Androgen Deprivation Therapy Is Associated With Prolongation of QTc Interval in Men With Prostate Cancer

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Context: Androgen deprivation therapy (ADT) for prostate cancer (PCa) is associated with increased cardiovascular mortality and sudden cardiac death, with some events occurring early after initiation of ADT. Testosterone levels are inversely associated with corrected QT (QTc) interval duration; therefore, prolongation of QTc duration could be responsible for some of these events during ADT.

Objective: To evaluate changes in QTc duration during ADT.

Design and Interventions: A 6-month prospective cohort study that enrolled men with PCa about to undergo ADT (ADT group) and a control group of men who previously underwent prostatectomy for PCa and never received ADT (non-ADT group).

Patients: At study entry, all participants were eugonadal and had no history of cardiac arrhythmias or complete bundle branch block.

Outcomes: Difference in change in QTc duration from baseline on a 12-lead electrocardiogram at 6, 12, and 24 weeks after initiation of ADT compared with electrocardiograms performed at the same intervals in the non-ADT group. PR, QRS, and QT interval durations were also evaluated.

Results: Seventy-one participants formed the analytical sample (33 ADT and 38 non-ADT). ADT was associated with prolongation of the QTc by 7.4 ms compared with the non-ADT group [95% confidence interval (CI) 0.08 to 14.7 ms; $P = 0.048$]. ADT was also associated with shortening of the QRS interval by 2.4 ms (95% CI -4.64 to -0.23; $P = 0.031$). Electrolytes did not change.

Conclusions: Men undergoing ADT for PCa experienced prolongation of the QTc. These findings might explain the increased risk of sudden cardiac death seen in these patients.

Prostate cancer (PCa) is the most common nondermatological cancer in men [1, 2]. As prostate is an androgen-dependent tissue [3], androgen deprivation therapy (ADT) has been the cornerstone of treatment in men with locally invasive and metastatic PCa [4, 5]. The goal of ADT is to lower serum testosterone levels into the castrate range (<50 ng/dL; to convert to nanomoles per liter, multiply by 0.0347) [6], which can be achieved surgically (bilateral orchiectomy) or medically [gonadotropin-releasing hormone (GnRH) agonists or antagonists]. Although ADT has beneficial effects in a subset of patients, the profound androgen deficiency that results from ADT is associated with a number of adverse effects including sexual dysfunction, osteoporosis, hot flashes, and changes in body composition [7, 8]. Additionally, ADT is also associated with insulin resistance, diabetes, and metabolic syndrome [9–11], as well as cardiovascular morbidity and mortality [12, 13]. Some studies have reported that cardiovascular events, including sudden cardiac death, occur early after initiation of ADT [13]. As metabolic changes and progression of atherosclerosis occur gradually over years, the mechanisms that predispose patients to these early events remain unclear.

Although much has been written about cardiovascular complications of ADT, one aspect that has not been investigated in a controlled setting is the potential effect of ADT on the cardiac conduction system. In an electrocardiogram (ECG), ventricular depolarization and repolarization are represented by the QRS complex and T wave, respectively. The QT interval duration corresponds to the total time from ventricular depolarization to repolarization. The QT interval corrected for heart rate (QTc) has been widely used in clinical settings to assess the risk of arrhythmias; indeed, prolongation in QTc is considered a risk factor for tachy-arrhythmias and sudden cardiac death [14–16]. Previous studies have shown that gonadal steroids, testosterone in particular, modulate QTc. Indeed, the QTc duration is similar in newborn male and female babies [17], and no sex-related differences are observed before 10 years of age [18]. However, after puberty, the QTc significantly shortens in boys compared with girls, suggesting a direct effect of testosterone production of cardiac conduction system [19]. Studies in young men have shown that endogenous serum testosterone levels are inversely associated with QTc duration [20]. However, as men age, their QTc durations also increase, which is associated with age-related decline in serum testosterone levels [21, 22]. Clinical trials in community-dwelling men with low serum testosterone levels have also shown that testosterone administration is associated with shortening of QTc [23]. Hence, it is conceivable that profound androgen deficiency that occurs because of ADT slows ventricular repolarization and consequently leads to QTc prolongation, which, in turn, might predispose these patients to cardiac arrhythmias [24]. Indeed, a previous small, uncontrolled study had also observed prolongation of QTc with ADT [25].

