Evaluation of novel hormonal agents in metastatic castration-resistant prostate cancer using real-world data in Quebec

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Abstract

In Canadian men, prostate cancer is the most commonly diagnosed cancer and has very high survival rates. However, a subset of patients will go on to develop an advanced and fatal form of the disease called metastatic castration-resistant prostate cancer (mCRPC). In the past decade, several new drugs with demonstrated survival benefits in clinical trials were approved. Among these newly approved treatments, two of them are novel hormonal agents (NHAs) and have been used widely: abiraterone and enzalutamide. Despite the prevalent use of abiraterone and enzalutamide in mCRPC, many questions still remain unanswered. The overarching aim of this thesis was to generate real-world evidence concerning current knowledge gaps regarding abiraterone and enzalutamide in mCRPC by examining the use and outcomes of these NHAs in the real-world.

In the first manuscript, the primary analyses sought to characterize the temporal patterns (2011-2016) of individuals initiating NHAs, categorized by their chemotherapy history (chemotherapy-naïve or post-chemotherapy) and the specialty of the prescribing physician (medical oncology, urology, or other specialties). While most patients were post-chemotherapy NHA initiators in 2012, this proportion decreased over time and accounted for only 13% of NHA initiators by the end of 2016. Medical oncologists were the most frequent prescribers of NHAs (upwards of 60%) throughout 2012 but fell to 45% by the end of 2016. Conversely, the proportion of prescriptions by urologists increased from 22% in 2012 to 42% in 2016. In summary, these findings suggests that the introduction of NHAs may have changed that the care pathways for mCRPC as urologists are increasingly prescribing the NHAs.

In the second manuscript, the objective was to assess the comparative cardiovascular safety of abiraterone and enzalutamide in patients with mCRPC in the real-world. First-time NHA users of abiraterone and enzalutamide between 2011 and 2016 were compared. The primary outcome of interest was cardiovascular-related hospitalization. Abiraterone initiators were at greater risk of cardiovascular-related hospitalization compared to enzalutamide initiators (HR 1.82; 95% confidence interval (95%CI) 1.09-3.05). When analyzing the individual subcomponents of the cardiovascular-related hospitalization, the risk of hospitalization for heart failure was greater in abiraterone initiators (HR 2.88; 95%CI 1.09-7.63) compared to enzalutamide users. These results provide clinicians with additional insight on the cardiovascular risks of mCRPC patients treated with NHAs in the real-world and further large studies are required to corroborate these findings.

In the third manuscript, the objective was to assess the association between the incidence of NHA-related complications and prescribing specialty in mCRPC patients treated with NHAs. First-time NHA users were grouped by their prescribing specialty (medical oncology (MO) vs urology (URO) vs other (OTH)). Outcomes of interest were overall NHA-related complications and its subtypes: cardiovascular, metabolic, infectious and general/non-specific. For overall NHA-related complications, the URO group (HR 0.97, 95%CI 0.72-1.31) and OTH group (HR 1.05, 95%CI 0.70-1.54) were not different compared to the MO group. While the URO group was associated with a greater incidence of cardiovascular complications compared to the MO group (HR 1.85, 95%CI 1.04-3.28), it was also at lower risk of infectious complications (HR 0.66, 95%CI 0.43-0.98). The results demonstrate the need for greater awareness in mCRPC clinical guidelines regarding management of NHA-related complications and drives the call to further promote multidisciplinary care in order to optimize patient outcomes.

Overall, this thesis provides additional data to understand how the NHAs, abiraterone and enzalutamide, are being used for mCRPC in clinical practice in Quebec and their outcomes.

Résumé

Chez les hommes canadiens, le cancer de la prostate est le cancer le plus fréquemment diagnostiqué et son taux de survie est très élevé. Cependant, un sous-ensemble de patients développera une forme avancée et mortelle de la maladie appelée cancer de la prostate métastatique résistant à la castration (mCRPC). Au cours de la dernière décennie, plusieurs nouveaux médicaments dont les effets bénéfiques sur la survie ont été démontrés lors d'essais cliniques ont été approuvés. Parmi ces traitements nouvellement approuvés, deux d'entre eux sont de nouveaux agents hormonaux (NHA) et ont été largement utilisés : l'abiratérone et l'enzalutamide. Malgré l'utilisation répandue de l'abiratérone et de l'enzalutamide dans le mCRPC, de nombreuses questions restent encore sans réponse. L'objectif primaire de cette thèse était de générer des preuves concrètes concernant les lacunes actuelles dans les connaissances concernant l'abiratérone et l'enzalutamide dans le mCRPC en examinant l'utilisation et les résultats de ces NHA dans le monde réel.

