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Risk for Cardiovascular Diseases in Prostate Cancer Patients Treated with Androgen Deprivation: A Population-based Cohort Study

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MPH Thesis

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Abstract

Background Previous studies evaluating the risk of cardiovascular diseases (CVD) in prostate cancer patients receiving androgen deprivation treatment (ADT) often did not distinguish different modalities of ADT.

Methods We conducted a large, retrospective cohort study using the linked Surveillance, Epidemiology and End Results - Medicare database, including patients with primary localized prostate cancer diagnosed in 2007-2013 and followed through the end of 2014. Time dependent multivariable Cox proportional hazards models with death as the competing risk were used to evaluate the association between ADT (overall, and two subtypes: gonadotropin-releasing hormone [GnRH] agonists and oral antiandrogens) and incidence of CVD.

Results Among 20,239 prostate cancer patients, 32% received ADT. Receipt of ADT was associated with a 28% increase in the risk of CVD (hazard ratio [HR] = 1.28, 95% confidence interval [CI]: 1.14-1.67). The HRs for GnRH agonists and oral antiandrogens were 1.22 (95% CI: 1.15-1.30) and 1.11 (95% CI: 1.04-1.20), respectively.

Conclusions In patients with primary, localized prostate cancer, ADT is associated with a significantly increased risk for CVD, and the magnitude of association appears higher for GnRH agonists than for oral antiandrogens.

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Introduction

Prostate cancer is the most common type of cancer and the second leading cause of cancer mortality among men in the United States (US).[1] An estimated 164,690 men will be diagnosed with prostate cancer in 2018 in the US[2] and will face a decision with respect to therapy. Androgen deprivation therapy (ADT) is the mainstay treatment for prostate cancer - 45% of prostate cancer patients are expected to receive some form of ADT in the course of their disease.[3] Although ADT has been shown to reduce cancer-specific mortality, it is also associated with several side effects including reduced libido, erectile dysfunction, gynaecomastasia, depression, metabolic alterations, dementia and kidney failure.[4-9] In addition, several studies have suggested that ADT, especially gonadotropin-releasing hormone (GnRH) agonists, may be associated with an increased risk of cardiovascular diseases (CVD).[10-14] Consequently, the US Food and Drug Administration issued a safety warning regarding the increased CVD risk of GnRH agonists in 2010.[15]

Previous studies on ADT and risk of CVD mainly investigated GnRH agonists. Oral antiandrogens, which has gained popularity in recent years.[16,17] Few studies are available on different modalities of ADT and risk of CVD. A recent French study suggests that CVD risk may differ across ADT modalities, but the difference may not be meaningful. However, this study only followed patients up to 4 years[18]. In addition, studies which combined different modalities of ADT have contradictory findings regarding the association between ADT and the risk of CVD in prostate cancer patients.[10,11,19,20] Punnen *et al.* observed no association between ADT and CVD specific mortality with patients matched by propensity scores,[19]

while Ziehr *et al.* reported that the association only existed in patients with preexisting CVD[20]. A Kaiser based study indicated a moderate association.[10,11] However, insufficient data were available on different types of ADT.

The purpose of this study is to fill the knowledge gaps identified above by assessing the potential association between the receipt of ADT (overall, as well as three subtypes: GnRH agonists, oral antiandrogens, and orchiectomy) and CVD risk in a large cohort of prostate cancer patients in the US.

Method

Data Source and Study Cohort

We used the Surveillance, Epidemiology and End Results (SEER) - Medicare database, which links patient-level information on incident cancer diagnoses reported to the SEER registries with Medicare claims for inpatient, outpatient, and physician services[21]. The SEER registries are population-based and account for approximately 28% of the US population[22]. The Yale human investigation committee determined this study did not directly involve human subjects.

We assembled a retrospective cohort of 32,234 patients newly diagnosed with first primary, localized prostate cancer (clinical stage T1 or T2) during 2007-2013 with the following eligibility criteria: 1) aged 66 to 99 years at diagnosis, 2) had known month of diagnosis, 3) were not reported from autopsy or death certificate only, and 4) had continuous Medicare fee-for-service coverage (Parts A and B) and was not enrolled in health

maintenance organizations from 12 months before diagnosis to the end of follow-up (i.e., the date a patient developed the first CVD event, the date a patient died, or December 31, 2014, whichever was earlier), and 5) continuously enrolled in Medicare Part D from diagnosis to the end of follow-up. To ensure all CVD events were newly developed after prostate cancer diagnosis, we further excluded patients who had Medicare claims indicative of CVD in the 12 months before (n = 9889) or during (n = 194) the month of their prostate cancer diagnosis. Additionally, we excluded patients who received ADT before their prostate cancer diagnosis (n = 84), and patients who developed CVD between the diagnosis of prostate cancer and when they received ADT for the first time (n = 1034). The final study cohort consisted of 20,239 patients (Figure 1).

Ascertainment of ADT

Using Medicare claims, we ascertained there different types of ADT: 1) GnRH analogists (Healthcare Common Procedure Coding System codes J9217, J9218, J9219, J1950, J9202, and relevant Medicare Part D drug national drug codes (NDCs) ; see Appendix Table 1); 2) orchiectomy (Common Procedure Terminology codes 54512, 54521, 54522, 54530, 54535, 54690, and ICD-9 Procedure codes 62.3, 62.4, 62.41, and 62.42; see Appendix Table 2); and 3) oral antiandrogens (Medicare Part D drug NDC codes; see Appendix Table 1-2). The use of ADT overall and the three different types of ADT were evaluated dichotomously (ever vs. never).

