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ORIGINAL REPORT

Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer

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See accompanying editorial on page 1232

A B S T R A C T

Purpose
Findings on the association between risk of cardiovascular disease (CVD) and the duration and type of androgen-deprivation therapy (ADT) in men with prostate cancer (PCa) are inconsistent.

Methods
By using data on filled drug prescriptions in Swedish national health care registers, we investigated the risk of CVD in a cohort of 41,362 men with PCa on ADT compared with an age-matched, PCa-free comparison cohort (n = 187,785) by use of multivariable Cox proportional hazards regression models.

Results
From 2006 to 2012, 10,656 men were on antiandrogens (AA), 26,959 were on gonadotropin-releasing hormone (GnRH) agonists, and 3,747 underwent surgical orchiectomy. CVD risk was increased in men on GnRH agonists compared with the comparison cohort (hazard ratio [HR] of incident CVD, 1.21; 95% CI, 1.18 to 1.25; and orchiectomy: HR, 1.16; 95% CI, 1.08 to 1.25). Men with PCa on AA were at decreased risk (HR of incident CVD, 0.87; 95% CI, 0.82 to 0.91). CVD risk was highest during the first 6 months of ADT in men who experienced two or more cardiovascular events before therapy, with an HR of CVD during the first 6 months of GnRH agonist therapy of 1.91 (95% CI, 1.66 to 2.20), an HR of CVD with AA of 1.60 (95% CI, 1.24 to 2.06), and an HR of CVD with orchiectomy of 1.79 (95% CI, 1.16 to 2.76) versus the comparison cohort.

Conclusion
Our results support that there should be a solid indication for ADT in men with PCa so that benefit outweighs potential harm; this is of particular importance among men with a recent history of CVD.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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INTRODUCTION

Androgen-deprivation therapy (ADT) is the first line of treatment for disseminated prostate cancer (PCa) and is also used as neoadjuvant and adjuvant therapy in conjunction with radiotherapy for locally advanced PCa.[1-3] Alongside its therapeutic benefits, ADT increases the risk of various metabolic aberrations including decreased insulin sensitivity, changes in lipid profiles, and an increased risk of cardiovascular disease (CVD).[4,5] The increased risk of CVD in men with PCa on ADT has been observed in a number of observational studies,[6-17] and one proposed explanation of this relationship is that ADT interferes with the cardioprotective property of testosterone, thereby increasing the risk for adverse events.[14-16,18]

In a previous study, we compared 76,000 men with PCa to the general Swedish male population and showed an increased risk of incident and fatal CVD among all men with PCa.[16] The highest relative risk was observed for those on ADT (eg, standardized incidence ratio for ischemic heart disease, 1.32; 95% CI, 1.27 to 1.36).[16] Together with six other studies, these data were used by the US Food and Drug Administration to require a risk label on gonadotropin-releasing hormone (GnRH) agonists for increased risk of diabetes and certain CVDs (heart attack, sudden cardiac death, and stroke).[19]

Nonetheless, there is considerable disagreement on the association between ADT and CVD in observational studies versus randomized clinical trials (Fig 1).[6-17,20-24] Some of the limiting factors have been lack of data on different types and duration of ADT, comparison to patients with PCa not treated with ADT rather than age-matched, PCa-free men, and not taking into account pre-existing CVD. Thus, to further elucidate the impact of ADT and its

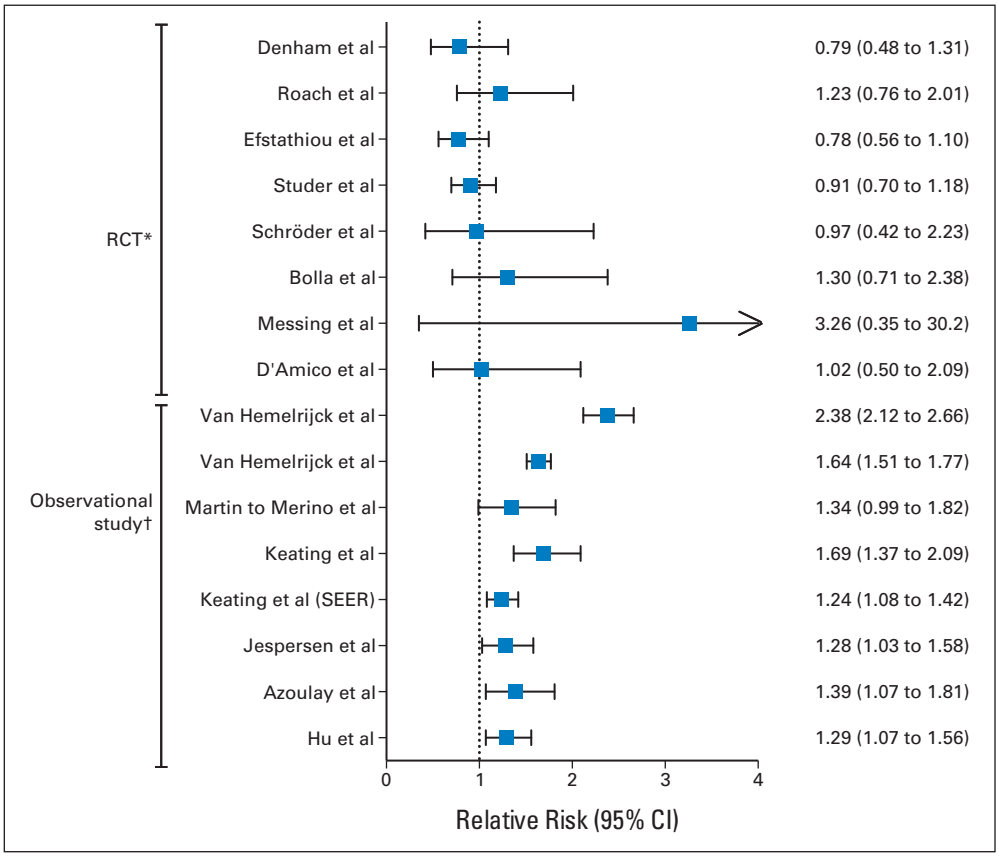

Fig 1. Relative risks of cardiovascular disease in men with prostate cancer on androgen-deprivation therapy in published randomized clinical trials (RCTs) versus observational studies. (*) Adopted from Nguyen et al.[24] (†) Adopted from Bosco et al (manuscript under review).

timing on the risk of CVD, we expanded our previous study cohort in the Prostate Cancer Database Sweden (PCBaSe) by extending follow-up time and adding a series of PCa-free comparison men and data on filled prescriptions from the National Prescribed Drug Register.

