The Cardiovascular Effects of Abiraterone and Enzalutamide Among Veterans Affairs Metastatic Castration-Resistant Prostate Cancer Patients

Onur Baser[1,2], Erdem Baser[2], Gabriela Samayoa, MD, MPH[2]

[1]City University of New York, NY, USA; [2]Columbia Data Analytics, New York, NY, USA

Columbia Data Analytics

 cdanyc.com

Conflict of Interest Statement/Disclosures

The authors have no conflicts of interest to disclose in relation to this presentation or the medications described herein.

Columbia Data Analytics

BACKGROUND

- Prostate cancer (PC) is the **second most common cancer in the US**,[1] comprising 14.7% of all new cancer cases and approximately 34,700 annual deaths[2] **and is the sixth-leading cause of cancer mortality in men.[3]**
- Metastatic castration-resistant prostate cancer (mCRPC) is the **most frequent cause of prostate cancer-related death.[3]**
- Men who progress to CRPC have a poor prognosis, with a median overall survival of <2 years.[2,4]
- **Cardiovascular disease (CVD) is the primary cause of non-cancer mortality in men with PC.**[5]
- **Androgen deprivation therapy (ADT)** is central to treating locally advanced and metastatic disease, aiming to inhibit testosterone production or its function and halt cancer growth.

Abiraterone and Enzalutamide

- **Abiraterone acetate** (AA; Zytiga®), an androgen biosynthesis inhibitor, and **enzalutamide** (ENZ; Xtandi®) an androgen receptor signaling inhibitor, standard hormonal therapies, are important additions to ADT in PC treatment**, showing efficacy and tolerability in various settings (pre- and post-chemotherapy).**[3]
- AA and ENZ have been proven to **increase survival for patients with CRPC and more recently for those with metastatic hormone-sensitive disease naive to hormonal agents**.[6,7]
- Concerns have arisen regarding treatment-related adverse metabolic and CV-related effects, particularly due to **the higher risk of CV adverse events (AEs) linked to ADT use in a population which is already susceptible to CVD.**

Columbia Data Analytics

Study Relevance

Objective

Examine incidence of CV AEs in patients using AA and ENZ in the VA PC population

CVD Morbidity

CVD: Predominant non-cancer cause of death in this population.[5]

CVD contributes to 30.2% of fatalities in patents with PC.[8]

Knowledge Gap

Limited availability of real-world data studies on ADT use

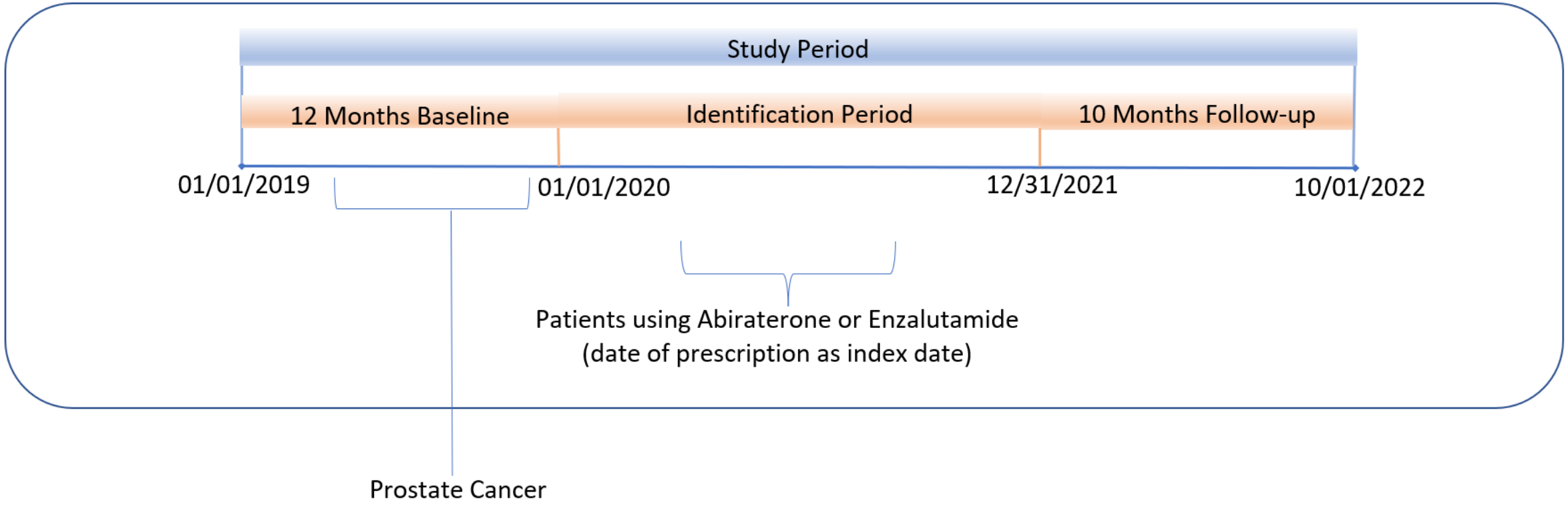
(e.g., AA and ENZ)

