COMPARATIVE EFFECTIVENESS OF ORAL ANDROGEN SIGNALING INHIBITORS IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS WITH AND WITHOUT PRE-EXISTING CARDIOVASCULAR COMORBIDITIES

by

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(Under the Direction of Ewan K. Cobran)

ABSTRACT

Oral androgen signaling inhibitors (OASI), Enzalutamide (ENZ) and Abiraterone Acetate (AA) are both first-line treatments for castration-resistant prostate cancer (CRPC) with chemotherapy, but the comparative effectiveness of these treatments has not been fully elucidated. Notably, men with mCRPC who received OASI were excluded from clinical trials if they had a pre-existing cardiovascular disease (CVD) and other comorbidities. Such practice limits the external validity of these trials, and findings may not be generalizable to patients with pre-existing comorbidities. This study sought to examine all-cause and prostate cancer-specific mortality, the incidence of new thromboembolic events (TE), and whether ENZ compared to AA is associated with a longer time to starting oral opioids and chemotherapy in CRPC patients.

An active comparator new-user design was used to identify 3,237 men diagnosed with likely CRPC using the Surveillance, Epidemiology, and End Results-Medicare Linked Database from 2011 to 2016. Patients were stratified by CVD history. Within each CVD stratum (pre-existing CVD versus no pre-existing CVD), patients were further divided into OASI versus

chemotherapy new-user groups. Furthermore, we compared AA versus chemotherapy, and ENZ versus chemotherapy in the subgroup analyses within each analytical cohort. To assess the difference between AA and ENZ in men with and without CVD history. Inverse probability treatment weights (IPTW)-adjusted time-varying Cox models and Fine-Gray competing risk models were used to evaluate associations between OASI and the outcomes of interest. Multiple sensitivity analyses were conducted.

A total of 2,147 patients had pre-existing CVD, of which 1,498 (70%) received OASI. Findings from this study suggested that OASI, both ENZ and AA, appeared comparatively with better effectiveness profile than chemotherapy. OASI was associated with preferable all-cause mortality, prostate cancer specific-cause mortality, and lower TE events than chemotherapy for all groups. ENZ and AA both showed beneficial effects compared to chemotherapy, with ENZ showing numerically greater benefits across groups, particularly among those with pre-existing CVD. When comparing ENZ vs. AA, patients who received ENZ showed a significant delay in using oral opioids and chemotherapy compared with other patients who received AA.

INDEX WORDS: Castration-Resistant Prostate Cancer, Cardiovascular Comorbidities, Comparative Effectiveness, Oral Androgen Signaling Inhibitor, Enzalutamide, Abiraterone Acetate

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DEDICATION

In memory of my father Mohammed Asiri (May Allah bless his soul with eternal peace). To my mother Helala Ammar, for always encouraging, supporting, and believing in me. To my daughter Alhanouf.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Prostate cancer (CaP) represents the highest incidence rate of cancer among men in the United States, with an estimated 248,530 (26%) new cases in 2021 alone.[1] CaP has the second-highest mortality rate, with 34,130 (11%) deaths among men with cancer.[1] In localized and regional CaP, the relative 5-year survival (2010-2016) rate is the highest, at > 99% compared with other types of cancer.[1] However, approximately 20–30% of treated patients by surgery or radiation therapy for localized CaP eventually ended up experiencing cancer recurrence.

This recurrence results from rising levels of androgen that drive CaP cell growth, known as hormone-sensitive prostate cancer.[2] Accordingly, traditional androgen-deprivation therapy (ADT) is the standard of care after recurrence; ADT functions by decreasing the testicular production of androgens, but the disease is most likely to progress beyond the phase of being hormone-sensitive in patients who receive such treatment.[3]

Lethal Prostate Cancer

Progression following traditional ADT is often observed, resulting in lethal CaP, known as castration-resistant prostate cancer (CRPC). There were approximately 36,100 new cases of CRPC in 2009, and the number was projected to rise in 2020 to 42,970 new cases in the United States.[4] CRPC is defined by cancer progression despite castrate levels of testosterone.[5] This transition from hormone-sensitive CaP to CRPC can occur in the absence of metastases (M0 CRPC) or the presence of metastases (M1 CRPC).[6]

mCRPC presents as one or any combination of a continuous rise in prostate-specific antigen (PSA), the progression of the pre-existing disease, or the appearance of new metastases. Characteristics of mCRPC include a conventionally defined testosterone level of <50 ng/dl, a rise in prostate-specific antigen (PSA) level for three consecutive tests, a PSA nadir > 2 ng/ml, and often a progression of disease after antiandrogen withdrawal.[7] Patients with mCRPC typically have a poorer prognosis, compared to patients with earlier-stage prostate cancer, and frequently develop bone metastases.[5,8-10]

Men with mCRPC who are resistant to docetaxel-based or other systemic therapy invariably progress and die from the disease.[5] The relative 5-year survival (2010-2016) rate drops dramatically to 30% among patients with advanced stages.[1] A systematic review reveals that 10–20% of prostate cancer patients develop mCRPC within approximately five years of follow-up.[11] Metastases present in ≥ 84% of patients at the time of mCRPC diagnosis.

In those without metastases at diagnosis, 33% of patients with CRPC eventually develop metastases within two years of their diagnosis. Although there is no major agreement on the median survival of mCRPC patients, the systematic review reports that the median survival from mCRPC diagnosis is 14 months.[11] Patients with mCRPC have the poorest prognosis; however, novel advances in treatment options have recently helped improve survival rates.[12]

Management of Lethal Prostate Cancer

Androgen deprivation therapy (ADT) is the standard of care for treating men with advanced prostate cancer.[13] ADT functions by decreasing the testicular production of androgens,[13] to improve outcomes in men with prostate cancer.[14] Unfortunately, disease

progression following ADT is often observed, resulting in mCRPC.[5] Different clinical guidelines provide some direction on incorporating these new agents and biomarkers in clinical practice since their first introduction in 2010.

The National Comprehensive Cancer Network (NCCN) recommends abiraterone acetate, enzalutamide, docetaxel, apalutamide, darolutamide, pembrolizumab, sipuleucel-T, olaparib, rucaparib, radium-223, or participation in clinical trials as treatment options for those patients.[15] The American Urological Association (AUA) guidelines provide similar recommendations, with the addition of ketoconazole plus steroids as a therapeutic option.[16,17] Most of the preceding listed agents are first-line treatments for mCRPC. Comparative effectiveness of these agents has not been fully elucidated, especially for oral androgen signaling inhibitors (OASI), abiraterone acetate (AA) and enzalutamide (ENZ).

Oral Androgen Signaling Inhibitors (OASI)

The NCCN recommends using two oral androgen signaling inhibitors (OASI), AA and ENZ, as a treatment option for men with mCRPC.[18] Abiraterone acetate (AA) is an androgen synthesis inhibitor in the adrenal glands, testes, and within the prostate tumor by blocking CYP17, a critical enzyme in testosterone synthesis.[19] Whereas, enzalutamide (ENZ) is an androgen receptor inhibitor that binds to the androgen receptor's ligand-binding domain and inhibits androgen-receptor translocation to the cell nucleus, androgen-receptor cofactors recruitment, and the binding of androgen-receptor to DNA.[20]

AA and ENZ are widely used to treat advanced prostate cancer with significant comorbidities. Both second-generation agents were initially approved by the United States Food and Drug Administration (FDA) in 2011 (AA) and 2012 (ENZ) in CRPC patients who had failed

prior docetaxel chemotherapy. Likewise, the FDA expanded the AA and ENZ indications to chemotherapy-naïve patients in 2013 and 2014, respectively.

Survival in Clinical Trials of Abiraterone Acetate and Enzalutamide

In the pivotal trial of AA (COU-AA-301) in patients with prior docetaxel chemotherapy, the median overall survival (OS) was more prolonged for the AA arm compared to the placebo arm (15.8 vs. 11.2 months, $p < 0.001$) after 20.2 months of median follow-up.[19,21] Similar results occurred in the chemotherapy-naïve patient trial (COU-AA-302): AA showed a more prolonged median OS compared with placebo (34.7 vs. 30.3 months, $p = 0.0027$) after 49.4 months of median follow-up.[22,23]

Although the pivotal trial of ENZ (AFFIRM) for patients who received prior docetaxel chemotherapy showed longer median OS in the ENZ arm compared with the placebo arm (18.4 vs. 13.6 months, $p < 0.001$), the median follow-up in the AFFIRM trial was shorter, at 14.4 months.[24] This OS improvement was not observed in the chemotherapy-naïve patients in the PREVAIL trial, as the median OS was not reached in the ENZ arm (median not reached vs. placebo 31.0 months, $p < 0.001$); nonetheless, the drug showed superiority in other endpoints such as radiographic progression-free survival (rPFS), with an 81% risk reduction after 12 months of follow-up.[20]

Cardiovascular and Thromboembolic Comorbidities After ADT

Along with the therapeutic benefits, ADT is associated with various metabolic aberrations, including decreased insulin sensitivity, changes in lipid profile, and increased risk of CVD.[25,26] The increased risk of CVD in men with prostate cancer on ADT has been observed in

a number of observational studies.[25-37] One proposed explanation of this relationship is that ADT interferes with testosterone's cardioprotective properties, thereby increasing the risk of adverse events.[25] In a previous study comparing 76,000 men with prostate cancer to the general Swedish population, O'Farrell et al.[25] showed an increased risk of incident and fatal CVD among all men with prostate cancer. The highest relative risk was observed for patients on ADT (e.g., standardized incidence ratio for ischemic heart disease, 1.32; 95% Confidence Interval [CI], 1.27 to 1.36).

The FDA used these findings, along with six other studies, to require a warning label on GnRH agonists for an increased risk of diabetes and certain CVDs (e.g., heart attack, sudden cardiac death, and Stroke). Nonetheless, there is divergence of opinion on the association between ADT and CVD in observational studies compared to randomized clinical trials.[25,38] Some of the limiting factors have been a lack of information on the various types and durations of ADT, comparison to patients with prostate cancer not treated with ADT rather than age-matched, and not taking into account pre-existing CVD comorbidites.[25]

In a recent study, Lu-Yao et al.[39] investigated the hypothesis that pre-existing CVDs were associated with higher 6-month mortality after AA and ENZ treatment. Among eligible patients of the study (2845 with AA and 1031 with ENZ), 67% had at least one pre-existing CVD.[39] Among post- and no-chemotherapy patients treated with AA or ENZ, having three or more CVD diagnoses was associated with 43% and 56% higher 6-month mortality relative risk [RR] (RR, 1.43; 95% CI, 1.04 to 1.98; RR, 1.56; 95% CI, 1.29 to 1.88), respectively, compared with those without CVDs. The elevated mortality risk associated with CVD attenuated within six months of treatment initiation.[39]

In another recent study, Deka et al.[40] conducted an observational cohort study of patients diagnosed with prostate cancer at the United States Department of Veterans Affairs between January 1, 2001, and October 31, 2015, who were treated with definitive radiation therapy. The authors sought to test the association between ADT use and transient ischemic attack (TIA), Stroke, pulmonary embolism (PE), and deep vein thrombosis (DVT) in localized prostate cancer patients. There was an overall significant association between ADT and stroke (sub-distribution Hazard Ratio (SHR), 1.19; 95% CI, 1.09 to 1.30; $p < 0.01$), TIA (SHR, 1.24; 95% CI, 1.08 to 1.41; $p < 0.01$), and DVT (SHR, 1.18; 95% CI, 1.04 to 1.34; $p < 0.01$).[40] However, there was no overall association between ADT and PE (SHR, 1.16; 95% CI, 0.98 to 1.39; $p = 0.08$). [40]

Palliative Care in Patients with CRPC

It is unquestionable that the ultimate goal of the management plan in patients with mCRPC is palliative care and should be considered in their treatment options.[41] The extension of symptom relief and the delay in initiating chemotherapy as long as possible are objectives of palliative care in patients with mCRPC.[41] AA and ENZ pivotal clinical trials incorporated time to opiate use as a secondary endpoint in their analyses for cancer-related pain.[20,21,23,24]

Furthermore, AA and ENZ trials of naïve patients in chemotherapy added another aspect of palliative care, time to initiating chemotherapy, as an important secondary endpoint in their analyses.[20,23] ASCO emphasizes the important point that palliative care should not be overlooked in the management plan, particularly for patients who exhibit symptoms or decreased HRQoL.[41] In addition to the late effect of CaP treatment, NCCN and ASCO guidelines recognize palliative care as an aspect that should be addressed within survivorship care.[42,43]

When patients with mCRPC on ENZ or AA experience cancer progression, starting oral opioids (due to pain from metastatic disease) and/or starting chemotherapy are clinical indicators that can be ascertained in real-world data. These are clinically meaningful outcomes for the patient, as shown in the OASIs pivotal clinical trials. Understanding the association of the OASIs with delaying time to use opioids and the initiation of chemotherapy helps to the success of the palliative care plan in prostate cancer patients aged 65 and over.

Medicare Population (Elderly)

The Medicare program is an insurer for individuals aged 65 and over. The median age of cancer patients at diagnosis is 66 years, while the median age of cancer patients at death was 80 years in 2011-2015.[44] Generally, novel treatment options have benefitted prostate cancer patients aged 50 to 64 years more than their older counterparts.[45] This discrepancy likely reflects less efficacy or utilization of new therapies in the elderly population.[45]

The treatment type provided may also be impacted by patients' demographics such as age, race, ethnicity, access to oncology services, and socioeconomic status.[46,47] Initial treatment patterns indicate that 25% of prostate cancer patients aged younger than 65 years are treated with radiation therapy, and 57% of this age segment received radical prostatectomy.[12] In contrast, among patients aged 65 to 74 years, 42% undergo radiation therapy, and 33% undergo radical prostatectomy.[12] It is evident that there are disparities in treatment options related to ages in localized prostate cancer, but the treatment pattern is still unclear in the elderly with lethal prostate cancer.

Problem Statement and Need for the Study

The United States Census Bureau projected the growth in the population aged 65 years and older to almost double in the near future, from 43.1 million in 2012 to 83.7 million in 2050.[48] This vast growth in the elderly population affects the prevalence of cancer and may reverse the declining incidence rates of cancer, as the incidence rate in the elderly population is the highest.[48] Specifically regarding mCRPC, approximately 36,100 new cases occurred in 2009 alone, and that number was projected to rise in 2020 up to 42,970 new cases in the US.[4] Therefore, the number of cancer survivors and the amount of cancer expenditure will likely increase in the future.[49]

Evidence projected the overall cost of cancer care in 2020 at $173 billion, an increase of 39% from 2010 if costs in the initial and final phases of cancer care increase by 2% annually. This substantial increase in the cost of total cancer care is driven by the high cost of treating prostate cancer (CaP); 42% of the expense comprises the continuous phase of CaP treatment.[49] This growth in the cost of CaP care is due to the introduction of advanced technology in disease diagnosis and treatment at the end-stage.[49]

Treating lethal CaP is notably expensive, especially with the new hormonal therapies that have been approved recently, AA and ENZ.[50-52] The average monthly cost of AA is $5,390, whereas ENZ costs $7,450 a month.[50] Contention and confusion still exist among clinicians about the best choice for initiating a treatment plan based on a patient's sociodemographic characteristics to improve clinical outcomes and survivorship experience.[15,16,53]

AA and ENZ are often used among prostate cancer patients who are elderly (≥65) and have significant comorbidities.[39] However, pivotal trials of AA excluded men with clinically

significant cardiovascular disease (CVD) conditions, serious coexisting nonmalignant disease, or uncontrolled hypertension.[21-23] Likewise, pivotal trials of ENZ excluded patients with significant comorbidities.[20,24] While the strict eligibility criteria for clinical trials may stem from legitimate concerns about comorbidities affecting response to or toxicity from trial medications, such practice limits the external validity of the trials, and the findings may not be generalizable to patients with pre-existing comorbidities.[54-56]

Further, there is still uncertainty among clinicians concerning the optimal prescribing of AA and ENZ in order to prolong survival.[16,53,57] The American Urological Association, National Comprehensive Cancer Network, and American Society for Clinical Oncology clinical guidelines acknowledge that there are no specific prescribing or combinations of AA and ENZ for patients with mCRPC.[16,53,57]

Since mCRPC patients receiving OASI are vulnerable to the cross-resistance between AA and ENZ, there is a narrow treatment window.[19,20,23,24] This lack of clarity in the prescribing of AA and ENZ for mCRPC patients may have an unintended impact on survival. In addition, men with existing CVDs had a higher risk of cardiovascular events and mortality in the first six months of starting traditional ADT.[58] Furthermore, the impact of OASI on thromboembolic events in mCRPC patients with a pre-existing history of cardiovascular disease is still under-investigated.

To date, research studies comparing the efficacy of ENZ and AA treatment in real-world patients are limited, especially among elderly mCRPC patients with coexisting comorbidities.[21-23] When patients with mCRPC on ENZ or AA experience cancer progression, starting oral opioids (due to pain from metastatic disease) and/or starting chemotherapy are clinical indicators that can be ascertained in real-world data. These are clinically meaningful outcomes for patients.

Therefore, the purpose of the study is to assess effectiveness of OASI in elderly mCRPC patients with and without a pre-existing history of cardiovascular disease. The following are the specific aims of this study.

Specific Aim 1: To examine all-cause and prostate cancer-specific mortality for mCRPC men, with and without a pre-existing history of CVD (e.g., acute myocardial infarction, atrial fibrillation, and heart failure), receiving oral androgen signaling inhibitors (OASI) versus chemotherapy.

Hypothesis: This study hypothesized that mCRPC patients with a pre-existing CVD history receiving OASI versus chemotherapy might show more improvement in all-cause and prostate cancer-specific mortality than mCRPC patients without a pre-existing CVD history.

Specific Aim 2: To investigate the incidence of new thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, and arterial embolism) in mCRPC patients with and without a pre-existing history of CVD (e.g., acute myocardial infarction, atrial fibrillation, and heart failure), receiving OASI versus chemotherapy.

Hypothesis: This study hypothesized that mCRPC patients with a pre-existing CVD history receiving OASI might have a higher incidence of new thromboembolic events than mCRPC patients without a pre-existing CVD history.

Specific Aim 3: To examine whether ENZ compared to AA is associated with a longer time to starting oral opioids and chemotherapy. This aim will further estimate the effect of switching from ENZ to AA, or from AA to ENZ, while investigating death as a competing risk.

Hypothesis: This study hypothesized that mCRPC patients on ENZ might significantly delay the time to use oral opioids and the initiation of chemotherapy. This study also hypothesized that mCRPC patients on ENZ might have a longer treatment duration before switching drugs than patients who started on AA.

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CHAPTER 2

MORTALITY IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS WITH AND WITHOUT PRE-EXISTING CARDIOVASCULAR COMORBIDITIES RECEIVING ORAL ANDROGEN SIGNALING INHIBITORS ⸸

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ABSTRACT

Purpose: Limited knowledge is available about the survival of men with castration-resistance prostate cancer (CRPC) who have a pre-existing history of cardiovascular disease (CVD) and are receiving newer forms of treatment. Notably, men with CRPC who received oral androgen signaling inhibitors (OASI) were excluded from clinical trials, if they had a pre-existing history of CVD and other comorbidities. Therefore, to address this limitation in the literature, this study compared all-cause and prostate cancer-specific mortality for CRPC men, with and without a pre-existing history of CVD, as a function of receiving OASI or chemotherapy.

Methods: An active comparator, new user design was used to identify 2,608 men with likely CRPC using the Surveillance, Epidemiology, and End Results-Medicare Linked Database from 2011 to 2015. Patients were grouped into two analytical cohorts by CVD history. Patients were compared based on OASI versus chemotherapy use within each analytical cohort (with and without a pre-existing history of CVD). Further, we compared Abiraterone Acetate (AA) versus chemotherapy and Enzalutamide (ENZ) versus chemotherapy in the subgroup analyses within each analytical cohort to assess the difference between AA and ENZ in men with and without CVD history. Inverse probability treatment weights (IPTW)-adjusted time-varying Cox models were used to evaluate associations between OASI and all-cause mortality. IPTW-adjusted Fine-Gray competing risk models were used to assess prostate cancer-specific mortality.

Results: Out of the entire cohort, nearly 64.5% of patients had pre-existing CVD history, and were numerically higher in the incidence of all-cause and prostate cancer-specific mortality than

patients with non-CVD history (all-cause mortality: 53% vs. 40%, prostate cancer-specific mortality: 42.5% vs. 33%, respectively). In the pre-existing CVD cohort, the IPTW-adjusted time-varying Cox model showed a significantly lower all-cause mortality in patients who received OASI, both enzalutamide and abiraterone, versus chemotherapy (IPTW-adjusted hazard ratio [AHR], 0.59; 95% Confidence Interval [CI], 0.54 to 0.64). Similarly, the adjusted model showed significantly lower all-cause mortality in patients who received ENZ. than those who received chemotherapy (IPTW-AHR, 0.47; 95% CI, 0.41 to 0.54). Patients who received AA had also a significantly lower all-cause mortality than those who received chemotherapy (IPTW-AHR, 0.63; 95% CI, 0.57 to 0.69). Findings were comparable to the sub-distribution hazard ratio for prostate cancer-specific mortality.