METHODS

Study Population and Data Collection

PCBaSe Sweden 2.0 is based on the National Prostate Cancer Register (NPCR) of Sweden, which became nationwide in 1998 and covers 98% of all newly diagnosed, biopsy-confirmed PCas, as compared with the Swedish Cancer Registry.[25] NPCR includes information on date of diagnosis, age at diagnosis, tumor stage and differentiation, serum levels of prostate-specific antigen (PSA) at time of diagnosis, and primary treatment within 6 months after date of diagnosis.[25] By use of the Swedish 10-digit personal identity number, five PCa-free men from the general population in Sweden were randomly selected within sets of men who matched the index patient on age (± 1 year) and county of residence from the PCBaSe cohort. Patients and the comparison cohort in PCBaSe were subsequently linked to a series of national health care registers and demographic databases to obtain data on discharge diagnoses, surgical procedures, socioeconomic status, and cause of death to be included in the PCBaSe database.[25] Comorbidities were measured by the Charlson comorbidity index (CCI), which assigns weights to a number of medical conditions, including diabetes and hypertension, allowing for a final comorbidity score to be calculated for each individual.[26] Each condition is assigned a score of 1, 2, 3, or 6, and the final CCI score is given as the sum of these scores. Individuals are grouped into CCI categories for final scores of 0, 1, 2, or 3+. Information on filled prescriptions of antiandrogens (AA) and GnRH agonists, including date of initiation, duration, and daily drug dose was obtained from the National Prescribed Drug Register.[27] The Research Ethics Board at Umeå University (Umeå, Sweden) approved this study.

Information in PCBaSe on age, serum PSA, treatment at time of diagnosis, tumor grade and stage, educational level, history of CVD (primary diagnoses), and cause and date of death was used. PCa risk category was defined according to a modification of the National Comprehensive Cancer Network guidelines,[28] as follows: low risk: T1-2, Gleason score of 2 to 6, and PSA less than 10 ng/mL; intermediate risk: T1-2, Gleason score of 7, and/or PSA of 10 to 20 ng/mL; high risk: T3 and/or Gleason score of 8 to 10 and/or PSA of 20 to 50 ng/mL; regionally metastatic/locally advanced: T4 and/or N1 and/or PSA of 50 to 100 ng/mL in the absence of distant metastases (M0 or MX); distant metastases: M1 and/or PSA more than 100 ng/mL.[25] For the current analysis, we selected men with PCa who received ADT as primary treatment or because of disease progression. Using information from the Patient Register and the National Prescribed Drug Register, ADT was grouped into AA monotherapy; GnRH agonist monotherapy, including men receiving short-term AA as flare protection or long-term AA (> 6 months) for combined androgen blockade (CAB); and surgical orchiectomy. We performed a sensitivity analysis whereby we excluded men receiving CAB from the GnRH group and saw negligible differences in risk of CVD; the results remained unchanged or changed in the second decimal, and thus, those on CAB therapy were included in the GnRH group for all analyses (Appendix Table A1, online only).

Analysis

Analysis was performed on the association between exposure to different types of ADT and incident and fatal overall CVD (International Classification of Diseases, Tenth Revision [ICD-10]: I00 through I99) and subtypes thereof, including ischemic heart disease (ICD-10: I20 through I25), arrhythmia (ICD-10: I44 through I49), heart failure (ICD-10: I50), and stroke (ICD-10: I60 through I64, G45). Because PCBaSe has detailed follow-up on five age- and county-matched PCa-free men for every patient with PCa, we conducted a prospective cohort study whereby men with PCa on ADT and PCa-free men

Table 1. Event Counts and HRs for Men With Prostate Cancer Who Did and Did Not Undergo TURP, Palliative RT, and Nephrostomy

Procedure	No. of Events	No. of Men Exposed	Crude		Multivariable*	
			HR	95% CI	HR	95% CI
TURP						
Incident CVD						
No	8,558	38,140	1.00	Reference	1.00	Reference
Yes	679	3,979	1.11	1.03 to 1.20	1.14	1.05 to 1.23
Fatal CVD						
No	3,958	40,258	1.00	Reference	1.00	Reference
Yes	369	4,870	1.15	1.04 to 1.28	1.14	1.03 to 1.27
Palliative RT						
Incident CVD						
No	8,446	38,504	1.00	Reference	1.00	Reference
Yes	791	6,519	1.25	1.17 to 1.35	1.35	1.25 to 1.46
Fatal CVD						
No	4,087	40,773	1.00	Reference	1.00	Reference
Yes	240	7,455	1.04	0.92 to 1.19	1.17	1.02 to 1.34
Nephrostomy						
Incident CVD						
No	9,102	38,922	1.00	Reference	1.00	Reference
Yes	135	1,276	1.64	1.38 to 1.95	1.47	1.24 to 1.74
Fatal CVD						
No	4,237	41,257	1.00	Reference	1.00	Reference
Yes	90	1,661	2.19	1.78 to 2.70	1.93	1.56 to 2.38

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; RT, radiotherapy; TURP, transurethral resection of the prostate.
*Adjusted for type of androgen-deprivation therapy, tumor risk category, Charlson comorbidity index, civil status, educational level, and baseline history of CVD (International Classification of Diseases, Tenth Revision: I00 through I99) using age as a timescale.

