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ARTICLE

Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy: Observational Study of Veterans With Prostate Cancer

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Background Previous studies indicate that androgen deprivation therapy for prostate cancer is associated with diabetes and cardiovascular disease among older men. We evaluated the relationship between androgen deprivation therapy and incident diabetes and cardiovascular disease in men of all ages with prostate cancer.

Methods We conducted an observational study of 37 443 population-based men who were diagnosed with local or regional prostate cancer in the Veterans Healthcare Administration from January 1, 2001, through December 31, 2004, with follow-up through December 31, 2005. Cox proportional hazards models were used to assess whether androgen deprivation therapy with gonadotropin-releasing hormone (GnRH) agonists, oral antiandrogens, the combination of the two (ie, combined androgen blockade), or orchiectomy was associated with diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, or stroke, after adjustment for patient and tumor characteristics. All statistical tests were two-sided.

Results Overall, 14 597 (39%) of the 37 443 patients were treated with androgen deprivation therapy. Treatment with GnRH agonists was associated with statistically significantly increased risks of incident diabetes (for GnRH agonist therapy, 159.4 events per 1000 person-years vs 87.5 events for no androgen deprivation therapy, difference=71.9, 95% confidence interval [CI]=71.6 to 72.2; adjusted hazard ratio [aHR]=1.28, 95% CI=1.19 to 1.38), incident coronary heart disease (aHR=1.19, 95% CI=1.10 to 1.28), myocardial infarction (12.8 events per 1000 person-years for GnRH agonist therapy vs 7.3 for no androgen deprivation therapy, difference=5.5, 95% CI=5.4 to 5.6; aHR=1.28, 95% CI=1.08 to 1.52), sudden cardiac death (aHR=1.35, 95% CI=1.18 to 1.54), and stroke (aHR=1.22, 95% CI=1.10 to 1.36). Combined androgen blockade was statistically significantly associated with an increased risk of incident coronary heart disease (aHR=1.27, 95% CI=1.05 to 1.53), and orchiectomy was associated with coronary heart disease (aHR=1.40, 95% CI=1.04 to 1.87) and myocardial infarction (aHR=2.11, 95% CI=1.27 to 3.50). Oral antiandrogen monotherapy was not associated with any outcome studied.

Conclusion Androgen deprivation therapy with GnRH agonists was associated with an increased risk of diabetes and cardiovascular disease.

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Androgen deprivation therapy is being prescribed increasingly for the treatment of local or regional prostate cancer (1,2). Although studies have reported improved survival for men who receive androgen deprivation in addition to radiation therapy for locally advanced tumors or in addition to radical prostatectomy for lymph node–positive tumors, androgen deprivation therapy is also frequently used for indications for which long-term data on the benefits and risks are lacking (such as primary treatment of early-stage prostate cancer and prostate-specific antigen-only recurrence) (3–8). We recently described an increased risk of diabetes and cardiovascular disease among men with local or regional prostate cancer who were treated with androgen deprivation therapy (9). Our findings have been confirmed in another study that used similar data and methods (10). These analyses were limited, however, by a focus on only older men and by lack of information about other medications, including oral antiandrogens, and they did not assess whether androgen deprivation therapy is associated with stroke (9,10).

We examined care for 37 443 men of all ages diagnosed and treated for prostate cancer within the Veterans Healthcare Administration to assess whether androgen deprivation therapy (including treatment with gonadotropin-releasing hormone [GnRH] antagonist, oral antiandrogen therapy, the combination of the two, or orchiectomy) is associated with an increased incidence of diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, and stroke.

CONTEXT AND CAVEATS

Prior knowledge

Androgen deprivation therapy for prostate cancer has been associated with diabetes and cardiovascular disease among older men.

Study design

Observational study of patients with local or regional prostate cancer in the Veterans Healthcare Administration to determine whether androgen deprivation therapy with gonadotropin-releasing hormone agonists, oral antiandrogens, the combination of the two (ie, combined androgen blockade), or orchiectomy was associated with diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, or stroke.