Study Outcomes

We identified CVD events after diagnosis based on the International Classification of Diseases, 9th edition [ICD-9] codes from Medicare claims (see Appendix 3). We required diagnosis codes must appear on one inpatient claim or at least two different claims that are more than 30 days apart. If a patient had multiple CVD events on the same date, the patient was assigned to a specific outcome group according to the sequence below: 1) acute myocardial infarction (AMI); 2) cardiac arrest; 3) stroke; 4) heart failure; 5) hypertensive heart disease with heart failure; 6) cardiomyopathy; 7) valvulopathy; 8) angina pectoris; and 9) conduction disorder. CVD events were first evaluated as a single entity and then classified into three separate categories: 1) cardiac ischemia (including AMI, cardiac arrest and angina pectoris); 2) stroke; and 3) other CVD (including heart failure, cardiomyopathy, conduction disorder, hypertensive heart disease and valvulopathy).

Other Variables of Interest

To assess comorbidity, all inpatient, outpatient and carrier claims within 12 months before the date of prostate cancer diagnosis were identified to calculate a modified Elixhauser comorbidity score (0, 1, >1)[23,24]. In addition, we abstracted information on a number of sociodemographic and clinical characteristics, including age at prostate cancer diagnosis (65-69, 70-74, 75-79, ≥80 years), race (white, non-white), marital status (married/unmarried), census division (northeast, midwest, south, west), residential area (urban/rural), percentage of residents living in poverty at the census tract level (<10%, ≥10%), clinical stage at diagnosis

(T1/T2), Gleason score (<7, 7, >7), level of prostate specific antigen (0.1-9.9, 10.0-20.0, ≥20.1), influenza vaccination in the last 12 months (yes/no, as a proxy measure for healthcare utilization), and radiotherapy for prostate cancer (yes/no).

Statistical Analysis

Frequency distributions of demographic and socioeconomic characteristics were compared between prostate cancer patients who received ADT and those who did not receive ADT, using Pearson's Chi-square tests. Death prior to the first CVD event was considered a competing risk event. All patients were followed till the development of their first CVD event, death, or December 31, 2014, whichever was earlier. The outcomes of interest were occurrences of the first CVD event. To account for patients transferring from one group to another group, Simon-Makuch method was used for a graphical representation of the probability of cardiovascular diseases according to the receipt of ADT, which was considered as a time-dependent variable.[25] Competing risk Cox proportional hazards regression models using the Find and Gray method were used to provide estimates of the crude and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CI) for the occurrence of CVD events.[26] To account for immortal bias[27], for a given patient, person-time before the receipt of the first ADT was considered unexposed to ADT and exposed thereafter. All variables described in the previous section were included in the models. In addition to analyzing ADT as one group, we also analyzed different types of ADT separately by including the three types of ADT in the same model simultaneously. As very few patients

received orchiectomy (either exclusively or in combination with GnRH agonists and/or oral antiandrogens, n = 89), we chose to adjust for orchiectomy in the model but did not present the results for orchiectomy separately. The proportional hazards assumption was tested by plotting Schoenfeld residuals.

All tests were two-sided with $p<0.05$ indicating statistical significance. SAS version 9.4 (SAS Inc. Cary, NC) was used to conduct the analyses.

Results

Baseline Characteristics

A total of 20,239 men with primary localized prostate cancer were included in the cohort. Patients who received ADT were more likely to be older, black, unmarried, poorer, in T1 stage and have received radiotherapy for prostate cancer (Table 1).

Of these 20,239 patients, 6490 (32.1%) received ADT. Specifically, 3121 (15.4%), 588 (2.9%), and 41 (0.2%) exclusively received GnRH agonists, oral antiandrogen, or orchiectomy, respectively; but a large number of prostate cancer patients (n = 2740, 13.5%) received combinations of two or three different types of ADT (Figure 2).

After a mean follow-up of 4.1 (range:1-8) years, 26.9% (n=5463) patients developed CVD. As shown in Figure 3, 2995 (14.8%), 611(3.0%), and 1857 (9.2%) patients experienced cardiac ischemia, stroke and other CVD events, respectively.

As shown in Figure 4, patients received ADT were more likely to develop CVD (p=0.003). In the multivariate models, prostate cancer patients treated with ADT had a

significantly higher risk of developing CVD events compared with patients who did not receive ADT (HR = 1.28, 95% CI: 1.22 - 1.36; P < .0001) (Table 2). When further evaluated three groups of CVD events, receipt of ADT increased risk of cardiac ischemia, stroke, and other CVDs by 20% (95% CI: 1.10 - 1.32), 38% (95% CI: 1.14 - 1.67) and 39% (95% CI: 1.25 - 1.54), respectively (Table 3). Among the nine specific types of CVD, significant associations were observed with angina pectoris, heart failure, hypertensive heart disease, and valvulopathy (Table 3).