Dans le premier manuscrit, les analyses primaires cherchaient à caractériser les tendances temporels (2011-2016) des individus initiant des NHA, classés en fonction de leurs antécédents de chimiothérapie (naïfs de chimiothérapie ou post-chimiothérapie) et de la spécialité du médecin prescripteur (oncologie médicale, urologie, ou autres spécialités). Alors que la plupart des patients étaient des initiateurs de NHA post-chimiothérapie en 2012, cette proportion a diminué au fil du temps et ne représentait que 13 % des initiateurs de NHA à la fin de 2016. Les oncologues médicaux étaient les prescripteurs les plus fréquents de NHA (plus de 60 %) tout au long de 2012, mais leur proportion est tombée à 45 % en fin 2016. À l'inverse, la proportion de

prescriptions émanant d'urologues a augmenté de 22 % en 2012 à 42 % en 2016. En résumé, ces résultats suggèrent que l'introduction des NHA a pu modifier les parcours de soins du mCRPC car les urologues prescrivent de plus en plus de NHA.

Dans le deuxième manuscrit, l'objectif était d'évaluer l'innocuité cardiovasculaire comparative de l'abiratérone et de l'enzalutamide chez les patients atteints de mCRPC dans le monde réel. Les nouveaux utilisateurs de NHA d'abiratérone et d'enzalutamide entre 2011 et 2016 ont été comparés. L'issue clinique d'intérêt était l'hospitalisation pour cause cardiovasculaire. Les initiateurs de l'abiratérone présentaient un risque plus élevé d'hospitalisation pour cause cardiovasculaire que les initiateurs de l'enzalutamide (HR 1,82 ; intervalle de confiance à 95 % (IC 95 %) 1,09-3,05). Lors de l'analyse des sous-composantes individuelles de l'hospitalisation pour cause cardiovasculaire, le risque d'hospitalisation pour l'insuffisance cardiaque était plus élevé chez les initiateurs de l'abiratérone (HR 2,88 ; IC à 95 % 1,09-7,63) que chez les utilisateurs de l'enzalutamide. Ces résultats fournissent aux cliniciens un aperçu supplémentaire des risques cardiovasculaires des patients mCRPC traités avec des NHA dans le monde réel et d'autres études à grande échelle sont nécessaires pour corroborer ces résultats.

Dans le troisième manuscrit, l'objectif était d'évaluer l'association entre l'incidence des complications liées aux NHA et la spécialité de prescripteur chez les patients mCRPC traités par NHA. Les nouveaux utilisateurs de NHA ont été regroupés selon la spécialité de leur médecin prescripteur (oncologie médicale (MO) vs urologie (URO) vs autre (OTH)). Les issues cliniques d'intérêt étaient les complications globales liées aux NHA et leurs sous-types : cardiovasculaires, métaboliques, infectieux et généraux/non spécifiques. Pour les complications globales liées à la NHA, le groupe URO (HR 0,97, IC 95 % 0,72-1,31) et le groupe OTH (HR 1,05, IC 95 % 0,70-1,54)

n'étaient pas différents du groupe MO. Alors que le groupe URO était associé à une incidence plus élevée de complications cardiovasculaires par rapport au groupe MO (HR 1,85, IC à 95 % 1,04-3,28), il présentait également un risque plus faible de complications infectieuses (HR 0,66, IC à 95 % 0,43-0,98). Les résultats démontrent la nécessité d'une plus grande sensibilisation aux lignes directrices cliniques du mCRPC concernant la gestion des complications liées à la NHA et incitent à promouvoir davantage les soins multidisciplinaires afin d'optimiser les résultats pour les patients.

Dans l'ensemble, cette thèse fournit des données supplémentaires pour comprendre comment les NHA, l'abiratérone et l'enzalutamide, sont utilisés pour le mCRPC dans la pratique clinique au Québec et leurs résultats cliniques.

