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TITLE: Improving Outcomes in Prostate Cancer Based on Comorbidities: Developing Personalized Medicine

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14. ABSTRACT Adverse events are common during treatment of metastatic prostate cancer, especially in elderly patients and those with comorbid medical diseases. In treatment of prostate cancer, there are several medicines that are used interchangeably and may have different rates of adverse events based on comorbidities; therefore, appropriate selection of therapies has the potential to improve outcomes. To identify adverse events associated with treatment of patients with metastatic prostate cancer and comorbid medical diseases. We will then compare rates of adverse events and survival. Aim 1. Determine the adverse events in men treated with different therapies for metastatic prostate cancer based on burden of comorbid medical disease. Aim 2. Analyze duration of therapy, treatment efficacy, and overall survival based on comorbid medical diseases, medicines and laboratory values. Aim 3. Develop an algorithm to select oral anti-androgen for metastatic prostate cancer based on based on patient comorbidities.					
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TABLE OF CONTENTS

PAGE

1. Introduction.....	4
2. Keywords	4
3. Accomplishments.....	4
4. Impact.....	14
5. Changes/Problems.....	15
6. Products.....	15
7. Participants & Other Collaborating Organizations.....	16
8. Special Reporting Requirements.....	17
9. Appendices	17

1. Introduction

Adverse events are common during treatment of metastatic prostate cancer, especially in elderly patients and those with comorbid medical diseases. Treatments for prostate cancer, include oral anti-androgens and chemotherapy are typically tested in fit patients who are eligible for clinical trials, therefore rates and severity of adverse events in real-world patients are not known. Additionally, there are interactions between treatments and patient comorbid diseases, such as heart failure and diabetes, that increase rates of adverse events or decrease the efficacy of treatment. In modern treatment of metastatic castration-resistant prostate cancer (mCRPC), there are several similar medicines that are used interchangeably and may have different rates of adverse events based on patient comorbidities, therefore appropriate selection of therapies has the potential to improve outcomes for all men with metastatic prostate cancer, but especially those with comorbid diseases.

Objective: To identify outcomes and adverse events with treatment of patients with metastatic prostate cancer and comorbid medical diseases. We will then compare rates of adverse events and overall survival between different treatments for prostate cancer at a similar stage of disease.

Methods: We have been using data from the Veteran Health Affairs, a nationwide network of medical facilities that maintains a complete set of data for analysis. We have created a retrospective cohort study using VHA patients treated for prostate cancer to determine rates of adverse events. ICD9/10 codes from inpatient hospitalizations and outpatient visits have been used to identify adverse events. Lab values, vital signs, and medicines for comorbid disease will be collected treatment initiation to model outcomes. Outcomes of importance include overall survival, time to next treatment, and hospitalizations.

2. Keywords

Metastatic prostate cancer, castration-resistant prostate cancer, adverse events, hospitalizations, veterans

3. Accomplishments

What were the major goals of the project?

As stated in the statement of the work the project has several major tasks and minor tasks

Specific Aim 1: Determine the frequency of adverse events in men treated with different therapies for metastatic prostate cancer based on burden of comorbid medical disease
Major Task 1: Regulatory approval and credentialing
Subtask 1: IRB Approval at STLVAMC
Subtask 2: Submit Human Research Protection Office (HRPO) Approval
Subtask 3: VA WOC Appointments for U of SC collaborators at Columbia VA
Subtask 4: Data sharing arrangements for U of SC and STLVAMC
Subtask 5: Coordinate with sites for annual IRB approval, continuing review
Milestone(s) Achieved: IRB Approval, credentialing and data sharing

Major Task 2: Create cohort of patients treated for metastatic castrate resistant prostate cancer and identify adverse events
Subtask 1: Request data from PBM and VINCI for patients treated with oral antiandrogens, IV chemotherapy, ADT, and bone agents (already done)
Subtask 2: Identify hospitalizations and outpatient visits after treatment start and collect ICD codes (already done)
Subtask 3: Collect PSA, testosterone testing, duration of ADT prior to treatment with oral anti-androgens, and ICD codes for castrate resistance and metastatic disease
Subtask 4: Validate causes for hospital admission and new ICD codes with manual chart review and verify metastatic castrate resistant prostate cancer
Subtask 5: Compile adverse events over time and associate with treatments
Subtask 6: Publish adverse events of treatment in VA data
Milestone(s) Achieved: Characterization of Adverse Events

Specific Aim 3: Develop and test an algorithm to select oral anti-androgen for metastatic prostate cancer based on based on patient comorbidities and medicines.
Major Task 4: Develop a classic regression based risk prediction model to predict survival and select treatment
Subtask 1: Establishment of candidate predictors from Aim 2
Subtask 2: Univariate analyses of candidate predictors
Subtask 3: Exclusion of covariate pair with strong correlation
Subtask 4: Multivariate analysis and finalization of the model
Milestone(s) Achieved: Derivation of the regression based model
Major Task 5: Develop an artificial intelligence (AI) model to predict risk for adverse events and select treatment
Subtask 1: Prepare data for AI protocols
Subtask 2: Utilization of neural network protocols in training dataset and comparison to other AI methods
Subtask 3: Refinement/tuning of neural network protocols
Subtask 4: Testing of ideal AI model in validation dataset
Subtask 5: Comparison of AI model to linear regression based model
Subtask 6: Manuscript preparation and publication of results
Milestone(s) Achieved: Creation of AI model for risk prediction of adverse events and to select treatment from existing medical comorbidity data

What was accomplished under these goals?

Aim 1: Determine the frequency of adverse events in men treated with different therapies for metastatic prostate cancer based on burden of comorbid medical disease.

We have been using a large database of patients treated for mCRPC from the Veterans Health Affairs to understand the role of comorbid disease in affecting overall survival. Since many men with mCRPC as elderly with comorbid diseases, there is likely to be significant differences in survival based on co-morbidities. Since these patients are not well represented in clinical trials, it is important to study these outcomes in real world patients. Additionally, there may interactions between treatments and comorbid disease that can results in increased number of adverse events.

Major Task 1: Regulatory approval and credentialing

Task Overview: All necessary regulatory approvals have been obtained. Due to changes in Federal staffing, we were unable to obtain WOC appointments for University of South Carolina collaborators. Therefore, data sharing agreements were made to facilitate sharing a limited dataset, which would allow for sharing of adequate data to facilitate analysis without obtaining a WOC.

- **Subtask 1: IRB Approvals at STLVAMC**

- This has been completed prior to start of task period

- **Subtask 2: Submit Human Research Protection Office (HRPO) Approval**

- This has been completed prior to start of task period and was research was approved by HRPO

- **Subtask 3: VA WoC Appointments for University of South Carolina collaborators**

- Due to changes in federal hiring practices combined with altered research methods, this goal was modified. WOC appointments will not be pursued for University of South Carolina collaborators. Instead data will be organized into a limited dataset and sharing using a Limited dataset Data Use Agreement (DUA)

- **Subtask 4: Data sharing arrangements between University of South Carolina and STLVAMC**

- A Limited Dataset Data Use Agreement was executed between University of South Carolina and STLVAMC to allowing sharing of a limited data set.

- **Subtask 5: Coordinated sites for annual IRB review and continuing review**

- Initial IRB review and continuing review has been obtained for the project and are current.

- **Milestones:** All milestones have been achieved

Major Task 2: Create cohort of patients treated for metastatic castrate resistant prostate cancer and identify adverse events

Task Overview: The creation of the initial cohort of men treated for mCRPC was has been performed via multiple methods. Initially the cohort was created be identifying patients who were originally treated for mCRPC with therapy beyond just ADT, as that was the primary focus of the effort. As the project has developed, we have begun to include patients with mCRPC who have been treated only with ADT or without any evidence of therapy in the VA.

- **Subtask 1: Request data from PBM and VINCI for patients treated with oral antiandrogens, IV chemotherapy, ADT, and bone agents**

- A complete record of all prostate cancer medicines including oral anti-androgens, injectable hormonal therapy, chemotherapy, and supportive care agents was obtained for all patients in the Veterans Health Affairs treated for metastatic castrate-resistant prostate cancer from multiple sources including PBM and the prostate cancer data core. At the beginning of the period all of the medicines were obtained that were used for treatment from years 2000 to 2021. As the data develops and time passes, we will add additional data from 2022 and 2023.

- **Subtask 2:** Identify hospitalizations and outpatient visits after treatment start and collect ICD codes.
 - We first started by identifying hospitalizations and collected the ICD codes from the hospitalizations. Instead of including all ICD codes that were associated with patients over time, we focused on the first three ICD codes associated with hospitalization. These would be the primary reason for hospitalization and would signify adverse events that were severe enough to warrant inpatient management. The number and frequency of these hospitalizations for patients treated with abiraterone and enzalutamide, the two most common treatments for mCRPC from 2011-2019 are shown in Table 1.
 - Since prostate cancer was the primary diagnosis in many patients we also assessed secondary diagnoses and tertiary diagnoses to look for non-prostate cancer causes of hospitalization to identify common adverse events.
 - We identified that among non-cancer causes for admission there were significant causes of admission related to cardiovascular causes, genitourinary causes and infections. We engages in further delineation of the types of hospitalizations in Figure 1.

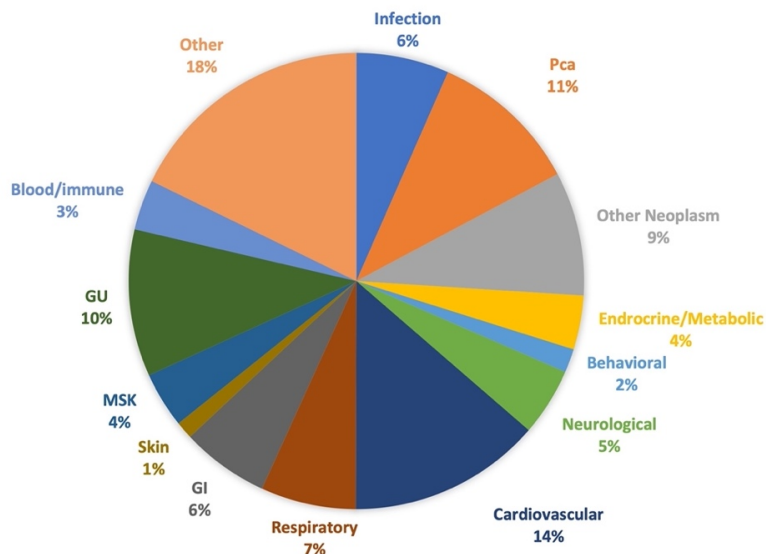
Table 1: Frequent diagnoses among hospitalization of patients with mCRPC

Primary Diagnosis	n	%
prostate cancer	1618	10.6
bone metastasis	666	4.4
sepsis	528	3.5
urinary tract infection	510	3.4
acute renal failure	408	2.7
cancer pain	330	2.2
pneumonia	236	1.6
gross hematuria	163	1.1
atrial fibrillation	159	1.0
acute coronary syndrome	147	1.0
other	10448	68.7

Secondary diagnosis if prostate cancer was primary diagnosis		
no secondary	103	6.4
liver metastasis	32	2.0
malnutrition	33	2.0
palliative care	44	2.7
pneumonia	39	2.4
urinary tract infection	35	2.2
acute renal failure	29	1.8
bone metastasis	652	40.3
other	650	40.2

Figure 1: Incidence of Primary ICD diagnosis codes for hospitalization among patients treated for metastatic prostate cancer with abiraterone or enzalutamide 2011-2019

HOSPITALIZATION DIAGNOSIS GROUP (ICD CODE) INCIDENCE



- In order to focus on infections, we included any diagnosis in the first three positions and identified a high rates of infections in Figure 2.

The three most common infections identified included urinary tract infections, sepsis, and pneumonia. Collectively these represent approximated 23% of the adverse events that resulted in hospitalization. Additionally we assess cardiovascular and other causes of hospitalization in table 2.

Figure 2: Infections among Hospitalizations in mCRPC

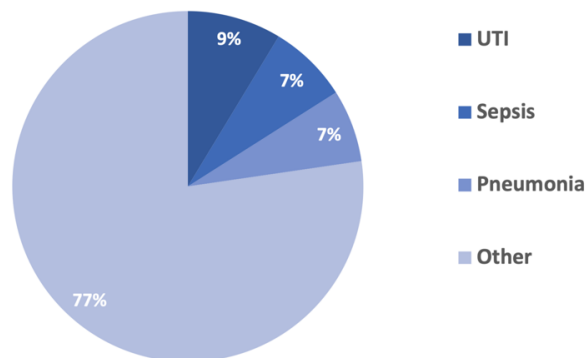


Table 2 Overall population N = 19955			Abiraterone n=13527
Outcome	n	person-year	Incidence per 1000 person-years (95% CI)
Heart Failure or decompensation	586	14638.9	40.0 (37.0 - 43.3)
Ischemic stroke	97	14638.9	6.6 (5.4 - 8.1)
Ischemic heart diseases	248	14638.9	16.9 (15.0 - 19.2)
Atrial fibrillation	372	14638.9	25.4 (23.0 - 28.1)
Torsade de pointe and QT interval prolongation	65	14638.9	4.4 (3.5 - 5.7)
Convulsion/seizure	158	14638.9	10.8 (9.2 - 12.6)
Acute kidney injury	1012	14638.9	69.1 (65.1 - 73.4)
Hepatitis	36	14638.9	2.5 (1.8 - 3.4)
			Enzalutamide n=6428
Outcome	n	person-year	Incidence per 1000 person-years (95% CI)
Heart Failure or decompensation	381	7428.2	51.3 (46.5 - 56.6)
Ischemic stroke	63	7428.2	8.5 (6.6 - 10.8)
Ischemic heart diseases	115	7428.2	15.5 (12.9 - 18.6)
Atrial fibrillation	136	7428.2	18.3 (15.5 - 21.6)
Torsade de pointe and QT interval prolongation	24	7428.2	3.2 (2.2 - 4.8)
Convulsion/seizure	24	7428.2	3.2 (2.2 - 4.8)
Acute kidney injury	348	7428.2	46.8 (42.3 - 51.9)
Hepatitis	6	7428.2	0.8 (0.4 - 1.8)

- **Subtask 3:** Collect PSA, testosterone testing, duration of ADT prior to treatment with oral anti-androgens, and ICD codes for castrate resistance and metastatic disease
 - We have been able to collect initial prostate-specific antigen levels in patients at the beginning of treatment as well as at the time of subsequent treatments. Additionally we have identified time of initial treatment with ADT if available in PBM or medical records. A sample of data that has been collected for the project related to use of abiraterone and enzalutamide for mCRPC is available in Table 3 that include PSA testing and ICD codes for metastatic disease. When attempting to identify testosterone testing and ICD codes for castrate resistant, we encountered significant heterogeneity in clinical practice and therefore those variables were no longer pursued.

Table 3: Characteristics of veterans first prescribed abiraterone and enzalutamide in prostate cancer from 5/13/2011 to 12/31/2019

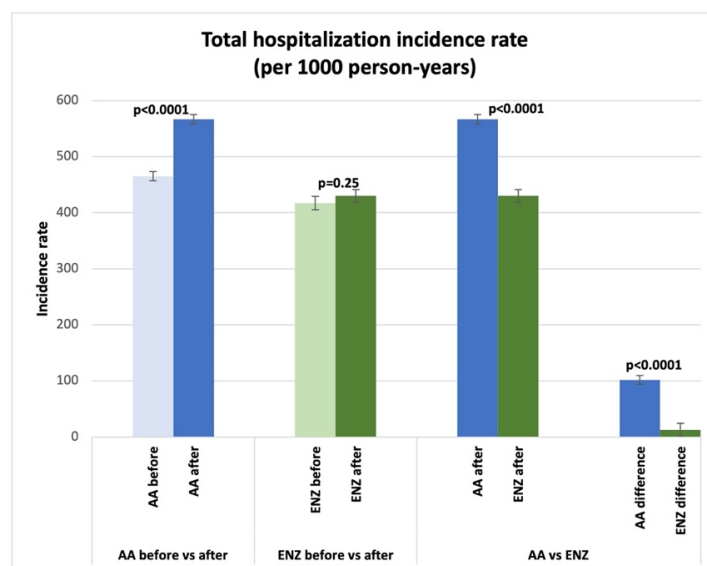
Demographic clinical characteristics	Total (N=19,775)		P-value
	first prescribed abiraterone n=13,527	first prescribed enzalutamide n=6,248	
Age (mean years)	74.5	75.8	<0.001†
Charlson Comorbidity index	4	4.4	<0.001†
Elixhauser comorbidities	5.8	6.3	<0.001†
Doxetaxel ever (%)	28	18.5	<0.0001*
Bone agent (%)	5.4	5.8	0.27*
Gleason score (mean, n)	7.8 (1602)	7.9 (1139)	0.23
PSA at treatment (median, n)	33.3 (11566)	21.6 (5086)	<0.0001‡
largest PSA at treatment (median, n)	37.3 (11566)	22.5(5086)	<0.0001‡
largest PSA when treated with doxetaxel (median, n)	83.2 (3576)	71.3 (1027)	0.0003
Duration from diagnosis to time 0 (mean months, n)	83.2(7934)	93.0 (3523)	<0.0001†
Duration from diagnosis to ADT (mean months, n)	42.6 (9744)	49.9(4518)	<0.0001†
Metastatic site 2 year before time0 (%)			
Bone	48	41.4	<0.0001*
Visceral	9.5	8.2	0.003*
Lung and Liver	4.9	4.3	0.052*
Visceral other than Lung and Liver	5.1	5.1	0.99*
Unspecified	7.9	5.7	<0.0001*

* Chi-square test

† T-test

‡ Wilcoxon Two-Sample Test

- **Subtask 4:** Validate causes for hospital admission and new ICD codes with manual chart review and verify metastatic castrate resistant prostate cancer
 - This task is ongoing based on the specific adverse events are the being studied. In order to focus on a multitude of outcomes, we have performed limited manual chart review. In the first effort, we manually reviewed heart failure admissions and outcomes. We will continue to manually review records as needed
- **Subtask 5:** Compile adverse events over time and associate with treatments
 - By looking at the rate of infections over time, we were able to detect and increased rate of hospitalizations for infections, cardiovascular events and genitourinary complications with abiraterone compared to enzalutamide. While there were fewer events overall with enzalutamide, the important findings was the change in the



rate of events.

- **Subtask 6:** Publish adverse events of treatment in VA data
 - We have published our initial findings in several conference abstracts and one publication thus far. The first manuscript related to adverse events is now available Riekhof F, Yan Y, Bennett CL, Sanfilippo KM, Carson KR, Chang SH, Georgantopoulos P, Luo S, Govindan S, Cheranda N, Afzal A, **Schoen MW**. Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer With Abiraterone or Enzalutamide. Clin Genitourin Cancer. 2023 Jul 11;. doi: 10.1016/j.clgc.2023.07.006. [Epub ahead of print] PubMed PMID: 37495480.

Milestones: Characterizations of adverse events is ongoing and we have made significant progress in identifying events and comparing events across populations.

Aim 2: Analyze duration of therapy, treatment efficacy and overall survival based on comorbid medical diseases, patient medicines and laboratory values.

The primary goal of this aim is to provide data to inform treatment choice based on comorbid diseases. There is considerable data related to the patient (host) with the prostate cancer and that data can be used to improve treatment selection.

Major Task 3: Identify comorbidities of patients and correlate to treatment duration and survival

Task Overview: This task is critical to the underlying premise that comorbid diseases drive outcomes and that patients treated in the real world are not similar to patients treated in trials. They are older, with more comorbid diseases. Therefore the survival is likely to be less and there may be important interactions between comorbid diseases and treatment that can be used to guide therapy.

