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Article

Risk of Metabolic and Cardiovascular Adverse Events With Abiraterone or Enzalutamide Among Men With Advanced Prostate Cancer

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Abstract

Background: Abiraterone and enzalutamide are the most common oral agents for the treatment of men with advanced prostate cancer. To understand their safety profiles in real-world settings, we examined the association between the use of abiraterone or enzalutamide and the risk of metabolic or cardiovascular adverse events while on treatment. **Methods:** Men with advanced prostate cancer and their use of abiraterone or enzalutamide were identified in a 20% sample of the 2010-2017 national Medicare claims. The primary composite outcome was the occurrence of a major metabolic or cardiovascular adverse event, defined as an emergency room visit or hospitalization associated with a primary diagnosis of diabetes, hypertension, or cardiovascular disease. The secondary composite outcome was the occurrence of a minor metabolic or cardiovascular adverse event, defined as an outpatient visit associated with a primary diagnosis of the aforementioned conditions. Risks were assessed separately for abiraterone and enzalutamide using Cox regression. All statistical tests were 2-sided. **Results:** Compared with men not receiving abiraterone, men receiving abiraterone were at increased risk of both a major composite adverse event (hazard ratio [HR] = 1.77, 95% confidence interval [CI] = 1.53 to 2.05; $P < .001$) and a minor composite adverse event (HR = 1.24, 95% CI = 1.05 to 1.47; $P = .01$). Compared with men not receiving enzalutamide, men receiving enzalutamide were at an increased risk of a major composite adverse event (HR = 1.22, 95% CI = 1.01 to 1.48; $P = .04$) but not a minor composite adverse event (HR = 1.04, 95% CI = 0.83 to 1.30; $P = .75$). **Conclusion:** Careful monitoring and management of men on abiraterone or enzalutamide through team-based approaches are critical.

One in 8 men in the United States will be diagnosed with prostate cancer in his lifetime, making prostate cancer the leading cause of nonskin cancer among men in the country (1). Men with metastatic castration-resistant prostate cancer, the most advanced form of the disease, were traditionally managed with cytotoxic chemotherapy in conjunction with androgen deprivation (2). Abiraterone and enzalutamide are oral targeted therapies that have provided alternative treatment options to cytotoxic chemotherapy for men with metastatic castration-resistant prostate cancer since 2011 and 2012, respectively.

Abiraterone and enzalutamide have demonstrated favorable safety profiles in clinical trials (3–6), however, they are not without potentially serious side effects related to their mechanism of action. Abiraterone exerts its anti-androgen properties by inhibiting cytochrome P450 17A1, a critical enzyme in androgen biosynthesis (7,8). Given the shared biochemical pathway between androgen and glucocorticoid biosynthesis, treatment with abiraterone leads to a decrease in glucocorticoid production with a compensatory increase in adrenocorticotrophic hormone and mineralocorticoid excess. In some patients, this can lead to new onset or worsening of hypertension, hypokalemia, and fluid retention. To reduce mineralocorticoid-related adverse events, abiraterone is co-administrated with a glucocorticoid, which in itself is associated with metabolic and cardiovascular consequences (9–11). Although enzalutamide is a nonsteroidal androgen receptor antagonist (12) that has been associated with central nervous system effects (13), its androgen receptor antagonism has also been shown to increase

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glucocorticoid levels (14). For men with advanced prostate cancer who are already at considerable risks for metabolic and cardiovascular events given their advanced age and concomitant use of chronic androgen deprivation (15–17), adverse events related to abiraterone or enzalutamide treatment may have a substantial impact on their overall health status and quality of life.

One particular concern is that differences in patient selection and safety monitoring between clinical trials and real-world settings (18,19) have the potential to amplify the risk of adverse events. To understand the safety of treatment with abiraterone or enzalutamide in everyday practice, we examined the relationship between abiraterone or enzalutamide use and the occurrence of metabolic and cardiovascular adverse events in a national sample of Medicare beneficiaries with advanced prostate cancer. We hypothesized that men receiving abiraterone or enzalutamide in conjunction with androgen deprivation had higher risks of metabolic and cardiovascular adverse events compared with men receiving androgen deprivation alone.