were observed to identify occurrence of CVD. Hazard ratios (HRs) for incident and fatal CVD were calculated for men with PCa versus the comparison cohort with left truncation using a Cox proportional hazards regression model with age as a timescale, accounting for tumor risk category, CCI, civil status, educational level, and baseline history of CVD (ICD-10: I00 to I99).[25] Left truncation was applied because the National Prescribed Drug Register started on July 1, 2005, and we allowed for a run-in period of 6 months. Because of its linkage with the National Prescribed Drug Register, PCBaSe provides information on both primary (recorded in the NPCR and the National Prescribed Drug Register) and secondary therapy (registered in the National Prescribed Drug Register only).[25] Furthermore, the National Prescribed Drug Register enables an accurate calculation of the start date of ADT. The association between duration of ADT and first CVD event, incident or fatal, was assessed using multivariable Cox proportional hazards models with left truncation, whereby follow-up time was divided into the following intervals: less than 6 months, 6 to 18 months, 18 to 36 months, and more than 36 months since start of ADT. We also compared the number of nonfatal CVD events before and after initiation of ADT for both men with PCa and PCa-free men. These crude comparisons are represented as risk ratios.[13] Finally, we also adjusted for PCa disease progression by using the following proxy variables as time-dependent covariates: transurethral resection of the prostate (TURP) indicating subvesical obstruction, palliative radiotherapy indicating pain from bone metastases, and use of nephrostomy indicating overgrowth on the ureter. We included these proxies of disease progression as covariates in the Cox proportional hazards model because we observed an increased risk of incident CVD for men with PCa who had one of these indications of disease progression versus men with PCa who did not (HR for CVD for TURP *v* no TURP, 1.11; 95% CI, 1.03 to 1.20; HR for CVD for palliative radiotherapy *v* no radiotherapy, 1.25; 95% CI, 1.17 to 1.35; HR for CVD for nephrostomy *v* no nephrostomy, 1.64; 95% CI, 1.38 to 1.95; Table 1).

All data management was performed using SAS version 9.3 (SAS Institute, Cary, NC). All data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 41,362 men with PCa, 10,656 were on AAs, 7,789 were on GnRH agonists, 18,166 were on GnRH agonists with flare protection, 1,004 were on CAB, and 3,747 underwent surgical orchiectomy (Table 2). Table 3 lists the HRs for overall incident and fatal CVD for different types of ADT compared with the comparison cohort. There was an increased risk of incident CVD for men on GnRH agonists (HR, 1.21; 95% CI, 1.18 to 1.25) and who underwent orchiectomy (HR, 1.16; 95% CI, 1.08 to 1.25) compared with the comparison cohort. Men on AA were at lower risk for CVD (HR, 0.87; 95% CI, 0.82 to 0.91).

To further disentangle the association between ADT and CVD, we performed an analysis for men with PCa who received ADT as primary treatment (Table 3). The HRs for incident and fatal CVD in men treated with GnRH agonists or orchiectomy remained similar, as in the analysis of the full study group. The HR of incident CVD was 1.19 (95% CI, 1.15 to 1.23) for men on GnRH agonists and 1.12 (95% CI, 1.04 to 1.21) for men who underwent orchiectomy. HRs in the AA group were marginally increased for incident and fatal CVD but were not statistically significant (HR for incident CVD, 0.89; 95% CI, 0.83 to 0.95) compared with the comparison cohort.

To account for additional CVD risk factors, we next ran an analysis for all men with PCa without a baseline history of CVD and men with a history of statin use before PCa diagnosis (Table 3). Men with no history of CVD receiving GnRH agonists were still at increased risk of incident and fatal CVD. The HR for incident CVD was 1.19 (95% CI, 1.14 to 1.24). Men who underwent surgical orchiectomy were also at an increased risk for CVD (HR for incident CVD, 1.13;

Table 2. Baseline Demographics and Clinical Characteristics of Patients With PCa on ADT and the Matched Comparison Cohort in PCBaSe Sweden 3.0

