





Adherence and Out-of-Pocket Costs Among Medicare Beneficiaries Who Are Prescribed Oral Targeted Therapies for Advanced Prostate Cancer

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BACKGROUND: Abiraterone and enzalutamide are high-cost oral therapies that increasingly are used to treat patients with advanced prostate cancer; these agents carry the potential for significant financial consequences to patients. In the current study, the authors investigated coping and material measures of the financial hardship of these therapies among patients with Medicare Part D coverage. **METHODS:** The authors performed a retrospective cohort study on a 20% sample of Medicare Part D enrollees who underwent treatment with abiraterone or enzalutamide between July 2013 and June 2015. The authors described the variability in adherence rates and out-of-pocket payments among hospital referral regions in the first 6 months of therapy and determined whether adherence and out-of-pocket payments were associated with patient factors and the socioeconomic characteristics of where a patient was treated. **RESULTS:** There were 4153 patients who filled abiraterone or enzalutamide prescriptions through Medicare Part D in 228 hospital referral regions. The mean adherence rate was 75%. The median monthly out-of-pocket payment for abiraterone and enzalutamide was \$706 (range, \$0-\$3505). After multilevel, multivariable adjustment for patient and regional factors, adherence was found to be lower in patients who were older (69% for patients aged ≥ 85 years vs 76% for patients aged < 70 years; $P < .01$) and in those with low-income subsidies (69% in those with a subsidy vs 76% in those without a subsidy; $P < .01$). Both Hispanic ethnicity and living in a hospital referral region with a higher percentage of Hispanic beneficiaries were found to be independently associated with higher out-of-pocket payments for abiraterone and enzalutamide. **CONCLUSIONS:** There were substantial variations in the adherence rate and out-of-pocket payments among Medicare Part D beneficiaries who were prescribed abiraterone and enzalutamide. Sociodemographic patient and regional factors were found to be associated with both adherence and out-of-pocket payments. *Cancer* 2020;126:5050-5059. © 2020 American Cancer Society.

KEYWORDS: hospital referral region (HRR), medication adherence, out-of-pocket cost, prostate cancer, urologists.

INTRODUCTION

Abiraterone and enzalutamide are oral androgen inhibitors that have been approved for the treatment of men with advanced prostate cancer. Both agents have demonstrated an improvement in survival and quality of life and generally are administered continuously until disease progression. These therapies increasingly are being used in earlier settings of advanced disease, with average treatment times of 2 to 3 years for patients with nonmetastatic castration-resistant and metastatic castration-sensitive prostate cancer.¹⁻³ With each passing year, abiraterone and enzalutamide also are being prescribed more often and by a greater number of providers.⁴ Novel oral androgen inhibitors are specialty medications covered under Medicare Part D, all with high list prices and the potential for considerable out-of-pocket costs to patients.⁵

Patients who are prescribed high-cost therapies for their cancer often experience significant financial toxicity and may engage in coping behaviors such as rationing their medications or discontinuing their medication all together. Although to our knowledge studies of adherence to treatments in patients with prostate cancer are lacking, there are studies in other cancers demonstrating that high out-of-pocket costs can lead to lower adherence to therapy and ultimately worse cancer-related and overall outcomes.⁶⁻¹¹ Patient characteristics such as age, race, and ethnicity have been associated with out-of-pocket expenses and adherence to therapy in other diseases, with African American and Hispanic patients observed to have lower adherence rates and out-of-pocket payments compared with White patients.¹²⁻¹⁸ Furthermore, health care resources within a particular market, such as regional policies, access to nurse

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care managers, or access to financial counselors, may have significant effects on adherence to treatment and out-of-pocket responsibilities.¹⁹

In the current study, we sought to describe adherence rates and out-of-pocket payments among Medicare beneficiaries who were treated across different health care markets, and the association between patient and regional sociodemographic variables and measures of financial hardship. Understanding the extent of variation in these measures of financial hardship and whether some patient groups and hospital referral regions (HRRs) are disproportionately affected will allow health care systems and policymakers to develop targeted strategies with which to improve adherence, reduce out-of-pocket payments, and ultimately improve patient outcomes and quality of life.