Based on a multivariable model that included GnRH agonists, oral antiandrogens, orchiectomy as binary variables simultaneously, we found that both GnRH agonists and oral antiandrogens were associated with a statistically significant, increased risk for CVD (Figure 5), while orchiectomy did not appear to influence CVD risk. The magnitude of association with CVD as a single entity was higher for GnRH agonists (HR = 1.22; 95% CI: 1.15 - 1.30) than for oral antihydrogens (HR = 1.11, 95% CI: 1.01 - 1.20). In addition, analyses by the three groups of CVD suggested that receipt of GnRH agonists was significantly associated with increased risks of cardiac ischemia and other CVDs, but not stroke, while taking oral antiandrogens was associated with an increased risk of stroke, but not cardiac ischemia or other CVD (details not shown).

Discussion

In this large population-based cohort of older prostate cancer patients, we found that ADT is significantly associated with an increased risk of CVD, and the magnitude of association appears higher for GnRH agonists than for oral antiandrogens.

Most previous studies on ADT and risk of CVD mainly focused on GnRH agonists solely ADT.[5,11,12,14,28-33] We were able to identify the use of GnRH agonists, oral antiandrogens, and orchiectomy from SEER-Medicare claims and accounted for a comprehensive set of sociodemographic and clinical characteristics of the patients as potential confounders. A previous study using SEER-Medicare database compared the 10-year rates of CVD between ADT users and non-ADT users, however, they did not include oral antiandrogens as ADT[12].

Utilizing the SEER-Medicare database, we found significantly increased risks of most CVD events among prostate cancer patients who received ADT. This finding is consistent with several other studies that were based on large databases[6,10,12-14,29]. A recent prospective cohort study from Kaiser Permanente only found an increased risk of heart failure in men without preexisting CVD[11]. However, the Kaiser study included patients at all ages, thus 38% of patients in the Kaiser cohort were under the age of 65 years, while our cohort consists of Medicare beneficiaries who were at least 66 years in age.

Our study evaluated the impact of ADT on CVD risk across modalities, with a focus on oral antiandrogens. Oral antiandrogens have been used more often in recent years but have not been systematically studied in terms of their impact on CVD risk[16]. Although oral antiandrogens are often used with other therapies, a recent randomized controlled trial

showed that there was no difference in all-cause mortality and prostate cancer related mortality between antiandrogen monotherapy and GnRH agonists[17]. In a French study, compared with GnRH agonists, combined androgen blockade was associated with an increased risk (HR= 1.6, 95% CI:1.3 - 2.0) and antiandrogen with a decreased risk (HR = 0.6, 95% CI: 0.4 - 0.9) of ischaemic events[18]. We found that patients who received GnRH agonists had a higher risk of most CVD outcomes including cardiac ischemia, heart failure, cardiomyopathy and hypertensive heart disease, compared with patients who received oral antiandrogens. These are similar to the findings by Keating et al[10]. However, we also found that the use of oral antiandrogens was associated with a significantly increased risk of stroke, while GnRH agonists did not appear to influence stroke risk. Given the paucity of studies on oral antiandrogens and the lack of confirmation, our findings should be interpreted with caution, but they do underscore the importance of studying different subtypes of ADT. It may not be reasonable to treat ADT as a single entity when evaluating its impact on CVD risk.

Our study has several strengths. First, the SEER-Medicare database enabled us to have a large sample size and a long follow-up of the patients, which is crucial for the ascertainment of CVD outcomes. Second, we take account a complete subtypes of ADT and include the information of oral antiandrogens, which have been used more often recently. Additionally, the time-dependent competing-risk Cox proportional hazards regression models allowed us to address immortal bias in the study.

Some limitations of our study should also be noted. With a retrospective cohort design, patients were not randomly assigned to treatment with ADT, and comparison of baseline

characteristics showed that sicker and older patients were more likely to receive ADT. Although we adjusted for a number of covariates in the model, residual confounding might still exist. Second, our study cohort only included older patients (age ≥ 66 years) who had continuous Medicare coverage and no pre-existing CVD, which likely limits the generalizability of our findings. In addition, multiple comparison problem may exist in this study as we have three major types of CVD outcomes and two subtypes of ADT. However, the p-values would be still significant after Bonferroni adjustment as almost all p-values for the three major types of CVD are smaller than 0.001. Finally, we were unable to analyze the association between orchiectomy and CVD risk due to the very small number of patients who underwent the surgical procedure.

In conclusion, receipt of ADT is associated with an increased risk of CVD events in older men with localized prostate cancer. Compared with oral antiandrogens, GnRH agonists appears to confer a higher CVD risk. It is important for prostate cancer patients and their physicians to take the association between ADT and CVD risk into account when making treatment decisions.