The Androgen Deprivation Therapy and Pain Perception (ADT and Pain) Study was a prospective observational study that evaluated the impact of ADT on clinical and experimental pain in men with nonmetastatic PCa and compared them to men with localized PCa who had previously undergone prostatectomy and were in remission [26]. The present substudy was designed to assess the impact of ADT-induced androgen deficiency on ECG parameters, in particular QTc. The prospective study design allowed us to follow participants prospectively in a systematic way by performing serial ECGs at the same time intervals in both cohorts.

1. Methods

A. Study Design and Participants

The ADT and Pain Study was a prospective cohort study designed to evaluate changes in pain perception and tolerance in men undergoing ADT for PCa. Thirty-seven men about to undergo medical ADT with GnRH agonist [22.5 mg leuprolide acetate (Lupron Depot; TAP

Pharmaceuticals)] every 3 months with a planned intervention of at least 6 months were enrolled from the Dana-Farber Cancer Institute (ADT group). All men received an androgen receptor antagonist (bicalutamide) during the first month of treatment to prevent tumor flare, and half of them also received concurrent radiation therapy. Additionally, 40 men with PCa who had undergone prostatectomy and/or radiation therapy for organ-confined PCa at least 6 months prior to enrollment and were in remission were also enrolled and served as the control group; they were recruited from the Brigham and Women's Hospital (non-ADT group). All men had normal serum total testosterone concentrations at the time of enrollment and were free of any chronic pain condition. Other exclusion criteria included orchiectomy, skeletal metastasis, use of opioid analgesics, peripheral neuropathy, painful inflammatory conditions, use of glucocorticoids, diabetes, and moderate to severe depression as assessed by the depression module of the Patient Health Questionnaire [27].

For the substudy described in this manuscript, participants with a history of cardiac arrhythmias or complete bundle branch block at baseline were also excluded from the analysis conforming to the American Heart Association recommendations regarding interpretation of ECG [28]. Seventy-one men (33 in the ADT group and 38 in the non-ADT group) formed the analytical sample for this substudy.

The ADT and Pain Study protocol was approved by the institutional review board at the Dana-Farber Cancer Institute (Boston, MA). Enrollment took place between July 2013 and April 2016; the last participant completed the study in November 2016. All participants provided written informed consent.

B. Laboratory Measurement

Fasting serum samples were collected in the morning at baseline and each of the follow-up visits for measurement of serum total testosterone levels using liquid chromatography-tandem mass spectrometry (the gold-standard method) that was performed in a Centers for Disease Control and Prevention–certified laboratory. The lowest detection limit with this method was 2 ng/dL [29]. Because sodium, potassium, and calcium play an important role in cardiac conduction system [30], these electrolytes were also measured at baseline and at all subsequent visits in all participants. Laboratory measurements and ECGs were performed on the same day (within the time frame of an hour) at all study visits.

C. ECG

ECGs were performed at baseline and at 6, 12, and 24 weeks into treatment in the ADT group. In the non-ADT group, ECGs were performed at similar intervals after enrollment. Standard 12-lead ECGs were performed using the same equipment (GE MAC 800; GE Healthcare, Marlborough, MA) and by the same technician at a speed of 25 mm/s and amplification of 0.1 mV/mm. The PR, QRS, and QT interval durations were measured electronically. The QTc was calculated using the Fridericia QT correction formula [31], which provides the best prediction of short- and long-term mortality [32].

