

ORIGINAL RESEARCH

# Reduced Cardiorespiratory Fitness and Increased Cardiovascular Mortality After Prolonged Androgen Deprivation Therapy for Prostate Cancer



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## ABSTRACT

**BACKGROUND** Prolonged androgen deprivation therapy (ADT) is favored over short-term use in patients with localized high-risk prostate cancer (PC).

**OBJECTIVES** This study sought to compare cardiorespiratory fitness (CRF) and cardiovascular (CV) mortality among patients with PC with and without ADT exposure and to explore how duration of ADT exposure influences CRF and CV mortality.

**METHODS** Retrospective cohort study of patients referred for exercise treadmill testing (ETT) after a PC diagnosis. PC risk classification was based on Gleason score (GS): high risk if GS  $\geq$ 8; intermediate risk if GS = 7; and low risk if GS <7. CRF was categorized by metabolic equivalents (METs): METs >8 defined as good CRF and METs  $\leq$ 8 as reduced CRF. ADT exposure was categorized as short term ( $\leq$ 6 months) versus prolonged (>6 months).

**RESULTS** A total of 616 patients underwent an ETT a median of 4.8 years (interquartile range: 2.0, 7.9 years) after PC diagnosis. Of those, 150 patients (24.3%) received ADT prior to the ETT; 99 with short-term and 51 with prolonged exposure. 504 patients (81.8%) had  $\geq$ 2 CV risk factors. Prolonged ADT was associated with reduced CRF (odds ratio [OR]: 2.71; 95% confidence interval [CI]: 1.31 to 5.61;  $p = 0.007$ ) and increased CV mortality (hazard ratio [HR]: 3.87; 95% CI: 1.16 to 12.96;  $p = 0.028$ ) in adjusted analyses. Although the association between short-term ADT exposure and reduced CRF was of borderline significance (OR: 1.71; 95% CI: 1.00 to 2.94;  $p = 0.052$ ), there was no association with CV mortality (HR: 1.60; 95% CI: 0.51 to 5.01;  $p = 0.420$ ) in adjusted Cox regression models.

**CONCLUSIONS** Among patients with PC and high baseline CV risk, prolonged ADT exposure was associated with reduced CRF and increased CV mortality. (J Am Coll Cardiol CardioOnc 2020;2:553–63) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: CardioOncology* [author instructions page](#).

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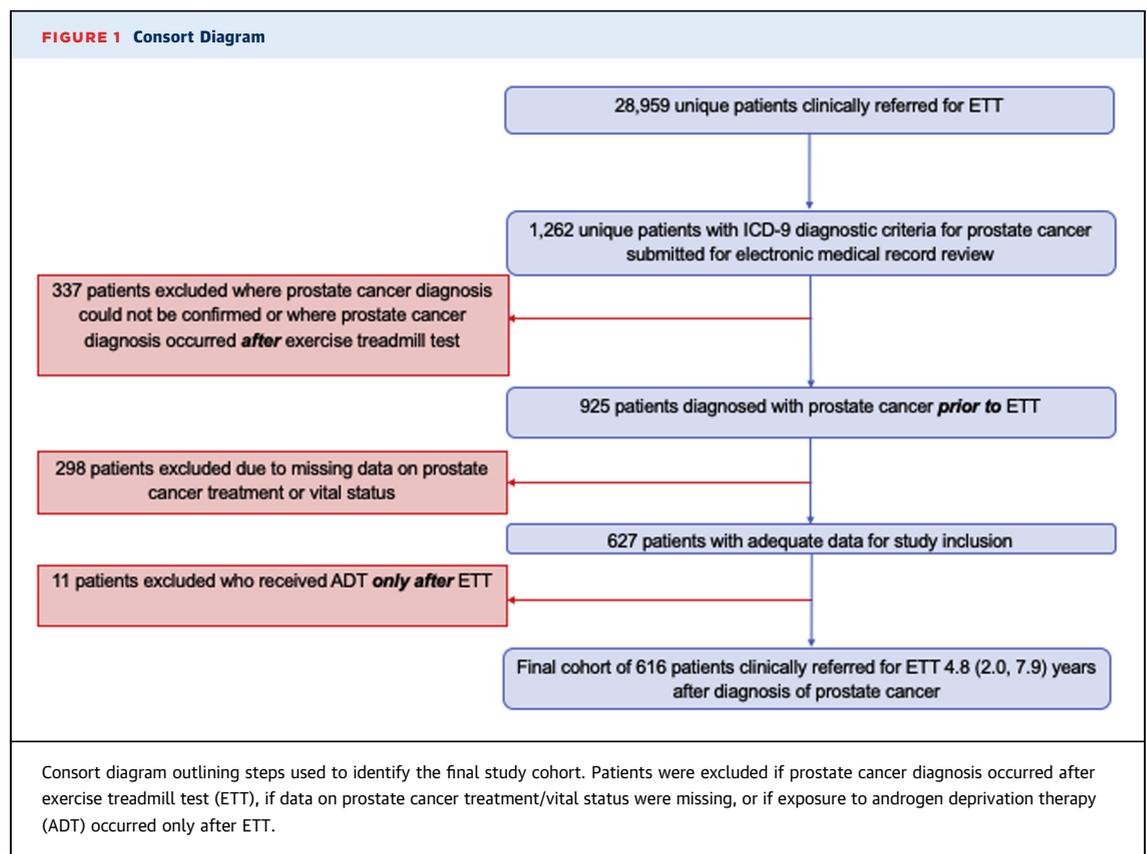
**ABBREVIATIONS  
AND ACRONYMS**

<b>ADT</b>	= androgen deprivation therapy
<b>BMI</b>	= body mass index
<b>CI</b>	= confidence interval
<b>CRF</b>	= cardiorespiratory fitness
<b>CV</b>	= cardiovascular
<b>ETT</b>	= exercise treadmill test
<b>HR</b>	= hazard ratio
<b>IQR</b>	= interquartile range
<b>MET</b>	= metabolic equivalent
<b>OR</b>	= odds ratio
<b>PC</b>	= prostate cancer

About 1 in 9 men will be diagnosed with prostate cancer (PC) during their lifetime, and it is the second leading cause of cancer death in American men. The population of survivors with PC in the United States is projected to increase from 3.3 million in 2016 to 4.5 million by 2026 (1). Cardiovascular (CV) disease is a leading cause of death in men with a history of PC (2). Androgen deprivation therapy (ADT) is a standard primary treatment for PC with radiation therapy as an alternative to surgery, and is widely used in patients with metastatic, recurrent, and localized high-risk tumors (3,4). ADT regimens of increased intensity and prolonged duration are increasingly applied in clinical practice following several studies that demonstrated superior cancer outcomes compared with those associated with shorter duration therapy in high-risk patients (5).