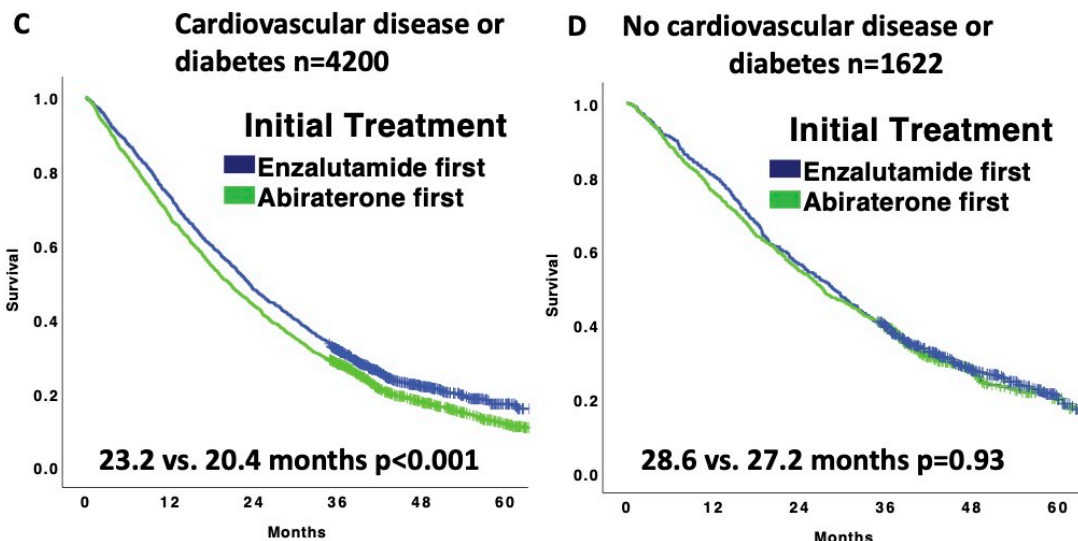
- **Subtask 1:** Identify patient comorbid conditions based on Charlson and Elixhauser methods
 - We have been able to use the Charlson comorbidity index and the Elixhauser classifications to identify comorbidities. Additionally, we have added the VA Frailty index, which is a new method of looking at frailty. A sample of comorbid conditions identified is shown in table 4.

Table 4 Comorbidity	Total n=20517	Percent	ABIRATERONE n=13906 N, %		ENZALUTAMIDE n=6611 N, %	
Heart Failure	3559	17.3%	2241	16.1%	1318	19.9%
Myocardial infarction	2042	10.0%	1300	9.3%	742	11.2%
Peripheral Vascular	4482	21.8%	2868	20.6%	1614	24.4%
Cerebrovascular	3598	17.5%	2322	16.7%	1276	19.3%
Dementia	760	3.7%	437	3.1%	323	4.9%
Pulmonary	6803	33.2%	4486	32.3%	2317	35.0%
Peptic ulcer disease	1069	5.2%	714	5.1%	355	5.4%
Mild Liver disease	2140	10.4%	1370	9.9%	770	11.6%
Mod-Severe Liver	167	0.8%	87	0.6%	80	1.2%
Diabetes	7510	36.6%	4786	34.4%	2724	41.2%
Hemiplegia	579	2.8%	407	2.9%	172	2.6%
Complicated Diabetes	3715	18.1%	2212	15.9%	1503	22.7%
Renal disease	8376	40.8%	5723	41.2%	2653	40.1%
Malignancy	4946	24.1%	3380	24.3%	1566	23.7%
HIV	88	0.4%	63	0.5%	25	0.4%
Rheumatic disease	643	3.1%	440	3.2%	203	3.1%

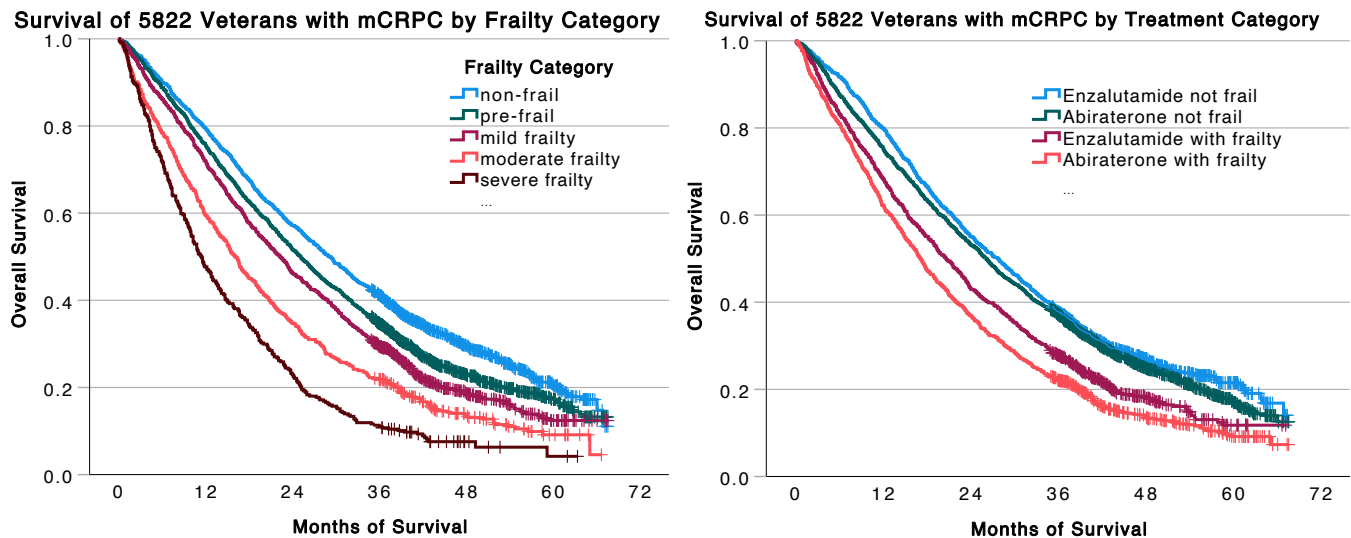
- **Subtask 2:** Collect laboratory values, vital signs, pathologic data and imaging findings at initiation of treatment
 - The collections of laboratory values and important vital signs has occurred. Some pathologic data related to Gleason score has been obtained via chart review and others via published NLP methods. Therefore, a majority of the work of this task is complete. Additional chart review is ongoing to supplement the data that is already collected.
- **Subtask 3:** Perform Cox proportional hazard risk prediction model based on established comorbid diseases
 - We have started this task using the data collected to report on the outcomes of treatment for mCRPC with the two main treatments during the period of interest, abiraterone and enzalutamide. In addition, we are adding data related to other treatments including docetaxel and cabazitaxel. In the primary analyses of data from abiraterone as enzalutamide we found several differences in overall survival and time to next treatment based on patients features, including comorbid conditions.

Variable	Median treatment duration (months)			Median survival (months)			
	abiraterone	enzalutamide	P-value*	abiraterone	enzalutamide	P-value#	
All patients (n=5822)	9.1	11.7	<0.001	22.1	24.2	0.001	Hazard Ratio enzalutamide better ← 1.0 → abiraterone better
One treatment for mCRPC (n=2553)	7.4	11.4	<0.001	13.8	19.3	<0.001	
Two or more treatments for mCRPC (n=3269)	9.9	11.8	0.006	27.9	28.0	0.35	
Age ≥ 75 years (n=2908)	8.1	10.7	<0.001	18.4	21.2	<0.001	
Age < 75 years (n=2914)	10.0	12.9	<0.001	26.6	28.5	0.097	
Charlson Comorbidities ≥ 4 (n=2565)	8.2	10.8	<0.001	18.2	21.5	0.003	
Charlson Comorbidities < 4 (n=3257)	9.8	12.4	<0.001	25.6	27.9	0.038	
Cardiovascular disease (n=3611)	8.5	10.9	<0.001	19.4	22.7	<0.001	
Diabetes (n=2203)	8.6	12.2	<0.001	20.8	23.7	0.002	
Cardiovascular disease and diabetes (n=1607)	8.2	11.5	<0.001	18.9	23.0	0.003	
Cardiovascular disease or diabetes (n=4207)	8.6	11.4	<0.001	20.5	23.2	<0.001	
Renal Failure (n=1240)	7.2	10.5	0.002	16.6	19.4	0.054	
Liver Disease (n=581)	9.7	12.0	0.026	23.8	28.3	0.17	

- Two of common comorbid conditions, cardiovascular disease and diabetes were predictive of survival and also predictive of benefit of enzalutamide over abiraterone



- Additionally, we conducted an analysis using frailty scores and found a similar effect. That frail patients had a shorter survival and that in patients who were frail as defined by a VA-FI score of >0.2 , there was longer survival with enzalutamide.



- **Subtask 4:** Conduct a competing risk analysis

- This task is ongoing. We are in the process of obtaining mortality data from our cohort in an attempt to define non-prostate cancer death as a competing risk. As all men in the cohort have metastatic prostate cancer, which is typically a fatal

- **Subtask 5:** Manuscript preparation and publication

- A manuscript related to outcomes of mCRPC treated with abiraterone vs. enzalutamide was published in prostate cancer and prostatic diseases.

Schoen MW, Carson KR, Eisen SA, Bennett CL, Luo S, Reimers MA, Knoche EM, Whitmer AL, Yan Y, Drake BF, Sanfilippo KM. Survival of veterans treated with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases. Prostate Cancer Prostatic Dis. 2022 Sep 14;. doi: 10.1038/s41391-022-00588-5

Deol ES, Sanfilippo KM, Luo S, Fiala MA, Wildes T, Mian H, Schoen MW. Frailty and survival among veterans treated with abiraterone or enzalutamide for metastatic castration-resistant prostate cancer. J Geriatr Oncol. 2023 Jun;14(5):101520. doi: 10.1016/j.jgo.2023.101520. Epub 2023 May 30.

Milestone(s) Achieved: As a result of this work we have improved understanding of the risk of comorbidities on outcomes in metastatic castrate resistant prostate cancer, including cardiovascular disease and diabetes.

Aim 3: Develop and test an algorithm to select oral anti-androgen for metastatic prostate cancer based on based on patient comorbidities and medicines.

The primary goal of this aim is to use traditional regression techniques as well as machine learning methods to develop a model/algorithm to select therapy based on comorbid diseases, patient characteristics and tumor features. The work on this AIM will be the focus of year 2-4

Major Task 4: Develop a classic regression based risk prediction model to predict survival and select treatment

Task Overview: This task is critical to the underlying premise that comorbid diseases drive outcomes and that patients treated in the real world are not similar to patients treated in trials. They are older, with more comorbid diseases. Therefore the survival is likely to be less and there may be important interactions between comorbid diseases and treatment that can be used to guide therapy.

- **Subtask 1, 2, 3:** Establishment of candidate predictors from Aim 2, Univariate analyses of candidate predictors, Exclusion of covariate pair with strong correlation.
 - Several univariate predictors from Aim 2 have been identified as having a large impact of outcomes. Important features such as age, Charlson index, BMI, Black race. In the process of variable selection we have performed many univariate analyses and have been excluding variable with high correlations/collinearity. This work is ongoing.
- **Subtask 4:** Multivariate analysis and finalization of the model
 - While the final model has not been fully developed, an example model of important covariates is shown in Table 5 with adjusted hazard ratios from the Cox proportional hazard model and the 95% confidence interval.

Table 5: Association between patient and treatment characteristics and mortality in U.S. Veterans treated for mCRPC

Variable	All Veterans n=5822		Veterans with cardiovascular disease or diabetes n=4200	
	aHR#	95% CI	aHR#	95% CI
Enzalutamide vs. Abiraterone	0.89	0.84-0.95	0.87	0.81-0.93
Age (per year increase)	1.02	1.01-1.02	1.01	1.01-1.02
Charlson Comorbidity Index, per point	1.05	1.04-1.06	1.04	1.03-1.06
Race: Non-black	Ref		Ref	
Black	0.76	0.70-0.81	0.76	0.70-0.83
PSA Category: 0-4	Ref		Ref	
4-10	1.2	1.05-1.38	1.18	1.01-1.39
10-20	1.47	1.29-1.68	1.37	1.18-1.60
20-50	1.64	1.45-1.86	1.52	1.32-1.76
50-100	2.15	1.89-2.45	2.05	1.76-2.38
100-200	2.39	2.08-2.75	2.23	1.90-2.63
200+	2.86	2.51-3.27	2.84	2.42-3.32
unknown	2.04	1.72-2.43	1.85	1.50-2.27
Prior docetaxel	1.36	1.23-1.50	1.28	1.14-1.43
Treated with bone therapy	0.73	0.65-0.83	0.78	0.68-0.91
BMI Category: < 18.5	1.57	1.29-1.91	1.49	1.19-1.87
18.5 ≤ BMI < 25	Ref		Ref	
25 ≤ BMI < 30	0.77	0.72-0.84	0.79	0.73-0.87
BMI ≥ 30	0.67	0.61-0.72	0.66	0.60-0.72
BMI unknown	0.81	0.72-0.91	0.79	0.69-0.91
Hemoglobin: Hgb ≥ 10.0 g/dL	Ref		Ref	
Hgb < 10 g/dL	1.77	1.60-1.97	1.73	1.55-1.94
unknown	0.88	0.76-1.01	0.87	0.74-1.03
eGFR: ≥ 30 ml/min	Ref		Ref	
< 30	1.08	0.93-1.25	1.03	0.88-1.21
unknown	1.01	0.82-1.24	1.07	0.84-1.37
Bilirubin: < 2 mg/dL	Ref		Ref	
≥ 2 mg/dL	1.96	1.13-3.38	1.43	0.71-2.86
unknown	1.02	0.89-1.18	1.08	0.92-1.26
Albumin: > 3.0 g/dL	Ref		Ref	
≤ 3.0 g/dL	1.86	1.64-2.10	1.88	1.64-2.15
unknown	1.11	0.98-1.25	1.15	0.99-1.32

aHR: Adjusted Hazard Ratio from Cox proportional hazard model. Variables include: Use of abiraterone vs. enzalutamide, Age, Charlson Comorbidity index Race (black vs. non-black), baseline PSA, prior treatment with docetaxel, treatment with bone directed therapy (zoledronic acid or denosumab), BMI, baseline hemoglobin (hgb), eGFR, bilirubin, albumin

Major Task 4: Develop an artificial intelligence (AI) model to predict risk for adverse events and select treatment

Task Overview: This task is will use artificial intelligence methods to select variables and develop a model to predict adverse events and survival. This task is scheduled for year 3&4, only preliminary work to create the datasets required has been performed. Further reporting on these tasks with occur in future annual reports.

What opportunities for training and professional development has the project provided?

This project has provide immense amounts of training and development for several participants, most notably Dr. Schoen. As a result of the efforts, Dr. Schoen has been able to collaborate and learn from several new mentors and was invited to be a Prostate Cancer Foundation Young Investigator. The techniques and methods that Dr. Schoen developed directly led to the PCF award. Furthermore, due to the availability of statistical expertise within Washington University and Saint Louis University, Dr. Schoen decided against additional formal coursework but instead joined the NIH CISNET prostate cancer modeling group. As a part of the NIH CISNET group, Dr. Schoen has received extensive mentoring and modeling experience.

How were the results disseminated to communities of interest?

The results of this study have been presented in multiple venues including local, national, and international conferences ranging from St. Louis University grand groups, St. Louis Big Data seminar, Missouri ACP meetings, NIH CISNET meetings, American Society of Clinical Oncology annual meeting and American Society of Clinical Oncology Genitourinary cancer meeting.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue with our develop of the clinical dataset to prepare for more regression models and the such of AI methods.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

The initial work of this study has shown the importance of comorbid diseases in both affecting the outcomes and interacting with treatments for prostate cancer. Future studies of prostate cancer medicines for mCRPC will likely have to better report and including comorbid conditions in clinical studies and study the interactions of comorbid conditions on outcomes and treatments.

What was the impact on other disciplines?

The hypothesis that patients in the real-world have more comorbid diseases and that because the disease burden is higher, there are more adverse events is also being shown to be correct.

What was the impact on technology transfer?

None to report

What was the impact on society beyond science and technology?

The overall impact on society and technology is that computational methods that use existing data from medical records, such as that available in the Veterans Health Affairs, can be used to guide patient treatment. These methods need to be tested and employed at a higher rate to augment clinician and patient decision making. Patients and clinicians will want to know their prognosis and

survival with different treatments as well as possible adverse events in order to make better decisions.

5. Changes/Problems

Changes in approach and reasons for change

Slight modifications in data sharing were made since some collaborators were unable to obtain a WOC appointment at the South Carolina VA

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

There was been minor changes in the use of funds for data abstraction and since Dr. Schoen is not doing additional coursework, there are more funds available. A major change that is in process but has not been completed is the addition of another site, Saint Louis University, as a sub-award. This is being done to increase the analytic capability of the project and better use project funds for data acquisition and analysis. As well, the Saint Louis University team has more capability in data visualization and creation of interactive web models that will be essential to increasing the impact of the this project.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

6. Products: Publications, conference papers, and presentations

Journal publications

1. Schoen MW, Carson KR, Eisen SA, Bennett CL, Luo S, Reimers MA, Knoche EM, Whitmer AL, Yan Y, Drake BF, Sanfilippo KM. Survival of veterans treated with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases. *Prostate Cancer Prostatic Dis.* 2022 Sep 14;. doi: 10.1038/s41391-022-00588-5. Published
2. Deol ES, Sanfilippo KM, Luo S, Fiala MA, Wildes T, Mian H, Schoen MW. Frailty and survival among veterans treated with abiraterone or enzalutamide for metastatic castration-resistant prostate cancer. *J Geriatr Oncol.* 2023 May 30;14(5):101520. doi: 10.1016/j.jgo.2023.101520. Epub ahead of print. PMID: 37263065. Published, acknowledged federal support
3. Riekhof F, Yan Y, Bennett CL, Sanfilippo KM, Carson KR, Chang SH, Georgantopoulos P, Luo S, Govindan S, Cheranda N, Afzal A, Schoen MW. Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer With Abiraterone or Enzalutamide. *Clin Genitourin Cancer.* 2023 Jul 11;. doi: 10.1016/j.clgc.2023.07.006. [Epub ahead of print] PubMed PMID: 37495480. Published, acknowledged federal support

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

American Society of Clinical Oncology: Genitourinary Cancers 2023

1. *Govindan S, Cheranda N, Luo S, Riekhof F, **Schoen MW**. Survival and hemoglobin A1c in metastatic castrate resistant prostate cancer. DOI: 10.1200/JCO.2023.41.6_suppl.75 Journal of Clinical Oncology 41, no. 6_suppl (February 20, 2023) 75-75.
 2. *Deol ES, Luo S, Sanfilippo KM, Eisen SA, **Schoen MW**. Frailty and overall survival in metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide. DOI: 10.1200/JCO.2023.41.6_suppl.71 Journal of Clinical Oncology 41, no. 6_suppl (February 20, 2023) 71-71. Published, acknowledged federal support
 3. Cheranda N, Luo S, Sanfilippo KM, Eisen SA, **Schoen MW**, Survival in Black and non-Black patients with metastatic prostate cancer. Journal of Clinical Oncology 2023 41:6_suppl, 101-101
- * denotes a manuscript has been produced

Websites or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

There have not been any changes in the participants in the projects to date. The key personnel at Site 1-2 are:

Name:	<i>Martin Schoen</i>
Project Role:	<i>PI</i>
Researcher Identifier (e.g. ORCID ID):	0000-0001-6388-5553
Nearest person month worked:	5
Contribution to Project:	<i>Dr. Schoen performed and overall this project.</i>
Funding Support:	<i>The Prostate Cancer Foundation</i>
Name:	<i>Suhong Luo</i>
Project Role:	<i>Analyst</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	5
Contribution to Project:	<i>Data processing and analysis</i>
Funding Support:	<i>National Institutes of Health R01 from Dr. Kristen Sanfilippo</i>
Name:	<i>Kelley Chadwick-Mansker</i>
Project Role:	<i>Analyst</i>
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	<i>Data processing and analysis</i>
Funding Support:	<i>National Institutes of Health R01 from Dr. Kristen Sanfilippo</i>

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last report?**

Yes, Dr. Schoen has received a Prostate Cancer Founding Young Investigator award. This award is complementary to this study and focuses on metastatic hormone sensitive prostate cancer, an earlier stage of the disease.