MATERIALS AND METHODS

Data and Study Population

We performed a retrospective cohort study on a 20% sample of patients who were eligible for Medicare Part D who had their first prescription for abiraterone or enzalutamide filled between July 2013 and June 2015, as well as survived and had sustained eligibility for at least 6 months after their first prescription fill. Six months was chosen as an appropriate follow-up time because the majority of patients undergo >6 months of therapy. In the disease setting with the fewest and shortest responses (ie, metastatic castration-resistant prostate cancer), patients are treated for a median of 8 to 9 months.⁵ Patients with any type of Medicare Part D plan (stand-alone coverage or Medicare Advantage), Medigap plans, and those with low-income subsidies were included to evaluate differences in outcomes by expected out-of-pocket payments among enrollees. We also restricted the current study cohort to patients who lived in an HRR in which at least 5 patients received treatment, a typical cutoff value that has been used in other studies that investigated outcomes associated with HRRs.^{20,21}

Outcomes

Outcomes included 2 primary and 2 secondary dimensions of financial hardship^{12,22} measured during the first 6 months of therapy. Adherence was chosen as our primary coping measure and monthly out-of-pocket payment was the primary material measure. To further characterize the financial consequences of these therapies, we also included the proportion of days covered (PDC) and total 6-month out-of-pocket payment as secondary coping and material outcomes, respectively. PDC was a continuous variable

calculated by summing the number of days of supply of prescriptions filled by the patient from initiation through 180 days after initiation and dividing by the number of days in the period of interest (180 days). Adherence was a binary outcome defined as a PDC $\geq 80\%$.¹² Monthly out-of-pocket payment was a continuous variable calculated by totaling the “patient pay amount” during the first 6 months, divided by their days receiving treatment within the first 6 months, multiplied by 30 days. Finally, total out-of-pocket payment was a continuous variable that was the sum of all patient pay amounts over the first 180 days of treatment. Only those payments in Medicare Part D that were associated with abiraterone and enzalutamide were included. We expected adherence and PDC to demonstrate similar associative patterns because adherence is determined from the PDC. In contrast, monthly and total 6-month out-of-pocket payment variables may differ slightly because of the Medicare Part D cost-sharing structure and based on a patient’s adherence to therapy. For example, because the first month of therapy generally is the most expensive until a patient reaches their catastrophic limit, a patient who discontinues therapy after 1 to 2 months may have a higher monthly out-of-pocket payment but a lower total 6-month payment compared with someone who remains on treatment for the full 6 months.

Adherence and both payment measures were quantified and illustrated across HRRs to demonstrate nationwide variation.

Covariates

We then investigated the association between several patient-level and regional-level variables and the measures of adherence and out-of-pocket payments. Patient-level variables that we expected to affect adherence included age, race, socioeconomic status, and whether a beneficiary received low-income subsidies. The low-income subsidy variable indicates whether a patient receives extra help with their copayments and premiums. Beneficiaries deemed eligible for low-income subsidies primarily are patients with Medicaid or automatic assistance and have the least out-of-pocket payments.²³⁻²⁵ Patients who need to “apply” for low-income subsidies may only have partial subsidies, and still may experience more difficulty paying for their medications or adhering to their medications compared with patients with no subsidies at all.²⁵ Based on prior studies, we expected race and ethnicity to be associated with lower out-of-pocket payments.^{12,13,15}

Varying local, state, and health system factors also may contribute to differences in adherence and

TABLE 1. Patient Characteristics

Characteristic	Frequency No. (%) N = 4153	
Patient Variables		
Age, y		
<70	913	(22.0)
70-74	849	(20.4)
75-79	938	(22.6)
80-84	768	(18.5)
≥85	685	(16.5)
Race		
White	3230	(77.8)
Black	635	(15.3)
Hispanic	106	(2.6)
Unknown	182	(4.4)
Socioeconomic status tertile		
Low	1348	(32.5)
Middle	1343	(32.3)
High	1373	(33.1)
Missing data	89	(2.1)
Low-income subsidy		
No	3353	(80.7)
Yes	800	(19.3)
Hospital Referral Region Variables: Quintiles of Overall Beneficiary Characteristics		
Percentage African American (mean, 6.5%; SD 7.6%)		
1 (<0.8% African American)	328	(7.9)
2 (0.8% to <2.3% African American)	704	(17.0)
3 (2.3% to <5.2% African American)	880	(21.2)
4 (5.2% to <11.3% African American)	1306	(31.5)
5 (≥11.3% African American)	935	(22.5)
Percentage Hispanic (mean, 4.7%; SD 8.8%)		
1 (<0.6% Hispanic)	550	(13.2)
2 (0.6% to <1.1% Hispanic)	701	(16.9)
3 (1.1% to <2.5% Hispanic)	847	(20.4)
4 (2.5% to <6.1% Hispanic)	892	(21.5)
5 (≥6.1% Hispanic)	1163	(28.0)
Percentage eligible for Medicaid (mean, 13.7%; SD 6.2%)		
1 (<9.5% eligible)	722	(17.4)
2 (9.5% to <11.3% eligible)	808	(19.5)
3 (11.3% to <13.8% eligible)	1003	(24.2)
4 (13.8% to <17.1% eligible)	688	(16.6)
5 (≥17.1% eligible)	932	(22.4)
Average HCC score (mean, 1.0; SD 0.1)^a		
1 (<0.89)	557	(13.4)
2 (0.89 to <0.94)	620	(14.9)
3 (0.94 to <0.98)	846	(20.4)
4 (0.98 to <1.02)	828	(19.9)
5 (≥1.02)	1302	(31.4)
Percentage first prescription by urology (mean, 14.3%; SD 14.4%)		
1 (0%)	779	(18.8)
2 (>0% to <10.5%)	1126	(27.1)
3 (10.5% to <16.7%)	747	(18.0)
4 (16.7% to <25.9%)	900	(21.7)
5 (≥25.9%)	601	(14.5)