Columbia Data Analytics

Methods: Study Design

Retrospective Cohort Study

US Veterans Affairs (VA) population, January 1, 2019 - October 1, 2022



Columbia Data Analytics

METHODS

Inclusion Criteria

A1. ≥1 pharmacy claim for AA during identification period (01JAN2020-12DEC2021)

A2. ≥1 pharmacy claim for ENZ during identification period

- For A1 and A2: First prescription claim date = treatment index date

B. ≥1 PC diagnosis claim prior to the index date

Exclusion Criteria

Patients were excluded if they had:

A. Claim for AA and/or ENZ prior to identification period (to identify new users)

B. Claim for both AA and ENZ on index date

C. CV-related comorbidities prior to index date (to distinguish new vs ongoing CVD cases)

METHODS

- **Baseline Characteristics:** Age, geographic region, and Charlson Comorbidity Index (CCI) score was used as a proxy for PC disease severity
- **Outcomes:** CVD was determined based on a composite of the following 15 CV conditions:

1. Hypertension
2. Ischemic heart disease
3. Myocardial infarction
4. Heart failure
5. Ventricular arrhythmias
6. Cerebrovascular accidents
7. Peripheral vascular disease
8. Pulmonary heart diseases
9. Atrial fibrillation
10. Paroxysmal tachycardia
11. Cardiomyopathy
12. Hypotension
13. Pulmonary embolism
14. Atherosclerosis
15. Aortic aneurysm

