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Mortality and Hospitalization Risk Following Oral Androgen Signaling Inhibitors Among Men with Advanced Prostate Cancer by Pre-existing Cardiovascular Comorbidities

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Abstract

Background: Elderly patients (≥ 65 yr) with advanced prostate cancer and cardiovascular disease (CVD) conditions are often excluded from clinical trials of abiraterone acetate (AA) or enzalutamide (ENZ). Consequently, little is known about the effects of these medications on these vulnerable patients.

Objective: To assess the short-term outcomes of AA and ENZ in patients with pre-existing CVDs.

Design, setting, and participants: A population-based retrospective study. The Surveillance, Epidemiology, and End Results-Medicare-linked database was used to identify prostate cancer patients using AA or ENZ.

Outcome measurements and statistical analysis: The primary endpoint was 6-mo all-cause mortality, analyzed using modified Poisson regression modeling of relative risk (RR) adjusted for confounders and comorbidities.

Results and limitations: Among eligible patients (2845 with AA and 1031 with ENZ), 67% had at least one pre-existing CVD. Compared with those without pre-existing CVDs, having one to two pre-existing CVDs was associated with 16% higher 6-mo mortality (RR = 1.16, 95% confidence interval [CI]: 1.00–1.36), and the risk increased further among those having three or more CVDs (RR = 1.56, 95% CI: 1.29–1.88). Most of the differences in survival of patients with pre-existing CVD condition occurred within the first 6 mo of treatment.

Conclusions: After treatment with AA or ENZ, elderly prostate cancer patients with pre-existing CVDs experienced higher short-term mortality than otherwise similar patients without CVDs. Mortality associated with CVDs did not depend on having received AA versus ENZ.

Patient summary: Patients with pre-existing cardiovascular diseases (CVDs) experienced higher short-term mortality after abiraterone acetate or enzalutamide than those without pre-existing CVDs. It is recommended that a multidisciplinary team, including a cardiologist, evaluate patients having pre-existing CVDs in the process of making treatment decisions and monitoring potential side effects.

Keywords

Prostate cancer; Population-based study; Elderly population; Short-term mortality; Hospitalization; Cardiovascular diseases

1. Introduction

Two second-generation oral androgen receptor signaling inhibitors, abiraterone acetate (AA) and enzalutamide (ENZ), are widely used to treat advanced prostate cancer (PCa) [1]. AA inhibits the biosynthesis of androgen, and ENZ competitively inhibits the androgen receptor. AA and ENZ are often used among PCa patients who are elderly (≥ 65 yr) and have significant comorbidities. However, pivotal trials of AA excluded men with clinically significant cardiovascular disease (CVD) conditions or serious coexisting nonmalignant disease [2], or uncontrolled hypertension; likewise, pivotal trials of ENZ excluded patients with significant comorbidities [3]. While the strict eligibility criteria for clinical trials may stem from legitimate concerns about frailty or comorbidities affecting response to or toxicity from trial medications, such practice limits the external validity of the trials, and the findings may not be generalizable to patients with existing comorbidities [4–6]. For example, adding androgen deprivation therapy (ADT) to radiotherapy improved overall survival (OS) in unfavorable localized PCa; however, the benefit was limited to patients with minimal comorbidities [7]. Among patients with a history of congestive heart failure (CHF) or acute myocardial infarction (AMI), adding ADT was associated with a 157% increase in all-cause mortality than brachytherapy only [8]. Furthermore, men with existing CVDs had a higher risk of cardiovascular events and mortality in the first 6 mo of starting ADT [8,9]. Similarly, AA is known to increase the levels of mineralocorticoids, thereby causing hypertension and hyperkalemia [10].

Based on these data, the potential benefit of AA and ENZ may depend on the health conditions of the patients [11]. However, information on this topic is limited due to the stringent trial eligibility criteria. To fill these knowledge gaps, we undertook a population-based study to provide outcome data by pre-existing CVDs and hypertension. Moreover, we tested the hypothesis that pre-existing CVDs are associated with higher 6-mo mortality after AA or ENZ treatment.

2. Patients and methods

The Institutional Review Board at Thomas Jefferson University approved the study.