Whether ADT is associated with increased CV mortality remains controversial. Specifically, some studies report increased risk of CV morbidity (6-9) and mortality (10) in ADT-exposed men (11,12),

whereas others have failed to demonstrate any significant association between ADT exposure and the development of CV disease (13) or mortality (14). Cardiorespiratory fitness (CRF) is a strong independent predictor of all-cause and CV mortality (15-17). Like the conflicting data on ADT and CV mortality, studies testing the association between ADT exposure and CRF are inconclusive (18-20). Furthermore, the influence of prolonged ADT exposure versus short-term exposure on CRF requires more comprehensive assessment. Some prior studies exploring ADT-mediated effects on CRF have focused on age-matched healthy individuals as the reference cohort rather than ADT-naive patients with PC (19,20). Therefore, to advance the current understanding of the influence of both ADT exposure and the duration of ADT exposure on CRF and CV mortality, the objectives of this study were: 1) to compare CRF and CV mortality in a large cohort of PC patients with and without ADT exposure; and 2) to explore the influence of prolonged versus short-term ADT usage on both CRF and CV mortality given the increasing use of prolonged ADT regimens in clinical practice.



**TABLE 1** Baseline Demographics of Study Cohorts

	Entire Cohort (N = 616)	ADT (n = 150)	Non-ADT (n = 466)	p Value	ADT ≤6 Months (n = 99)	ADT >6 Months (n = 51)	p Value
Age at ETT, yrs	69.6 ± 7.8	70.3 ± 7.7	69.4 ± 7.8	0.232	70.2 ± 7.7	70.6 ± 7.7	0.768
Interval from PC diagnosis to ETT, yrs	4.8 (2.0-7.9)	4.0 (1.7-6.9)	5.0 (2.1-8.2)	0.056	3.2 (1.3-6.3)	4.6 (2.7-7.9)	0.015
<b>Cardiovascular history</b>							
Body mass index, kg/m <sup>2</sup>	27.7 ± 4.1	28.3 ± 4.4	27.5 ± 4.0	0.040	28.2 ± 4.5	28.5 ± 4.3	0.722
Diabetes mellitus	127 (20.6)	36 (24.0)	91 (19.5)	0.247	23 (23.2)	13 (25.5)	0.841
Hypertension	426 (69.2)	107 (71.3)	319 (68.5)	0.543	71 (71.7)	36 (70.6)	1.000
Hypercholesterolemia	454 (73.7)	113 (75.3)	341 (73.2)	0.670	76 (76.8)	37 (72.6)	0.690
Ischemic heart disease	208 (33.8)	57 (38.0)	151 (32.4)	0.234	39 (39.4)	18 (36.3)	0.723
Heart failure	64 (10.4)	18 (12.0)	46 (9.9)	0.445	11 (11.1)	7 (13.7)	0.791
LVEF, %*	59 (54-64)	60 (54-63)	59 (54-64)	0.790	59 (54-63)	60 (53-65)	0.679
Active smoking	42 (6.8)	8 (5.3)	34 (7.3)	0.462	4 (4.0)	4 (7.8)	0.444
Morise risk score	12.9 ± 1.7	13.0 ± 1.7	12.9 ± 1.8	0.399	13.0 ± 1.8	13.1 ± 1.5	0.734
≥1 Cardiovascular risk factors†	591 (96.0)	144 (96.0)	447 (96.0)	0.205	94 (95.0)	50 (98.0)	0.821
≥2 Cardiovascular risk factors†	504 (81.8)	127 (84.7)	377 (80.9)	0.085	80 (80.8)	47 (92.2)	0.210
<b>Cardiovascular medications</b>							
Statin	396 (64.3)	98 (65.3)	298 (64.0)	0.770	64 (64.7)	34 (66.7)	0.858
Aspirin	373 (60.6)	94 (62.7)	279 (59.9)	0.566	66 (66.7)	28 (54.9)	0.212
ACE inhibitor/ARB	231 (37.5)	55 (36.7)	176 (37.8)	0.847	33 (33.3)	22 (43.1)	0.284
Atrioventricular nodal blockade	348 (56.5)	94 (62.7)	254 (54.5)	0.089	59 (59.6)	35 (68.8)	0.292

Values are mean ± SD, median (interquartile range), or n (%). \*Available for 438 patients (71.1%): 330 (70.8%) in non-ADT cohort and 108 (72.0%) in ADT cohort. †Active smoking, diabetes, hypertension, hypercholesterolemia, overweight (body mass index ≥25 kg/m<sup>2</sup>).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ADT = androgen deprivation therapy; ETT = exercise treadmill test; LVEF = left ventricular ejection fraction; PC = prostate cancer.

**METHODS**

**STUDY DESIGN.** This was a single-center, retrospective cohort study approved by the Partners Healthcare Institutional Review Board. Using ICD-9-CM codes, 1,262 subjects with a diagnosis of PC were identified from 28,959 consecutive patients who underwent exercise treadmill tests (ETTs). Subjects were excluded if PC diagnosis could not be confirmed, if PC diagnosis occurred after ETT, or if ADT exposure occurred only after an ETT. Following additional exclusion of patients with insufficient data available on PC treatment, vital status, and/or CV comorbidities, 616 subjects who underwent ETTs between March 7, 2002, and August 18, 2015, were included in the final cohort (Figure 1).