Contribution

Androgen deprivation therapy with gonadotropin-releasing hormone agonists was associated with an increased risk of diabetes and cardiovascular disease, including coronary heart disease, myocardial infarction, sudden cardiac death, or stroke.

Implications

Although additional studies are needed to elucidate the effects of gonadotropin-releasing hormone agonists in the clinical setting, the potential increased risks of diabetes and cardiovascular disease associated with such agents should be considered in treatment decisions for prostate cancer.

Limitations

Patients were not randomly assigned to treatment. Administrative data were used to obtain information about treatments and outcomes. Patients who were receiving regular treatment with androgen deprivation therapy may have been diagnosed with diabetes or coronary disease because of their more frequent contact with health-care providers.

From the Editors

Patients and Methods

Patient Data

We used data from the Veterans Healthcare Administration for the analyses. Since 1998, the Veterans Healthcare Administration has collected uniformly reported data from each Veterans Healthcare Administration medical center on incident cancers diagnosed or treated within the system. These data have been linked to inpatient and outpatient encounter data, pharmacy data on medications administered by the Veterans Healthcare Administration and outpatient prescriptions filled, and Medicare administrative data for patients who are also eligible for Medicare. Patients were observed until death or December 31, 2005.

Study Cohort

We identified 42 573 men who were diagnosed with invasive prostate cancer from January 1, 2001, through December 31, 2004. We excluded 154 patients with cancers diagnosed at autopsy or only reported on their death certificate and 186 with no claims from 45 days before diagnosis through 195 days after diagnosis or who had multiple Medicare records (because we were concerned their claims were incomplete). We then excluded 4790 patients with metastatic or unknown stage, for a final cohort of 37 443 men with local or regional prostate cancer.

Ascertainment of Diabetes, Coronary Heart Disease, Myocardial Infarction, and Sudden Cardiac Death

As described previously, we used *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnosis codes associated with inpatient or physician office visits (depending on the condition) to ascertain the dependent variables of interest: diabetes (codes 250.xx, 357.2, 362.0–362.0x, and 366.41), coronary heart disease (codes 411–414.9, except for 414.1x), myocardial infarction (codes 410.xx, except for 410.x2), and sudden cardiac death or life-threatening ventricular arrhythmia (codes 798, 798.1, 798.2, 427.1, 427.4, 427.41, 427.42, and 427.5) (Appendix Table 1) (9). In addition, we ascertained stroke based on an inpatient admission or emergency room encounter with a primary diagnosis of ischemic stroke or transient ischemic attack (codes 433.x, 434.x, and 435.x) (Appendix Table 1).

So as not to identify diabetes or coronary heart disease diagnosed before diagnosis or during visits related to prostate cancer diagnosis, we defined prevalent diabetes or coronary heart disease for men who met the criteria for diagnosis of either condition that began 12 months before diagnosis through 6 months after diagnosis. The 15 087 (40.3%) men with prevalent diabetes and the 14 375 (29.5%) men with coronary heart disease were excluded from analyses of incident diabetes or coronary heart disease, respectively. We defined incident diabetes and coronary heart disease when the condition was identified at least 6 months after diagnosis in men without prevalent disease.

Androgen Deprivation Therapy

As described previously, we used administrative data to ascertain receipt of androgen deprivation therapy, including GnRH agonists and bilateral orchiectomy (Healthcare Common Procedure Coding System J9217, J9218, J9219, J1950, J9292; Common Procedure Terminology 54520, 54521, 54522, 54530, 54535, 54690, 49510; and *ICD-9* Procedure codes 62.3, 62.4, 62.41, and 62.42) (Appendix Table 1); men were considered to be on treatment for 6 months after each dose of GnRH agonist (9). We estimated duration of GnRH agonist exposure by summing the number of 1-month equivalent doses (9,11). We used prescription data to assess use of oral antiandrogens and considered men to be on treatment for the 30 days after each prescription plus an additional 8 weeks to account for any persistent antiandrogen effects of treatment. When men were being treated with androgen deprivation therapy, they could be classified as being in one of the following groups: orchiectomy, GnRH agonist alone (which includes men who received up to 6 weeks of oral antiandrogen treatment at the start of therapy), combined androgen blockade (for men treated with both GnRH agonist and more than 6 weeks of an oral antiandrogen), or oral antiandrogen monotherapy. Men could move from one state to another over time, although once treated with orchiectomy, they were permanently in that group.