What other organizations were involved as partners? (Subcontract, Site 3)

Organization Name: University of South Carolina

Location of Organization: Columbia, South Carolina

Partner's contribution to the project: Dr. Hoque and the team at University of South Carolina have been providing key support related to artificial intelligence and neural network methods.

8. Special Reporting Requirements

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. Appendices Published journal articles

ARTICLE OPEN



Clinical Research

Survival of veterans treated with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases

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BACKGROUND: Comorbid diseases influence patient outcomes, yet little is known about how comorbidities interact with treatments for metastatic castrate-resistant prostate cancer (mCRPC). No head-to-head trials have compared the efficacy of abiraterone and enzalutamide - oral androgen-receptor targeted agents (ARTAs) for mCRPC. In patients with comorbid disease, outcomes with ARTAs may differ due to disparate mechanisms of action, adverse events, and drug interactions.

METHODS: Retrospective observational study of US veterans initiating treatment for mCRPC with abiraterone or enzalutamide between September 2014 and June 2017. Treatment duration and overall survival (OS) was compared based on age and comorbid diseases. The association between ARTA and OS was assessed using Cox proportional hazards and propensity-score matched modeling while adjusting for potential confounders. Sensitivity analyses were performed based on patient age, comorbidities, and subsequent treatments for mCRPC.

RESULTS: Of 5822 veterans treated for mCRPC, 43.0% initially received enzalutamide and 57.0% abiraterone. Veterans initially treated with enzalutamide versus abiraterone were older (mean 75.8 vs. 75.0 years) with higher mean Charlson comorbidity index (4.4 vs. 4.1), and higher rates of cardiovascular disease or diabetes (74.2% vs. 70.6%). In the entire population, veterans initially treated with enzalutamide had longer median OS compared to those initially treated with abiraterone (24.2 vs. 22.1 months, $p = 0.001$). In veterans with cardiovascular disease or diabetes, median treatment duration with enzalutamide was longer (11.4 vs. 8.6 months, $p < 0.001$) with longer median OS compared to abiraterone (23.2 vs. 20.5 months, $p < 0.001$). In a propensity score matched cohort, enzalutamide was associated with decreased mortality compared to abiraterone (HR 0.90, 95% CI 0.84–0.96).

CONCLUSIONS: Veterans with cardiovascular disease or diabetes had longer treatment duration and OS with enzalutamide compared to abiraterone. Further study of ARTA selection may benefit men with metastatic castrate resistant prostate cancer and likely hormone sensitive prostate cancer, especially among patients with comorbid diseases.

Prostate Cancer and Prostatic Diseases; <https://doi.org/10.1038/s41391-022-00588-5>

INTRODUCTION

Metastatic castrate resistant prostate cancer (mCRPC) remains difficult to treat despite availability of multiple therapies. The oral androgen-receptor targeting agents (ARTAs) abiraterone and enzalutamide improve overall survival (OS) in mCRPC [1, 2] and due to more tolerable safety profiles compared to cytotoxic chemotherapy such as docetaxel, ARTAs are frequently administered to patients with comorbid diseases treated within the Veterans Health Administration (VHA) [3]. Although there have been small trials testing drug sequencing, no large clinical trial has compared outcomes between ARTAs [4, 5]. Meta-analyses have not revealed large differences in disease response with these agents [6–8] and they are used interchangeably due to similar results from trials that included patients with few comorbid diseases [9].

Comorbid diseases and age can interact with treatments to affect survival in prostate cancer [10–12]. High rates of short-term mortality and hospitalization have been noted among prostate cancer patients with cardiovascular disease receiving ARTAs [13]. Because the abiraterone and enzalutamide have different mechanisms of action, in patients with complex medical conditions, the drugs may have disparate treatment outcomes and adverse events [14]. Abiraterone acetate inhibits steroid hormone biosynthesis to reduce production of androgens, requires co-administration of prednisone to prevent adrenal insufficiency, and may interact with diabetes [1]. In contrast, enzalutamide blocks hormone signaling directly by inhibiting the androgen receptor and does not require prednisone [2]. These differences may explain the increased

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rate of hospitalizations in patients treated with abiraterone [15, 16] and increased acute kidney injury, hepatic injury, and atrial fibrillation [17]. Since many men with prostate cancer have cardiovascular disease with inadequately controlled risk factors [18], understanding the interaction between cardiovascular disease and ARTAs may guide treatment decisions.

Large data analyses of real-world treatment can inform clinical practice in situations of clinical equipoise and identify potential differences in survival among patients who are not routinely included in clinical trials. Prior studies showed benefit of enzalutamide over abiraterone using real-world data from the VHA [19] and a French cohort [20]. However, analyses of patients with comorbidities such as cardiovascular disease and diabetes have not been performed and could determine which patients benefit from careful selection of ARTA therapy. Since many veterans with prostate cancer have multiple comorbidities, data from the VHA provides a crucial opportunity to compare treatment duration and survival in high-risk patient populations with cardiovascular disease or diabetes.

METHODS

Study population

The Veterans Health Administration Informatics and Computing Infrastructure (VINCI) system contains clinical and administrative data from the Corporate Data Warehouse (CDW) from veterans treated across the United States. Using VINCI, we identified patients with an initial prescription for abiraterone or enzalutamide between September 10, 2014 and June 2, 2017. During these years, these medications had the same FDA indications for treatment of mCRPC and were similarly priced with no generic available. On June 2, 2017, abiraterone was reported to improve survival in metastatic hormone sensitive prostate cancer, therefore patients starting treatment after that date were not included [21]. This study was reviewed by the Saint Louis Veterans Affairs Medical Center Institutional Review Board and was performed in accordance with the Declaration of Helsinki.

Measurements and covariates

We obtained ICD-9/10 codes and laboratory data with the VINCI platform. Pathologic data from the cancer diagnosis was obtained from CDW oncology files, including Gleason score. Pharmacy Benefits Management (PBM) records were accessed to ascertain treatments for all other types of prostate cancer therapy including androgen deprivation therapy (ADT), chemotherapy, and bone-directed therapy of zoledronic acid or denosumab. ADT included treatment with leuprolide, triptorelin, goserelin, histrelin, and degarelix, or ICD codes for orchiectomy. Treatment start date was determined as the first date of the initial prescription for abiraterone or enzalutamide. Patients were considered to have received one treatment for mCRPC if they were prescribed either abiraterone or enzalutamide only and were not prescribed docetaxel, cabazitaxel, mitoxantrone, radium-223, or sipuleucel-T. Patients were considered to have received multiple therapies for mCRPC if they were prescribed two or more of the following: abiraterone, enzalutamide, docetaxel, cabazitaxel, mitoxantrone, or sipuleucel-T.

Baseline demographics collected include race and age at first prescription for abiraterone or enzalutamide. Body-mass index (BMI) was calculated using height and weight within one month of initial treatment. Laboratory data included prostate specific antigen (PSA), albumin, creatinine, and hemoglobin closest to and prior to treatment start, within six months of therapy initiation. Creatinine clearance was calculated using the CKD-Epi formula. The Romano adaptation of the Charlson comorbidity index (CCI) [22] and the Quan modification of the Elixhauser index [23] were calculated based on two ICD9/10 codes obtained any time prior to initiation of abiraterone or enzalutamide. Cardiovascular disease was identified by the presence of any ICD codes in the Charlson and Elixhauser indices for myocardial infarction, heart failure, cardiac arrhythmia, valvular disease, complicated hypertension, peripheral vascular disease, and cerebrovascular disease. Diabetes mellitus was identified by ICD codes for diabetes or complicated diabetes. Sites of metastases was determined by presence of ICD9/10 codes in one year prior to treatment initiation [24] and time from first diagnosis was calculated from first pathologic diagnosis of prostate cancer available in CDW-Oncology Raw.

Outcome measures

Date of death was identified using the VHA Vital Status File and OS was calculated as the time from date of initial prescription of abiraterone or enzalutamide to date of death or April 30, 2020 the last date of follow up. Duration of initial treatment was calculated from the difference in days between the first and last prescription plus the number of days of treatment in the last prescription.

Statistical analyses

Demographic and clinical characteristics were compared between patients using Chi-square, Student's *t*, or Wilcoxon two-sample tests as appropriate. Cox proportional hazards regression modeling was used to assess the association between initial treatment and OS while adjusting for confounding variables. The following variables were included in the full model: age, CCI, black race [25], BMI [26], prior treatment with docetaxel, PSA at time of first treatment, prior bone-directed therapy, bone-directed after starting ARTA as a time-varying variable, anemia (hemoglobin < 10 g/dL), impaired creatinine clearance (CrCL < 30 mL/min), bilirubin $\geq$ 2 mg/dL and albumin $\leq$ 3 g/dL. Propensity score matching was also performed using age, heart failure, cardiac arrhythmia, uncomplicated hypertension, valvular abnormality, myocardial infarction, complicated diabetes, uncomplicated diabetes and renal failure variables to match patients and determine outcome with abiraterone or enzalutamide. Sub-group analyses of patients who had a pathologic record of prostate cancer available were performed to identify patients who primarily received treatment within the VHA.

SAS 9.4 (SAS Inc., Cary NC) and SPSS (IBM, Armonk NY) were used for analyses and to create figures. All *p*-values were 2-tailed with *p* < 0.05 determined as significant.

RESULTS

From September 10, 2014 to June 2, 2017, 5822 veterans with prostate cancer were initially treated with abiraterone or enzalutamide by VHA medical facilities. The mean age of patients included was 75.4 years, 1351 (23.2%) were African American, and mean CCI was 4.2 (standard deviation 2.7). A comparison of baseline patient characteristics is shown in Table 1. Fewer patients were initially treated with enzalutamide than abiraterone (2504 vs. 3318) and 2804 (48.2%) received only one of the two drugs during the study period. Veterans first treated with enzalutamide were older (75.8 vs. 75.0 years, *p* = 0.002), had higher mean CCI (4.4 vs. 4.1, *p* < 0.001), and had lower median baseline PSA values (27.8 vs. 32.0, ng/mL *p* = 0.03). There were no significant differences in treatment based on race/ethnicity or use of docetaxel prior to treatment with abiraterone or enzalutamide.

Treatment pattern

Table 2 shows treatment duration and OS among all patients and key mCRPC patient subgroups. During a median follow up period of 23.2 months, duration of treatment for veterans initially treated with enzalutamide was 2.6 months longer compared to patients treated initially with abiraterone (11.7 vs. 9.1, *p* < 0.001), and veterans treated with enzalutamide had 2.1 months longer median OS (24.2 vs. 22.1 months, *p* = 0.001) (Fig. 1). Significantly fewer veterans treated with enzalutamide received subsequent treatment for mCRPC (49.1% vs. 54.9%, *p* < 0.001), and time from the start of initial ARTA to subsequent treatment was longer with enzalutamide (15.3 vs. 14.7 months, *p* < 0.001).

Age and comorbidities

Because age and comorbid diseases effect treatment duration and survival in prostate cancer, we conducted analyses in these important sub-groups. Among 2908 patients age 75 years or older at start of ARTA therapy, median treatment duration with enzalutamide was 2.6 months longer compared to abiraterone, with 2.8 months longer median survival (21.2 vs. 18.4 months, *p* < 0.001, Fig. 2A). Among the 2565 patients with a CCI of 4 or higher, median treatment duration with enzalutamide was 2.6 months longer compared to abiraterone, with 2.3 month longer median survival (21.5 vs. 18.2 months, *p* = 0.003, Fig. 2B).

Table 1. Baseline Characteristics of US Veterans treated with abiraterone and enzalutamide in prostate cancer from 9/10/2014 to 6/2/2017.

Demographic clinical characteristics	Total (N = 5822)		P-value
	first prescribed abiraterone n = 3318	first prescribed enzalutamide n = 2504	
Age (mean years)	75	75.8	0.002 ^a
Charlson Comorbidity index	4.1	4.4	< 0.001 ^a
Elixhauser comorbidities	5.9	6.3	0.002 ^a
Race (% , n)			0.91 ^b
White	75.0 (2487)	74.6 (1867)	
Black	23.1 (765)	23.4 (586)	
Other	1.8 (60)	1.9 (48)	
Unknown	0.2 (6)	0.1 (3)	
eGFR (%)			0.003 ^b
> = 30 mL/min	90.2	88.3	
<30 mL/min	3.8	3.4	
Unknown	6.1	8.3	
Anemia (%)			< 0.001 ^b
Hgb > =10 g/dL	79.3	75	
Hgb < 10 g/dL	11.2	10.6	
Unknown	9.5	14.4	
Bilirubin (%)			0.045 ^b
<2	88.9	86.9	
>=2	0.2	0.4	
Unknown	11	12.7	
Albumin (%)			0.37 ^b
>3 g/dL	81	79.6	
<=3 g/dL	6	6.3	
Unknown	13	14.2	
Docetaxel prior (% , n)	10.3 (343)	9.0 (224)	0.08 ^b
Docetaxel ever (%)	28.4	24.4	< 0.001 ^b
Bone directed therapy prior (% , n)	23.5 (780)	21.2 (530)	0.03 ^b
Bone directed therapy after (% , n)	39.9 (1324)	37.1 (930)	0.03 ^b
Gleason score (n)	7.8 (1602)	7.9 (1139)	0.23 ^c
PSA closest to start of ARTA (median, n)	32.0 (3063)	27.8 (2245)	< 0.001 ^c
Received both abiraterone and enzalutamide (% , n)	50.6 (1678)	45.0 (1126)	< 0.001 ^b
Received subsequent treatment for mCRPC (% , n)	54.9 (1821)	49.1 (1230)	< 0.001 ^b
Time from diagnosis to start of ARTA (mean months, n)	93.8 (2076)	91.0 (1508)	0.29 ^a
Time between start of ARTA and subsequent treatment for mCRPC (mean months)	13.7	15.3	< 0.001 ^a
Metastatic site 1 year prior (%)			
Bone	44.7	42.3	0.07 ^b
Visceral	7.5	7.1	0.50 ^b
Lung and Liver	4.0	4.2	0.59 ^b
Visceral other than Lung and Liver	3.8	3.9	0.93 ^b
Unspecified	6.6	6	0.40 ^b

^aT-test.^bChi-square test.^cWilcoxon Two-Sample Test.

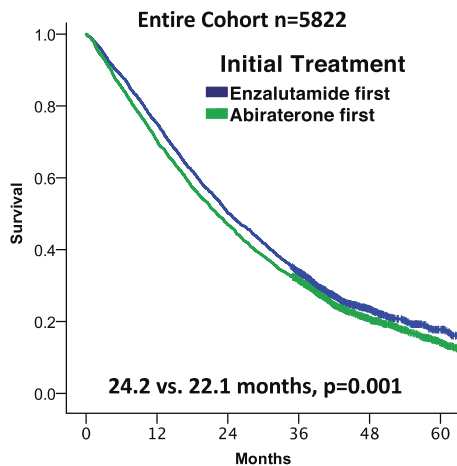
ARTA: androgen receptor targeting agent.

Among 3611 patients who only had cardiovascular disease (61.9% of the entire cohort), median treatment duration with enzalutamide was 2.4 months longer compared to abiraterone with 3.3 months longer median OS (22.7 vs. 19.4 months, $p = 0.006$). Additionally, among 2203 veterans with diabetes (37.8%), median

treatment duration with enzalutamide was 3.6 months longer compared to abiraterone with 2.9 months longer median OS (23.7 vs. 20.8 months, $p = 0.002$). In 4207 patients who had either cardiovascular disease or diabetes, median treatment duration with enzalutamide was 2.8 months longer compared to

Table 2. Treatment duration and survival of U.S. Veterans treated for mCRPC between 9/10/2014 to 6/3/2017.

Variable	Median treatment duration (months)			Median survival (months)			Forest plot with adjusted Hazard Ratios for death. Adjustment for all variables in full model
	abiraterone	enzalutamide	P-value*	abiraterone	enzalutamide	P-value#	
All patients (n=5822)	9.1	11.7	<0.001	22.1	24.2	0.001	
One treatment for mCRPC (n=2553)	7.4	11.4	<0.001	13.8	19.3	<0.001	
Two or more treatments for mCRPC (n=3269)	9.9	11.8	0.006	27.9	28.0	0.35	
Age ≥ 75 years (n=2908)	8.1	10.7	<0.001	18.4	21.2	<0.001	
Age < 75 years (n=2914)	10.0	12.9	<0.001	26.6	28.5	0.097	
Charlson Comorbidities ≥ 4 (n=2565)	8.2	10.8	<0.001	18.2	21.5	0.003	
Charlson Comorbidities < 4 (n=3257)	9.8	12.4	<0.001	25.6	27.9	0.038	
Cardiovascular disease (n=3611)	8.5	10.9	<0.001	19.4	22.7	<0.001	
Diabetes (n=2203)	8.6	12.2	<0.001	20.8	23.7	0.002	
Cardiovascular disease and diabetes (n=1607)	8.2	11.5	<0.001	18.9	23.0	0.003	
Cardiovascular disease or diabetes (n=4207)	8.6	11.4	<0.001	20.5	23.2	<0.001	
Renal Failure (n=1240)	7.2	10.5	0.002	16.6	19.4	0.054	
Liver Disease (n=581)	9.7	12.0	0.026	23.8	28.3	0.17	

**Fig. 1** Kaplan-Meier plot of overall survival of all patients based on initial treatment with either enzalutamide or abiraterone. Median months of survival reported. P-values calculated via Log-rank.

abiraterone with 2.7 months longer median OS (23.2 vs. 20.5 months, $p < 0.001$, Fig. 2C). In 1622 patients without cardiovascular disease or diabetes, there was no difference in survival (28.6 vs. 27.2 months, $p = 0.93$, Fig. 2D).

In an exploratory analyses, veterans who received only one treatment in addition to ADT for mCRPC were compared to veterans who received multiple subsequent treatments for mCRPC. Among 2550 veterans (43.8%) who received only an ARTA for mCRPC and no further treatments, median treatment duration with enzalutamide was 4.0 months longer compared to abiraterone (11.4 vs. 7.4 months, $p < 0.001$), with 5.5 months longer median OS (19.3 vs. 13.8 months, $p < 0.001$, Supplemental Fig. 1A). Veterans who received only one mCRPC treatment were older (78.2 vs. 73.1 years, $p < 0.001$) with higher mean CCI (4.6 vs.

3.9, $p < 0.001$) than veterans who received two or more mCRPC therapies. Among 3272 veterans (56.2%) who received two or more treatments for mCRPC, median treatment duration with enzalutamide versus abiraterone was longer (11.8 vs. 9.9 months, $p = 0.006$); however there was no significant difference in median survival (28.0 vs. 27.8 months, $p = 0.34$, Supplemental Fig. 1B).

Multivariable models

To account for baseline differences between veterans, we created both a Cox proportional hazards and propensity score matched model. In the multivariable Cox model, enzalutamide was associated with 11% decreased mortality versus abiraterone (adjusted Hazard Ratio (aHR) 0.89, 95% CI 0.84–0.95). In 4207 (72%) patients with cardiovascular disease and diabetes, enzalutamide was associated with a 13% decreased mortality (aHR 0.87, 95% CI 0.81–0.93, Table 3). Using age and cardiac comorbidities, a propensity score matched model with mCRPC was created (Supplementary Table 1). In 5006 matched Veterans, enzalutamide was associated with 10% decreased mortality versus abiraterone (aHR 0.90, 95% CI 0.84–0.96) and an increased treatment duration of 1.6 months (15.0 vs. 13.6, $p < 0.001$). In the matched cohort, enzalutamide was associated with 2.1 months longer survival than abiraterone (24.2 months vs. 22.1, $p < 0.001$).