Conclusion: This study found that OASI compared to chemotherapy was associated with a significant improvement in the all-cause and prostate cancer-specific mortality across groups. This improvement was even more pronounced in patients with concomitant CVD comorbidities than in those without pre-existing CVD. The current research supports the use of OASIs in this group who were not well-represented in the randomized trials, which led to the FDA approval of OASIs.

INTRODUCTION

Historically, treatment for patients with castration-resistance prostate cancer (CRPC) has been limited to palliative care.[1,2] However, in recent years, treatment options for CRPC have expanded, including taxane-based chemotherapy, immunotherapy, radiotherapy, and hormonal therapy.[3] The US Food and Drug Administration approved two oral androgen signaling inhibitors (OASI) abiraterone acetate (AA) and enzalutamide (ENZ) for CRPC patients with prior chemotherapy in April 2011 and August 2012, respectively.[4,5]

In clinical trials, both treatments have prolonged overall survival in chemotherapy-naïve patients with CRPC compared with placebo (ENZ 35.3 vs. 31.3 months with placebo; AA plus prednisone, 34.7 vs. 30.3 months with placebo plus prednisone).[4,6,7] ENZ and AA have also received the highest recommendation in the National Comprehensive Cancer Network guidelines for the treatment of CRPC.[8]

Although the results of clinical trials demonstrate the efficacy of ENZ and AA for CRPC under controlled conditions, men with pre-existing cardiovascular disease (CVD) were excluded from these trials. Because a sizable proportion of prostate cancer patients have CVD, it is important to evaluate the effectiveness of treatments in these patients using real-world data.[4] Therefore, the objective of this study is to examine all-cause and prostate cancer-specific mortality for mCRPC men, with and without a pre-existing history of CVD, receiving OASI versus chemotherapy.

PATIENTS AND METHODS

Data Source

A population-based retrospective cohort was created from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Explaining the SEER-Medicare linked database has been described elsewhere.[9] Briefly, the Medicare program affords health insurance to 97% of the United States (US) population aged 65 years and older, covering inpatient care (Part A), outpatient care and physician service (Part B), and prescription drugs (Part D).[9] The SEER Program of the National Cancer Institute (NCI) collects information about cancer incidence and survival statistics from 19 population-based state or regional cancer registries.[10] The SEER-Medicare linked database provides comprehensive health care utilization data for Medicare beneficiaries with cancer that represent approximately 28% of the US population.[9]

In this study, several SEER-Medicare data files were utilized. The Patient Entitlement and Diagnosis Summary File (PEDSF) was used to obtain clinical and demographic characteristics. The Carrier file (NCH) was utilized to capture claims for inpatient and outpatient beneficiaries who were served by physicians and non-institutional provider services (Part B). Information regarding inpatient cancer care and hospital outpatient services were obtained through the Medicare Provider Analysis and Review file (MEDPAR, institutional, through Part A) and the Outpatient files (OUTPAT, institutional, through Part B), respectively. Further, Medicare Part D Event files (PDE) were utilized to extract information regarding orally used drugs. Finally, Chronic Condition Flags file was used to identify comorbidities and define the analytical subgroups (pre-existing CVDs versus no pre-existing CVDs). This study received IRB waiver from the University of Georgia Institutional Review Board.

Analytical Design

An active comparator, new user (ACNU) design was used to identify OASI versus chemotherapy use in likely CRPC patients in the SEER-Medicare database between January 1, 2011, through December 31, 2015. Considering men diagnosed with prostate cancer between the years 2004 to 2014 for ACNU enrollment eligibility. The new user concept has been recommended to be implemented whenever possible[11] to overcome some of the inherited weaknesses in nonexperimental observational studies such as indication bias, healthy initiator bias, and selection bias.[12-14]

The purpose of adding the active comparator element in this study design [OASI (Abiraterone Acetate [AA] and Enzalutamide [ENZ]) vs. chemotherapy (Docetaxel [DOX] and Cabazitaxel [CAB])] was to mitigate confounding by indication and other unmeasured patient characteristics such as frailty.[12,13] The active comparators (DOX and CAB) were chosen based on the time and the availability of the treatment options for CRPC patients in the NCCN guideline.[15] A new user was defined based on the first claim date that showed a patient had no prior use of the drugs of interest. We considered the switching between CRPC drugs during the follow-up period "as-treated analysis".[12] Therefore, the discontinuation date of the orally taken drugs (AA and ENZ) was defined as (the last dispensing date + the days' supply [30 days] + a grace period [15 days]) to ensure drug utilization period was correctly captured.[12,8]

Further, we stratified the CRPC cohort into having pre-existing CVDs versus no pre-existing CVDs based on the CMS. Chronic Conditions Data Warehouse (CCW) algorithms using the Chronic Condition Flags file.[16] Pre-existing CVDs were defined as having atrial fibrillation, acute myocardial infarction, congestive heart failure, stroke, or ischemic heart disease before CRPC treatment initiation by ascertained period. We defined the ascertained period as a 6-month

fixed window prior to the first use of any of the drugs of interest. If a CRPC patient did not have any of the defined CVDs before the index time, the patient would be included in the no pre-existing CVDs analytical cohort. For each patient, follow-up continued until the occurrence of death (from any cause and prostate cancer-specific death), end of the study period (December 31, 2015), or the participant was lost, whichever occurred first.

Study Cohort

The study cohort included patients 65 years of age and older, who were first and only diagnosed with prostate cancer between the years January 1, 2004, through December 31, 2014 (International Classification of Diseases, 9th Revision, Clinical Modification, [ICD-9-CM] code 185.xx, [ICD-10-CM] code C61.xx). We further restricted the inclusion criteria of the study to CRPC patients, which was defined based on treatments (DOX, CAB, AA, or ENZ) administered after prostate cancer became resistant to surgical castration or Androgen Deprivation Therapy (ADT).[15,17] The exposure arm was defined as CRPC patients receiving OASI (AA or ENZ) from January 1, 2011, through December 31, 2015.

The comparison arm was defined as CPRC patients receiving chemotherapy (DOX or CAB.) January 1, 2011, through December 31, 2015.[15,17] Healthcare Common Procedure Coding System (HCPC) codes were used to identify DOX (J9171 and J9170) and CAB (J9043 and C9276). Patients were excluded from the study if they had: (1) other cancer at diagnosis time or following prostate cancer; (2) diagnosis at death or autopsy; (3) no Medicare Parts A, B, and D through study period & 12 months pre-index date; (4) Medicare HMO through study period & 12 months pre-index date; and (5) first drug initiation date was not between the predefined study period; and (6) enrollment because of End-Stage Renal Disease (ESRD) or disability. Figure A1

in Appendix presents the details on the inclusion and exclusion criteria to create the analytical cohorts.

Outcomes

CRPC patients were followed from the date of the first drugs of interest use until the end of December 2015. Survival time and cause of death were obtained from the SEER record in the PEDSF file. The cause of death was determined using the recode variable (CODPUB = 28010 for prostate cancer-specific mortality). We compared between AA versus chemotherapy and ENZ. versus chemotherapy separately within each analytical cohort (pre-existing history of CVD cohort and no pre-existing CVD cohort).

Covariates

Demographic characteristics including race (grouped into four categories: White, Black, Asian/Hispanic/North American Native, and Other/Unknown), age at diagnosis (grouped into four categories: 65-69 years, 70-74 years, 75-79 years, and ≥ 80 years), marital status (grouped into married and unmarried/unknown), and population location (urban vs. rural) were obtained from the SEER records. SEER regions were grouped into Northeast (Connecticut, New Jersey), South (Atlanta, rural Georgia, Kentucky, Louisiana), Central (Detroit, Iowa, New Mexico, Utah), and West (San Francisco, Hawaii, Seattle, San Jose, Los Angeles, greater California. As in previous population-based studies, the Medicaid state buy-in variable was classified as yes or no for identifying Medicare and Medicaid dual enrollees.[18-20]

Men were also grouped into four groups based on census tract poverty indicator (0%-<5%, 5%-<10%, 10%-<20%, and 20%-100%). For clinical characteristics, the initial diagnosis was categorized into localized/regional, metastatic, and unknown. The age at first CRPC treatment

was divided into < 75 vs. ≥ 75 years. Other Comorbidities (diabetes mellitus, chronic lower respiratory diseases, and dementia & Alzheimer's diseases) were chosen to be included in the analysis as shown to be from the top ten causes of death in the elderly.[21] Other causes of death in elderly patients were not included as they were not available in the Chronic Condition Flags file. In the pre-existing CVD cohort, a CVD variable indicator was created with one and two or more CVDs because these conditions were not mutually exclusive.

Statistical analysis

Descriptive statistics were conducted for each analytical cohort (pre-existing vs. no pre-existing CVD) separately to describe the baseline characteristics of the entire study sample. To address the issue of selection bias and heterogeneity among patients, the propensity scores using inverse probability treatment weights (IPTWs) were utilized for each analytical cohort (pre-existing and no pre-existing CVD) separately.[22] In brief, propensity scores were estimated by multivariable logistic regression, generating a covariate summary score (initial weight), which was defined as the probability of a CRPC patient to receive either OASI or chemotherapy conditional on all the identified covariates.[22,23]

Then, pseudo populations were created that represent weighting each patient's contribution by the inverse probability (IPTW) of receiving the drug received in each analytical cohort. To assess the limits of the potential for influential patients to bias results, such as those in these groups treated contrary to prediction, checks of the maximum weights (≤10) and the closeness of the mean weights to 1.0,[24] were conducted. If the maximum IPTWs were (>10), trimming procedures were utilized and recalculated the IPTWs to avoid treatment comparisons outside a common range of the propensity score.

Afterward, the final weights were implemented to adjust the time-varying Cox Models (Extended Cox Model) and the competing risk model (Fine-Gray sub-distribution hazard competing risk regression model).[25] However, in each patient who was included in the analytical cohorts based on the first drug use (OASI vs. chemotherapy), we considered the switching between CRPC drugs during the follow-up period "as-treated analysis".[12] Thus, the treatment status was accounted as a time-varying covariate for each patient until the occurrence of the outcome, end of the study period, or the patient was lost, whichever occurred first. Time-varying Cox models were performed to assess associations between OASI and all-cause mortality. For the prostate cancer-specific mortality, regression on cumulative incidence functions was conducted by using Fine and Gray's method accounting for any other cause of death as a competing risk. Gray's test was used to evaluate differences in the cumulative incidence curves between patients with OASI and chemotherapy.

We were interested in assessing the outcome differences between AA and ENZ. versus chemotherapy. Therefore, we further repeated the all-cause mortality and the prostate cancer-specific mortality for AA and ENZ. subgroups separately. When calculating the IPTW, the procedure was repeated for each outcome when comparing between AA and ENZ. versus chemotherapy separately within each analytical cohort. For example, when comparing AA versus chemotherapy in patients with a pre-existing CVD history, patients who were included in the study as new users of ENZ were excluded to eliminate their weight contribution in the subgroup that might bias the findings. Further, Gray's test was used to evaluate differences in the cumulative incidence curves between patients with AA and ENZ. versus chemotherapy separately.

In sensitivity analyses, we took into consideration the possibility of misclassification in the patients' history of CVD in the study design. At first, we considered an ascertainment period of 6-months before the index date (i.e., enrollment date in the analytical cohort) as a cut-off that if a patient's first CVD date was after that date, the patient would be assumed to be in the no pre-existing CVD cohort. This assumption was based on the notion that some patients might see their doctors without having a complete medical history because of technical delays in sharing patient's medical records. Therefore, in the sensitivity analyses, we tested our assumption and changed the ascertainment period from 6-months to 1-year and 1-day before the index date. All of the primary analyses were repeated for the sensitivity analyses. Statistical significance thresholds were set at significance level $\alpha = 0.05$; all tests were 2-tailed. All analyses were conducted using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics in CRPC Patients Stratified by CVD History

The study cohort included 2,608 men with mCRPC who met the inclusion criteria (Fig 1). Around 64.5% of patients had pre-existing CVD. Baseline demographic and clinical characteristics comparing mCRPC patients with pre-existing CVD and those without pre-existing CVD are listed in Tables 1 and 2. The median follow-up time in months was lower in patients with CVD history compared to patients without CVD history (Median time (IQR): 10.3 (14.1) vs. 12.1 (15.8), respectively; Table 2). The incidence rates of all-cause and prostate cancer-specific mortality were higher in patients with pre-existing CVD history than patients without

pre-existing CVD history (all-cause mortality: 53% vs. 40%, prostate cancer-specific mortality: 42.5% vs. 33%, respectively; Tables 3 & 4).

A total of 1,683 patients had a history of pre-existing CVD, of which 1,162 (69%) received OASI. Likewise, A total of 925 patients had no history of pre-existing CVD, of which 636 (69%) received OASI. In the pre-existing CVD cohort, patients who received OASI were more likely to be White, more elderly at first prostate cancer diagnosis, more likely to live in urban areas, more likely to enroll in Medicaid state buy-in programs, and more likely to live in less poor regions compared with those who received chemotherapy (all $P < .05$; Table 1). In the cohort without pre-existing CVD history, patients who received OASI were more elderly at first prostate cancer diagnosis and more likely to enroll in Medicaid state buy-in programs than those who received chemotherapy (all $P < .05$; Table 1).

Risk of Mortality Associated with OASI Use in Patients with pre-existing CVD History

In the pre-existing CVD cohort, the IPTW-adjusted time-varying Cox model showed a significantly lower all-cause mortality in patients who received OASI compared with those who received chemotherapy (IPTW-adjusted hazard ratio [AHR], 0.59; 95% Confidence Interval [CI], 0.54 to 0.64; Table 3). Correspondingly, the adjusted model showed significantly lower all-cause mortality in patients who received ENZ. than those who received chemotherapy (IPTW-AHR, 0.47; 95% CI, 0.41 to 0.54; Table 4). Patients who received AA had a significantly lower all-cause mortality than those who received chemotherapy (IPTW-AHR, 0.63; 95% CI, 0.57 to 0.69; Table 4). Findings were comparable to the sub-distribution hazard ratio for the prostate cancer-specific mortality in the appendix Tables A1 and A2.

Risk of Mortality Associated with OASI Use in Patients without pre-existing CVD History

In the non-CVD cohort, the adjusted time-varying Cox model showed a significantly lower all-cause mortality in patients who received OASI than those who received chemotherapy (IPTW-AHR, 0.68; 95% CI, 0.59 to 0.78; Table 3). Similarly, patients who received ENZ had a significantly lower all-cause mortality than those who received chemotherapy (IPTW-AHR, 0.57; 95% CI, 0.46 to 0.71; Table 4). The adjusted model showed a significantly lower all-cause mortality in patients who received AA than those who received chemotherapy (IPTW-AHR, 0.71; 95% CI, 0.61 to 0.83; Table 4). The results were also comparable to the sub-distribution hazard ratios for prostate cancer-specific mortality in Appendix Tables A1 and A2.

All the previous findings were for the assumption of ascertainment period of 6-months before the index date. Findings of the all-cause mortality were consistent in patients with pre-existing CVD when in the 1-day ascertainment period (IPTW-AHR, 0.58; 95% CI, 0.53 to 0.63; Appendix Table A3) and the 1-year ascertainment period (IPTW-AHR, 0.59; 95% CI, 0.54 to 0.64; Appendix Table A3). Furthermore, results of the all-cause mortality were showed to be consistent in patients with no history of pre-existing CVD when in the 1-day ascertainment period (IPTW-AHR, 0.71; 95% CI, 0.62 to 0.82; Appendix Table A3) and the 1-year ascertainment period (IPTW-AHR, 0.65; 95% CI, 0.57 to 0.75; Appendix Table A3). Results were also comparable to the sub-distribution hazard ratio for the prostate cancer-specific mortality, as presented in Appendix Table A4.

DISCUSSION

The treatment options offering survival benefits for patients with mCRPC have expanded in recent years.[2] However, few published studies assess real-world outcomes among CVD patients with mCRPC, even though treatment response may depend on patients' pre-existing comorbidities.[4,26-28] The current study is important because the pivotal trials that led to the FDA approval of OASIs excluded men with clinically significant CVD conditions, serious coexisting nonmalignant disease, or uncontrolled hypertension.[29-31] Thus, the generalizability of results from these trials to the overall mCRPC patient population is unknown. Another standard option for mCRPC treatment is chemotherapy, but head-to-head comparisons between OASI vs. chemotherapy have not been studied in a randomized fashion. The current study, therefore, addresses clinically meaningful current knowledge gaps: comparative effectiveness of OASI vs. chemotherapy in mCRPC patients with and without pre-existing CVD. Notably, two-thirds of mCRPC patients in this Medicare cohort had pre-existing CVD.

To our knowledge, this is the first head-to-head observational comparison study between OASI and chemotherapy examining all-cause and prostate cancer-specific mortality in mCRPC patients with pre-existing CVD history using a real-world population. We found that in the CVD cohort, patients who received OASI had lower all-cause mortality compared with those who received chemotherapy (IPTW- AHR, 0.59; 95% CI, 0.54 to 0.64). Similarly, in the non-CVD cohort, patients with OASI had lower all-cause mortality compared with those who received chemotherapy (IPTW- AHR, 0.68; 95% CI, 0.59 to 0.78). These findings suggest the higher effectiveness of OASIs, both enzalutamide and abiraterone, compared to chemotherapy.

A recent population-based cohort study assessed short-term outcomes in advanced prostate cancer patients with pre-existing CVD comorbidities.[28] The study found that among post- and no-chemotherapy advanced prostate cancer patients treated with OASI, having three or more CVD diagnoses was associated with 43% and 56% higher 6-month mortality relative risk (RR 1.43; 95% CI, 1.04 to 1.98; RR 1.56; 95% CI, 1.29 to 1.88), respectively, compared with those without CVDs. It is worth noting that the increased mortality risk associated with CVD was reduced within 6 months of starting treatment.[28] Both the current study and the study conducted by Lu-Yao et al. emphasize the importance of evaluating outcomes in patients who do not meet pivotal trial eligibility criteria in the real-world setting.[28] The current extends the study from Lu-Yao by including additional years of data (2014-2015) and providing clinically relevant comparisons between AA vs. chemotherapy and ENZ. vs. chemotherapy.

An observational study also found that patients treated with ENZ vs. AA had a longer median treatment duration (9.93 vs. 8.47 months, respectively; P = 0.0008).[27] Furthermore, patients treated with ENZ had better overall survival (OS) than patients treated with AA (HR, 0.71; 95% CI, 0.62 to 0.82).[27] In comparison to the previous study, which used the VHA database, the current study used the SEER-Medicare linked database, representing roughly 97% aged 65 and older and 28% of the total US population.[9] In the pivotal trials, toxicity associated with AA was primarily driven by corticosteroid use, including volume overload and electrolyte abnormalities that impact CVD,[30,31]. In contrast, significant fatigue, diarrhea, and a risk of seizures were associated with ENZ. use. [32,33]

There are several limitations of this study. First, this observational study cannot rule out the possibility of confounding by indication. It is possible that medical oncologists are choosing chemotherapy over OASI for patients with more advanced mCRPC. We utilized sophisticate

analytic methods in an attempt to account for differences across comparison groups, but residual confounding may exist. Another limitation of our study is that we cannot directly identify patients with mCRPC because testosterone and PSA levels are not available in the dataset. We believe that our inclusion of patients who have received an OASI between 2011-2015 closely approximates an mCRPC patient population because few other patients would be able to access this treatment via Medicare during that time. On the other hand, a strength of this study is the inclusion of a population-based group of patients who may not all meet the strict criteria of randomized clinical trials; thereby, this study provides results that are likely more generalizable to the mCRPC patient population overall.

CONCLUSION

This study, using real-world data of prostate cancer patients aged 65 and over, found that OASI vs. chemotherapy is associated with a significant improvement in the all-cause and prostate cancer-specific mortality for all groups, including those with pre-existing CVD. Indeed, those with pre-existing CVD should numerically better relative risk in response to OASIs; ENZ and AA both showed beneficial effects relative to chemotherapy, with ENZ showing numerically greater benefits across groups, particularly among those with pre-existing CVD. Given a lack of randomized data directly comparing OASI vs. chemotherapy, this observational study provides clinically meaningful results that can inform patient and clinician decision-making for CRPC with concomitant CVD comorbidities.