Abbreviation: HCC, hierarchical condition category.

^aThe HCC score is an index for the overall health of patients; a higher score indicates poorer health.

out-of-pocket payments among patients. The characteristics of where a person is treated can capture differences related to policy (eg, eligibility for low-income subsidies) and access to programs that address

treatment adherence (eg, nurse-directed education, reminder packaging), or reduce out-of-pocket payments through third-party mechanisms.^{19,26-29} Therefore, to understand more about the region or environment in which a patient resides, we assigned patients to their HRR (regional markets for tertiary medical care) based on the zip code of their residence. Regional variables included: 1) percentage of African American beneficiaries; 2) percentage of Hispanic beneficiaries; 3) percentage of Medicaid-eligible beneficiaries; and 4) the average health in the HRR measured using hierarchical condition category scores.³⁰ The percentage of beneficiaries in the hospital system who are African American or Hispanic has been demonstrated to affect health outcomes in prior studies.³¹⁻³³ We expected that living in an HRR with a greater percentage of African American or Hispanic patients may result in fewer resources being available to lower out-of-pocket payments, similar to the literature that demonstrated regional differences in quality of care among hospitals with a greater percentage of African American patients.^{31,33} Last, because medical oncology and urology offices may differ in their experience navigating these resources to address financial burdens and factors that may influence patient adherence,³⁴⁻³⁶ we included a regional-level variable that describes the percentage of abiraterone and enzalutamide prescriptions within an HRR that were being prescribed by urologists. Characteristics of the HRRs were determined using data from all Medicare beneficiaries within that HRR; characteristics of HRRs were analyzed as continuous variables in the models and displayed as quintiles in Table 1.

Statistical Analysis

We first described the characteristics of the current study cohort and the distribution of outcomes across the different HRRs to demonstrate the magnitude of variability. To characterize this variation further and determine whether patient and regional factors were associated with adherence and out-of-pocket payments, we conducted several regression analyses. We fit a multilevel, mixed-effects logistic regression model for adherence and multilevel mixed-effects negative binomial regression models for both out-of-pocket payment measures. Payment models were stratified further by low-income subsidy status. Models were constructed at the patient level, and included covariates for patient age, race, socioeconomic status at the zip code level, low-income subsidy status (adherence only), and market-level variables as described above. All models included HRR-level random effects. We then

used the margins postestimation command in Stata statistical software (StataCorp LLC, College Station, Texas) to obtain adjusted adherence, monthly out-of-pocket payments, and total 6-month out-of-pocket payments from regression results. All statistical analyses were performed using Stata 15 statistical software (StataCorp LLC). The current study was deemed exempt by the institutional review board.

Sensitivity Analyses

Although rationing behavior or discontinuing treatment after 1 to 2 months without a subsequent switch may be financially motivated, we considered other patient scenarios that may affect adherence to therapy, including drug intolerance or disease progression. Because drug intolerance or disease progression commonly are followed by a switch to the other oral therapy or a dose adjustment, we considered abiraterone and enzalutamide interchangeably, accounting for the potentially higher PDC a drug switch may cause by resetting the prescription fill date.³⁷ Furthermore, because some patients who are intolerant to therapy may undergo dose adjustments, we determined PDC and adherence among patients who were maintained on full-dose therapy without dose reductions. We also considered whether a switch to chemotherapy for possible disease progression rather than the other oral agent may have affected adherence by identifying the use of docetaxel or cabazitaxel within Medicare Part B claims in the latter one-half of the 6-month study time frame. Discontinuation of oral agents for disease progression generally occurs after 3 months of therapy, whereas discontinuation before 3 months could be due to financial reasons.