D. Statistical Analysis

The study was designed to insure, conservatively, 80% power to detect a 24-week standardized difference in outcomes between ADT and non-ADT arms of at least 0.5, corresponding to a difference in QTc duration of ~12 ms, provided the baseline and 24-week measurements had intraindividual Pearson correlations of at least 0.5. This threshold was well exceeded in practice; for instance, QTc durations at baseline and 24 weeks had Pearson correlations of 0.67, and use of all three follow-up measurements (at 6, 12, and 24 weeks postrandomization) increased the information available for analysis. Tabular and graphical summaries were used to assess empirical evidence in favor of differences in ECG measurements between ADT and non-ADT arms at baseline and over time. Outcome trends with time were estimated using group- and time-specific means and 95% confidence intervals (CIs).

Mixed-effects regression was used to estimate group differences at baseline and follow-up (the latter was the average effect over the 24 weeks of intervention) using terms for group (ADT vs non-ADT), time, and the interaction between the two and incorporating a random intercept at the participant level to acknowledge serial correlation of repeated measurements. Statistical significance was evaluated using Wald-type tests of the hypothesis that the true interaction between treatment and time—that is, the influence of treatment on the trajectory of mean change in outcomes with time—is zero.

2. Results

Seventy-one men (33 in the ADT group and 38 in the non-ADT group) met all eligibility criteria for the present work and formed the analytical sample. The median age of the participants was 66 years (range 53 to 89 years), and mean body mass index was 28.1 kg/m^2 (range 21.9 to 37.7 kg/m^2). Baseline characteristics of the participants are detailed in Table 1.
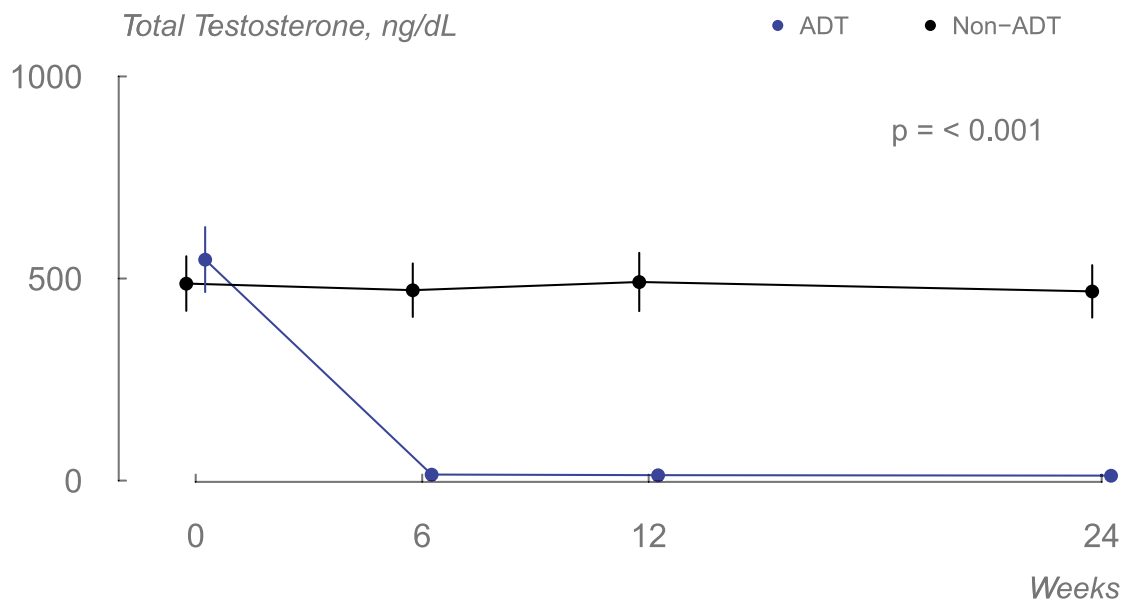
A. Serum Testosterone and Electrolytes

ADT successfully suppressed testosterone production [mean (standard deviation [SD]) 13 (8) ng/dL], whereas testosterone levels did not change in the non-ADT group [mean (SD) 473 (188) ng/dL] (Fig. 1).