Patient Characteristics

We documented each man's age at diagnosis (<55, 56–60, 61–65, 66–70, 71–75, or >75 years), race or ethnicity (white, black,

Hispanic, or other or unknown), marital status (married, unmarried, or unknown), year of diagnosis (2001, 2002, 2003, or 2004), Census division (New England, Mid Atlantic, East North Central, West North Central, Pacific, Mountain, West South Central, East South Central, or South Atlantic), median household income and average proportion of residents who are high school graduates in the zip code of residence at diagnosis (categorized in quartiles), tumor stage (local or regional), tumor grade (well differentiated, moderately differentiated, poorly or undifferentiated, or unknown), type of primary treatment (surgery [Common Procedure Terminology codes 55810–55815, 55840–55845 or *ICD-9* Procedure code 60.5], radiation [Common Procedure Terminology codes 77261–77431, 77499, 77750–77799 or *ICD-9* Procedure codes 92.2–92.29], or neither [Appendix Table 1]), and comorbid illness that was based on Diagnostic Cost Groups, a risk-adjustment tool used by the Centers for Medicare and Medicaid Services to predict future costs and disease burden for Medicare beneficiaries on the basis of diagnoses from inpatient and ambulatory claims during the 12-month period preceding diagnosis (categorized in quartiles) (9,12). We also included prostate-specific antigen levels at diagnosis, total cholesterol levels at diagnosis, and use of finasteride or a statin at diagnosis. Missing data for each variable were categorized as separate categories.

Statistical Analyses

We calculated incidence rates of diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, and stroke during treatment with GnRH agonists, orchiectomy, combined androgen blockade, oral antiandrogen monotherapy, or no therapy. Men contributed information to the treatment groups only when on treatment. We used two-sample z tests to assess whether rates of outcomes while on treatment with GnRH agonists, orchiectomy, combined androgen blockade, or oral antiandrogen monotherapy differed from rates under no treatment, accounting for censoring.

Next, as described previously, we used Cox proportional hazards models with time-varying treatment variables and time-varying covariates to assess the direct effect of GnRH agonists, orchiectomy, combined androgen blockade, or oral antiandrogen monotherapy on time to developing each dependent variable (9). This time-varying approach to survival analysis allows the proportional hazards assumption to be easily tested against a range of reasonable alternatives. For example, in our previous analysis (9), we allowed the effects of predictors to change at specified survival times and tested whether the resulting model fit the data statistically significantly better than the proportional hazards model. In all cases, the null hypothesis (proportional hazards) was not rejected. Furthermore, it is important to note that with time-varying covariates, the range of covariate values over which proportional hazards must hold is on average shorter than for the regular fixed-covariate case and so the associated model fit is more robust to any covariate-by-time interactions. We adjusted these analyses for patient age, race or ethnicity, marital status, Census division, area-level measures of income and education, tumor stage, tumor grade, year of diagnosis, primary surgery, comorbidity, prostate-specific antigen level at diagnosis, total cholesterol level at diagnosis, and use of finasteride or a statin at diagnosis and included time-varying variables controlling for the development of new diabetes, heart disease, sudden cardiac death, or stroke. For each analysis, men were observed from the date of prostate cancer diagnosis until the end of 2005 or until they died, disenrolled from parts A and B of Medicare, or developed an event of interest. For example, for the diabetes analysis, follow-up ended if the man developed diabetes.

Because effects of androgen deprivation therapy could persist even after the medications were stopped, in a series of sensitivity analyses, we also fit models in which we considered men on treatment indefinitely once treatment began, even if treatment was only short term. For these models, we considered all types of androgen deprivation therapy in a single variable.

All tests of statistical significance were two-sided. We used SAS statistical software, version 9 (SAS Institute, Inc, Cary, NC) for analyses. Because the study used deidentified previously collected data, it was considered exempt by the Harvard Medical School Committee on Human Studies.

