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Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism

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Abstract

Background—Previous studies demonstrate that androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) agonists and orchiectomy for prostate cancer is associated with cardiovascular disease. However, few studies have examined its effect on the peripheral vascular system.

Objective—To study the risk of peripheral arterial disease and venous thromboembolism associated with androgen deprivation therapy for prostate cancer.

Design, Settings and Participants—Population-based observational study of 182,757 U.S. men aged 66 years and older who were diagnosed with loco-regional prostate cancer from 1992 to 2007, of whom 47.8% received GnRH agonists and 2.2% orchiectomy.

Measurements—We used Cox proportional hazards models with time-varying treatment variables to assess whether treatment with GnRH agonists or orchiectomy was associated with peripheral arterial disease and/or venous thromboembolism.

Results and limitations—Overall, 47.8% of men received a GnRH agonist during follow-up and 2.2% underwent orchiectomy. GnRH agonist use was associated with an increased risk of incident peripheral arterial disease (adjusted hazard ratio [HR], 1.15, 95% confidence interval [CI] 1.11–1.19) and incident venous thromboembolism (adjusted HR, 1.1, 95% CI 1.04–1.16). In addition, orchiectomy was associated with an increased risk of peripheral arterial disease (adjusted HR, 1.14, 95% CI 1.03–1.27) and venous thromboembolism (adjusted HR, 1.22, 95% CI 1.07–1.40). Limitations include the observational study design, inability to assess the use of oral anti-androgens as monotherapy or combined androgen deprivation.

Conclusions—Androgen deprivation therapy for loco-regional prostate cancer is associated with an increased risk of peripheral artery disease and venous thromboembolism. Additional research is needed to better understand the potential risks and benefits, so that these treatments can be targeted to patients where the benefits are most clear.

Keywords

Prostate cancer; androgen deprivation therapy; peripheral vascular disease; venous thromboembolism

1. INTRODUCTION

Although prostate cancer remains the most commonly diagnosed non-cutaneous malignancy in U.S. men,¹ the five-year prostate cancer specific survival is almost 100%.² For metastatic disease, androgen deprivation therapy, i.e. bilateral orchiectomy or gonadotropin releasing hormone (GnRH) agonists, relieves urinary obstruction and pain.³ While a retrospective study found an association between androgen deprivation therapy and improved survival for metastatic disease,⁴ a large population-based study failed to demonstrate a survival benefit in elderly men with localized prostate cancer.⁵ For locally advanced disease, radiotherapy with adjuvant hormonal therapy versus without improves prostate cancer specific mortality.^{6, 7} Moreover, immediate androgen deprivation therapy versus observation has a survival benefit for men with positive lymph nodes at radical prostatectomy.⁸

While the role of androgen deprivation therapy for local or regional prostate cancer has not been clearly defined,⁹ its use as primary therapy for localized prostate cancer has increased in recent decades, with primary androgen deprivation therapy second to radical prostatectomy as the most frequent treatment for localized prostate cancer.¹⁰ Utilization decreased somewhat following Medicare reimbursement reductions in 2005.¹¹ Observational studies have shown no survival advantage¹² or a survival disadvantage¹³ associated with primary androgen deprivation for localized prostate cancer. Androgen deprivation therapy is also commonly used following biochemical recurrence after primary treatment with radical prostatectomy or radiation therapy,¹⁴ another setting where data are lacking to support improved outcomes. However, androgen deprivation may cause atherosclerotic plaque progression and instability,¹⁵ and its use has been associated with an increased risk of coronary heart disease.^{16–20}

Consistent with evidence that aging²¹ and cancer²² are associated with an increased risk of venous thromboembolism (i.e., pulmonary embolism and deep venous thrombosis), a population-based study of the Swedish National Prostate Cancer Register demonstrated that prostate cancer was associated with an increased risk of venous thromboembolism, and men with prostate cancer treated with androgen deprivation therapy were at greatest risk for venous thromboembolism.²³ We sought to corroborate the association of androgen deprivation therapy with venous thromboembolism among older Americans with prostate cancer. In addition, given the increased risk of coronary heart disease associated with testosterone suppression, we questioned whether androgen deprivation therapy was associated with an increased risk of peripheral arterial disease.