RESULTS

Between July 1, 2013, and June 30, 2015, a total of 4153 patients received their first prescription fill for abiraterone or enzalutamide in 228 HRRs. Supporting Figure 1 details cohort selection. At least 1 urologist wrote a prescription for abiraterone or enzalutamide in each of the 164 HRRs. There were 800 patients (19%) who received low-income subsidies; the majority of patients with low-income subsidies were deemed eligible (88%) (eg, through Medicaid), and 12% had to apply.

The majority of patients (3289 patients; 79%) continued treatment with abiraterone or enzalutamide for at least 6 months. There were 334 patients (8%) who discontinued treatment after 1 to 2 months. Figure 1 illustrates

the mean unadjusted adherence, monthly out-of-pocket payment, and total out-of-pocket payment in the first 6 months of therapy by HRR. There was considerable variability across all HRRs for all financial hardship outcomes before adjusting for any covariates.

Adherence

The overall mean adherence (having a PDC of $\geq 80\%$ over 6 months) was 75%. After adjusting for patient-level and regional-level variables, patients who were aged ≥ 85 years were found to have a predicted adherence of 69% versus 76% in patients aged < 70 years ($P < .01$). Similarly, patients with low-income subsidies had a predicted adherence of 69% versus 76% in patients without low-income subsidies ($P < .01$). Living in an HRR with a higher percentage of Hispanic patients was found to be predictive of having lower adherence ($P = .01$) (Table 2). Conversely, living in an HRR with a higher percentage of Medicaid-eligible patients trended toward an association with increased adherence ($P = .09$). No association was found between living in an environment with a high percentage of urologists prescribing these therapies and adherence.

Out-of-Pocket Payment in Patients With No Low-Income Subsidies

Among patients without low-income subsidies (3353 patients), the median monthly out-of-pocket payment was \$706 (range, \$0-\$3505). After adjustment for other patient-level and regional-level variables, African American patients had a lower predicted monthly out-of-pocket payment of \$625 ($P < .01$), and Hispanic patients trended toward a higher predicted monthly payment of \$1102 ($P = .07$) compared with White patients (\$747) (Table 2). Furthermore, living in an HRR with a higher percentage of Hispanic patients was associated with a higher monthly out-of-pocket payment after controlling for patient-level variables ($P < .01$).

The median total out-of-pocket payment over the first 6 months of treatment was \$4498 (range, \$0-\$8398). African American patients had a predicted total out-of-pocket payment of \$3289 ($P < .01$), whereas that for Hispanic patients was \$5380 ($P < .01$) versus \$3964 for White patients. Patients who lived in HRRs in which beneficiaries had higher hierarchical condition category scores (ie, more illnesses) had lower total out-of-pocket payments ($P = .02$) (Table 2). No association was found between living in an environment with a high percentage of urologists prescribing these therapies and out-of-pocket payments.