Demographic or Clinical Characteristic	Comparison Cohort (n = 187,785)		Patients With PCa (n = 41,362)		Patients on Antiandrogens (n = 10,656)		Patients on GnRH Agonists (n = 7,789)		Patients on GnRH Agonists With Flare Protection (n = 18,166)		Patients on Combined Androgen Blockade (n = 1,004)		Patients With Surgical Orchiectomy (n = 3,747)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Follow-up time, years														
Mean	4.4		4.0		3.5		5.3		3.8		3.3		4.3	
SD	3.2		3.1		2.6		3.5		3.0		2.6		3.4	
Age, years														
Mean	75.3		75.7		73.7		75.8		76.4		70.4		78.6	
SD	8.1		8.0		7.6		7.8		8.0		9.5		7.2	
< 65	19,533	10.4	3,997	9.7	1,308	12.3	683	8.8	1,556	8.6	283	28.2	167	4.5
65-74	59,847	31.9	12,774	30.9	4,121	38.7	2,424	31.1	5,108	28.1	377	37.5	744	19.9
75-84	86,039	45.8	19,328	46.7	4,539	42.6	3,701	47.5	8,732	48.1	272	27.1	2,084	55.6
≥85	22,366	11.9	5,263	12.7	688	6.5	981	12.6	2,770	15.2	72	7.2	752	20.1
Year of PCa diagnosis														
1997-2001	19,979	10.6	6,020	14.6	1,215	11.4	1,958	25.1	2,127	11.7	77	7.7	643	17.2
2002-2005	54,757	29.2	12,420	30.0	2,837	26.6	2,988	38.4	5,154	28.4	199	19.8	1,242	33.1
2006-2009	73,117	38.9	14,908	36.0	4,178	39.2	2,074	26.6	6,867	37.8	478	47.6	1,311	35.0
2010-2012	39,932	21.3	8,014	19.4	2,426	22.8	769	9.9	4,018	22.1	250	24.9	551	14.7
Charlson comorbidity index at onset of ADT														
0	125,199	66.7	26,946	65.1	7,480	70.2	5,052	64.9	11,438	63.0	706	70.3	2,270	60.6
1	31,063	16.5	7,382	17.8	1,707	16.0	1,390	17.8	3,338	18.4	160	15.9	787	21.0
2	17,967	9.6	4,003	9.7	882	8.3	761	9.8	1,901	10.5	81	8.1	378	10.1
≥3	13,556	7.2	3,031	7.3	587	5.5	586	7.5	1,489	8.2	57	5.7	312	8.3
Risk category														
No PCa	187,785	100.0												
Low risk			2,458	5.9	1,195	11.2	439	5.6	687	3.8	36	3.6	101	2.7
Intermediate risk			6,902	16.7	3,051	28.6	1,284	16.5	2,173	12.0	75	7.5	319	8.5
High risk			14,806	35.8	4,367	41.0	3,210	41.2	5,867	32.3	248	24.7	1,114	29.7
Regionally metastatic			5,955	14.4	1,200	11.3	1,386	17.8	2,682	14.8	158	15.7	529	14.1
Distant metastases			10,888	26.3	713	6.7	1,397	17.9	6,647	36.6	481	47.9	1,650	44.0
Missing data			353	0.9	130	1.2	73	0.9	110	0.6	6	0.6	34	0.9
Initial treatment														
No PCa	187,785	100.0												
ADT			31,149	75.3	5,266	49.4	6,075	78.0	15,565	85.7	827	82.4	3,416	91.2
Curative treatment			4,848	11.7	3,103	29.1	869	11.2	700	3.9	105	10.5	71	1.9
Active surveillance or watchful waiting			5,365	13.0	2,287	21.5	845	10.8	1,901	10.5	72	7.2	260	6.9
No. of previous CVD events (ICD-10: I00-I99)														
0	161,064	85.8	35,487	85.8	9,191	86.3	6,676	85.7	15,491	85.3	891	88.7	3,238	86.4
1	8,527	4.5	1,923	4.6	427	4.0	407	5.2	880	4.8	38	3.8	171	4.6
2	11,569	6.2	2,487	6.0	668	6.3	424	5.4	1,142	6.3	42	4.2	211	5.6
3+	6,625	3.5	1,465	3.5	370	3.5	282	3.6	653	3.6	33	3.3	127	3.4
Statin use before ADT initiation														
ADT before drug registry start	50,808	27.1	12,246	29.6	1,235	11.6	3,895	50.0	5,321	29.3	165	16.4	1,630	43.5
No	98,780	52.6	20,899	50.5	6,565	61.6	2,804	36.0	9,297	51.2	630	62.7	1,603	42.8
Yes	38,197	20.3	8,217	19.9	2,856	26.8	1,090	14.0	3,548	19.5	209	20.8	514	13.7
Level of education														
Low	89,824	47.8	20,200	48.8	4,290	40.3	4,068	52.2	9,173	50.5	413	41.1	2,256	60.2
Middle	62,552	33.3	13,880	33.6	3,938	37.0	2,517	32.3	6,003	33.0	352	35.1	1,070	28.6
High	31,549	16.8	6,719	16.2	2,337	21.9	1,088	14.0	2,707	14.9	227	22.6	360	9.6
Missing	3,860	2.1	563	1.4	91	0.9	116	1.5	283	1.6	12	1.2	61	1.6
Civil status														
Married	122,236	65.1	27,385	66.2	7,506	70.4	5,209	66.9	11,736	64.6	640	63.7	2,294	61.2
Single	65,549	34.9	13,977	33.8	3,150	29.6	2,580	33.1	6,430	35.4	364	36.3	1,453	38.8

Abbreviations: ADT, androgen-deprivation therapy; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; ICD-10, International Classification of Diseases, Tenth Revision; PCa, prostate cancer; PCBaSe, Prostate Cancer Database Sweden; SD, standard deviation.

Table 3. Event Counts and HRs for CVD in All Men With PCa, Men Who Received ADT at Time of Diagnosis, Men With No History of CVD Before Starting ADT, and Men With a History of Statin Use