2. METHODS

2.1 Data

We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data for analyses, a linkage of population based tumor registry data that currently covers areas representing 28% of the United States population with Medicare administrative data.²⁴ Medicare provides health insurance to most elderly Americans.

2.2 Study Cohort

We identified 249,977 men aged 66 years or older diagnosed with prostate cancer during 1992 to 2007 with follow-up through 2009 who were continuously enrolled in Medicare Parts A and B in the year before diagnosis. We excluded 3,372 men diagnosed at death or autopsy and 6411 with no claims from 45 days before through 195 days after diagnosis because we were concerned about incomplete data, since all patients with newly diagnosed prostate cancer should have had at least one claim during that time. We then excluded 14,597 men with metastatic disease and 39,486 men with unknown stage at diagnosis, 54 men who received the GnRH agonist abarelix during follow up, and 2295 patients who received chemotherapy within six months of diagnosis (because we were concerned that they may have had metastatic cancer), resulting in a final cohort of 182,757.

We excluded men with evidence of prevalent peripheral arterial disease (n=8147) or venous thromboembolism (deep vein thrombosis and/or pulmonary embolus, n=2318) during 12 months before through six months after prostate cancer diagnosis from their respective cohorts.

2.3 Peripheral arterial disease, venous thromboembolism

To identify our dependent variables of interest, we used International Classification of disease, 9th edition (ICD-9) diagnosis or procedure codes and Healthcare Common Procedure Coding System (HCPCS) codes for peripheral arterial disease²⁵ and venous thromboembolism²⁶ (Appendix Table 1). We required at least 2 claims on different dates with diagnosis codes associated with outpatient face-to-face office visits, emergency department visits, or inpatient admissions; or one claim with a procedure code. Because surgery is a risk factor for venous thromboembolism,²² for men who underwent orchiectomy, we ascertained venous thromboembolism beginning 90 days after the orchiectomy. Moreover, because we were concerned that development of metastatic prostate cancer might be associated with venous thromboembolism, we identified men who received chemotherapy (suggesting metastatic progression) and censored them six months before the first dose of chemotherapy.

2.4 Androgen Deprivation Therapy

We identified the use of androgen deprivation therapy, GnRH agonists and bilateral orchiectomy, using corresponding administrative codes (Appendix). Because the hypogonadotropic effect may persist after discontinuing GnRH agonists, we considered men to be actively treated for six months following the delivery of GnRH agonists. Results were similar in sensitivity analyses where we considered men permanently on therapy once treatment was started (data not shown).

2.5 Sociodemographic and tumor characteristics

For each patient, we characterized year of diagnosis, age, race, Hispanic ethnicity, marital status, urban residence, census-tract level income and education (categorized as quartiles within registries), SEER region, type of primary treatment (radiation, surgery, or neither), tumor extent, and comorbid conditions based on the Klabunde modification of the Charlson score, using inpatient and ambulatory claims during the year prior to prostate cancer diagnosis.²⁷

2.6 Analyses

Men were censored on December 31, 2009, (the last date for which data were available) or sooner if they died or disenrolled from Parts A and B of fee-for-service Medicare, or, for the venous thromboembolism analysis, 6 months before a first dose of chemotherapy for men

who underwent chemotherapy during follow up (due to concern for development of metastatic cancer). We first describe receipt of androgen deprivation therapy by sociodemographic and tumor characteristics. We then calculated incidence rates of peripheral arterial disease and venous thromboembolism during treatment with GnRH agonists, orchiectomy, or no therapy. Men contributed information to the treatment groups only when on treatment. We used two-sample hypotheses tests to assess whether rates with orchiectomy and GnRH agonist treatment differed from rates without these therapies (assuming censoring to be ignorable).

Next, we constructed Cox proportional hazards models with time-varying treatment variables to assess the effect of GnRH agonists or orchiectomy on time to developing peripheral arterial disease and venous thromboembolism. The time-varying treatment variables allowed men at risk to contribute information to the treatment groups when on treatment and to the no treatment group when off treatment. We adjusted for the independent variables in Table 1. For each analysis, men were followed until they developed an event of interest or were censored.

Because the development of new conditions during follow-up may affect the risk of developing peripheral arterial disease and venous thromboembolism, we performed sensitivity analyses where we included time-varying independent variables in the models. In both models, we included variables for diabetes, coronary heart disease, myocardial infarction, and stroke. We also included venous thromboembolism in the peripheral arterial disease model and peripheral arterial disease in the venous thromboembolism model.