**CARDIOVASCULAR RISK FACTOR ASSESSMENT.** Demographics, indication for ETT, medical history, and medication usage were prospectively recorded at the time of the ETT. Ischemic heart disease was defined as any history of myocardial infarction, coronary revascularization, or coronary artery disease. Heart failure was defined as any history of heart failure, cardiomyopathy, left ventricular ejection fraction <40%, or loop diuretic use. Hyperlipidemia was defined as any history of hyperlipidemia or statin use. Diabetes was defined as any history of diabetes

or use of insulin or oral hypoglycemic agents. Morise clinical score was calculated based on age, sex, smoking, hyperlipidemia, diabetes, hypertension, estrogen status, body mass index (BMI), family history of coronary artery disease, and symptoms (21). A Morise score of 0 to 8 indicates low pre-test probability of a positive stress test, 9 to 15 indicates an intermediate probability, and 16 to 24 indicates a high probability (21).

**ONCOLOGY HISTORY.** Oncologic data were collected, including PC treatment regimens used before and after the ETTs. Gleason score categorized patients as high (score ≥8), intermediate (score = 7), or low (score <7) cancer risk. Details of ADT treatment were recorded, including agent used and duration of ADT exposure prior to the ETT. Short-term and prolonged ADT exposures were defined as use of ADT for ≤6 and >6 months, respectively (22,23).

**EXERCISE PROTOCOL.** All patients underwent a symptom-limited ETT according to the standard Bruce protocol (24). Heart rate and blood pressure were recorded at rest and periodically during exercise and recovery. ETTs were performed, analyzed, and reported as normal, abnormal, or inconclusive per international standards (25). Resting left ventricular ejection fraction was recorded for ETTs performed

**TABLE 2 Oncology Characteristics of the Study Cohorts**

	Entire Cohort (N = 616)	ADT (n = 150)	Non-ADT (n = 466)	P Value	ADT ≤6 Months (n = 99)	ADT >6 Months (n = 51)	p Value
Age at diagnosis, yrs	64.1 ± 7.5	65.3 ± 7.6	63.7 ± 7.4	0.022	65.8 ± 7.1	64.3 ± 8.5	0.268
Nodal status at time of initial treatment							
Pathologically positive	17 (2.8)	15 (10.0)	2 (0.4)	<0.001	4 (4.1)	11 (21.6)	0.002
Pathologically negative	323 (52.4)	67 (44.7)	256 (55.0)		44 (44.4)	23 (45.1)	
Clinically negative*	276 (44.8)	68 (45.3)	208 (44.6)		51 (51.5)	17 (33.3)	
Metastatic status at time of initial treatment							
Yes	39 (6.3)	8 (5.3)	31 (6.7)	0.045	1 (1.0)	7 (13.7)	0.006
No	509 (82.7)	117 (78.0)	392 (84.1)		80 (80.8)	37 (72.6)	
Unknown	68 (11.0)	25 (16.7)	43 (9.2)		18 (18.2)	7 (13.7)	
Prostate cancer risk group							
High-risk PC (GS ≥8)	67 (10.9)	44 (29.3)	23 (4.9)	<0.001	20 (20.2)	24 (47.1)	0.001
Intermediate-risk PC (GS = 7)	245 (39.8)	90 (60.0)	155 (33.3)		66 (66.7)	24 (47.1)	
Low-risk PC (GS <7)	304 (49.3)	16 (10.7)	288 (61.8)		13 (13.1)	3 (5.8)	
Prostatectomy as initial therapy							
Yes	333 (54.1)	37 (24.7)	296 (63.5)	<0.001	17 (17.2)	20 (39.2)	0.001
No	278 (45.1)	110 (73.3)	168 (36.1)		81 (81.8)	29 (57.9)	
Unknown	5 (0.8)	3 (2.0)	2 (0.4)		1 (1.0)	2 (3.9)	
External radiation/brachytherapy as initial therapy							
Yes	235 (38.2)	109 (72.7)	126 (27.0)	<0.001	81 (81.8)	28 (54.9)	0.001
No	376 (61.0)	38 (25.3)	338 (72.5)		18 (18.2)	20 (39.2)	
Unknown	5 (0.8)	3 (2.0)	2 (0.4)		0	3 (5.9)	
Any chemotherapy							
Yes	30 (4.9)	15 (10.0)	15 (3.2)	0.002	9 (9.1)	6 (11.8)	0.581
No	583 (94.6)	135 (90.0)	448 (96.1)		90 (90.9)	45 (88.2)	
Unknown	3 (0.5)	0	3 (0.7)		0	0	
Recurrence or progression							
Yes	74 (12.0)	30 (20.0)	44 (9.4)	0.003	8 (8.1)	22 (43.1)	<0.001
No	532 (86.4)	120 (80.0)	412 (88.4)		91 (91.9)	29 (56.9)	
Unknown	10 (1.6)	0	10 (2.2)		0	0	
Biochemical recurrence							
Yes	99 (16.1)	52 (34.7)	47 (10.1)	<0.001	20 (20.2)	32 (62.7)	<0.001
No	515 (83.6)	98 (65.3)	417 (89.5)		79 (79.8)	19 (37.3)	
Unknown	2 (0.3)	0	2 (0.4)		0	0	

Values are mean ± SD or n (%). "Unknown" or "inconclusive" rows excluded from hypothesis tests. \*No evidence of lymph node metastasis on imaging studies or physical examination. GS = Gleason score; other abbreviations as in Table 1

with echocardiography (n = 86, 14.0%), nuclear imaging (n = 351, 57.0%), or computed tomography (n = 1, 0.002%).

**CARDIORESPIRATORY FITNESS.** CRF was expressed in units of metabolic equivalents (METs), calculated from peak treadmill speed and grade (26). CRF was stratified as reduced (≤8 METs) or good (>8 METs), as established in prior works (15,16,27,28).