TABLES

Table 2.1: Baseline Demographics of Castration-Resistance Prostate Cancer (CRPC) Patients Stratified by Pre-existing CVD History

Characteristics	Pre-existing CVD Comorbidities				No Pre-existing CVD Comorbidities			
	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*
Total	1,683 (100)	1,162 (69)	521 (31)		925 (100)	636 (69)	289 (31)	
Age at Diagnosis, y								
65-69	318 (19)	223 (19)	95 (18)	**0.007**	322 (35)	230 (36)	92 (32)	**0.0012**
70-74	469 (28)	298 (26)	171 (33)		290 (31)	186 (29)	104 (36)	
75-79	438 (26)	302 (26)	136 (26)		172 (19)	107 (17)	65 (22)	
≥ 80	458 (27)	339 (29)	119 (23)		141 (15)	113 (18)	28 (10)	
Race								
White	1,380 (82)	937 (81)	443 (85)	**0.0019**	718 (78)	492 (77)	226 (78)	0.1914
Black	146 (9)	96 (8)	50 (10)		114 (12)	73 (11)	41 (14)	
Asian/Hispanic/N. Am. Native	113 (7)	95 (8)	18 (3)		60 (6)	48 (8)	12 (4)	
Other/Unknown	44 (2)	34 (3)	10 (2)		33 (4)	23 (4)	10 (4)	
Marital Status								
Married	1,099 (65)	743 (64)	356 (68)	0.0804	623 (67)	420 (66)	203 (70)	0.2063
Not Married/Unknown	584 (35)	419 (36)	165 (32)		302 (33)	216 (34)	86 (30)	
SEER Region								
South	328 (19)	220 (19)	108 (21)	0.6902	199 (22)	137 (22)	62 (21)	0.9531
Northeast	403 (24)	285 (25)	118 (23)		160 (17)	109 (17)	51 (18)	
Central	267 (16)	188 (16)	79 (15)		168 (18)	113 (18)	55 (19)	
West	685 (41)	469 (40)	216 (41)		398 (43)	277 (43)	121 (42)	
Population								
Urban	1,411 (84)	970 (84)	441 (85)	0.5472	740 (80)	513 (81)	227 (79)	0.4563
Rural	272 (16)	192 (16)	80 (15)		185 (20)	123 (19)	62 (21)	
Medicaid State Buy-in Status								
Yes	250 (15)	203 (17)	47 (9)	**<.0001**	97 (10)	76 (12)	21 (7)	**0.0312**
No	1,433 (85)	959 (83)	474 (91)		828 (90)	560 (88)	268 (93)	
Census Tract Poverty Indicator								
0% to < 5% poverty	445 (26)	320 (28)	125 (24)	**0.0412**	242 (26)	177 (28)	65 (23)	0.2917
5% to < 10% poverty	468 (28)	332 (29)	136 (26)		253 (28)	165 (26)	88 (30)	
10% to < 20% poverty	481 (29)	308 (26)	173 (33)		263 (28)	181 (28)	82 (28)	
20% to 100% poverty	289 (17)	202 (17)	87 (17)		167 (18)	113 (18)	54 (19)	

Abbreviations: CRPC, castration-resistant prostate cancer; CVD, cardiovascular disease; SEER, Surveillance, Epidemiology, and End Results; N. Am. Native, North America Native; *p*, p-value; y, year.

Statistically significant results are bolded

Table 2.2: Baseline Clinical Characteristics of Castration-Resistance Prostate Cancer (CRPC) Patients Stratified by Pre-existing CVD History

Characteristics	Pre-existing CVD Comorbidities				No Pre-existing CVD Comorbidities			
	Entire Cohort	Treatment Group	Control Group	*P*	Entire Cohort	Treatment Group	Control Group	*P*
	No. (%)	No. (%)	No. (%)		No. (%)	No. (%)	No. (%)	
Median follow-up time (IQR), m	10.3 (14.1)	10.3 (13.5)	10.4 (16.4)		12.1 (15.8)	12 (15.2)	12.7 (17.7)	
Age at First CRPC Treatment, y								
< 75	307 (18)	200 (17)	107 (21)	0.1024	331 (36)	225 (35)	106 (37)	0.7021
≥ 75	1,376 (82)	962 (83)	414 (79)		594 (64)	411 (65)	183 (63)	
Clinical Stage at Diagnosis								
Localized/Regional	1,080 (64)	756 (65)	324 (62)	0.4145	579 (63)	393 (62)	186 (64)	0.6411
Metastatic	455 (27)	303 (26)	152 (29)		298 (32)	211 (33)	87 (30)	
Unknown	148 (9)	103 (9)	45 (9)		48 (5)	32 (5)	16 (6)	
Other Comorbidities ‡								
Diabetes mellitus	758 (45)	535 (46)	223 (43)		225 (24)	148 (23)	77 (27)	
Chronic lower respiratory diseases	549 (33)	394 (34)	155 (30)		120 (13)	84 (13)	36 (12)	
Dementia & Alzheimer diseases	202 (12)	158 (14)	44 (8)		34 (4)	27 (4)	⸸	
Number of cardiovascular conditions								
1	750 (45)	505 (43)	245 (47)	0.1737	***	***	***	***
≥ 2	933 (55)	657 (57)	276 (53)		***	***	***	

Abbreviations: CRPC, castration-resistant prostate cancer; CVD, cardiovascular disease; *p*, p-value; IQR, interquartile range; y, year; m, month.

⸸ Cell size less than 11 are not shown in accordance with SEER-Medicare data use agreement

‡ percentages are not added up

*** Excluded

Statistically significant results are bolded

Table 2.3: Crude and Adjusted HRs for the Association Between Use of Oral Androgen Signaling Inhibitors and the Risk of All-Cause Mortality

	No. of Deaths	No. of Person-Years	Death Rate (per 100 person-years)	95% CI (per 100 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Pre-existing CVD Comorbidities Cohort						
Chemotherapy	373	1,331	28.02	25.32 to 31.02	Ref.	Ref.
Oral Androgen Signaling Inhibitors	517	4,399	11.75	10.78 to 12.81	**0.65 (0.57-0.74)**	**0.59 (0.54-0.64)**
No Pre-existing CVD Comorbidities Cohort						
Chemotherapy	156	815	19.14	16.36 to 22.39	Ref.	Ref.
Oral Androgen Signaling Inhibitors	212	2,415	8.78	7.67 to 10.04	**0.72 (0.58-0.89)**	**0.68 (0.59-0.78)**

Abbreviations: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results.

*Covariates adjusted in the IPTW for the treatment group: age at diagnosis, marital status, SEER region, population location, census tract poverty indicator, Medicaid state buy-in status, clinical stage at diagnosis, race, other comorbidity history (Diabetes Mellitus, Dementia and Alzheimer diseases, and Chronic Lower Respiratory Diseases), and number of cardiovascular conditions (only in pre-existing CVD cohort).

Statistically significant results are bolded

Table 2.4: Subgroup Analysis of the Oral Androgen Signaling Inhibitors of the Risk of All-Cause Mortality

	No. of Deaths	No. of Person-Years	Death Rate (per 100 person-years)	95% CI (per 100 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Pre-existing CVD Comorbidities Cohort						
Chemotherapy	373	1,331	28.02	25.32 to 31.02	Ref.	Ref.
Abiraterone Acetate	420	2,866	14.65	13.32 to 16.13	**0.69 (0.60-0.79)**	**0.63 (0.57-0.69)**
Enzalutamide	97	1,533	6.33	5.19 to 7.72	**0.51 (0.42-0.62)**	**0.47 (0.41-0.54)**
No Pre-existing CVD Comorbidities Cohort						
Chemotherapy	156	815	19.14	16.36 to 22.39	Ref.	Ref.
Abiraterone Acetate	184	1,647	11.17	9.67 to 12.91	**0.75 (0.60-0.93)**	**0.71 (0.61-0.83)**
Enzalutamide	28	768	3.65	2.52 to 5.28	**0.54 (0.40-0.74)**	**0.57 (0.46-0.71)**

Abbreviations: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results.

*Covariates adjusted in the IPTW for the treatment group: age at diagnosis, marital status, SEER region, population location, census tract poverty indicator, Medicaid state buy-in status, clinical stage at diagnosis, race, other comorbidity history (Diabetes Mellitus, Dementia and Alzheimer diseases, and Chronic Lower Respiratory Diseases), and number of cardiovascular conditions (only in pre-existing CVD cohort).

Statistically significant results are bolded

APPENDIX

Table 2.A1: Crude and Adjusted SHRs for the Association Between Use of Oral Androgen Signaling Inhibitors and the Risk of Prostate Cancer Mortality

	No. of PCa Deaths	No. of Person-Years	PCa Death Rate (per 100 person-years)	95% CI (per 100 person-years)	Crude SHR (95% CI)	Adjusted SHR (95% CI)*
Pre-existing CVD Comorbidities Cohort						
Chemotherapy	306	1,331	23	20.55 to 25.72	Ref.	Ref.
Oral Androgen Signaling Inhibitors	409	4,399	9.3	8.44 to 10.24	**0.62 (0.54-0.72)**	**0.60 (0.55-0.66)**
No Pre-existing CVD Comorbidities Cohort						
Chemotherapy	135	815	16.56	13.99 to 19.61	Ref.	Ref.
Oral Androgen Signaling Inhibitors	169	2415	7	6.02 to 8.14	**0.69 (0.55-0.87)**	**0.68 (0.59-0.80)**

Abbreviations: PCa, prostate cancer; SHR, sub-distribution hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results.

*Covariates adjusted in the IPTW for the treatment group: age at diagnosis, marital status, SEER region, population location, census tract poverty indicator, Medicaid state buy-in status, clinical stage at diagnosis, race, other comorbidity history (Diabetes Mellitus, Dementia and Alzheimer diseases, and Chronic Lower Respiratory Diseases), and number of cardiovascular conditions (only in pre-existing CVD cohort).

Statistically significant results are bolded

Table 2.A2: Subgroup Analysis of Oral Androgen Signaling Inhibitors of the Risk of Prostate Cancer Mortality

	No. of PCa Deaths	No. of Person-Years	PCa Death Rate (per 100 person-years)	95% CI (per 100 person-years)	Crude SHR (95% CI)	Adjusted SHR (95% CI)*
Pre-existing CVD Comorbidities Cohort						
Chemotherapy	306	1,331	23	20.55 to 25.72	Ref.	Ref.
Abiraterone Acetate	338	2,866	11.79	10.60 to 13.12	**0.68 (0.58-0.79)**	**0.66 (0.59-0.73)**
Enzalutamide	71	1,533	4.63	3.67 to 5.84	**0.51 (0.41-0.62)**	**0.46 (0.40-0.54)**
No Pre-existing CVD Comorbidities Cohort						
Chemotherapy	135	815	16.56	13.99 to 19.61	Ref.	Ref.
Abiraterone Acetate	149	1,647	9.05	7.70 to 10.62	**0.74 (0.59-0.93)**	**0.73 (0.62-0.86)**
Enzalutamide	20	768	2.6	1.68 to 4.04	**0.56 (0.40-0.78)**	**0.53 (0.42-0.68)**

Abbreviations: PCa, prostate cancer; SHR, sub-distribution hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results.

*Covariates adjusted in the IPTW for the treatment group: age at diagnosis, marital status, SEER region, population location, census tract poverty indicator, Medicaid state buy-in status, clinical stage at diagnosis, race, other comorbidity history (Diabetes Mellitus, Dementia and Alzheimer diseases, and Chronic Lower Respiratory Diseases), and number of cardiovascular conditions (only in pre-existing CVD cohort).

Statistically significant results are bolded

Table 2.A3: Sensitivity Analysis for the Time Difference between CVD Diagnosis Date and CRPC Treatment Initiation Date (All-Cause Mortality)

	No. of Patients	No. of Deaths	Crude HR (95% CI)	Adjusted HR (95% CI)*
1-Day before Cohort Index Enrollment				
Pre-existing CVD Comorbidities Cohort (Total)	**1,742**	**912**		
Chemotherapy	546	384	Ref.	Ref.
Oral Androgen Signaling Inhibitors	1,196	528	**0.64 (0.56-0.73)**	**0.58 (0.53-0.63)**
No Pre-existing CVD Comorbidities Cohort (Total)	**866**	**346**		
Chemotherapy	264	145	Ref.	Ref.
Oral Androgen Signaling Inhibitors	602	201	**0.75 (0.60-0.94)**	**0.71 (0.62-0.82)**
6-Months before Cohort Index Enrollment				
Pre-existing CVD Comorbidities Cohort (Total)	**1,683**	**890**		
Chemotherapy	521	373	Ref.	Ref.
Oral Androgen Signaling Inhibitors	1,162	517	**0.65 (0.57-0.74)**	**0.59 (0.54-0.64)**
No Pre-existing CVD Comorbidities Cohort (Total)	**925**	**368**		
Chemotherapy	289	156	Ref.	Ref.
Oral Androgen Signaling Inhibitors	636	212	**0.72 (0.58-0.89)**	**0.68 (0.59-0.78)**
1-Year before Cohort Index Enrollment				
Pre-existing CVD Comorbidities Cohort (Total)	**1,624**	867		
Chemotherapy	501	363	Ref.	Ref.
Oral Androgen Signaling Inhibitors	1,123	504	**0.65 (0.57-0.75)**	**0.59 (0.54-0.64)**
No Pre-existing CVD Comorbidities Cohort (Total)	**984**	**391**		
Chemotherapy	309	166	Ref.	Ref.
Oral Androgen Signaling Inhibitors	675	225	**0.72 (0.58-0.88)**	**0.65 (0.57-0.75)**

Abbreviations: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results.

*Covariates adjusted in the IPTW for the treatment group: age at first prostate cancer diagnosis, marital status, SEER region, population location, census tract poverty indicator, Medicaid state buy-in status, clinical stage at diagnosis, race, other comorbidity history (Diabetes Mellitus, Dementia and Alzheimer diseases, and Chronic Lower Respiratory Diseases), and number of cardiovascular conditions (only in pre-existing CVD cohort).

Statistically significant results are bolded

Table 2.A4: Sensitivity Analysis for the Time Difference between CVD Diagnosis Date and CRPC Treatment Initiation Date (Prostate Cancer-Specific Mortality)

	No. of Patients	No. of Deaths	Crude SHR (95% CI)	Adjusted SHR (95% CI)*
1-Day before Cohort Index Enrollment				
Pre-existing CVD Comorbidities Cohort (Total)	**1,742**	**734**		
Chemotherapy	546	316	Ref.	Ref.
Oral Androgen Signaling Inhibitors	1,196	418	**0.62 (0.54-0.72)**	**0.60 (0.54-0.66)**
No Pre-existing CVD Comorbidities Cohort (Total)	**866**	**285**		
Chemotherapy	264	125	Ref.	Ref.
Oral Androgen Signaling Inhibitors	602	160	**0.71 (0.56-0.90)**	**0.71 (0.61-0.83)**
6-Months before Cohort Index Enrollment				
Pre-existing CVD Comorbidities Cohort (Total)	**1,683**	**890**		
Chemotherapy	521	373	Ref.	Ref.
Oral Androgen Signaling Inhibitors	1,162	517	**0.62 (0.54-0.72)**	**0.60 (0.55-0.66)**
No Pre-existing CVD Comorbidities Cohort (Total)	**925**	**368**		
Chemotherapy	289	156	Ref.	Ref.
Oral Androgen Signaling Inhibitors	636	212	**0.69 (0.55-0.87)**	**0.68 (0.59-0.80)**
1-Year before Cohort Index Enrollment				
Pre-existing CVD Comorbidities Cohort (Total)	**1,624**	**695**		
Chemotherapy	501	297	Ref.	Ref.
Oral Androgen Signaling Inhibitors	1,123	398	**0.62 (0.54-0.72)**	**0.60 (0.54-0.66)**
No Pre-existing CVD Comorbidities Cohort (Total)	**984**	**324**		
Chemotherapy	309	144	Ref.	Ref.
Oral Androgen Signaling Inhibitors	675	180	**0.69 (0.55-0.86)**	**0.67 (0.58-0.78)**

Abbreviations: SHR, sub-distribution hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results.

*Covariates adjusted in the IPTW for the treatment group: age at first prostate cancer diagnosis, marital status, SEER region, population location, census tract poverty indicator, Medicaid state buy-in status, clinical stage at diagnosis, race, other comorbidity history (Diabetes Mellitus, Dementia and Alzheimer diseases, and Chronic Lower Respiratory Diseases), and number of cardiovascular conditions (only in pre-existing CVD cohort).

Statistically significant results are bolded

FIGURES

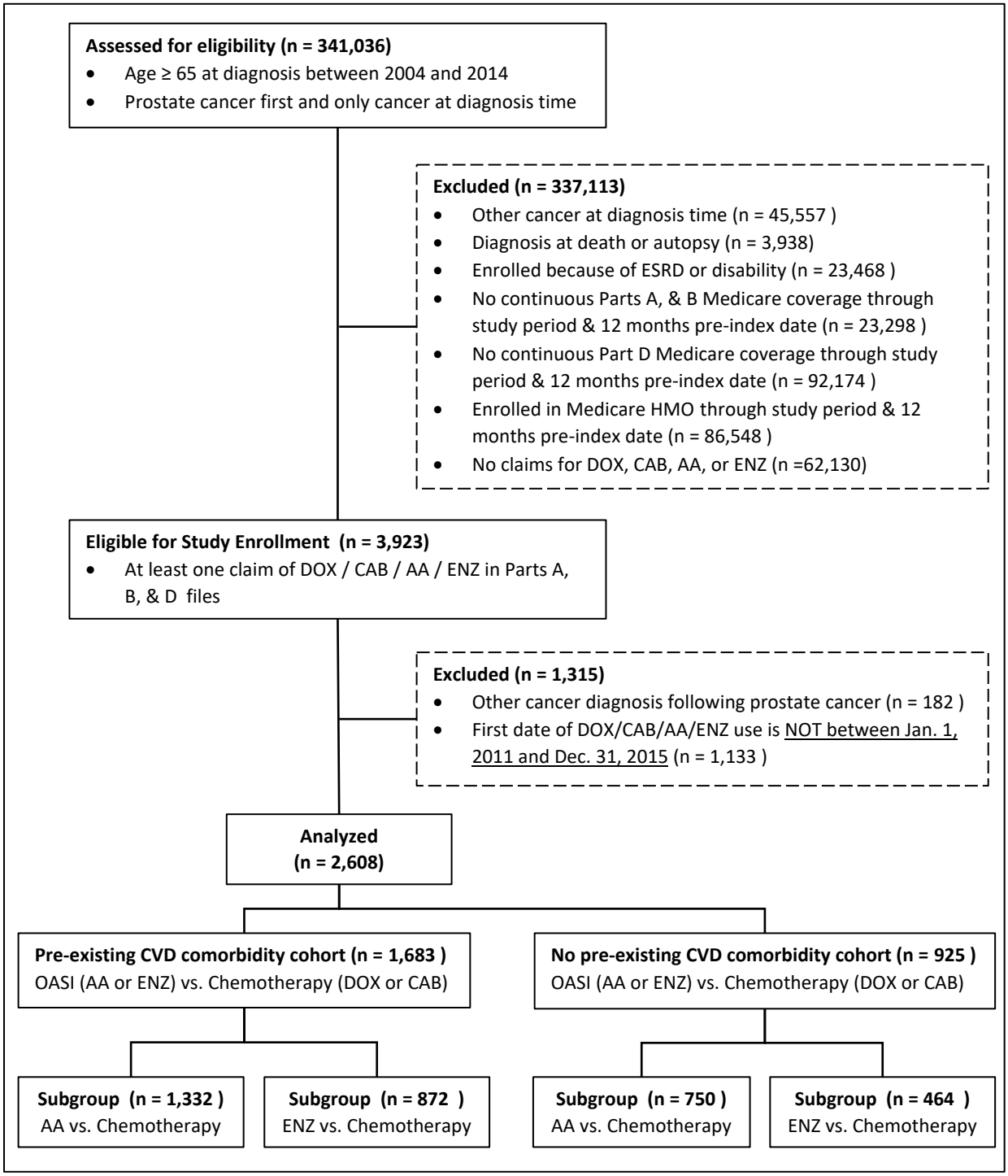
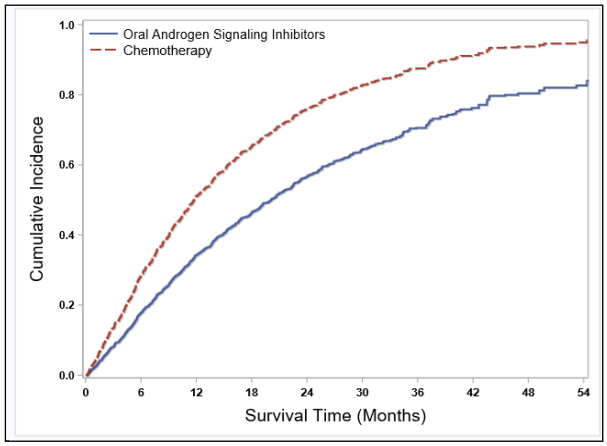


Fig 2.1: Study flow diagram displaying the sample counts for included and excluded observations. Abbreviations: ESRD, end-stage renal disease; CVD, cardiovascular disease; HMO, health maintenance organization; OASI, oral androgen signaling inhibitor; DOX, docetaxel; CAB, cabazitaxel; AA, abiraterone acetate; ENZ, enzalutamide.

