placebo or testosterone gel for 14 weeks (TAP) or 36 months (TEAAM). ECGs were performed at baseline and at the end of interventions in both trials; in the TEAAM trial ECGs were also obtained at 12 and 24 months.

Outcomes: Difference in change in the QTcF between testosterone and placebo groups was assessed in each trial. Association of changes in testosterone levels with changes in QTcF was analyzed in men assigned to the testosterone group of each trial.

Results: Mean total testosterone levels increased in the testosterone group of both trials. In the TAP trial, there was a nonsignificant reduction in mean QTcF in the testosterone group compared with placebo (effect size = −4.72 ms; $P = 0.228$) and the changes in QTcF were negatively associated to changes in circulating testosterone ($P = 0.036$). In the TEAAM trial, testosterone attenuated the age-related increase in QTcF seen in the placebo group (effect size= −6.30 ms; $P < 0.001$).

Conclusion: Testosterone replacement attenuated the age-related increase in QTcF duration in men. The clinical implications of these findings require further investigation. (***J Clin Endocrinol Metab*** **102: 1478–1485, 2017)**

The rising number of testosterone prescriptions (1) in parallel with some, but not all, studies reporting an increased incidence of cardiovascular events associated with testosterone treatment (2–6) has raised concerns about the cardiovascular safety of testosterone replacement. However, the mechanisms by which testosterone increases cardiovascular events remain unclear. Some studies that have reported increased cardiovascular

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Abbreviations: BBB, bundle branch block; CI, confidence interval; QTc, corrected QT interval; ECG, electrocardiogram; FT, free testosterone; QTcF, Fridericia QT correction formula; TAP, Testosterone and Pain; TEAAM, Testosterone Effects on Atherosclerosis in Aging Men; TT, total testosterone.

events in men on testosterone have shown events occur shortly after initiation of testosterone therapy and the risk decreases soon after its interruption (4, 5). These findings suggest that mechanisms other than atherosclerosis progression might be involved. Indeed, a recent large randomized controlled trial showed that subclinical atherosclerosis progression over 3 years in older men with low or low-normal testosterone was similar in placebo and testosterone arms (7). However, other potential causes for cardiovascular events on testosterone therapy, such as ventricular arrhythmias, have not been investigated.

The ventricular depolarization and repolarization are represented in the electrocardiogram (ECG) by the QRS complex and the T wave, respectively. The QT interval duration corresponds to the time from initial depolarization to the end of repolarization of both right and left ventricles. After correction for heart rate, the corrected QT interval (QTc) has been used as a clinical tool for assessing arrhythmia risk, with prolonged times reflecting an increased risk of ventricular tachyarrhythmias and sudden death (8–10). Indeed, the Food and Drug Administration guidelines that are used to evaluate the arrhythmogenic potential of new drugs are also based on the changes in QTc interval duration as QTc prolongation predisposes an individual to the risk of tachyarrhythmias (especially torsade des pointes) (11).

Several factors are associated with QTc interval duration, including serum electrolytes levels (12), age, sex, and medications (13–15). The QTc interval increases with aging, a demographic that is increasingly being prescribed testosterone therapy (16, 17). Previous population studies have shown that men have shorter QTc compared with women, and this sex difference in QTc duration has been attributed to the higher endogenous testosterone levels in men (18). Indeed, endogenous serum testosterone levels have been negatively correlated with QTc duration in small case series (19–22). However, the effect of testosterone replacement on QTc interval duration in men has not been studied in randomized controlled trials.

Accordingly, we determined the effects of testosterone replacement therapy on QTc interval and other ECG parameters by performing secondary analyses of electrocardiographic data from 2 recent randomized, placebo-controlled trials: The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) Trial, a 3-year randomized controlled trial to evaluate subclinical atherosclerosis progression in older men with low to low-normal testosterone levels (7); and the Testosterone and Pain (TAP) trial, a 14-week trial of testosterone replacement to evaluate pain perception and sexual function in men with opioid-induced androgen deficiency (23). These trials provided the opportunity to evaluate QTc changes over 3 years in older men (TEAAM Trial) and the effects of testosterone replacement in men with opioid-induced androgen deficiency (TAP Trial).