**STUDY OUTCOMES.** Study outcomes were reduced CRF, as just defined, and CV mortality. Cause-specific mortality data were collected using National Death Index.

**STATISTICAL ANALYSIS.** Categorical demographic variables were compared using Pearson chi-squared

tests or Fisher exact tests. Continuous normal data were compared using 2-independent samples Student's *t*-tests. Continuous, non-normal variables were compared using Wilcoxon rank-sum tests. Logistic regression was used to assess the relationships among reduced CRF and ADT exposure or ADT duration in crude analyses, and analyses adjusted for age, ETT result, PC risk group, Morise risk score, and BMI. Survival analyses were performed using Cox proportional hazards models. Thirteen patients in the short-term ADT cohort who received additional ADT after their ETTs to bring their cumulative ADT exposure to >6 months were excluded from CV mortality analyses. As CV mortality is measured in the presence of competing

**TABLE 3 ETT Indications and Results**

	Entire Cohort (N = 616)	ADT (n = 150)	Non-ADT (n = 466)	p Value	ADT ≤6 Months (n = 99)	ADT >6 Months (n = 51)	p Value
<b>Indication for ETT*</b>							
Chest pain	166 (27.0)	40 (26.7)	126 (27.0)	1.000	25 (25.3)	15 (29.4)	0.697
Dyspnea	94 (15.3)	24 (16.0)	70 (15.0)	0.794	16 (16.2)	8 (15.7)	1.000
Arrhythmia	40 (6.5)	12 (8.0)	28 (6.0)	0.445	8 (8.1)	4 (7.8)	1.000
Other	316 (51.3)	74 (49.3)	242 (51.9)	0.638	50 (50.5)	24 (47.1)	0.732
<b>CRF</b>							
Exercise duration, mins	7.9 ± 2.8	7.0 ± 2.4	8.2 ± 2.9	<0.001	7.3 ± 2.5	6.5 ± 2.2	0.083
METs completed	9.5 ± 3.0	8.5 ± 2.5	9.8 ± 3.1	<0.001	8.7 ± 2.6	8.1 ± 2.3	0.127
Good CRF (METs >8)	391 (63.5)	77 (51.3)	314 (67.4)	<0.001	54 (54.6)	23 (45.1)	0.304
Reduced CRF (METs ≤8)	225 (36.5)	73 (48.7)	152 (32.6)	<0.001	45 (45.4)	28 (54.9)	0.304
<b>Heart rate response, beats/min</b>							
Heart rate at rest	66 ± 13	65 ± 13	66 ± 13	0.275	63 ± 12	67 ± 14	0.091
Heart rate at peak	134 ± 23	130 ± 22	136 ± 24	0.018	130 ± 22	131 ± 22	0.936
<b>Blood pressure, mm Hg</b>							
SBP at rest	134 ± 17	134 ± 18	134 ± 17	0.854	134 ± 16	135 ± 20	0.799
DBP at rest	77 ± 10	77 ± 11	77 ± 10	0.935	76 ± 10	78 ± 12	0.435
SBP at peak exercise	168 ± 26	166 ± 26	169 ± 26	0.200	166 ± 26	165 ± 27	0.860
DBP at peak exercise	74 ± 11	74 ± 12	75 ± 10	0.403	72 ± 12	76 ± 12	0.077
<b>ETT result</b>							
Normal	450 (73.1)	103 (68.7)	347 (74.5)	0.359	68 (68.7)	35 (68.6)	1.000
Abnormal	103 (16.7)	29 (19.3)	74 (15.9)		19 (19.2)	10 (19.6)	
Inconclusive	63 (10.2)	18 (12.0)	45 (9.6)		12 (12.1)	6 (11.8)	

Values are n (%) or mean ± SD. "Unknown" or "inconclusive" rows excluded from hypothesis tests. \*Cumulative percentages may exceed 100% as categories are not mutually exclusive.  
 CRF = cardiorespiratory fitness; DBP = diastolic blood pressure; ETT = exercise treadmill test; METs = metabolic equivalents; SBP = systolic blood pressure.

risks, cause-specific hazard ratios (HRs) were used. Crude HR with 95% confidence intervals (CIs) were calculated in addition to HRs adjusting for the same set of potential confounders included in the CRF analysis. An inverse probability of treatment-weighted propensity score analysis was performed to check model stability. Martingale residuals were used to assess the proportional hazards assumption. Individuals were right-censored if they did not experience a CV event by the end of follow-up or were lost to follow-up. Cumulative incidence of CV deaths was compared among ADT-naive patients, patients who received ≤6 months of ADT, and those who received >6 months of ADT using Gray test of equality. Analyses were performed using SAS (version 9.4, SAS Institute, Cary, North Carolina). All p values <0.05 were considered statistically significant, and all testing was 2-tailed.

**RESULTS**

**BASELINE DEMOGRAPHICS AND CV RISK.** The mean age at time of ETT was 69.6 ± 7.8 years. The median interval from PC diagnosis to ETT was 4.8 years (interquartile range [IQR]: 2.0 to 7.9 years). The intermediate to high baseline CV risk of these men is

highlighted by the following: 504 patients (81.8%) had ≥2 CV risk factors, the mean Morise score was 12.9 ± 1.7, and there was a high frequency of CV medication usage (Table 1).

**ONCOLOGY HISTORY AND ADT.** Almost one-half (n = 304, 49.3%) of the entire cohort were low risk from a PC perspective based on Gleason score <7 at time of diagnosis; 245 (39.8%) were intermediate risk (score = 7) and only 67 (10.9%) were high risk (score ≥8). Prostatectomy, radiation therapy, and adjuvant chemotherapy were employed in 54.1%, 38.2%, and 4.9% of patients, respectively (Table 2).