Table 1. Baseline Characteristics of Participants in Each Group

	Non-ADT (n = 38)	ADT (n = 33)
Demographics		
Age, mean ± SD, y	66 ± 7	67 ± 8
Weight, mean ± SD, kg	85.2 ± 12.4	87.1 ± 12.5
Height, mean ± SD, cm	174 ± 7	175 ± 6
BMI, mean ± SD, kg/m^2	27.9 ± 3.1	28.4 ± 3.7
Medical history		
Hypertension, %	39.5	45.5
CAD, %	15.8	3.0
Stroke, %	5.3	3.0
Myocardial infarction, %	5.3	0
Congestive heart failure, %	2.6	0
Obesity, %	26.3	30.3
Hyperlipidemia, %	39.5	51.5
PCa history		
Prostatectomy, %	95	73
Radiation, %	5	52
Gleason score, mean ± SD	6.5 ± 1.1	7.4 ± 1.0
ECG		
PR, mean ± SD, ms	171 ± 16	175 ± 32
QRS, mean ± SD, ms	89 ± 10	88 ± 10
QT, mean ± SD, ms	415 ± 32	431 ± 32
QTc, mean ± SD, ms	412 ± 20	422 ± 17
Laboratory parameters		
Total testosterone, mean ± SD, ng/dL	486 ± 196	545 ± 196
Sodium, mean ± SD, mEq/L	140 ± 2	140 ± 2
Potassium, mean ± SD, mEq/L	4.3 ± 0.3	4.3 ± 0.3
Calcium, mean ± SD, mg/dL	9.5 ± 0.3	9.3 ± 0.4
Creatinine, mean ± SD, mg/dL	1.04 ± 0.17	1.04 ± 0.15

There were no substantial between-group differences. To convert total testosterone to nmol/L, multiply by 0.0347. To convert calcium to mmol/L, multiply by 0.25. To convert creatinine to μmol/L, multiply by 88.4.
Abbreviations: BMI, body mass index; CAD, coronary artery disease.

Figure 1. Changes in serum total testosterone levels in the two groups during the course of the study (data displayed as means, and error bars are 95% CI).

No meaningful changes were seen in any of the electrolytes in either group (Fig. 2).

B. ECG Parameters

B-1. QT and QTc intervals

Significant prolongation in the QTc was seen in men receiving ADT (estimated change 12 ms; 95% CI 6.4 to 17.5 ms; $P < 0.001$). This effect was still significant when compared with the non-ADT group (treatment difference of 7.4 ms; 95% CI 0.08 to 14.7; $P = 0.048$; Table 2; Fig. 3).

As a QTc of >440 ms is considered abnormal in men [33], we analyzed those participants who had normal QTc duration at baseline but exceeded this threshold during follow-up. Only 4 participants (12%) in the non-ADT group exceeded this threshold, whereas 12 subjects receiving ADT (44%) exceeded a QTc of 440 ms during the course of the study (Fig. 4). Furthermore, among subjects with a QTc >440 ms at baseline, there was a continued increase in QTc in five out of six subjects in the ADT group, whereas no further increase was seen in the non-ADT group (Fig. 4).

ADT did not affect QT interval duration (Table 2; Fig. 3), with average time remaining unchanged in both groups (treatment difference 3.6 ms; 95% CI −6.9 to 14.0 ms; $P = 0.5$).

B-2. QRS complex interval

Men undergoing ADT experienced significant shortening of the QRS complex interval (treatment difference −2.4 ms; 95% CI −4.6 to −0.23 ms; $P = 0.031$; Table 2; Fig. 3) compared with the participants not receiving ADT.

B-3. PR interval

ADT did not affect PR interval duration (Table 2; Fig. 3), with average time remaining unchanged in both groups (treatment difference 0.84 ms; 95% CI −4.3 to 6.0 ms; $P = 0.75$).