Because our analyses can control only for observed characteristics, we examined the robustness of estimated treatment effects to potential *unobserved* confounders.^{2, 28, 29} To do this, we assumed there exists an unobserved variable, such as smoking, associated with both receipt of ADT and development of peripheral arterial disease or venous thromboembolism. We then updated estimates of ADT on the outcomes after adjusting for these additional unmeasured variables under specific assumptions regarding the prevalence of the confounder in men who were and were not treated and the confounder's relationship with treatment choice. Based on prior evidence, smoking increases risk of peripheral arterial disease approximately 4-fold³⁰ and risk of venous thromboembolism approximately 1.5-fold.³¹ Overall, about 10% of Americans older than 65 are smokers.³² We assumed that smoking rates in men not on ADT were 10%, and in men on ADT were 15% to 20%.

We used SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina) for analyses. All tests of statistical significance were two-sided. The study was considered exempt from review by the institutional review board at Harvard Medical School (Boston, MA).

3. RESULTS

The mean age of the cohort at diagnosis was 74.2 years (standard deviation, 5.9), 8.9% were black, 5% were Hispanic, and 69.1% were married (Table 1). Overall 47.8% of men received GnRH agonist therapy and 2.2% of men underwent bilateral orchiectomy during follow-up. The median time (interquartile range) from prostate cancer diagnosis to primary surgery or radiation among treated men was 57 days (33–96). The median (interquartile range) time from diagnosis to first dose of androgen deprivation therapy was 38 days (19–100).

For the peripheral arterial disease cohort, men were observed for a median of 5.1 years (range zero to 18.0 years). On average, men treated with GnRH agonists were on treatment for 40.6% of the time from diagnosis through censoring; men treated with orchiectomy were on treatment for 73.4% of the time from diagnosis through censoring. For the venous

thromboembolism cohort, men were observed for a median of 4.1 years (range 0 to 15.0 years). On average, men treated with GnRH agonists were on treatment for 45.2% of the time from diagnosis through censoring; men treated with orchiectomy were on treatment for 74.7% of the time from diagnosis through censoring.

The unadjusted rates per 1,000 person-years for developing peripheral arterial disease or venous thromboembolism during treatment versus no treatment are presented in Table 2. Rates of peripheral arterial disease and venous thromboembolism were significantly higher for men being treated with GnRH agonists or orchiectomy compared with men not receiving hormonal therapy.

Using time-varying Cox proportional hazards models that adjusted for socio-demographic and tumor characteristics, current treatment with a GnRH agonist or orchiectomy was associated with an increased risk for peripheral arterial disease and venous thromboembolism compared with men not receiving hormonal therapy (Table 3).

The increased risk for peripheral arterial disease was observed with as little as one to four months of androgen deprivation therapy, while the risk for venous thromboembolism was only evident after at least five months of treatment with a GnRH agonist (Table 4).

In sensitivity analyses including time-varying variables reflecting onset of diabetes, myocardial infarction, coronary heart disease, stroke and peripheral arterial disease or venous thromboembolism (where appropriate), results for both models were unchanged (data not shown).

In analyses assessing the sensitivity of our findings to unobserved confounders, we considered a confounder, such as smoking status, and assumed that the prevalence of smoking was 1.5 to 2 times higher in men on androgen deprivation therapy (~15–20%) than in men not on treatment (~10%). If 15% of men on androgen deprivation therapy smoked, the association between androgen deprivation therapy and risk of peripheral arterial disease would still be statistically significant (AHR 1.03, 95% CI 1.00–1.07). However, if the rate of smoking among men on androgen deprivation therapy were higher, this association would lose statistical significance. If 15% of men on androgen deprivation therapy smoked (versus 10% of men not on androgen deprivation therapy), the association of androgen deprivation therapy with venous thromboembolism would remain statistically significant (AHR 1.07, 95% CI 1.02–1.13). If 20% of men on androgen deprivation smoked, the association would be of borderline significance (AHR 1.05, 95% CI 0.99–1.11).