Methods

Using a 20% random sample of fee-for-service Medicare beneficiaries from 2010 to 2017 national Medicare claims, men with advanced prostate cancer were identified through their use of chronic androgen deprivation. The use of chronic androgen deprivation was defined as a history of bilateral orchiectomy or 6 or more months of continuous coverage of a gonadotropin-releasing hormone analog (ie, leuprolide, goserelin, degarelix, or triptorelin). For instance, men with 6 claims of monthly depot of leuprolide or 2 claims of a 3-month depot of leuprolide within 6 months were considered on chronic androgen deprivation. Men on androgen deprivation who had radiation to the prostate in the 12-month period preceding or the 6-month period following the first claim for androgen deprivation were excluded, because these men were likely to be on neoadjuvant or adjuvant androgen deprivation and may not have advanced disease.

The exposure was abiraterone or enzalutamide use, identified using Medicare Part D claims. Because 83.6% of the study cohort treated with abiraterone and 87.2% of the study cohort treated with enzalutamide had commenced their therapy at least 6 months after their initiation of androgen deprivation, the study start date was indexed to 6 months after the initiation of androgen deprivation. Men without continuous enrollment in Medicare Parts A and B for at least 12 months prior to the study start date and men participating in Medicare-managed care plans were excluded to ensure the availability of complete claims.

The primary composite outcome was the occurrence of a major metabolic or cardiovascular adverse event, defined as an emergency room visit or hospitalization associated with a primary International Classification of Diseases diagnosis of diabetes, hypertension, or cardiovascular disease (ie, congestive heart failure, dysrhythmia, or coronary artery disease), while on treatment with abiraterone or enzalutamide. The relevant International Classification of Diseases codes are presented in Supplementary Table 1 (available online). Given that the events comprising the composite outcome are not uncommon in an older cohort of men and that new events are more likely to be attributable to abiraterone or enzalutamide use, men who had an emergency room visit or hospitalization for diabetes, hypertension, and cardiovascular disease in the 12 months prior to the study start date were excluded. Cohort selection is illustrated in Supplementary Figure (available online).

The secondary composite outcome was the occurrence of a minor metabolic or cardiovascular adverse event, defined as an outpatient visit associated with a primary diagnosis of diabetes, hypertension, or cardiovascular disease, while on treatment with abiraterone or enzalutamide. In additional analyses, the occurrence of adverse events by specific diagnoses was examined individually. Similar to the approach used to construct the primary outcome cohort, men who had had an occurrence of the relevant event outcome in the 12 months prior to the study start date were excluded.

Statistical Analysis

First, the characteristics of men with advanced prostate cancer were compared in 2 ways: 1) between those who ever received abiraterone and those who ever received enzalutamide and 2) between those who ever received abiraterone or enzalutamide and those who never received abiraterone or enzalutamide.

Next, event-free survival curves were constructed with abiraterone or enzalutamide use analyzed as a time-dependent variable (ie, a patient's on-drug status was determined each time a patient had an adverse event) (20). Statistical inference was made using the log-rank test. The incidence rate of each outcome per 100 person-years during periods of receiving abiraterone, not receiving abiraterone, receiving enzalutamide, and not receiving enzalutamide was calculated.

Then, separate Cox proportional hazards regression models were used to assess the risk of the primary composite outcome associated with abiraterone use, adjusting for age, race (Black, Other [Asian, Hispanic, North American Native, other, and unknown], or White) as reported in Medicare data, socioeconomic status based on the area that the patient resided in (21), and comorbidity score based on the Klabunde modification of the Charlson comorbidity index (22). To account for possible differences in disease trajectory, the models were also adjusted for the cumulative time on androgen deprivation, categorized as 0 to less than 6 months, 6 to less than 12 months, or 12 months or more. Patients were censored at death, loss of eligibility, or end of the study period. A separate model was fit to measure the risk of the primary composite outcome associated with enzalutamide use. Using a similar approach, additional models were fit to examine the risks of secondary composite outcome and diagnosis-specific adverse events. For all outcomes, we hypothesized that men receiving abiraterone and men receiving enzalutamide, in conjunction with androgen deprivation, were at a significantly increased risk of adverse events compared with those receiving androgen deprivation alone.