Almost one-quarter (n = 150, 24.4%) of the entire cohort received ADT prior to the ETT. Compared with ADT-naive patients, these patients were older at time of PC diagnosis (65.3 ± 7.6 vs. 63.7 ± 7.4 years; p = 0.022) with higher BMI (28.3 ± 4.4 vs. 27.5 ± 4.0 kg/m<sup>2</sup>; p = 0.040). Other CV risk factors and medication usage were similar across ADT-naive and ADT-exposed cohorts (Table 1). Treatment of ADT-exposed patients was more likely to have included radiation therapy (72.7% vs. 27.0%, p < 0.001) and chemotherapy (10.0% vs. 3.2%, p = 0.002), but less likely to have included prostatectomy (24.7% vs. 63.5%, p <0.001).

**TABLE 4** Associations Among ADT of Any Duration, Short-Term Use, and Prolonged Use With Reduced CRF and CV Mortality

	Reduced CRF (METs $\leq$ 8)		CV Mortality	
	Unadjusted OR (95% CI), p Value	Adjusted OR* (95% CI), p Value	Unadjusted Cause-Specific HR (95% CI), p Value	Adjusted Cause-Specific HR* (95% CI), p Value
No ADT (n = 466)	1.00	1.00	1.00	1.00
ADT (n = 150)	1.96 (1.35-2.85), <0.001	1.97 (1.21-3.20), 0.006	2.36 (1.10-5.06), 0.027	2.14 (0.83-5.50), 0.115
ADT $\leq$ 6 months (n = 99)†	1.72 (1.11-2.67), 0.016	1.71 (1.00-2.94), 0.052	1.83 (0.68-4.98), 0.234	1.60 (0.51-5.01), 0.420
ADT >6 months (n = 51)	2.52 (1.40-4.51), 0.002	2.71 (1.31-5.61), 0.007	3.60 (1.31-9.84), 0.013	3.87 (1.16-12.96), 0.028

\*Adjusted for age, ETT result, prostate risk group, Morise risk score, and body mass index (quadratic). †Thirteen patients in the short-term cohort who received additional ADT after ETT to bring their cumulative ADT exposure to >6 months were excluded from CV mortality analyses.  
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; OR = odds ratio; other abbreviations as in Tables 1 and 3.

**PROLONGED ADT EXPOSURE.** Of 150 ADT-exposed patients, ADT use was prolonged (>6 months) in 51 patients (34.0%) with a median exposure duration of ADT 28 months (IQR: 12 to 52 months). There were no significant differences in baseline demographics, CV risk factors, or medication usage when patients with prolonged ADT exposure were compared with those exposed to ADT for  $\leq$ 6 months (Table 1). Patients treated with prolonged ADT were more likely to have been treated with prostatectomy (39.2% vs. 17.2%;  $p = 0.001$ ), but less likely to have received radiation therapy (54.9% vs. 81.8%;  $p = 0.001$ ) (Table 2).

**EXERCISE TREADMILL TEST.** Indications for ETT were similar across cohorts (Table 3). ETT was normal in 450 patients (73.1%), abnormal in 103 (16.7%), and inconclusive in 63 (10.2%). The distribution of ETT results did not differ significantly based on ADT exposure or duration of exposure (Table 3).

**REDUCED CARDIORESPIRATORY FITNESS.** The mean METs achieved by the entire cohort were  $9.5 \pm 3.0$  METs, and CRF was reduced ( $\leq$ 8 METs) in 225 patients (36.5%). The frequency of reduced CRF was significantly higher among ADT-exposed patients compared with ADT-naive patients (48.7% vs. 32.6%;  $p < 0.001$ ) (Figure 2). ADT exposure was associated with an almost 2-fold increased likelihood of reduced CRF among PC patients (odds ratio [OR]: 1.96; 95% CI: 1.35 to 2.85;  $p < 0.001$ ) (Table 4); this association remained statistically significant after adjusting for potential confounders, including age, ETT result, PC risk group, Morise risk score, and BMI (Table 4). Additional multivariable models that included atrioventricular blocking medications, prostatectomy, or PC nonchemical recurrence and/or progression did not yield significantly different results (data not shown). In exploratory unadjusted analyses, a relative inverse linear dose-response effect of ADT exposure on CRF was observed (Supplemental Figure 1).

In unadjusted analysis, both short-term ADT exposure (OR: 1.72; 95% CI: 1.11 to 2.67;  $p = 0.016$ ) and prolonged ADT exposure (OR: 2.52; 95% CI: 1.40 to 4.51;  $p = 0.002$ ) were each associated with increased risk of reduced CRF among PC patients as compared to those with no exposure to ADT. However, in adjusted analyses, only prolonged ADT exposure (OR: 2.71; 95% CI: 1.31 to 5.61;  $p = 0.007$ ) remained significantly associated with reduced CRF, whereas the strength of the association with short-term exposure was attenuated and of borderline statistical significance (OR: 1.71; 95% CI: 1.00 to 2.94;  $p = 0.052$ ) (Table 4).

**CARDIOVASCULAR MORTALITY.** There were 28 CV deaths over a median follow-up of 4.2 years (IQR: 2.3 to 7.1 years) after the ETT; 17 occurred in ADT-naive patients and 11 in ADT-exposed patients. Any ADT therapy was associated with a >2-fold increased risk of CV death (HR: 2.36; 95% CI: 1.10 to 5.06;  $p = 0.027$ ). However, this association was not statistically significant after adjusting for age, ETT result, PC risk group, Morise risk score, and BMI (HR: 2.14; 95% CI: 0.83 to 5.50;  $p = 0.115$ ) (Table 4). Prolonged ADT exposure was associated with a significantly higher hazard of CV mortality in unadjusted (HR: 3.60; 95% CI: 1.31 to 9.84;  $p = 0.013$ ) and adjusted (HR: 3.87; 95% CI: 1.16 to 12.96;  $p = 0.028$ ) analyses (Table 4, Figure 3). Short-term ADT exposure was not significantly associated with CV mortality in unadjusted or adjusted analyses (Table 4, Figure 3). Across the entire study cohort, reduced CRF ( $\leq$ 8 METs) was associated with a significantly higher risk of CV mortality (HR: 4.60; 95% CI: 2.03 to 10.46;  $p < 0.001$ ).