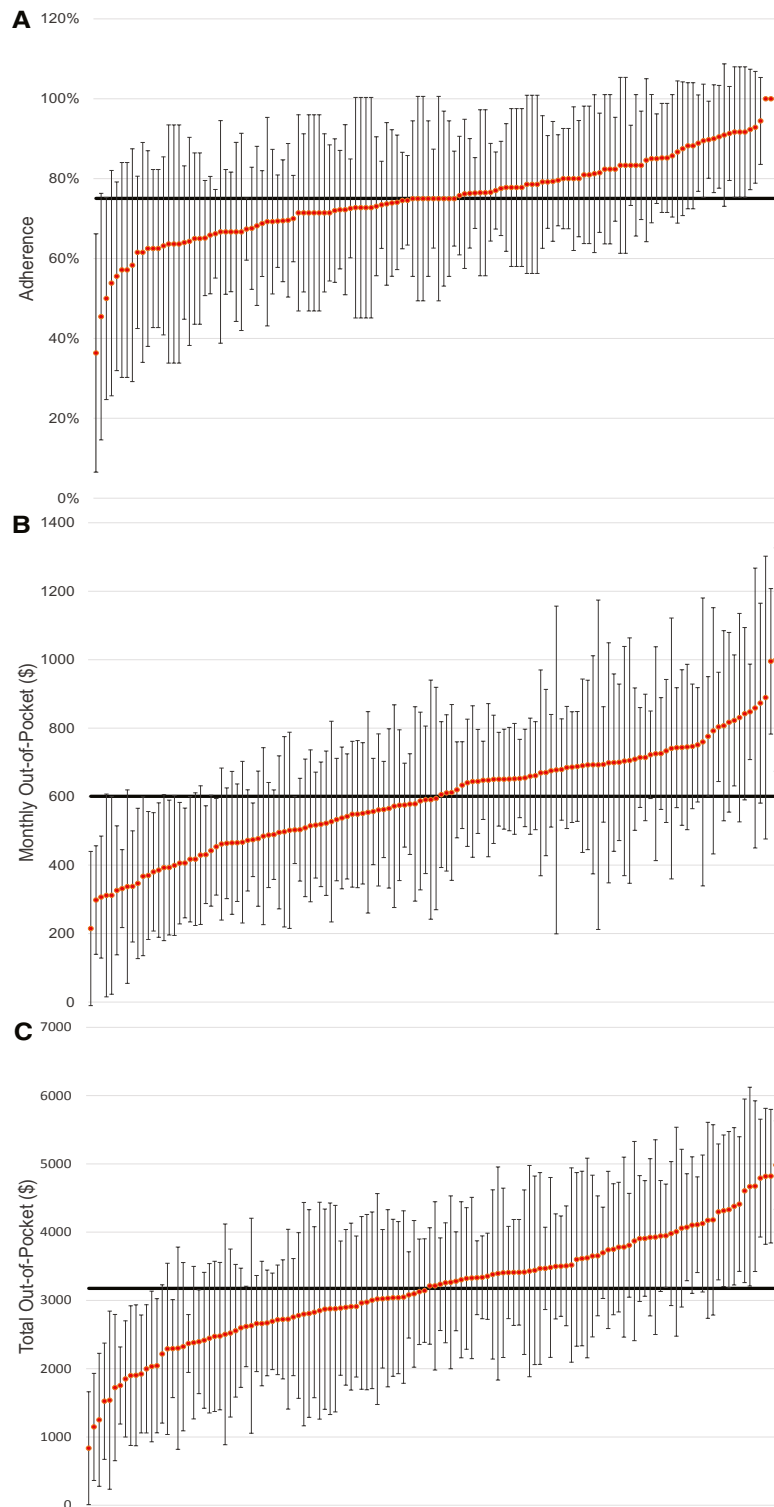


FIGURE 1. Unadjusted mean adherence rate and out-of-pocket payments by hospital referral region (HRR). Those HRRs with at least 11 patients who were being treated with abiraterone or enzalutamide during the study time frame (134 HRRs) were included and were listed along the x-axis. It is interesting to note that fewer HRRs were included in the figure than were used in the current analysis due to privacy limitations. The black horizontal line indicates the mean among the HRRs. Red dots represent the mean of the individual HRR. (A) Adherence (mean, 75%), defined as the proportion of days covered >80%. (B) Monthly out-of-pocket payment (mean, \$601), defined as the total amount the patient paid out of pocket divided by the number of days filled multiplied by 30 days. (C) Total out-of-pocket payment (mean, \$3176), defined as the total out-of-pocket payment within the first 180 days of treatment.

TABLE 2. Predicted Margins of Financial Hardship Measures After Multilevel, Multivariable Adjustment^a