Methods

These secondary analyses used demographic, electrocardiographic, and the relevant laboratory data of men who had participated in the TAP (23) and the TEAAM Trials (7).

Study design and participants

The design, eligibility criteria, and procedures of both trials have been previously published (7, 23). A brief summary of each trial is presented here:

The TAP trial

The TAP Trial was a randomized, placebo-controlled, double-blind, single-center parallel-group trial involving men, 18 to 64 years, with opioid-induced androgen deficiency (total testosterone <350 ng/dL). The primary outcomes of the trial were pain perception and tolerance. Participants were taking at least 20 mg hydrocodone (or equivalent dose of another opioid) daily for at least 4 weeks. Men with a previous history of hypogonadism, use of androgens or other anabolic drugs, any malignancy, prostate-specific antigen level >4 ng/mL, severe lower urinary tract symptoms, myocardial infarction within 3 months before enrollment, unstable angina, uncontrolled congestive heart failure, peripheral vascular disease, uncontrolled hypertension, or oxygen-requiring chronic obstructive pulmonary disease were excluded. The study protocol was approved by the institutional review board of the Boston University Medical Center and the Brigham and Women's Hospital.

Men were randomly assigned to receive 5 g daily of either 1% transdermal testosterone gel or placebo gel. Two weeks after randomization, testosterone levels were measured and daily dose was increased by 2.5 g gel if the mean total testosterone (TT) concentration was <500 ng/dL. The adjusted dose was maintained for the remainder of the 14-week intervention period.

The TEAAM trial

The TEAAM Trial was a randomized, placebo-controlled, double-blind, multicenter parallel-group trial in men, 60 years or older, with TT level between 100 and 400 ng/dL or calculated free testosterone (FT) <50 pg/mL, to determine the effects of testosterone replacement on progression of subclinical atherosclerosis. Men were excluded if they had prostate or breast cancer; a lower urinary tract symptom score >21; prostate-specific antigen >4 ng/mL; untreated major depression; hematocrit >48%; unstable angina; uncontrolled congestive heart failure; myocardial infarction in the past 6 months; body mass index >35 kg/m^2; or diseases of the testes, pituitary, or hypothalamus. Study recruitment took place at 3 medical centers in Boston, Phoenix, and Los Angeles, from September 2004 to February 2009, with the last participant completing the study in May 2012. The study protocol was approved by institutional review boards at the 3 participating institutions and Brigham and Women's Hospital.

Men were randomly assigned to receive 7.5 g daily of either 1% transdermal testosterone gel or placebo gel. Two weeks

Table 1. Baseline Characteristics of Participants in Each Trial

	TAP		TEAAM	
	Placebo	Testosterone	Placebo	Testosterone
	n = 28	*n* = 34	*n* = 85	*n* = 88
Demographics				
Age (y)	50 ± 6	47 ± 9	68 ± 5	67 ± 5
Weight (kg)	106.8 ± 31.7	95.5 ± 19.9	86.4 ± 11.1	85.9 ± 10.9
Height (cm)	177 ± 8	175 ± 6	176 ± 7	174 ± 7
BMI (kg/m^2)	33.6 ± 8.0	31.1 ± 6.1	28.0 ± 2.8	28.3 ± 2.9
Medical history				
Hypertension (%)	53.6	32.4	39.5	48.9
Diabetes (%)	7.1	17.7	18.8	9.1
Obesity (%)	64.3	64.7	29.4	27.3
Hyperlipidemia (%)	46.4	20.6	57.7	61.4
CAD (%)	14.3	0	9.41	15.9
Medications				
Beta-blockers (%)	21.4	5.9	12.9	23.9
Ca^{2+}-channel blockers (%)	28.6	2.9	11.8	10.2
ACE-I/ARA (%)	28.6	23.5	28.2	29.6
Diuretics (%)	32.1	17.7	18.8	20.5
Statins (%)	35.7	20.6	48.2	50.0
ECG				
PR (ms)	161 ± 16	161 ± 20	174 ± 26	181 ± 30
QRS (ms)	94 ± 8	92 ± 11	90 ± 10	90 ± 10 (87)[a]
QT (ms)	400 ± 38	396 ± 41	403 ± 32	398 ± 30
QTcF (ms)	416 ± 26	415 ± 22	399 ± 20	398 ± 20
Blood levels				
Hematocrit (%)	42.3 ± 3.8	43.1 ± 4.5	43.7 ± 3.3	43.9 ± 3.9
Total testosterone (ng/dL)	233 ± 96	216 ± 87	304 ± 66	313 ± 65
Free testosterone (pg/mL)	44 ± 20	44 ± 23	61 ± 17	66 ± 17
SHBG (nmol/L)	37 ± 14	39 ± 32	33 ± 11	31 ± 11
Sodium (mmol/L)	139 ± 3	139 ± 2	140 ± 2	140 ± 3
Potassium (mmol/L)	4.6 ± 0.7	4.6 ± 0.8	4.4 ± 0.4	4.3 ± 0.4
Calcium (mg/dL)	9.6 ± 0.6	9.3 ± 0.3	9.4 ± 0.3	9.3 ± 0.4
Creatinine (mg/dL)	0.98 ± 0.24	0.95 ± 0.15	1.04 ± 0.18	1.03 ± 0.18
Glucose (mg/dL)	113 ± 64	93 ± 19	107 ± 28	102 ± 19
HbA1c (%)	6.2 ± 1.6	5.7 ± 0.5	5.7 ± 0.6	5.6 ± 0.5