(A) Pre-existing Cardiovascular Comorbidity



(B) No Pre-existing Cardiovascular Comorbidity

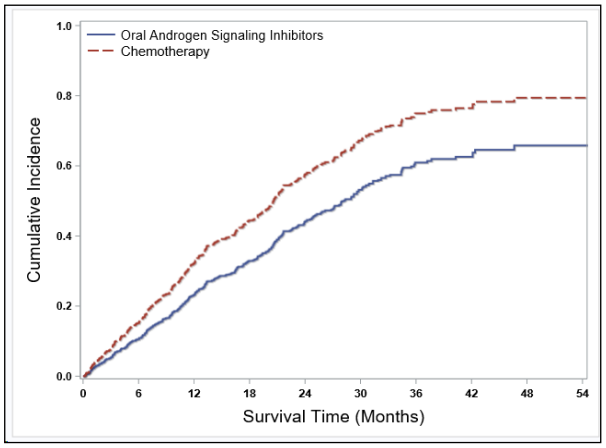
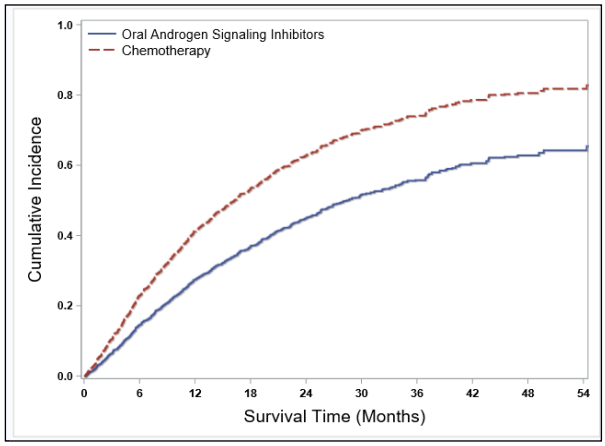


Fig 2.2: Comparing cumulative incidence between new-users of OASI and chemotherapy in all-cause mortality (Gray's test P < .001). Abbreviations: OASI, Oral Androgen Signaling Inhibitors.

(A) Pre-existing Cardiovascular Comorbidity



(B) No Pre-existing Cardiovascular Comorbidity

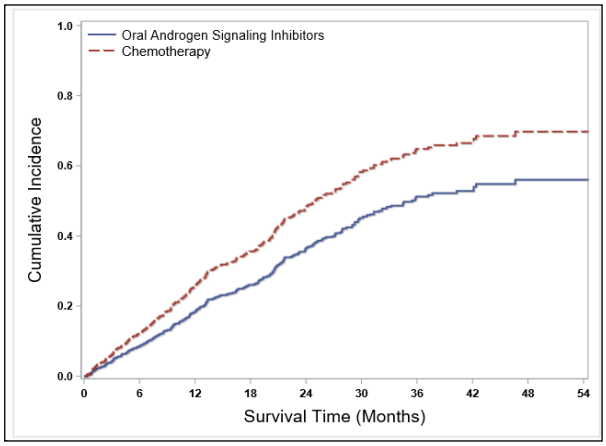


Fig 2.3: Comparing cumulative incidence between new-users of OASI and chemotherapy in prostate cancer specific-cause mortality (Gray's test P < .001). Abbreviations: OASI, Oral Androgen Signaling Inhibitors.

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CHAPTER 3

THROMBOEMBOLIC EVENTS IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS WITH AND WITHOUT PRE-EXISTING CARDIOVASCULAR COMORBIDITIES RECEIVING ORAL ANDROGEN SIGNALING INHIBITORS ⸸

⸸ Asiri, I.M., Cobran, E.K., Young, H.N., et al. To be submitted to *The Journal of Urology*.

ABSTRACT

Background: Most clinical trials for thromboembolic events (TE) in with metastatic castration-resistance prostate cancer (mCRPC) patients receiving oral androgen signaling inhibitors (OASI) excludes patients with pre-existing comorbidities. However, such practice limits the external validity of these trials and findings may not be generalizable to patients with pre-existing comorbidities. This study examine the incidence of new TE in mCRPC patients receiving OASI compared to chemotherapy, with and without a pre-existing history of cardiovascular disease (CVD).

Methods: An active comparator new-user design was used to identify 3,237 men diagnosed with CRPC using the Surveillance, Epidemiology, and End Results-Medicare Linked Database from 2011 to 2016. Patients were stratified by CVD history. Within each CVD stratum (pre-existing CVD vs. no pre-existing CVD), patients were further divided into OASI vs. chemotherapy new-user groups. Inverse probability treatment weights (IPTW)-adjusted Fine-Gray competing risk models were used to evaluate the potential association of OASI and TE. Multiple sensitivity analyses were conducted.

Results: Overall, TE events and crude death incidence rates were higher in patients with prior CVD history than no prior CVD (TE: 3.31% vs. 3.21%; Death: 50% vs. 37%, respectively). The IPTW-adjusted competing risk analysis showed a statistically significant decrease in the sub-distribution Hazard Ratio (SHR) for the TE events associated with OASI compared to chemotherapy in patients with a prior CVD history (SHR 0.24; 95% Confidence Interval [CI],

0.16 to 0.34; P < .001). Likewise, the competing risk analysis revealed that OASI was associated with a lower sub-distribution hazard ratio for TE events than chemotherapy among patients with and without prior CVD history (SHR 0.22; 95% CI, 0.13 to 0.38; P < .001). Findings were consistent in the sensitivity analysis.

Conclusion: This active comparator new-user design study found that OASI was associated with a lower sub-distribution hazard ratio for TE events than chemotherapy among patients with and without pre-existing CVD history.

INTRODUCTION

The National Comprehensive Cancer Network recommends the use of two oral androgen signaling inhibitors (OASI), abiraterone acetate (AA) and enzalutamide (ENZ), as a treatment option for men with metastatic castration-resistant prostate cancer (mCRPC).[1] Both medications were initially approved by the United States Food and Drug Administration in 2011 (AA) and 2012 (ENZ) for CRPC patients who had failed prior docetaxel chemotherapy. Patients with CRPC typically have a poorer prognosis, with a median survival of 15 to 36 months.[2-6] AA and ENZ are often used among prostate cancer patients who are elderly (≥65) and have significant comorbidities.[7]

To date, research studies investigating AA and ENZ treatment are limited, especially among CRPC patients with pre-existing cardiovascular disease (CVD), leaving physicians with little guidance regarding optimal treatment selection. Further, pivotal trials evaluating whether AA prolongs overall survival among patient with mCRPC, excluded men with clinically significant CVD conditions, serious coexisting nonmalignant disease, or uncontrolled hypertension.[8-10] Whereas, pivotal trials of evaluating whether ENZ prolongs overall survival among patients with CRPC excluded patients with significant comorbidities.[11,12]

Cancer-associated venous thromboembolism (VTE) is the second leading cause of death in ambulatory cancer patients, second only to progression of disease.[13] VTE in this population can occur as a result of cancer treatment or secondary to the hypercoagulable state associated with malignancy, with a significantly increased risk of development within the metastatic setting.[14,15] Active prostate malignancy is an increased risk factor for VTE development, especially when patients are undergoing ADT treatment. Along with the therapeutic benefits, ADT increases various metabolic aberrations, including decreased insulin sensitivity, changes in lipid profile,

and increased risk of CVD.[16,17] The increased risk of CVD in men with prostate cancer on ADT has been noted in several observational studies,[16-20] and a proposed explanation of this relationship is that ADT interferes with the cardioprotective property of testosterone, thereby increasing the risk for adverse CVD events.[16]

In a recent study Deka et al.,[21] sought to test the association between ADT use and stroke, transient ischemic attack (TIA), deep vein thrombosis (DVT), and pulmonary embolism (PE) in localized prostate cancer patients. The authors found that there was an overall significant association between ADT and stroke (Sub-distribution Hazard Ratio (SHR) 1.19; 95% CI, 1.09 to1.30), TIA (SHR 1.24; 95% CI, 1.08 to1.41), and DVT (SHR1.18; 95% CI, 1.04 to1.34).[21] However, there was no overall association between ADT and PE (SHR1.16; 95% CI, 0.98 to1.39). [21] These results highlight concerns regarding long-term risks of ADT on stroke and thromboembolic (TE) events in the treatment of prostate cancer.[21]

While the strict eligibility criteria for clinical trials may stem from legitimate concerns about comorbidities affecting response to or toxicity from trial medications, such practice limits the external validity of the trials and findings may not be generalizable to patients with pre-existing CVD and cancer-associated TE.[22-24] To fill this gap, the objective of this study was to examine outcomes associated with OASI in mCRPC patients with a pre-existing history of cardiovascular disease. Specifically, we assessed the incidence of new TE with OASI use compared to chemotherapy. To provide a more stringent analysis, we evaluated the incidence of TE with OASI use compared to chemotherapy in mCRPC patients without a pre-existing history of cardiovascular disease.

METHODS

Data Source

A population-based retrospective cohort was created from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. More detail regarding the SEER-Medicare linked database has been described elsewhere.[25] In brief, The SEER Program of the National Cancer Institute (NCI) collects information about cancer incidence and survival statistics from 19 population-based state or regional cancer registries.[26] Medicare program affords health insurance to 97% of the United States (US) population aged 65 years and older, covering inpatient care (Part A), outpatient care and physician service (Part B), and prescription drugs (Part D).[25] The SEER-Medicare linked database provides comprehensive health care utilization data for Medicare beneficiaries with cancer that represent approximately 28% of the US population.[25]

In this study, several SEER-Medicare data files were utilized. Cancer clinical information at diagnosis, Medicare status, and patients' demographics were obtained from the Patient Entitlement and Diagnosis Summary File (PEDSF). Claims for inpatient and outpatient beneficiaries were served by physicians, and non-institutional provider services (Part B) were captured from the Carrier file (NCH). Further, the Medicare Provider Analysis and Review file (MEDPAR, institutional, through Part A) and the Outpatient files (OUTPAT, institutional, through Part B) were utilized to extract information regarding inpatient cancer care and hospital outpatient services, respectively. Medicare Part D Event files (PDE) was used to capture orally utilized drugs (e.g., Abiraterone Acetate [AA] and Enzalutamide [ENZ]). Chronic Condition Flags file was used to define CRPC patients with pre-existing CVDs versus no pre-existing

CVDs. Finally, the hospice files were used to identify NCH patient status such as death, as well as for capturing procedures, supplies, products, or services provided to Medicare beneficiaries. This study received IRB waiver from the University of Georgia Institutional Review Board.

Analytical Design

An active comparator new user (ACNU) design was conducted to identify OASI use in CRPC patients and chemotherapy initiation in the SEER-Medicare Linked Database between January 1, 2011, through December 31, 2016 (Fig A1; Appendix). This study design was developed to avoid biases such as indication bias, healthy initiator bias, and selection bias in nonexperimental observational studies[27-29] that have been recommended to be implemented whenever possible.[30] The purpose of the active comparator arm [OASI (AA and ENZ) vs. chemotherapy (Docetaxel [DOX] and Cabazitaxel [CAB])] was to mitigate confounding by indication and other unmeasured patient characteristics such as frailty.[27,28] The chemotherapy (DOX and CAB) alternatives were chosen based on the time and the availability of the treatment options for CRPC patients in the NCCN guideline.[31] In the new user design arm, we defined treatment initiation based on a 6-month washout period that represents a fixed window prior to the first use of any of the drugs of interest.

A 6-month washout period was selected based on previous evaluations of periods greater than 12 months and shorter than 6 months that revealed misclassifications of true new use.[32] For the washout period in the orally taken drugs (AA and ENZ), the discontinuation date of the last prescription before the index date was defined as (the last dispensing date + the days' supply [30 days] + a grace period [15 days]) to ensure there was no previous use of the drug (Fig A1; Appendix).[27,8] Further, we stratified the CRPC cohort into having pre-existing CVDs versus no pre-existing CVDs based on the CMS Chronic Conditions Data Warehouse (CCW) algorithms

using Chronic Condition Flags file.[33] Pre-existing CVDs were defined as having atrial fibrillation, acute myocardial infarction, congestive heart failure, stroke, or ischemic heart disease 12 months before CRPC treatment initiation. If a CRPC patient did not have any of the defined CVDs before the index time, the patient would be enrolled in the no pre-existing CVDs stratum. For each patient, follow-up continued until the occurrence of TE, death from any cause, end of the study period (December 31, 2016), or the participant is lost, whichever occurred first.

Study Cohort

Patients were included in the study cohort if they had: (1) first and only prostate cancer diagnosis (International Classification of Diseases, 9th Revision, Clinical Modification, [ICD-9-CM] code 185.xx, [ICD-10-CM] code C61.xx); (2) at least 12 months of continuous eligibility Part A, B, and D pre-index (baseline period). Patients were excluded from the study if they had: (1) other cancer diagnoses; (2) diagnosis at death or autopsy; (3) Medicare HMO through study period & 12 months pre-index date; and (4) no predefined therapy agent claims; and (5) enrollment because of End-Stage Renal Disease (ESRD) or disability.

CRPC patients were defined based on the clinical guidelines for the treatments received (DOX, CAB, AA, or ENZ) during the period of the FDA approval for CRPC condition (2011-2016).[31,34] Since our drugs of interest have not yet expanded their FDA approval to cover other castration sensitive prostate cancer, we assumed these patients were diagnosed with CRPC based on this study timeline (2011-2016). The exposure cohort was defined as CRPC patients receiving OASI (AA or ENZ) from January 1, 2011, through December 31, 2016. The comparison cohort was defined as CPRC patients receiving chemotherapy (DOX or CAB) January 1, 2011, through December 31, 2016.[31,34] Healthcare Common Procedure Coding System (HCPC) codes were

used to identify DOX (J9171 and J9170) and CAB (J9043 and C9276). Figure 1 presents the details on the inclusion and exclusion criteria to create the analytical cohort.

Outcomes

We examined outcomes associated with OASI in CRPC patients with a pre-existing history of cardiovascular disease. Specifically, we assessed the association of new TE with OASI use compared to chemotherapy. In order to conduct a conservative follow-up analysis, we also examined the burden of new TE associated with OASI use in patients without a pre-existing CVD compared to CRPC patients with a pre-existing history of CVD separately. The definition of new TE events was based on the presence of deep vein thrombosis (DVT), pulmonary embolism (PE), or arterial embolism (AE) after the date of initiation of OASI and chemotherapy (Table A1; Appendix).[21] Since the analytical cohort of this study was a geriatric population who were in their end-stage of prostate cancer; we considered death from any cause as a competing risk to the primary outcome.[35] We excluded cardiovascular death from the competing risk analysis.

Covariates

Demographic characteristics including race (White, Black, Asian/Hispanic/North American Native, and Other/Unknown), age at first CRPC treatment (66-70 years, 71-75 years, 76-79 years, and ≥ 80 years), marital status (grouped into married and not married or missing / unknown), and population density (urban vs. rural) were obtained from the SEER. SEER regions were grouped into Northeast (Connecticut, New Jersey), South (Atlanta, rural Georgia, Kentucky, Louisiana), Central (Detroit, Iowa, New Mexico, Utah), and West (San Francisco, Hawaii, Seattle, San Jose, Los Angeles, greater California). Medicaid state buy-in variable was

categorized to yes or no for identifying Medicare and Medicaid dual enrollees as used previously in population-based studies.[36-38] Men were also categorized into four groups based on census tract poverty indicator for income percentile 0%-<5%, 5%-<10%, 10%-<20%, and 20%-100%.

For clinical characteristics, other comorbidities (diabetes mellitus, chronic lower respiratory diseases, and dementia & Alzheimer's diseases) were chosen to be included in the analysis as shown to be from the top ten causes of death in the elderly.[39] Other causes of death in elderly patients were not included as they were not available in the Chronic Condition Flags file. In the pre-existing CVD stratum, a CVD variable indicator was created with one and two or more CVDs because these conditions were not mutually exclusive. The use of the anticoagulants at the first time of the CRPC treatment was defined as yes versus no. Anticoagulant use was defined as having at least one prescription in the past six months before the study's enrollment date.

Statistical analysis

Descriptive statistics were conducted for each stratum (pre-existing vs. no pre-existing CVD) separately to describe the baseline characteristics of the study cohort. To address the issue of selection bias and heterogeneity among patients, propensity scores using inverse probability treatment weights (IPTWs) were utilized for each stratum (pre-existing vs. no pre-existing CVD) separately.[40] Propensity scores were estimated by multivariable logistic regression, generating a covariate summary score (initial weight) which was defined as the probability of a CRPC patient to receive either OASI or chemotherapy conditional on all the identified covariates.[40,41] Covariates used in the logistic regression included a race, age at first CRPC treatment use, marital status, SEER region, population density, regional poverty indicator, Medicaid state buy-in status, other comorbidities (diabetes mellitus, chronic lower respiratory diseases, and dementia

& Alzheimer diseases), number of cardiovascular conditions (only in pre-existing CVD patients), and anticoagulant use (only in pre-existing CVD patients).

Then, pseudo populations were created that represent weighting each patient's contribution by the inverse probability (IPTW) of receiving the drug actually received in each stratum. To assess the limits of the potential for influential patients to bias results, such as those in these groups treated contrary to prediction, checks of the maximum weights (≤10) and the closeness of the mean weights to 1.0,[42] were conducted. To ensure well-balanced variables, we followed the conservative approach that recommended the absolute standardized mean difference should be less than or equal to 0.1.[43]

The final weights were implemented to the Fine-Gray sub-distribution hazard competing risk model.[44] The model was used to evaluate any potential association of the OASI and TE accounting for death from any cause as a competing risk. Cumulative incidence function graphs were estimated for TE events in each stratum (pre-existing vs. no pre-existing CVD) separately. Gray's test was used to evaluate differences in the cumulative incidence function graphs between patients with OASI and chemotherapy.

Sensitivity analyses

Since we focused our analysis on stratifying likely CRPC patients based on whether they had CVD history, men in the pre-existing CVD group may have previously experienced thromboembolic (TE) events that may have an impact on evaluating a new incident of TE. A study showed that men with a history of TE events who currently use androgen deprivation therapy (ADT) were more likely to have future TE events.[45] Other studies that have sought to

explore the association between ADT and TE events excluded men with a history of TE events to eliminate their impact on evaluating a new incident of TE.[46,47]

Additionally, given the nature of the research context, these patients would have already been placed on before or concomitantly used ADT with the CRPC treatment. Therefore, in our first sensitivity analysis approach, we excluded men with a history of TE events looking back one year before the first date of the CRPC treatment. Table A2 shows the distribution of the incidence of TE diagnoses and deaths based on the exclusion criteria. In the second sensitivity analysis approach, we incorporated a time-varying definition of the exposure variable. This approach allowed patients to transition across OASI and chemotherapy during the follow-up period of the "as-treated analysis" study.[27] Statistical significance thresholds were set at significance level $\alpha = 0.05$; all tests were 2-tailed. All analyses were performed using SAS Statistical Software Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics and TE in CRPC Patients Stratified by CVD History

The study cohort included 3,237 men with CRPC who met the inclusion criteria (Fig 1). A total of 2,147 patients (66%) and 1,090 patients (34%) had pre-existing CVD and no pre-existing CVD, respectively. Baseline demographic and clinical characteristics comparing likely CRPC patients who had pre-existing CVD and those without pre-existing CVD are listed in Tables 1 and 2. The median follow-up time in months was lower in patients with pre-existing CVD compared with no pre-existing CVD (Median time (IQR): 11.6 (16.2) vs. 14.3 (17.5), respectively; Table 2). The crude incidence rates of TE events and death were higher in patients

with pre-existing CVD compared with no pre-existing CVD (TE: 3.31% vs. 3.21%; Death: 50% vs. 37%, respectively; Appendix Table A2).

Baseline and Risk of TE Associated with OASI in Patients with Pre-existing CVD

A total of 2,147 patients had pre-existing CVD, of which 1,498 (70%) received OASI. Baseline characteristics of CRPC patients who had pre-existing CVD and received OASI comparing those who received chemotherapy are listed in Tables 1 and 2. Patients who received OASI were more likely aged ≥ 80 at the first CRPC treatment, Asian/Hispanic/North American Native, not married or missing/unknown, had Medicaid state buy-in status, and had anticoagulant use history in the past six months compared with those who received chemotherapy (all $P < .05$; Tables 1 and 2).

The IPTW-adjusted competing risk analysis showed a statistically significant decrease in the sub-distribution Hazard Ratio (SHR) for the TE events associated with OASI (SHR 0.24; 95% Confidence Interval [CI], 0.16 to 0.34; $P < .001$, Table 3) compared with chemotherapy. This association was found to be consistent in the two sensitivity analyses. In the first sensitivity analysis, men with a history of TE events were excluded (SHR 0.23; 95% CI, 0.16 to 0.37; $P < .001$, Table 3). In the second sensitivity analysis, switching between drugs was considered time-varying exposure during the study's follow-up period (SHR 0.25; 95% CI, 0.17 to 0.36; $P < .001$, Table 3).

Chi-square test revealed that the crude incidence rates of TE events and death were higher in patients who received chemotherapy compared with patients on OASI (TE: 7% vs. 2%; Death: 51% vs. 37%, respectively; Appendix Table A2). The cumulative incidence curves for OASI and

chemotherapy were statistically different in the TE events taking into account death (Gray's test P < .001, Fig. 2).

Baseline and Risk of TE Associated with OASI in Patients without Pre-existing CVD

There was a total of 1,090 patients without pre-existing CVD, of which 726 (67%) received OASI. Baseline characteristics comparing CRPC patients who had no pre-existing CVD and received OASI to those who received chemotherapy are listed in Tables 1 and 2. Patients who received OASI were more likely to be not married or missing/unknown and had Medicaid state buy-in status compared with those who received chemotherapy (all P < .05; Table 1).