Models were repeated with the inclusion of an interaction term to examine whether the risks of the primary composite outcome and the secondary composite outcome differed based on the cumulative time on androgen deprivation. Models with and without the interaction term were compared to assess their fit using the likelihood ratio χ^2 test (data not shown given that models with the interaction term did not significantly fit better than the models without the interaction term).

Lastly, to account for possible lag in the development or detection of adverse events, such as a long appointment wait time for outpatient care, sensitivity analyses were performed in which the period at risk attributable to abiraterone or enzalutamide was extended to 3 months after the last prescription fill of the drug of interest.

All analyses were carried out using Stata 14 (College Station, TX, USA). All tests were 2-sided with probability of type 1 error

(alpha) set at 0.05. This study was determined to not be regulated by the University of Michigan institutional review board as the research did not interact with or obtain identifiable private information about human participants.

Results

Of the 56 230 men with advanced prostate cancer in our primary composite outcome study cohort, 2736 received treatment with abiraterone, and 2466 received treatment with enzalutamide. Men who ever received abiraterone and men who ever received enzalutamide were similar in age, race, socioeconomic status, and comorbidity (Table 1). Men who received abiraterone or enzalutamide were modestly younger (median age of 76.8 years vs 78.8 years) and healthier (49.6% vs 44.0% with comorbidity score of zero) than men who never received either drug.

As shown in Figure 1, men receiving abiraterone had lower event-free rates for both primary and secondary composite outcomes compared with men not receiving abiraterone (log-rank test $P < .001$ and $P = .01$, respectively). In contrast, men receiving enzalutamide and men not receiving enzalutamide had similar event-free rates for both primary and secondary composite outcomes (log-rank test $P = .11$ and $P = .84$, respectively) (Figure 2). The unadjusted incidence rates of adverse events per 100 patient-years among men receiving treatment and men not receiving treatment are presented in Supplementary Table 2 (available online).

The associations of abiraterone or enzalutamide use with the primary composite outcome, adjusted for patient characteristics, are presented in Table 2. Compared with men not receiving abiraterone, men receiving abiraterone had an increased risk of the primary composite outcome (hazard ratio [HR] = 1.77, 95% confidence interval [CI] = 1.53 to 2.05; $P < .001$). Compared with men not receiving enzalutamide, men receiving enzalutamide were at an increased risk of the primary composite outcome (HR = 1.22, 95% CI = 1.01 to 1.48; $P = .04$). Older age and higher comorbidity score were also associated with an increased risk of the primary composite outcome, whereas cumulative time on androgen deprivation was not associated with an increased risk.

Men receiving abiraterone also had an increased risk of the secondary composite outcome (HR = 1.24, 95% CI = 1.05 to 1.47) (Table 3). Examining individual diagnoses separately, men receiving abiraterone had increased risks of a diabetic event (HR = 1.84, 95% CI = 1.04 to 3.27 for major diabetic events; HR = 1.37, 95% CI = 1.08 to 1.75 for minor diabetic events) and a cardiovascular event (HR = 1.91, 95% CI = 1.64 to 2.23 for major cardiovascular events; HR = 1.75, 95% CI = 1.51 to 2.03 for minor cardiovascular events) (Table 3).

In contrast, men receiving enzalutamide were not at an increased risk of the secondary composite outcome (HR = 1.04, 95% CI = 0.83 to 1.03), relative to men not receiving enzalutamide. Examining risks by individual diagnosis, men receiving enzalutamide were at an increased risk of a major cardiovascular event (HR = 1.31, 95% CI = 1.08 to 1.59). Neither men receiving abiraterone nor men receiving enzalutamide were at an increased risk of hypertensive adverse events compared with their counterparts not receiving abiraterone or enzalutamide.