4. DISCUSSION

Our study has several important findings. First, androgen deprivation therapy to treat loco-regional prostate cancer was associated with an increased risk of peripheral arterial disease. To our knowledge, this has not been previously described. GnRH agonists are known to increase fat mass, increase fasting insulin levels, decrease insulin sensitivity and alter serum lipoproteins which lead to increased arterial stiffness.^{33–36} While the exact mechanism by which GnRH agonists and bilateral orchiectomy exert their effect on central and peripheral arteries remains unknown, men considering androgen deprivation therapy should be counseled concerning the potential risk of peripheral arterial disease.

Conversely, Van Hemelrijck et al did not observe an association between androgen deprivation therapy and an increased risk of peripheral arterial disease. This may be due to differences in the study populations. First, our study was restricted to older U.S. men while the Swedish study included men of all ages (although 90% of the androgen deprivation therapy cohort was aged 65 and older). Secondly, we focused on men with non-metastatic

disease because the indication for androgen deprivation therapy remains unclear for many men treated in this setting, and thus the risk of harm is potentially greater.

Second, use of GnRH agonists and bilateral orchiectomy to treat prostate cancer was associated with an increased risk of venous thromboembolism, consistent with Van Hemelrijck et al's finding²³ as well as another preliminary analysis.³⁷ Higher testosterone concentrations are associated with increased levels of antithrombin-3,^{38,39} and androgen deprivation therapy and testosterone suppression may induce a hyper-coagulable state. We excluded men with previous venous thromboembolism, and controlled for pre-existing diabetes and other medical conditions in establishing the association between androgen deprivation therapy and increased risk of venous thromboembolism, which the Swedish study was unable to do. We also censored men who were treated with chemotherapy 6 months before their first dose of chemotherapy to lower the chance that we would be identifying venous thromboembolism associated with metastatic disease. Although the risk of venous thromboembolism in our study was more modest than in the Swedish study, our study was limited to men with loco-regional prostate cancer; the higher rate of venous thromboembolism from the Swedish study may be because 40% of the Swedish cohort had metastatic prostate cancer, a known risk factor for venous thromboembolism. Similarly, while estrogen therapy exerts antitumor activity in androgen independent prostate cancer, 6.7% of treated men developed venous thromboembolism.⁴⁰ In our study, androgen deprivation therapy was associated with a 9% increased risk of venous thromboembolism. The thromboembolic mechanism of androgen deprivation therapy and estrogen therapy remains to be discerned.

We observed an increased risk of peripheral arterial disease with as little as one to four months of androgen deprivation therapy, similar to the increased risk of coronary heart disease observed previously.¹⁶ This finding suggests that the mechanism is unlikely to be solely via diabetes and atherosclerosis, although plaque progression and instability may still contribute.¹⁵ For venous thromboembolism, the increased risk was not evident until at least five months of therapy, and we actually observed fewer venous thromboembolic events in the first months after therapy. Although we attempted to minimize bias, this could be a result of unobserved confounding if men with risk factors for VTE, such as hospitalization, for example, are not started on GnRH agonist therapy until after other medical conditions have stabilized. Overall, we did not observe a cumulative risk for either condition associated with longer duration of androgen deprivation therapy. Additional research is needed to understand the mechanisms behind the associations we observed.

Our findings must be interpreted in the context of the study design. First, this is an observational study demonstrating associations, and we are limited in our ability to determine causality. The analysis is subject to bias from unmeasured confounders, although we found that our findings were robust to rather large differences in a potential unmeasured confounder (smoking status). In addition, informative censoring may also bias our results. However, use of the time-varying treatment variable approach to survival analysis helps alleviate both concerns as individuals can contribute information to both treatment and no treatment groups. In order for censoring to be informative, their survival times must be independent of their censoring times. In our case, most of the censoring was related to the end of follow up and not to any patient characteristics. Second, our study is restricted to older men, and our findings may not be generalizable to younger men with prostate cancer. Furthermore, approximately 40% of men in the current study did not receive curative primary therapy and only 15% underwent radical prostatectomy. Therefore our findings may not be generalizable to all men considering ADT. However, our findings of increased risk of venous thromboembolism are consistent with the Swedish population-based study which included younger men.²³ Moreover, a study including patients of all ages with prostate