2.1. Data sources

The main data source for this study was the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked files. As of 2013, the SEER program covers approximately 31% of the US population, with a 98% case ascertainment rate, and collects data on cancer status at diagnosis, primary cancer therapy, demographics, and cause of death for persons with cancer [12]. Medicare provides health insurance for the majority of Americans aged 65 yr and over [13].

2.2. Study participants

The study cohort consisted of men diagnosed between January 1, 1991, and December 31, 2013, with primary PCa. Patients were excluded if they were diagnosed at death, were enrolled in health maintenance organizations, or had no Medicare part A, B, or D coverage during the study period. We excluded those with AA or ENZ treatment before chemotherapy

due to a small sample size. A flowchart of the cohort creation is shown in Supplementary Figure 1.

2.3. Drug exposure

AA was identified using prescriptions for “abiraterone acetate” (Zytiga) and ENZ using prescriptions for “enzalutamide” (Xtandi). Docetaxel chemotherapy was identified using Healthcare Common Procedure Coding System codes “J9170” and “J9171.” Patients with documented docetaxel use prior to AA/ENZ initiation were included in the postchemotherapy group. The no-chemotherapy group had no docetaxel use. The AA group included patients treated with only AA or with AA before ENZ. Similarly, the ENZ group included patients treated with only ENZ or with ENZ before AA, with continuous part A and part B 12 mo before and 6 mo after drug initiation or until death, and part D coverage 6 mo before drug initiation.

2.4. Study endpoints

The primary endpoint was 6-mo all-cause mortality from the day of AA or ENZ initiation. The secondary endpoint was inpatient hospitalization 6 mo before and 6 mo after AA or ENZ initiation, defined as the number of short- or long-stay hospital admissions. These 6-mo endpoints were chosen because the risk of CVD is known to rise within the first 6 mo of starting ADT in patients with existing CVDs [8,9]. Patients were followed through the death date or the last follow-up date (December 31, 2015).

2.5. Identification of CVD conditions and medication use

In this study, pre-existing CVDs were defined as having AMI, atrial fibrillation, CHF, stroke, or ischemic heart disease before AA or ENZ initiation. These conditions were identified from the Chronic Condition Flags file, based on the International Classification of Diseases, ninth revision [14]. Since the CVD conditions were not mutually exclusive, a CVD indicator was created with zero, one to two, or three or more CVDs.

2.6. Descriptive variables

Demographic variables included age at the time of first AA or ENZ treatment, race, marital status, income, SEER region, year of diagnosis, year of first treatment, and state buy-in. Clinical variables included presence of diabetes mellitus or hypertension before AA or ENZ initiation, and variables included presence of diabetes mellitus or hypertension before AA or ENZ initiation, and clinical stage at diagnosis [15].

2.7. Statistical analysis

Descriptive statistics were generated using Kruskal-Wallis tests (presented as median and interquartile range) for continuous variables and chi-square tests for categorical variables. The crude 6-mo mortality rates were estimated as the number of deaths divided by the number of patients by CVD condition, and 99% confidence intervals (CIs) were generated using the Clopper-Pearson method [16]. The difference in OS between the CVDs was illustrated with Kaplan-Meier plots. A modified Poisson regression model was used to assess the associations between CVD and 6-mo mortality, adjusting for demographics and

all clinical variables [17]. An interaction term between CVD indicator and drug (AA vs ENZ) was added to the model to test the differences in 6-mo mortality between groups.

The incidence rates of hospitalization were estimated as the total number of hospital admissions offset by the total time at risk (defined as total time alive in the 6-mo period minus the amount of time spent in the hospital). Poisson regression was used to generate crude incidence rate ratios (IRRs) and 99% CI to compare incidence rate of hospitalization 6 mo before and after AA or ENZ initiation. Separate negative binomial models were used to compare the change in hospitalization rates, adjusting for baseline hospitalization rate, demographics, and all clinical variables. An interaction term between the CVD indicator and the drug (AA vs ENZ) was introduced in the models to compare the change between the two drugs. All multivariable analyses were stratified by chemotherapy status. Owing to the small sample size for some CVD conditions (eg, AMI) and to avoid overfitting, multivariable analysis by each CVD was not performed. To account for multiple comparisons for unadjusted analyses, adjustment for maintaining a 5% false discovery rate (FDR) using the Benjamini-Hochberg method was performed to control for type I errors [18]. A *p* value of <0.05 was considered statistically significant. The 99% CIs were generated to be more conservative and closely align with the FDR-adjusted *p* values. For multivariable analyses, 95% CIs are reported. All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and the figures were generated using R v3.4.2.