Results

The mean age at diagnosis of the 37 443 men in the cohort was 66.9 years (SD = 8.6 years), 8896 (24%) were black, 2138 (6%) were Hispanic, and 20 578 (55%) were married (Table 1). Men were observed for a median of 2.6 years (range = 0 days to 5.0 years). Overall, 14 597 (39%) of the 37 443 men received some form of androgen deprivation therapy during follow-up (Table 1), primarily with GnRH agonists (14 037 or 37.5%). Few were treated with bilateral orchiectomy (308 or 0.8%) or oral antiandrogen monotherapy (1229 or 3.3%) at any time. Use of combined androgen blockade (for more than 6 weeks at the start of GnRH agonist therapy) was also infrequent (1838 or 4.9%). Overall rates of androgen deprivation therapy were highest for men diagnosed in 2001 because they had the longest duration of follow-up.

After prostate cancer diagnosis, 847 (2.3%) of the 37 443 men had a myocardial infarction, 1337 (3.6%) had sudden cardiac death or life-threatening ventricular arrhythmia, and 1188 (3.2%) had an ischemic stroke or transient ischemic attack during follow-up. Among the 22 356 men without prevalent diabetes, 4967 (22.2%) developed diabetes, and among the 23 068 without prevalent coronary heart disease, 4775 (20.7%) developed coronary heart disease.

The unadjusted rates per 1000 person-years for developing diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, or stroke during treatment or no treatment with androgen deprivation therapy are included in Table 2. We found higher unadjusted rates for each outcome for men who were receiving GnRH agonists therapy or orchiectomy than for men who were not (Table 2). For example, rates of incident diabetes were 159.4 (95% confidence interval [CI] = 150.6 to 158.3) per 1000 person-years for men on GnRH agonist treatment vs 87.5 (95% CI = 84.6 to 90.4) per 1000 person-years for men on no therapy, and rates of myocardial infarction were 12.8 (95% CI = 11.1 to 14.4) per 1000 person-years for men on GnRH agonist treatment vs 7.3 (95% CI = 6.4 to 7.9) per 1000 person-years

Table 1. Patient characteristics and receipt of androgen deprivation therapy (ADT)*

Characteristic	No. (%)	% who received ADT during follow-up
Total	37443 (100)	39.0
Age at diagnosis, y		
≤55	4110 (11)	23.6
56–60	5369 (14)	24.9
61–65	6412 (17)	33.0
66–70	8036 (21)	39.5
71–75	7173 (19)	46.7
>75	6343 (17)	57.6
Race or ethnicity		
White	24979 (67)	38.1
Black	8896 (24)	39.2
Hispanic	2138 (6)	50.1
Other or unknown	1430 (4)	36.3
Marital status		
Married	20578 (55)	39.4
Unmarried	16040 (43)	38.5
Unknown	825 (2)	38.4
Census division		
New England	1483 (4)	40.4
Mid Atlantic	3949 (11)	35.4
East North Central	3751 (11)	37.1
West North Central	3156 (9)	38.1
Pacific	3507 (10)	26.2
Mountain	2273 (6)	36.4
West South Central	5288 (15)	40.5
East South Central	3010 (9)	44.8
South Atlantic	8680 (25)	45.4
Median household income in zip code of residence at diagnosis		
Quartile 1 (lowest)	8852 (24)	43.5
Quartile 2	8855 (24)	40.9
Quartile 3	8849 (24)	37.3
Quartile 4 (high)	8850 (24)	34.1
Unknown	2037 (5)	39.8
% High school graduates in census tract of residence at diagnosis		
Quartile 1 (lowest)	8852 (24)	40.6
Quartile 2	8849 (24)	42.1
Quartile 3	8854 (24)	38.1
Quartile 4 (high)	8846 (24)	34.9
Unknown	2042 (5)	39.8
Tumor grade (Gleason score)		
Well differentiated (2–4)	1552 (4)	28.8
Moderately differentiated (5–7)	22626 (60)	31.4
Poorly differentiated or undifferentiated (8–10)	11688 (31)	54.7
Unknown	1577 (4)	41.5
DCG comorbidity score		
Quartile 1 (lowest)	9418 (25)	36.3
Quartile 2	9315 (25)	37.9
Quartile 3	9353 (25)	39.9
Quartile 4 (high)	9357 (25)	41.8
Year of diagnosis		
2001	9240 (25)	45.1
2002	9479 (25)	41.0
2003	9387 (25)	37.6
2004	9337 (25)	32.3
Primary treatment received in the 6 months after diagnosis		
Radical prostatectomy	9025 (24)	15.2
Radiation therapy	13490 (37)	44.3
Neither	14478 (39)	48.8
Prevalent diabetes		
No	22356 (60)	33.3
Yes	15087 (40)	47.4
Prevalent coronary heart disease		
No	26387 (70)	34.9
Yes	11056 (30)	48.7