	Comparison Cohort		Patients on Antiandrogens		Patients on GnRH Agonists ± Flare Protection		Patients With Surgical Orchiectomy		Comparison Cohort		Antiandrogens		GnRH Agonists ± Flare Protection		Surgical Orchiectomy	
CVD	No.	%	No.	%	No.	%	No.	%	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All men with PCa																
All incident CVD	42,235	23.5	1,511	14.4	6,830	24.9	896	26.1	1.00	Reference	0.87	0.82 to 0.91	1.21	1.18 to 1.25	1.16	1.08 to 1.25
Ischemic heart disease	13,808	7.5	514	4.9	2,143	7.5	259	7.1	1.00	Reference	0.94	0.86 to 1.03	1.17	1.11 to 1.24	1.08	0.94 to 1.22
Arrhythmia	10,263	5.5	369	3.5	1,537	5.3	183	5.0	1.00	Reference	0.90	0.81 to 1.00	1.12	1.05 to 1.19	1.03	0.88 to 1.20
Heart failure	10,468	5.6	281	2.6	1,868	6.4	257	7.0	1.00	Reference	0.80	0.71 to 0.90	1.24	1.16 to 1.32	1.10	0.97 to 1.26
Stroke	13,916	7.5	465	4.4	2,118	7.3	262	7.2	1.00	Reference	0.90	0.82 to 0.99	1.11	1.05 to 1.18	0.99	0.87 to 1.13
All fatal CVD	21,654	11.5	359	3.4	3,373	11.4	595	15.9	1.00	Reference	0.57	0.51 to 0.64	1.06	1.01 to 1.11	1.09	1.00 to 1.20
Ischemic heart disease	9,720	5.2	179	1.7	1,640	5.5	271	7.2	1.00	Reference	0.62	0.53 to 0.72	1.16	1.08 to 1.23	1.14	1.00 to 1.30
Arrhythmia	1,601	0.9	15	0.1	227	0.8	51	1.4	1.00	Reference	0.36	0.22 to 0.61	1.00	0.84 to 1.18	1.25	0.92 to 1.69
Heart failure	2,386	1.3	39	0.4	371	1.3	69	1.8	1.00	Reference	0.64	0.46 to 0.88	0.94	0.81 to 1.08	0.90	0.69 to 1.17
Stroke	2,807	1.5	46	0.4	460	1.6	67	1.8	1.00	Reference	0.53	0.39 to 0.71	1.12	0.99 to 1.27	0.99	0.76 to 1.28
Men who received ADT at time of diagnosis																
All incident CVD	42,235	23.5	877	8.4	5,628	20.5	803	23.4	1.00	Reference	0.89	0.83 to 0.95	1.19	1.15 to 1.23	1.12	1.04 to 1.21
Ischemic heart disease	13,808	7.5	309	2.9	1,798	6.3	233	6.4	1.00	Reference	0.99	0.88 to 1.12	1.18	1.11 to 1.26	1.06	0.92 to 1.22
Arrhythmia	10,263	5.5	226	2.1	1,263	4.3	166	4.5	1.00	Reference	0.98	0.86 to 1.13	1.10	1.02 to 1.19	1.02	0.86 to 1.20
Heart failure	10,468	5.6	182	1.7	1,597	5.5	225	6.1	1.00	Reference	0.83	0.71 to 0.97	1.22	1.14 to 1.31	1.03	0.90 to 1.19
Stroke	13,916	7.5	286	2.7	1,806	6.2	243	6.7	1.00	Reference	0.94	0.83 to 1.06	1.12	1.05 to 1.20	1.00	0.87 to 1.14
All fatal CVD	21,654	11.5	235	2.2	2,967	10.0	550	14.7	1.00	Reference	0.58	0.51 to 0.66	1.09	1.03 to 1.14	1.10	1.01 to 1.21
Ischemic heart disease	9,720	5.2	130	1.2	1,443	4.9	249	6.6	1.00	Reference	0.70	0.59 to 0.84	1.19	1.11 to 1.28	1.15	1.00 to 1.32
Arrhythmia	1,601	0.9	10	0.1	198	0.7	45	1.2	1.00	Reference	0.37	0.20 to 0.69	1.01	0.83 to 1.21	1.18	0.85 to 1.64
Heart failure	2,386	1.3	23	0.2	329	1.1	66	1.8	1.00	Reference	0.54	0.36 to 0.83	0.95	0.82 to 1.11	0.93	0.71 to 1.23
Stroke	2,807	1.5	29	0.3	405	1.4	62	1.7	1.00	Reference	0.52	0.36 to 0.76	1.15	1.01 to 1.32	0.99	0.76 to 1.30
Men with no history of CVD before starting ADT																
All incident CVD	23,810	13.2	800	7.6	3,972	14.5	542	15.8	1.00	Reference	0.81	0.75 to 0.87	1.19	1.14 to 1.24	1.13	1.03 to 1.24
Ischemic heart disease	7,680	4.2	266	2.5	1,145	4.0	146	4.0	1.00	Reference	0.87	0.77 to 0.99	1.10	1.02 to 1.19	1.02	0.86 to 1.22
Arrhythmia	5,499	3.0	175	1.6	856	2.9	106	2.9	1.00	Reference	0.81	0.69 to 0.94	1.10	1.01 to 1.21	0.96	0.78 to 1.18
Heart failure	4,717	2.5	110	1.0	926	3.2	136	3.7	1.00	Reference	0.68	0.56 to 0.83	1.23	1.13 to 1.35	1.06	0.88 to 1.27
Stroke	8,674	4.7	302	2.8	1,333	4.6	154	4.2	1.00	Reference	0.93	0.83 to 1.05	1.09	1.01 to 1.17	0.85	0.72 to 1.01
All fatal CVD	11,379	6.1	191	1.8	1,861	6.3	347	9.3	1.00	Reference	0.57	0.49 to 0.66	1.07	1.00 to 1.13	1.08	0.96 to 1.22
Ischemic heart disease	4,944	2.6	91	0.9	846	2.9	147	3.9	1.00	Reference	0.61	0.49 to 0.75	1.14	1.04 to 1.24	1.10	0.92 to 1.31
Arrhythmia	846	0.5	7	0.1	126	0.4	29	0.8	1.00	Reference	0.34	0.16 to 0.71	1.01	0.80 to 1.27	1.19	0.79 to 1.79
Heart failure	1,264	0.7	19	0.2	222	0.7	40	1.1	1.00	Reference	0.57	0.36 to 0.91	0.98	0.81 to 1.18	0.83	0.58 to 1.17
Stroke	1,600	0.9	29	0.3	283	1.0	46	1.2	1.00	Reference	0.57	0.39 to 0.84	1.15	0.98 to 1.35	1.07	0.78 to 1.47
Men with a history of statin use																
All incident CVD	9,594	5.3	491	4.7	1,443	5.3	139	4.1	1.00	Reference	0.86	0.78 to 0.95	1.20	1.12 to 1.28	1.06	0.89 to 1.26
Ischemic heart disease	3,529	1.9	196	1.8	560	1.9	54	1.5	1.00	Reference	0.98	0.84 to 1.14	1.31	1.18 to 1.46	1.25	0.95 to 1.66
Arrhythmia	2,229	1.2	117	1.1	270	0.9	20	0.5	1.00	Reference	0.95	0.78 to 1.15	1.01	0.87 to 1.17	0.78	0.49 to 1.22
Heart failure	2,369	1.3	99	0.9	382	1.3	41	1.1	1.00	Reference	0.81	0.65 to 1.01	1.18	1.04 to 1.35	1.01	0.73 to 1.40
Stroke	2,505	1.4	111	1.0	366	1.3	38	1.0	1.00	Reference	0.80	0.66 to 0.98	1.16	1.02 to 1.32	1.18	0.84 to 1.65
All fatal CVD	3,159	1.7	99	0.9	481	1.6	70	1.9	1.00	Reference	0.62	0.50 to 0.76	1.01	0.90 to 1.13	1.15	0.89 to 1.48
Ischemic heart disease	1,671	0.9	55	0.5	279	0.9	41	1.1	1.00	Reference	0.63	0.48 to 0.85	1.11	0.95 to 1.30	1.28	0.92 to 1.79
Arrhythmia	152	0.1	3	0.0	25	0.1	5	0.1	1.00	Reference	0.43	0.13 to 1.40	1.28	0.78 to 2.08	2.18	0.84 to 5.68
Heart failure	290	0.2	15	0.1	43	0.1	8	0.2	1.00	Reference	1.20	0.68 to 2.11	0.93	0.63 to 1.39	1.25	0.58 to 2.70
Stroke	376	0.2	13	0.1	57	0.2	5	0.1	1.00	Reference	0.57	0.31 to 1.04	0.95	0.67 to 1.35	0.65	0.26 to 1.66

Abbreviations: ADT, androgen-deprivation therapy; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; PCa, prostate cancer.