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This marks the end of an engrossing couple of years, and I am indebted to many people that have facilitated my journey here.

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Contribution of Authors

This thesis was written in a manuscript-based format.

Manuscript 1: Hu J, Aprikian AG, Saleh RR, Dragomir A. Utilization Trends of Novel Hormonal Agents in Metastatic Castration-Resistant Prostate Cancer in Quebec. Current Oncology. 2022 Nov 12;29(11):8626-37.

I conceptualized and developed the objective with Dr Alice Dragomir. I was responsible for study design, methodology, data management, programming, data analysis, drafting manuscript. All authors contributed to interpretation of results and revision of the manuscript.

Manuscript 2: Hu J, Aprikian AG, Vanhuyse M, Dragomir A. Comparative cardiovascular safety of novel hormonal agents in metastatic castration-resistant prostate cancer using real-world data. Clinical genitourinary cancer. 2022 Feb 1;20(1):17-24.

I conceptualized and developed the objective with Dr Alice Dragomir. I was responsible for study design, methodology, data management, programming, data analysis, drafting manuscript. All authors contributed to interpretation of results and revision of the manuscript.

Manuscript 3: Hu J, Aprikian AG, Dragomir A. Association between prescribing specialty and treatment-related complications in patients using novel hormonal agents for metastatic castration-resistant prostate cancer: an observational study. (submission in progress)

I conceptualized and developed the objective with Dr Alice Dragomir. I was responsible for study design, methodology, data management, programming, data analysis, drafting manuscript. All authors contributed to interpretation of results and revision of the manuscript.

Statement of Contribution of Original Knowledge

This work makes several novel contributions to the knowledge of the utilization and outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC) treated by abiraterone and enzalutamide, which are novel hormonal agents (NHAs).

Despite the prevalent use of abiraterone and enzalutamide in mCRPC, many questions still remain unanswered. Although randomized controlled trials (RCTs) are the standard in generating evidence about the efficacy and safety of treatments, observational studies using real-world data can provide complementary evidence whenever RCT data is not available or the RCT is not feasible. Certain knowledge gaps regarding the NHAs in mCRPC can potentially be remedied with real-world data such as administrative healthcare data. Specifically, the use of real-world data also allows for the study of prescribing patterns and outcomes of patients in actual clinical practice which provides something that data from clinical trials cannot. For the first manuscript, I was able to describe the utilization patterns of abiraterone and enzalutamide in terms of temporal patterns, by chemotherapy exposure/indication, and by prescribing specialty. No previous study described the utilization of these NHAs in the province of Quebec, nor have previous studies examined the prescribing specialties in this manner. I also attempted to identify whether prescribing specialty may preferentially prefer one agent over the other. In the second manuscript, although there were studies examining the cardiotoxicity of the NHAs via meta-analyses of aggregate data from RCTs, using disproportionality analysis with pharmacovigilance data, this manuscript was the first epidemiological study the issue in a comparative manner. Using a new-user active comparator approach with administrative healthcare data from Quebec, my findings suggest that abiraterone is associated with greater risk of cardiovascular-related

hospitalization compared to enzalutamide. In my third manuscript, I examined the association between the risk of treatment complications from NHAs and prescribing specialty. Although a previous study examined this issue as well, they only considered NHA complications as a composite outcome encompassing all complications together. However, given the wide range of complications associated with NHAs, there is interest in examining if certain types of complications are associated with prescribing specialty.

I declare that the conception, execution, and drafting of the manuscripts and thesis were entirely my own and that I received guidance from my supervisor in regard to my thesis objectives, methodological and substantive aspects of my thesis.