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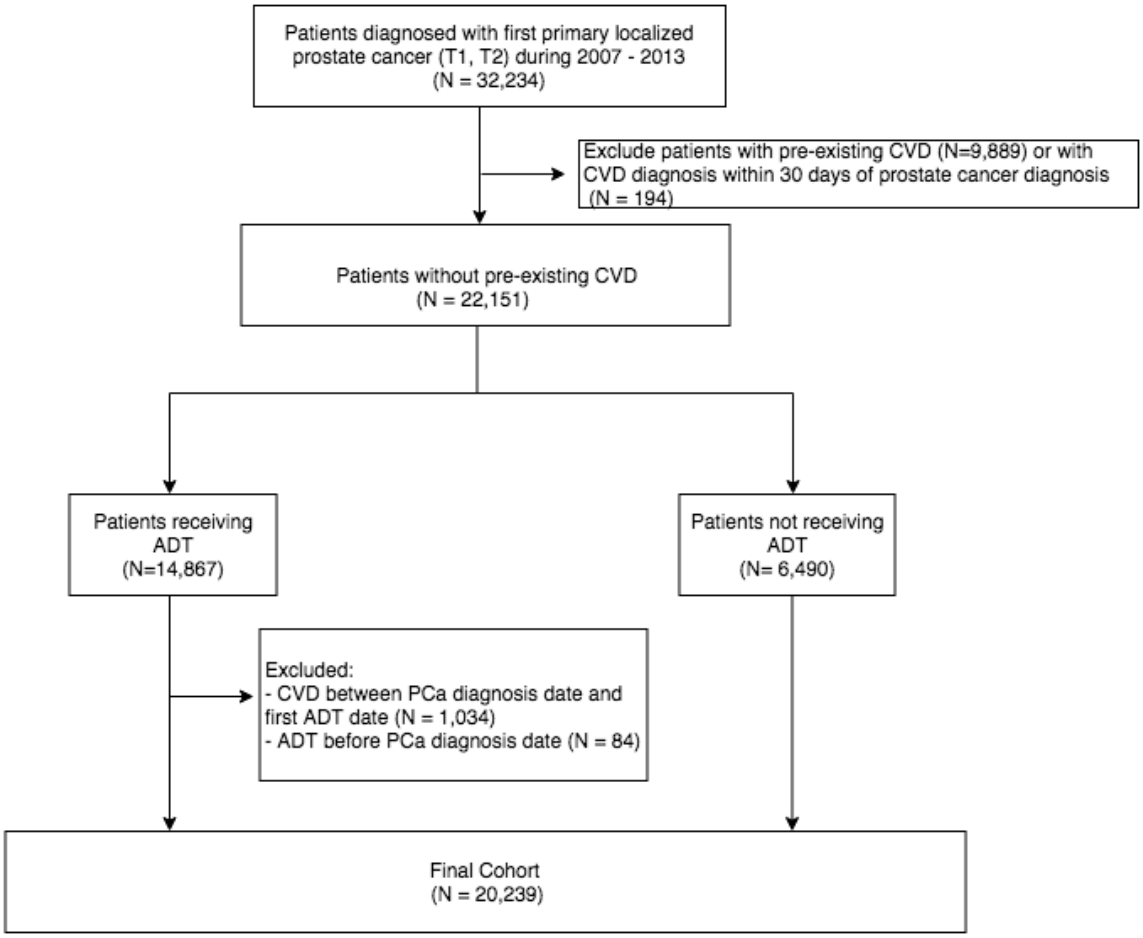


Figure 1. Construction of Study Cohort Using the Linked SEER-Medicare Database. * CVD indicates cardiovascular diseases; PCa, prostate cancer; ADT, androgen deprivation therapy.

Table 1. Sociodemographic and Clinical Characteristics of Prostate Cancer Patients at Baseline by Receipt of Androgen Deprivation Therapy

	Overall	Androgen Deprivation Therapy		P-value*
		Never	EVER	
Total	20239	13749	6490	
Age (years)				
<70	6992 (34.6)	5440 (39.6)	1552 (23.9)	<0.0001
70 – 74	7336 (36.3)	5174 (37.6)	2162 (33.3)	
75 – 79	3805 (18.8)	2231 (16.2)	1574 (24.3)	
≥80	2106 (10.4)	904 (6.6)	1202 (18.5)	
Race				
White	16480 (81.4)	11458 (83.3)	5022 (77.4)	<0.0001
Non-white	3759 (18.6)	2291 (16.7)	1468 (22.6)	
Marital status				
Married	13320(65.8)	9312 (67.7)	4008 (61.8)	<0.0001
Unmarried	3977 (19.7)	2548 (18.5)	1429 (22.0)	
Census Region				
Northeast	3603 (17.8)	2277 (16.6)	1326 (20.4)	<0.0001
Midwest	2672 (13.2)	1719 (12.5)	953 (14.7)	
South	4898 (24.2)	3406 (24.8)	1492 (23.0)	
West	9066 (44.8)	6347 (46.2)	2719 (41.9)	
Residential Area				
Urban	16189 (80.0)	11651 (81.2)	5028 (77.5)	<0.0001
Rural	4046 (20.0)	2584 (18.8)	1462 (22.5)	
% of Residents Living Under Census Tract				
<10%	10659(52.7)	7461 (54.3)	3198 (49.3)	<0.0001
≥10%	9348 (46.2)	6125 (44.6)	3223 (49.7)	
Clinical stage at diagnosis				
T1	12684 (62.7)	9097 (66.2)	3587 (55.3)	<0.0001
T2	7555 (37.3)	4652 (33.8)	2903 (44.7)	
Gleason score				
<7	7913 (39.1)	6678 (48.6)	1235 (19.0)	<0.0001
7	7971 (39.4)	5308 (38.6)	2663 (41.0)	
>7	3101 (15.3)	905 (6.6)	2196 (33.8)	
Prostate Specific Antigen				
0.1-9.9	15890 (78.5)	11782 (85.7)	4108 (63.3)	<0.0001
10.0-20.0	2869 (14.2)	1528 (11.1)	1341 (20.7)	
≥20.1	1480 (7.3)	439 (3.2)	1041 (16.2)	
Elixhauser Score				
0	13418 (63.8)	8968 (65.2)	3937 (60.0)	<0.0001

1	5032 (24.9)	3312 (24.1)	1720 (26.5)	
≥2	2343 (11.6)	1469 (10.7)	874 (13.5)	
Influenza vaccine before diagnosis				
Yes	9816 (48.5)	6641 (48.3)	3175 (48.9)	0.41
No	10423 (51.5)	7108 (51.7)	3315 (51.1)	
Radiotherapy				
Yes	10801 (53.4)	5971 (43.4)	4830 (74.4)	<0.0001
No	9438 (46.6)	7778 (56.6)	1660 (25.6)	

*P-values were calculated using Pearson's Chi-square test

Column totals may not equal to the total due to missing values.