Data are expressed as mean ± standard deviation (*n*). No significant between-group differences were present in both the trials for any of the baseline parameters.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARA, angiotensin receptor antagonist; BMI, body mass index; CAD, coronary artery disease; HbA1c, glycated hemoglobin; SHBG, sex hormone-binding globulin.

[a]One participant did not have QRS measurement at baseline.

after randomization, testosterone level was measured and the dose was either increased or decreased by 2.5 g if the mean TT concentration was <400 ng/dL or >900 ng/dL, respectively. The adjusted dose was maintained until the end of treatment, 3 years after the initiation of therapy.

Serum sex steroids

Fasting serum samples were collected in the morning for the measurement of total and free testosterone levels in both trials at baseline and at the end of treatments. Additionally, participants of the TEAAM trial also had testosterone measured at 6 and 18 months. In the TAP trial, total testosterone was measured using a liquid chromatography coupled to tandem mass spectrometry assay performed in a Centers for Disease Control and Prevention–certified laboratory, with a sensitivity of 2 ng/dL (24). In the TEAAM trial, a Bayer Advia Centaur immunoassay (Siemens Health Care Diagnostics, Malvern, PA) was used after extraction of serum with ethyl acetate and hexane, followed by celite chromatography. This assay has a sensitivity of 10 ng/dL and has been validated against LC-MS/MS (25). Sex hormone binding globulin was measured in both trials using an immunofluorometric assay with sensitivity of 2.5 nmol/L (26). Free testosterone was calculated from TT and sex hormone-binding globulin concentrations using a law-of-mass-action equation (27, 28).

Electrocardiogram

Standard 12-lead ECGs were performed using the same machine (GE MAC 800) at a speed of 25 mm/s and amplification of 0.1 mV/mm. The PR, QRS, and QT interval durations were electronically measured by the ECG machine. The QT interval duration was calculated after correcting for heart rate using the Fridericia QT correction formula (QTcF) (29), which has been shown to provide the best prediction of short- and long-term mortality (30). The ECGs were performed at baseline and after 14 weeks of treatment in the TAP trial, and at baseline, 12, 24, and 36 months in the TEAAM trial. Each subject had his