METHODS: STATISTICAL ANALYSIS

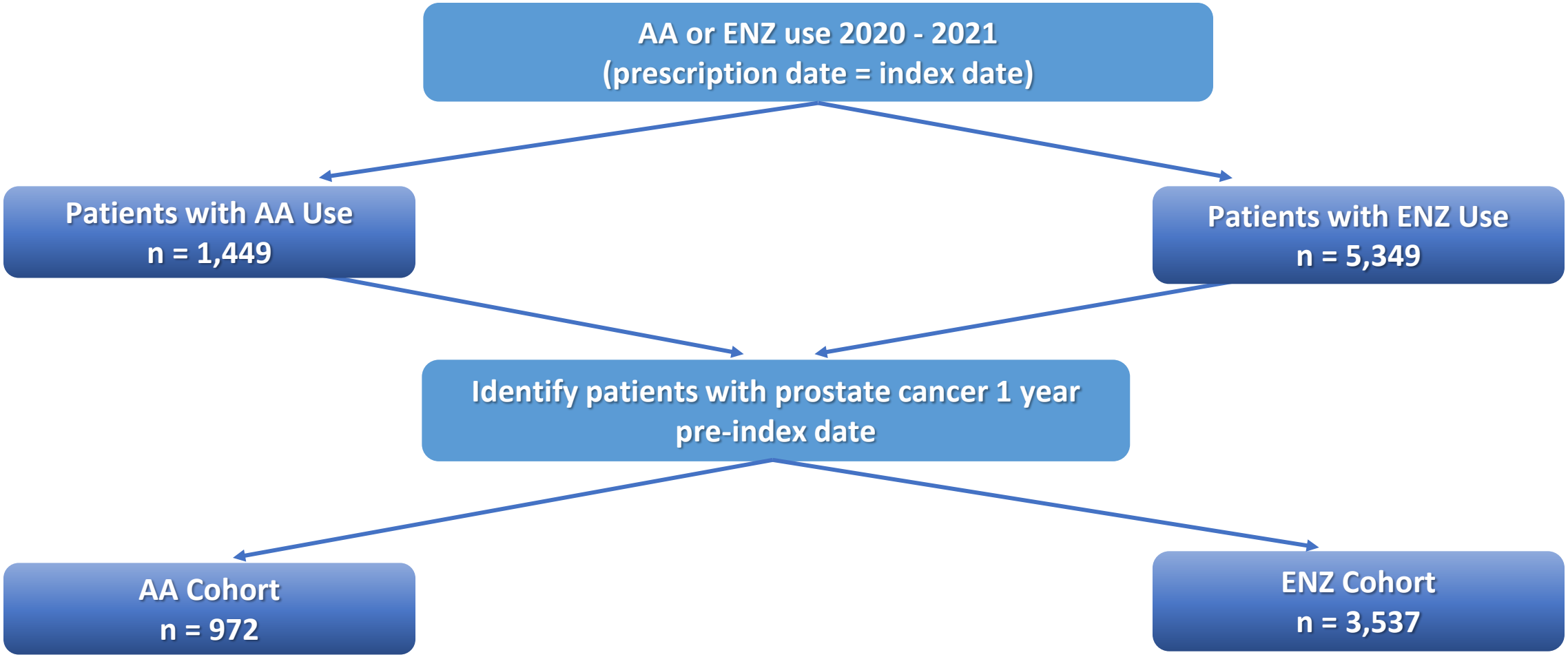
Descriptive Analysis: Numbers, percentages, means, and standard deviations; *t*-tests and Pearson chi-squared tests were employed to assess differences.

Multivariate Analysis: To control the non-random assignment of patients, we constructed logistic regression models that predict the likelihood of using each medication (**the propensity score**) and matched patients in each cohort by this score. We control for **confounders** (age, US region, CCI score).

Analysis Tools: All analyses were conducted using Pyspark and SparkR on Databricks, ensuring rigorous statistical analysis and control for non-random patient assignment.

COLUMBIA DATA ANALYTICS

Results: Study Attrition



Columbia Data Analytics

PSM-Adjusted Baseline Characteristics

Characteristics	Patients with PC and AA Use n = 956		Patients with PC and ENZ Use n = 956		*P* Value
	N/Mean	%/SD	N/Mean	%/SD	
Age Group	**73.13**	8.60	**73.13**	8.60	1.0000
46-54 years	14	1.46%	14	1.46%	1.0000
55-64 years	135	14.12%	135	14.12%	1.0000
65+ years	807	**84.41%**	807	**84.41%**	1.0000
US Region					
Northeast	107	11.19%	95	9.94%	0.3720
South	402	**42.05%**	414	**43.31%**	0.5790
Midwest	202	21.13%	202	21.13%	1.0000
West	244	25.52%	244	25.52%	1.0000
Other	1	0.10%	1	0.10%	1.0000
Baseline CCI Score	**2.63**	1.47	**2.54**	1.49	0.1834

AA: abiraterone acetate; CCI: Charlson Comorbidity Index; ENZ: enzalutamide; PC: prostate cancer; SD: %/standard deviation.

PSM-Adjusted Outcomes

There is no difference among the AA cohort and ENZ cohort in the incidence of CV-related AEs.

Hypertension was the most common CV AE, slightly higher in the AA cohort than in the ENZ cohort (46.03% vs 45.40%, *P*=0.7830.

Atrial fibrillation (13.18% vs 11.92%. *P*=0.4075) and **heart failure** (10.77% vs 9.62%, *P*=0.4058) were slightly higher in the AA cohort.

Ischemic heart disease (17.26% vs 16.84%, *P*=0.8078) was slightly higher in the ENZ cohort than the AA cohort.