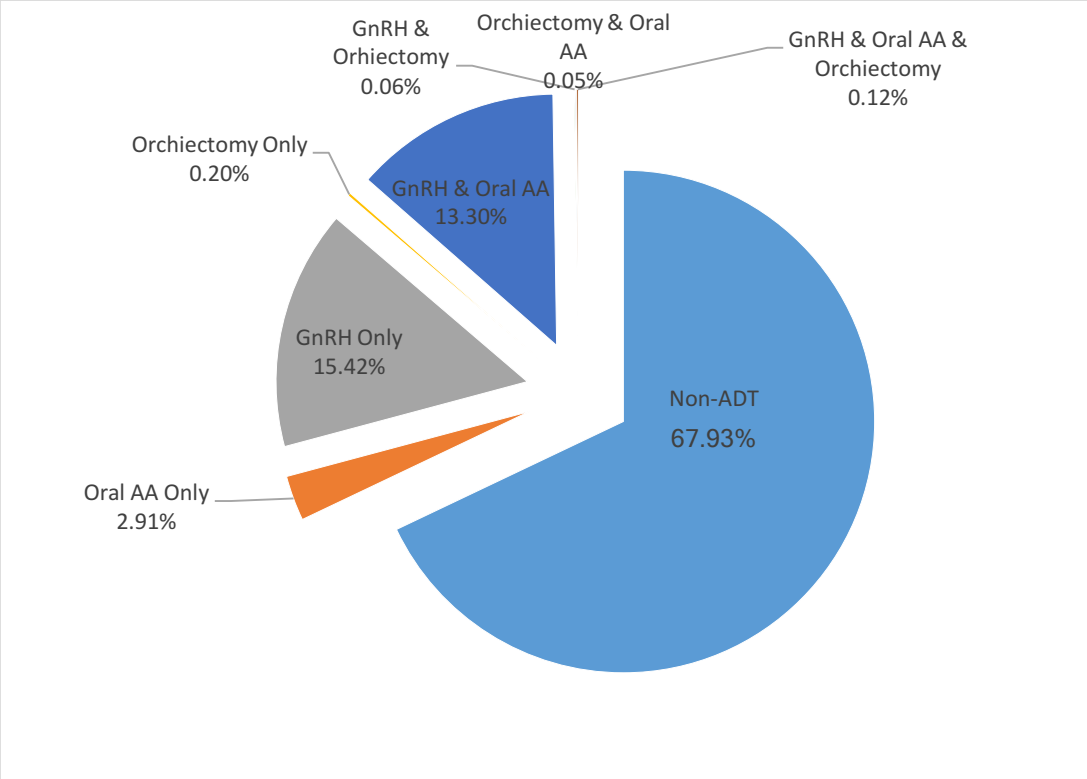


Figure 2. Types of Androgen Deprivation Therapy Received by Prostate Cancer Patients (n = 20,239)

* GnRH: gonadotropin-releasing hormone agonists; Oral AA: oral antiandrogens; ADT: androgen deprivation treatment

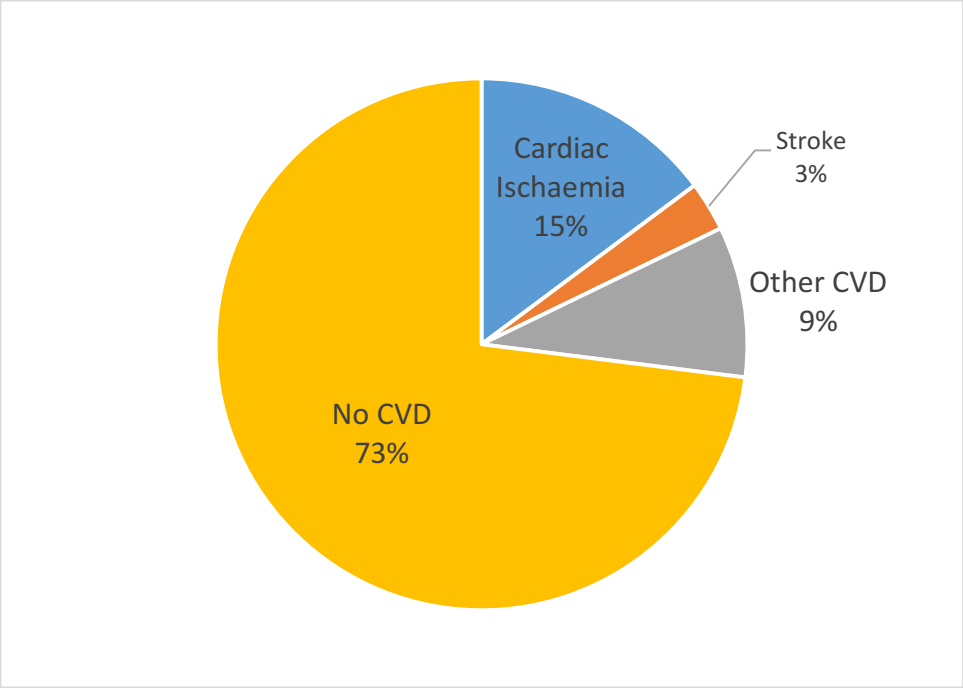


Figure 3. Types of Cardiovascular Diseases Occurred in Prostate Cancer Patients (n = 20,239)