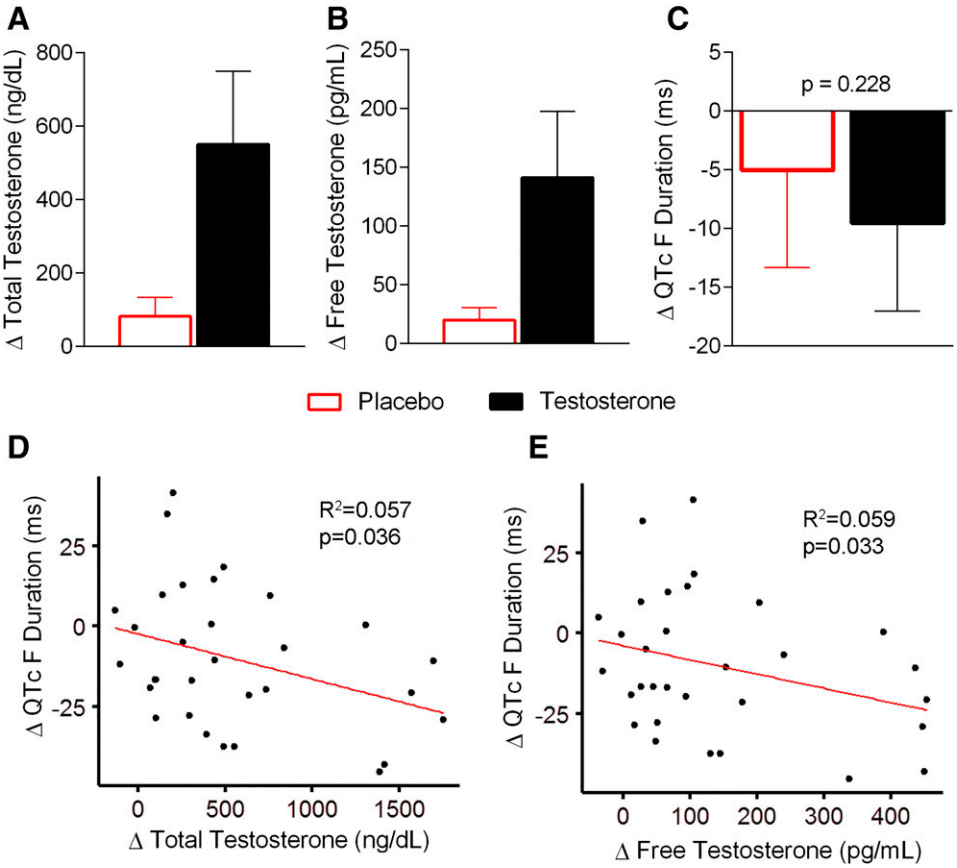

Figure 1. Data for the TAP trial displayed as means and error bars are 95% CI for (A) change from baseline in total testosterone levels; (B) change from baseline in free testosterone levels; and (C) change from baseline in QTcF duration. (D) Linear regression of the association of change in total testosterone levels with changes in QTcF in the testosterone arm of the TAP trial. (E) Linear regression of the association of change in free testosterone levels with changes in QTcF in the testosterone arm of the TAP trial.

pre- and postrandomization ECGs performed on the same machine. The effects of testosterone treatment on PR, QRS, QT, and QTcF duration were analyzed in both trials.

Participants who had complete bundle branch block (BBB) at baseline were excluded from the analyses (31). Participants who developed BBB after randomization had their ECGs with BBB excluded from the analyses. Subjects with a pacemaker or those who did not have any postrandomization ECG results were also excluded.

Statistical analysis

Primary analyses were performed on randomized subjects who had baseline and at least 1 postrandomization ECG examination. Baseline characteristics were reported separately for both clinical trials using means and standard deviations, or proportions for continuous and categorical data, respectively. In the TAP trial, changes from baseline in ECG parameters between groups were compared using analysis of covariance models with treatment effect factor. Estimated mean changes within and between groups and 95% confidence intervals (CI) were provided. In the TEAAM trial, intervention effect was analyzed using mixed-effects linear regression models allowing for within-subject correlation between measurements at each postrandomization visit. The models were adjusted for baseline measurements, and included a site factor as a random effect, and randomization assignment, visit, and visit-by-randomization interaction as fixed effects. Estimated mean changes and corresponding 95% CIs, within and between arms, were calculated as an average of changes from baseline for 3 postrandomization visits. In both trials, the association between the change in testosterone level from baseline and the study outcomes was performed using linear regression models; *R*-squared and the associated *P* values were reported.

All hypotheses were tested using type I error $\alpha = 0.05$. No adjustments were made for multiplicity of outcomes. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC), GraphPad Prism version 6 (GraphPad Software, La Jolla, CA), and R software version 2.15.1.

Results

The TAP trial

Of the 84 subjects randomized in the TAP trial, 65 completed the 14 weeks of intervention. Of those, 62 subjects had both pre- and postrandomization ECGs and satisfied all inclusion criteria. The median age of the participants was 48 years (range 27 to 63 years), and mean body mass index was 32.2 kg/m^2 (range 19.0 to 62.3 kg/m^2). Testosterone and placebo groups had similar baseline characteristics (Table 1).