## DISCUSSION

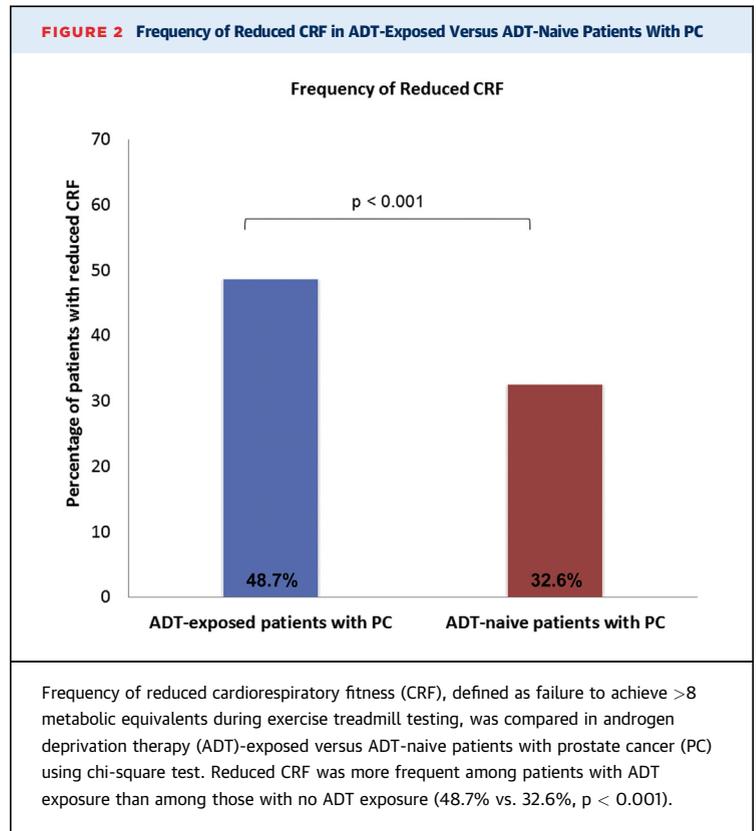
This study investigated the effect of ADT exposure on CRF and CV mortality in 616 patients with PC and a high prevalence of baseline CV risk factors. We

observed that any ADT exposure was associated with reduced CRF. Additional analyses stratified by duration of ADT exposure prior to ETT suggest that this observation was driven largely by prolonged ADT use (>6 months). Similarly, prolonged ADT exposure was associated with an almost 4-fold increased adjusted risk of CV mortality.

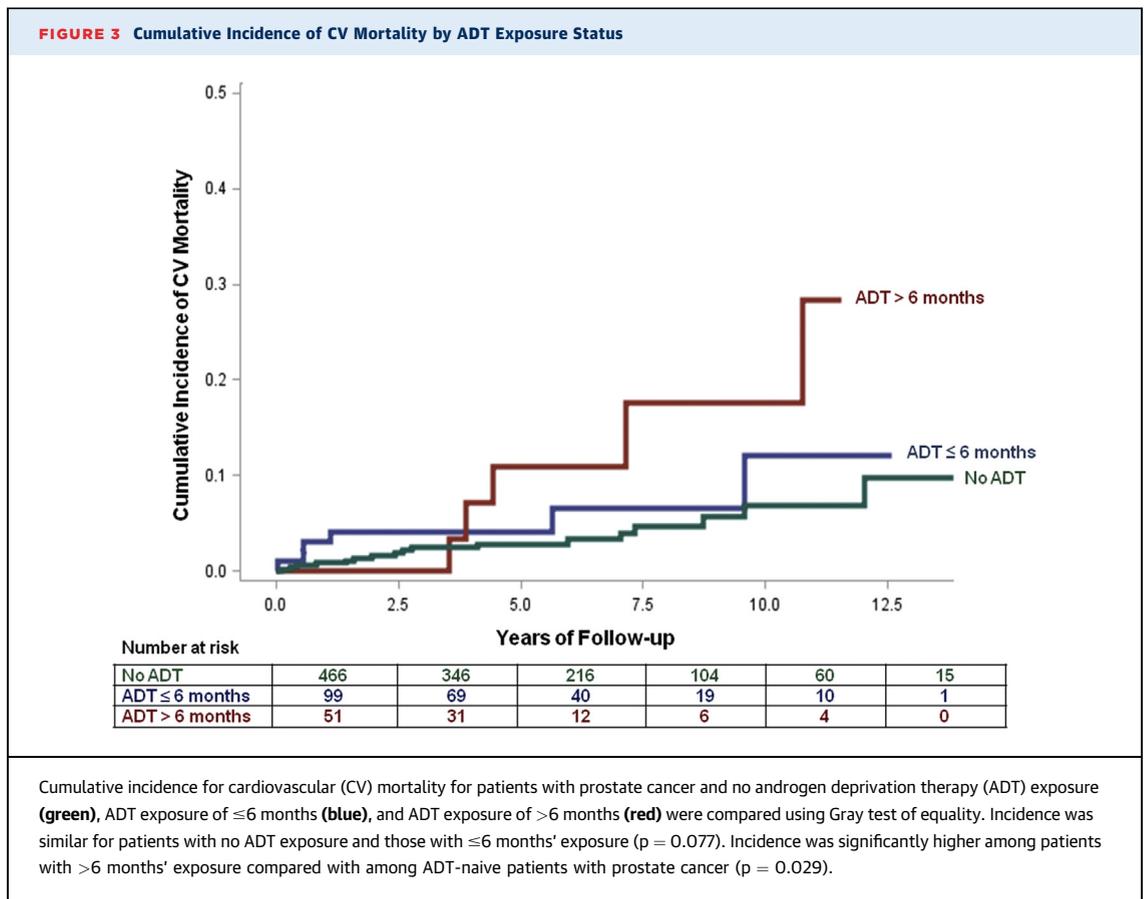
Our findings advance the current understanding of the influence of both ADT exposure and the duration of ADT exposure on CRF. Use of ADT-naive patients with PC as the control group rather than age-matched healthy individuals to explore ADT-mediated effects on CRF is a key strength of this study. Wall et al. (20) demonstrated lower maximal oxygen uptake (10th to 15th percentiles) during ETTs in a comparison of 112 patients with PC treated with ADT and age-matched healthy individuals. The same group reported significantly lower CRF in those who received  $\geq 3$  months of ADT compared with those with <3 months of ADT exposure in analyses that did not control for potential confounders (20,29). Our larger study offers additional insight by demonstrating that whereas prolonged ADT exposure was associated with a 2.7-fold increased likelihood of reduced CRF compared with in ADT-naive patients with PC after adjusting for key confounders, the association with short-term ADT exposure was of borderline significance ( $p = 0.052$ ) with a smaller effect size (OR: 1.71).