cancer in the Veterans Healthcare Administration corroborated previous findings among older patients of a greater risk of incident diabetes, coronary heart disease, acute myocardial infarction, and sudden cardiac death associated with androgen deprivation therapy.¹⁷ Third, we were unable to assess the use of oral anti-androgens as monotherapy or combined androgen deprivation using Medicare data, which lacks outpatient oral prescription data. Van Hemelrijck et al demonstrated that combined androgen deprivation increased the risk of deep vein thrombosis and pulmonary embolism while anti-androgen monotherapy only increased the risk of deep vein thrombosis.²³ In the study of veterans, the use of combined androgen blockade had relatively similar risks to those of GnRH agonist therapy, and oral anti-androgens alone (which are used infrequently in the U.S.) did not influence risks of outcomes.¹⁷ Finally, we ascertained peripheral arterial disease and venous thromboembolism based on procedure or diagnosis codes, and may be subject to bias due to poor documentation or incomplete coding.

5. CONCLUSIONS

Our findings contribute to the body of evidence demonstrating potential harms of androgen deprivation therapy. Prior studies have shown that androgen deprivation therapy causes insulin resistance³⁴, weight gain³³, and adverse lipid profiles³³ and it is associated with an increased risk of diabetes, cardiovascular disease, acute myocardial infarction, sudden cardiac death, and stroke.^{16, 17} Although the benefits of androgen deprivation therapy for loco-regional prostate cancer almost certainly outweigh risks in the adjuvant setting,⁷ the risk benefit profile may differ when used in other settings where there has been no proven benefit, such as primary androgen deprivation therapy. Additional research is needed to better understand the potential risks and benefits, so that these treatments can be targeted to patients where the benefits are most clear.

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Table 1

Characteristics of the study population.

Characteristic	n	%	Received GnRH Agonist During Follow-Up (%)	Received Orchiectomy During Follow-Up (%)
Total	182,757	-	47.8	2.2
Age, years				
66–69	45,326	24.8	35.9	1.1
70–74	57,703	31.6	45.0	1.6
75–79	44,764	24.5	54.0	2.4
80–84	23,722	13.0	59.9	4.0
85	11,242	6.1	59.8	5.3
Race/ethnicity				
Race				
White	155,009	84.8	47.3	2.3
Black	16,309	8.9	48.3	2.0
Other	7,204	3.9	53.6	2.4
Unknown	4,235	2.3	53.9	0.7
Hispanic ethnicity				
No	173,595	95.0	47.6	2.2
Yes	9,162	5.0	50.3	3.0
Marital status				
Unmarried	36,601	20.0	48.4	2.8
Married	126,328	69.1	46.4	2.1
Unknown	19,828	10.9	55.6	1.5
Residence				
Major metropolitan area	103,677	56.7	47.8	1.7
Metropolitan county	51,135	28.0	47.2	2.3
Urban	10,706	5.9	49.4	3.5
Less urban	14,183	7.8	48.3	4.1
Rural	3,056	1.7	48.5	4.0
SEER region				
San Francisco, CA	8,248	4.5	45.0	2.6
Connecticut	14,510	7.9	52.2	2.1
Detroit, MI	21,224	11.6	44.3	1.7
Hawaii	3,244	1.8	54.3	3.5
Iowa	14,599	8.0	48.0	4.3
New Mexico	6,123	3.4	36.18	5.6
Seattle, WA	13,878	7.6	39.0	2.8
Utah	8,290	4.5	39.8	3.3
Atlanta, GA	6,684	3.7	35.6	1.6
San Jose, CA	5,005	2.7	58.4	2.9
Los Angeles, CA	16,447	9.0	46.8	2.1