* CVD: cardiovascular diseases

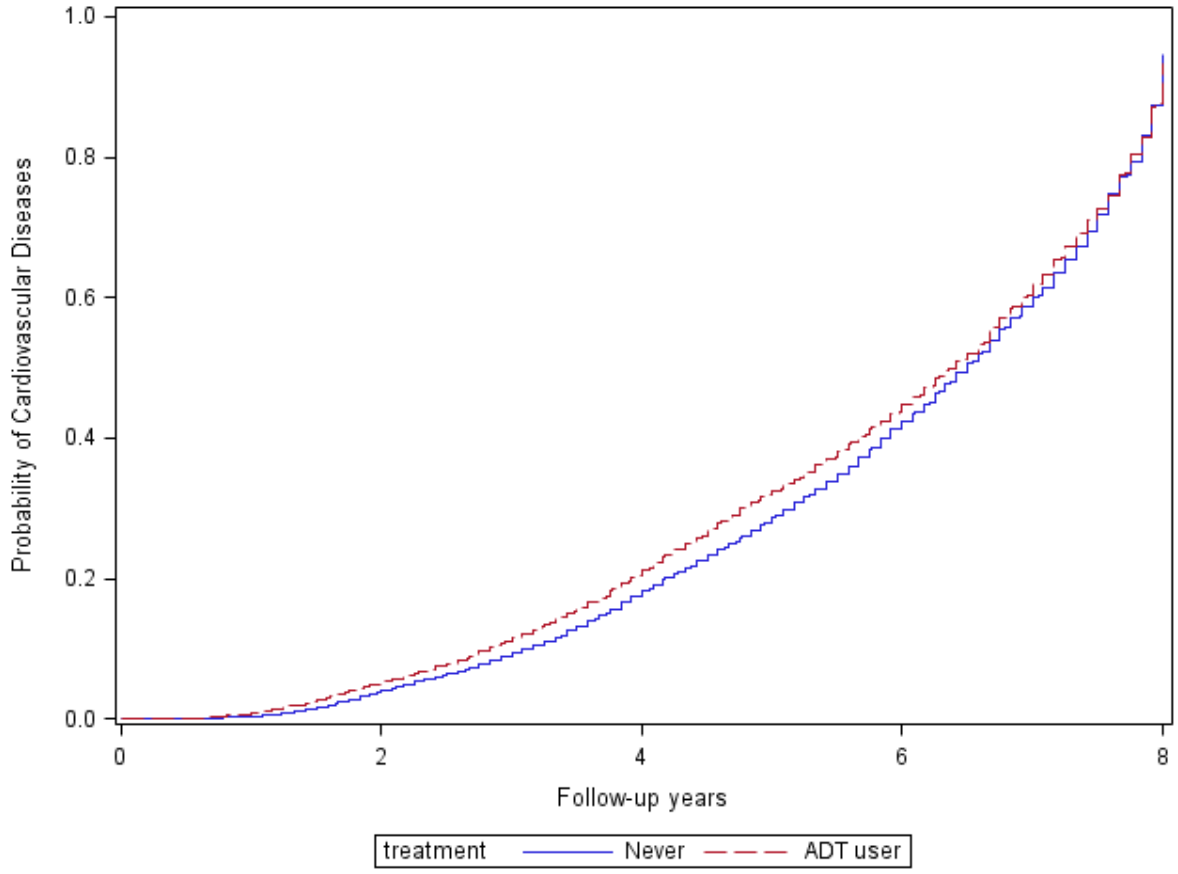


Figure 4. Probability of Cardiovascular Diseases by Androgen Deprivation Therapy according to the Simon-Makuch method[25]

Table 2. Sociodemographic and Clinical Characteristics, Androgen Deprivation Therapy, and Risk of Cardiovascular Diseases in Prostate Cancer Patients*