To account for possible lag in the development or detection of adverse events, a sensitivity analysis was performed in which the period at risk attributable to the drugs was extended to 3 months after the last prescription fill (Supplementary Table 3, available online). The magnitudes of effect size were generally larger, with abiraterone use associated with a further increased risk of the primary composite outcome (HR = 1.94, 95% CI = 1.71 to 2.19), a major diabetic event (HR = 2.21, 95% CI = 1.32 to 3.40), and a major cardiovascular event (HR = 2.10, 95% CI = 1.85 to 2.38). The risks of the primary composite outcome and, specifically, a major cardiovascular event associated with enzalutamide use increased modestly (HR = 1.34, 95% CI = 1.14 to 1.57, and HR = 1.43, 95% CI = 1.21 to 1.68, respectively).

Discussion

This study presents the first assessment of the real-world safety of abiraterone and enzalutamide in a national sample of Medicare beneficiaries with advanced prostate cancer. As hypothesized, men receiving abiraterone with androgen deprivation were at a significantly increased risk of metabolic and cardiovascular adverse events necessitating emergency room

Table 1. Comparisons of characteristics of men with advanced prostate cancer, according to abiraterone or enzalutamide use[a]

Characteristics	Ever received abiraterone (n = 2736)	Ever received enzalutamide (n = 2466)	Ever received abiraterone or enzalutamide (n = 3942)	Never received abiraterone or enzalutamide (n = 52 288)
Age at study start date, median (IQR), y	76.7 (10.1)	76.4 (10.2)	76.8 (10.2)	78.3 (11.1)
Race, No. (%)				
Black	238 (8.7)	231 (9.4)	364 (9.2)	5991 (11.5)
Other	142 (5.2)	103 (4.2)	187 (4.7)	2298 (4.4)
White	2356 (86.1)	2132 (86.5)	3391 (86.0)	4399 (84.1)
Socioeconomic status, No. (%)				
Low	828 (30.3)	749 (30.4)	1211 (30.7)	17 529 (33.5)
Medium	863 (31.5)	789 (32.0)	1240 (31.5)	17 509 (33.5)
High	1045 (38.2)	928 (37.6)	1491 (37.8)	17 250 (33.0)
Comorbidity score, No. (%)				
Zero	1380 (50.4)	1252 (50.8)	1957 (49.6)	23 026 (44.0)
One	597 (21.8)	552 (22.4)	865 (21.9)	12 171 (23.3)
Two	384 (14.0)	343 (13.9)	569 (14.4)	7997 (15.3)
Three or more	375 (13.7)	319 (12.9)	551 (14.0)	9094 (17.4)

[a]After excluding those who had an emergency room visit or hospitalization for diabetes, hypertension, or cardiovascular disease in the 12 months prior to the study start date. IQR = interquartile range.