Table 4. Incidence per 1,000 Person-Years and RRs for All Types of CVD Assessed Before and After Initiation of ADT in Men With PCa Versus the Comparison Cohort

CVD	Antiandrogens						GnRH Agonists						Orchiectomy					
	Patients With PCa		Comparison Cohort				Patients With PCa		Comparison Cohort				Patients With PCa		Comparison Cohort			
	No.	Incidence per 1,000 Person-Years	No.	Incidence per 1,000 Person-Years	RR	95% CI	No.	Incidence per 1,000 Person-Years	No.	Incidence per 1,000 Person-Years	RR	95% CI	No.	Incidence per 1,000 Person-Years	No.	Incidence per 1,000 Person-Years	RR	95% CI
CVD																		
2 years before ADT initiation	934	52.1	4,587	55.8	0.93	0.87 to 1.00	2,409	73.2	9,946	63.7	1.15	1.10 to 1.20	287	72.4	1,421	75.5	0.96	0.84 to 1.08
2 years after ADT initiation	1,628	139.7	7,939	143.7	0.97	0.91 to 1.03	4,349	216.4	18,099	169.2	1.28	1.23 to 1.33	530	234.3	2,585	204.7	1.14	1.02 to 1.28
Ischemic heart disease																		
2 years before ADT initiation	293	15.8	1,576	18.5	0.86	0.76 to 0.97	762	22.1	3,292	20.2	1.10	1.01 to 1.19	91	22.0	420	21.1	1.04	0.83 to 1.30
2 years after ADT initiation	289	20.4	1,401	20.4	1.00	0.87 to 1.13	802	30.1	3,314	24.1	1.24	1.15 to 1.34	94	31.2	505	29.6	1.05	0.84 to 1.31
Arrhythmia																		
2 years before ADT initiation	216	11.6	1,106	12.9	0.90	0.77 to 1.04	520	15.0	2,298	14.0	1.07	0.98 to 1.18	53	12.7	335	16.8	0.76	0.56 to 1.00
2 years after ADT initiation	188	13.2	1,029	14.9	0.88	0.76 to 1.03	463	17.2	2,363	17.1	1.00	0.90 to 1.11	64	21.1	324	18.8	1.12	0.84 to 1.47
Heart failure																		
2 years before ADT initiation	111	5.9	644	7.5	0.79	0.65 to 0.96	379	10.9	1,613	9.8	1.11	1.00 to 1.25	60	14.4	267	13.3	1.08	0.82 to 1.41
2 years after ADT initiation	147	10.3	843	12.2	0.84	0.71 to 1.00	661	24.6	2,401	17.4	1.42	1.30 to 1.54	82	27.0	393	22.8	1.18	0.92 to 1.50
Stroke																		
2 years before ADT initiation	246	13.2	1,193	13.9	0.95	0.83 to 1.09	617	17.8	2,610	15.9	1.12	1.03 to 1.22	72	17.3	393	19.7	0.88	0.68 to 1.13
2 years after ADT initiation	225	15.8	1,184	17.2	0.92	0.80 to 1.06	657	24.4	3,038	22.1	1.11	1.02 to 1.20	81	26.6	440	25.7	1.04	0.81 to 1.30

Abbreviations: ADT, androgen-deprivation therapy; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; PCa, prostate cancer; RR, risk ratio.

95% CI, 1.03 to 1.24). The risk of CVD remained high for men with a history of statin use in the GnRH group (HR for incident CVD, 1.20; 95% CI, 1.12 to 1.28; Table 3).

To assess the impact of ADT on CVD risk in more detail, we also calculated risk ratios of incident CVD in the 2 years before and after initiation of ADT (Table 4). An even more increased risk of CVD was observed after initiation of GnRH agonists (HR for incident CVD before initiation, 1.15; 95% CI, 1.10 to 1.20; HR after initiation, 1.28; 95% CI, 1.23 to 1.33). Men receiving AA were not at statistically significantly increased risk of CVD before or after commencing ADT. Those who underwent orchiectomy were at increased risk of CVD after castration (HR for incident CVD before surgery, 0.96; 95% CI, 0.84 to 1.08; HR after surgery, 1.14; 95% CI, 1.02 to 1.28).

The association of ADT duration and number of previous CVD events is shown in Figure 2. Men with two or more CVD events, with the latest occurring within a year before initiation of ADT, were at the highest risk of CVD within the first 6 months of ADT (HRs for first CVD event since start of ADT: AA HR, 1.60; 95% CI, 1.24 to 2.06; GnRH agonists HR, 1.91; 95% CI, 1.66 to 2.20; and orchiectomy HR, 1.79; 95% CI, 1.16 to 2.76). This risk then decreased in the AA and GnRH groups, whereas those who underwent orchiectomy were still at high risk of CVD during months 6 to 12 after castration (HR, 1.91; 95% CI, 1.31 to 2.78; Fig 2C). Minimal changes in risk of CVD over ADT duration were observed in men with no history of CVD and those who experienced an event 1 or more years before initiation of ADT.

DISCUSSION

In this large observational study, we found a consistent increase in risk of CVD for men with PCa on GnRH agonists compared with a matched PCa-free cohort. The HR for CVD peaked sharply during the first 6 months of ADT. This association was particularly strong among men with a history of multiple CVD events, with the most recent event occurring within 1 year before ADT.

Results on the association between ADT and CVD have been inconsistent in previous studies. An observational study conducted by Martin-Merino et al[12] found an adjusted odds ratio for acute myocardial infarction of 1.13 (95% CI, 0.66 to 1.94) in men on GnRH agonists compared with controls. Jespersen et al[10] found a similar association between ADT and CVD, but there was no detailed information on type of ADT. In contrast, a recent meta-analysis of eight randomized trials of 4,141 men with high-risk nonmetastatic PCa did not find such an association.[24] Because data on history of CVD were not available, the risk for men with pre-existing CVD could not be assessed.[24,29,30] Thus, it currently cannot be excluded that there may be an increased risk of CVD for men on ADT, and our data suggest that this risk is higher for men with a history of CVD during the first 6 months of treatment, as has previously been reported for men on GnRH agonists versus antagonists.[31]

In our previous study, relative risks of CVD in men with PCa were increased in men with PCa treated with ADT compared with the general Swedish male population.[16] Moreover, the data suggested an increased risk of CVD in men with a history of CVD before cancer diagnosis.[16] By use of data on age- and county-matched PCa-free men and detailed information on ADT duration, the current study confirms these findings but also adds information to the temporal association between ADT and CVD risk.