	All Patients		No Low-Income Subsidies				Low-Income Subsidies			
	Adherence N = 4153		Monthly Out-of-Pocket Cost N = 3353		Total Out-of-Pocket Cost N = 3353		Monthly Out-of-Pocket Cost N = 800		Total Out-of-Pocket Cost N = 800	
	Margin, <i>P</i>		Margin, <i>P</i>		Margin, <i>P</i>		Margin, <i>P</i>		Margin, <i>P</i>	
Age, y										
<70	76.4%	Ref	\$779	Ref	\$4157	Ref	\$34	Ref	\$155	Ref
70-74	77.2%	.69	\$740	.36	\$3972	.13	\$35	.88	\$141	.74
75-79	77.2%	.71	\$762	.69	\$4154	.98	\$28	.53	130	.53
80-84	73.4%	.15	\$689	.03	\$3539	<.01	\$69	.02	\$299	.03
≥85	68.8%	<.01	\$693	.05	\$3494	<.01	\$57	.10	\$257	.11
Race										
White	75.2%	Ref	\$747	Ref	\$3964	Ref	\$61	Ref	\$271	Ref
African American	73.9%	.51	\$625	<.01	\$3289	<.01	\$27	<.01	\$112	<.01
Hispanic	77.5%	.60	\$1102	.07	\$5380	<.01	\$13	<.01	\$59	<.01
Missing data	72.2%	.35	\$721	.73	\$3591	.15	\$8	<.01	\$42	<.01
Socioeconomic status tertile										
Low	74.5%	Ref	\$735	Ref	\$3935	Ref	\$41	Ref	\$199	Ref
Medium	75.9%	.42	\$764	.40	\$3967	.79	\$39	.80	\$173	.58
High	74.7%	.91	\$704	.35	\$3764	.15	\$48	.62	\$175	.64
Missing data	73.7%	.88	\$779	.65	\$3915	.95	\$16	.11	\$71	.07
Low-income subsidy										
No	76.3%	Ref	—	—	—	—	—	—	—	—
Yes	69.4%	<.01	—	—	—	—	—	—	—	—
Percentage African American		.42		.59		.20		.42		.35
1 (0.3%)	74.3%		\$727		\$3796		\$47		\$209	
2 (1.7%)	74.4%		\$728		\$3814		\$46		\$203	
3 (3.5%)	74.6%		\$731		\$3837		\$44		\$196	
4 (7.4%)	74.9%		\$735		\$3890		\$41		\$181	
5 (18.7%)	75.9%		\$749		\$4042		\$33		\$144	
Percentage Hispanic		.01		<.01		.10		.59		.98
1 (0.4%)	76.6%		\$703		\$3793		\$38		\$183	
2 (0.8%)	76.5%		\$706		\$3801		\$38		\$183	
3 (1.7%)	76.2%		\$712		\$3820		\$39		\$183	
4 (3.8%)	75.6%		\$726		\$3860		\$40		\$182	
5 (10.8%)	73.6%		\$775		\$4003		\$43		\$182	
Percentage eligible for Medicaid		.09		.12		.09		.32		.43
1 (8.0%)	73.2%		\$763		\$4023		\$55		\$223	
2 (10.5%)	73.8%		\$751		\$3963		\$50		\$209	
3 (12.7%)	74.4%		\$741		\$3912		\$47		\$198	
4 (14.9%)	74.9%		\$731		\$3860		\$44		\$187	
5 (20.4%)	76.2%		\$706		\$3736		\$36		\$163	
Average HCC score		.12		.19		.02		.98		.99
1 (0.86)	77.0%		\$767		\$4127		\$42		\$183	
2 (0.91)	76.2%		\$753		\$4021		\$41		\$182	
3 (0.95)	75.5%		\$742		\$3938		\$41		\$182	
4 (0.99)	74.9%		\$731		\$3856		\$41		\$182	
5 (1.05)	73.9%		\$716		\$3737		\$41		\$182	
Percentage prescrip- tions by urologist		.99		.23		.53		.28		.17
1 (0.0%)	74.9%		\$716		\$3849		\$49		\$226	
2 (7.7%)	75.0%		\$727		\$3869		\$44		\$197	
3 (14.3%)	75.0%		\$735		\$3884		\$41		\$178	
4 (21.6%)	75.0%		\$743		\$3899		\$37		\$161	
5 (40.0%)	75.0%		\$763		\$3937		\$30		\$124	

Abbreviations: HCC, hierarchical condition category; Ref, referent.

Outcome measures (adherence, monthly out-of-pocket payment, total out-of-pocket payment) were modeled over the first 6 months of treatment. Payment models (ie, monthly out-of-pocket and total out-of-pocket costs) were modeled separately by low-income subsidy status. Models were constructed at the patient level and included covariates for patient age, race, socioeconomic status at the zip code level, low-income subsidy status (as an adherence measure only), and geographic variables that characterized the different hospital referral regions (HRRs) in which patients resided. Characteristics of HRRs were based on all HRRs, except for the percentage of urologists, which was based on HRRs in which at least 1 urologist wrote a prescription. HRR characteristics were modeled as continuous variables, but predictive margins were shown for the median of each quintile.

^aStatistically significant findings ($P < .05$) are set in bold type.

Out-of-Pocket Payment in Patients With Low-Income Subsidies

Among patients with low-income subsidies (800 patients), the median monthly out-of-pocket payment was \$1 (range, \$0-\$2635). After adjusting for patient-level and regional-level variables, African American patients and Hispanic patients with low-income subsidies had lower predicted monthly out-of-pocket payments compared with White patients (\$27 and \$13, respectively vs \$61; $P < .01$).