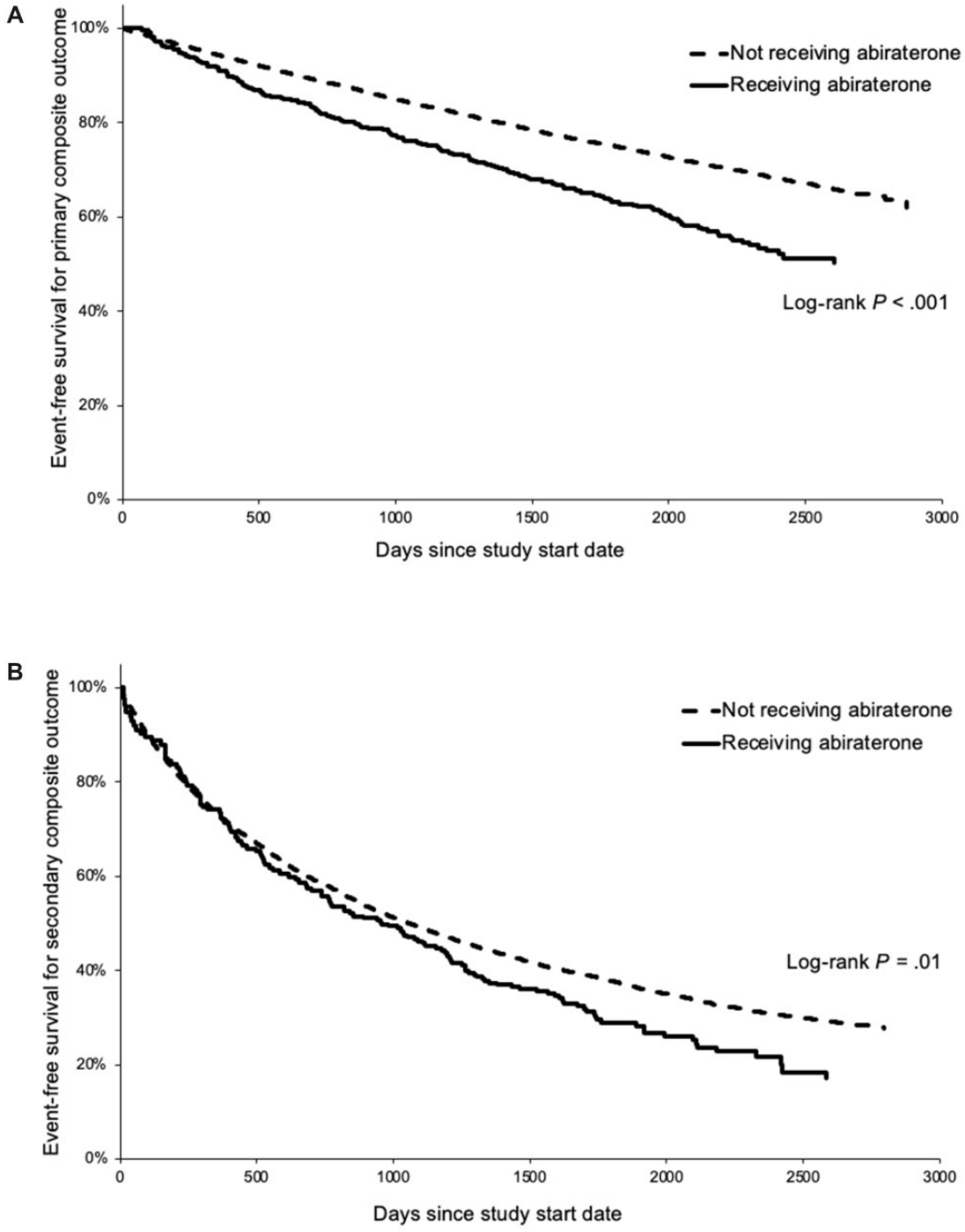

Figure 1. Event-free survival rates for (**A**) primary composite outcome and (**B**) secondary composite outcome among men with advanced prostate cancer according to abiraterone use. Men receiving abiraterone had lower event-free rates for both primary and secondary composite outcomes compared with men not receiving abiraterone (log-rank test $P < .001$ and $P = .01$, respectively). All statistical tests were 2-sided.

visits and hospitalizations compared with those only on androgen deprivation. Though also statistically significant, the evidence supporting the risks of enzalutamide was weaker, with a smaller magnitude of effect size compared with that associated with abiraterone use.

The risks associated with abiraterone and enzalutamide use could have a large impact as these therapies have outpaced cytotoxic chemotherapy as the most commonly prescribed treatment in conjunction with androgen deprivation for men with advanced prostate cancer (23). Based on unadjusted incidence rates (Supplementary Table 2, available online), men receiving abiraterone had 1 additional major cardiovascular event for every 29 men treated over a median time on the drug of 4.7 months. In clinical trials, men on abiraterone had 1