Similar to the patients with pre-existing CVD history, the IPTW-adjusted competing risk analysis revealed that a statistically significant decrease in the sub-distribution hazard ratio for the TE events associated with OASI compared with chemotherapy (SHR 0.22; 95% CI, 0.13 to 0.38; P < .001, Table 3). Results of the association were consistent in the sensitivity analysis (Table 3). Likewise, the cumulative incidence curves for OASI and chemotherapy were statistically different in the TE events taking into account death (Gray's test P < .001, Fig. 2).

DISCUSSION

The National Comprehensive Cancer Network recommends the use of two OASI, AA and ENZ, as a treatment option for men with CRPC.[1] Both medications are often used among prostate cancer patients who are elderly (≥65) and have significant comorbidities.[48] The potential benefit of AA and ENZ may depend on the health conditions of the patient.[49] To date, research studies investigating AA and ENZ treatment are limited, especially among CRPC patients with pre-existing CVD, leaving physicians with little guidance regarding optimal

treatment selection. To our knowledge, this is one of two US-based large population-based cohort studies assessing outcomes of OASI in CRPC patients with pre-existing CVD. Our study revealed an overall significant association in decreasing the sub-distribution hazard ratio for the TE events associated with OASI compared with chemotherapy. The overall direction of these associations did not differ between patients with and without a history of CVD. There was a decrease in the overall significant association between OASI and TE events in patients with a CVD history (SHR 0.24; 95% CI, 0.16 to 0.34; P < .001). Similarly, in the patients with no history of CVD (SHR 0.22; 95% CI, 0.13 to 0.38; P < .001). This reflects the overall decrease in TE events for patients who have started their OASI treatment plan and have not yet experienced an outcome event, taking into account the competing death event.

In large data sets such as in this study, where the number of events is small relative to the number of patients at risk, the cumulative incidence of the TE event is equal to the cumulative probability of occurrence of TE event in the presence of competing death.[50] In other words, the cumulative incidence of TE event is highly significantly lower among the new user patients of OASI in both cohorts (pre-existing vs. no pre-existing CVD; Gray's test P < .001). However, when the TE event's cumulative probability of occurrence was compared between the pre-existing CVD cohort and the no-pre-existing CVD cohort, the pre-existing CVD cohort had a faster cumulative probability of occurrence. Further, the divergence in cumulative incidence curves was evident before the first six months of starting CRPC treatment in the pre-existing CVD cohort, but not in the no pre-existing CVD cohort. Results of the association were consistent in the sensitivity analyses.

In the other US-based large population-based cohort study assessing short-term outcomes with OASI use, Lu-Yao et al.,[48] found among post- and no-chemotherapy advanced prostate

cancer patients treated with OASI, having three or more CVD diagnoses was associated with 43% and 56% higher 6-month mortality relative risk (RR 1.43; 95% CI, 1.04 to 1.98; RR 1.56; 95% CI, 1.29 to 1.88), respectively, compared with those without CVDs. The elevated mortality risk associated with CVD attenuated within 6 months of treatment initiation.[48] Both the current study and the investigation conducted by Lu-Yao et al., highlight the importance of conducting outcomes evaluation among patients not meeting pivotal trial eligibility criteria in the real-world setting.[48]

Since clinical trials investigating AA and ENZ among CRPC patients, excludes men with clinically significant CVD conditions, serious coexisting nonmalignant disease, or uncontrolled hypertension.[8-10] The external validity of these trials and findings may not be generalizable to patients with pre-existing comorbidities.[22-24] The current study allowed for the comparison of pre-existing CVDs versus no pre-existing CVDs separately to appropriately reflect real-world clinical practice. This study revealed a significant decrease in the sub-distribution hazard ratio for the TE events associated with OASI compared with chemotherapy. However, the potential TE effects of OASI did not differ between patients with and without a history of prior CVD, warrants further investigation. One reason that might explain the hinder of the potential TE effects of OASI is that all CRPC patients may remain on their pervious ADT treatment and OASI or chemotherapy is added on top of ADT treatment. Since all of these patients might get ADT, this might explain why there is no difference in TE outcomes between patients with and without a history of prior CVD.

Klil-Drori et al.,[47] conducted a large population-based cohort study to determine whether the use of different types of ADT in patients with prostate cancer is associated with an increased incidence of venous thromboembolism (VTE). Current ADT use was associated with an 84%

increased risk of VTE (incidence rates: 10.1 vs. 4.8 per 1000 person-years; HR 1.84; 95% CI, 1.50 to 2.26), whereas, there was no association with past use (HR: 1.07; 95% CI, 0.81 to 1.42).[47] The use of ADT likely increase thrombosis via a perturbed equilibrium between clot formation and fibrinolysis, induced by the testosterone-lowering effect of ADT therapy.[47] Klil-Drori et al.,[47] concluded that the increased risk of VTE calls for careful consideration of ADT use in low-risk prostate cancer population for whom the benefits of this therapy are less certain. It is well established that ADT treatment has potential TE effects on prostate cancer patients.[16-21]

A population-based case-control study sought to estimate the magnitude of risk factors for deep vein thrombosis and pulmonary embolism.[51] The study revealed that a diagnosis with cancer alone was associated with a 4-fold increased risk of vein TE, and receiving chemotherapy increased cancer-associated risk to more than 6-fold.[51] It is worth noting that our study found that OASI, compared to chemotherapy, was associated with a lower sub-distribution hazard ratio for TE events. Furthermore, the cumulative incidence curves demonstrated that the TE event's cumulative probability of occurrence was much higher in patients with a pre-existing CVD history compared to patients with no pre-existing CVD history. This finding suggested that starting or adding chemotherapy to the treatment regimen of CRPC patients who were previously treated with ADT increased the risk of TE events when compared to OASI.

This study has limitations that warrant mention. The validated combined NCI comorbidity score for claims data has not been used in this study since the calculated score included cardiovascular conditions that may overestimate the model's composite comorbidity score. Some patients may use ADT concurrently with or after the initiation of OASI or chemotherapy that perhaps adds to the risk of a new TE incident. Nevertheless, we used an active comparator, new user design to identify OASI use in CRPC patients and chemotherapy initiation. This study

design was developed to avoid biases such as indication bias, healthy initiator bias, and selection bias in nonexperimental observational studies.[27-29]

Further, we stratified the CRPC cohort into having pre-existing CVDs versus no pre-existing CVDs based on the CMS Chronic Conditions Data Warehouse (CCW) algorithms using the Chronic Condition Flags file.[33] This allowed for the comparison of pre-existing CVDs versus no pre-existing CVDs separately to fully assess a new incident of TE in CRPC patients and drawing the right conclusion about the TE burden in the pre-existing CVD cohort. In this study, we further considered death from any cause as a competing risk to the new incidence of TE to appropriately reflect real-world clinical practice. Finally, to address the issue of selection bias and heterogeneity among patients, propensity scores using inverse probability treatment weights (IPTWs) were utilized for pre-existing versus no pre-existing CVD stratum separately.

CONCLUSIONS

The current study found that OASI was associated with a lower sub-distribution hazard ratio for TE events compared with chemotherapy among patients with and without pre-existing CVD history. However, the divergence in the cumulative incidence curves was much higher and evident before the first six months of starting CRPC treatment in the pre-existing CVD cohort, but not in the no pre-existing CVD cohort.

TABLES

Table 3.1: Demographics Characteristics of Castration-Resistance Prostate Cancer (CRPC) Patients Stratified by Pre-existing CVD History

Characteristics	Pre-existing CVD Comorbidities				No Pre-existing CVD Comorbidities			
	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*
Total	2,147 (100)	1,498 (70)	649 (30)		1,090 (100)	726 (67)	364 (33)	
Age at First CRPC Treatment, y								
66-70	66 (3)	46 (3)	20 (3)	<.01**	122 (11)	79 (11)	43 (12)	0.4
71-75	365 (17)	233 (16)	132 (20)		300 (28)	201 (28)	99 (27)	
76-79	509 (24)	321 (21)	188 (29)		289 (26)	183 (25)	106 (29)	
≥ 80	1,207 (56)	898 (60)	309 (48)		379 (35)	263 (36)	116 (32)	
Race								
White	1,753 (82)	1,194 (80)	559 (86)	<.01**	847 (78)	559 (77)	288 (79)	0.07
Black	195 (9)	133 (9)	62 (10)		129 (12)	80 (11)	49 (13)	
Asian/Hispanic/N. Am. Native	136 (6)	120 (8)	16 (2)		73 (7)	58 (8)	15 (4)	
Other/Unknown	63 (3)	51 (3)	12 (2)		41 (4)	29 (4)	12 (3)	
Marital Status								
Married	1,418 (66)	961 (64)	457 (70)	<.01**	713 (65)	453 (62)	260 (71)	<.01**
Not Married or Missing/Unknown	729 (34)	537 (36)	192 (30)		377 (35)	273 (38)	104 (29)	
SEER Region								
South	403 (19)	268 (18)	135 (21)	0.38	230 (21)	145 (20)	85 (23)	0.32
Northeast	523 (24)	367 (24)	156 (24)		190 (18)	136 (19)	54 (15)	
Central	324 (15)	234 (16)	90 (14)		186 (17)	122 (17)	64 (18)	
West	897 (42)	629 (42)	268 (41)		484 (44)	323 (44)	161 (44)	
Population Density								
Urban	1,814 (84)	1,268 (85)	546 (84)	0.76	873 (80)	582 (80)	291 (80)	0.93
Rural	333 (16)	230 (15)	103 (16)		217 (20)	144 (20)	73 (20)	
Medicaid State Buy-in Status								
Yes	429 (20)	359 (24)	70 (11)	<.01**	193 (18)	154 (21)	39 (11)	<.01**
No	1,718 (80)	1,139 (76)	579 (89)		897 (82)	572 (79)	325 (89)	
Regional Poverty Indicator								
0% to < 5% poverty	569 (26)	396 (26)	173 (27)	0.07	282 (26)	197 (27)	85 (23)	0.37
5% to < 10% poverty	601 (28)	430 (29)	171 (26)		305 (28)	196 (27)	109 (30)	
10% to < 20% poverty	613 (29)	405 (27)	208 (32)		301 (28)	194 (26)	107 (29)	
20% to 100% poverty	364 (17)	267 (18)	97 (15)		202 (18)	139 (19)	63 (17)	

Abbreviations: CRPC, castration-resistant prostate cancer; CVD, cardiovascular disease; SEER, Surveillance, Epidemiology, and End Results; N. Am. Native, North America Native; *p*, p-value; y, year.

* p-value < .05; ** p-value < .01

Table 3.2: Clinical Characteristics of Castration-Resistance Prostate Cancer (CRPC) Patients Stratified by Pre-existing CVD History

Characteristics	Pre-existing CVD Comorbidities				No Pre-existing CVD Comorbidities			
	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*
Median follow-up time (IQR), m	11.6 (16.2)	12.2 (15.9)	9.9 (15.7)		14.3 (17.5)	15.4 (17.0)	11.3 (16.7)	
Other Comorbidities ‡								
Diabetes mellitus	984 (46)	701 (47)	283 (44)		280 (26)	183 (25)	97 (27)	
Chronic lower respiratory diseases	721 (34)	526 (35)	195 (30)		149 (14)	105 (15)	44 (12)	
Dementia & Alzheimer diseases	282 (13)	222 (15)	60 (9)		46 (4)	40 (6)	⸸	
Number of cardiovascular conditions								
1	933 (43)	634 (42)	299 (46)	0.11	***	***	***	
≥ 2	1,214 (57)	864 (58)	350 (54)		***	***	***	
Anticoagulants use								
No - use at 1st CRPC Treatment	1,996 (93)	1,359 (91)	637 (98)	<.01**	***	***	***	
Yes - use at 1st CRPC Treatment	152 (7)	139 (9)	12 (2)		***	***	***	

Abbreviations: CRPC, castration-resistant prostate cancer; CVD, cardiovascular disease; *p*, p-value; IQR, interquartile range; m, month.

⸸ Cell size less than 11 are not shown in accordance with SEER-Medicare data use agreement

‡ percentages are not added up

* p-value < .05; ** p-value < .01

Table 3.3: Crude and Adjusted SHRs for the Association Between the Use of Oral Androgen Signaling Inhibitors and the Risk of Thromboembolic Events

	Pre-existing CVD Comorbidities		No Pre-existing CVD Comorbidities	
	Unadjusted model	IPTW-adjustment Competing Risk Model ‡	Unadjusted model	IPTW-adjustment Competing Risk Model ‡
	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)	SHR (95% CI)
Primary Analysis	0.23 (0.14-0.38)	0.24 (0.16-0.34)	0.21 (0.10-0.44)	0.22 (0.13-0.38)
Sensitivity Analyses				
1. Excluded patients with TE events history *	0.23 (0.14-0.37)	0.23 (0.16-0.37)	0.21 (0.10-0.43)	0.22 (0.13-0.37)
2. Time-dependent exposure variable δ	0.26 (0.15-0.42)	0.25 (0.17-0.36)	0.26 (0.13-0.53)	0.27 (0.16-0.46)

Abbreviations: CVD, cardiovascular disease; TE, thromboembolic event; SHR, sub-distribution hazard ratio; CI, confidence interval; IPTW; inverse probability treatment weight.

‡Covariates adjusted in the IPTW were race, age at first CRPC treatment use, marital status, SEER region, population density, regional poverty indicator, Medicaid state buy-in status, other comorbidities (diabetes mellitus, chronic lower respiratory diseases, and dementia & Alzheimer diseases), number of cardiovascular conditions (only in pre-existing CVD patients), and anticoagulant use (only in pre-existing CVD patients).

* In the first sensitivity analysis, we excluded patients who had at least one TE event one year back before the study enrollment date.

δ In the second sensitivity analysis, we incorporated a time-dependent exposure variable that allowed patients to transition from oral androgen signaling inhibitors to chemotherapy and vice versa.

APPENDIX

Table 3.A1: Codes and Terms for Thromboembolic Events	
Codes	Terms
Pulmonary Embolism	
ICD-9-CM	
415x	Acute pulmonary heart disease
415.0	Acute cor pulmonale
415.1x	Pulmonary embolism and infarction
415.11	Latrogenic pulmonary embolism and infarction
415.12	Septic pulmonary embolism
415.13	Saddle embolus of pulmonary artery
415.19	Other pulmonary embolism and infarction
ICD-10-CM	
I26.0x	Pulmonary embolism with acute cor pulmonale
I26.01	Septic pulmonary embolism with acute cor pulmonale
I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale
I26.09	Other pulmonary embolism with acute cor pulmonale
I26.9x	Pulmonary embolism without acute cor pulmonale
I26.90	Septic pulmonary embolism without acute cor pulmonale
I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale
I26.99	Other pulmonary embolism without acute cor pulmonale
Arterial Embolism	
ICD-9-CM	
444.0x	Embolism and thrombosis of abdominal aorta
444.01	Saddle embolus of abdominal aorta
444.09	Other arterial embolism and thrombosis of abdominal aorta
444.1	Embolism and thrombosis of thoracic aorta
444.2x	Embolism and thrombosis of arteries of the extremities
444.21	Arterial embolism and thrombosis of upper extremity
444.22	Arterial embolism and thrombosis of lower extremity
444.8x	Embolism and thrombosis of other specified artery
444.81	Embolism and thrombosis of iliac artery
444.89	Embolism and thrombosis of other specified artery
444.9	Embolism and thrombosis of unspecified artery
ICD-10-CM	
I74.0x	Embolism and thrombosis of abdominal aorta
I74.01	Saddle embolus of abdominal aorta

I74.09	Other arterial embolism and thrombosis of abdominal aorta
I74.1x	Embolism and thrombosis of other and unspecified parts of aorta
I74.10	Embolism and thrombosis of unspecified parts of aorta
I74.11	Embolism and thrombosis of thoracic aorta
I74.19	Embolism and thrombosis of other parts of aorta
I74.2	Embolism and thrombosis of arteries of the upper extremities
I74.3	Embolism and thrombosis of arteries of the lower extremities
I74.4	Embolism and thrombosis of arteries of extremities, unspecified
I74.5	Embolism and thrombosis of iliac artery
I74.8	Embolism and thrombosis of other arteries
I74.9	Embolism and thrombosis of unspecified artery
Deep Vein Thrombosis	
ICD-9-CM	
453.4x	Acute venous embolism and thrombosis of deep vessels of lower extremity
453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
453.5x	Chronic venous embolism and thrombosis of deep vessels of lower extremity
453.50	Chronic venous embolism and thrombosis of unspecified deep vessels of lower extremity
453.51	Chronic venous embolism and thrombosis of deep vessels of proximal lower extremity
453.52	Chronic venous embolism and thrombosis of deep vessels of distal lower extremity
ICD-10-CM	
I82.4xx	Acute embolism and thrombosis of deep veins of lower extremity
I82.40x	Acute embolism and thrombosis of unspecified deep veins of lower extremity
I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity
I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity
I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral
I82.409	Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity
I82.41x	Acute embolism and thrombosis of femoral vein
I82.411	Acute embolism and thrombosis of right femoral vein
I82.412	Acute embolism and thrombosis of left femoral vein
I82.413	Acute embolism and thrombosis of femoral vein, bilateral
I82.419	Acute embolism and thrombosis of unspecified femoral vein
I82.42x	Acute embolism and thrombosis of iliac vein
I82.421	Acute embolism and thrombosis of right iliac vein
I82.422	Acute embolism and thrombosis of left iliac vein
I82.423	Acute embolism and thrombosis of iliac vein, bilateral
I82.429	Acute embolism and thrombosis of unspecified iliac vein
I82.43x	Acute embolism and thrombosis of popliteal vein
I82.431	Acute embolism and thrombosis of right popliteal vein
I82.432	Acute embolism and thrombosis of left popliteal vein
I82.433	Acute embolism and thrombosis of popliteal vein, bilateral
I82.439	Acute embolism and thrombosis of unspecified popliteal vein
I82.44x	Acute embolism and thrombosis of tibial vein

I82.441	Acute embolism and thrombosis of right tibial vein
I82.442	Acute embolism and thrombosis of left tibial vein
I82.443	Acute embolism and thrombosis of tibial vein, bilateral
I82.449	Acute embolism and thrombosis of unspecified tibial vein
I82.49x	Acute embolism and thrombosis of other specified deep vein of lower extremity
I82.491	Acute embolism and thrombosis of other specified deep vein of right lower extremity
I82.492	Acute embolism and thrombosis of other specified deep vein of left lower extremity
I82.493	Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral
I82.499	Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity
I82.4Yx	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity
I82.4Y1	Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity
I82.4Y2	Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity
I82.4Y3	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral
I82.4Y9	Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity
I82.4Zx	Acute embolism and thrombosis of unspecified deep veins of distal lower extremity
I82.4Z1	Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity
I82.4Z2	Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity
I82.4Z3	Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral
I82.4Z9	Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity
I82.5xx	Chronic embolism and thrombosis of deep veins of lower extremity
I82.50x	Chronic embolism and thrombosis of unspecified deep veins of lower extremity
I82.501	Chronic embolism and thrombosis of unspecified deep veins of right lower extremity
I82.502	Chronic embolism and thrombosis of unspecified deep veins of left lower extremity
I82.503	Chronic embolism and thrombosis of unspecified deep veins of lower extremity, bilateral
I82.509	Chronic embolism and thrombosis of unspecified deep veins of unspecified lower extremity
I82.51x	Chronic embolism and thrombosis of femoral vein
I82.511	Chronic embolism and thrombosis of right femoral vein
I82.512	Chronic embolism and thrombosis of left femoral vein
I82.513	Chronic embolism and thrombosis of femoral vein, bilateral
I82.519	Chronic embolism and thrombosis of unspecified femoral vein
I82.52x	Chronic embolism and thrombosis of iliac vein
I82.521	Chronic embolism and thrombosis of right iliac vein
I82.522	Chronic embolism and thrombosis of left iliac vein
I82.523	Chronic embolism and thrombosis of iliac vein, bilateral
I82.529	Chronic embolism and thrombosis of unspecified iliac vein
I82.53x	Chronic embolism and thrombosis of popliteal vein
I82.531	Chronic embolism and thrombosis of right popliteal vein
I82.532	Chronic embolism and thrombosis of left popliteal vein
I82.533	Chronic embolism and thrombosis of popliteal vein, bilateral
I82.539	Chronic embolism and thrombosis of unspecified popliteal vein
I82.54x	Chronic embolism and thrombosis of tibial vein
I82.541	Chronic embolism and thrombosis of right tibial vein
I82.542	Chronic embolism and thrombosis of left tibial vein
I82.543	Chronic embolism and thrombosis of tibial vein, bilateral
I82.549	Chronic embolism and thrombosis of unspecified tibial vein

I82.59x	Chronic embolism and thrombosis of other specified deep vein of lower extremity
I82.591	Chronic embolism and thrombosis of other specified deep vein of right lower extremity
I82.592	Chronic embolism and thrombosis of other specified deep vein of left lower extremity
I82.593	Chronic embolism and thrombosis of other specified deep vein of lower extremity, bilateral
I82.599	Chronic embolism and thrombosis of other specified deep vein of unspecified lower extremity
I82.5Yx	Chronic embolism and thrombosis of unspecified deep veins of proximal lower extremity
I82.5Y1	Chronic embolism and thrombosis of unspecified deep veins of right proximal lower extremity
I82.5Y2	Chronic embolism and thrombosis of unspecified deep veins of left proximal lower extremity
I82.5Y3	Chronic embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral
I82.5Y9	Chronic embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity
I82.5Zx	Chronic embolism and thrombosis of unspecified deep veins of distal lower extremity
I82.5Z1	Chronic embolism and thrombosis of unspecified deep veins of right distal lower extremity
I82.5Z2	Chronic embolism and thrombosis of unspecified deep veins of left distal lower extremity
I82.5Z3	Chronic embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral
I82.5Z9	Chronic embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity
Abbreviations: ICD-9-CM, the international classification of diseases, ninth revision, clinical modification; ICD-10, the international classification of diseases, tenth revision, clinical modification.	