Sensitivity analyses

To account for differences among veterans with mCRPC who were treated within the VHA versus those receiving care at non-VHA facilities, a cohort of veterans who had pathology results in VHA was evaluated. Among the 3584 veterans with pathology results (61.5%), initial treatment with enzalutamide versus abiraterone was associated with 2.7 months longer median treatment duration (12.1 vs. 9.4 months, $p < 0.001$) and 1.7 months longer median OS (24.7 vs. 23.0 months, $p = 0.025$), similar to the overall findings. Additionally, in 2625 patients with who had pathologic results and had cardiovascular disease or diabetes, initial treatment with enzalutamide versus abiraterone was associated with 2.8 months longer median treatment duration (11.9 vs. 9.1 months, $p < 0.001$)

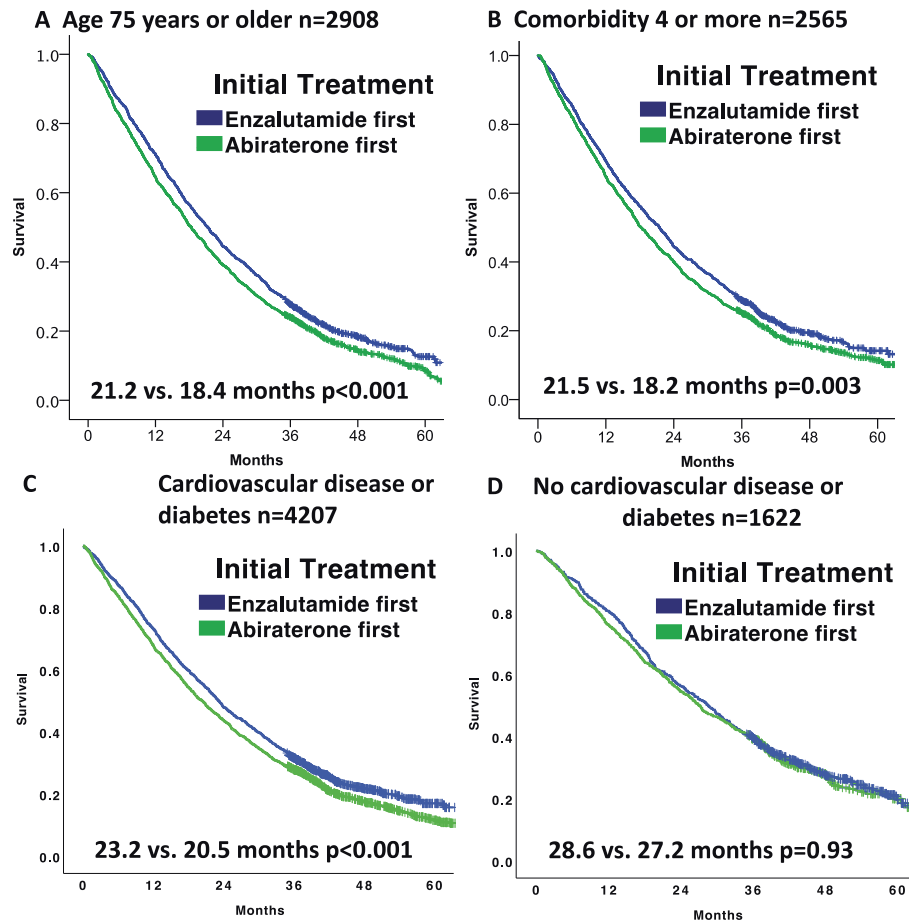


Fig. 2 Kaplan-Meier plots of overall survival in subgroups of patients treated initially with enzalutamide or abiraterone for mCRPC with median months of survival reported. *P*-values calculated via Log-rank. **A** 2908 patients aged 75 years or older when first treated. **B** 2565 patients with a Charlson comorbidity index of four or more. **C** 4207 patients with cardiovascular disease or diabetes. **D** 1622 patients without cardiovascular disease or diabetes.

and 2.3 months longer median OS (23.6 vs. 21.3 months, $p = 0.002$).

DISCUSSION

In this large, nation-wide study of mCRPC, US veterans with pre-existing cardiovascular disease or diabetes who received enzalutamide had longer treatment duration and median overall survival compared to those who received abiraterone. This difference highlights an important heterogeneity that can be used by clinicians to select treatments in patients with comorbid diseases. A similar difference was noted in older veterans (≥ 75 years of age) and veterans with a Charlson comorbidity index of ≥ 4 , in whom treatment with enzalutamide had longer treatment duration and OS compared to abiraterone. In multivariable models and propensity-score matched analyses, initial use of enzalutamide was also associated with a reduced risk of death, particularly in patients with cardiovascular disease or diabetes.

The increased treatment duration and longer OS with enzalutamide may result from improved efficacy or fewer adverse events, especially among veterans with cardiovascular disease and other comorbid diseases [13, 27]. Clinical trials of abiraterone and enzalutamide excluded patients with uncontrolled hypertension and clinically significant heart disease, therefore outcomes in these patients are unknown [1, 2]. In prior studies of mCRPC, treatment with enzalutamide was associated with lower rates of myocardial infarction, stroke, new or worsening hypertension,

heart failure, arrhythmia, and diabetes compared to abiraterone [28–30]. Observational studies have linked uncontrolled diabetes with poor response to abiraterone [31]. In our study, we identified an important interaction between veterans with mCRPC and cardiovascular disease or diabetes resulting in decreased survival with abiraterone, highlighting potential toxicity or decreased efficacy. In these veterans, enzalutamide was associated with a median of 2.4 months longer (28%) duration of treatment and a median of 3.3 months longer survival (17%).

Our analyses highlight additional important associations between other patient factors and OS. Black veterans ($n = 1351$, 23%) had improved survival (aHR 0.75) similar to other analyses [32] but were 3 years younger (mean 72.9 vs. 76.1 years, $p < 0.001$). While these differences have been proposed to be from testosterone levels and response to hormone treatment [33], prior studies of chemotherapy have also shown improved survival in Black patients with mCRPC [34] and improved survival and younger age at diagnosis in Black men is observed in lung cancer [35] and hematologic malignancies in the VHA [36, 37]. It is also interesting to note that increased BMI was associated with improved survival, which has been previously been seen in clinical trials in mCRPC [26, 38] and observational data in veterans with non-metastatic CRPC [39], but not in localized disease [40].

It is important for clinicians to consider the first choice of ARTA in a sequence of care. In this study, 52.4% of veterans with mCRPC received subsequent therapy after an ARTA, similar to other studies [41]. In veterans who received only one treatment and

Table 3. Association between patient and treatment characteristics and mortality in U.S. Veterans treated for mCRPC.

Variable	All Veterans <i>n</i> = 5822		Veterans with cardiovascular disease or diabetes <i>n</i> = 4207	
	aHR ^a	95% CI	aHR ^a	95% CI
Enzalutamide vs. Abiraterone	0.89	0.84–0.95	0.87	0.81–0.93
Age (per year increase)	1.02	1.01–1.02	1.01	1.01–1.02
Charlson Comorbidity Index, per point	1.05	1.04–1.06	1.04	1.03–1.06
Race: Non-black	Ref		Ref	
Black	0.75	0.70–0.80	0.76	0.70–0.83
PSA Category: 0–4	Ref		Ref	
4–10	1.18	1.03–1.36	1.18	1.01–1.39
10–20	1.46	1.28–1.67	1.37	1.18–1.60
20–50	1.63	1.44–1.84	1.52	1.32–1.76
50–100	2.12	1.86–2.41	2.05	1.76–2.38
100–200	2.38	2.07–2.74	2.23	1.90–2.63
200 +	2.80	2.45–3.20	2.84	2.42–3.32
unknown	2.08	1.75–2.47	1.85	1.50–2.27
Prior docetaxel	1.36	1.23–1.50	1.28	1.14–1.43
Prior bone-directed therapy	0.91	0.84–0.99	0.78	0.68–0.91
Bone-directed therapy after	1.17	1.09–1.25		
BMI Category: < 18.5	1.63	1.34–1.99	1.49	1.19–1.87
18.5 ≤ BMI < 25	Ref	0.72–0.84	Ref	0.73–0.87
25 ≤ BMI < 30	0.78	0.62–0.73	0.79	0.60–0.72
BMI ≥ 30	0.70	0.74–0.93	0.66	0.69–0.91
BMI unknown	0.83		0.79	
Hemoglobin: Hgb ≥ 10.0 g/dL	Ref		Ref	
Hgb < 10 g/dL	1.83	1.66–2.02	1.73	1.55–1.94
unknown	0.87	0.76–1.00	0.87	0.74–1.03
eGFR: ≥ 30 ml/min	Ref		Ref	
< 30	1.08	0.93–1.25	1.03	0.88–1.21
unknown	1.01	0.82–1.24	1.07	0.84–1.37
Bilirubin: < 2 mg/dL	Ref		Ref	
≥ 2 mg/dL	1.94	1.12–3.34	1.43	0.71–2.86
unknown	1.03	0.89–1.18	1.08	0.92–1.26
Albumin: > 3.0 g/dL	Ref		Ref	
≤ 3.0 g/dL	1.85	1.61–2.13	1.88	1.64–2.15
unknown	1.10	0.97–1.25	1.15	0.99–1.32

^aaHR Adjusted Hazard Ratio from Cox proportional hazard model. Variables include: Use of abiraterone vs. enzalutamide, Age, Charlson Comorbidity index Race (black vs. non-black), baseline, PSA Prior treatment with docetaxel, treatment with bone directed therapy (zoledronic acid or denosumab), treatment with bone-directed therapy after ARTA (time varying), BMI, baseline hemoglobin (hgb), eGFR, bilirubin, albumin.

never received docetaxel previously, enzalutamide was associated with 5.5 months longer median survival, a 40% increase versus abiraterone. It is possible that veterans who never received subsequent treatment either died or were medically unfit for

therapy due to adverse events or high comorbidity burdens. Among veterans with mCRPC who received abiraterone first and then received a second mCRPC treatment, there was no difference in OS compared to veterans who received enzalutamide. In this situation, the veterans who receive a second treatment could be considered to 'cross-over' and benefit from salvage treatment for mCRPC. Enzalutamide has activity after abiraterone in randomized trials [4] and observational studies [42]. However, sequential treatment with a second ARTA is not ideal if the patient is eligible for cytotoxic chemotherapy and maximizing the benefit of the first therapy is appropriate [43].

There are scant randomized, comparative data to inform treatment selection for patients with mCRPC. Furthermore, there are no published randomized trials that include patients with significant comorbidities similar to patients with mCRPC treated in the real world. Future trials comparing ARTAs are unlikely to identify differences in survival among patients of older age and/or with comorbid diseases (the subset of veterans associated with the largest treatment benefit), since these patients are unlikely to be included [5]. Therefore, observational large data analyses have the potential to guide treatment where clinical equipoise exists and comparative data is unavailable. Our study builds on prior studies [19, 20] by comparing abiraterone and enzalutamide treatment during a time period when the drugs had the same FDA indications, includes patients who received prior chemotherapy, and provides multiple analyses and models that adjust for a range of patient factors. By focusing on patients who are older and/or who have comorbid illnesses, our analyses give potentially actionable information from real-world data to guide treatment decisions.

LIMITATIONS

The primary limitation of this study is its retrospective observational design and unmeasured confounding. However, we adjusted our analyses for known confounders, performed sensitivity analyses, and included a time period where the two treatments had the same FDA-approved indications, similar rates of use, and no publicly reported studies had identified benefit of either agent among prostate cancer patients with hormone sensitive disease [44]. While there may be unknown biases in treatment selection, in patients without diabetes or cardiovascular disease, or who received two or more treatments, there were no differences in outcomes between the ARTAs, which supports the hypothesis that these medicines can be used interchangeably and have little differences in outcomes in fit patients. In addition, our data is subject to errors associated with studies of administrative datasets where diagnoses and comorbidities were based on ICD-9 or ICD-10 codes. We also performed analysis of veterans with pathologic diagnoses of mCRPC, excluding veterans who received care at non-VA medical centers and therefore a complete record of comorbid diseases may not be available.

CONCLUSIONS

These findings suggest that initial treatment with enzalutamide for mCRPC was associated with 2–3 months longer treatment duration and 10–20% overall longer survival compared to abiraterone. The benefit of enzalutamide was most notable among veterans with cardiovascular disease or diabetes, were 75 years or older, or with high comorbidity burdens. These data may guide treatment in metastatic hormone sensitive prostate cancer, where ARTAs are now commonly used and comorbidities likely have a similar impact on outcomes and adverse events in patients treated outside of clinical trials. Future studies are warranted to assess the effect of age and comorbidities on treatment duration and survival among men with metastatic hormone sensitive prostate cancer.

DATA AVAILABILITY

The dataset supporting the conclusions of this article will be shared upon request and execution of an agreement of use. Members of the scientific community can request a copy of the final dataset by e-mailing Dr. Martin Schoen at martin.schoen@va.gov. The investigator should state their reason for requesting the data and analysis plans. De-identified data will be provided after requestors sign a letter of agreement detailing the mechanisms by which the data will be kept secure and access restricted to their study team. The agreements will also state the recipient will not attempt to identify any individual whose data are included and will not share the data with anyone outside of their research team. Acknowledgement and attribution of scholarly effort is expected for any publication arising from shared data.

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AUTHOR CONTRIBUTIONS

Concept and design: MWS, KRC, KMS, SAE, BFD, YY. Data Analysis SL and MWS. Initial drafting of the manuscript: MWS. Critical manuscript review and approval by all authors. MWS takes responsibility for all aspects of the work.

COMPETING INTERESTS

All authors declare no competing financial interests or conflicts of interest related to this manuscript. Dr. Whitmer contributed to this work as an

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ADDITIONAL INFORMATION

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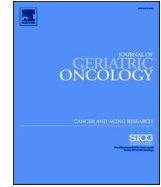
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Research Paper

Frailty and survival among veterans treated with abiraterone or enzalutamide for metastatic castration-resistant prostate cancer

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ABSTRACT

Introduction: Abiraterone and enzalutamide are treatments for metastatic castration-resistant prostate cancer (mCRPC). Due to a lack of head-to-head trials, they are prescribed interchangeably. However, the drugs have different pharmacokinetics and thus may have differing efficacy and adverse effects influenced by patient functional status and comorbid diseases. Additionally, mCRPC mainly affects older adults and since the prevalence of frailty increases with age, frailty is an important patient factor to consider in personalizing drug selection.

Materials and Methods: We conducted a retrospective observational study of US veterans treated with abiraterone or enzalutamide for mCRPC from September 2014 to June 2017. Frailty was assessed using the Veterans Affairs Frailty Index (VA-FI), which utilizes administrative codes to assign a standardized frailty score. Patients were categorized as frail if VA-FI scores were > 0.2 . The primary outcome was difference in overall survival (OS) between the two treatment groups. Cox regression modeling and propensity score matching was used to compare between abiraterone and enzalutamide treatments.

Results: We identified 5,822 veterans, 57% of whom were initially treated with abiraterone and 43% with enzalutamide. Frail patients ($n = 2,314$; 39.7%) were older, with a mean age of 76.1 versus 74.9 years in the non-frail group ($n = 3,508$; 60.3%, $p < 0.001$) and had shorter OS compared to non-frail patients regardless of treatment group (18.5 vs. 26.6 months, $p < 0.001$). Among non-frail patients there was no significant difference in OS between abiraterone and enzalutamide treatment (27.7 vs 26.1 months, $p = 0.07$). However, frail patients treated with enzalutamide versus abiraterone had improved OS (20.7 vs 17.2 months, $p < 0.001$). In a propensity score matched analysis of frail patients ($n = 2,070$), enzalutamide was associated with greater median OS (24.1 vs 20.9 months, $p < 0.001$). In patients with dementia, enzalutamide was associated with longer OS (19.4 vs. 16.6 months, $p = 0.003$).

Discussion: In this study of 5822 US veterans with mCRPC, treatment with enzalutamide was associated with improved OS compared to abiraterone among frail veterans and veterans with dementia, but not among non-frail veterans. Future studies should evaluate interactions between frailty and cancer treatments to optimize selection of therapy among frail adults.

1. Introduction

Prostate cancer is the most common cancer among men in both North America and Europe [1,2]. Despite having generally favorable outcomes, a subgroup of patients will develop metastatic disease. Although

this form of disease is initially responsive to androgen-deprivation therapy (ADT), commonly the cancer progresses to metastatic castration-resistant prostate cancer (mCRPC). Over the past decade, the development of oral therapies targeting the androgen receptor axis, androgen signaling inhibitors (ASIs), have improved overall survival

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(OS) among patients with mCRPC [3].

The two ASIs that have been available the longest are abiraterone (given in combination with prednisone) and enzalutamide. However, there has never been a randomized trial directly comparing treatment efficacy of these two drugs. Analyses of indirect comparisons have had mixed outcomes, with some suggesting similar efficacy [4,5] while others suggest that enzalutamide may be the preferred choice [6]. Since these drugs have different mechanisms of action and pharmacokinetics, it is conceivable that patient characteristics and comorbid diseases may selectively impact the safety and efficacy of either drug. Compared to abiraterone, enzalutamide has been associated with more psychiatric and vascular disorders, whereas abiraterone is associated with higher levels of cardiac and hepatobiliary disorders. Evidence from US veterans with cardiovascular disease or diabetes mellitus showed that enzalutamide was associated with longer OS compared to abiraterone, while patients without these comorbidities had no difference in OS [7]. Knowledge of safety and efficacy of the ASIs in comorbid populations could inform sequencing of the drugs and improve patient outcomes.

The risk of prostate cancer increases with age, with the median age of treatment for mCRPC is 75 years in the Veterans Health Administration (VHA) [2]. Thus, it is important to consider the effects of treatments in older patients who may be frail. Prior evidence suggests that abiraterone may be associated with improved quality of life in patients >75 years compared to enzalutamide [8] and some studies also associated enzalutamide with increased risk of falls [9] and cognitive impairment [10]. The risk of comorbid illnesses and frailty also increase with age [11]. Frailty is characterized by a loss of strength, endurance, physical ability, and cognitive function, resulting in impaired homeostasis maintenance abilities and decreased physiological reserve [12]. As such, frailty is associated with increased adverse outcomes and decreased OS in older adult patients with cancer [13]. In this study, we aimed to assess the association between frailty and treatment with abiraterone or enzalutamide and OS in US veterans with mCRPC using the Veterans Affairs Frailty Index (VA-FI) [14].

2. Methods

2.1. Study Population

The VHA Informatics and Computing infrastructure (VINCI) was used to identify patients treated with abiraterone or enzalutamide from September 2014 to June 2017. Patients were followed until April 2020 – the date of censoring. This period of time was selected since abiraterone and enzalutamide were only approved for the treatment of mCRPC and had the same indications prior to the release of data related to the use of abiraterone in metastatic hormone sensitive prostate cancer on June 2, 2017. This study was reviewed by the Saint Louis Veterans Affairs Medical Center Institutional Review Board and was performed in accordance with the Declaration of Helsinki.