Randomization to testosterone was associated with a mean increase (95% CI) in TT and FT of 550 (351 to

Table 2. Estimated Changes From Baseline and 95% CIs for ECG Interval Times in the TAP Trial

Variables	Testosterone	Placebo	Difference	*P* Value
PR	1.31 (−4.65, 2.02)	0.23 (−3.39, 3.85)	−1.54 (−6.46, 3.38)	0.534
QRS	0.08 (−1.74, 1.90)	−0.09 (−2.10, 1.91)	0.17 (−2.54, 2.89)	0.900
QT	−15.78 (−24.51, −7.04)	−12.91 (−22.54, 3.28)	−2.86 (−15.87, 10,15)	0.661
QTcF	−9.63 (−14.84, −4.43)	−4.94 (−10.65, 0.82)	−4.72 (−12.47, 3.03)	0.228

Data are expressed as estimated interval time change from baseline in milliseconds (95% CIs). *P* value for treatment effect and estimated changes from baseline are extracted from analysis of covariance model.

750) ng/dL and 141 (85 to 198) pg/mL, respectively [Fig. 1(A) and 1(B)]. There was a small increase in TT and FT in the placebo group. Serum sodium, potassium, and calcium concentrations did not differ between treatment groups during the intervention period (data not shown).

The mean QTcF at baseline in both groups was higher than the average for age-matched men in the population (13), reflecting the known effect of opioids on QTc duration. Mean QTcF trended lower in the testosterone group compared with placebo (−9.63 *versus* −4.94 ms; Fig. 1C; Table 2). However, between-group difference was not statistically significant ($P = 0.228$). In the testosterone group, changes in TT and FT levels were significantly negatively associated with changes in QTcF [Fig. 1(D) and 1(E)].

The changes in PR and QRS interval durations did not differ significantly between the 2 arms (Table 2). No significant association was observed between changes in TT or FT levels and changes in PR or QRS duration (Supplemental Fig. 1).

The TEAAM trial

Of the 308 subjects randomized in the TEAAM trial, 173 had postrandomization ECGs and met eligibility criteria for these secondary analyses. The median age of participants was 66 years (range 60 to 80 years), and mean body mass index was 28.1 kg/m^2 (21.5 to 35.1 kg/m^2). Testosterone and placebo groups had similar baseline characteristics (Table 1).

Testosterone treatment increased TT and FT levels. The mean (95% CI) increase in TT levels from baseline at 6, 18, and 36 months was 213 (164 to 261) ng/dL for TT and 30 (19 to 42) pg/mL for FT. Neither TT nor FT changed significantly in men assigned to the placebo arm [Fig. 2(A) and 2(B)]. Serum sodium, potassium, and calcium concentrations did not differ between treatment groups during the duration of the trial (data not shown).

Mean QTcF increased in the placebo group during the trial (mean change = 9.97; 95% CI = 7.26 to 12.67). In the testosterone group, mean QTcF initially decreased at the 12-month ECG, but returned toward baseline values at the 24- and 36-month evaluations [Fig. 2(C)]. The mixed-effects linear regression model showed a small but significant effect of testosterone treatment *versus* placebo on QT and QTcF duration [effect size (95% CI) −6.30 (−9.29, −3.30), $P \leq 0.001$]. Thus, testosterone therapy attenuated the age-related increase in QTcF. In the testosterone group, there was no association between average change in TT ($P = 0.256$, $R^2 = 0.016$), or FT ($P = 0.216$; $R^2 = 0.019$), and QTcF.

The changes in PR and QRS duration did not differ between the testosterone and placebo groups (Table 3). There was also no association between the changes in TT or FT levels and changes in PR, QRS, or QT intervals (Supplemental Fig. 2).

Discussion

The current study showed that testosterone treatment did not induce QTcF prolongation in either of the 2 trials. Fourteen weeks of testosterone treatment had no significant effect on QTcF in the TAP Trial, whereas, in the TEAAM trial, testosterone treatment attenuated the age-related increase in QTcF that was seen in the placebo group. Importantly, no participant in the testosterone arm had QTcF duration of 500 msec or more or an increment of 60 ms or greater, remaining below the threshold of regulatory concern (11). We do not know whether this attenuation of the age-related increase in QTc duration by testosterone is beneficial; the clinical significance of this observation remains to be determined.