Table 3.A2: Crude Distribution of Incidence of Thromboembolic Event Diagnoses and Deaths

	Pre-existing CVD Comorbidities				No Pre-existing CVD Comorbidities			
	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*	Entire Cohort No. (%)	Treatment Group No. (%)	Control Group No. (%)	*P*
Primary Analysis, total	2,147 (100)	1,498 (70)	649 (30)		1,090 (100)	726 (67)	364 (33)	
TE events	71 (3.31)	25 (1.67)	46 (7.09)	<.0001	35 (3.21)	11 (1.52)	24 (6.59)	<.0001
Deaths	880 (40.99)	547 (36.52)	333 (51.31)		399 (36.61)	241 (33.20)	158 (43.41)	
Sensitivity Analysis (Excluded patients with TE events history), total	2,129 (100)	1,493 (70)	636 (30)		1,086 (100)	725 (67)	361 (33)	
TE events	71 (3.33)	25 (1.67)	46 (7.23)	<.0001	35 (3.22)	11 (1.52)	24 (6.65)	<.0001
Deaths	869 (40.82)	545 (36.50)	324 (50.94)		398 (36.65)	241 (33.24)	157 (43.49)	

Abbreviations: CVD, cardiovascular disease; TE, thromboembolic event; p, p-value.

FIGURES

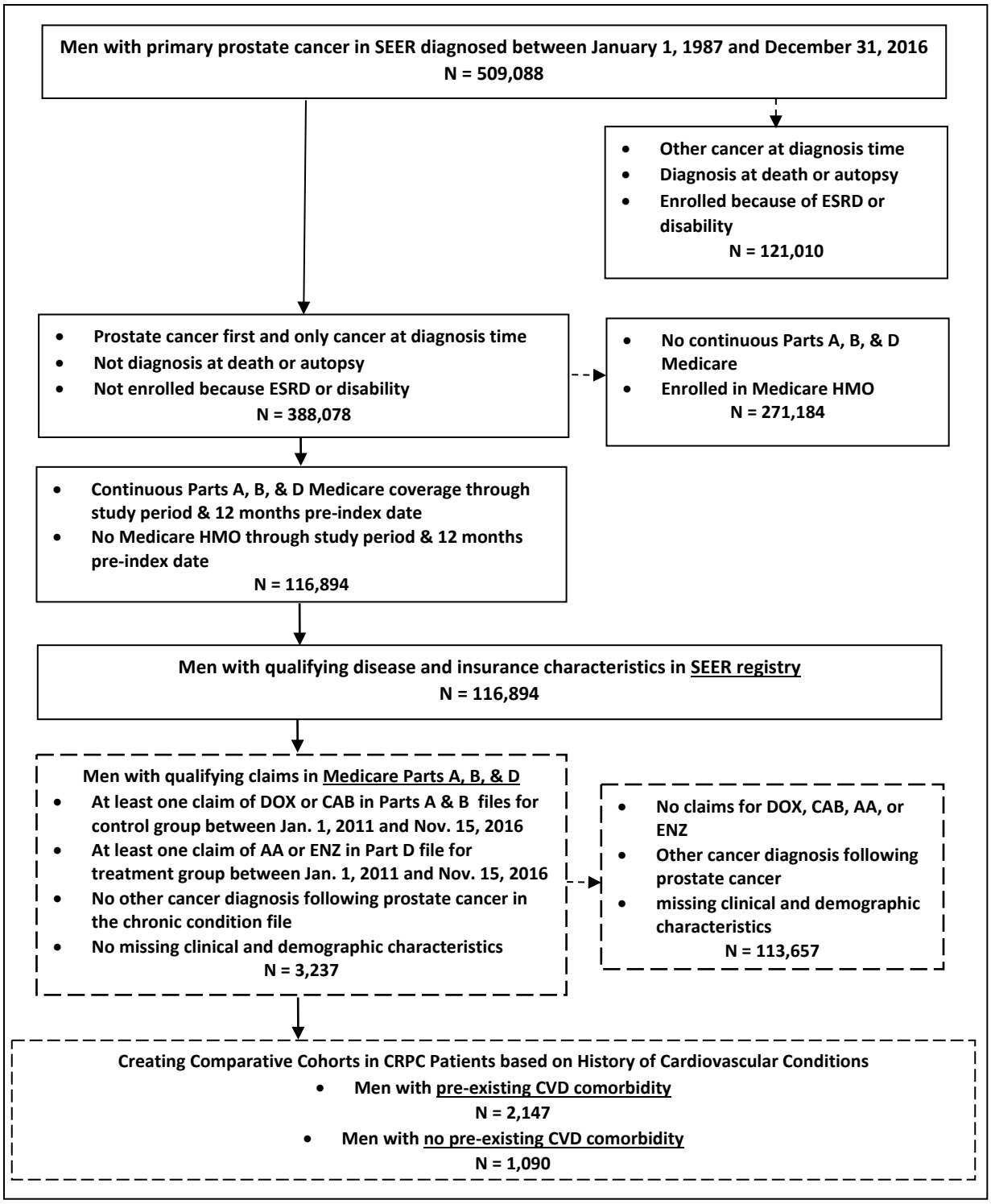

Fig 3.1: Study flow diagram displaying the sample counts for included and excluded observations, with the number of men excluded at each stage in the sample creation process. Abbreviations: CRPC, castration-resistant prostate cancer; ESRD, end-stage renal disease; CVD, cardiovascular disease; TE; thromboembolic event, HMO, health maintenance organization; SEER, Surveillance, Epidemiology, and End Results; DOX, docetaxel; CAB, cabazitaxel; AA, abiraterone acetate; ENZ, enzalutamide.

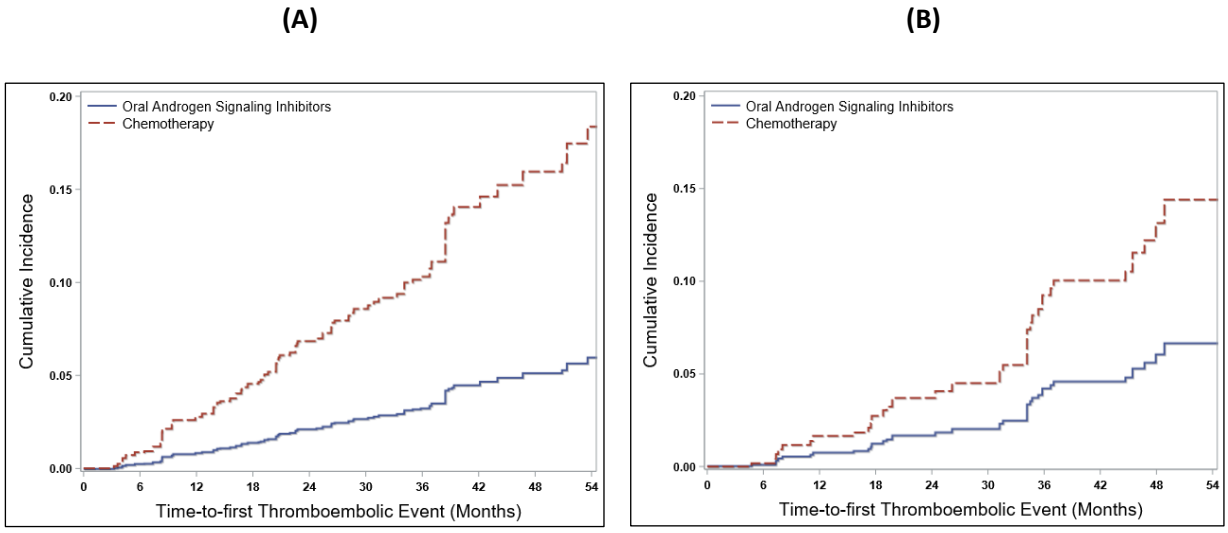

Fig 3.2: Graphs (A) and (B) display the comparison of cumulative incidence curves between OASI and chemotherapy new-users in time to the first TE event in months. **Graph (A)** shows the cumulative incidence curves in patients ***with*** pre-existing CVD history (Gray's test P < .001). **Graph (B)** indicates the cumulative incidence curves in patients ***without*** pre-existing CVD history (Gray's test P < .001). *Abbreviations*: OASI; oral androgen signaling inhibitors; TE, thromboembolic event; CVD, cardiovascular disease.

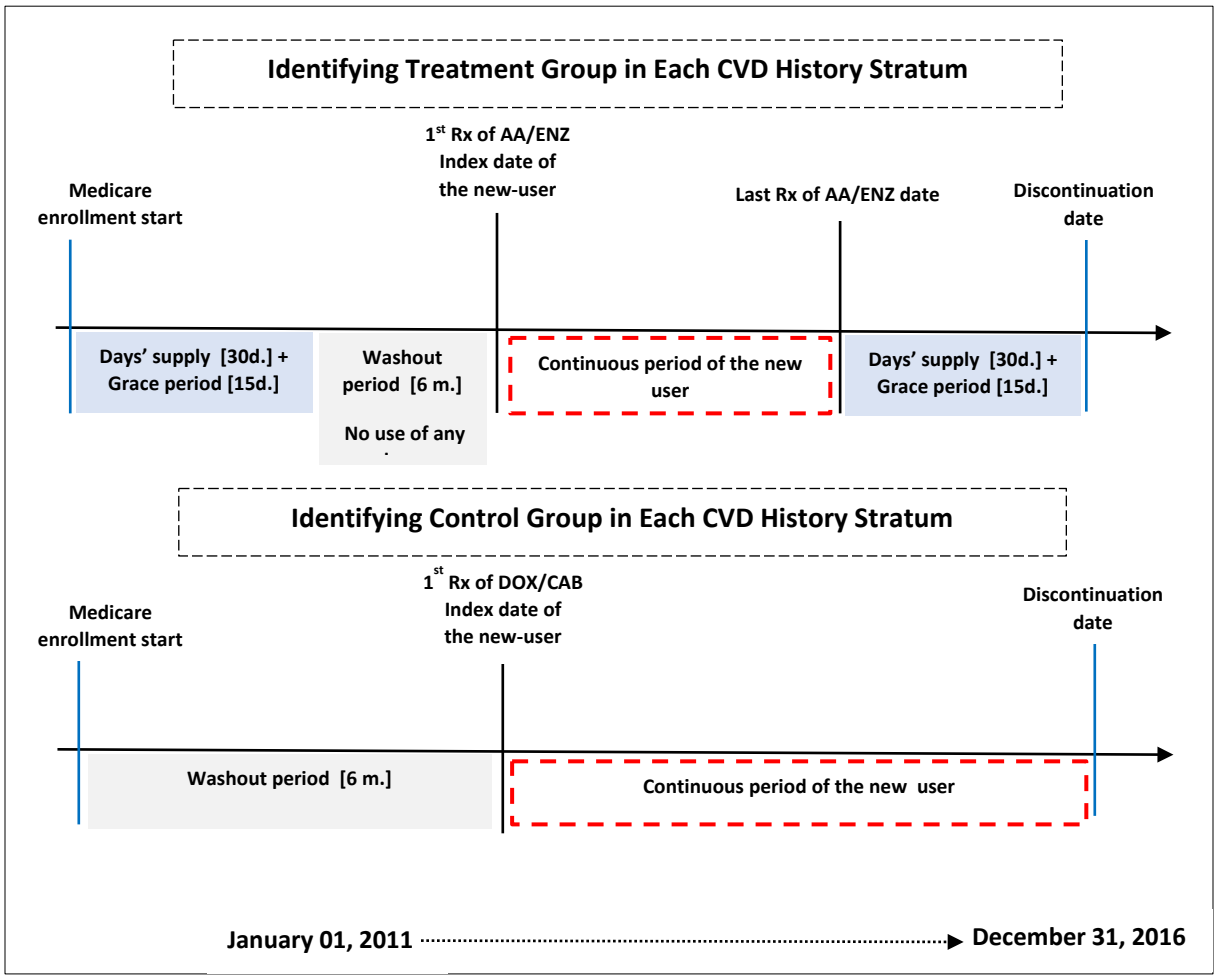

Fig 3.A1: An Active Comparator, new-user (ACNU) Diagram shows identifying CRPC patients based on their treatment regimen in each CVD history stratum. These patients were first time initiated oral androgen signaling inhibitors (AA/ENZ) and chemotherapy (DOX/CAB) in the SEER-Medicare linked database between January 1, 2011, and December 31, 2016. Patients who were new-users on (AA/ENZ) were actively compared with patients who were new-users on (DOX/CAB) in each CVD history stratum. The diagram also illustrates the way of calculating the continuous median period of the new use of drugs based on the discontinuation date. The washout periods were considered and included to eliminate any previous potential use due to other cancers. Abbreviations: CRPC, castration-resistant prostate cancer; CVD, cardiovascular disease; DOX, docetaxel; CAB, cabazitaxel; AA, abiraterone acetate; ENZ, enzalutamide; m., months; d., days.

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CHAPTER 4

TIME-TO-FIRST USE OF ORAL OPIOIDS AND CHEMOTHERAPY AFTER INITIATING ENZALUTAMIDE VERSUS ABIRATERONE ACETATE IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS ⸸

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ABSTRACT

Background: Enzalutamide (ENZ) and Abiraterone Acetate (AA) are both first-line treatments for metastatic castration-resistant prostate cancer (mCRPC), however, research studies comparing the time-to-first use of oral opioids and chemotherapy after initiating ENZ and AA in real-world patients are limited. Using SEER-Medicare data, this study examine whether ENZ compared to AA is associated with a longer time to starting oral opioids and chemotherapy.

Methods: An active comparator new-user design was used to identify 2,160 men diagnosed with likely CRPC who received ENZ and AA using the SEER-Medicare Linked Database from 2012 to 2016. Patients were divided into ENZ vs. AA, new-user groups. Inverse probability treatment weights (IPTW)-adjusted time-varying Cox models were used to compare the time-to-first use of oral opioids and chemotherapy after initiating ENZ and AA. IPTW-adjusted Fine-Gray competing risk model was used to examine switching drugs from ENZ to AA or AA to ENZ.

Results: Overall, the crude incidence rates of receiving oral opioids and chemotherapy were lower in patients who received ENZ than in patients with AA (e.g., receiving oral opioids: 51% vs. 63%, receiving chemotherapy: 12% vs. 20%, respectively). The adjusted time-dependent Cox model showed a statistically significant delay of time-to-first initiate oral opioids in patients who received ENZ compared with those who received AA (IPTW-adjusted hazard ratio [AHR], 0.84; 95% Confidence Interval [CI], 0.74 to 0.92; $P < .001$). Likewise, patients who received ENZ showed a statistically significant delay of time-to-first initiate chemotherapy by 40% compared with those who received AA (IPTW-AHR, 0.60; 95% CI, 0.49 to 0.73; $P < .001$). In the adjusted

Fine-Gray competing risk model, ENZ has shown a statistically significant decrease of the Sub-distribution Hazard Ratio (SHR) for switching drugs (IPTW- adjusted SHR, 0.67; 95% CI, 0.61 to 0.74; $P < .001$). The sensitivity analysis revealed that the results were consistent.

Conclusion: Patients who received ENZ showed a significant delaying time to use oral opioids and chemotherapy compared with other patients who received AA.

INTRODUCTION

Enzalutamide (ENZ) and Abiraterone Acetate (AA), oral androgen signaling inhibitors (OASI), were recommended by clinical guidelines such as the American Urology Association (AUA), National Comprehensive Cancer Network (NCCN), and American Society for Clinical Oncology/Cancer Care Ontario (ASCO/CCO) as first-line treatment options for men with metastatic castration-resistant prostate cancer (mCRPC).[1-4] These published guidelines do not indicate whether ENZ or AA is preferred due to a lack of comparative effectiveness data.[3,4] Both medications were initially approved by the United States Food and Drug Administration (FDA) in 2011 (AA) and 2012 (ENZ) for mCRPC patients who had failed prior docetaxel chemotherapy.[5] The FDA then expanded the AA and ENZ indications to chemotherapy-naïve patients in 2013 and 2014, respectively.[5] Patients with mCRPC typically have a poorer prognosis, with a median survival time of 15 to 36 months.[6-10]

To date, research studies comparing the efficacy of ENZ and AA treatment in real-world patients are limited, especially among elderly mCRPC patients with coexisting comorbidities.[11-13] When patients with CRPC on ENZ or AA experience cancer progression, starting oral opioids (due to pain from metastatic disease) and/or starting chemotherapy are clinical indicators that can be ascertained in claims data. These are also clinically meaningful outcomes for the patient. Therefore, we examine whether ENZ compared to AA is associated with a longer time to starting oral opioids and chemotherapy. We further estimated the effect of switching drugs from ENZ to AA, or from AA to ENZ on the sub-distribution hazard function while investigating death as a competing risk into account.

PATIENTS AND METHODS

Data Source

A population-based retrospective cohort was created from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The SEER-Medicare linked database has been described elsewhere.[14] Briefly, the Medicare program affords health insurance to 97% of the United States (US) population aged 65 years and older, covering inpatient care (Part A), outpatient care and physician service (Part B), and prescription drugs (Part D).[14] The SEER Program of the National Cancer Institute (NCI) collects information about cancer incidence and survival statistics from 19 population-based state or regional cancer registries.[15] The SEER-Medicare linked database provides comprehensive health care utilization data for Medicare beneficiaries with cancer that represent approximately 28% of the US population.[14]

In this study, several SEER-Medicare data files were utilized. The Patient Entitlement and Diagnosis Summary File (PEDSF) was used to obtain clinical and demographic characteristics. The Carrier file (NCH) was utilized to capture claims for inpatient and outpatient beneficiaries who were served by physicians and non-institutional provider services (Part B). Information regarding inpatient cancer care and hospital outpatient services were obtained through the Medicare Provider Analysis and Review file (MEDPAR, institutional, through Part A) and the Outpatient files (OUTPAT, institutional, through Part B), respectively. Further, Medicare Part D Event files (PDE) were utilized to extract information regarding orally used drugs. This study received IRB waiver from the University of Georgia Institutional Review Board.

Analytical Design

An active comparator, new user (ACNU) design was used to identify CRPC patients who received OASI in the SEER-Medicare database between Jan. 1, 2012, through Dec. 31, 2016. Men who were diagnosed with prostate cancer between the years 2004 to 2015 were considered for ACNU enrollment eligibility. The start year was carefully chosen to be in 2012 because the ENZ was approved by the FDA in that year, given that the enrolled patients have an equal probability of receiving either ENZ or AA. The new user concept has been recommended to be implemented whenever possible[16] to overcome some of the inherited weaknesses in non-experimental observational studies such as indication bias, healthy initiator bias, and selection bias.[17-19] The purpose of utilizing the active comparator element in this study design was to mitigate confounding by indication and other unmeasured patient characteristics such as frailty.[17,18]

ENZ and AA were chosen based on the time and the availability of the treatment options between the years 2012 and 2016. They were the only available OASI for CRPC patients in the clinical guidelines during the study period.[1-4] The new user was defined on the basis of the first claim date, which showed that the patient had no prior use of drugs of interest. The switching of drugs from ENZ to AA or from AA to ENZ was considered in two analytical approaches during the follow-up period of the "as-treated analysis" study.[17] The first approach considered switching status to be a time-varying exposure variable for the outcomes of interest: time to initiating oral opioid and chemotherapy. The second approach considered switching status to be an outcome variable with taking death into account as a competing event. Therefore, the discontinuation date of the orally taken drugs (AA and ENZ) was defined as (the last dispensing date + the days' supply [30 days] + a grace period [15 days]) to ensure the drug utilization period was correctly

captured.[17,8] For each patient, follow-up continued until the outcome occurrence (time-to-first initiate oral opioids and chemotherapy), end of the study period (Dec. 31, 2016), death, or the participant was lost, whichever occurred first.