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Chapter 1. General Introduction

1.1 Introduction

In Canadian men, prostate cancer (PCa) is the most commonly diagnosed cancer and has very high survival rates.[1] However, a subset of patients will go on to develop an advanced and fatal form of the disease called metastatic castration-resistant prostate cancer (mCRPC).[2] Up until 2010, only docetaxel chemotherapy was shown to prolong survival in this advanced form of prostate cancer.[3] In the past decade, several new drugs with demonstrated survival benefits in clinical trials were approved. Among these newly approved treatments, two of them are novel hormonal agents (NHAs) and have been used widely: abiraterone and enzalutamide.[4] Both treatments possess similarities: both are oral drugs that were approved for the same indications in mCRPC. Although their specific mechanism of action is different, they both target androgen signaling pathways. They both showed similar efficacy against placebo in their respective randomized trials that led to their regulatory approval.[5-8] However, direct head-to-head comparisons from randomized trials are lacking. Additionally, evaluation of their adoption in clinical practice has also not yet been thoroughly investigated, especially regarding the uptake of these NHAs by the different physician specialties. Contrary to the management of many other types of cancers, the care of patients with PCa is distinct. It often involves the oversight, to varying extents, of different clinicians such as urologists, radiation specialists, and medical oncologists throughout a disease course that may span several years. Additionally, there is concern about the cardiovascular safety in real-world patients for both of these agents as their RCTs excluded patients with significant cardiovascular disease. Finally, there remains limited data regarding the management and incidence of treatment complications with NHAs in the real-world by

considering prescribing specialty, this is particularly important given the wide range of complications that NHA treatment can incur and the different prescribing specialties managing patients today.

1.2 Research Objectives

The overall aim of this thesis is to address knowledge gaps regarding the utilization and outcomes of the NHAs in mCRPC in the real-world. There are 3 objectives to address the overall aim:

1. To describe the utilization of the NHAs (abiraterone and enzalutamide) for mCRPC in clinical practice in Quebec, by describing the overall temporal trends (2011-2016), by chemotherapy status/indication, and by prescribing specialty.
2. To determine the comparative cardiovascular safety of abiraterone and enzalutamide in patients with mCRPC in the real-world.
3. To evaluate the association between prescribing specialty and the incidence of overall NHA-related complications, as well as the different subtypes of NHA-related complications, in mCRPC patients treated with NHAs.

All 3 objectives will be completed using a study population of NHA users from 2011 to 2016 extracted from the administrative healthcare databases from the province of Quebec in Canada.

1.3 Thesis Organization

This thesis is prepared in a manuscript-based format and each manuscript is contained in their own specific chapters (chapters 3, 4, 5). Prior to the manuscript chapters, chapter 2 presents the background knowledge overarching the main research objective, including the epidemiology of PCa, the management of initial/localized PCa, the advanced PCa states, and the epidemiology, management and treatment of mCRPC. Chapter 3 presents the first manuscript which is an observational study describing the utilization patterns of novel hormonal agents in the province of Quebec. Chapter 4 presents the second manuscript which is an observational study evaluating the comparative cardiovascular safety of abiraterone and enzalutamide. Chapter 5 presents the third manuscript which is an observational study to evaluate the association between prescribing specialty and the incidence of NHA-related complications, overall and by subtypes, in patients receiving NHAs for mCRPC. Chapter 6 summarizes the findings of the 3 manuscripts, discusses the implications of the findings and future directions of the research. References for Chapters 1, 2 and 7 are presented at the end of the thesis. References for the manuscript chapters (Chapter 3, 4, 5) are presented in the corresponding chapters.

Chapter 2. Background

2.1 Epidemiology of Prostate Cancer

PCa is one of the most commonly diagnosed and fatal malignancies in males worldwide; it ranks second in terms of incidence with an estimated 1.4 million new cases and is fifth in terms of cancer mortality in males.[9] It should be noted that the incidence of PCa varies between geographic areas, with likely some influence from biological, genetic, and behavioral factors. Moreover, regional guidelines pertaining to the recommendations on screening and diagnosis likely play a large role. The incidence in Eastern and South-Central Asia is over 6 times lower compared to those in Western and Northern Europe, and Northern America.[10]

The Canadian Cancer Society estimates that 1 in 8 males will be diagnosed in their lifetime, making it the most commonly diagnosed cancer in males.[1] From 2016 to 2020, the age-standardized incidence rate of PCa in Canada was estimated at approximately 120 per 100,000 males. These levels are lower than what was observed from the 1990s throughout the early 2000s which corresponded to the period with the highest incidence levels in Canada (peaked at approximately 190 cases per 100,000 males). In the 1990s, prostate-specific antigen (PSA) testing was introduced in North America and was widely used as screening tool to detect early PCa.[11] However, although elevated PSA levels can be suggestive of PCa, they can also indicate noncancerous conditions such as prostatitis (inflamed prostate) or benign prostatic hyperplasia.[12,13] The phenomenon of widespread PSA testing likely contributed to the overdiagnosis of low grade cancers which subsequently led to overtreatment of indolent or non-aggressive cancers.[14] This eventually led to recommendations against population screening using