3. Results

We identified 3876 eligible patients (2845 treated with AA and 1031 treated with ENZ). The demographic and clinical characteristics for AA- and ENZ-treated patients were comparable (Table 1). About 67% of eligible patients had one or more CVD conditions before receiving AA or ENZ.

3.1. Short-term mortality

Figure 1 shows that postchemotherapy patients treated with AA or ENZ experienced higher 6-mo mortality than those reported by the pivotal trials. In patients treated with AA or ENZ with no chemotherapy, the crude 6-mo mortality was substantially higher among patients with pre-existing CVD than among those without it (Fig. 1). Among post- and no-chemotherapy patients treated with AA or ENZ, having three or more CVD diagnoses was associated with 43% and 56% higher 6-mo mortality relative risk (RR = 1.43, 95% CI: 1.04–1.98; RR = 1.56, 95% CI: 1.29–1.88), respectively, compared with those without CVDs (Table 2). The elevated mortality risk associated with CVD attenuated within 6 mo of treatment initiation (Fig. 2; the survival curves diverge within 6 mo and become approximately parallel afterward).

3.2. Hospitalization rate changes

Based on crude IRRs, AA was associated with higher hospitalization rates regardless of pre-existing CVD conditions in the no-chemotherapy group (Fig. 3). In negative binomial regression models, among postchemotherapy patients, there were no significant differences in hospitalization rates between the two drugs; however, those with one to two CVDs had a

43% higher hospitalization rate compared with no CVD (IRR 1.43, 95% CI: 1.15–1.78). Among no-chemotherapy patients with three or more CVDs, those treated with ENZ had a 41% lower hospitalization rate than the patients treated with AA (IRR = 0.59, 95% CI: 0.44–0.79). Additionally, pre-existing hypertension was associated with a higher post-treatment hospitalization rate in the no-chemotherapy or no-CVD group (Table 3). Furthermore, AA was associated with a significant increase in post-treatment hospitalization in patients taking various classes of medications (unadjusted IRRs ranging from 1.29 to 2.09; Supplementary Fig. 2).

4. Discussion

To date, outcome data following AA or ENZ treatment are limited, especially among those with preexisting CVDs, leaving physicians with little guidance regarding optimal treatment selection. To our knowledge, this is the first large-scale population-based study presenting outcome data following the use of AA and ENZ among elderly patients with advanced PCa and a history of significant CVDs. Our study revealed that two-thirds of the community-dwelling Medicare patients treated with AA or ENZ had pre-existing CVDs, and these patients experienced higher 6-mo mortality (23–37%) than those without existing CVDs and those from the pivotal trials [1,19]. Our findings highlight the importance of conducting outcome evaluation among patients not meeting pivotal trial eligibility criteria in the real-world setting. Furthermore, our data suggest that treatment choice (AA or ENZ) may impact post-treatment hospitalization risk. We found that AA was associated with a significant increase in hospitalization among patients with several CVD conditions, although the same patterns were not observed in ENZ users.

Our findings are consistent with published reports showing an increased risk of grade 3 (severe) or grade 4 (life-threatening) cardiac adverse events (AEs) after AA in the general population and clinical trials [20]. A meta-analysis of published randomized controlled trials found that AA was associated with a 2.2-fold risk of cardiovascular toxicity (RR = 2.2, 95% CI: 1.60–3.27); a similar pattern was not observed in ENZ users (RR = 1.32, 95% CI: 0.85–2.06) [21]. The STAMPEDE trial, which evaluated the use of AA with standard ADT among patients over the age of 70 yr, found that the gain in OS was minimal and not statistically significant (hazard ratio [HR] = 0.94, 95% CI: 0.69–1.29) despite the improvement in cancer-free survival (HR = 0.36, 95% CI: 0.28–0.47) [11]. The potential survival advantage might have been offset by increased noncancer mortality: the most common toxicities associated with AA were CVDs (grade 3; 10% of the combination group [AA/ADT] vs 4% in the ADT-alone group) [11]. ADT is also associated with an increased risk of CHF (HR = 1.81), arrhythmia (HR = 1.44), and conduction disorder (HR = 3.11) [22]. Our findings further revealed that AA was associated with a significant increase in post-treatment hospitalization across all CVD categories examined (Fig. 3) and several classes of medications (Supplementary Fig. 2); similar patterns of post-treatment hospitalization were not observed among ENZ users. As AA and ENZ have been approved for earlier-stage disease, their toxicity profiles become even more crucial because the AEs may have a lasting impact on quality of life.