In the analysis of the association between ADT and CVD for men who received primary ADT, the strength of the associations increased slightly compared with the comparison cohort. Speculatively, high-risk PCa where treatment with ADT is indicated may itself contribute to the increased risk of CVD, consistent with our previous work where the risk of CVD was higher for men on ADT than those on surveillance or curative treatment compared with the general Swedish male population.[16]

Time on ADT also affected risk of CVD in our study. HRs for CVD peaked sharply during the first year of ADT for men on AA, men on GnRH agonists, and men who underwent surgical orchiectomy. This is consistent with previous data on the immediate risk of cardiovascular events in men with PCa on peroral estrogens.[32-36] These observations imply that the majority of cardiovascular events occur shortly after the start of ADT, potentially because of an acute direct drug effect, as previously proposed.[37] Interestingly, men with a strong

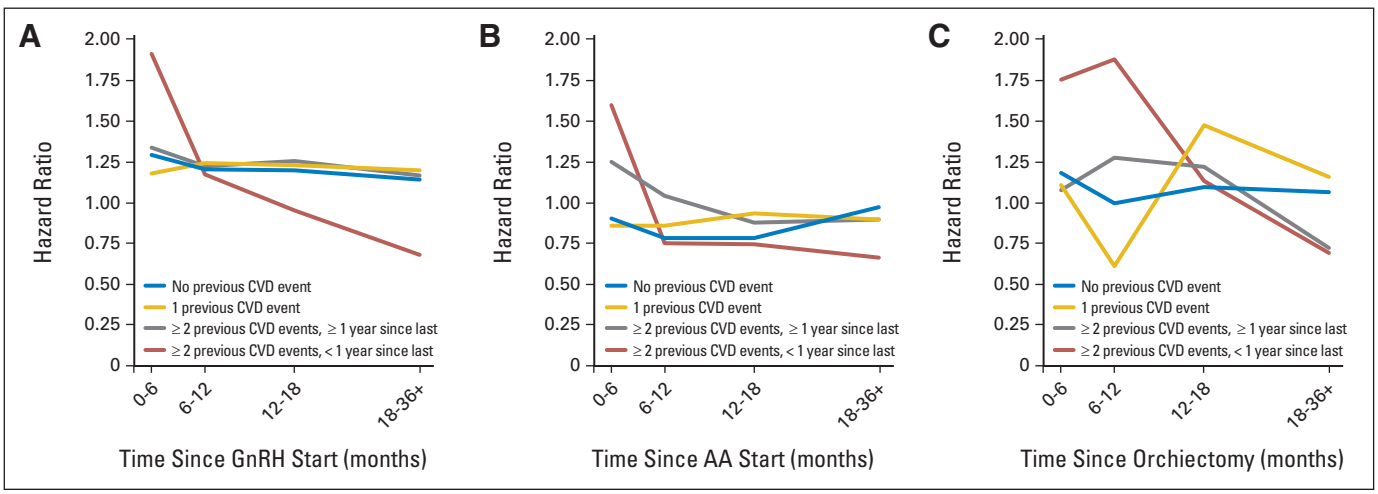

Fig 2. Hazard ratios at selected time intervals since the start of androgen-deprivation therapy for first cardiovascular disease (CVD) event in men with differing baseline CVD over duration of (A) gonadotropin-releasing hormone (GnRH) agonist, (B) antiandrogen (AA) therapy, and (C) surgical orchiectomy versus the comparison cohort.

history of CVD on AA were at increased risk of CVD during the first 6 months of pharmacologic ADT, suggesting that the stress of PCa diagnosis may also contribute to the early increase in risk of CVD. This temporal pattern with an increase shortly after start of treatment also has implications for the use of neoadjuvant and adjuvant ADT as well as palliative ADT.

The mechanism by which ADT may increase risk of CVD is currently poorly understood. A possible explanation for this association may be that the cardioprotection provided by testosterone is being interrupted by ADT.[14-16,18] Alternatively, GnRH agonist–mediated immune activation has also been linked to CVD via fibrous cap disruption and plaque destabilization by activated circulating T cells with the capacity to express the GnRH receptor.[38-40] Risk of CVD was also comparatively high in the orchiectomy group, thus suggesting an association between removal of testosterone from the circulation and increased risk of CVD. In further support of this, risk of CVD was markedly lower in the AA group in which there is no reduction of circulating testosterone. Indeed, decreased levels of androgens have been shown to increase low-density lipoprotein, triglycerides, and insulin, which are components of the metabolic syndrome, a strong risk factor of CVD.[41] Our data set does not contain any information about these factors, but speculatively, these mechanisms may, in part, play a role in the associations observed.

Finally, history of CVD was a contributing factor for the increased risk of CVD after ADT. Men who experienced a CVD event within 1 year before the start of ADT were at the highest risk during the first 6 months of therapy compared with the comparison cohort. This suggests that ADT rapidly increases risk of CVD in men with a recent history of CVD. Thus, it may be contemplated that some clinical effort should be focused on modification of CVD risk factors in these men.

Strengths of the study are its large size, complete follow-up, and comparison to an age- and county-matched cohort free of PCa. The National Prescribed Drug Register allowed us to accurately and directly assess the filling of prescriptions for specific drug therapies with detailed information on doses and iterations. We also adjusted our multivariable regression models for proxies of PCa progression, including TURP, palliative radiotherapy, and nephrostomy. Limitations of our study include that we did not have information about lifestyle factors, but all results were corrected for CCI, which accounts for other morbidities.[42,43] There may still be residual confounders, such as confounding by indication of treatment, which could not be accounted for.

Our study suggests an increased risk of CVD within the first year from starting GnRH agonist therapy or orchiectomy, especially in men with history of a CVD event within 1 year before ADT. There should be solid indication of use of ADT so that the perceived benefit outweighs possible harm. This is particularly important in men with a recent history of CVD.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

androgen-deprivation therapy (ADT): treatment that suppresses or blocks the production or action of male hormones.