C. Adverse Events

Few adverse events were observed during the 24-week duration of the study. Three cardiovascular events were observed in participants in the non-ADT group (one exacerbation
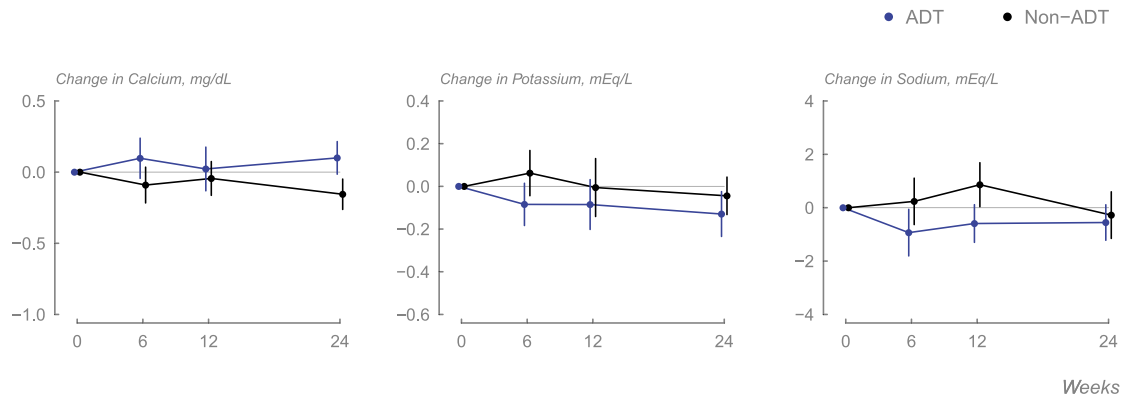
Figure 2. Changes in (A) serum calcium, (B) serum potassium, and (C) serum sodium levels in each group during the course of the study (data displayed as means, and error bars are 95% CI).

of hypertension, one syncope, and one atrial fibrillation), whereas two events were seen in the ADT group (one ventricular tachycardia and one exacerbation of hypertension). No deaths occurred in either group. Vasomotor symptoms were seen in men undergoing ADT.

3. Discussion

ADT is increasingly being used in the management of PCa [1–4]. Although ADT improves survival in a subset of patients, it has been associated with cardiovascular morbidity and mortality in some studies [34]. Some reports have suggested that cardiovascular events, including sudden death, occur soon after initiation of ADT [13, 35]. As atherosclerosis is a slow process [7, 9], these early events suggest effects of ADT on the cardiac conduction system. Population studies have shown that endogenous serum testosterone levels are inversely associated with QTc duration [36–38]. Indeed, clinical trials have shown that testosterone administration is associated with shortening of QTc [23, 39]. Therefore, withdrawal of testosterone could lead to prolongation of QTc, which in turn could predispose these patients to arrhythmias. We found that ADT with GnRH agonists leads to marked prolongation of QTc (mean increase of 7 ms), and the US Food and Drug Administration considers this increase in QTc clinically relevant [40]. Indeed, prolongation of QTc is independently associated with cardiovascular mortality and sudden death [15, 41–44]. More participants in the ADT group experienced increases in QTc that led to durations >440 ms, the threshold beyond which the risk of arrhythmias increases [16, 40, 45, 46] compared with men in the non-ADT group. Furthermore, the QTc duration continued to increase in those androgen-deprived participants who already had baseline QTc of ≥440 ms, suggesting that ADT leads to prolongation of QTc irrespective of baseline value. Another important finding of the study was the shortening of QRS complex duration, suggesting rapid ventricular depolarization.

Table 2. Estimated Changes from Baseline and 95% CIs for ECG Interval Times

| Variables	Non-ADT	ADT	Difference	*P* value
PR	−1.5 (−4.8 to 1.9)	−0.6 (−4.5 to 3.3)	0.8 (−4.3 to 6.0)	0.75
QRS	0.3 (−1.1 to 1.7)	−2.1 (−3.8 to −0.5)	−2.4 (−4.6 to −0.2)	0.031
QT	7.6 (0.8–14.4)	11.2 (3.3 to 19.1)	3.6 (−6.8 to 14.0)	0.50
QTc	4.6 (−0.2 to 9.3)	12.0 (6.4–17.5)	7.4 (0.1–14.6)	0.048