	Non-ADT (N=13749)	ADT (N=6490)	Hazard Ratio	95% Confidence Interval	P-value
ADT			1.28	1.22 - 1.36	<.0001
Age (years)					
<70	5440 (39.6)	1552 (23.9)	1.00		
70 – 74	5174 (37.6)	2162 (33.3)	1.16	1.10 - 1.23	<.0001
75 – 79	2231 (16.2)	1574 (24.3)	1.36	1.27 - 1.45	<.0001
≥80	904 (6.6)	1202 (18.5)	1.63	1.51 - 1.76	<.0001
Race					
White	11458 (83.3)	5022 (77.4)	1.00		
Non-white	2291 (16.7)	1468 (22.6)	1.09	1.03 - 1.16	0.003
Marital status					
Married	9312 (67.7)	4008 (61.8)	1.00		
Unmarried	2548 (18.5)	1429 (22.0)	1.06	1.00 - 1.12	0.047
Missing	1889 (13.7)	1053 (16.2)	0.99	0.93 - 1.06	0.874
Census Region					
Northeast	2277 (16.6)	1326 (20.4)	1.00		
Midwest	1719 (12.5)	953 (14.7)	1.02	0.94 - 1.11	0.652
South	3406 (24.8)	1492 (23.0)	1.02	0.95 - 1.09	0.647
West	6347 (46.2)	2719 (41.9)	0.89	0.83 - 0.94	<.0001
Residential Area					
Urban	11651 (81.2)	5028 (77.5)	1.00		
Rural	2584 (18.8)	1462 (22.5)	0.90	0.85 - 0.96	0.001
% of Residents Living Under Census Tract					
<10%	7461 (54.3)	3198 (49.3)	1.00		
≥10%	6125 (44.6)	3223 (49.7)	0.97	0.92 - 1.02	0.187
Gleason score					
<7	6678 (48.6)	1235 (19.0)	1.00		
7	5308 (38.6)	2663 (41.0)	1.01	0.96 - 1.07	0.616
>7	905 (6.6)	2196 (33.8)	0.94	0.87 - 1.01	0.097
Prostate-specific antigen					
0.1-9.9	11782 (85.7)	4108 (63.3)	1.00		
10.0-20.0	1528 (11.1)	1341 (20.7)	0.95	0.89 - 1.01	0.100
≥20.1+	439 (3.2)	1041 (16.2)	0.80	0.73 - 0.88	<.0001
Elixhauser Score					
0	8968 (65.2)	3937 (60.0)	1.00		

1	3312 (24.1)	1720 (26.5)	1.28	1.22 - 1.35	<.0001
2	1469 (10.7)	874 (13.5)	1.58	1.48 - 1.69	<.0001
Radiotherapy					
No	7778 (56.6)	1660 (25.6)	1.00		
Yes	5971 (43.4)	4830 (74.4)	0.94	0.89 - 0.98	0.008

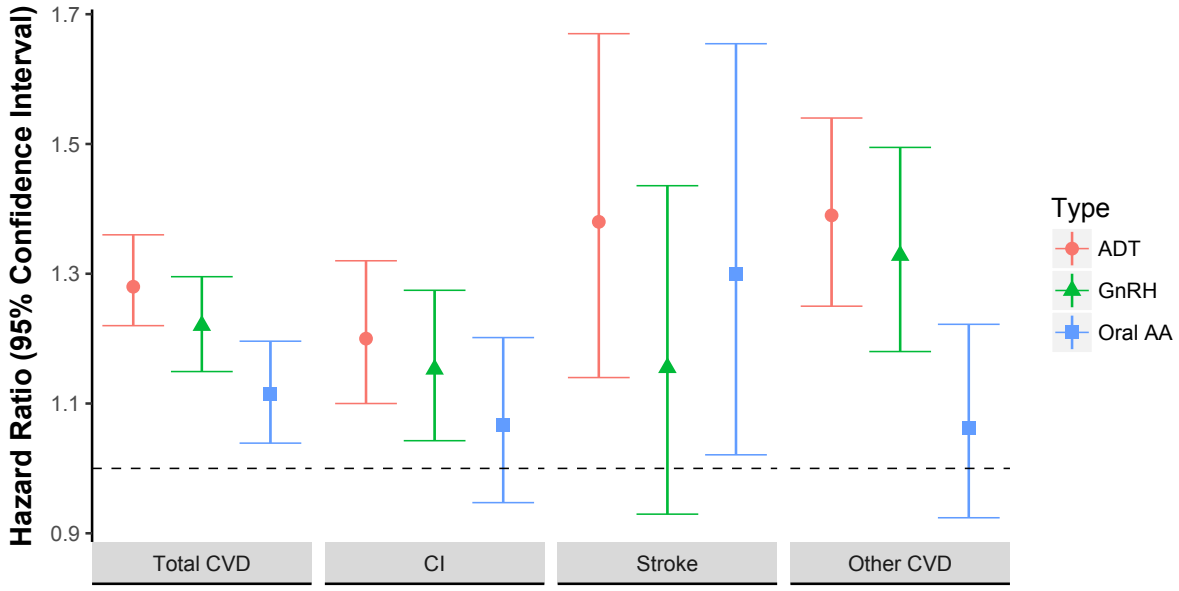
Adjusted hazard ratios and 95% confidence intervals were derived from a multivariate, competing-risk Cox proportional hazards regression model. All variables listed were mutually adjust for each other.

Table 3. Androgen Deprivation Therapy for Prostate Cancer and Risk of Cardiovascular Diseases

	N	% of patients who have the event	Adjusted HR (95% CI)*	P-value
Overall	5463	26.9	1.28 (1.22- 1.36)	<0.001
Cardiac Ischemia	2995	14.8	1.20 (1.10- 1.32)	<0.001
AMI	314	1.55	1.00 (0.76- 1.31)	1.00
Angina Pectoris	2646	13.07	1.22 (1.11- 1.35)	<0.001
Cardiac arrest	35	0.17	1.88 (0.97- 3.63)	0.06
Stroke	611	3.02	1.38 (1.14- 1.67)	<0.001
Other heart diseases	1857	9.18	1.39 (1.25- 1.54)	<0.001
Heart failure	672	3.32	1.59 (1.34- 1.90)	<0.001
Cardiomyopathy	114	0.56	1.34 (0.89- 2.02)	0.16
Conduction disorder	18	0.09	1.06 (0.39- 2.91)	0.90
Hypertensive heart disease	36	0.18	3.04 (1.24- 7.49)	0.02
Valvulopathy	1017	5.02	1.22 (1.05- 1.41)	0.01

*Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were derived from a single multivariable, competing-risk Cox proportional hazards regression model that adjusted for the following covariates: age at prostate cancer diagnosis (65-69, 70-74, 75-79, ≥80 years), race (white, non-white), marital status (married/unmarried), census division (northeast, midwest, south, west), percentage of residents living in poverty at the census tract level (<10%, ≥10%), Elixhauser score (0, 1, >1) and radiotherapy for prostate cancer (yes/no).