2.2. Measurements and Covariates

We obtained international classification of diseases (ICD)-9/10 codes and laboratory data with the VINCI platform using the corporate data warehouse (CDW). Using data from the prior three years, we calculated the VA-FI score as reported using a publicly available code repository, except that we excluded codes for prostate cancer (185.x, C61.x) [14]. Updated in 2021 [14], the VA-FI is a deficit-accumulation method of determining frailty that uses administrative data codes to assign a frailty score based on the presence or absence 31 different disease categories as a cumulation of deficits (Table 1). Scores range from 0 (no deficit present) to 1 (all deficits present); see Supplemental Table 1 for list of deficits assessed. The redundancy in number of applicable codes and deficit categories was designed such that the final frailty score is accurate even if coding data is missing. Based on validated cut-points the VA-FI categorize patients as: non-frail (VA-FI ≤ 0.2) and frail (VA-FI > 0.2)

Table 1

Baseline characteristics of frail (VA-FI > 0.2) and non-frail (VA-FI ≤ 0.2) US veterans treated with abiraterone and enzalutamide for metastatic prostate cancer from 9/2014 to 6/2017, including prostate cancer diagnosis in VA registry and Gleason score. Abbreviations: BMI = Body-Mass Index, eGFR = estimated Glomerular Filtration Rate, ADT = Androgen Deprivation Therapy, VHA = Veterans Health Affairs, ASI = Androgen Signaling Inhibitor, PSA = Prostate Specific Antigen.

Demographic clinical characteristics	Total (n = 5822)		P-value
	Non-frail n = 3508	Frail n = 2314	
Age (mean years)	74.9	76.1	<0.001†
Charlson Comorbidity index (mean)	3.1	5.8	<0.001†
Elixhauser comorbidities (mean)	4.3	8.8	0.002‡
BMI (mean)	28.6	28.3	0.08
Race (% , n)			<0.001*
White	78.0 (2737)	69.9 (1617)	
Black	20.0 (703)	28.0 (648)	
Other	1.8 (63)	1.9 (45)	
Unknown	0.1 (5)	0.2 (4)	
eGFR (%)			<0.001*
≥ 30 mL/min	87.8	91.7	
<30 mL/min	2.3	5.6	
Unknown	9.9	2.7	
Anemia (%)			<0.001*
Hgb ≥ 10 g/dL	78.0	76.6	
Hgb < 10 g/dL	6.9	17.1	
Unknown	15.2	6.3	
Bilirubin (%)			<0.001*
<2 mg/dL	84.7	93.0	
≥ 2 mg/dL	0.2	0.3	
Unknown	15.1	6.7	
Albumin (%)			<0.001*
>3 g/dL	80.5	83.9	
≤ 3 g/dL	2.6	7.8	
Unknown	16.9	8.3	
ADT in VHA prior to ASI (% , n)	58.9 (2067)	78.2 (1809)	<0.001*
Docetaxel prior to ASI (% , n)	7.6 (268)	13.0 (300)	<0.001*
Docetaxel after ASI (% , n)	20.0 (703)	16.4 (379)	<0.001*
Prostate cancer diagnosis in VHA registry (% , n)	57.2 (2005)	68.2 (1579)	<0.001*
Gleason score (n)	7.9 (1535)	7.8 (1206)	0.82‡
PSA closest to start of ASI (median ng/mL, n)	27.1 (3063)	34.4 (2245)	0.056‡

† t-test.

* Chi-square test.

‡ Wilcoxon Two-Sample Test.

[15]. VA-FI has previously been shown to predict mortality among veterans with multiple myeloma and patients with cancer taking immune checkpoint inhibitors [15,16]. We further explored the varying degrees of frailty severity on OS by defining non-frail patients as VA-FI ≤ 0.1 , pre-frail as $0.1 < \text{VA-FI} \leq 0.2$, mildly frail as $0.2 < \text{VA-FI} \leq 0.3$, moderately frail as $0.3 < \text{VA-FI} \leq 0.4$, and severely frail as VA-FI > 0.4 [15].

VA Pharmacy Benefits Management (VA PBM) records were accessed to ascertain treatments for prostate cancer. ADT included treatment with leuprolide, triptorelin, goserelin, histrelin, and degarelix, or codes for orchiectomy. ASI treatment start date was determined as the date of the initial prescription for abiraterone or enzalutamide. Baseline demographics, including age and race, were collected at first prescription of enzalutamide and abiraterone. Laboratory data included prostate specific antigen (PSA), albumin, creatinine, and hemoglobin closest to and prior to treatment start, within six months prior to initiation. Creatinine clearance was calculated using the CKD-Epi formula. The Romano and Quan adaptations of the CCI was calculated based on ICD-9/10 codes obtained any time prior to treatment initiation with exclusion of prostate cancer [17,18]. Gleason score was calculated from first pathologic diagnosis of prostate cancer available in the CDW-Oncology registry for the subset of the population with a prostate biopsy

Table 2

Association between frailty and patient characteristics on mortality in U.S. veterans treated for mCRPC.

Variable	All Veterans n = 5822		Frail Veterans n = 2314	
	aHR#	95% CI	aHR#	95% CI
Enzalutamide vs. Abiraterone	0.88	0.83–0.94	0.87	0.79–0.95
VA-FI score	5.25	4.02–6.84	7.23	4.31–12.14
Age (per year increase)	1.01	1.01–1.02	1.01	1.00–1.01
Race: Non-Black	Ref		Ref	
Black	0.75	0.70–0.80	0.79	0.71–0.88
PSA Category: 0–4 ng/mL	Ref		Ref	
4–10 ng/mL	1.19	1.04–1.36	1.19	0.96–1.47
10–20 ng/mL	1.46	1.28–1.66	1.42	1.15–1.75
20–50 ng/mL	1.62	1.43–1.83	1.6	1.32–1.94
50–100 ng/mL	2.12	1.86–2.41	2.03	1.66–2.48
100–200 ng/mL	2.34	2.04–2.70	2.18	1.75–2.71
200+ ng/mL	2.8	2.48–3.24	2.65	2.14–3.26
unknown	2.09	1.76–2.48	2.22	1.64–3.00
Prior docetaxel	1.28	1.16–1.41	1.25	1.09–1.43
BMI Category: < 18.5	1.61	1.32–1.96	1.42	1.07–1.87
18.5 ≤ BMI < 25	Ref		Ref	
25 ≤ BMI < 30	0.79	0.73–0.85	0.84	0.75–0.95
BMI ≥ 30	0.67	0.62–0.73	0.66	0.59–0.75
BMI unknown	0.85	0.76–0.95	0.83	0.67–1.02
Hemoglobin: Hgb ≥ 10.0 g/dL	Ref		Ref	
Hgb < 10 g/dL	1.75	1.58–1.94	1.78	1.56–2.03
unknown	0.88	0.77–1.01	0.79	0.62–1.01
eGFR: ≥30 ml/min	Ref		Ref	
<30	1.1	0.95–1.28	0.99	0.81–1.20
unknown	1.02	0.83–1.25	0.95	0.65–1.39
Bilirubin: <2 mg/dL	Ref		Ref	
≥2 mg/dL	1.94	1.12–3.34	2.43	1.15–5.13
unknown	1.03	0.89–1.18	1.13	0.90–1.41
Albumin: >3.0 g/dL	Ref		Ref	
≤3.0 g/dL	1.8	1.57–2.07	1.83	1.53–2.18
unknown	1.13	1.00–1.27	1.31	1.07–1.59

aHR: Adjusted Hazard Ratio from Cox proportional hazard model. Variables include: Use of abiraterone vs. enzalutamide, VA-FI, Age, Race (Black vs. non-Black), baseline PSA, prior treatment with docetaxel, BMI, baseline hemoglobin (hgb), eGFR, bilirubin, albumin.

Table 2: Cox proportional hazard model of all patients (n = 5822) and frail patients with VA-FI > 0.2 (n = 2314) that shows the association between patient characteristics at baseline prior to treatment with abiraterone or enzalutamide and mortality. Abbreviations: aHR = adjusted Hazard Ratio, VA-FI = Veterans Affairs Frailty Index, PSA = Prostate Specific Antigen, BMI = Body-Mass Index, eGFR = estimated Glomerular Filtration Rate.

conducted at the VA.

2.3. Outcome Measures

The primary outcome was the difference in overall survival (OS) between the abiraterone and enzalutamide treatment groups. OS was defined as the time from date of initial prescription of abiraterone or enzalutamide to date of death or censoring. Secondary outcomes included: duration of treatment, calculated as the difference in days between the first and last prescription plus the number of days of treatment in the last prescription, and subsequent therapy for mCRPC, a second ASI (abiraterone or enzalutamide), docetaxel, cabazitaxel, sipuleucel-T, or mitoxantrone.

2.4. Statistical Analyses

Demographic and clinical characteristics were compared between patients using Chi-square, Student's t, Wilcoxon two-sample, or Kaplan-Meier curves with log-rank tests as appropriate. Cox proportional hazards regression modeling was used to assess the association between initial treatment and OS. The proportional hazard assumption was tested by using a time-dependent variable as an interaction term, which had a p value of 0.276; therefore, the proportional hazard assumption was not

violated. The following variables were clinically selected for inclusion in the full model: age, Black race [19], body-mass index (BMI) [20], prior treatment with docetaxel, PSA at time of first treatment, anemia (hemoglobin <10 g/dL), impaired creatinine clearance (CrCl <30 mL/min), bilirubin ≥2 mg/dL, and albumin <3 g/dL. Collinearity was tested in multivariate models by determining the variance inflation factor (VIF). No VIF values were >3 in final models. Missing variables were treated as a category and included in tables as 'unknown.' A multivariate cox model among the total population was used to assess the hazard risk of each frailty domain. A landmark analysis was conducted among frail patients with a minimum OS of six months to compare survival among abiraterone and enzalutamide treatment groups. For frail patients, a propensity score matched cohort was also created by matching age, race, CCI, and total VA-FI between abiraterone and enzalutamide treatment groups. Matching was 1:1 using a caliper of 0.01 with priority to exact matches. SAS 9.4 (SAS Inc., Cary NC) and SPSS 28 (IBM, Armonk NY) were used for analyses and to create figures. All p-values were 2-tailed with $p < 0.05$ determined as significant.

3. Results

Of the 5,822 patients identified, 57% were initially treated with abiraterone and 43% with enzalutamide as the initial ASI for mCRPC. The mean age was 75.4 years and 1,351 (23.2%) were Black. The median CCI was 3 (interquartile range [IQR] 3); see Supplemental Table 2 for complete listing of CCI categories. Based on the definition of frail patients as those with a VA-FI >0.2, there were 2,314 frail patients, representing 39.7% of the cohort. The median VA-FI score was 0.194 (IQR 0.161), which correlates to a median number of 6 VA-FI deficits per patient (IQR 5) (Fig. 1).

Compared to non-frail patients, frail patients were older: mean 76.1 years vs. 74.9 years ($p < 0.001$) and more likely to identify as Black (28% vs. 20%, $p < 0.001$). There was no significant difference in PSA level at initiation of treatment between frail and non-frail patients and, in patients with available pathologic data, there was no difference in Gleason score between frail and non-frail patients (Table 1). Frail patients were more likely to have received docetaxel prior to ASI (13.0% vs. 7.6%, $p < 0.001$) and more likely to have received ADT within the VHA prior to treatment with an ASI. Additional baseline characteristics of frail and non-frail patients are listed in Table 1.

Supplemental Table 3 lists the baseline VA-FI components in patients who were first treated with enzalutamide versus those treated with abiraterone. Patients who received enzalutamide as their first ASI were more likely to be frail compared to those prescribed abiraterone (44.8% vs. 41.8%, $p = 0.03$) and higher VA-FI score (0.203 vs. 0.192, $p = 0.004$). Also, patients with diabetes, heart failure, or kidney disease were more likely to be prescribed enzalutamide (see Supplemental Tables 2 and 3). Due to the potential association of enzalutamide with fatigue and impaired cognition, it is important to note that patients with cognition and mood deficits based on the VA-FI scores were prescribed abiraterone and enzalutamide at equal rates (33.4% vs. 34.4%, $p = 0.58$). However, patients with a diagnosis of dementia were more likely to be prescribed enzalutamide (13.5% vs. 10.3%, $p < 0.001$). There was no difference in prescriptions for abiraterone or enzalutamide based on falls (4.3% vs. 4.6%, $p = 0.65$). Median duration of first ASI treatment was 7.5 months (IQR 3.0–16) in frail patients, while non-frail patients were initially treated for a median of 9.2 months (IQR 4.0–19.7). Frail patients were less likely to receive any subsequent treatment for mCRPC compared to non-frail patients (47.6% vs. 56.1%, $p < 0.001$); see Supplemental Table 4.

Frail patients had decreased OS compared to non-frail patients (18.5 vs. 26.6 months, $p < 0.001$, hazard ratio [HR] 1.44, 95% confidence interval [CI] 1.35–1.52). Furthermore, increased severity of VA-FI frailty score was associated with an increased risk of mortality (Fig. 2). In patients with a score in the non-frail range (VA-FI ≤0.1, $n = 1471$) median survival was 29.1 months, pre-frail score range (VA-FI

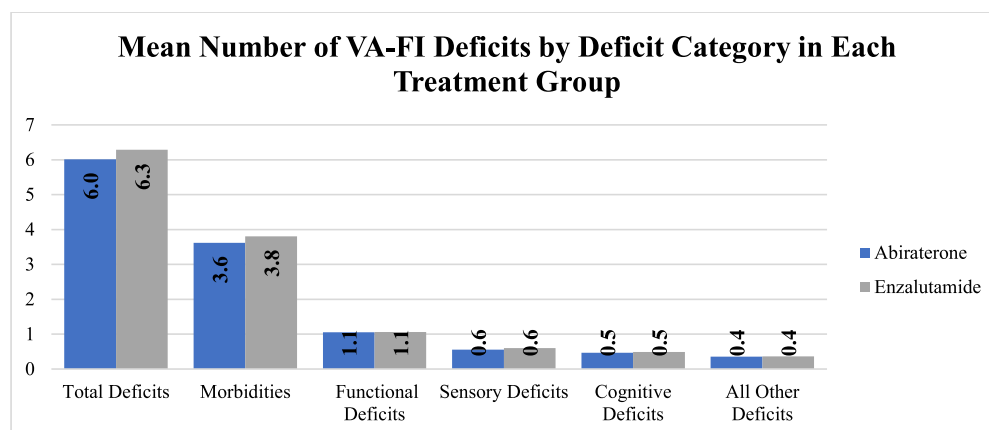


Fig. 1. Bar graph of mean number of baseline deficits present in patients treated with abiraterone and enzalutamide. Patients can have a total of 31 deficits from 5 subcategories (morbidities, function, sensory, cognition and mood, other). Abbreviations: VA-FI = Veterans Affairs Frailty Index.

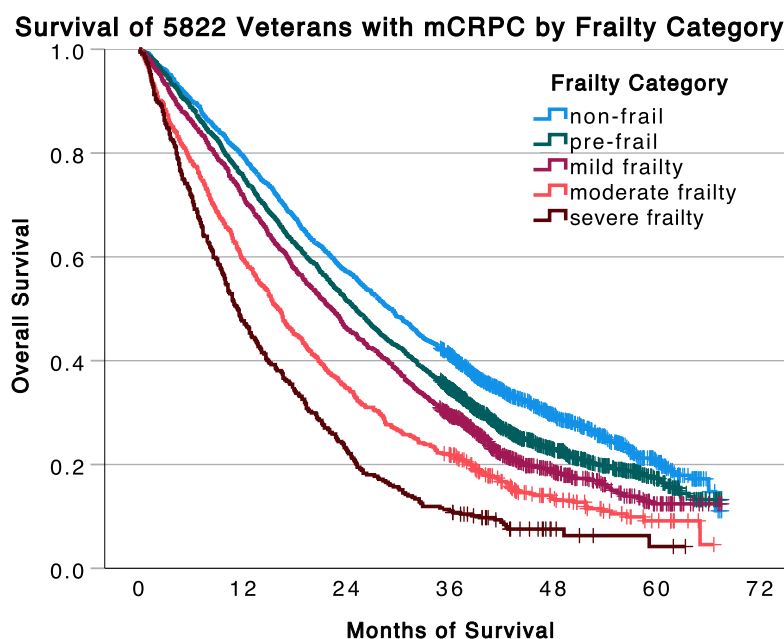


Fig. 2. Kaplan-Meier plot of overall survival of patients based on their frailty group. Patients were grouped as either non-frail, pre-frail, mildly frail, moderately frail, or severely frail. Among non-frail patients ($n = 1471$) median survival was 29.1 months, in pre-frail ($n = 2037$) patients 25.2 months, in mildly frail patients ($n = 1341$) 22.3 months, in moderately frail patients ($n = 629$) 16.1 months, and in severely frail patients ($n = 344$) 11.4 months ($p < 0.001$).

0.1–0.2, $n = 2037$) 25.2 months, mildly frail score range (VA-FI 0.2–0.3, $n = 1341$) 22.3 months, moderately frail score range (VA-FI 0.3–0.4, $n = 629$) 16.1 months, and severely frail score (VA-FI >0.4 , $n = 344$) 11.4 months ($p < 0.001$). In a multivariable Cox model, each increased frailty deficit was associated with increased mortality (adjusted hazard ratio [aHR] 1.33, 95% CI 1.25–1.41). In a Cox model that included all VA-FI domains as separate continuous variables, the HR for each increased deficit category are as follows; morbidities: aHR 1.05 (95% CI 1.04–1.07), functional: aHR 1.06 (95% CI 1.03–1.09), sensory loss aHR: 1.00 (95% CI 0.96–1.05), cognition and mood: aHR 1.05 (95% CI 1.00–1.09), and Other: aHR 1.11 (95% CI 1.05–1.17).

Among non-frail patients ($n = 3508$, 60.3%) there was no significant difference in OS between first ASI treatment with abiraterone versus enzalutamide (26.1 vs. 27.7 months, $p = 0.07$, HR 0.93, 95% CI 0.86–1.01) in univariate analyses. However, among frail patients ($n = 2314$, 39.7%), 1036 (45%) of patients treated with enzalutamide had a

3.5-month longer median OS compared to 1278 patients (55%) treated with abiraterone (20.7 vs. 17.2 months, $p < 0.001$, HR 0.85, 95% CI 0.77–0.93) (Fig. 3). Frail patients remained on enzalutamide longer than abiraterone (median 9.0 vs. 7.0 months, $p < 0.001$). In 2014 frail patients who had not previously received docetaxel, enzalutamide was associated with longer survival (21.5 vs. 17.6 months, $p < 0.001$).