While the exact mechanisms leading to increased hospitalization after AA are unclear, potential hypotheses include drug-drug interactions (DDIs), drug-disease interactions, and potential AEs associated with the drugs. In our study, we found that hypertension was associated with a higher post-treatment hospitalization rate (Table 3). AA is a major substrate and inhibitor of the cytochrome p450 pathway involved in the metabolism of numerous widely used medications [23,24]. For example, the concurrent use of AA with a major CYP2D6 substrate (eg, metoprolol) may increase metoprolol toxicity [23,24]. It is thus important to monitor patients treated with AA while taking medications that affect the p450 pathways. Similarly, close monitoring of patients treated with ENZ while taking gemfibrozil [25] is needed due to potential DDIs.

It is important to recognize that during the study period, AA and ENZ were primarily used in castration-resistant disease, and thus these patients were more likely to have ADT, which is associated with an increase in fat mass, a loss of muscle mass, changes in lipid balance, and an increased risk of metabolic syndrome [26]. This is a known contributor to CVDs and thus a likely contributor in the observed outcomes.

Our findings raise important questions regarding the potential toxicity of AA or ENZ in “real-world” patients, and should spur clinicians to integrate this knowledge into their clinical decision making for patients with PCa and CVD. These findings also suggest that more careful patient selection and monitoring of outcomes following the administration of AA or ENZ are essential for achieving optimal outcomes. Furthermore, these findings call for a multidisciplinary team approach in the treatment of PCa patients.

The American Society of Clinical Oncology (ASCO) has attempted to use a value framework to assess the utility of various cancer treatment regimens [27,28]. However, because its current value frameworks contain data generated from relevant clinical trials only, it might not apply to a large portion of PCa patients who are likely excluded from clinical trials. The findings of this study can be useful for extending the ASCO value framework to address the special situation faced by PCa patients with pre-existing CVDs.

4.1. Strengths and limitations

This study has several limitations. We could not address treatment efficacy given our study’s retrospective nature, potential misclassification of comorbidities, unmeasured confounders, and lack of ability to identify appropriate control patients not receiving AA or ENZ. We could not directly compare our study population against the inclusion/exclusion criteria of the pivotal AA and ENZ trials due to insufficient clinical information from the SEER database. In addition, the CVD conditions were derived from the Medicare files [29], and misclassification might occur. However, the misclassification was unlikely to be related to the use of AA or ENZ [30]. Nonsystematic misclassifications often bias the results toward the null; that is, this study might have underestimated the effects of existing CVD conditions due to misclassifications.

The major strength of this study is that it was derived from a large, rich, population-based database with broad representation of various racial/ethnic groups treated in many different clinical settings; therefore, the findings are likely to apply to a majority of patients. Another

major strength of this study is the availability of longitudinal data at the individual level. By adjusting for the hospitalization rate before the drug treatment, we were able to estimate post-treatment hospitalization IRRs comparing ENZ versus AA among patients having the same pretreatment hospitalization rate, while accounting for other potential confounders.

5. Conclusions

A substantial portion of AA and ENZ users in the real-world setting had pre-existing CVDs and was unlikely to meet the eligibility criteria of clinical trials. Pre-existing CVDs in PCa patients receiving AA or ENZ were associated with a higher 6-mo mortality rate. Furthermore, we found that pre-existing hypertension is associated with an increased risk of hospitalization after AA or ENZ treatment. For PCa patients to receive these medications, assessment of CVD risk and/or comorbidities is vital to help inform treatment decision making. Moreover, if AA is used by patients with a high risk for treatment-related AEs, then close monitoring is required. Further studies are warranted to understand the potential mechanisms and to develop appropriate guidelines to manage this significant subset of men with advanced PCa and comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Pre-existing cardiovascular conditions are associated with higher short-term mortality after abiraterone acetate or enzalutamide. The survival benefit observed in the pivotal clinical trials might not hold for patients with significant pre-existing cardiovascular conditions.