The number of testosterone prescriptions written has increased substantially over the past few years, mainly in middle-aged men with low testosterone levels (16, 17). Some studies of testosterone replacement have reported increased cardiovascular events in men treated with testosterone, whereas others have not shown an increase (2, 4–6, 32). In some of the studies reporting an increase in cardiovascular events, the events have tended to occur soon after initiation of testosterone therapy, and the risk decreased soon after interruption of treatment, suggesting that this is an acute process (4, 5). Indeed, testosterone treatment has been shown not to affect atherosclerosis progression, suggesting that mechanisms

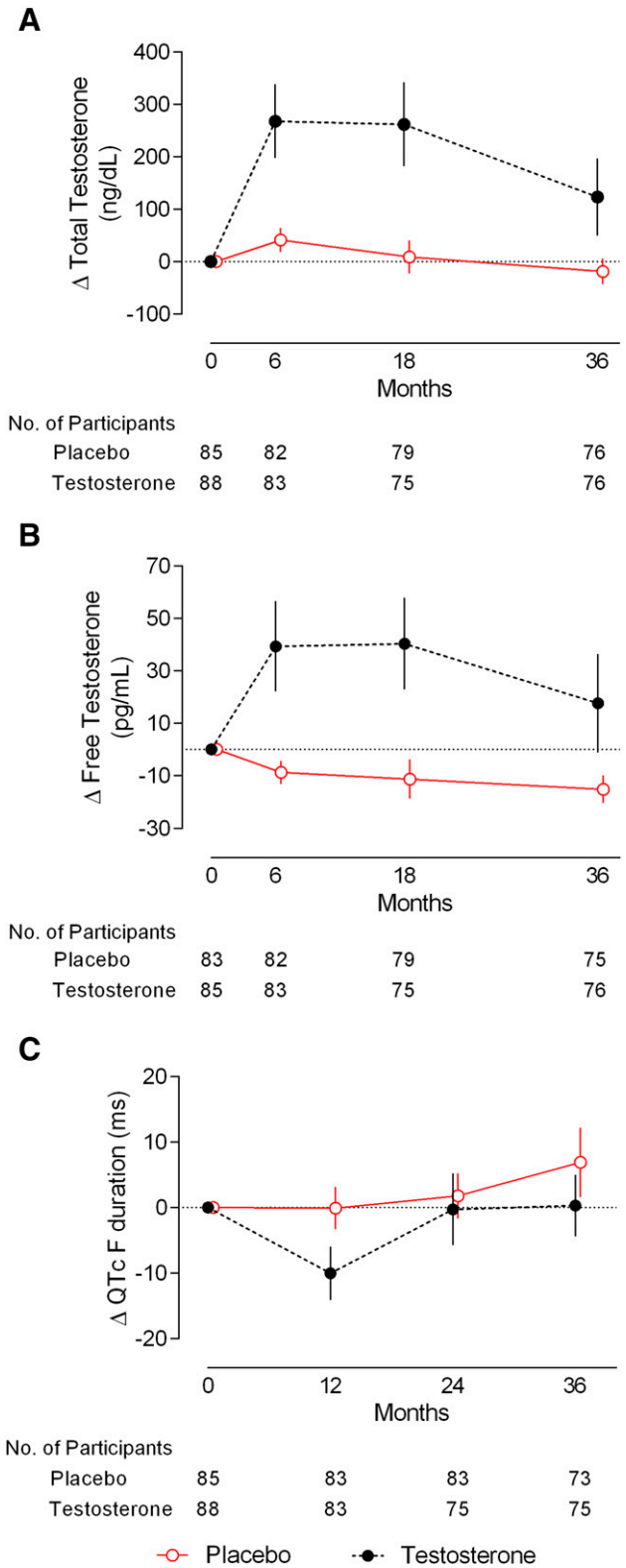

Figure 2. Changes from baseline in (A) total testosterone; (B) free testosterone; and (C) QTcF duration in the TEAAM trial. Data expressed as means and error bars are 95% CI.

other than atherosclerotic plaque progression might play a role. As the QTc interval duration increases with age (13, 14) and this prolongation of QTc interval has been associated with cardiovascular mortality (9, 33–36), the effect of testosterone therapy on electrocardiographic parameters deserved investigation. The results of the present analyses indicate that testosterone does not prolong QTc interval duration, which could affect arrhythmogenic risk.