* DCG = Diagnostic Cost Groups.

for men on no therapy. Higher rates of diabetes, coronary heart disease, and sudden cardiac death were observed during periods when men were on combined androgen blockade (Table 2). Higher rates of diabetes and coronary heart disease were observed for men during periods on oral antiandrogen monotherapy (Table 2).

By use of Cox proportional hazards models that adjusted for patient and tumor characteristics, we found that current use of a GnRH agonist, compared with no androgen deprivation therapy, was associated with a statistically significantly increased risk of developing incident diabetes (adjusted hazard ratio [aHR] = 1.28, 95% CI = 1.19 to 1.38), incident coronary heart disease (aHR = 1.19, 95% CI = 1.10 to 1.28), myocardial infarction (aHR = 1.28, 95% CI = 1.08 to 1.52), sudden cardiac death (aHR = 1.35, 95% CI = 1.18 to 1.54), and stroke (aHR = 1.22, 95% CI = 1.10 to 1.36) (Table 3). Orchiectomy was statistically significantly associated with an increased risk of incident coronary heart disease (aHR = 1.40, 95% CI = 1.04 to 1.87) and myocardial infarction (aHR = 2.11, 95% CI = 1.27 to 3.50). Oral antiandrogen use via combined androgen blockade, compared with no androgen deprivation therapy, was associated with an increased risk of incident coronary heart disease (aHR = 1.27, 95% CI = 1.05 to 1.53) but not with risk for diabetes, myocardial infarction, sudden cardiac death, or stroke. Oral antiandrogen monotherapy was not associated with any outcome examined.

When we repeated analyses by comparing ever use of androgen deprivation therapy with no androgen deprivation therapy, we found that, after adjustment for patient and tumor characteristics, ever use of androgen deprivation therapy was associated with diabetes (aHR = 1.28, 95% CI = 1.20 to 1.37, $P < .001$), coronary heart disease (aHR = 1.17, 95% CI = 1.09 to 1.25, $P < .001$), sudden cardiac death (aHR = 1.44, 95% CI = 1.28 to 1.64, $P < .001$), and stroke (aHR = 1.17, 95% CI = 1.03 to 1.33, $P = .02$). The risk for myocardial infarction was no longer statistically significant (aHR = 1.11, 95% CI = 0.95 to 1.30, $P = .18$) in this analysis, indicating that the association with myocardial infarction may be more directly related to current use of androgen deprivation therapy than any use.

Discussion

In this population-based study of men of all ages with local or regional prostate cancer in the Veterans Healthcare Administration, we observed that androgen deprivation therapy

Table 2. Unadjusted rate of incident diabetes, coronary heart disease, myocardial infarction, sudden death, and stroke associated with androgen deprivation therapy (ADT)*