Fig. 1 -

All-cause crude mortality at 6 mo after treatment: (A) abiraterone users—postchemotherapy status; (B) enzalutamide—postchemotherapy status; (C) abiraterone—no chemotherapy status; and (D) enzalutamide—no chemotherapy status. The vertical bars represent 99% confidence intervals. All CVD conditions may or may not include other CVD conditions.

Figure 1 A shows that 24% of all postchemotherapy patients treated with AA died within 6 mo, compared with 17% in the pivotal trial COU-AA 301 [1]. Figure 1B shows that 28% of all postchemotherapy patients treated with enzalutamide died within 6 mo, compared with 12% in the pivotal trial AFFIRM [19]. Figure 1C shows that among patients with no documented chemotherapy, 18% of patients died within 6 mo of initiation of abiraterone. Figure 1D shows that among patients with no documented chemotherapy, 17% of patients died within 6 mo of initiation of enzalutamide. AA = abiraterone acetate; AFIB = atrial fibrillation; AMI = acute myocardial infarction; CHF = congestive heart failure; CVD = cardiovascular disease; IHD = ischemic heart disease.

Fig. 2 -

Survival among patients treated by (A) abiraterone and (B) enzalutamide by pre-existing cardiovascular conditions. Kaplan-Meier survival curves by pre-existing cardiovascular conditions and polypharmacy status 6 mo before the initiation of study drug among patients without documented chemotherapy. Most significant differences in survival were observed in the first 6 mo, following which the survival curves become almost parallel. Survival curves for patients using the drugs after chemotherapy are not presented to comply with the National Cancer Institute's (NCI) minimum cell size requirements. CVD = cardiovascular disease.

Fig. 3 -

Incidence rate ratios of hospitalization by chemotherapy status and pre-existing CVD conditions. Among no-chemotherapy group, AA is associated with a higher post-treatment hospitalization rate among patients with a history of AMI, AFIB, CHF, stroke, and IHD. All CVD conditions may or may not include other CVD conditions. AA = abiraterone; AMI = acute myocardial infarction; AFIB = atrial fibrillation; CHF = congestive heart failure; CI = confidence interval; CVD = cardiovascular disease; ENZ=enzalutamide; IHD = ischemic heart disease.

Table 1 -
Demographic and clinical characteristics of prostate cancer patients treated with abiraterone or enzalutamide

Characteristic	Abiraterone (<i>n</i> = 2845)		Enzalutamide (<i>n</i> = 1031)	
	Abiraterone After chemotherapy (<i>n</i> = 586)	No chemotherapy (<i>n</i> = 2259)	Enzalutamide After chemotherapy (<i>n</i> = 264)	Enzalutamide No chemotherapy (<i>n</i> = 767)
Age at first treatment (yr), median (IQR)	74 (70–79)	76 (71–82)	74 (70–78)	76 (70–82)
Age groups at first treatment (yr), <i>n</i> (%)				
<75	294 (50.2)	960 (42.5)	139 (52.7)	342 (44.6)
75	292 (49.8)	1299 (57.5)	125 (47.3)	425 (55.4)
Race, <i>n</i> (%)				
White	489 (83.4)	1832 (81.1)	228 (86.4)	626 (81.6)
Black	61 (10.4)	267 (11.8)	25 (9.5)	94 (12.3)
Other	36 (6.1)	160 (7.1)	11 (4.2)	47 (6.1)
Marital status, <i>n</i> (%)				
Married	377 (64.3)	1513 (67.0)	194 (73.5)	514 (67.0)
Not married	137 (23.4)	523 (23.2)	48 (18.2)	159 (20.7)
Unknown	72 (12.3)	223 (9.9)	22 (8.3)	94 (12.3)
Zip code-level income (\$), median (IQR)	57 963 (43 218–77 648)	58 085 (44 180–79 710)	59 920 (47 044–81 878)	59 525 (44 219–81 899)
SEER region, <i>n</i> (%)				
Northeast	99 (16.9)	456 (20.2)	46 (17.4)	200 (26.1)
South	115 (19.6)	454 (20.1)	59 (22.3)	123 (16.0)
North central	66 (11.3)	256 (11.3)	45 (17.0)	105 (13.7)
West	306 (52.2)	1093 (48.4)	114 (43.2)	339 (44.2)
Year of diagnosis, <i>n</i> (%)				
1991–2000	114 (19.5)	399 (17.7)	59 (22.3)	143 (18.6)
2001–2005	198 (33.8)	587 (26.0)	73 (27.7)	198 (25.8)
2006–2009	187 (31.9)	655 (29.0)	66 (25.0)	183 (23.9)
2010	87 (14.8)	618 (27.4)	66 (25.0)	243 (31.7)
Year of first treatment ^a , <i>n</i> (%)				
2011–2012	423 (72.2)	643 (28.5)	65 (24.6)	72 (9.4)
2013–2014	163 (27.8)	1616 (71.5)	199 (75.4)	695 (90.6)