The median total out-of-pocket payment over 6 months for those with low-income subsidies was \$6 (range, \$0-\$6193). After adjusting for patient-level and regional-level variables, predicted total out-of-pocket payments for African American and Hispanic patients were lower than those among White patients (\$112 and \$59, respectively, vs \$271; $P < .01$) (Table 2). No HRR characteristics were found to be associated with out-of-pocket payments among patients with low-income subsidies.

Sensitivity Analyses

A drug switch (ie, abiraterone to enzalutamide or enzalutamide to abiraterone) was observed in 464 patients (11%) during the first 6 months of treatment. To ensure dose adjustments did not affect adherence, we calculated adherence among those who were maintained on full-dose therapy and found it to be similar to the total at 76% versus 75%. After excluding patients who discontinued therapy after 1 to 2 prescription fills (334 patients; 8%), adherence went up to 81%, indicating that adherence was affected by patients who discontinued therapy quickly. To determine whether a switch to chemotherapy for disease progression would have impacted the results, we evaluated whether the non-adherent patients who also were eligible for Medicare Part B received docetaxel or cabazitaxel during months 4 to 6. A switch to chemotherapy during the first 3 months may have been likely for financial reasons because out-of-pocket payments are lower for intravenous chemotherapy than these oral therapies. We found that approximately 1% of the total number of patients switched to docetaxel or cabazitaxel during months 4 to 6 and therefore we did not expect this small number of patients to have affected the current study results.

DISCUSSION

The results of the current study demonstrated substantial variations in adherence and out-of-pocket payments among patients with Medicare Part D who were prescribed abiraterone and enzalutamide for advanced

prostate cancer. We also demonstrated that patient age, race, and ethnicity as well as the sociodemographic characteristics of the HRR in which a patient lived were associated with varying adherence and out-of-pocket payments. Beneficiaries who were older or who received low-income subsidies were found to have lower adherence. Furthermore, living in a region with a greater percentage of Hispanic beneficiaries was associated with lower adherence, potentially reflecting unmeasured structural, policy, or differences in resources. Out-of-pocket payments varied substantially by whether patients had low-income subsidies or not. African American or Hispanic beneficiaries who received low-income subsidies had lower monthly and total out-of-pocket payments compared with White beneficiaries within the same group. In contrast, Hispanic beneficiaries without low-income subsidies had higher total out-of-pocket payments compared with White patients without low-income subsidies, and living in an HRR with a greater percentage of Hispanic beneficiaries was associated with higher out-of-pocket payments.

There are several potential explanations for why some patient and regional factors were predictive of varying adherence. Being adherent to a medication requires regular physician visits, which involves transportation and potentially time off work for the patient or caregiver. Thus, a lack of transportation to the physician's office or the pharmacy may explain why older patients and those with low-income subsidies may have lower adherence to therapy. Furthermore, environmental factors such as living in a region that has a higher percentage of African American or Hispanic patients may reflect market-level variables that can capture structural issues, policy differences, and access to different programs.^{19,26} Prior studies have demonstrated lower adherence and specifically lower cost-related adherence in African American and Hispanic patients in younger populations, with a narrowing of the disparity among patients with Medicare.³⁸ The fact that our adjusted analysis did not demonstrate an impact of race or ethnicity on adherence could be because the current study cohort included patients with Medicare in whom disparities were narrower. Alternatively, the adjustment for regional-level variables could reflect the fact that prior racial and ethnic disparities in adherence may be explained somewhat by regional characteristics. It is interesting to note that despite having lower adherence, living in an HRR with a higher percentage of Hispanic beneficiaries was found to be associated with higher monthly out-of-pocket payments among those

without low-income subsidies. In prior studies, the percentage of beneficiaries in hospital systems who were African American or Hispanic was demonstrated to affect health outcomes.³¹⁻³³ Markets with more Hispanic patients may have differing levels of resources and policy-driven interventions to address financial hardship compared with those with fewer Hispanic patients. There also may be something unique regarding the clinic infrastructure in HRRs with greater percentages of Hispanic patients that we were unable to capture in the current study data.