PSA testing in both the United States and Canada in the early 2010s.[15,16] A substantial reduction in the incidence rate of PCa in Canada has been observed since 2011, coinciding with the publication of those recommendations, and appears to have stabilized since 2016.[1,17]

According to Canadian statistics, 1 in 30 males will die from PCa.[1] It ranks third in terms of cancer mortality as it accounts for 10.5% of male cancer deaths, behind lung cancer and colorectal cancer. The 5-year and 10-year survival rates are estimated at 91% and 88%, respectively, owing to the fact that most PCa cases are diagnosed at an early stage.[1] While the 5-year survival rate for those who present with localized disease is around 98%, for those who present with metastatic disease at diagnosis it falls to approximately 40%.[1] Prostate cancer-specific mortality reached a peak in the early 1990s and has been decreasing ever since, more specifically, the age-standardized mortality rate has decreased from 45 per 100,000 males in 1992 to 25 per 100,000 males in 2015.[11] This consistent decrease in PCa mortality across the years coupled with the decreased incidence rate of the disease suggests that recommendations against PSA testing have not adversely impacted survival although additional long term studies are needed.

2.2 Risk Factors for Prostate Cancer

The most important non-modifiable risk factors include age, race/ethnicity, and family history. The incidence of PCa increases dramatically with age, as the quasi-totality (98%) of PCa cases occur in males aged over 50.[1] In both the United States and Canada, the incidence of PCa in those aged over 75 ranges from 400 to 600 per 100,000 males while the incidence in those aged less than 60 ranges from 200 to 300 per 100,000 males.[17,18] There is evidence that race and ethnicity are associated with PCa incidence.[19-21] As mentioned earlier, there is substantial geographic variation in terms of incidence, but this is likely accounted by differences in PCa screening and

diagnosis practices, medical practices, and access to healthcare since developed countries typically possess the highest incidence rates.[10] Beyond that, in studies conducted in the United States, there is evidence that non-Hispanic Black males are at higher risk of PCa incidence and mortality relative to non-Hispanic White males.[21,22] Some research suggests that the poorer outcomes in the non-Hispanic Black population are driven by socioeconomic status,[23] while others show that socioeconomic status alone does not sufficiently explain the observed disparities in outcomes.[24,25] Studies investigating the role of familial history in PCa have demonstrated that hereditary PCa is associated with earlier disease onset; however, the impact on disease prognosis is still unclear.[26-28]

Across the past decades, a large number of studies investigating modifiable risk factors were undertaken.[29] A non-exhaustive list includes the following: physical exercise, smoking, obesity, metabolic syndrome, cholesterol levels, dietary factors. In terms of dietary factors, there has been a wide array of research examining the role in PCa development of: lycopene, vitamin E and selenium, alcohol, caffeine, soy products, meat intake, among others. However, no conclusive data currently exists to support any form of behavioral or dietary intervention that can mitigate the risk of PCa.

2.3 Classification and Diagnosis of Prostate Cancer

Classification of PCa is based on patient and tumour characteristics which typically comprises TMN staging, Gleason grade grouping, and PSA level. These three have been shown to be independently and in combination to predict cancer outcomes in non-metastatic disease.

The Tumor, Node, Metastasis (TMN) system from the American Joint Committee on Cancer (AJCC) is frequently used for staging PCa.[30] The T stage component of AJCC staging represents the extent of spread of the primary tumor, the N stage component represents the extent of spread of the regional lymph nodes, and the M stage component represents distant spread (metastasis). The T stage ranges from T0 to T4 with various sub-stages denoted by letters. Briefly speaking, T0 is assigned when there is no evidence of the primary tumour, T1 represents tumours that are not palpable, T2 is assigned to tumours that are confined to the prostate, T3 represents extraprostatic tumour, i.e. that has pierced through the prostate capsule but without invading surrounding structures (except seminal vesicles), and T4 is assigned to tumours that have invaded surrounding structures (bladder, rectum, external sphincter, etc.). The same principle applies to the N stage and M stage but with no or less sub-staging options, respectively. N0 is defined as no evidence of disease in regional lymph nodes, whereas N1 represents presence of disease in regional lymph nodes. M0 represents no evidence of distant metastasis, and M1 is attributed when distant metastasis is detected.