	Patients with PC and AA Use (n = 956)		Patients with PC and ENZ Use (n = 956)		
	N/Mean	%/SD	N/Mean	%/SD	*P* Value
Follow-up CV-related AEs					
Hypertension	440	**46.03%**	434	**45.40%**	0.7830
Ischemic heart disease	161	16.84%	165	**17.26%**	0.8078
Myocardial infarction	18	1.88%	22	2.30%	0.5227
Heart failure	103	**10.77%**	92	9.62%	0.4058
Ventricular arrhythmias	48	5.02%	51	5.33%	0.7568
Cerebral infarction	20	2.09%	24	2.51%	0.5418
Peripheral vascular diseases	36	3.77%	39	4.08%	0.7238
Pulmonary heart diseases	9	0.94%	13	1.36%	0.3910
Atrial fibrillation	126	**13.18%**	114	11.92%	0.4075
Paroxysmal tachycardia	18	1.88%	16	1.67%	0.7293
Cardiomyopathy	25	2.62%	30	3.14%	0.4939
Hypotension	38	3.97%	47	4.92%	0.3180
Pulmonary embolism	24	2.51%	17	1.78%	0.2691
Atherosclerosis	40	4.18%	35	3.66%	0.5558
Aortic aneurysm	23	2.41%	21	2.20%	0.7603

AA: abiraterone acetate; CVD: cardiovascular disease; ENZ: enzalutamide; PC: prostate cancer; SD: standard deviation.

CONCLUSIONS

- **Provides RWE of the risk of CV events related to AA and ENZ utilization that may not have appeared in clinical trial settings**
- **Addresses the incidence of many CV-related AEs in a population identified without pre-existing CVD, which differs from previous studies**
- **Adjusting for age, US region, and CCI score, the likelihood of CV-related AEs did not differ between the AA and ENZ user groups, in agreement with existing literature.[9-11]**

Guidance for Physicians

These insights provide more well-informed decisions on patient care for PC and improve outcomes.

REFERENCES

1 Rawla P. Epidemiology of prostate cancer. *World J Oncol*. 2019;10(2):63-89.

2 National Cancer Institute. Cancer Stat Facts: Prostate Cancer, 2023. https://seer.cancer.gov/statfacts/html/prost.html. Accessed January3, 2024.

3 Zhang W, Wu T-Y, Chen Q, et al. Indirect comparison between abiraterone acetate and enzalutamide for the treatment of metastatic castration-resistant prostate cancer: A systematic review. *Asian J Androl*. 2017;19(2):196.

4 Freedland SJ, Davis M, Epstein AJ, Arondekar B, Ivanova JI. Real-world treatment patterns and overall survival among men with metastatic castration-resistant prostate cancer (mCRPC) in the US Medicare population. *Prostate Cancer Prostatic Dis*. 2023. 10.1038/s41391-023-00725-8;

5 Kakarla M, Ausaja Gambo M, et al. Cardiovascular effects of androgen deprivation therapy in prostate cancer patients: A systematic review. *Cureus*. 2022;14(6):e26209.

6 Recine F, Sternberg CN. Hormonal therapy and chemotherapy in hormone-naive and castration resistant prostate cancer. *Transl Androl Urol.* 2015;4(3):355-364.

7 American Urological Association. Advanced prostate cancer: AUA/SUO guideline 2023. https://www.auanet.org/guidelines-and-quality/guidelines/advanced-prostate-cancer. Accessed January 4, 2024.

8 Ye Y, Zheng Y, Miao Q, Ruan H, Zhang X. Causes of death among prostate cancer patients aged 40 years and older in the United States. *Front Oncol.* 2022;12:914875.

9 Iacovelli R, Ciccarese C, Bria E, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. *Clin Genitourin Cancer*. 2018;16(3):e645-e53;

10 Cao B, Kim M, Reizine NM, Moreira DM. Adverse events and androgen receptor signaling inhibitors in the treatment of prostate cancer: A systematic review and multivariate network meta-analysis. *Eur Urol Oncol.* 2023;6(3):237-250;

11 Conover MM, Weaver J, Fan B, et al. Cardiovascular outcomes among patients with castration-resistant prostate cancer: a comparative safety study using US administrative claims data. *Prostate*. 2023;83(7):729-739.

Contact Information

Gabriela Samayoa, MD, MPH

 gabriela@cdanyc.com

 145 Hudson Street, Suite 205, New York, NY 10013

 cdanyc.com

Columbia Data Analytics