In a multivariable Cox model of all patients that included overall frailty score but not CCI, enzalutamide was associated with a reduced risk of death (aHR 0.88, 95% CI 0.83–0.94). In a multivariable Cox model including only frail patients, enzalutamide was associated with reduced risk of death (aHR 0.87, 95% CI 0.80–0.96) when accounting for covariates. In a landmark analysis among frail patients who survived at least six months from start of first ASI ($n = 1901$), patients in the enzalutamide treatment group had an OS of 25.2 months versus 21.8 months in the abiraterone treatment group ($p < 0.001$). In a propensity matched cohort of 1988 frail patients, the enzalutamide treatment group

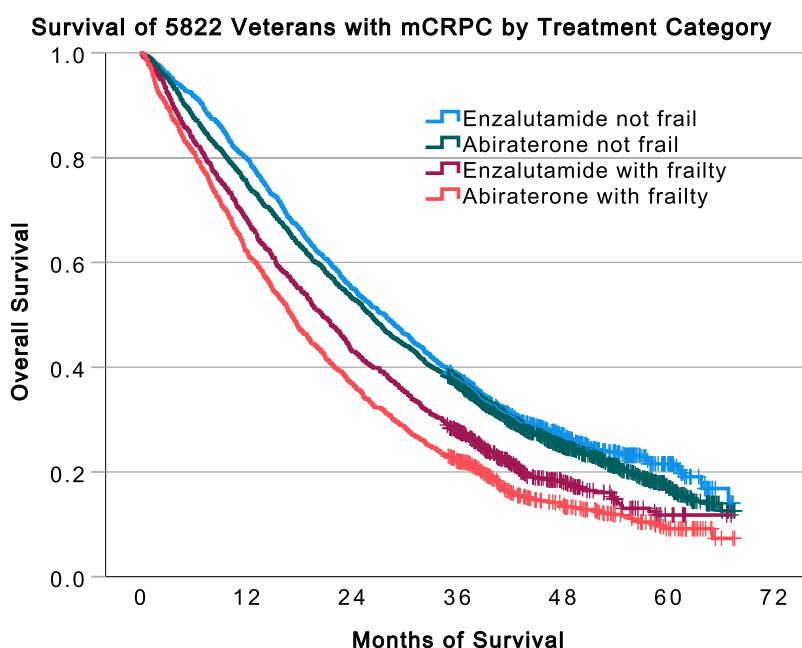


Fig. 3. Kaplan-Meier plot of overall survival of patients based on their treatment group (abiraterone vs. enzalutamide) and their frailty status (non-frail with VA-FI < 0.2 vs. frail with VA-FI > 0.2). The survival of 1036 veteran patients treated with enzalutamide was longer than 1278 frail veterans treated with abiraterone (20.6 vs. 17.1 months, $p < 0.001$). There was no difference in survival between 1468 non-frail veterans treated with enzalutamide compared to 2040 non-frail veterans treated with abiraterone (27.7 vs. 26.1 months, $p = 0.07$). Abbreviations: VA-FI = Veterans Affairs Frailty Index.

($n = 994$) had a 3.5-month greater median OS than the abiraterone group ($n = 994$) (20.7 months vs 17.2 months, $p < 0.001$). Matching was successful based on standardized differences of <0.1 in the matched variables and there were 326 unmatched frail patients, 42 treated with enzalutamide, and 284 with abiraterone. Characteristics of the propensity score matched analysis are available in Supplemental Table 5.

Due to the concern for changes in cognition with enzalutamide, a

Table 3

Association of patient characteristics on mortality in a propensity matched cohort of frail U.S. veterans treated for mCRPC.

Variable	Frail Propensity Matched Veterans ($n = 1988$)	
	aHR#	95% CI
Enzalutamide vs. Abiraterone	0.86	0.78–0.94
VA-FI score	5.25	4.02–6.84
Age (per year increase)	1.01	1.00–1.02
Race: Non-Black	Ref	
Black	0.76	0.68–0.85
PSA Category: 0–4 ng/mL	Ref	
4–10 ng/mL	1.24	0.99–1.57
10–20 ng/mL	1.49	1.19–1.86
20–50 ng/mL	1.66	1.35–2.04
50–100 ng/mL	2.16	1.74–2.68
100–200 ng/mL	2.41	1.90–3.07
200+ ng/mL	2.82	2.25–3.54
unknown	2.27	1.65–3.12
Prior docetaxel	1.24	1.07–1.45
BMI Category: < 18.5	1.43	1.07–1.91
18.5 ≤ BMI < 25	Ref	
25 ≤ BMI < 30	0.82	0.72–0.93
BMI ≥ 30	0.67	0.59–0.77
BMI unknown	0.76	0.61–0.95
Hemoglobin: Hgb ≥ 10.0 g/dL	Ref	
Hgb < 10 g/dL	1.87	1.62–2.16
unknown	0.8	0.62–1.03
eGFR: ≥30 ml/min	Ref	
<30	0.95	0.77–1.17
unknown	0.88	0.59–1.32
Bilirubin: <2 mg/dL	Ref	
≥2 mg/dL	1.93	0.86–4.33
unknown	1.19	0.93–1.53
Albumin: >3.0 g/dL	Ref	
≤3.0 g/dL	1.96	1.62–2.36
unknown	1.27	1.02–1.59

subgroup analysis of 1981 patients with deficits in the cognitive VA-FI domain was performed. In this group, enzalutamide was associated with similar survival to abiraterone (22.6 vs. 21.0 months, $p = 0.064$) and increased treatment duration (16.8 vs. 14.0 months, $p < 0.001$). In a subset of 680 patients with dementia based on VA-FI ICD codes, enzalutamide was associated with longer survival (19.4 vs. 16.6 months, $p = 0.003$) and increased treatment duration (16.2 vs. 12.7 months, $p = 0.002$). Additionally, in 257 patients with falls based on VA-FI, enzalutamide was associated with longer survival (19.6 vs. 14.4 months, $p = 0.048$) and increased treatment duration (15.0 vs. 11.1 months, $p = 0.036$). Additional subgroup analyses of frail patients who received ADT prior to ASI ($n = 1,809$) had longer survival with enzalutamide (21.7 vs. 18.0 months, $p = 0.003$) and frail patients who were entered in the CDW Oncology registry ($n = 1,919$) had longer survival with enzalutamide (21.7 vs. 18.2 months, $p = 0.004$).

4. Discussion

This study reports the overall survival of one of the largest cohorts of frail men treated for mCRPC. In veterans with mCRPC, frailty as determined by the VA-FI score was associated with increased mortality. In veterans, frailty was more predictive of mortality than choice of ASI. However, among frail patients (VA-FI > 0.2), treatment with enzalutamide compared to abiraterone was associated with improved OS in unadjusted and adjusted analyses using several different methods of accounting for covariates. Importantly, in men with dementia, enzalutamide was associated with longer survival. We found no deleterious effects in patients with falls or fatigue nor differential prescribing in patients with falls and fatigue, a common concern with enzalutamide [21,22]. These findings of similar or improved outcomes with enzalutamide in patients with frailty and cognitive disorders using real-world data may allay concerns that enzalutamide may lead to falls and cognitive decline.

Clinical trials of therapeutic agents often exclude patients with significant comorbidities, thus restricting the generalizability of their findings to the broader population [23]. This is especially important in mCRPC as it is a disease of older adults with a mean age of 75 years, of whom 40% were frail in this analysis. When adequately powered comparative studies are not available, retrospective cohorts can offer insight into risks and benefits in the real-world usage of these

medications. In patients not traditionally eligible for clinical trials or with limited access, such as frail or marginalized populations, large observational trials provide needed guidance for clinicians and can help to clarify outcomes in at-risk patients.

No large clinical trials have directly compared enzalutamide to abiraterone, although there have been trials of sequencing the two agents that shows that enzalutamide has activity after abiraterone [24]. In this cohort of veterans, only 47.6% of frail patients received another treatment for mCRPC, significantly less than non-frail patients, and therefore maximizing the benefit of the first ASI may be the most prudent strategy in frail patients. In this study, frail men were treated with enzalutamide for a longer period of time, likely reflecting improved efficacy or improved tolerance of this agent. Studies in the past have widely shown that enzalutamide tends to have a faster and greater PSA response, although concomitant survival benefit was only occasionally identified [25]. While sequencing agents is possible in patients who are younger with less comorbid disease, frail patients have significant competing risks for mortality, thus maximizing the benefit of the first therapy for mCRPC is a prudent strategy.

The inferior survival among frail patients with abiraterone may lie in the differing adverse effect profiles of abiraterone and enzalutamide. Studies have shown associations between ASI toxicities and comorbidities such as metabolic, cardiovascular, or neurological diseases, which are all more prevalent in frail populations than non-frail populations [26,27]. In particular, cardiovascular disease (CVD) is the most common comorbidity among the general population, and it is the greatest cause of death in men with prostate cancer. Among patients with prostate cancer, CVD incidence is high [28,29]. Abiraterone has been shown to significantly increase cardiac complications, an effect not seen in enzalutamide [23,27,30,31]. Furthermore, abiraterone is associated with higher hospitalization rates among those with pre-existing CVD compared to enzalutamide [32]. Specific cardiovascular toxicities associated with abiraterone use include hypertension, heart failure, fluid retention, and hypokalemia [31]. Thus, exacerbation of underlying CVD may be a mechanism for worsening OS among frail patients prescribed abiraterone.

Given concerns of polypharmacy among older adults, drug-drug interactions between ASIs and other prescription medications may be a contributing factor to disparate adverse events. Older adults with cancer are frequently subject to polypharmacy. In one UK study of patients with metastatic cancer (38% prostate), patients reported using a median of seven medications (range 1–17) [33]. Furthermore, frail adults take a greater number of prescription medications than non-frail adults [34]. While relatively safe, both enzalutamide and abiraterone affect numerous physiological pathways and thus present a major concern for drug-drug interactions in older adults with polypharmacy. Adverse outcomes include hospitalization, mortality, and increased odds of ASI discontinuation [35].

Both abiraterone and enzalutamide have significant drug-drug interactions, and abiraterone interacts with several cardiac medications largely due to differential inhibition of cytochrome p450 enzymes [36,37]. Abiraterone is a strong inhibitor of CYP2C8 (amiodarone drug interaction), and 2D6 (hydrocodone drug interaction); enzalutamide is a strong inducer of CYP3A4 (apixaban, clopidogrel, nimodipine, and warfarin drug interaction) and p-glycoprotein (dabigatran, edoxaban) [38]. Thus lower OS among frail older adults prescribed abiraterone may be attributable to underlying drug interactions and related adverse events. Abiraterone treatment is coupled with low dose prednisone, usually at 10 mg/day. Abiraterone is a CYP3A17 inhibitor that impairs both production of cortisol and androgens, resulting in an increase of mineralocorticoid related adverse effects, including hypertension, hypokalemia, and fluid retention. Glucocorticoid replacement at near physiologic levels with prednisone suppresses the production of mineralocorticoid precursors. Although the dose of prednisone is low relative to other indications, the dosing is still above the upper end of the physiological level and does not follow physiological diurnal variation

[39]. The use of prednisone for prolonged periods has been shown to lead to increased incidence of glucocorticoid related adverse events, including hyperglycemia and diabetes as well as adrenal insufficiency.

This study showed that veterans with dementia had inferior overall survival and survival was worse among patients taking abiraterone compared to enzalutamide. Medication adherence is a concern among cognitively impaired individuals [40]. Medication non-adherence is more likely to negatively impact abiraterone over enzalutamide due to differences in medication dosing and pharmacokinetics. The mean half-life of enzalutamide is 5.8 days, when compared to abiraterone, which is 12 h. Furthermore, enzalutamide has decreased pill burden since it is only taken only once per day, whereas abiraterone requires one pill a day plus prednisone once or twice a day. Thus, among cognitively impaired patients who are more likely to be non-adherent to medications, the impact of missed doses would be greater in abiraterone than enzalutamide.

5. Limitations

The primary limitation of this study is that the data is observational, and associations in observational data may be impacted by residual confounding and missing data. Additionally, the VA-FI only uses administrative data to assess frailty, which is less precise compared to directly measured comprehensive frailty assessments. However, this assessment is readily available across a large group of real-world patients and can be easily integrated in medical records software. While there may be unknown biases in treatment selection, including a slight preference for physicians selecting frail patients for enzalutamide, we found no significant differences in outcomes between the ASIs in non-frail patients, which supports the hypothesis that these medicines can be used interchangeably and have little differences in outcomes in fit patients. Additionally, our population of frail patients with dementia was limited, therefore this study has limited ability to discern differences in this subgroup.

It is important to note that frail patients were included in the VA Oncology registry and received ADT within the VHA at a higher rate than non-frail patients. While this could represent increased use of VA services by frail patients, it also could represent that many patients receive care outside of the VHA and, therefore, additional codes to determine frailty were not available within the VHA. This study classifies patients based on their initial ASI in the VA; it is possible patients may have received prior ASI treatment outside the VA. Additionally, diagnosis of mCRPC was assumed since only veterans initially treated from September 2014 to June 2017 were included. During this time abiraterone and enzalutamide had the exact same FDA indications for mCRPC and off-label use of these drugs in the VA is limited. Coding for mCRPC and ‘hormone resistant malignancy’ is poor in VA records and therefore cannot be confirmed using administrative data. Lastly, this cohort comprised US veterans treated within the VHA and may not apply to other populations.

6. Conclusions

In this large cohort of veterans treated for mCRPC with abiraterone and enzalutamide, many patients were frail and increased frailty was highly associated with decreased overall survival. In frail men, enzalutamide was associated with longer survival than abiraterone, including patients with dementia. Future studies should evaluate frailty assessment for clinical decision-making to identify patterns of deficits and their impact on cancer outcomes to refine treatment selection. A more detailed assessment of frailty phenotypes or classes [41] may elucidate treatment effect heterogeneity and facilitate personalization of drug regimens based on patient characteristics. Further studies should assess adverse events with ASIs in frail patients and the outcomes of treatment of metastatic hormone sensitive prostate cancer, where ASIs are now commonly used.

Authorship Contributions

Conceptualization: ED, MS, KS
 Study design: MS, ED, KS, MF
 Data acquisition: MS, SL
 Quality control of data and algorithms MS, SL
 Data analysis and interpretation: all authors
 Statistical analysis: MS, SL, ED, MF
 Manuscript preparation: ED, MS
 Manuscript editing: all authors
 Manuscript review: all authors

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Table 3: Cox proportional hazard model of matched frail patients with VA-FI > 0.2 ($n = 1988$) that shows the association between patient characteristics at baseline prior to treatment with abiraterone or enzalutamide and mortality. Abbreviations: aHR = adjusted Hazard Ratio, VA-FI = Veterans Affairs Frailty Index, PSA = Prostate Specific Antigen, BMI = Body-Mass Index, eGFR = estimated Glomerular Filtration Rate.

Declaration of Competing Interest

Tanya M. Wildes reports consulting fees from Sanofi, Carevive Systems, and grants from Janssen. Hira Mian reports honoraria and consulting fees from Janssen, GlaxoSmithKline, Pfizer, Sanofi, Takeda, Amgen, and Abbvie. Martin W. Schoen reports an honorarium from Pfizer for a lecture on Real-World Data in Oncology.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jgo.2023.101520>.

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Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer With Abiraterone or Enzalutamide

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Abstract

Abiraterone and enzalutamide are used to treat advanced or metastatic prostate cancer. We compared hospitalizations during initial treatment among 19,775 U.S. veterans. We found that when accounting for prior hospitalizations, patients started on enzalutamide were hospitalized less frequently compared to abiraterone.

Background: Abiraterone and enzalutamide are second generation androgen receptor pathway inhibitors (ARPIs) used to treat advanced or metastatic prostate cancer. Without head-to-head comparative studies identifying 1 agent as preferred initial therapy, physician preferences guide initial ARPI choice. This study compares hospitalizations among patients treated initially with abiraterone versus enzalutamide. **Patients and Methods:** United States veterans treated with abiraterone or enzalutamide between May 13, 2011 and December 31, 2019; then compared hospitalization rate during first treatment with ARPI in the Veterans Healthcare Administration. Baseline incidence rate of hospitalization was determined from data 1 year prior to ARPI. Incidence Rate Difference (IRD) was calculated using χ^2 test and difference in IRD using Poisson Regression. **Results:** 19,775 veterans were identified; 13,527 (68.4%) were initially treated with abiraterone and 6248 (31.6%) initially with enzalutamide. The enzalutamide cohort was older (75.8 vs. 74.5 years, $P < .001$) and had higher baseline comorbidities at ARPI initiation (4.4 vs. 4.0, $P < .001$). Patients were treated with enzalutamide longer than abiraterone (median 9.0 vs. 8.0 months, $P < .001$). Total hospitalizations increased from 465 per 1000 person-years in the year prior to treatment with abiraterone to 567 during treatment. Total hospitalizations increased from 417 per 1000 person-years in the year prior to treatment with enzalutamide to 430 during treatment. Total rate of hospitalization increased 22% for abiraterone compared to a 3% increase for enzalutamide in the 12 months after ARPI initiation ($P < .0001$). Abiraterone was associated with greater increase in rates of acute heart failure, atrial fibrillation, acute kidney injury, urinary tract infections, sepsis, and pneumonia. **Conclusion:** By comparing the rate of hospitalization before vs. during treatment, real world analyses identified a 22% versus 3% increase in hospitalizations with abiraterone compared to enzalutamide respectively, despite being used in a younger population with less comorbid disease. Abiraterone was also associated with higher risk of infections, a novel finding.

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Key words: Adverse events, Toxicity, Comparative effectiveness, Veterans, Oncology outcomes

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Introduction

Two next generation oral androgen receptor pathway inhibitors (ARPI) abiraterone and enzalutamide became available in the U.S. in 2011 and 2012 respectively after demonstrating improvement in overall survival (OS) among patients with mCRPC.^{1,2} Currently these therapies are used interchangeably due to lack of head-to-head randomized phase 3 trials, but there may be differences in outcomes due to toxicities. In real-world observational studies, enzalutamide is associated with longer OS,³ especially among patients with cardiovascular disease, diabetes, older age, or higher comorbidity burdens.⁴ More research is needed to determine risks associated with these therapies in patients outside of clinical trials.

Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer

Adverse event (AE) profiles for these drugs differ in real-world studies, which may result from their different mechanisms of action. Abiraterone blocks androgen biosynthesis by inhibiting steroid 17-hydroxylase/17, 20-lyase [CYP17A1], thereby inhibiting synthesis of testosterone.¹ However, blockade of androgen synthesis shunts steroid precursors away from testosterone, resulting in additional production of mineralocorticoids that can result in hypokalemia, hypertension, fluid retention, and heart failure.⁵ Therefore abiraterone is administered with prednisone to suppress the adrenal axis and prevent mineralocorticoid excess.⁶ Due to prednisone, patients treated with abiraterone are at risk of infections due to immune suppression and adrenal insufficiency during acute illness.⁷ Adrenal insufficiency is associated with a 1.5 times higher incidence of infections and hospitalizations, potentially increasing infectious complications in patients treated with abiraterone.⁸

Enzalutamide is an androgen-receptor–signaling inhibitor that inhibits nuclear translocation of the androgen receptor, DNA binding, and coactivator recruitment.² Adverse events associated with enzalutamide include hypertension, falls/fractures, ischemic heart disease, seizures, diarrhea, and fatigue.^{9,10} Enzalutamide does not result in excess mineralocorticoid production and therefore does not require concurrent prednisone, which could contribute to better tolerability among people who are at high risk for developing mineralocorticoid excess or adrenal insufficiency.

Most safety recommendations for abiraterone and enzalutamide rely on adverse events in phase III registration trials.^{11–13} However, patients in clinical trials are screened and have fewer comorbid diseases and risk of AEs compared to real-world patients. Prior studies have identified that hospitalizations occur at high rates among patients taking abiraterone,¹⁴ more than those treated with enzalutamide.^{15,16} In patients with cardiovascular disease, increased rates of hospitalization and mortality were found with abiraterone compared to enzalutamide.¹⁷ Observational cohort studies of patients receiving abiraterone or enzalutamide have not always included a large enough cohort of patients with comorbid conditions to assess if adverse event profiles differed between medicines.¹⁸

The US Veterans Health Administration (VHA) treats many men with advanced prostate cancer and comorbid disease in an integrated care delivery system. This large cohort facilitates the study of known adverse events, such as cardiovascular AEs while also allowing for investigation new AEs, such as infections that may result from prednisone use and adrenal insufficiency. Therefore, we studied the frequency and cause of hospitalizations before and during treatment with abiraterone versus enzalutamide to understand AEs among patients treated for metastatic castrate-resistant prostate cancer to guide clinical decision making.

Materials and Methods

Data and Study Population

The VHA Informatics and Computing Infrastructure (VINCI) was used to access the Corporate Data Warehouse (CDW) database to identify patients with prostate cancer treated with abiraterone or enzalutamide. Veterans were included if the first prescription of abiraterone or enzalutamide was between May 13, 2011 and December 31, 2019 with no evidence of prior ARPI therapy.