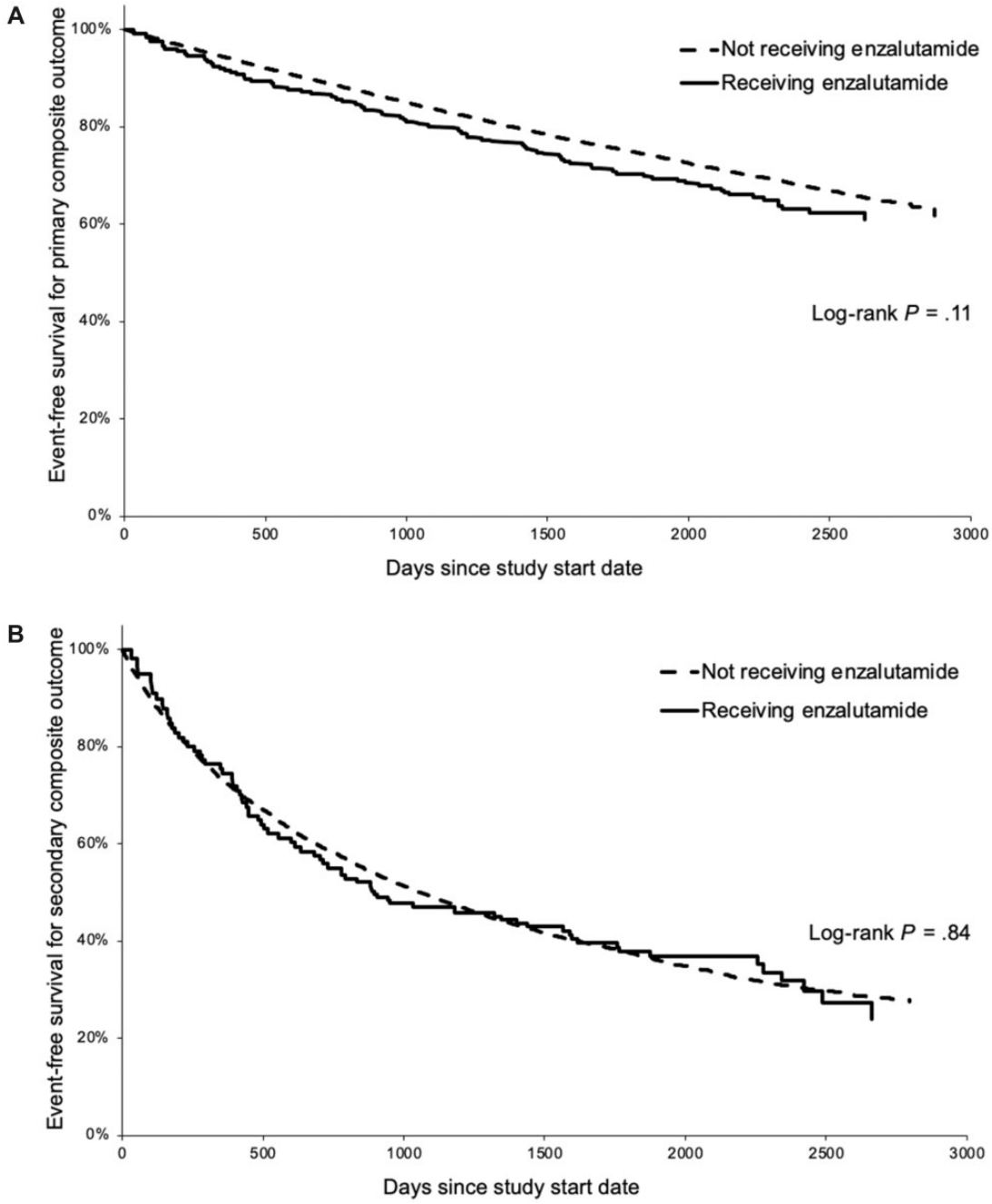

Figure 2. Event-free survival rates for (**A**) primary composite outcome and (**B**) secondary composite outcome among men with advanced prostate cancer according to enzalutamide use. Men receiving enzalutamide and men not receiving enzalutamide had similar event-free rates for both primary and secondary composite outcomes (log-rank test $P = .11$ and $P = .84$, respectively). All statistical tests were 2-sided.

additional cardiac adverse event of any grade for every 33 men treated in the prechemotherapy setting over a median follow-up of 22.2 months (4) and for every 50 men treated in the postchemotherapy setting over a median follow-up of 12.8 months (3). The difference in the number needed to harm may reflect the more liberal patient selection criteria in real-world settings relative to clinical trials in which patients with serious coexisting nonmalignant disease were excluded. In addition, men included in our study who ever received abiraterone were notably older adults than participants of the COU-AA-302 trial (4) and the COU-AA-301 trial (3) (median age of 76, 71, and 69 years, respectively) and might be more vulnerable to adverse events, as suggested by the significant association between age and risk of the primary composite outcome noted in our study. Another key difference is the rigorous safety evaluation of trial participants, which could lead to detection of adverse events that would otherwise be clinically silent; such evaluation would have lowered the number needed for harm for trial participants compared with real-world evaluations. Despite the potential ascertainment bias, the number needed for harm for men receiving abiraterone included in our study was lower than that of trial participants, which further heightens the concern for adverse events associated with abiraterone use.