Treatment	Incident diabetes		Incident CHD		Myocardial infarction		Sudden cardiac death		Stroke	
	Rate (95% CI)	*P* value†	Rate (95% CI)	*P* value†	Rate (95% CI)	*P* value†	Rate (95% CI)	*P* value†	Rate (95% CI)	*P* value†
No ADT	87.5 (84.6 to 90.4)	—	81.4 (78.7 to 84.2)	—	7.3 (6.4 to 7.9)	—	11.5 (10.7 to 12.3)	—	10.8 (10.0 to 11.5)	—
GnRH agonist	159.4 (150.6 to 168.3)	<.001	144.0 (135.7 to 152.2)	<.001	12.8 (11.1 to 14.4)	<.001	21.6 (19.4 to 23.7)	<.001	18.5 (16.5 to 20.5)	<.001
Orchiectomy	190.4 (137.6 to 243.2)	<.001	210.5 (150.9 to 270.0)	<.001	24.3 (12.4 to 36.3)	.005	23.3 (11.5 to 35.1)	.05	26.2 (13.8 to 38.7)	.015
Combined androgen blockade	144.6 (117.2 to 172.0)	<.001	157.7 (129.4 to 186.0)	<.001	10.2 (5.2 to 15.2)	.26	20.1 (13.0 to 27.2)	.02	14.8 (8.8 to 20.9)	.19
Oral antiandrogen	126.8 (82.9 to 170.8)	.08	143.2 (97.1 to 189.4)	.009	11.2 (2.3 to 20.1)	.40	18.8 (7.2 to 30.5)	.22	14.9 (4.6 to 25.2)	.43

* CHD = coronary heart disease; GnRH = gonadotropin-releasing hormone; Rate = number of events per 1000 person-years.

† *P* values were based on two-sample *z* tests that evaluated whether the rate of each outcome for men during treatment with any of the treatments differed from the rate under no androgen deprivation therapy, accounting for censoring. Patients with prevalent diabetes and coronary heart disease did not contribute data to the rates for incident diabetes and coronary heart disease, respectively. All statistical tests were two-sided.

with GnRH agonists was associated with increased risk of incident diabetes, coronary heart disease, acute myocardial infarction, and sudden cardiac death. These results are consistent with our previous findings in a population of older men enrolled in fee-for-service Medicare. Moreover, the associations we observed persisted after accounting for oral antiandrogen use and additional clinical information (such as baseline prostate-specific antigen values, cholesterol levels, and use of statins and finasteride) (9). In addition, we identified an association of GnRH agonists with stroke, which, to our knowledge, has not been previously described.

This study allowed us to examine the use of oral antiandrogens, in combination with GnRH agonists and when used as monotherapy. Use of combined androgen blockade, compared with no androgen deprivation therapy, was associated with incident coronary heart disease. However, neither combined androgen blockade nor oral antiandrogen monotherapy was associated with the other outcomes studied. Although the relatively small numbers of men receiving these treatments limited the power to observe differences, these findings provide some reassurance that use of oral antiandrogens was not associated with substantial increases in risks in addition to those observed for GnRH agonists.

Recently, other studies have examined the association between androgen deprivation therapy and diabetes and/or cardiovascular disease, and the findings remain somewhat mixed (10,13). A study of men in fee-for-service Medicare that used data and methods that were similar to those in our previous study found a similar increase in cardiovascular disease associated with androgen deprivation therapy (3,10). A preliminary report from a population-based observational study of Canadian men with prostate cancer observed an association between androgen deprivation therapy and increased incidence of diabetes but not of myocardial infarction or sudden cardiac death (13).

Other studies have examined cardiovascular mortality (6,14–18). A population-based observational study with few events reported increased cardiovascular mortality in a subset of men who underwent prostatectomy but not in a subset of men treated with radiation therapy (14). Secondary analyses of four large randomized controlled trials from the Radiation Therapy Oncology Group or European Organization for Research and Treatment of Cancer have found no association between neoadjuvant or adjuvant androgen deprivation therapy and cardiovascular mortality, although a pooled analysis of three small randomized controlled trials of men with clinically localized prostate cancer suggested that 6 months of androgen deprivation therapy led to earlier onset of fatal myocardial infarction in the subset of men who were aged at least 65 years (6,15–18). It is important to note that none of these studies were primarily designed to assess cardiovascular mortality and, therefore, were underpowered to study cardiovascular mortality.