Data are expressed as estimated interval time change from baseline in milliseconds (95% CIs).
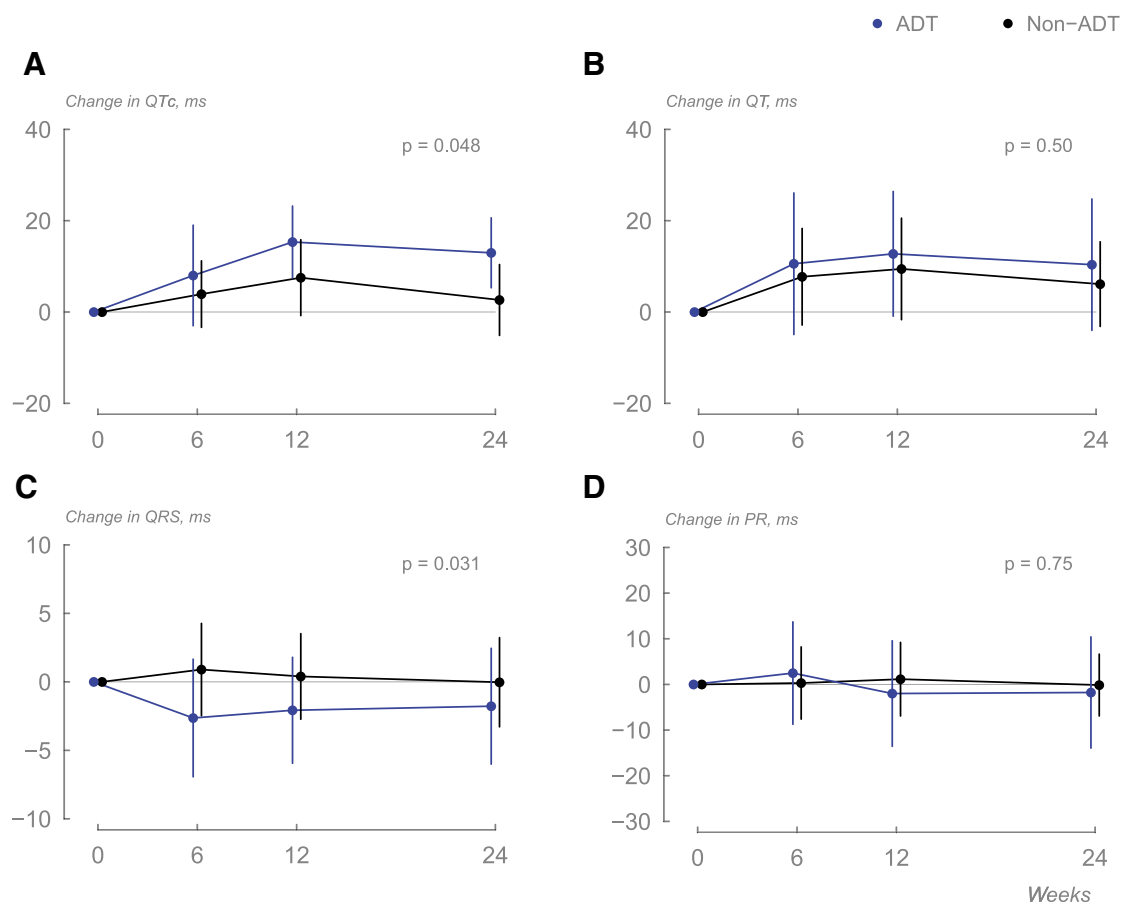
Figure 3. Changes in (A) QTc, (B) QT interval, (C) QRS complex, and (D) PR interval duration in the two groups during the study (data displayed as means, and error bars are 95% CI).

These findings are important and provide insight regarding the potential mechanisms by which ADT might predispose patients to cardiac arrhythmias and sudden death. These findings, however, require further investigation.