Consistent with recent data based on the Quebec (24) and French (25) health-care claims, the risks associated with

Table 2. Associations of abiraterone or enzalutamide use with the risk of the primary composite outcome[a]

Characteristics	Abiraterone cohort		Enzalutamide cohort	
	HR (95% CI)	P[b]	HR (95% CI)	P[b]
Receiving abiraterone				
No	Referent		NA	NA
Yes	1.77 (1.53 to 2.05)	<.001	NA	NA
Receiving enzalutamide				
No	NA	NA	Referent	
Yes	NA	NA	1.22 (1.01 to 1.48)	.04
Cumulative time on androgen deprivation, mo				
0 to <6	Referent		Referent	
6 to <12	0.93 (0.77 to 1.12)	.44	0.93 (0.78 to 1.12)	.45
12 or more	1.06 (0.88 to 1.28)	.55	1.07 (0.89 to 1.29)	.50
Age at study start date[c]				
Per 5-year increase	1.26 (1.24 to 1.28)	<.001	1.26 (1.24 to 1.28)	<.001
Race				
Black	0.98 (0.92 to 1.05)	.62	0.98 (0.92 to 1.05)	.58
Other	0.73 (0.65 to 0.82)	<.001	0.73 (0.65 to 0.82)	<.001
White	Referent		Referent	
Socioeconomic status				
Low	Referent		Referent	
Medium	0.89 (0.84 to 0.93)	<.001	0.89 (0.84 to 0.93)	<.001
High	0.80 (0.76 to 0.84)	<.001	0.80 (0.76 to 0.84)	<.001
Comorbidity score				
Zero	Referent		Referent	
One	1.34 (1.27 to 1.41)	<.001	1.34 (1.27 to 1.41)	<.001
Two	1.72 (1.62 to 1.82)	<.001	1.72 (1.62 to 1.82)	<.001
Three or more	2.38 (2.25 to 2.51)	<.001	2.38 (2.25 to 2.51)	<.001

[a]Primary composite outcome: diabetes, hypertension, or cardiovascular disease (congestive heart failure, cardiac dysrhythmia, or coronary artery disease) requiring an emergency room visit or hospitalization. CI = confidence interval; HR = hazard ratio; NA = not applicable.
[b]Statistical differences (2-sided *P* values) were estimated using Wald χ^2 statistics for testing the null hypothesis that the model parameter estimates equal zero.
[c]Study start date was indexed at 6 months after the initiation of androgen deprivation.

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enzalutamide use were smaller in magnitude than with abiraterone use. Whereas men receiving abiraterone had 1 additional major cardiovascular event for every 29 men treated, the number needed to harm associated with a major cardiovascular event was 88 for men receiving enzalutamide included in our study (median time on the drug of 3.9 months). Given that the characteristics of men who ever received enzalutamide and men who ever received abiraterone were nearly identical, the substantially lower magnitude of risks further highlights the credibility that abiraterone use may be a major contributor to metabolic and cardiovascular adverse events. In clinical trials, the number needed to harm associated with cardiac adverse events of any grade among men receiving enzalutamide in the prechemotherapy setting was 50 (6), and men receiving enzalutamide in the postchemotherapy setting did not have a higher incidence of cardiac adverse events than men in the placebo group (5).

The study findings have important implications for men with advanced prostate cancer as use of abiraterone and enzalutamide continues to evolve. Both these drugs are now used to treat men with metastatic castration-sensitive disease (26–28), abiraterone for locally advanced, lymph node–positive disease (29), and enzalutamide for nonmetastatic castration-resistant disease (30). With continued expansion of the indications for abiraterone and enzalutamide to earlier stages of the disease continuum (26–28,30), increasing numbers of men will be receiving these therapies for longer periods of time. This will potentially amplify the scope of men affected and increase the magnitude of the risks of adverse events, making careful attention to management of these issues crucial. One practical consideration is patient selection for particular drugs. As the risks of metabolic and cardiovascular adverse events are more pronounced with abiraterone than with enzalutamide, abiraterone may be a less preferred option for men at higher risk of metabolic and cardiovascular adverse events. Another consideration is that metabolic and cardiovascular conditions are generally managed by primary care providers. Team-based care involving patients' primary care providers may help mitigate these adverse events so that men with advanced prostate cancer can remain on life-prolonging cancer therapies longer and with less disruption to their quality of life.