Results of existent studies that have investigated the association between ADT and CV mortality are conflicting. One large observational cohort study showed that gonadotropin-releasing hormone agonist use leads to increased risk of sudden cardiac death following exposure for 5 to 12 months, but not after treatment regimens lasting 1 to 4 months (30). Similarly, an increased risk of sudden cardiac death was observed with ADT use in the veteran population (8); elevated CV mortality was reported with ADT use in patients who received radical prostatectomy as initial treatment (10); and a shorter time to fatal myocardial infarction was noted in patients receiving 6 months of ADT compared with ADT-naive patients from a post hoc analysis combining data from 3 randomized control trials (31). These studies are consistent with our findings that ADT use is associated with increased CV mortality, although we were able to demonstrate this association only for patients exposed to ADT for >6 months.

Conversely, other studies have failed to demonstrate any association between ADT use and CV mortality. A meta-analysis of 8 trials showed no significant difference in CV mortality between patients receiving ADT and control individuals (14). However, the control individuals in some of these trials did



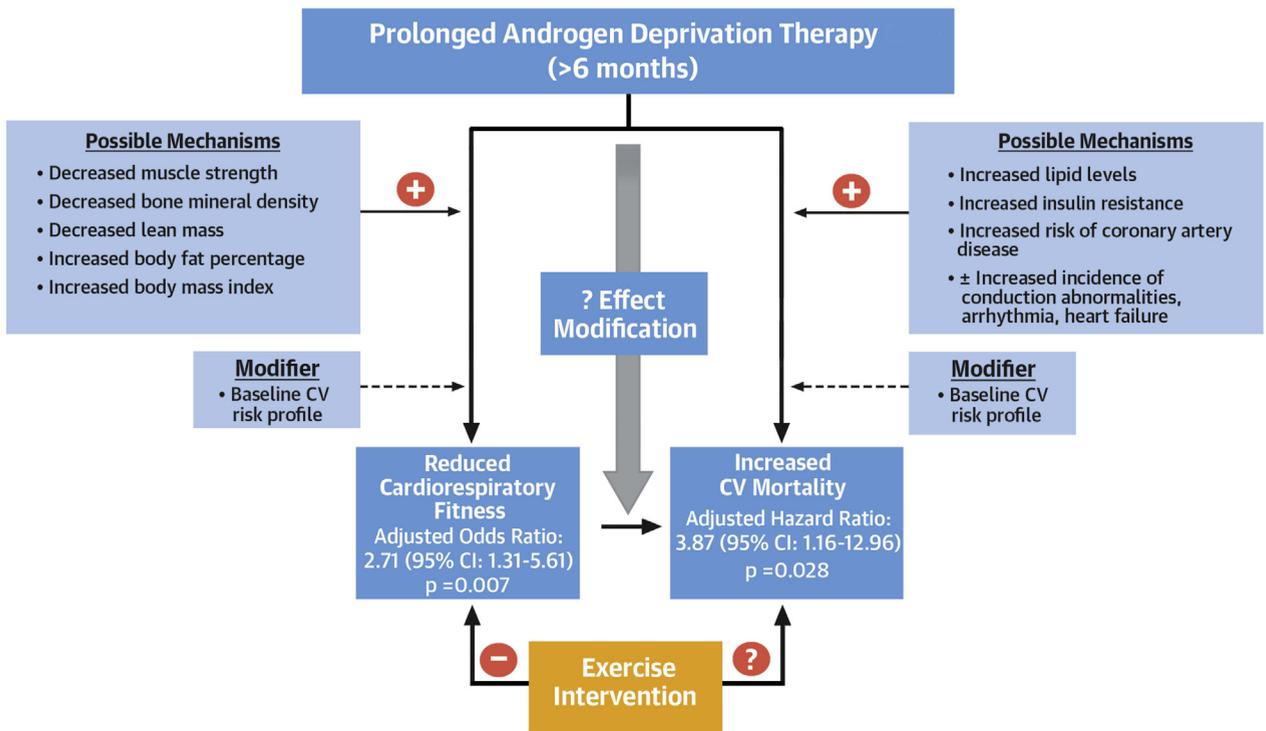
receive ADT after the initial treatment phase following randomization, which may have limited the ability to detect a treatment effect on CV mortality (32). A matched cohort study comparing the impact of  $\geq 6$  months ADT or bilateral orchiectomy in patients with PC versus in ADT-naive patients with PC did not find any association with increased risk of either myocardial infarction or sudden cardiac death (13). A reanalysis of patients treated with the combination of goserelin and radiation therapy versus radiation therapy alone found no increased risk of CV mortality with goserelin (33). Our finding that CV mortality risk may be a function of duration of ADT exposure might in part explain why some studies failed to demonstrate any association with CV mortality. In our study, ADT exposure within the entire cohort was not independently associated with increased CV mortality ( $p = 0.115$ ), and it was only after stratifying analyses by duration of ADT exposure that an independent association between prolonged ADT exposure and CV mortality was observed. Whether the CV implications of ADT-associated metabolic perturbations are cumulative over duration of exposure is uncertain. Alternatively, in contrast with large population studies that report incident CV disease



within 6 months of starting ADT (11,30), it is important to acknowledge that the absence of significant associations between short-term ADT use and CV mortality in this study may simply reflect the relatively small sample size and number of events. Other reasons why our results may differ from these studies include differences in the definition of CV mortality and in the range of ADT agents considered. Moreover, baseline CV risk was higher in our study and may have modified the association of ADT exposure and CV mortality. In support of this, a retrospective study found that the use of hormonal therapy was associated with increased all-cause mortality in patients with pre-existing heart failure or ischemic heart disease but not in those with  $< 2$  risk factors for coronary artery disease (12). In our study, the majority of the patients (81.8%) had  $\geq 2$  CV risk factors. Although baseline CV risk may well potentiate the CV risk of ADT exposure, multivariable analyses confirmed an independent association of prolonged ADT exposure with both reduced CRF and CV mortality after controlling for this baseline CV risk using the aggregate Morise score.