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

Gleason score: a pathologic description of prostate cancer grade on the basis of the degree of abnormality in the glandular architecture. Gleason patterns 3, 4, and 5 denote low, intermediate, and high levels of histologic abnormality and tumor aggressiveness, respectively. The score assigns primary and secondary numbers on the basis of the most common and second most common patterns identified.

hazard ratios: the ratio of the hazard rate in one group (for example, a group of treated patients) to the hazard rate in another group (for example, an untreated control group of patients). The hazard rate is the probability of a specified event, such as death or cancer recurrence, occurring during a short time interval. The hazard ratio, therefore, is a measure of the relative probability of an event occurring at any given point in time.

prostate-specific antigen (PSA): a protein produced by cells of the prostate gland. The blood level of prostate-specific antigen (PSA) is used as a tumor marker for men who may be suspected of having prostate cancer. Most physicians consider 0 to 4.0 ng/mL to be the normal range. Levels of 4 to 10 and 10 to 20 ng/mL are considered slightly and moderately elevated, respectively. PSA levels have to be complemented with other tests to make a firm diagnosis of prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer

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Appendix

Table A1. Event Counts and HRs for CVD in Men With PCa on GnRH Agonists Excluding Those on Combined Androgen Blockade Versus the Comparison Cohort for All Men With PCa, Men Who Received ADT at Time of Diagnosis, Men With No History of CVD Before Starting ADT, and Men With a History of Statin Use

	Control Population		Patients on GnRH Agonists ± Flare Protection		Control Population		Patients on GnRH Agonists ± Flare Protection	
CVD	No.	%	No.	%	HR	95% CI	HR	95% CI
All men with PCa								
All incident CVD	42,235	23.5	6,657	25.2	1.00	Reference	1.21	1.18 to 1.25
Ischemic heart disease	13,808	7.5	2,084	7.5	1.00	Reference	1.17	1.11 to 1.24
Arrhythmia	10,263	5.5	1,502	5.3	1.00	Reference	1.12	1.05 to 1.20
Heart failure	10,468	5.6	1,831	6.5	1.00	Reference	1.24	1.16 to 1.31
Stroke	13,916	7.5	2,081	7.4	1.00	Reference	1.12	1.06 to 1.18
All fatal CVD	21,654	11.5	3,316	11.6	1.00	Reference	1.06	1.01 to 1.11
Ischemic heart disease	9,720	5.2	1,606	5.6	1.00	Reference	1.15	1.08 to 1.23
Arrhythmia	1,601	0.9	225	0.8	1.00	Reference	1.00	0.84 to 1.19
Heart failure	2,386	1.3	368	1.3	1.00	Reference	0.94	0.82 to 1.08
Stroke	2,807	1.5	453	1.6	1.00	Reference	1.12	0.99 to 1.27
Men who received ADT at time of diagnosis								
All incident CVD	42,235	23.5	5,488	20.8	1.00	Reference	1.19	1.15 to 1.23
Ischemic heart disease	13,808	7.5	1,749	6.3	1.00	Reference	1.17	1.10 to 1.25
Arrhythmia	10,263	5.5	1,235	4.4	1.00	Reference	1.10	1.02 to 1.19
Heart failure	10,468	5.6	1,567	5.5	1.00	Reference	1.22	1.14 to 1.31
Stroke	13,916	7.5	1,774	6.3	1.00	Reference	1.12	1.05 to 1.20
All fatal CVD	21,654	11.5	2,922	10.2	1.00	Reference	1.09	1.03 to 1.14
Ischemic heart disease	9,720	5.2	1,416	4.9	1.00	Reference	1.19	1.11 to 1.28
Arrhythmia	1,601	0.9	198	0.7	1.00	Reference	1.02	0.84 to 1.23
Heart failure	2,386	1.3	326	1.1	1.00	Reference	0.96	0.82 to 1.11
Stroke	2,807	1.5	398	1.4	1.00	Reference	1.14	1.00 to 1.31
Men with no history of CVD before starting ADT								
All incident CVD	23,810	13.2	3,871	14.7	1.00	Reference	1.19	1.14 to 1.24
Ischemic heart disease	7,680	4.2	1,111	4.0	1.00	Reference	1.09	1.01 to 1.18
Arrhythmia	5,499	3.0	841	3.0	1.00	Reference	1.11	1.01 to 1.21
Heart failure	4,717	2.5	910	3.2	1.00	Reference	1.24	1.13 to 1.35
Stroke	8,674	4.7	1,308	4.7	1.00	Reference	1.09	1.01 to 1.17
All fatal CVD	11,379	6.1	1,832	6.4	1.00	Reference	1.07	1.01 to 1.14
Ischemic heart disease	4,944	2.6	829	2.9	1.00	Reference	1.14	1.04 to 1.25
Arrhythmia	846	0.5	125	0.4	1.00	Reference	1.01	0.80 to 1.27
Heart failure	1,264	0.7	221	0.8	1.00	Reference	0.98	0.82 to 1.18
Stroke	1,600	0.9	279	1.0	1.00	Reference	1.15	0.98 to 1.35
Men with a history of statin use								
All incident CVD	9,594	5.3	1,390	5.3	1.00	Reference	1.20	1.12 to 1.28
Ischemic heart disease	3,529	1.9	535	1.9	1.00	Reference	1.30	1.17 to 1.44
Arrhythmia	2,229	1.2	259	0.9	1.00	Reference	1.01	0.88 to 1.18
Heart failure	2,369	1.3	371	1.3	1.00	Reference	1.18	1.04 to 1.35
Stroke	2,505	1.4	357	1.3	1.00	Reference	1.17	1.03 to 1.34
All fatal CVD	3,159	1.7	468	1.6	1.00	Reference	1.01	0.90 to 1.14
Ischemic heart disease	1,671	0.9	269	0.9	1.00	Reference	1.11	0.95 to 1.29
Arrhythmia	152	0.1	25	0.1	1.00	Reference	1.30	0.80 to 2.13
Heart failure	290	0.2	41	0.1	1.00	Reference	0.93	0.63 to 1.39
Stroke	376	0.2	57	0.2	1.00	Reference	0.98	0.69 to 1.38

Abbreviations: ADT, androgen-deprivation therapy; CVD, cardiovascular disease; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; PCa, prostate cancer.