Grading refers to the appearance of cancer cells examined microscopically. For PCa, the Gleason grading system is used worldwide to determine whether the histological patterns observed microscopically range from well-differentiated (normal appearance) cells to poorly differentiated (abnormal appearance) cells with the latter being associated with more aggressive disease and worse prognosis.[31-34] Cells are assigned a grade (1 to 5) based on their level of differentiation/abnormality with a higher number indicating greater abnormality. A grade lower than 3 represents normal looking cells. Since the tumour may have cells of different grades, a Gleason score, is determined for each tumour by summing the two most common grades

(primary and secondary patterns) in the tumour sample. Hence, Gleason scores for PCa range from 6 to 10. A relatively recent development is the re-classification of Gleason scores into the International Society for Urological Pathology (ISUP) Grade Group system (or more simply known the Grade Group system). Grade Groups range from 1 (less aggressive PCa) to 5 (most aggressive PCa).[35] Table 1 summarizes the comparison of the Gleason scores and Grade Groups.

Gleason score	ISUP Grade Group	Histological appearance	Cancer aggressiveness
6 (3+3)	1	Well differentiated, all uniform glands	Low likelihood of spread
7 (3+4)	2	Moderately differentiated, mostly uniform glands and small proportion of poorly formed glands	Likely to spread slowly
7 (4+3)	3	Moderately differentiated, mostly poorly formed glands and small proportion of uniform glands	More likely to spread relative to Grade 2
8 (4+4; 3+5; 5+3)	4	Poorly differentiated, poorly formed glands and/or with parts lacking glands	Likely to spread quickly
9 to 10 (4+5; 5+4; 5+5)	5	Poorly differentiated, all lacking glands or lacking glands with parts with poorly formed glands	More likely to spread relative to Grade 3

Table 1: Summary of Gleason scores and ISUP Grade Groups
Abbreviation: ISUP: International Society of Urological Pathology.

As mentioned previously, PSA testing has been widely used as a screening tool in the diagnosis of PCa, but it is also important as a prognostic tool and in the monitoring of response during and following treatment.[36] PSA is a glycoprotein produced by the epithelial cells of the prostate in both normal cells and malignant cells. Detection of PSA is done through a blood test which is typically measured in nanograms per millimeter (ng/ml). Once the diagnosis of PCa is confirmed, PSA levels have prognostic value and can help assist in the risk stratification of patients with PCa.[37] Used in conjunction with other clinical and tumour characteristics, pretreatment PSA levels are predictive of treatment response, especially after treatment for localized disease.[38-41]

2.4 Risk Stratification Systems for Localized Disease

Risk stratification systems are critical in assisting clinicians and patients to make better informed decisions. The ability to differentiate between clinically significant disease from indolent disease is essential in the context of a heterogeneous disease like PCa. There are numerous risk stratification systems for localized and locally advanced disease, [42-45] As mentioned earlier, the 3 classical prognostic biomarkers are usually included in the risk stratification systems that predict a variety of clinical outcomes following treatment. The most frequently used risk stratification systems in are all broadly similar since they are mostly based on the D'Amico classification system, developed in 1998, to predict the likelihood of recurrence after surgery.[42] In the D'Amico classification system, patients were stratified into low, intermediate, or high risk group.

2.5 Treatments for Localized Prostate Cancer

Once the disease is diagnosed and adequately classified in the appropriate risk group, several management options are available to patients with localized disease. The three most common treatments for localized disease are active surveillance, radical prostatectomy, and radiation therapy.

Active Surveillance

Active surveillance is a type of deferred treatment, and as its name implies, it entails actively monitoring disease progression with the intention of administering local curative therapy if the cancer advances. It is primarily suitable for younger patients with apparently indolent cancer, aiming to delay or forgo treatment and its associated side effects. Given the longer life

expectancy of these patients, close monitoring is essential, and prompt initiation of treatment is crucial if cancer progresses to ensure the opportunity for a cure is not missed.