In the TAP trial, mean QTcF at baseline in both treatment groups was higher than the average for age-matched men in the population (13). This is most likely due to the chronic use of opioids, which are known to prolong QTcF by inhibiting the potassium currents derived from the human ether-a-go-go–related gene (37–39). At the end of the 14-week intervention, men in the testosterone group showed a trend to a greater reduction in QTcF duration, with the mean value returning to the normal range for their age group, although the between-group differences were not statistically significant. It is conceivable that the concurrent use of opioids might have mitigated the effects of testosterone on cardiomyocyte repolarization, which could explain the lack of a statistically significant effect. It is also possible that the study may have lacked the statistical power to detect a small treatment effect. The regression analyses showed a negative association between changes in testosterone levels and changes in QTcF duration, supporting that testosterone shortens QTc duration. In the TEAAM trial, testosterone treatment attenuated the age-related increase in QTcF that was seen in the placebo group. Participants receiving testosterone showed an initial decrease in QTcF at 12 months, followed by a trend toward returning to baseline. At the final evaluation, 36 months after randomization, QTcF had returned to baseline levels in men receiving testosterone, whereas the placebo group had an increase in mean QTcF. These results are in agreement with previous observational and cross-sectional studies that showed inverse correlation between testosterone levels and QTc duration (20, 21). Furthermore, in a small open-label trial, a single injection of a testosterone ester in hypogonadal men was associated with shortening of QTc interval (40).

It has been suggested that the age-related prolongation of QTc in men might, at least in part, be due to the decline in serum testosterone levels (13). Although the mechanisms behind testosterone-induced shortening of QTc interval remain unclear, it is thought to be partially mediated by the increase in human ether-a-go-go–related gene potassium currents via activation of the androgen receptor (41). Testosterone also inhibits the depolarizing delayed calcium current in cardiomyocytes of mammals *in vitro* (42, 43). Vicente *et al.* (13) have proposed that the lower testosterone-induced inhibition of the depolarizing delayed calcium current was the major mediator of the

Table 3. Estimated Changes From Baseline and 95% CIs for ECG Interval Times in the TEAAM Trial

Variables	Testosterone	Placebo	Difference	*P* Value
PR	−2.61 (−4.61, −0.60)	−2.33 (−4.25, −0.42)	−0.27 (−2.48, 1.94)	0.810
QRS	2.17 (1.08, 3.27)	1.17 (0.13, 2.22)	1.00 (−0.17, 2.18)	0.095
QT	−3.86 (−7.70, −0.03)	2.06 (-1.60, 5.71)	−5.91 (−9.98, −1.85)	0.004
QTcF	3.67 (0.84, 6.50)	9.97 (7.26, 12.67)	−6.30 (−9.29, −3.30)	<0.001

Data are expressed as estimated interval time change from baseline in milliseconds (95% CIs). *P* value for treatment effect and estimated changes from baseline, calculated as average outcome change across all postrandomization visits, are extracted from mixed model framework.

effects of aging on QTc in men. The effects of testosterone on QTcF duration observed in the TEAAM trial are consistent with their proposal.

The TAP and TEAAM trials had many attributes of good trial design, as follows: double-blind, subject allocation using concealed randomization, parallel group design, and inclusion of placebo control. Additionally, the 3-year intervention duration of the TEAAM trial allowed for the first time the observation of the age-associated QTc prolongation in a prospective interventional trial. The current study also has some limitations. These analyses represent secondary analyses of data from these trials. Because these hypotheses were not prespecified, the findings must be viewed cautiously.

In summary, testosterone replacement attenuates the age-related increase in QTc interval duration in men. The clinical implications of these findings require further investigation.

Acknowledgments

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Clinical Trial Registry: ClinicalTrials.gov no. NCT00351819 (12 July 2006; TAP trial) and NCT00287586 (6 February 2006; TEAAM trial).

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