This study has several limitations. First, the use of Medicare claims data limits the generalizability of our findings to younger men with advanced prostate cancer. However, we expect this to have minimal impact as the vast majority of men with advanced prostate cancer are within the Medicare age group (31). Second, differences in the risks of adverse events might be related to differences in baseline health status between men who were receiving abiraterone or enzalutamide and men who were not receiving the drug. We mitigated this issue through robust adjustment for patient characteristics, including comorbidity and disease trajectory, in our models. In addition, our use of time-dependent variables allowed men to serve as their own control when not receiving abiraterone or enzalutamide, reducing the unadjusted differences between the treatment group and the nontreatment group. Third, given the exclusion of men

Table 3. Risks of primary (major) and secondary (minor) composite outcomes and diagnosis-specific adverse events among men receiving abiraterone vs men not receiving abiraterone (reference group) and among men receiving enzalutamide vs men not receiving enzalutamide (reference group)

Severity[a]	Adverse event	Abiraterone cohort HR (95% CI)	Enzalutamide cohort HR (95% CI)
Major	Composite[b]	1.77 (1.53 to 2.05)	1.22 (1.01 to 1.48)
	Diabetes	1.84 (1.04 to 3.27)	1.40 (0.69 to 2.82)
	Hypertension	0.98 (0.59 to 1.63)	0.78 (0.42 to 1.46)
	Cardiovascular disease[c]	1.91 (1.64 to 2.23)	1.31 (1.08 to 1.59)
Minor	Composite[b]	1.24 (1.05 to 1.47)	1.04 (0.83 to 1.03)
	Diabetes	1.37 (1.08 to 1.75)	0.66 (0.45 to 0.98)
	Hypertension	1.07 (0.90 to 1.26)	1.09 (0.89 to 1.33)
	Cardiovascular disease[c]	1.75 (1.51 to 2.03)	1.11 (0.91 to 1.37)

[a]Major: requiring an emergency room visit or hospitalization; minor: requiring an outpatient visit. CI = confidence interval; HR = hazard ratio.
[b]Composite: diabetes, hypertension, or cardiovascular disease.
[c]Cardiovascular disease: congestive heart failure, cardiac dysrhythmia, or coronary artery disease.

who had an occurrence of the relevant event outcome in the 12 months prior to the study start date, the true risks of adverse events might be actually higher than those estimated in our study. Nevertheless, our conservative estimates still demonstrated clinically relevant numbers needed to harm. Lastly, the findings should be interpreted with the consideration that we did not correct for multiple testing. However, we only made planned comparisons supported by biological plausibility, and the analyses were hypothesis generating, which warrant further investigation.

In a national sample of men with advanced prostate cancer, men receiving abiraterone and men receiving enzalutamide in conjunction with androgen deprivation were at an increased risk of metabolic and cardiovascular adverse events, relative to their counterparts on androgen deprivation alone. The management of men with advanced prostate cancer tends to focus on cancer outcomes, however, it is critical for providers to be aware of the risks associated with treatment with abiraterone and enzalutamide. Multidisciplinary involvement and clear designation of monitoring responsibilities with optimal care coordination may help ensure the safety of men receiving abiraterone or enzalutamide.

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Notes

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Author contributions: Conceptualization and Methodology: All authors. Data curation and Resources: LYL, MKO, BKH, VBS. Formal analysis and Visualization: LYL, MKO, SRK, BKH, VBS. Writing—original draft: LYL, BKH, VBS. Writing—review & editing: All authors. Supervision: BKH, VBS.

Data Availability

This study used Medicare claims data, provided by the Centers for Medicare & Medicaid Services (CMS) under license/by permission. Data may be shared on request to the corresponding author with permission of the CMS.

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