There is no formal RCT comparing modern active surveillance protocols to local curative treatment. Numerous cohorts have documented active surveillance in cases of organ-confined disease, with a recent systematic review consolidating their findings.[46] The results indicate that the long-term overall survival and cancer-specific survival of patients undergoing active surveillance are notably positive. However, during follow-up, over one-third of patients are 'reclassified,' and a majority of them undergo curative treatment due to factors such as disease upgrading, increased disease extent, advanced disease stage, progression, or patient preference.

Radical Prostatectomy

Radical prostatectomy is the surgical removal of the prostate and seminal vesicles. It is appropriate for men with localized disease and considered to be local curative therapy. However, due to potential perioperative morbidity, it should be reserved for patients with at least 10 years of life expectancy.[43] In a large RCT enrolling males with low and intermediate risk PCa during the early years of PSA testing (1994-2002), the cancer-specific mortality in males treated with radical prostatectomy is estimated at 7.4% through 19 years of follow-up.[47] Another more recent RCT, enrolling patients with low and intermediate risk disease from 1999 to 2009, found a cancer-specific mortality rate of approximately 1% at 10 years of follow-up.[48]

Radiation therapy

Different types of radiation therapy techniques are available to treat PCa, including external beam radiation therapy, brachytherapy, and proton radiation therapy.[43] In a relatively recent RCT, which compared monitoring, external-beam radiation and radical prostatectomy in patients with low and intermediate risk disease, no difference was found in terms of cancer-specific mortality rate of approximately 1%-2% at 10 years of follow-up.[48] However, the monitoring group had a higher rate of progression to metastatic disease at 6.3 cases per 1000 person-years, while no difference was found for the radical prostatectomy group (2.4 per 1000 person-years) and external-beam radiation therapy group (3.0 per 1000 person-years).

2.6 Advanced Prostate Cancer

Disease states that can be included as advanced PCa comprise a wide range from biochemical recurrence without metastatic disease after local treatment, metastatic hormone-sensitive prostate cancer (mHSPC), non-metastatic castration-resistant prostate cancer (nmCRPC), and metastatic castration-resistant prostate cancer (mCRPC). The states of biochemical recurrence without metastatic disease after local treatment, mHSPC and nmCPRC will only be briefly described but mCRPC will be discussed in greater depth as it is the most relevant to the thesis work. Figure 1 illustrates the various advanced PCa states.