Characteristic	n	%	Received GnRH Agonist During Follow-Up (%)	Received Orchiectomy During Follow-Up (%)
Rural Georgia	538	0.3	37.4	3.0
Greater California	22,756	12.4	45.2	1.3
Kentucky	9465	5.2	50.6	1.8
Louisiana	10,050	5.5	54.9	1.9
New Jersey	21,696	11.9	60.5	0.7
Median household income in census tract of residence				
Quartile 1 (lowest)	45,237	24.8	50.3	2.8
Quartile 2	45,356	24.8	48.6	2.3
Quartile 3	45,521	24.9	47.0	2.2
Quartile 4 (high)	45,522	24.9	45.5	1.5
Unknown	1,121	0.6	40.0	5.1
High school graduates in census tract of residence				
Quartile 1 (lowest)	45,538	24.9	50.0	2.8
Quartile 2	45,416	24.9	48.3	2.3
Quartile 3	45,375	24.8	47.4	2.0
Quartile 4 (high)	45,307	24.8	45.5	1.6
Unknown	1,121	0.6	40.0	5.1
Clinical stage				
Clinically inapparent	77,684	42.5	42.1	1.5
Organ confined	95,460	52.2	51.6	2.3
Extracapsular extension	5,708	3.1	62.1	5.3
Invading bladder and/or rectum	3,839	2.1	46.4	10.5
Unknown	66	0.1	63.6	7.6
Tumor grade (Gleason)				
Well differentiated (2–4)	8,167	4.5	32.2	2.5
Moderately differentiated (5–7) *	107,229	58.7	41.7	1.7
Poorly differentiated/undifferentiated (8–10)	61,526	33.7	61.0	3.0
Unknown	5,835	3.2	42.1	3.2
Year of diagnosis				
1992	3,324	1.8	27.6	7.8
1993	2,498	1.4	29.7	7.4
1994	2,116	1.2	29.8	6.3
1995	8,497	4.7	38.6	7.5
1996	8,185	4.5	43.7	5.7
1997	8,435	4.6	46.2	4.1
1998	7,916	4.3	49.9	3.2
1999	8,400	4.6	52.6	2.6
2000	15,913	8.7	56.0	2.0
2001	16,992	9.3	54.8	1.5
2002	17,710	9.7	53.9	1.2

Characteristic	n	%	Received GnRH Agonist During Follow-Up (%)	Received Orchiectomy During Follow-Up (%)
2003	16,753	9.2	53.0	1.1
2004	16,845	9.2	50.1	1.1
2005	16,107	8.8	44.7	0.9
2006	16,728	9.1	42.6	0.7
2007	16,338	8.9	39.9	0.7
Primary treatment received in the 6 months after diagnosis				
Neither radiation or radical prostatectomy	72,471	39.7	48.3	3.9
Radiation	81,859	44.8	56.1	0.9
Radical prostatectomy	28,427	15.5	22.3	1.7
Charlson Index				
0	129,459	70.8	46.5	2.2
1	34,936	19.1	50.5	2.3
2	11,347	6.2	52.3	2.2
3	7,015	3.8	50.9	2.3

* Gleason grade 7 was categorized as poorly differentiated as of January 1, 2003

Rate of incident peripheral artery disease and venous thromboembolism with androgen deprivation therapy, unadjusted.

Table 2

Treatment	Events per 1,000 person-years					
	Peripheral Arterial Disease			Venous Thromboembolism		
	n	95% CI	p-value*	n	95% CI	p-value*
No treatment	21.0	20.7–21.3	Ref	10.4	10.2–10.6	Ref
GnRH agonist	30.5	29.6–31.4	<0.001	13.4	12.8–14.0	<0.001
Orchiectomy	27.1	24.4–29.7	<0.001	14.0	12.2–15.9	<0.001

* p values based on two-sample hypotheses tests evaluating whether the rate for men during GnRH agonist treatment differed from the rate under no treatment and whether the rate for men treated with orchiectomy differed from the rate under no treatment.

Adjusted hazard ratios for peripheral artery disease and venous thromboembolism among men receiving ADT.

Table 3

Treatment	Incident Peripheral Arterial Disease			Incident Venous Thromboembolism		
	Adjusted HR	95% CI	p-value*	Adjusted HR	95% CI	p-value*
No Treatment	Ref		-	Ref		-
GnRH agonist	1.15	1.11–1.19	<0.001	1.09	1.04–1.15	<0.001
Orchiectomy	1.14	1.03–1.26	0.013	1.21	1.05–1.38	0.007

* Using time-varying Cox proportional hazards models adjusting for all variables in Table 1.

Table 4

Adjusted association of the duration of GnRH Agonist therapy and outcomes*

Duration of GnRH Agonist Treatment (Months) [†]	Incident Peripheral Arterial Disease			Incident Venous Thromboembolism		
	Adjusted HR	95% CI	p-value*	Adjusted HR	95% CI	p-value*
No Treatment	Ref		-	Ref		-
1-4	1.10	1.04 - 1.17	0.002	0.88	0.80 - 0.96	0.003
5-12	1.21	1.14 - 1.28	<0.001	1.18	1.08 - 1.29	<0.001
13-24	1.11	1.03 - 1.19	0.008	1.27	1.15 - 1.41	<0.001
>25	1.15	1.07 - 1.24	<0.001	1.17	1.06 - 1.30	0.002

* Using time-varying Cox proportional hazards models adjusting for all variables in Table 1.