Characteristic	Abiraterone (<i>n</i> = 2845)		Enzalutamide (<i>n</i> = 1031)	
	Abiraterone After chemotherapy (<i>n</i> = 586)	Abiraterone No chemotherapy (<i>n</i> = 2259)	Enzalutamide After chemotherapy (<i>n</i> = 264)	Enzalutamide No chemotherapy (<i>n</i> = 767)
State buy in ^b , <i>n</i> (%)				
Yes	164 (28.0)	640 (28.3)	40 (15.2)	150 (19.6)
No	422 (72.0)	1619 (71.7)	224 (84.8)	617 (80.4)
Clinical stage at diagnosis, <i>n</i> (%)				
Localized	339 (57.8)	1455 (64.4)	177 (67.0)	486 (63.4)
Regional	29 (4.9)	141 (6.2)	16 (6.1)	34 (4.4)
Metastatic	168 (28.7)	523 (23.2)	56 (21.2)	198 (25.8)
Unknown	50 (8.5)	140 (6.2)	15 (5.7)	49 (6.4)
Cardiovascular conditions, <i>n</i> (%)				
Acute myocardial infarction	26 (4.4)	138 (6.1)	13 (4.9)	59 (7.7)
Atrial fibrillation	101 (17.2)	448 (19.8)	38 (14.4)	145 (18.9)
Congestive heart failure	200 (34.1)	739 (32.7)	67 (25.4)	240 (31.3)
Stroke	70 (12.0)	314 (13.9)	22 (8.3)	114 (14.9)
Ischemic heart disease	351 (59.9)	1319 (58.4)	149 (56.9)	450 (54.2)
Any of the above CVD conditions ^c	406 (69.3)	1518 (67.2)	167 (63.3)	530 (69.1)
Number of cardiovascular conditions, <i>n</i> (%)				
0	180 (30.7)	741 (32.8)	97 (36.7)	237 (30.9)
1–2	313 (53.4)	1097 (48.6)	135 (51.1)	393 (51.2)
3	93 (15.9)	421 (18.6)	32 (12.1)	137 (17.9)
Diabetes mellitus, <i>n</i> (%)	253 (43.2)	959 (42.5)	102 (38.6)	331 (43.2)
Hypertension, <i>n</i> (%)	480 (81.9)	1930 (85.4)	219 (82.9)	635 (82.8)
Medications, <i>n</i> (%)				
Thiazide diuretics	97 (16.6)	362 (16.0)	45 (17.0)	136 (17.7)
Loop diuretics	128 (21.8)	384 (17.0)	63 (23.9)	122 (15.9)
Calcium channel blockers	106 (18.1)	527 (23.3)	49 (18.6)	194 (25.3)
Beta blockers	176 (30.0)	761 (33.7)	92 (34.8)	251 (32.7)
Statins	221 (37.7)	959 (42.4)	97 (36.7)	326 (42.5)