Figure 5. Adjusted Hazard Ratios and 95% Confidence Intervals for Risk of CVD Events in Prostate Cancer Patients Who Received GnRH Agonists or Oral Antiandrogens*



*Competing-risk Cox proportional hazards model were adjusted for the following covariates: age at prostate cancer diagnosis (65-69, 70-74, 75-79, ≥80 years), race (white, non-white), marital status (married/unmarried), census division (northeast, midwest, south, west), percentage of residents living in poverty at the census tract level (<10%, ≥10%), Elixhauser score (0, 1, >1), radiotherapy for prostate cancer (yes/no) and orchiectomy(ever/never). Abbreviations: AA: antiandrogens; ADT: androgen deprivation therapy; CVD: cardiovascular disease; CI: cardiac ischemia; GnRH: gonadotropin-releasing hormone

Appendix

Appendix 1. Codes Used to Identify Androgen Deprivation Therapy (Healthcare Common Procedure Coding System [HCPCS], Current Procedural Terminology [CPT], International Classification of Disease, Ninth Version [ICD-9])

Diagnosis or procedure	HCPCS	CPT	ICD-9 procedure	Comments
GnRH (Leuprolide injection)	J9217			Leuprolide acetate (for depot suspension), 7. 5 mg
	J9218			Leuprolide acetate, per 1 mg
	J9219			Leuprolide acetate implant, 65 mg
	J1950			Injection, leuprolide acetate (for depot suspension), per 3. 75 mg
GnRH (Goserelin injection)	J9202			Goserelin acetate implant, per 3. 6 mg
Orchiectomy		54512		Excise lesion testis
		54520		Removal of testis
		54522		Orchiectomy partial
		54530		Removal of testis
		54535		Extensive testis surgery
		54690		Laparoscopy orchiectomy
			62.3	Unilateral orchiectomy
			62.4	Bilateral Orchiectomy
			62.41	Removal of both testes at same operative episode
			62.42	Removal of both testes at same operative episode

Appendix 2. Drugs Identified for Androgen Deprivation Therapy Using Medicare Part D Claims

Type	GNN(Generic Name)	BRN (Brand Name)
GnRH agonists	Buserelin	Suprecur
	Buserelin	Suprefact injectable
	Goserelin	Zoladex
	Leuprolide Acetate	Lupron Depot
	Leuprolide Acetate	Prostap SR
	Leuprolide Acetate	Enantone
	Leuprolide Acetate	Lucrin Depot
	Leuprolide Acetate	Trenantone-Gyn
	Leuprolide	Lupron Depot
	Leuprolide	Prostap SR
	Leuprolide	Enantone
	Leuprolide	Lucrin Depot
	Leuprolide	Trenantone-Gyn
	Leuprorelin	Lupron Depot
	Leuprorelin	Prostap SR
	Leuprorelin	Enantone
	Leuprorelin	Lucrin Depot
	Leuprorelin	Trenantone-Gyn
	Naferelin	Synarel
	Naferelin	Synarella
	Triptorelin	Decapeptyl SR
	Triptorelin	Gonapeptyl
	Triptorelin	Supprelin LA
	Triptorelin	Trelstar Depot
	Degarelix	Firmagon
	Abarelix	Plenaxis
	Histrelin	Vantas
Oral antiandrogens	Flutamide	Eulexin
	Bicalutamide	Casodex
	Nilutamide	Nilandron
	Enzalutamide	Xtandi
	Abiraterone	Zytiga

Appendix 3. International Classification of Disease, Ninth Version [ICD-9] Codes Used to Identify Cardiovascular Diseases from Medicare Part B Claims

CVD diagnoses	ICD9	Comment
Acute Myocardial Infarction	410	Acute myocardial infarction
Cardiac Arrest	427.5	Cardiac arrest
Stroke	430	Subarachnoid hemorrhage
	431	Intracerebral hemorrhage
	432	Other and unspecified intracranial hemorrhage
	434	Occlusion of cerebral arteries
	436	Acute, but ill-defined, cerebrovascular disease
Heart Failure (HF)	428	Heart failure
Hypertensive Heart Disease with HF	402.01	Malignant hypertensive heart disease with heart failure
	402.11	Benign hypertensive heart disease with heart failure
	402.91	Unspecified hypertensive heart disease with heart failure
Cardiomyopathy	425.1	Hypertrophic cardiomyopathy
	425.3	Endocardial fibroelastosis
	425.4	Endocardial fibroelastosis
	425.8	Cardiomyopathy in other diseases classified elsewhere
	425.9	Secondary cardiomyopathy, unspecified
Arrhythmias	427	Cardiac dysrhythmias
Valvulopathy	424	Other diseases of endocardium
Angina Pectoris	411	Other acute and subacute forms of ischemic heart disease
	413	Angina pectoris
	414	Other forms of chronic ischemic heart disease
Conduction Disorder	426.9	Conduction disorder, unspecified