Multiple mechanisms likely mediate the negative association of ADT and CRF observed in this study. ADT has been associated with decreased muscular strength (18,34) that can occur after only 3 months of exposure (18). ADT has also been linked to decreases in bone mineral density and lean muscle mass and to increases in BMI and body fat percentage (34,35); these changes in body composition could also undermine CRF. Similarly, many factors likely contribute to the increased risk of CV mortality associated with prolonged ADT exposure observed in our study. Studies have linked ADT use to increased incidence of conduction disorders (36), arrhythmias (36,37), heart failure (36), and coronary artery disease (8,30,38). Predisposition to CV events is greater among patients with PC and pre-existing CV disease (11,36). Furthermore, metabolic side effects of ADT, including increased lipid levels (38), insulin resistance (39), and higher incidence of diabetes (6,30,38), may also mediate increased CV mortality. Our study proposes an additional mechanism through which ADT use could contribute to increased CV mortality, namely reduced CRF (Central Illustration). The influence of ADT-independent factors prevalent in cancer

**CENTRAL ILLUSTRATION** Potential Mechanisms Underlying Association of Prolonged ADT Exposure With Reduced CRF and Increased CV Mortality



Gong, J. et al. *J Am Coll Cardiol CardioOnc.* 2020;2(4):553-63.

Association of prolonged androgen deprivation therapy (ADT) exposure with reduced cardiorespiratory fitness (CRF) and increased cardiovascular (CV) mortality are presented together with some proposed mechanisms. Baseline CV risk modifies these associations. Reduced CRF may also in part mediate increased risk of CV mortality. ADT exposure may not only directly influence CRF and CV mortality but may also modify the association between CRF and CV mortality. An exercise intervention concurrent with ADT may mitigate against reduced CRF, and whether this could offset some of the increased risk of CV mortality warrants investigation.

patients such as chronic fatigue, sleep disorders, depression, pain, anemia, and deconditioning on CRF and associated adverse CV outcomes must also be considered (40,41).

Previous studies have demonstrated strong associations among CRF and all-cause and CV mortality, CV morbidity, and CV risk factors (15-17). It is possible that ADT exposure might modify this association of CRF with mortality. Two prospective randomized clinical trials (n = 57 and n = 100, respectively) have shown that structured exercise programs can rescue the adverse effects of ADT use including functional performance, muscle strength, lean muscle mass (42-44), with greater beneficial effects seen with prolonged ADT exposure (44). Whether such exercise interventions can reduce CV morbidity and mortality in ADT-exposed patients requires further evaluation.

**STUDY LIMITATIONS.** The retrospective nature of this study poses limitations. Missing data precluded inclusion of all patients who were referred for ETTs after a diagnosis of PC (Figure 1). However, missing data were considered random and noninformative. This PC cohort had high baseline CV risk reflecting selection bias introduced by studying patients clinically referred for ETTs. This facilitated an assessment of prolonged ADT exposure in a CV risk-enriched cohort but does limit the generalizability of findings to the broader PC population. However, we present multivariable analyses that attempt to control for key potential confounders in a more comprehensive manner than prior similar studies did. We were unable to explore the influence of time from ADT completion on CRF assessment, which limits inference on the relative contribution of duration of ADT

exposure versus time from ADT exposure on CRF. The relatively small sample size and number of events could have limited the ability to detect significant associations among short-term ADT use and reduced CRF (a trend was observed) or CV mortality, respectively. This study was not designed to test whether ADT exposure is an effect modifier of the association between CRF and mortality.

**CLINICAL IMPLICATIONS.** This study highlights that patients with PC and high baseline CV risk are at increased risk of reduced CRF and CV mortality when exposed to prolonged ADT regimens. Whereas prolonged ADT certainly plays a role in the treatment of PC, these findings emphasize the need to consider CV surveillance and risk modification during and after ADT exposure. A clinical trial is warranted to determine whether exercise interventions concurrent with ADT prescription can mitigate CRF impairment and CV risk.

## CONCLUSIONS

Among patients with PC and high baseline CV risk, prolonged ADT exposure was independently associated with reduced CRF and increased CV mortality. Reduced CRF may in part mediate the increased CV risk that we observed and may represent a therapeutic target. The potential merit of exercise interventions concurrent with prolonged ADT prescription in patients with PC and high CV risk warrants investigation.

## AUTHOR DISCLOSURES

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Prolonged ADT exposure in patients with high baseline CV risk is associated with reduced CRF and increased CV mortality among patients with PC. Patients with PC treated with prolonged ADT should be advised of increased CV risk and strategies to mitigate CV risk and maintain CRF should be considered.

**TRANSLATIONAL OUTLOOK:** Mechanisms that underlie reduced CRF and higher CV mortality in the setting of prolonged ADT exposure in patients with PC require additional study. Interventions to preserve CRF and mitigate CV risk in patients with PC exposed to prolonged ADT, adapted before, during, and after ADT, merit further investigation.

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**KEY WORDS** androgen deprivation therapy, cardio-oncology, cardiorespiratory fitness, cardiovascular mortality, cardiovascular risk, prostate cancer

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**APPENDIX** For a supplemental figure, please see the online version of this paper.



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