[†] For the peripheral artery disease cohort, the proportion of patient time contributed by duration categories no treatment was 84.3%; 1-4 months was 4.5%; 5-12 months was 4.7%; 13-24 months was 3.0%; and >25 months was 3.5%. For the venous thromboembolism cohort, the proportion of patient time contributed by duration categories no treatment was 84.2%; 1-4 months was 4.6%; 5-12 months was 4.8%; 13-24 months was 3.0%; and >25 months was 3.5%.

Appendix Table 1

Identification of androgen deprivation therapy, peripheral arterial disease and venous thromboembolism.

Description	ICD-9 Diagnosis	ICD-9 Procedure	HCPCS
Androgen Deprivation Therapy			
Leuprolide Injection			J9217, J9218, J9219, J1950
Goserelin Injection			J9202
Orchiectomy		62.3, 62.4, 62.41, 62.42	54520, 54521, 54522, 54530, 54535, 54690, 49510
Peripheral Arterial Disease			
Diagnosis Codes			
Peripheral Arterial Disease*	443.9		
Atherosclerosis*	440.xx		
Procedure Codes			
Incision of vessel, embolectomy, or thrombectomy, lower limb arteries*		38.08	
Endarterectomy, upper-limb vessels*		38.13	
Endarterectomy, lower limb vessels*		38.18	
Aorta-iliac-femoral bypass*		39.25	
Other intra-abdominal shunt or bypass*		39.26	
Peripheral Arterial shunt or bypass*		39.29	
Angioplasty*		39.50	
Insertion of non-coronary stent(s) or stent graft(s)*		39.90	
Open revascularization			35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35621, 35623, 35641, 35646, 35647, 35654, 35656, 35661, 35663, 35665, 35666
Peripheral angioplasty and atherectomy			35470, 35473, 35474, 35482, 35483, 35492, 35493, 35495
Venous Thromboembolism			
Deep vein thrombosis	444.x, 445.x, 451.x, 452, 453.x		34401–34451, 34471–34490
Pulmonary embolism	415.x		

Appendix Table 2

Full results of multivariable models

Characteristic	Peripheral Arterial Disease		Venous Thromboembolism	
	Adjusted HR	95% CI	Adjusted HR	95% CI
GnRH agonist therapy	1.15	1.11–1.19	1.09	1.04–1.15
Orchiectomy	1.14	1.03–1.26	1.21	1.05–1.38
Age (continuous in years)	1.03	1.02–1.03	1.02	1.01–1.02
Baseline diabetes mellitus	1.36	1.32–1.41	1.01	0.96–1.06
Baseline coronary artery disease	1.80	1.75–1.86	1.13	1.09–1.18
Race/ethnicity				
Race				
White	1.0		1.0	
Black	1.18	1.12–1.24	1.28	1.19–1.37
Other	0.71	0.65–0.78	0.40	0.34–0.48
Unknown	1.21	1.05–1.39	1.13	0.91–1.39
Hispanic ethnicity				
No	1.0		1.0	
Yes	0.95	0.89–1.02	1.25	1.13–1.39
Unknown	0.84	0.73–0.97	1.02	0.82–1.27
Marital status				
Married	1.0		1.0	
Unmarried	1.06	1.02–1.09	0.97	0.92–1.02
Unknown	0.97	0.92–1.02	0.88	0.82–0.94
Residence				
Major metropolitan area	1.0		1.0	
Metropolitan county	1.04	0.99–1.09	0.94	0.88–1.01
Urban	1.17	1.09–1.26	0.94	0.85–1.04
Less urban	0.95	0.88–1.02	0.92	0.83–1.02
Rural	0.93	0.82–1.05	0.99	0.84–1.17
SEER region				
San Francisco, CA	0.90	0.83–0.97	0.78	0.70–0.88
Connecticut	0.75	0.70–0.81	0.91	0.83–1.01
Detroit, MI	1.00	0.95–1.07	1.03	0.95–1.11
Hawaii	0.56	0.48–0.65	0.59	0.45–0.76
Iowa	0.87	0.80–0.94	0.87	0.77–0.97
New Mexico	0.80	0.72–0.89	1.21	1.07–1.38
Seattle, WA	0.72	0.82–0.94	0.90	0.82–0.99
Utah	0.82	0.50–0.61	1.16	1.03–1.31
Atlanta, GA	0.50	0.84–0.61	0.83	0.74–0.93
San Jose, CA	0.84	0.84–1.00	0.71	0.61–0.82
Rural Georgia	0.82	0.82–1.35	0.64	0.42–0.98