As serum testosterone levels are inversely associated with QTc, it is likely that prolongation of QTc duration in men undergoing ADT is a direct consequence of testosterone suppression. Studies have shown that testosterone shortens ventricular cardiomyocyte repolarization time by two mechanisms: it increases potassium currents derived from the human ether-a-go-go–related gene via the androgen receptor [47], and it inhibits the depolarizing delayed calcium current via a nonandrogen receptor–mediated pathway [48]. Therefore, in men undergoing ADT, profound androgen deficiency favors ventricular depolarization, as seen by a shortened QRS complex, and prolongation of QTc. In a previous trial of testosterone replacement in community-dwelling older men [23], we had observed a reduction in QTc and a trend toward prolongation of QRS complex duration; this supports our current finding that withdrawal of testosterone during ADT leads to prolongation of the QTc and shortening of the QRS complex. Previous cross-sectional studies that have evaluated QRS complex duration in men and women have found that men have longer QRS complex duration compared with women, which they attributed to sex differences in cardiac size [49, 50]. Our observation of QTc prolongation because of ADT confirms findings from a previous uncontrolled prospective study [25]. Unlike QTc prolongation, which has consistently been associated with risk of cardiac arrhythmias, the clinical implications of QRS complex shortening remain unclear and deserve further investigation.
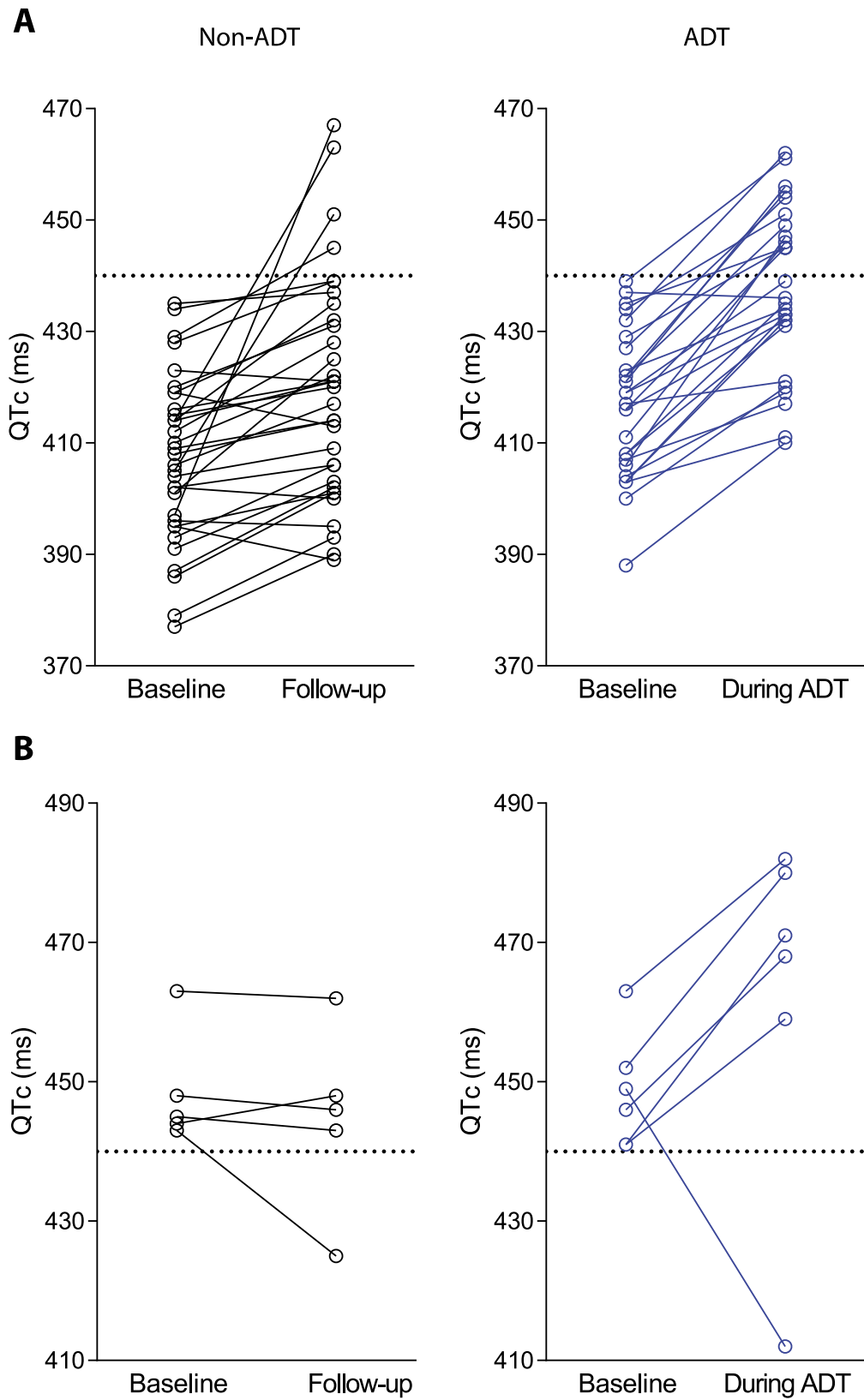
Figure 4. (A) Increase in QTc >440 ms among participants who had normal QTc (<440 ms) at baseline. (B) Increase in QTc among participants who had QTc >440 ms at baseline.