Study Cohort

The study cohort included patients 65 years of age and older, who were diagnosed with a first and only cancer (being prostate cancer) between January 1, 2004, through December 31, 2015 (International Classification of Diseases, 9th Revision, Clinical Modification, [ICD-9-CM] code 185.xx, [ICD-10-CM] code C61.xx). We further restricted the inclusion criteria of the study to patients who received OASI and had at least a one-year window between the date of prostate cancer diagnosis and the study enrollment date (new user of ENZ or AA) to ensure having enough data for the washout periods. OASI treatment was defined using Part D data.[2,4] The exposure arm was defined as patients receiving ENZ as the initial OASI from Jan. 1, 2012, through Dec. 31, 2016; the comparison arm was defined as patients receiving AA as the initial OASI during the same period.[2,4] Patients were excluded from the study if they had: (1) other cancer at diagnosis time or following prostate cancer; (2) diagnosis at death or autopsy; (3) no Medicare Parts A, B, and D through study period & 12 months pre-index date; (4) Medicare HMO through study period & 12 months pre-index date; and (5) first drug initiation date was not between the predefined study period; and (6) enrollment because of End-Stage Renal Disease (ESRD) or disability. Figure 1 illustrates the inclusion and exclusion criteria to create the analytical cohorts.

Outcomes

Patients were followed from the first drugs of interest use (new-user) until the end of December 2016. The outcome time-to-first initiate oral opioids were identified based on the drug prescription dates from the Part D file (see Appendix Table A1). The outcome time-to-first initiates chemotherapy was identified based on the first claim date of Healthcare Common Procedure Coding System (HCPC) codes from the Carrier files, Medicare Provider Analysis and Review files; and Outpatient files (see Appendix Table A1). To ensure that the patient is not a prevalent chemotherapy user, the patient should not receive chemotherapy one year prior to the first use of the ENZ and AA. The outcome switching drugs from ENZ to AA, or from AA to ENZ was coded for all patients as switching drugs (Coded as 1), died before switching drugs (Coded as 2), or end of the study period or the participant was lost without switching drugs (Coded as 0).

The definition of the new event date of oral opioids (time-to-first use) is based on washout periods before and after the index date of patient enrollment (new user time of OASI to treat CRPC). These two washout periods were introduced in this study design to ensure that a patient is not a prevalent user of oral opioid prescription; further details are explained in the appendix (Fig. A1). Briefly, if the new event date for oral opioids was within one of or both the washout periods, this was not considered a time-to-first use. This patient was considered to be a prevalent oral opioid user. The washout periods were defined as (the last dispensing date + the days' supply [30 days] + a grace period [15 days]) to ensure that the drug utilization period was correctly captured.[17,8]

Covariates

Demographic characteristics including race (grouped into four categories: White, Black, Asian/Hispanic/North American Native, and Other/Unknown), age at first CRPC treatment (66-70 years, 71-75 years, 76-79 years, and ≥ 80 years), marital status (married, unmarried/unknown), and population location (urban vs. rural) were obtained from SEER. SEER regions were grouped into Northeast (Connecticut, New Jersey), South (Atlanta, rural Georgia, Kentucky, Louisiana), Central (Detroit, Iowa, New Mexico, Utah), and West (San Francisco, Hawaii, Seattle, San Jose, Los Angeles, greater California).

Medicaid state buy-in variable was categorized to yes or no for identifying Medicare and Medicaid dual enrollees as used previously in population-based studies.[20-22] Census-level poverty indicator was used to indicate socioeconomic status and analyzed in quartiles. For clinical characteristics, baseline oral non-opioid drugs for cancer pain management were identified and categorized as yes or no (see Appendix Table A2). Medicare claims data from the 12 months preceding the first OASI treatment were used to obtain a combined National Cancer Institute (NCI) comorbidity score validated specifically for claims data.[23]

Statistical analysis

Descriptive statistics were conducted to describe baseline characteristics. The propensity scores using inverse probability treatment weights (IPTWs) were utilized to address the issue of selection bias and heterogeneity among patients.[24] In brief, propensity scores were estimated by multivariable logistic regression, generating a covariate summary score (initial weight), which was defined as the probability of a patient to receive either ENZ or AA conditional on all the

identified covariates.[24,25] Covariates used in the logistic regression included age at first CRPC treatment, marital status, SEER region, population density, regional poverty indicator, state buy-in status, race, NCI Comorbidity Index at first CRPC treatment, and use of non-opioid drugs for cancer pain.

Then, pseudo populations were created, representing weighting each patient's contribution by the inverse probability of receiving the drug actually received in each study arms. To assess the limits of the potential for influential patients to bias results, such as those in these groups treated contrary to prediction, checks of the maximum weights (≤10) and the mean weights' closeness to 1.0,[26] were conducted. If the maximum IPTWs were (>10), trimming procedures were utilized and recalculated the IPTWs to avoid treatment comparisons outside a common range of the propensity score. To ensure that having well-balanced variables, we followed the conservative approach that recommended the absolute standardized mean difference should be less than or equal to 0.1.[27]

Afterward, the final weights were implemented to adjust the time-varying Cox Models (Extended Cox Model) and the competing risk model (Fine-Gray sub-distribution hazard competing risk regression model).[28,29] The extended Cox models were utilized to examine whether ENZ versus AA is associated with a longer time to starting oral opioids and chemotherapy, separately. The Fine-Gray competing risk model was used to estimates the effect of switching drugs from ENZ to AA, or from AA to ENZ on the sub-distribution hazard function. The cumulative incidence function (CIF) was estimated to describe the incidence of the occurrence of switching drugs while taking death as a competing risk into account.[29] Gray's test was used to evaluate differences in the cumulative incidence function graph between patients with ENZ and AA.

Sensitivity Analyses

In the sensitivity analyses, consideration was given to the possibility of misclassification in the capture of oral opioids. At first, the outcome time-to-first use oral opioid was determined only on the basis of the first date of prescription of the drug in the Part D file. In order to ensure that a patient had enough oral opioid prescriptions, the time-to-first oral opioid outcome was defined as having at least two oral opioid prescription dates within 3 months from the first opioid prescription. Additionally, we expanded the definition into having at least two oral opioid prescription dates within 6 months from the first opioid prescription. We examined whether the time to starting oral opioids changed on the basis of the three assumptions for ENZ compared to AA (see Appendix Table A3). Statistical significance thresholds were set at significance level $\alpha = 0.05$; all tests were 2-tailed. All analyses were performed using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

RESULTS

The study cohort included 2,160 men who received OASIs and met the inclusion criteria (Fig. 1). Approximately 63% and 37% of patients received AA and ENZ, respectively, likely reflect on the fact that AA received FDA approval before ENZ. Baseline demographic and clinical characteristics before and after applying IPTWs are listed in Tables 1 and 2. Tables 1 and 2 showed that after using IPTWs, all variables were balanced (all the absolute standardized mean differences < 0.1).

The crude incidence rates of receiving oral opioids after initiating OASI were lower in patients who received ENZ than patients who received AA (51% vs. 63%, respectively; Table 3). Further, the median time-to-first oral opioid use was longer in patients who received ENZ (7.6 months) compared to those who received AA (4.9 months). Similarly, the crude incidence rates of receiving chemotherapy after initiating OASI were lower in patients who received ENZ compared to AA (12% vs. 20%, respectively; Table 3). The median time-to-first chemotherapy use was 12.8 months for ENZ patients and 11.8 months for AA patients.

The adjusted time-dependent Cox model showed a statistically significant delay of time-to-first initiate oral opioids in patients who received ENZ compared with those who received AA (IPTW-adjusted hazard ratio [AHR], 0.84; 95% Confidence Interval [CI], 0.74 to 0.92; $P < .001$; Table 3). Correspondingly, the adjusted time-dependent Cox model showed a statistically significant delay in starting chemotherapy in patients who received ENZ than those who received AA (IPTW-AHR, 0.60; 95% CI, 0.49 to 0.73; $P < .001$; Table 3).

ENZ showed a statistically significant decrease in the Sub-distribution Hazard Ratio (SHR) for switching drugs (IPTW- adjusted SHR, 0.67; 95% CI, 0.61 to 0.74; $P < .001$; Table 4). This reflects the overall decrease in switching drugs for patients who have started their ENZ treatment plan and have not yet experienced an outcome event, considering the competing death event. The cumulative incidence curves for ENZ and AA were statistically different in the time to switch drugs considering death (Gray's test $P < .001$, Fig. 2).

In the sensitivity analysis, changing the assumption of the time-to-first oral opioid outcome definition as having at least two oral opioid prescriptions within 3 and 6 months of the first prescription did not affect the results. Patients who received ENZ compared to those who

received AA experienced a statistically significant delay in initiating oral opioids for all assumptions (Appendix Table A3).

DISCUSSION

In this analysis of SEER-Medicare data, ENZ was found to be associated with a statistically significant delay in time to use oral opioids (median time to the event, 7.6 vs. 4.9 months), as compared with AA. Patients with ENZ compared with AA were also found to have a longer time to chemotherapy initiation (median time to the event, 12.8 months vs. 11.8 months). Further, patients with ENZ had decreased SHR for switching drugs (SHR, 0.67; 95% CI, 0.61 to 0.74; P < .001). To our knowledge, this is the first head-to-head observational comparison study between ENZ and AA in these clinically meaningful endpoints using a real-world population.

In patients with mCRPC, both ENZ and AA have been shown to be able to improve patient outcomes. In the PREVAIL trial, which compared ENZ to placebo for mCRPC patients, ENZ was found to lengthen the time to chemotherapy (28.0 vs. 10.8 months for placebo).[30,31] In the COU-AA-302 trial, which compared AA plus prednisone to prednisone alone in mCRPC patients, AA was found to increase median time to opioid use (not reached vs. 23.7 months for prednisone) and initiation of cytotoxic chemotherapy (25.2 vs. 16.8 months).[12,13] These trials helped establish both ENZ and AA as first-line treatments for mCRPC patients, but no large randomized trial has compared ENZ vs. AA in a head-to-head fashion.

This study helps provide data on clinically-relevant outcomes to inform this current knowledge gap. Our results are consistent with other published observational studies.[32-34] Schultz et al. investigated chemotherapy-naive mCRPC patients treated with ENZ or AA using Truven Health MarketScan Commercial Claims and Encounters and Medicare Supplemental

Databases.[33] They found that patients initiating ENZ stayed on treatment longer compared with AA (median, 10.7 vs. 8.8 months, respectively; P = 0.008).[33] In comparison to Schultz et al. (2012-2015), our study included an additional year of data (2012-2016). This significant difference showed more included patients in this study with no enrollment in Medicare HMO. Another observational study looked into the same patients' criteria using the Veterans Health Administration (VHA) database.[32] The study also found that ENZ treated patients had a longer median treatment duration than AA treated patients (9.93 vs. 8.47 months, respectively; P = 0.0008).[32] Further, patients treated with ENZ had improved overall survival (OS) versus AA treated patients (HR, 0.71; 95% CI, 0.62 to 0.82).[32]

The current study utilized the SEER-Medicare linked database, representing approximately 97% of the US population aged 65 years and older and 28% of the total US population compared with the previous study that used the VHA database.[14] A recent French observational study compared the OS of new ENZ users and AA among chemotherapy-naive mCRPC patients using the French National Health Data System.[34] The study also suggested that ENZ treated patients had longer median OS than AA treated patients (34.2 vs. 31.7 months, respectively; HR, 0.90; 95% CI, 0.85 to 0.96).[34] Nevertheless, this French observational study represents a different population in terms of healthcare system experience, which may influence treatment outcomes. The current study, on the other hand, looked at whether ENZ, as compared to AA, was associated with a longer time to start oral opioids and chemotherapy, which were not looked at in previous observational studies.[32-34]

Our finding that ENZ is associated with delayed chemotherapy and opioids compared to AA, after adjusting for multiple measured covariates, suggests that ENZ may be more effective in delaying cancer progression. However, this observational study cannot rule out the possibility of

confounding by indication – that is, medical oncologists may selectively choose ENZ for patients with less aggressive mCRPC and AA for more aggressive mCRPC. We do not believe this is common clinical practice. In addition, no large, randomized trial directly comparing ENZ vs. AA is planned, and our study does provide data on clinically meaningful outcomes to inform a current knowledge gap. Another limitation of our study is that we cannot directly identify patients with mCRPC because testosterone and PSA levels are not available in the dataset. We believe that our inclusion of patients who have received an OASI between 2012-2016, closely approximates an mCRPC patient population because few other patients would be able to access this treatment via Medicare during that time. On the other hand, a strength of this study is the inclusion of a population-based group of patients who may not all meet the strict criteria of randomized clinical trials, thereby this study provides results that are likely more generalizable to the mCRPC patient population overall.

CONCLUSION

This study, using real-world data of prostate cancer patients over age 65, found that ENZ vs. AA is associated with a significant delaying time to use oral opioids and the initiation of chemotherapy. Further, patients who started on ENZ had a longer treatment duration before switching drugs than patients who started on AA. Given a lack of randomized data directly comparing ENZ vs. AA, this observational study provides clinically meaningful results that can inform patient and clinician decision-making for mCRPC.

TABLES

Table 4.1: Baseline Demographics of Castration-Resistance Prostate Cancer (CRPC) Patients

	Unweighted Population			Weighted Population*		
	Abiraterone Acetate No. (%)	Enzalutamide No. (%)	*SMD‡*	Abiraterone Acetate No. (%)	Enzalutamide No. (%)	*SMD‡*
Total of Entire Cohort (n = 2,160)	1,352 (63)	808 (37)		2,158 (100)	2,166 (100)	
Age at First CRPC Treatment, y						
66-70	77 (6)	44 (6)	0.01088	121 (6)	119 (6)	0.00387
71-75	251 (19)	176 (22)	0.08023	433 (20)	441 (20)	0.00704
76-79	316 (23)	173 (21)	0.04708	485 (22)	474 (22)	0.01344
≥ 80	708 (52)	415 (51)	0.02012	1,119 (52)	1,131 (52)	0.00734
Race						
White	1,071 (79)	645 (80)	0.01514	1,713 (79)	1,713 (79)	0.00540
Black	137 (10)	68 (8)	0.05923	206 (10)	212 (10)	0.00810
Asian/Hispanic/N. Am. Native	102 (8)	61 (8)	0.00019	163 (8)	164 (8)	0.00072
Other/Unknown	42 (3)	34 (4)	0.05867	76 (4)	76 (4)	0.00192
Marital Status						
Married	883 (65)	491 (61)	0.09418	1,377 (64)	1,385 (64)	0.00440
Not Married/Unknown	469 (35)	317 (39)	0.09423	782 (36)	779 (36)	0.00440
SEER Region						
South	259 (19)	136 (17)	0.06056	396 (18)	403 (18)	0.00763
Northeast	283 (21)	217 (27)	0.13927	500 (23)	501 (23)	0.00024
Central	202 (15)	145 (18)	0.08113	342 (16)	336 (16)	0.00844
West	608 (45)	310 (38)	0.13419	922 (43)	924 (43)	0.00019
Population Density						
Urban	1,136 (84)	662 (82)	0.05571	1,795 (83)	1,800 (83)	0.00033
Rural	216 (16)	146 (18)	0.05568	364 (17)	364 (17)	0.00033
Medicaid State Buy-in Status						
Yes	234 (17)	126 (16)	0.04621	358 (17)	359 (17)	0.00041
No	1,118 (83)	682 (84)	0.04623	1,801 (83)	1,805 (83)	0.00041
Regional Poverty Indicator						
0% to < 5% poverty	355 (26)	229 (28)	0.04680	580 (27)	574 (27)	0.00763
5% to < 10% poverty	374 (28)	230 (28)	0.01786	601 (28)	595 (28)	0.00761
10% to < 20% poverty	368 (27)	218 (27)	0.00537	589 (27)	592 (27)	0.00224
20% to 100% poverty	255 (19)	131 (16)	0.06964	390 (18)	403 (18)	0.01531

Abbreviations: CRPC, castration-resistant prostate cancer; SEER, Surveillance, Epidemiology, and End Results; N. Am. Native, North America Native; *SMD*, Standardized Mean Difference; y, year.

*Baseline characteristics for the weighted populations were obtained by using inverse probability of treatment weights (IPTWs). The IPTWs were estimated based on the propensity score. Covariates adjusted in the IPTW for the treatment group: age at first CRPC treatment, marital status, SEER region, population density, regional poverty indicator, state buy-in status, race, NCI Comorbidity Index at first CRPC treatment, and use of non-opioid drugs for cancer pain.

‡Absolute value of the standardized mean difference

Table 4.2: Baseline Clinical Characteristics of Castration-Resistance Prostate Cancer (CRPC) Patients

	Unweighted Population			Weighted Population*		
	Abiraterone Acetate No. (%)	**Enzalutamide No. (%)**	***SMD‡***	**Abiraterone Acetate No. (%)**	**Enzalutamide No. (%)**	***SMD‡***
Median time from initial diagnosis of prostate cancer to first CRPC treatment (IQR), m	52.0 (53.5)	54.0 (65.0)		NA	NA	
Non-Opioids Drugs for Cancer Pain						
Yes	872 (65)	368 (46)	0.38789	1,242 (58)	1,249 (58)	0.00397
No	480 (36)	440 (54)	0.38808	917 (42)	915 (42)	0.00397
NCI Comorbidity Index at First CRPC Treatment						
0	725 (54)	442 (55)	0.02165	1,166 (54)	1,166 (54)	0.00289
> 0	627 (46)	366 (45)	0.02164	993 (46)	998 (46)	0.00289

Abbreviations: CRPC, castration-resistant prostate cancer; NCI, National Cancer Institute; *SMD,* Standardized Mean Difference*;* IQR, interquartile range; y, year; m, month; NA, not applicable.

*Baseline characteristics for the weighted populations were obtained by using inverse probability of treatment weights (IPTWs). The IPTWs were estimated based on the propensity score. Covariates adjusted in the IPTW for the treatment group: age at first CRPC treatment, marital status, SEER region, population density, regional poverty indicator, state buy-in status, race, NCI Comorbidity Index at first CRPC treatment, and use of non-opioid drugs for cancer pain.

‡Absolute value of the standardized mean difference

Table 4.3: Crude and Adjusted HRs for the Association Between Use of Oral Androgen Signaling Inhibitors and the Time-to-First Oral Opioid and Chemotherapy Use

	Patients No. (%)	Outcome Event No. (%)	Median Time-to-First Event (IQR), m	Crude HR (95% CI)	Adjusted HR (95% CI)*
Time-to-first oral opioid use					
Abiraterone Acetate	1,352 (63)	854 (63)	4.9 (12.5)	Ref.	Ref.
Enzalutamide	808 (37)	410 (51)	7.6 (13.5)	**0.74 (0.65-0.84)**	**0.84 (0.74-0.92)**
Time-to-first chemotherapy use					
Abiraterone Acetate	1,352 (63)	276 (20)	11.8 (16.9)	Ref.	Ref.
Enzalutamide	808 (37)	100 (12)	12.8 (14.5)	**0.52 (0.39-0.71)**	**0.60 (0.49-0.73)**

Abbreviations: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results; NCI, National Cancer Institute.

*Covariates adjusted in the IPTW for the treatment group: age at first CRPC treatment, marital status, SEER region, population density, regional poverty indicator, state buy-in status, race, NCI Comorbidity Index at first CRPC treatment, and use of non-opioid drugs for cancer pain.

Statistically significant results are bolded

Table 4.4: Crude and Adjusted HRs for the Association Between Use of Oral Androgen Signaling Inhibitors and the Time-to-First Drug Switch

	Patients No. (%)	Outcome Event No. (%)	Competing Event No. (%)	Crude Sub-distribution HR (95% CI)	Adjusted Sub-distribution HR (95% CI)*
Time-to-first Drug Switch					
Abiraterone Acetate	1,352 (63)	645 (48)	250 (19)	Ref.	Ref.
Enzalutamide	808 (37)	232 (29)	111 (14)	**0.65 (0.56-0.75)**	**0.67 (0.61-0.74)**

Abbreviations: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results; NCI, National Cancer Institute.

*Covariates adjusted in the IPTW for the treatment group: age at first CRPC treatment, marital status, SEER region, population density, regional poverty indicator, state buy-in status, race, NCI Comorbidity Index at first CRPC treatment, and use of non-opioid drugs for cancer pain.