Characteristic	Peripheral Arterial Disease		Venous Thromboembolism	
	Adjusted HR	95% CI	Adjusted HR	95% CI
Greater California	0.80	0.80–0.91	0.86	0.79–0.95
Kentucky	0.88	0.88–1.05	0.94	0.83–1.06
Louisiana	0.94	0.94–1.11	0.82	0.72–0.92
New Jersey	0.96	0.96–1.09	0.90	0.82–0.98
Median household income in census tract of residence				
Quartile 1 (lowest)	1.0		1.0	
Quartile 2	0.96	0.91–1.00	0.99	0.93–1.06
Quartile 3	0.94	0.89–0.98	0.97	0.90–1.04
Quartile 4 (high)	0.93	0.87–0.96	1.06	0.97–1.15
Unknown	0.91	0.77–1.08	1.09	0.88–1.35
High school graduates incensus tract of residence				
Quartile 1 (lowest)	1.0		1.0	
Quartile 2	0.98	0.94–1.02	1.02	0.96–1.08
Quartile 3	0.96	0.92–1.01	0.98	0.91–1.05
Quartile 4 (high)	0.90	0.85–0.96	0.97	0.89–1.05
Unknown				
Clinical stage				
Clinically inapparent	1.0		1.0	
Organ confined	1.02	0.99–1.05	1.02	0.98–1.06
Extracapsular extension	1.07	0.99–1.16	1.12	1.00–1.25
Invading bladder and/or rectum	1.02	0.92–1.13	1.25	1.10–1.42
Unknown	0.58	0.19–1.80	1.91	0.79–4.58
Tumor grade (Gleason)				
Well differentiated	1.0		1.0	
Moderately differentiated (5–7) *	0.93	0.88–0.99	1.03	0.94–1.12
Poorly differentiated/ undifferentiated (8–10)	0.94	0.88–1.01	1.17	1.06–1.28
Unknown	0.95	0.86–1.04	1.05	0.92–1.21
Year of diagnosis				
1992	1.48	1.31–1.67	1.19	1.02–1.40
1993	1.33	1.16–1.53	1.13	0.95–1.36
1994	1.45	1.27–1.67	1.07	0.89–1.29
1995	1.33	1.20–1.46	1.06	0.93–1.21
1996	1.36	1.23–1.49	1.17	1.03–1.33
1997	1.33	1.21–1.47	1.10	0.97–1.25
1998	1.34	1.22–1.48	1.06	0.93–1.21
1999	1.29	1.17–1.42	1.13	0.99–1.28
2000	1.26	1.16–1.37	1.14	1.01–1.27
2001	1.24	1.14–1.35	1.06	1.02–1.28
2002	1.18	1.09–1.29	1.11	0.95–1.20
2003	1.18	1.09–1.29	1.08	0.99–1.25

Characteristic	Peripheral Arterial Disease		Venous Thromboembolism	
	Adjusted HR	95% CI	Adjusted HR	95% CI
2004	1.13	1.04–1.24	1.08	0.96–1.21
2005	1.04	0.95–1.14	1.04	0.92–1.18
2006	0.93	0.88–1.05	1.04	0.92–1.18
2007	1.0		1.0	
Primary treatment received in the 6 months after diagnosis				
Neither radiation or prostatectomy	1.0		1.0	
Radiation	1.02	0.99–1.06	0.91	0.87–0.95
Radical prostatectomy	0.83	0.79–0.88	0.93	0.87–0.99
Charlson Index				
0	1.0		1.0	
1	1.37	1.32–1.42	1.23	1.17–1.30
2	1.63	1.54–1.72	1.47	1.36–1.60
3	1.93	1.80–2.07	1.72	1.56–1.91

* Gleason grade 7 was categorized as poorly differentiated as of January 1, 2003