Although suppressed serum testosterone levels are likely responsible for the alterations seen in the cardiac conduction system, one cannot exclude a direct effect of GnRH agonists on cardiac electrophysiology. Indeed, some previous reports have suggested that use of GnRH agonists is associated with a greater risk of cardiovascular disease compared with bilateral orchiectomy, whereas other reports have not confirmed these findings [12, 13, 51, 52]. A possible explanation for these discrepant observations might be the small number of men who underwent bilateral orchiectomy in these compared with those receiving GnRH agonists. However, GnRH receptors are expressed in the cardiac tissue [53, 54], and stimulation of GnRH receptors by GnRH agonists *in vitro* has shown an increase in intracellular Ca^{2+} and prolongation of intracellular Ca^{2+} decay in mouse cardiomyocytes [55]. Mechanistic studies are needed to further understand the drug effect of both GnRH agonists and antagonists on cardiac conduction.

Serum electrolytes sodium, potassium, and calcium, in particular, have an effect on cardiac conduction [30]. Hypokalemia and hypocalcemia can result in QTc prolongation, whereas hypercalcemia leads to shortening of QTc duration [56]. We measured these electrolytes at the same time intervals (and on the same day) that the ECG was performed to exclude any potential effect on ECG parameters. We found no meaningful changes in these electrolytes, suggesting that QTc prolongation is likely related to profound androgen deficiency as a result of ADT.

The current study has several strengths: (1) the study had a prospective design that allowed us to carefully follow changes in ECG parameters; (2) all ECGs were performed by the same technician using the same equipment; (3) enrollment of eugonadal men provided an opportunity to determine the direct effect of testosterone suppression on cardiac electrophysiology; (4) serum testosterone was measured using liquid chromatography-tandem mass spectrometry (the gold-standard method); (5) none of the participants had history of cardiac arrhythmias or bundle branch block, allowing us to accurately measure QTc; (6) all men received medical ADT with GnRH agonists, and no one underwent orchiectomy, thus providing a homogenous sample; (7) enrollment of a non-ADT group as controls who were well matched with the ADT group; and (8) QTc was calculated using the Fridericia QT correction formula, which is known to provide the best prediction of short- and long-term mortality [32]. The present work also has some limitations. This work was a secondary analysis of the ADT and Pain Study. Furthermore, we only enrolled men undergoing ADT with GnRH agonists (this was by design to have a homogenous sample of participants); future mechanistic studies should evaluate the various modalities of ADT (GnRH agonists, GnRH antagonists, and orchiectomy) on ECG parameters.

In conclusion, ADT with GnRH agonists results in considerable prolongation in QTc in men with PCa. These changes in cardiac electrophysiology might explain cardiovascular events, including sudden cardiac death, that are seen soon after initiation of ADT. These findings should guide both physicians and patients to make informed decisions regarding their treatment.

Acknowledgments

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