Previous studies have not assessed the relationship between androgen deprivation therapy and stroke. The mechanism(s) responsible for the novel association between GnRH agonists and stroke observed in this study are unknown but may result from the same physiological changes proposed to underlie the risk of coronary vascular disease. These mechanisms include, but are likely not

Table 3. Association between androgen deprivation therapy and diabetes, coronary heart disease, myocardial infarction, sudden death, and stroke*

Treatment	Adjusted hazard ratio (95% CI)				
	Diabetes	Coronary heart disease	Myocardial infarction	Sudden cardiac death	Stroke
No androgen deprivation therapy	Reference	Reference	Reference	Reference	Reference
GnRH agonist	1.28 (1.19 to 1.38)	1.19 (1.10 to 1.28)	1.28 (1.08 to 1.52)	1.35 (1.18 to 1.54)	1.21 (1.05 to 1.40)
Orchiectomy	1.16 (0.87 to 1.54)	1.40 (1.04 to 1.87)	2.11 (1.27 to 3.50)	1.29 (0.76 to 2.18)	1.49 (0.92 to 2.43)
Combined androgen blockade	1.17 (0.96 to 1.42)	1.27 (1.05 to 1.53)	1.03 (0.62 to 1.71)	1.22 (0.85 to 1.76)	0.93 (0.61 to 1.42)
Oral antiandrogen	1.02 (0.72 to 1.45)	1.10 (0.80 to 1.53)	1.05 (0.47 to 2.35)	1.06 (0.57 to 1.99)	0.86 (0.43 to 1.73)

* Cox proportional hazards models were adjusted for age; race or ethnicity (white, black, Hispanic, or other or unknown); marital status (married, unmarried, or unknown); Census division; zip code–level measures of income and education (categorized in quartiles); tumor grade (well differentiated, moderately differentiated, poorly differentiated, or unknown); comorbidity score; year of diagnosis; stage (regional or local); primary therapy (radical prostatectomy or radiation therapy); prostate-specific antigen level at diagnosis (categorized in quintiles or unknown); cholesterol level at baseline (categorized in quintiles or unknown); baseline statin use; baseline finasteride use; prevalent coronary heart disease; prevalent diabetes; and development of new diabetes, coronary heart disease or myocardial infarction, sudden cardiac death, and stroke during follow-up, except that the diabetes, coronary heart disease, and sudden death models do not control for past occurrences of the same condition. The diabetes and coronary heart disease models excluded patients with prevalent diabetes and coronary heart disease, respectively. CI = confidence interval; GnRH = gonadotropin-releasing hormone.

limited to, treatment-related central obesity, lipid alterations, and insulin resistance (19–23).

We found that ever use and current use of androgen deprivation therapy were associated with similar risks of diabetes, coronary heart disease, and sudden cardiac death. The hazard ratio for the association between ever use of androgen deprivation therapy and risk of myocardial infarction was smaller than the hazard ratio for current use. This difference suggests that there may be a direct effect of androgen deprivation therapy on thrombosis formation in addition to the hypothesized risks of central obesity and diabetes that may develop during androgen deprivation therapy and may persist after therapy. Further investigation of this hypothesis is needed.

Although the risks associated with androgen deprivation therapy remain incompletely defined, the potential for harm from this treatment underscores the importance of better understanding its benefits. To date, short-term use of androgen deprivation therapy for local or regional prostate cancer has been shown to be beneficial in men with locally advanced disease who are treated with radiation therapy or men with lymph node–positive disease who are treated with radical prostatectomy (3–6,8). In addition, a recent study observed that 3 years of androgen suppression with radiation therapy for locally advanced prostate cancer was superior to 6 months of treatment (7). Nevertheless, data are lacking about benefits for use of androgen deprivation therapy as primary therapy or to treat asymptomatic biochemical recurrences identified only by increasing levels of prostate-specific antigen after primary treatment. Until the benefits and risks of androgen deprivation therapy in such settings are more completely defined, it may be best for physicians and patients to exercise caution in the use of androgen deprivation therapy. Indeed, observational data suggest that older men with low-risk tumors who were treated with primary androgen deprivation therapy appear to have poorer survival than those who received no treatment in the 6 months after diagnosis (24). Moreover, in post hoc subset analyses of randomized controlled trials, androgen deprivation therapy combined with radiation therapy for intermediate-risk disease may actually be associated with worse survival in men with moderate or severe comorbidity at baseline, perhaps underscoring the associated toxicities of this therapy (25).