Patients in this dataset were followed until April 2022. This study was reviewed by the Saint Louis Veterans Affairs Medical Center Institutional Review Board and was performed in accordance with the Declaration of Helsinki.

Outcomes and Covariates

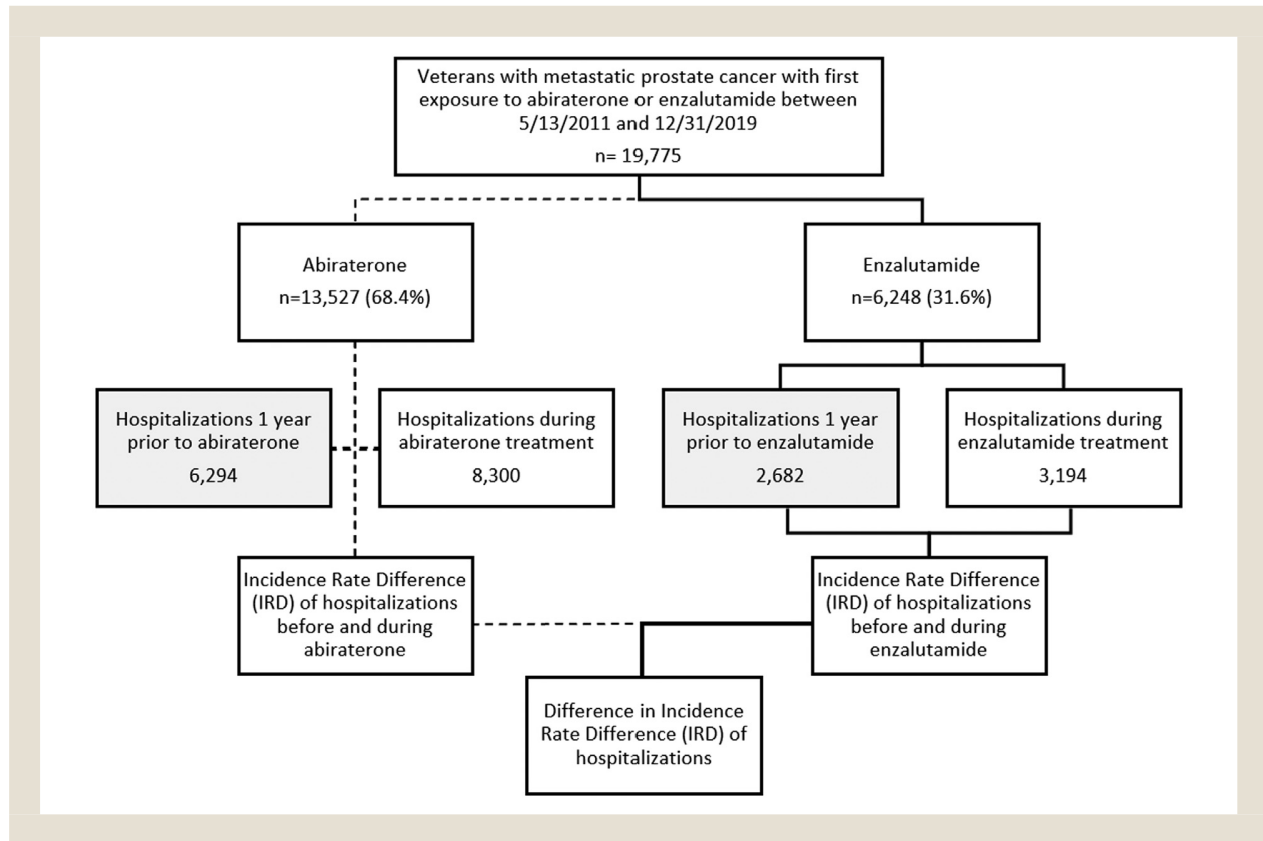
Using the CDW inpatient MedSAS¹⁹ file, hospitalizations of patients were identified during the study period and the ICD-9/10 codes associated with each hospitalization were collected. The first 3 ICD-9/10 codes were used to identify the cause(s) for hospitalization. The number of ICD code occurrences in the top 3 positions were summed to determine the prevalence of each code (first code only data in Table S3). We define 2 time periods for hospitalization, a 1-year period prior to treatment initiation and the time during treatment with abiraterone or enzalutamide. The treatment duration was calculated from date of the first prescription to the date of the last prescription plus the number of days included in the last prescription.

Using ICD codes, patients hospitalized for the following reasons were identified: (1) acute heart failure or decompensation, (2) ischemic stroke, (3) ischemic heart disease, (4) atrial fibrillation (Afib), (5) Torsade de Pointe/QT prolongation, (6) seizure or convulsion, (7) acute kidney injury (AKI), (8) hepatitis, and (9) infections. Infections were defined by ICD 9 or 10 codes falling into the following 3 categories: pneumonia²⁰, urinary tract infection, and sepsis (Supplemental Table 1). Incidence rates for hospitalization were calculated as the number of hospital admissions (events) per 1000 person-years of exposure to the drug while on treatment with an active prescription. Additionally, rates of hospitalization were calculated during the 1 year look back period prior to ARPI initiation so the difference in the rate of hospitalization before and after treatment could be calculated for each cohort, similar to previously published methods²¹ and thus use patients as their own controls to manage known and unknown confounders that lead to hospitalization.

Baseline demographics collected at initiation of treatment included race, age, prostate specific antigen (PSA), and prior docetaxel use. Laboratory data included PSA, albumin, creatinine, and hemoglobin prior to treatment start and within 6 months of therapy initiation. Missing laboratory data was reported as unknown. Creatinine clearance was calculated using the CKD-Epi formula. The Romano and Quan adaptations of the Charlson Comorbidity index were calculated based on ICD-9/10 codes obtained any time prior to treatment initiation while excluding prostate cancer from the malignancy category.^{22,23} Months of filled prescriptions were collected from Pharmacy Benefits Management and were used to determine length of treatment. Patients were assigned to the abiraterone or enzalutamide cohort based on which treatment they received first. Subsequent therapy for mCRPC was also collected including a second ARPI (abiraterone or enzalutamide), docetaxel, cabazitaxel, sipuleucel-T, or mitoxantrone.

Statistical Analyses

Demographic and clinical characteristics were compared between abiraterone and enzalutamide cohorts using chi-square, Student's t-test, ANOVA, or Wilcoxon 2-sample tests. The incidence rate differ-

Figure 1 Overall study schema.

ences (IRD) in the rate of hospitalization 1 year prior to initial treatment compared to during treatment with either abiraterone or enzalutamide were calculated with the χ^2 method with a 95% confidence interval. To compare the IRD between abiraterone and enzalutamide, a Poisson regression with treatment by time period interaction was used to estimate the difference in incidence rate difference (IRD) between the rate of hospitalizations during treatment with abiraterone or enzalutamide, see Figure 1 for a schema of cohort creation and analytic plan. If a patient received the opposite agent as a second treatment, that period of time was not included in the analysis. SAS 9.4 (SAS Inc., Cary NC) was used for analyses and SPSS 28 and Microsoft Excel were used to create figures. All *P*-values were 2-tailed with *P* < .05 determined as statistically significant.

Results

A cohort of 19,775 US veterans diagnosed with prostate cancer between May 13, 2011 and December 31, 2019 who received treatment with either abiraterone or enzalutamide was identified. Among them, 13,527 (68.4%) patients were treated with abiraterone and 6248 (31.6%) with enzalutamide as initial ARPI treatment (Figure 1). The mean age of patients treated with abiraterone and enzalutamide was 74.5 and 75.8 years respectively (*P* < .001, Table 1) and 23% identified as black. The mean Charlson comorbidity index was 4.0 and 4.4 for the abiraterone and enzalutamide

cohort respectively (*P* < .001). A comparison of baseline characteristics can be found in Table 1. Notably, the enzalutamide cohort had higher baseline rates of prior myocardial infarction (MI), congestive heart failure (CHF), hypertension (HTN), diabetes mellitus (DM), cardiac arrhythmias, cerebrovascular disease (CVD), peripheral vascular disease (PVD), renal disease, and liver disease.

Patients were prescribed abiraterone for a median of 8.0 months (intraquartile range (IQR) 3.5-15) compared to 9.0 months (IQR 4.0-17) with enzalutamide (*P* < .001 by ANOVA). Crossover occurred more frequently in the patients initially prescribed abiraterone, with 40.6% later treated with enzalutamide, compared to those initially treated with enzalutamide, with 33.1% later treated with abiraterone (*P* < .001). Patients initially treated with abiraterone were more likely to receive subsequent therapy for mCRPC (45.4% vs. 37.1%, *P* < .001).

Of the 11,494 hospitalizations that occurred in 5320 veterans (26.9% of cohort) during first ARPI treatment, 8300 (72.2%) occurred while on abiraterone during 14,639 person-years of observation, which is a rate of 567 hospitalizations per 1000 person-years. With enzalutamide 3194 (27.8%) hospitalizations occurred during 7428 person-years of observation, which is a rate of 437 hospitalizations per 1000 person-years. Both the abiraterone and enzalutamide cohorts had a median of 1 hospitalization during treatment (IQR 0-3). Compared to patients with no hospitalizations in the year prior to treatment, hospitalized patients were younger (mean

Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer

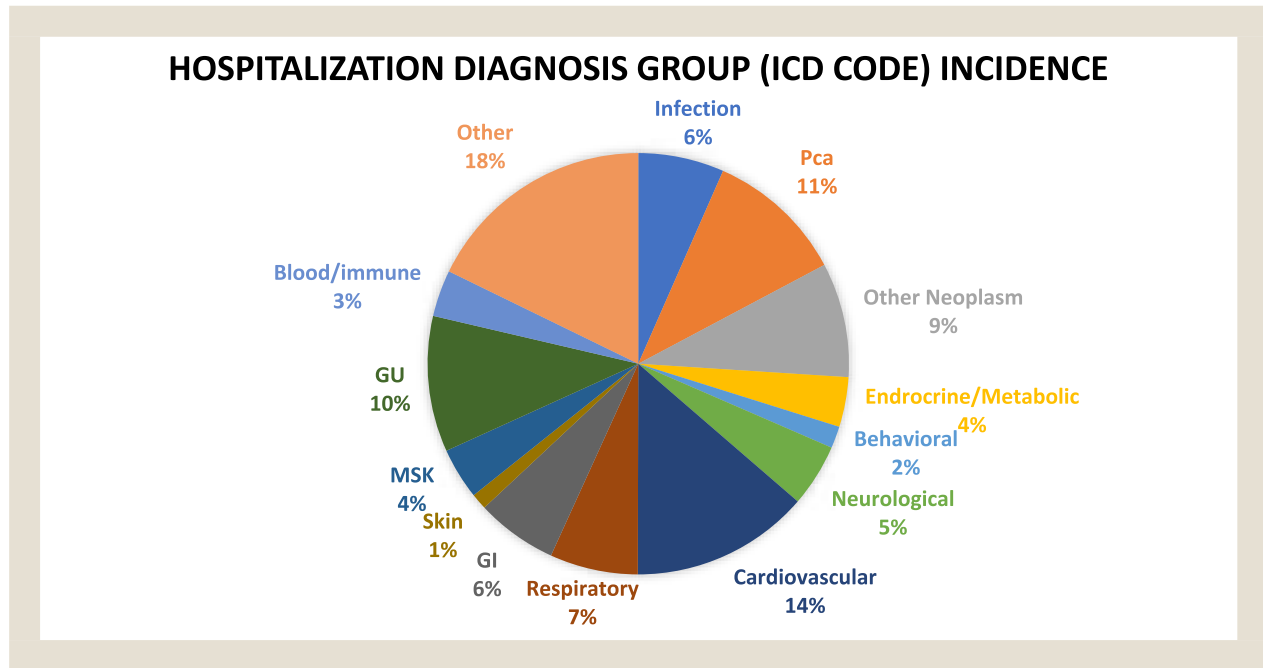
Table 1 Comparison Between Veterans First Prescribed Abiraterone Versus Enzalutamide From May 13, 2011 to December 31, 2019

Demographic Clinical Characteristics	Total (N = 19,775)		P-value
	First Prescribed Abiraterone n = 13,527	First Prescribed Enzalutamide n = 6248	
Age (mean years)	74.5	75.8	< .001 ^b
Charlson comorbidity index	4.0	4.4	< .001 ^b
Elixhauser comorbidities	5.8	6.3	< .001 ^b
Race (%)			.40 ^a
White	74.8	73.7	
Black	23	23.9	
Other	2.0	2.2	
Unknown	0.2	0.2	
EGFR (%)			.03 ^a
≥30	86.2	86	
<30	3.8	3.2	
Unknown	10	10.8	
Anemia (%)			< .0001 ^a
Hgb ≥ 10	75.7	74.4	
Hgb < 10	10.9	9	
Unknown	13.4	16.7	
Bilirubin (%)			< .0001 ^a
<2	86.9	83.8	
≥2	0.3	0.4	
Unknown	12.8	15.8	
Albumin (%)			< .0001 ^a
>3	78.7	77.6	
≤3	6.2	28.2	
Unknown	15	17.2	
Docetaxel prior to ARPI (%)	15.6	7.9	< .0001 ^a
Received subsequent treatment for mCRPC (%), n	45.4 (6142)	37.1 (2321)	< .0001 ^a
Charlson comorbidity categories			
Myocardial infarction (%)	9.4	11.3	< .0001 ^a
Diabetes (%)	35.1	41.9	< .0001 ^a
Hypertension (%)	81.1	83.9	< .0001 ^a
Congestive heart failure (%)	16.2	20.1	< .0001 ^a
Peripheral vascular disease (%)	20.7	24.4	< .0001 ^a
Cerebrovascular disease (%)	16.6	19.1	< .0001 ^a
Renal disease (%)	19.8	21.7	.002 ^a
Liver disease (%)	10.2	11.6	.002 ^a

^a χ^2 test.^b T-test.

74.5 vs. 75.2 years, $P = .002$) with higher mean Charlson comorbidity scores (5.2 vs. 3.9, $P < .001$). Admissions due to prostate cancer and cancer metastasis were the most frequent diagnosis for hospitalization contributing approximately 1/5th of total hospitalizations. Cardiovascular, genitourinary, respiratory, and infections were the most frequent non-neoplastic diagnoses among hospitalizations (Figure 2).

In the year prior to treatment with an ARPI, there were a total of 6294 hospitalizations out of 13,527 person-years in the abiraterone cohort (rate of 465 per 1000 person-years) compared to 2682 hospitalizations out of 6428 person-years (rate of 417 per 1000 person years) in the enzalutamide cohort. Total hospitalization incidence rate difference (IRD) increased by 103 per 1000 person years (22%) with abiraterone versus 20 per 1000 person years

Figure 2 Incidence of ICD diagnosis codes for hospitalization among entire cohort.

(3%) with enzalutamide (Figure 3), indicating a 19% larger increase in hospitalization rate from baseline among the abiraterone cohort ($P < .001$).

In the 1 year prior to initiation of ARPI, 8976 hospitalizations occurred in 4683 of the veterans (23.7% of cohort). This high rate of hospitalization indicates a high baseline risk of adverse events in the population prior to treatment. Compared to patients with no hospitalizations in the year prior to treatment, hospitalized patients were younger (mean 73.8 vs. 75.3 years, $P < .001$) with higher mean Charlson comorbidity score (5.5 vs. 3.7, $P < .001$). Veterans who were hospitalized in the year prior to ARPI treatment were at higher risk of being hospitalized in the year after initiation of an ARPI (41.9% vs. 15.0%, relative risk 2.79, 95% confidence interval 2.65-2.93).

When assessing indication for hospitalization during the treatment period, hospitalizations for heart failure increased by 65% in the abiraterone cohort, compared to 23% in the enzalutamide. Acute kidney injury also increased by 4.6% in patients treated with abiraterone compared to a 21% decrease in patients treated with enzalutamide. Atrial fibrillation increased by 67% in the abiraterone cohort compared to a decrease of 8.5% in the enzalutamide cohort. The 3 infections of interest showed a significant difference in difference, there was a 44% increase in urinary tract infections, a 114% increase in sepsis, and a 93% increase in pneumonia with abiraterone vs. enzalutamide when comparing the rate of infections during treatment to 1 year prior. (Table 2 and S2, Figure 4 and 5)

Discussion

In this cohort of 19,755 patients who initiated abiraterone or enzalutamide, we found that there was a larger increase in the rate of hospitalization in veterans treated with abiraterone compared to

Table 2 Difference in Incidence Rate Difference (IRD) Between Abiraterone and Enzalutamide Cohorts Using Poisson Regression to Compare Rate of Outcome in 1 Year Prior to Treatment Versus During Treatment With ARPI. Higher Numbers Indicate Increased Risk With Abiraterone

Outcome	diff of IRD	P-Value
Acute heart failure or decompensation	6.3	.005
Ischemic stroke	-1.7	.44
Ischemic heart disease	3	.17
Atrial fibrillation (Afib)	11.9	< .0001
Torsades de pointe and QT interval prolongation	0.7	.58
Convulsion/seizure	0.9	.45
Acute kidney injury (AKI)	15.9	.001
Hepatitis	0.8	.72
Urinary Tract Infections (UTI)	17.4	.008
Sepsis	15.3	< .0001
Pneumonia	19.6	< .0001
Total hospitalization	88.9	< .0001

enzalutamide. By comparing the rate of hospitalizations in the 1 year before treatment to the rate of hospitalizations during treatment in a large integrated healthcare system, this analysis allows veterans to serve as their own controls to study the rate of hospitalization during treatment with ARPIs. In addition to total hospitalizations, there were statistically greater increases in hospitalization for certain diagnoses that could result from AEs from abiraterone including congestive heart failure, atrial fibrillation, acute kidney injury, and common infections (eg, urinary tract infections, sepsis, pneumo-

Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer

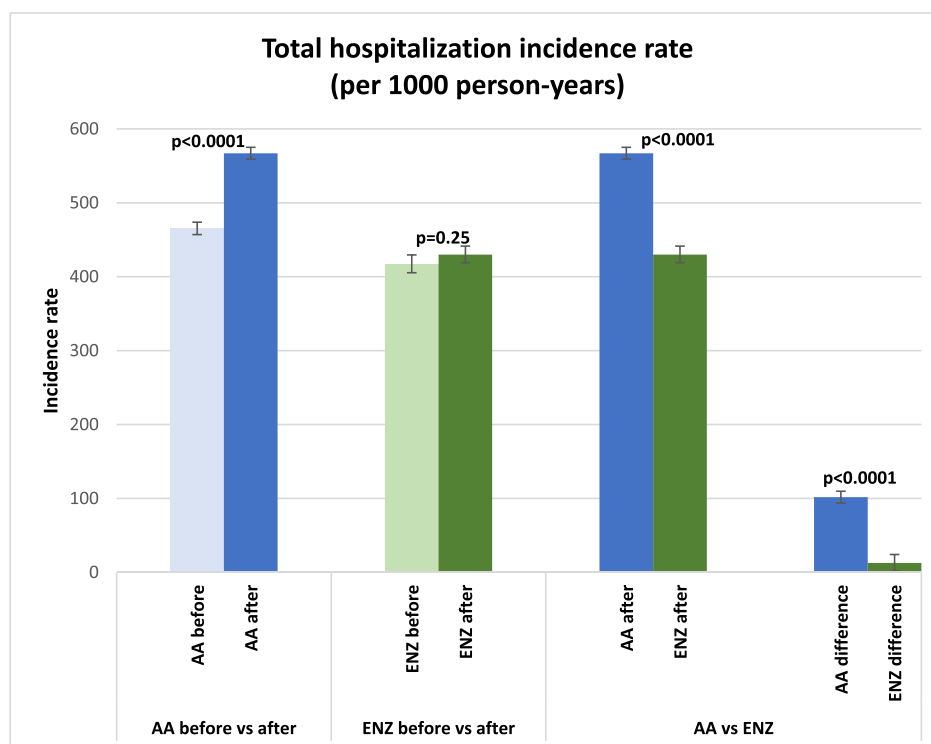
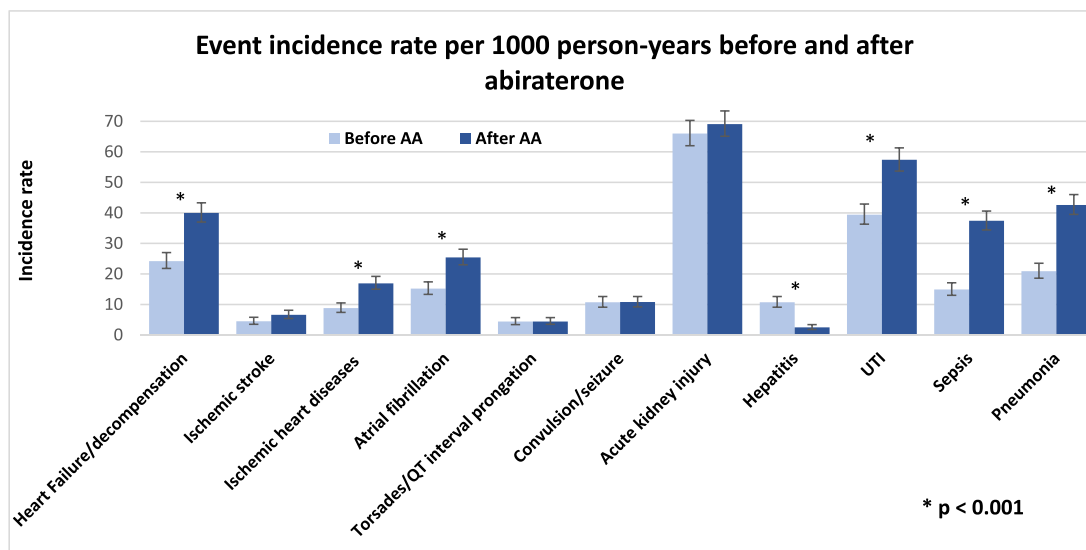
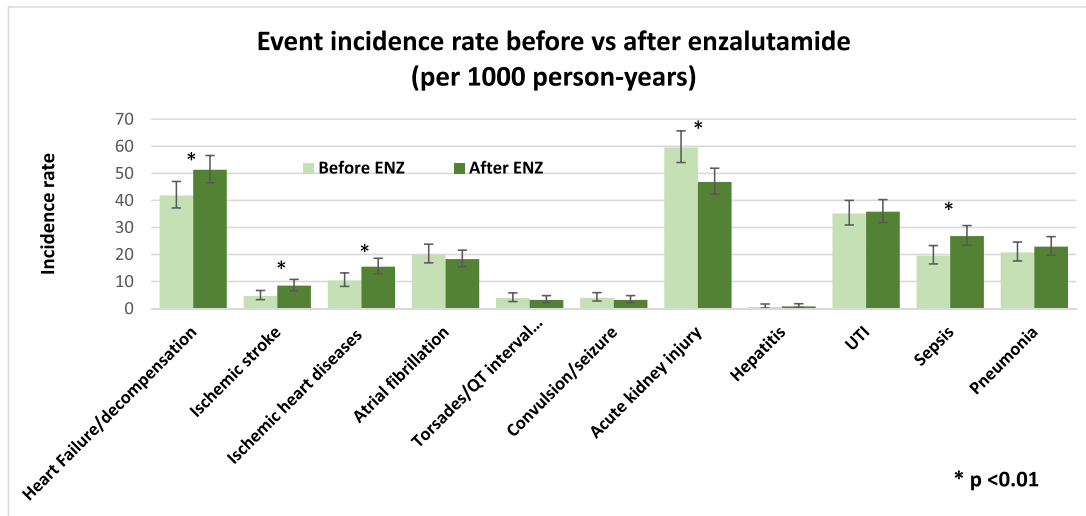
Figure 3 Hospitalization Incidence Rate before and after ARPI initiation between abiraterone (AA) and enzalutamide (ENZ).**Figure 4** Specific event incidence rate before and after abiraterone (AA) initiation.

Figure 5 Specific event incidence rate before and after enzalutamide (ENZ) initiation.

nia) among people who initially received abiraterone compared to enzalutamide.

It is important to consider these data in a larger context. In this study, we show that patients treated with abiraterone have more adverse events and are then later treated at a higher rate with subsequent treatments for mCRPC. Prior studies have shown that abiraterone is associated with inferior survival in real-world data,^{3,4,24} particularly in patients who are frail.²⁵ The mechanism of the association between impaired survival and abiraterone may result from increased adverse events. Our study supports the finding of increased adverse events with abiraterone that has been identified by others using similar methods.¹⁶ Possible etiologies for this difference include fewer drug-drug interactions and drug-disease interactions. For example, abiraterone is both a substrate and inhibitor of the cytochrome P450 pathway, which could lead to increased drug-drug interactions.²⁶

While increased risk of cardiovascular events with abiraterone has been well described in numerous observational studies,^{14,27} our study is the first to highlight an increased risk of infection with abiraterone compared to enzalutamide. In patients treated with abiraterone, patients had a higher incidence rate difference of urinary tract infections, sepsis, and pneumonia. Chronic corticosteroid therapy can lead to both immunosuppression as well as adrenal insufficiency, which can increase risk of infection.²⁸ In addition, patients who become corticosteroid dependent need an increase in corticosteroid dosage when they acquire an infection or have increased stress, which may increase likelihood of hospitalization for simple infections.²⁹ This suggests that the difference in mechanism of action of abiraterone and co-administration of corticosteroids while on abiraterone may be of clinical significance affecting infection frequency and severity.

It is important to note that there was significant heterogeneity in the populations treated with ARPIs. In the abiraterone cohort, there was higher rate of previous docetaxel use while the enzalutamide cohort was older with higher rates of comorbid conditions. These baseline differences in population effect the baseline rate of hospitalization in each group. Patients initiated on enzalutamide had a 25%-higher baseline of heart failure related hospitalizations (20.1% vs.16.2%) compared to abiraterone. Despite this higher risk at baseline, during the first year of ARPI therapy, patients on abiraterone had a 65% increase in heart failure admissions compared to 23% increase in the enzalutamide cohort. Both abiraterone and glucocorticoids are associated with worsening heart failure, which could explain the greater increase in IRD during the first year of ARPI therapy.^{9,30} Atrial fibrillation was also common among men in this cohort and is associated with use of both ARPIs.⁹ The incidence of atrial fibrillation increased 67% among the abiraterone cohort after treatment initiation, with no significant increase among the enzalutamide cohort (difference in IRD from baseline of 11.9, $P < .001$). Corticosteroid use could be contributing to the increase in atrial fibrillation in the abiraterone cohort as corticosteroids are associated with increased risk of atrial fibrillation and flutter.³¹

There was a strong association between comorbidity score and risk of hospitalization before and after ARPI treatment. Prior hospitalization was strongly associated with future hospitalization. Patients who were hospitalized in the year prior were 2.8-times more likely to be hospitalized during treatment with an ARPI compared to those who were not hospitalized in the year prior. Interestingly, younger age was associated with increased hospitalizations before and after treatment with an ARPI. Clinicians could consider comorbidities and assess the number of hospitalizations in the year prior to determine which patients are at risk for increased hospitalization with ARPI treatment.

Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer

Limitations

Our study is limited by its retrospective observational design; therefore, causation cannot be determined. Another limitation is potential misclassification of ICD codes in determining reason of hospitalization; however, the methods used in this study has been previously used²⁰ and are unlikely to lead to a systematic difference in coding between patients treated with abiraterone compared to enzalutamide. Additionally, it was not possible to determine if patients developed new medical complications of treatment compared to exacerbation of chronic disease because ICD codes such as heart failure and atrial fibrillation fail to distinguish between initial versus chronic presentation at hospitalization.

Additionally, data from patients who may have been hospitalized outside of the VA with no claims for reimbursement by the VA were not available. This limitation was minimized by including only those veterans that fill their ARPI through the VA and are therefore more likely to receive care through the VA. Additionally, there is unlikely to be a difference in non-VA hospitalizations between abiraterone and enzalutamide. Lastly, we were unable to determine the exact prostate cancer diagnosis for which the ARPI was used as the drugs acquired different indications over time. However, the stage of prostate cancer and slight differences in the timing of drug approvals are unlikely to change the risk of hospitalizations, which are likely driven by comorbid conditions, not stage of prostate cancer.

Strengths

This is one of the largest cohorts of patients treated with ARPIs and was derived from a diverse population that has more equitable access to medical care and oncologic treatments. The number of patients and complete medical records available for review allow for robust determination of differences in hospitalizations of patients who are prescribed these medications in a real-world cohort of patients with mCRPC. Additionally, patients in this cohort were elderly, with high rates of comorbidities, which reflects real-world use of the ARPIs for prostate cancer. Therefore, the results from this study are generalizable to many patients treated in routine clinical practice. Another strength of this study is the determination of baseline hospitalization rates (assessed 1 year prior to treatment) to allow longitudinal comparison of hospitalizations before and after treatments, thus allowing patients to serve as their own controls and minimizing heterogeneity of patient characteristics and prior treatment between ARPIs.

Conclusion

This large retrospective analysis provides real-world data on adverse events during ARPI treatment. Despite the older age and higher comorbidity burden among enzalutamide users at baseline, the rate of hospitalization was higher among patients treated with abiraterone. Abiraterone was associated with increased rates of hospitalization for heart failure, atrial fibrillation, acute kidney injury, as well as 3 common infections (urinary tract infection, pneumonia, and sepsis) compared to enzalutamide. The increased risk of hospitalization and adverse events may explain the inferior survival seen in real-world studies of these agents that include elderly patients with higher burden of comorbid conditions. Clinicians

should be aware that hospitalizations are common in this patient population and appropriately select treatments based on individual patient risk of drug-specific adverse events.

Clinical Practice Points

- In US veterans, enzalutamide was prescribed to older patients with higher rates of comorbid conditions.
- Abiraterone was associated with increased rates of hospitalization for cardiac, renal, and infectious events compared to enzalutamide.
- Clinicians should consider patient comorbid conditions and treatment adverse event profiles when selecting therapies for metastatic castrate-resistant prostate cancer.

CRedit authorship contribution statement

Forest Riekhof: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Yan Yan:** Methodology, Formal analysis. **Charles L. Bennett:** Conceptualization, Writing – review & editing. **Kristen M. Sanfilippo:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Kenneth R. Carson:** Conceptualization, Writing – review & editing. **Su-Hsin Chang:** Methodology, Formal analysis, Writing – review & editing. **Peter Georgantopoulos:** Methodology, Writing – review & editing. **Suhong Luo:** Formal analysis, Data curation. **Srinivas Govindan:** Data curation. **Nina Cheranda:** Data curation. **Amber Afzal:** Writing – review & editing. **Martin W. Schoen:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

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Disclosure

The authors have stated that they have no conflicts of interest.

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Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer

Supplementary materials

Table S1 ICD 9 and ICD 10 codes used to define specified events of interest

Event	ICD 10	ICD 9
Hospitalization for acute heart failure	I50.x	428.x
Hospitalization for ischemic stroke	I63.xx, G45.xx	434.01, 434.11, 434.91, 433.01, 433.11, 433.21, 433.91, 433.90, 433.31, 433.81, 997.02,
Hospitalization for ischemic heart diseases	I21.x, I22.x, I23.x, I24.x, I20.x	410.x, 411.x
Hospitalization for atrial fibrillation	I48.x	427.3x,
Hospitalization for convulsion/seizure	G40.x, G41.x, R56.9	345.x, 780.x
Hospitalization for acute renal failure	N14.1, N14.2, N14.4, N99.0, N17.x, N19.x, R392	584.x, 586.x, 583.89
Hospitalization for hepatitis	K71.0, K71.1, K71.2, K71.6, K71.8, K71.9, K72.0, K75.2, K75.9, K76.2, K76.7, Z94.4	573.3, 070.x, 571.42, 570.x, 572.4, V42.7
Hospitalization for infections	J13.x-J18.x, N39.0, A40.x-A41.x, R65.20	480.x-486.x, 599.0, 995.91, 995.92

Table S2 Number of events and crude incidence rates in the overall population first 3 ICD codes

Adverse event hospitalization outcome	Total events in overall population N = 19,955	Abiraterone treatment n=13,527			Enzalutamide treatment n=6428		
		Events during treatment	person-years	Incidence per 1000 person-years (95% CI)	Events during treatment	person-years	Incidence per 1000 person-years (95% CI)
Acute Heart Failure	967	586	14638.9	40.0 (37.0 - 43.3)	381	7428.2	51.3 (46.5 - 56.6)
Ischemic stroke	160	97	14638.9	6.6 (5.4 - 8.1)	63	7428.2	8.5 (6.6 - 10.8)
Ischemic heart diseases	363	248	14638.9	16.9 (15.0 - 19.2)	115	7428.2	15.5 (12.9 - 18.6)
Atrial fibrillation	508	372	14638.9	25.4 (23.0 - 28.1)	136	7428.2	18.3 (15.5 - 21.6)
Torsades de pointe and QT interval prolongation	89	65	14638.9	4.4 (3.5 - 5.7)	24	7428.2	3.2 (2.2 - 4.8)
Convulsion/seizure	182	158	14638.9	10.8 (9.2 - 12.6)	24	7428.2	3.2 (2.2 - 4.8)
Acute kidney injury	1360	1012	14638.9	69.1 (65.1 - 73.4)	348	7428.2	46.8 (42.3 - 51.9)
Hepatitis	42	36	14638.9	2.5 (1.8 - 3.4)	6	7428.2	0.8 (0.4 - 1.8)
Urinary Tract Infection	1106	840	14638.9	57.4 (53.7 - 61.3)	266	7428.2	35.8 (31.8, 40.3)
Sepsis	746	547	14638.9	37.4 (34.4 - 40.6)	199	7428.2	26.8 (23.4 - 30.7)
Pneumonia	794	624	14638.9	42.6 (39.5 - 46.0)	170	7428.2	22.9 (19.7 - 26.6)
Total hospitalization	11494	8300	14638.9	567.0 (559.0 - 575.1)	3194	7428.2	430.0 (418.9 - 441.4)
1 year prior to treatment							
Adverse event hospitalization outcome	Total events in overall population N = 19,955	Events prior to treatment	person-years	Incidence per 1000 person-years (95% CI)	Events prior to treatment	person-years	Incidence per 1000 person-years (95% CI)
Acute Heart Failure	597	328	13527.0	24.2 (21.8 - 27.0)	269	6428	41.8 (37.2 - 47.0)
Ischemic stroke	91	61	13527.0	4.5 (3.5 - 5.8)	30	6428	4.7 (3.3 - 6.7)
Ischemic heart diseases	186	119	13527.0	8.8 (9.4 - 10.5)	67	6428	10.4 (8.2 - 13.2)
Atrial fibrillation	335	206	13527.0	15.2 (13.3 - 17.4)	129	6428	20.0 (16.9 - 23.8)
Torsades de pointe and QT interval prolongation	85	60	13527.0	4.4 (3.4 - 5.7)	25	6428	3.9 (2.6 - 5.8)
Convulsion/seizure	171	145	13527.0	10.7 (9.1 - 12.6)	26	6428	4.0 (2.8 - 5.9)
Acute kidney injury	1276	893	13527.0	66.0 (62.0 - 70.3)	383	6428	59.6 (54.0 - 65.7)
Hepatitis	149	145	13527.0	10.7 (9.1 - 12.6)	4	6428	0.6 (0.2 - 1.7)
Urinary Tract Infection	760	534	13527.0	39.4 (36.3 - 42.9)	226	6428	35.2 (30.9 - 40.0)
Sepsis	328	202	13527.0	14.9 (13.0 - 17.1)	126	6428	19.6 (16.5 - 23.3)
Pneumonia	417	283	13527.0	20.9 (18.6 - 23.5)	134	6428	20.8 (17.6 - 24.6)
Total hospitalization	8976	6294	13527.0	465.3 (457.0 - 473.8)	2682	6428	417.2 (405.4 - 429.5)

Hospitalizations Among Veterans Treated for Metastatic Prostate Cancer

Table S3 Number of events and crude incidence rates in the overall population first ICD code only

Adverse event hospitalization outcome	Abiraterone treatment n=13,527				Enzalutamide treatment n=6428			
	Events during treatment	person-years	Incidence per 1000 person-years	Incidence per 1000 person-years (95% CI)	Events during treatment	person-years	Incidence per 1000 person-years	Incidence per 1000 person-years (95% CI)
Acute Heart Failure	128	14638.9	8.7	7.4 - 10.4	90	7428.2	12.1	8.8 - 13.6
Ischemic stroke	70	14638.9	4.8	3.8 - 6.0	45	7428.2	6.1	4.5 - 8.1
Ischemic heart diseases	107	14638.9	7.3	6.0 - 8.8	45	7428.2	6.1	4.5 - 8.1
Atrial fibrillation	172	14638.9	11.7	10.1 - 13.6	48	7428.2	6.5	4.9 - 8.6
Torsades de pointe and QT interval prolongation	34	14638.9	2.3	1.7 - 3.3	8	7428.2	1.1	0.5 - 2.2
Convulsion/seizure	88	14638.9	6	4.9 - 7.4	19	7428.2	2.6	1.6 - 4.0
Acute kidney injury	257	14638.9	17.6	15.5 - 19.8	74	7428.2	10	7.9 - 12.5
Hepatitis	7	14638.9	0.5	0.2 - 1.0	2	7428.2	0.3	0.1 - 1.1
Urinary Tract Infection	291	14638.9	19.9	17.7 - 22.3	96	7428.2	12.9	10.6 - 15.8
Sepsis	334	14638.9	22.8	20.5 - 25.4	140	7428.2	18.8	16.0 - 22.2
Pneumonia	248	14638.9	16.9	15.0 - 19.2	55	7428.2	7.4	5.7 - 9.6
Total hospitalization	8300	14638.9	567	554.9 - 579.3	3194	7428.2	430	415.3 - 445.2
1 year prior to treatment								
Adverse event hospitalization outcome	Events during treatment	person-years	Incidence per 1000 person-years	Incidence per 1000 person-years (95% CI)	Events during treatment	person-years	Incidence per 1000 person-years	Incidence per 1000 person-years (95% CI)
Acute Heart Failure	81	13527	6	4.8 - 7.4	83	6428	12.9	10.4 - 16.0
Ischemic stroke	49	13527	3.6	2.7 - 4.8	22	6428	3.4	2.3 - 5.2
Ischemic heart diseases	55	13527	4.1	3.1 - 5.3	40	6428	6.2	4.6 - 8.5
Atrial fibrillation	84	13527	6.2	5.0 - 7.7	45	6428	7	5.2 - 9.4
Torsades de pointe and QT interval prolongation	12	13527	0.9	0.5 - 1.6	11	6428	1.7	0.9 - 3.1
Convulsion/seizure	88	13527	6.5	5.3 - 8.0	14	6428	2.2	1.3 - 4.7
Acute kidney injury	272	13527	20.1	19.9 - 22.6	96	6428	14.9	12.2 - 18.2
Hepatitis	0	13527	0	0	0	6428	0	0
Urinary Tract Infection	173	13527	12.8	11.0 - 14.8	62	6428	9.6	7.5 - 12.4
Sepsis	109	13527	8.1	6.7 - 9.7	85	6428	13.2	10.7 - 16.4
Pneumonia	111	13527	8.2	6.8 - 9.9	52	6428	8.1	6.2 - 10.6
Total hospitalization	6294	13527	465.3	453.9 - 476.9	2682	6428	417.2	401.7 - 433.3