Characteristic	Abiraterone (<i>n</i> = 2845)		Enzalutamide (<i>n</i> = 1031)	
	Abiraterone After chemotherapy (<i>n</i> = 586)	Abiraterone No chemotherapy (<i>n</i> = 2259)	Enzalutamide After chemotherapy (<i>n</i> = 264)	Enzalutamide No chemotherapy (<i>n</i> = 767)
Prostate-specific antigen (ng/ml), median (IQR)	26.8 (8.5–98.0)	24.0 (8.5–98.0)	22.8 (7.6–98.0)	28.0 (8.3–98.0)
Prostate cancer-specific death as of December 31, 2015, <i>n</i> (%)				
Dead	399 (68.1)	1031 (45.6)	174 (65.9)	304 (39.6)
Alive	187 (31.9)	1228 (54.4)	90 (34.1)	463 (60.4)
All-cause death as of December 31, 2015, <i>n</i> (%)				
Dead	492 (84.0)	1358 (60.1)	199 (75.4)	406 (52.9)
Alive	94 (16.0)	901 (39.9)	65 (24.6)	361 (47.1)

CVD = cardiovascular disease; IQR = interquartile range; SEER = Surveillance, Epidemiology, and End Results. Column percentage.

^aFor enzalutamide group, the category “2011–2012” for the year of first treatment represents only 2012, since the drug was approved in 2012.

^bIndicating that the state pays part or all of the patient’s Medicare part B premium or the person is in the Medicaid program.

^cCVD is defined as having any of acute myocardial infarction, atrial fibrillation, congestive heart failure, or stroke ischemic heart disease.

Table 2 -
Relative risks of 6-mo mortality by chemotherapy status based on modified Poisson regression

Characteristic	After chemotherapy RR (95% CI)	No chemotherapy, RR (95% CI)
Hypertension (yes vs no)	1.00 (0.76–1.32)	1.10 (0.90–1.35)
CVD (1–2 CVD vs no CVD)	1.14 (0.90–1.44)	1.16 (1.00–1.36)
CVD (3 CVD vs no CVD)	1.43 (1.04–1.98)	1.56 (1.29–1.88)
Drug (ENZ vs AA)	1.21 (0.96–1.53)	1.08 (0.94–1.25)

AA = abiraterone acetate; CI = confidence interval; CVD = cardiovascular disease; ENZ = enzalutamide; RR = relative risk. Interaction between CVD and drug was tested in both the models. Since the interaction was not significant in both the models, the interaction terms were removed from the model, and the main terms of CVD and drug were estimated without interactions. Model: CVD + drug + hypertension + demographics (age + race + marital status + income + region) + clinical (year of diagnosis + year of first treatment + clinical stage at diagnosis) + diabetes mellitus.

Table 3 -
Incidence rate ratio (IRR) of post- versus pretreatment hospitalization by chemotherapy status based on negative binomial models

Characteristic	After chemotherapy, IRR (95% CI)	No chemotherapy, IRR (95% CI)
Hypertension (yes vs no)	1.38 (1.04–1.82)	1.11 (0.93–1.32)
CVD (1–2 CVD vs no CVD)	1.43 (1.15–1.78)	NA
CVD (at least 3 CVD vs no CVD)	1.36 (0.99–1.85)	NA
Drug (ENZ vs AA)	0.82 (0.66–1.03)	NA
Drug (ENZ vs AA) no CVD	NA	0.89 (0.69–1.15)
Drug (ENZ vs AA) 1–2 CVDs	NA	0.85 (0.71–1.01)
Drug (ENZ vs AA) 3 CVDs	NA	0.59 (0.44–0.79)

AA = abiraterone acetate; CI = confidence interval; CVD = cardiovascular disease; ENZ = enzalutamide; NA = not applicable based on the presence of interaction in the model.

Interaction between CVD and drug was tested for both the models. Since the interaction was not significant in the postchemotherapy group, the interaction term was removed from the model, and the main effects of CVD and drug were estimated without interaction. Model: CVD + drug + hypertension + baseline hospitalization rate + demographics (age + race + marital status + income + region) + clinical (year of diagnosis + year of first treatment + clinical stage at diagnosis) + diabetes mellitus. Since the interaction was significant in the no-chemotherapy group, we applied linear contrasts to the interaction model to estimate IRRs for drug that depended on the CVD level. Model: CVD + drug + (CVD × drug interaction) + hypertension + baseline hospitalization rate + demographics (age + race + marital status + income + region) + Clinical (year of diagnosis + year of first treatment + clinical stage at diagnosis) + diabetes mellitus.