Our study has some limitations. First, patients were not randomly assigned to treatment with androgen deprivation therapy, and so it is possible that factors associated with treatment might also be associated with the outcomes of interest. We controlled for numerous potential confounders, and we used time-varying treatment variables to allow men to serve as their own control when not on androgen deprivation therapy to minimize the likelihood of selection effects influencing our findings. Second, we used administrative data to ascertain exposures and outcomes. Nevertheless, previous research in the Veterans Healthcare Administration has documented a high degree of sensitivity in administrative data for cardiac procedures compared with that in medical record abstraction (26). Third, it is possible that men receiving regular injections or prescriptions might be more likely to be diagnosed with diabetes or coronary heart disease because of more frequent interactions with health-care providers. However, patients treated with GnRH agonists were also more often hospitalized for myocardial infarction and hospitalized or seen in emergency rooms for stroke, and these events are likely to be identified even among men without regular outpatient care. Finally, although we studied only men cared for in the Veterans Healthcare Administration, the cohort included men of all ages with prostate cancer living throughout the United States.

In conclusion, our findings from this observational study and those from a cohort of older men residing in Surveillance, Epidemiology, and End Results areas suggest that concerns regarding use of GnRH agonists are warranted (9). Additional research is needed to understand the effects of GnRH agonists for clinical settings where benefits have not yet been established, to identify populations of men at highest risk of complications associated with GnRH agonists, and to investigate strategies to prevent treatment-related morbidity. Nevertheless, patients and physicians considering initiation of GnRH agonist treatment for local or regional prostate cancer should factor the potential increased risks of diabetes and cardiovascular disease as they make treatment decisions.

Appendix Table 1. Codes used to identify diagnoses and procedures

Diagnosis or procedure	*ICD-9* diagnosis	HCPCS	CPT	*ICD-9* procedure	Comments
Diabetes (9,27–29)					Required two or more outpatient encounters with a primary or secondary diagnosis code or one hospitalization with a primary diagnosis of diabetes
Diabetes mellitus	250.xx				
Diabetic polyneuropathy	357.2				
Diabetic retinopathy	362.0–362.0x				
Diabetic cataract	366.41				
Coronary heart disease (9,27)	411–414.9 except 414.1x				Required two or more outpatient visits with a primary or secondary diagnosis code or one hospitalization with a primary diagnosis code for ischemic heart disease
Acute myocardial infarction (9,27,30,31)	410.xx except 410.x2				Required an inpatient admission with a primary diagnosis of acute myocardial infarction
Sudden cardiac death or life-threatening arrhythmia (9,32)					Required an inpatient admission with a relevant primary or secondary diagnosis code
Sudden death, cause unknown	798				
Instantaneous death	798.1				
Death <24 h after symptoms	798.2				
Paroxysmal ventricular tachycardia	427.1				
Ventricular fibrillation and flutter	427.4				
Ventricular fibrillation	427.41				
Ventricular flutter	427.42				
Cardiac arrest	427.5				
Stroke (33,34)					Required an inpatient admission or emergency room encounter with primary diagnosis of stroke
Ischemic	433.x–434.x				
Transient ischemic attack	435.x				
Leuprolide injection*		J9217, J9218, J9219, J1950			
Goserelin injection*		J9202			
Orchiectomy			54520, 54521, 54522, 54530, 54535, 54690, 49510	62.3, 62.4, 62.41, 62.42	
Radical prostatectomy†			55810–55815, 55840–55845	60.5	
Radiation therapy†	V58.0, V67.1, V66.1		77261–77431, 77499, 77750–77799	92.2–92.29	

* To calculate duration of use, we added the number of months on therapy. We considered men continuously on therapy for 6 months after each dose.
CPT = Common Procedure Terminology; HCPCS = Healthcare Common Procedure Coding System; *ICD-9 = International Classification of Diseases, Ninth Revision.*

† Radical prostatectomy and radiation therapy were identified based on claims in the 6 months after diagnosis or data from the Veterans Healthcare Administration registry data indicating use of these treatments (35,36).

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