It is important to note that out-of-pocket payments for beneficiaries with low-income subsidies were not impacted by the same socioeconomic variables as were observed for beneficiaries without subsidies. Some of the differences in out-of-pocket payments among those with low-income subsidies may reflect differences in Medicaid eligibility. The majority of patients who are deemed eligible for low-income subsidies have Medicaid and are fully subsidized, whereas many of those who apply and are only partially subsidized still are expected to pay coinsurance for medications.²⁵ There is a higher percentage of African American and Hispanic beneficiaries among Medicare beneficiaries who are Medicaid eligible (33%) than among all patients with Medicare (18%).³⁹

One limitation of the current study was that we only were able to capture those prescriptions that were filled through Medicare Part D. Low-income patients who were eligible for Medicare Part D but who took advantage of free drug assistance programs would not be included in the current study; only approximately 20% of patients in the current study cohort had low-income subsidies compared with 29% of patients in Medicare overall. This difference may reflect the percentage of patients with Medicare Part D who sought out free drug assistance from manufacturers.⁴⁰ However, although the differential use of free drug assistance programs would affect the overall cohort number in the current study, it would not necessarily affect the trends in predictors of financial hardship measures among those observed in the data. Furthermore, to maximize the number of included beneficiaries and ensure that the current study cohort was representative of all patients with Medicare Part D coverage, we did not restrict the cohort only to those patients with traditional Medicare and included all of those patients with Medicare Part D, including those with Medicare Part C (eg, Medicare Advantage). For this reason, we only were able to evaluate the use of docetaxel and cabazitaxel for potential disease

progression as a sensitivity analysis in a subset of patients in the current study cohort who were eligible for traditional Medicare Part B. Assuming a similar rate of use among beneficiaries in whom we did not have information available regarding chemotherapy, the number affected still was negligible and thus was not expected to affect the results of the current study. Finally, although we accounted for some scenarios unrelated to financial toxicity that may impact adherence, such as disease progression and drug intolerance, there were some unmeasured variables that could have been associated with adherence. For example, we were unable to measure patient and provider beliefs and attitudes toward treatments. We also did not evaluate social factors such as employment, childcare, and family dynamics that potentially could impact adherence and may be considered to be indirectly related to financial toxicity.⁴¹ Nevertheless, prior work has demonstrated that these factors have less effect on adherence among patients with Medicare than among a younger population of patients with cancer.³⁸

Conclusions

The results of the current study demonstrated significant variations in adherence and out-of-pocket payments among Medicare Part D beneficiaries with advanced prostate cancer who were prescribed abiraterone and enzalutamide throughout HRRs. Measures of financial hardship such as coping behaviors (adherence) and direct material measures of financial toxicity (out-of-pocket payments) will become increasingly salient to those patients in the coming years as the use of abiraterone and enzalutamide continues to expand dramatically and as additional newly approved oral therapies (apalutamide, darolutamide, olaparib, rucaparib) are adopted. Thus, the stakes for understanding and further mitigating the financial hardships experienced by this growing population of patients deserve urgent attention. Understanding the effects of patient-level and market-level variables on measures of adherence and out-of-pocket payments for patients with advanced prostate cancer and trying to minimize the financial consequences of treatment will allow more patients to access and benefit from these and other important treatments.

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CONFLICT OF INTEREST DISCLOSURES

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Conceptualization: **Megan E. V. Caram, Parth K. Modi, Brent K. Hollenbeck, and Vahakn Shahinian.** Data curation: **Mary K. Oerline and Samuel R. Kaufman.** Formal analysis: **Megan E. V. Caram and Mary K. Oerline.** Funding acquisition: **Brent K. Hollenbeck and Vahakn Shahinian.** Investigation: **Megan E. V. Caram, Mary K. Oerline, Brent K. Hollenbeck, and Vahakn Shahinian.** Methodology: **Megan E. V. Caram, Mary K. Oerline, Samuel R. Kaufman, Brent K. Hollenbeck, and Vahakn Shahinian.** Project administration: **Megan E. V. Caram.** Resources: **Brent K. Hollenbeck and Vahakn Shahinian.** Software: **Mary K. Oerline and Samuel R. Kaufman.** Supervision: **Stacie Dusetzina, Ted A. Skolarus, Brent K. Hollenbeck, and Vahakn Shahinian.** Validation: **Mary K. Oerline, Stacie Dusetzina, Lindsey A. Herrel, Parth K. Modi, Samuel R. Kaufman, and Ted A. Skolarus.** Visualization: **Megan E. V. Caram and Mary K. Oerline.** Writing—original draft: **Megan E. V. Caram and Mary K. Oerline.** Writing—review and editing: All authors.

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