Statistically significant results are bolded

FIGURES

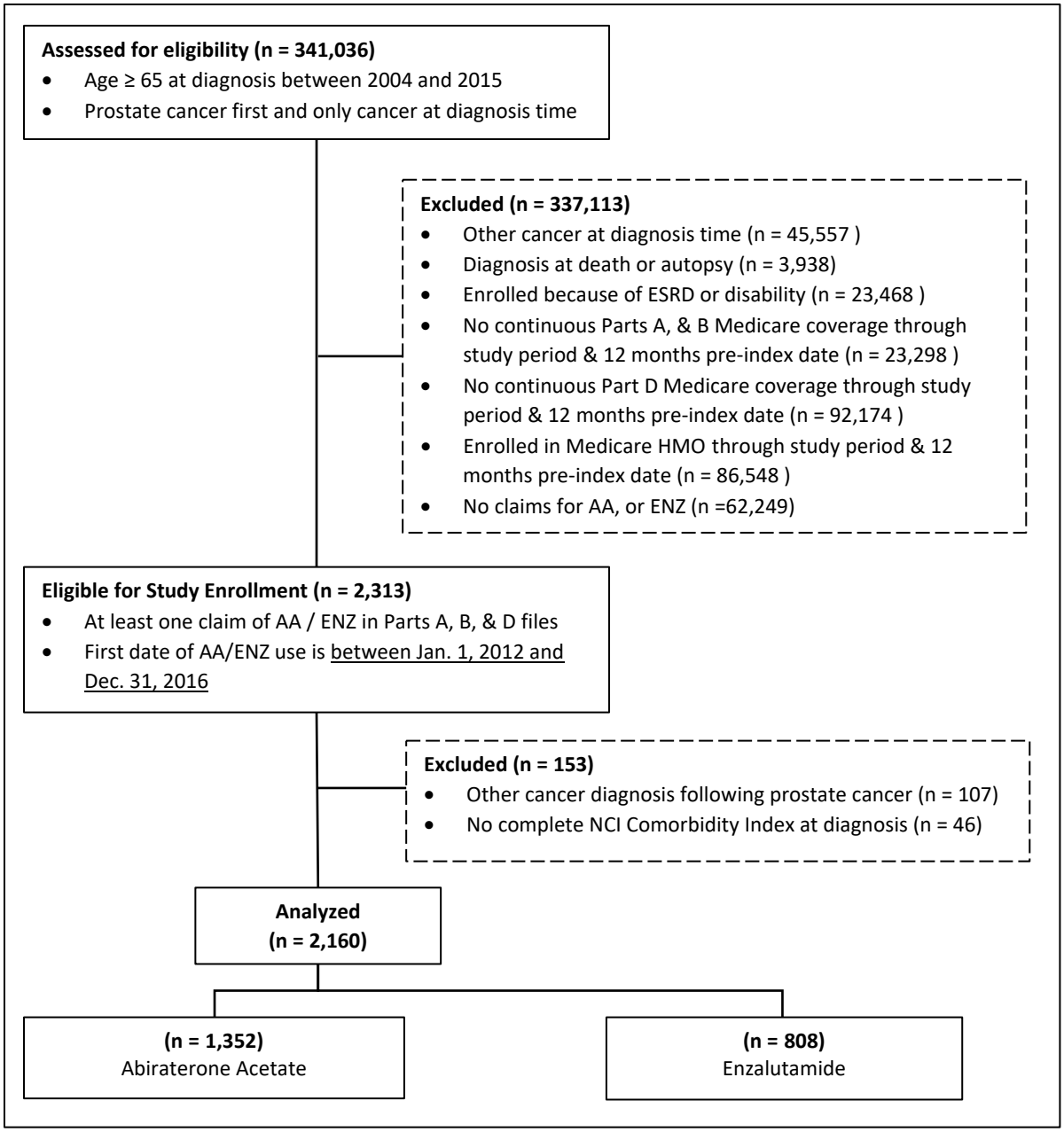

Fig 4.1: Study flow diagram displaying the sample counts for included and excluded observations. Abbreviations: ESRD, end-stage renal disease; CVD, cardiovascular disease; HMO, health maintenance organization; NCI, National Cancer Institute; OASI, oral androgen signaling inhibitor; AA, abiraterone acetate; ENZ, enzalutamide.

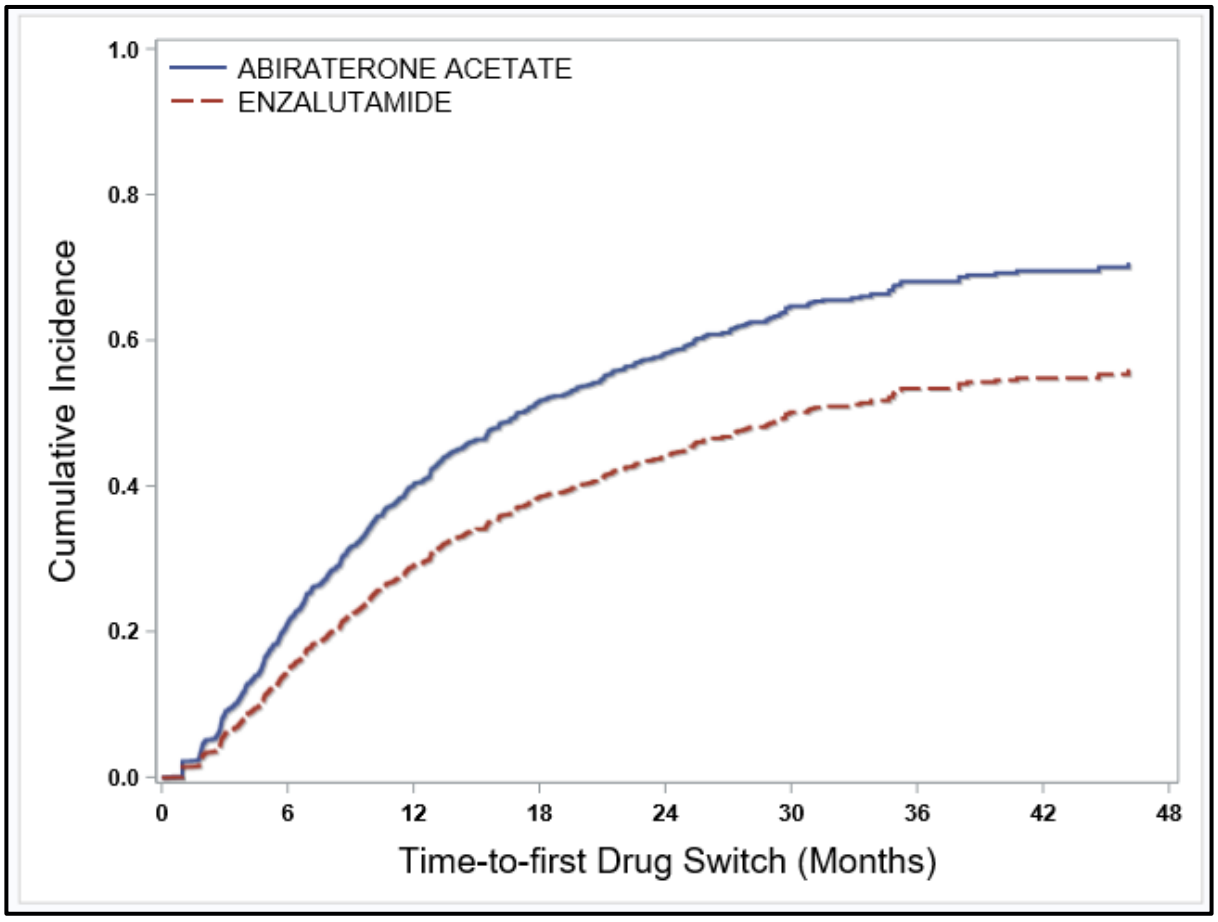

Fig 4.2: Comparing cumulative incidence between new-users of ENZ and AA in time to switch drugs (Gray's test P < .001). Time to switch drugs was defined as switching from ENZ to AA, or from AA to ENZ. *Abbreviations*: ENZ, Enzalutamide; AA, Abiraterone Acetate.

APPENDIX

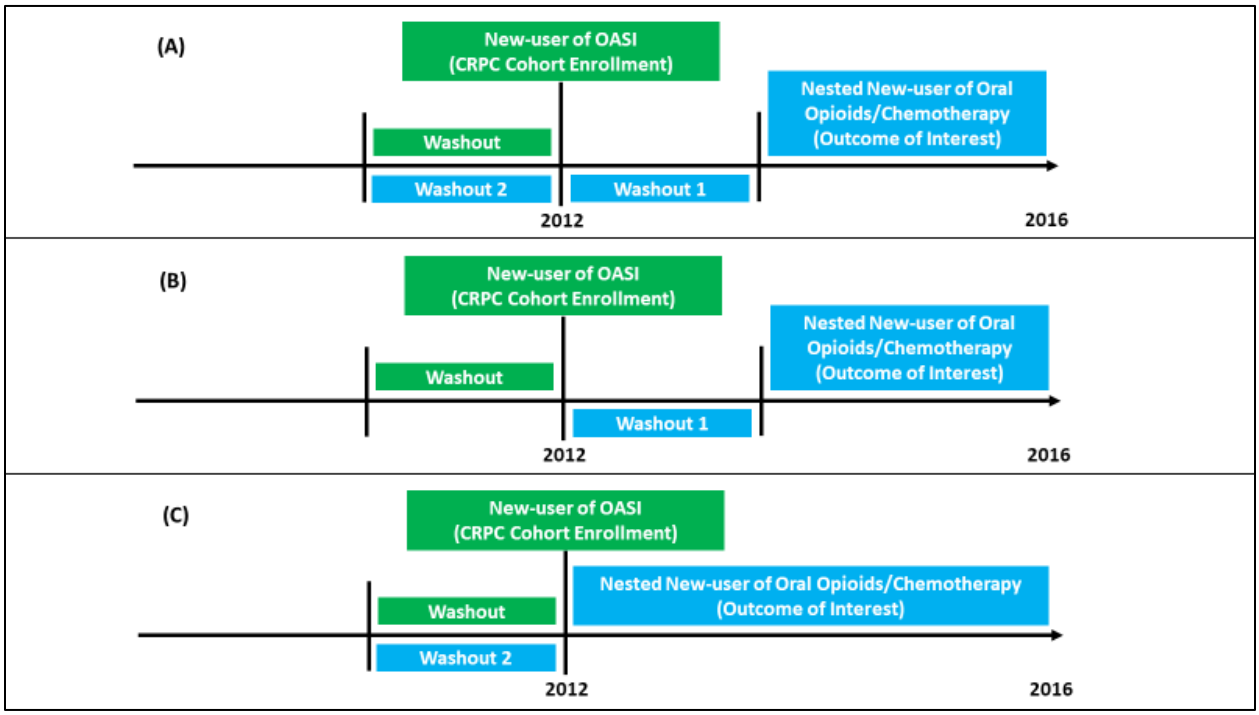

Fig 4.A1: Depiction of the introduced nested new-user design to measure the outcome of interest (time-to-first initiate oral opioids and chemotherapy). Abbreviations: OASI, oral androgen signaling inhibitor; CRPC, castration-resistant prostate cancer.

The Nested New-User is a complementary component to the well-known Active Comparator New User (ACNU) design when the outcome of interest we want to estimate is a time-to-first receive a drug (oral opioids and chemotherapy). This added component to the study design helps to ensure that a patient does not carry out a prevalent usage of the outcome of interest before enrollment in the study. The unique part of this design is introducing two washout periods, as seen in (A) for the nested new-user (which is receiving oral opioid and chemotherapy as outcomes of interest that we want to estimate). However, in (B) and (C), only one washout period was considered, leading to different findings.

In this study, we identified an analytical cohort with a total of 2,160 patients from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, who received AA and ENZ between 2012 and 2016. These patients were identified as new users (green color). Therefore, we looked at this washout period (green color) and defined it as the number of supply days of the drug + grease period, which is considered 50% of the supply days.

The nested new-user design is introduced here to identify the time-to-first use of opioids (blue color). As we emphasized before, the key element in the nested new-user design is the definition of the washout period that we need to mitigate the prevalent user bias. So, the first idea that comes to mind is this washout period 1. It has the same definition criteria for the number of supply days + the grease period. However, we might have a situation where a patient is still receiving the oral opioid or chemotherapy within the washout period (green color) of identifying the new-user patients. This may still carry out some of the treatment effects even with the existence of the washout period 1. Therefore, we added the washout period 2 with the same definition criteria in this design to ensure that a patient does not carry out the effect of the opioids.

Table 4.A1: Codes for Identifying Outcome Variables

Outcome Variable	File	Description
Oral Opioid	PDE	Codeine, Hydrocodone, Hydromorphone, Methadone, Morphine, Oxycodone, Oxymorphone, Tapentadol, Tramadol, and Meperidine
Chemotherapy	NCH MEDPAR OUTPAT	• Docetaxel [DOX] (J9171 and J9170)* • Cabazitaxel [CAB] (J9043 and C9276)*

Abbreviations: PDE, Medicare Part D Event file; NCH, Carrier files; MEDPAR, Medicare Provider Analysis and Review files; OUTPAT, Outpatient files.

* Healthcare Common Procedure Coding System (HCPC) codes

Table 4.A2: Non-opioids and Other Drugs Used to Treat Cancer Pain

Drug Class	Generic Name
OTC NSAIDs	Acetaminophen, Aspirin, Ibuprofen, Naproxen
Prescription NSAIDs	Celecoxib, Diclofenac, Indomethacin, Ketorolac, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac
Antidepressants	Amitriptyline, Bupropion, Imipramine, Nortriptyline, Desipramine, Doxepin, Duloxetine, Venlafaxine
Antihistamines	Hydroxyzine, Diphenhydramine
Anti-anxiety drugs	Diazepam, Lorazepam
Stimulants and amphetamines	Caffeine, Dextroamphetamine, Methylphenidate, Modafinil
Anti-convulsant	Carbamazepine Clonazepam, Gabapentin, Pregabalin
Steroids	Dexamethasone, Prednisone

Abbreviations: OTC, over the counter; NSAID, non-steroidal anti-inflammatory drugs

Table 4.A3: Sensitivity Analysis of Crude and Adjusted HRs for the Association Between Use of Oral Androgen Signaling Inhibitors and the Time-to-First Oral Opioid Use

	Crude HR (95% CI)	Adjusted HR (95% CI)*
Time-to-first oral opioid use (Only the First Opioid Prescription)		
Abiraterone Acetate	Ref.	Ref.
Enzalutamide	**0.74 (0.65-0.84)**	**0.84 (0.74-0.92)**
Time-to-first opioid use (At least 2 Opioid Prescriptions within 3 Months)		
Abiraterone Acetate	Ref.	Ref.
Enzalutamide	**0.74 (0.59-0.92)**	**0.83 (0.72-0.97)**
Time-to-first opioid use (At least 2 Opioid Prescriptions within 6 Months)		
Abiraterone Acetate	Ref.	Ref.
Enzalutamide	**0.74 (0.61-0.89)**	**0.82 (0.73-0.93)**

Abbreviations: HR, hazard ratio; CI, confidence interval; IPTW, inverse probability treatment weight; SEER, Surveillance, Epidemiology, and End Results; NCI, National Cancer Institute.

*Covariates adjusted in the IPTW for the treatment group: age at first CRPC treatment, marital status, SEER region, population density, regional poverty indicator, state buy-in status, race, NCI Comorbidity Index at first CRPC treatment, and use of non-opioid drugs for cancer pain.

Statistically significant results are bolded

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CHAPTER 5
CONCLUSION AND FUTURE DIRECTIONS

In the last decade, the number of treatment options available to patients with mCRPC that improve their chances of survival and better health-related outcomes has grown.[1] However, few published studies examine real-world outcomes in mCRPC patients with concurrent CVD comorbidities, despite the fact that treatment response may be affected by patients' pre-existing comorbidities.[2-5] The current research is important because the pivotal studies leading to the approval by the FDA of OASIs (ENZ and AA) excluded men with concurrent CVD conditions.[6-8] Notably, two-thirds of the mCRPC patients in this Medicare cohort (2011-2016) had pre-existing CVD conditions.

As a result, the generalizability of these trials' findings to the overall mCRPC patient population is unknown. Chemotherapy is another standard treatment option for mCRPC, but no randomized comparisons of OASI vs. chemotherapy have been conducted. Thus, the current study, using real-world data of prostate cancer patients aged 65 and over, addresses clinically significant gaps: effectiveness of OASI vs. chemotherapy with and without pre-existing CVD in mCRPC patients.

Findings from this study suggested that OASI, both ENZ and AA, appeared comparatively with better effectiveness profile than chemotherapy. OASI was associated with preferable all-cause mortality, prostate specific-cause mortality, and lower thromboembolic events than chemotherapy for all groups, including those with pre-existing CVD. In fact, those with pre-existing CVD showed numerically better relative risk in response to OASIs. ENZ and

AA both showed beneficial effects compared to chemotherapy, with ENZ showing numerically greater benefits across groups, particularly among those with pre-existing CVD. When comparing ENZ vs. AA, patients who received ENZ showed a significant delay in using oral opioids and chemotherapy compared with other patients who received AA.

Given a lack of randomized data directly comparing OASI vs. chemotherapy, this observational study provides clinically meaningful results that can inform patient and clinician decision-making for mCRPC with pre-existing CVD comorbidities. A survey was conducted in 2017 by the Cancer Support Community revealed that while 84% of patients were involved in treatment decision-making, only 48% of them felt fully prepared to make a decision.[9] It is evident that the findings of this study help to inform mCRPC patients when making their decision about treatment choices.

The survey also revealed that prostate cancer patients rated the following factors based on the most important when selecting their treatment plan: a higher chance for survival (27%), a higher chance for cure (20%), recommendations from a doctor (16%), and fewer side effects (14%).[9] This study provides findings of effectiveness for patients when discussing their treatment options with clinicians. One strength of this study is the inclusion of a population-based group of patients who may not all meet the strict criteria of randomized clinical trials (RCTs); thereby, this study provides results that are likely more generalizable to the overall mCRPC patient population, which helps in informing patients.

Although RCTs' recommended findings are the gold standard for clinicians when treating their patients, the generalizability of these results is restricted by the RCT design.[10] According to the 21st Century Cures Act (Cures Act) by the FDA, findings from real-world data, such as SEER-Medicare linked database, are complementary to RCTs.[11] This study contributes to the

knowledge gap in clinical decision-making to clinicians in several ways. The study draws attention to the notion that chemotherapy has greater TE and mortality burden on mCPRC patients. It is noteworthy that chemotherapy is often preferred over OASI in patients with a high disease burden and symptoms. However, the study points out the importance of close monitoring of the chemotherapy patients and implies the need for thromboprophylaxis. This is consistent with the recent review by the American College Of Cardiology that outlines a practical approach to anticoagulation management of Venous Thromboembolism (VTE) and atrial fibrillation (AF) in high-risk cancer patients on chemotherapy.[12]

Another contribution of this study is that ENZ showed better effectiveness than AA. Those on ENZ with pre-existing CVD showed to have delaying time to use oral opioids and chemotherapy compared with other patients who received AA. This knowledge contributes to the mCRPC treatment management plan. Cancer pain is a statistically significant predictor of overall survival, representing an adverse prognostic factor in patients with metastatic CRPC.[13] Hence, ENZ might be more effective than AA in delaying cancer progression since it showed better helping in managing cancer pain. Further, these patients who had better cancer pain management may not need to start their chemotherapy as early as other patients with higher metastatic disease volume.

However, the RCTs of AA pointed out the importance of being cautious when treating patients with pre-existing CVD.[6-8] With that knowledge illustrated in this study, clinicians might use this study findings to guide their decisions on which treatment choice is better for their patients with concomitant CVD. Recently, the American Medical Association (AMA) adopted a new policy supporting the use of real-world evidence to improve clinical care and patient

outcomes.[14] Therefore, this real-world study consistent with the AMA policy of using real-world data enhances evidence from RCTs to provide and guide clinicians to proper patient care.

Future Directions

This study can be extended in different future directions. One direction is confirming the findings of this study on different populations by investigating different data sources. The long-term goal is to inform clinical practice better and enhance the development of clinical guidelines. Several clinical factors, including cancer characteristics, body mass index (BMI), and metabolic disease are not available in SEER-Medicare data. These clinical factors may affect the increased risk of having new TE events and the cancer burden. One way to obtain these variables by using Electronic Health Records (EHR) that provides opportunities to track patients disease changes during the course of the study. Utilizing the same methodology as in this study allows for a more efficient and cost-effective study.

Another future direction is conducting a cost-effectiveness study to have a complete picture of comparative effectiveness between these agents. Treating mCRPC is notably expensive.[15-17] The average monthly cost of AA is $5,390, whereas ENZ costs $7,450 a month.[15] The Cancer Support Community survey further showed that more than half of respondents suffering from having monthly prostate cancer-related out-of-pocket costs of more than $100. Also, approximately 25% of responded patients reported having over $500 of out-of-pocket costs per month.[9]

A study suggested that the number of cancer patients and the amount of cancer expenditure is likely to increase in the future.[18] The study also projected the overall cost of cancer care in 2020 at $173 billion, increasing 39% from 2010. This substantial increase in the

cost of total cancer care is driven by the high cost of treating prostate cancer that might impact the decision-making process of the treatment plan.[18]

Knowing this information highlights the significance of conducting cost-effectiveness analyses (CEA). CEA is one tool that policymakers and other decision-makers can use to assess and potentially improve the performance of their healthcare systems. The findings of this study can contribute to filling the gap of the effectiveness point of estimate. To my knowledge, this study is the first study to compare OASI versus chemotherapy on TE and time to first initiate oral opioids and chemotherapy in head to head fashion. As a result, this study contributes to the expand and conduct of other cost-effectiveness studies by providing findings of population-based clinically relevant outcomes.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD LETTER

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Office of Research
Institutional Review Board

EXEMPT DETERMINATION

May 31, 2018

Dear Ewan Cobran:

On 5/31/2018, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Utilization of Prognostic Genetic Testing and Immunotherapy for Prostate Cancer: A Secondary Data Analysis of The Surveillance, Epidemiology, and End Results-Medicare Claims Linked Database
Investigator:	Ewan Cobran
IRB ID:	STUDY00006182
Funding:	None
Review Category:	Exempt 4

The IRB approved the protocol from 5/31/2018 to 5/30/2023. The IRB has approved the waiver of HIPAA Authorization.

Please close this study when it is complete.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103).

Sincerely,

Kate Pavich, IRB Analyst
Human Subjects Office, University of Georgia