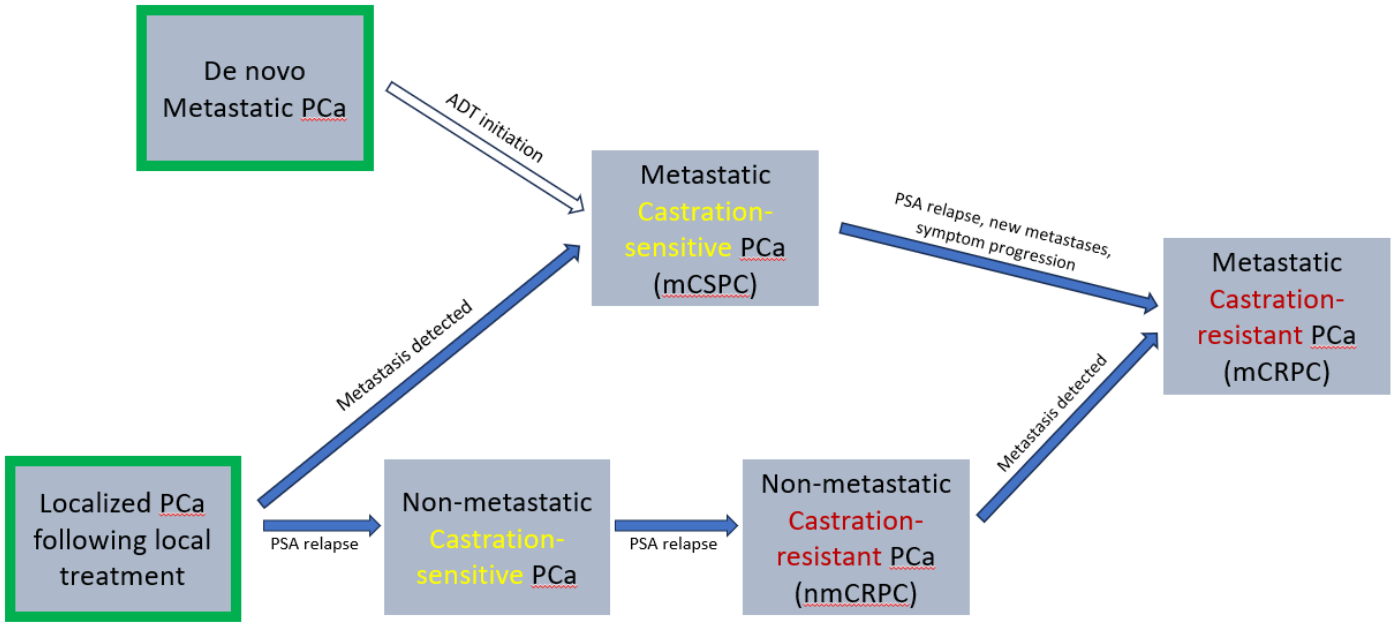

Figure 1. Progression of advanced prostate cancer

2.6.1 Biochemical Recurrence Without Metastasis After Local Treatment

This clinical state, also known as non-metastatic castration-sensitive prostate cancer, defined by the American Urological Association as patients experiencing PSA relapse after radical prostatectomy or radiation therapy. Approximately 30% of patients undergoing radical prostatectomy and 40% of patients undergoing radiation therapy will experience biochemical recurrence within 10 years.[49-51] The median metastasis-free survival for patients with biochemical recurrence after local treatment is estimated at 10 years, but can vary largely depending on prognostic variables such as the Gleason score (Gleason score 8-10: 6 years vs Gleason score 7: 12 years).[52]

The definition of biochemical recurrence is different for patients treated with radical prostatectomy and radiation therapy. Following radical prostatectomy, biochemical recurrence is frequently defined as PSA >0.2ng/ml (at least 2 consecutive measures) although there is variation in the litterature.[45,53] Following radiation therapy, biochemical recurrence is defined as nadir PSA + 2.0ng/ml.[54]

Treatment options depend on a variety of factors and include the following: salvage radiation therapy after radical prostatectomy, salvage prostatectomy after external radiation therapy, and androgen deprivation therapy (ADT).[55] Initiation of ADT is not routinely recommended in patients, however it may be considered to those at higher risk of progressing to metastasis (Gleason score, initial PSA, etc.).[55,56]

2.6.2 Metastatic Prostate Cancer

Patients with PCa can present with metastases after local treatment (also known as metachronous metastatic disease) or be diagnosed de novo with metastatic disease (also known as synchronous metastatic disease).[57,58] Among all patients diagnosed with incident PCa, those who present de novo with metastasis only account for around 8-9% of cases in the United States and Canada and approximately 14% in Western European nations.[59-61] Patients with de novo metastatic disease have worse prognosis and survival from diagnosis ranges from 43 to 52 months, while survival for patients who develop metastases after local treatment varies from 55 to 92 months.[58]

The most frequent site of metastasis in PCa is the bone by a wide margin (around 65% to 84% of patients have at least one bone lesion).[62,63] Distant lymph node involvement varies from 10% to 15%, followed by liver, lung, and brain metastases.[62,63] The presence of visceral lesions is associated with worse survival (relative to only nodal metastases).[64] Concomitant visceral, bone and nodal involvement carries the worse prognosis.[65]

Patients with metastatic PCa experience significant symptomatic burden, including fatigue (73% of patients), urinary symptoms (63%), and bone pain (52%).[66] Moreover, over half (54%) of patients report they agree that their pain often limit their daily activities. Several studies report significant declines in a variety of health-related quality-of-life measures.[67,68] Skeletal-related events are particularly highlighted in metastatic PCa, given the high prevalence of bone lesions in this disease, include events such as pathologic fractures, spinal cord compression, need for palliative radiation to bone, and bone surgery.[69,70] Among patients with metastatic disease, approximately 44% reported skeletal-related events.[71] These events are associated with decreased health-related quality-of-life and worse survival.[71-74]

2.6.3 Role of Androgens in Prostate Cancer

In the 1940s, Huggins et al. established the role of the endocrine system, in particular androgens, in PCa progression.[75] In patients with metastatic PCa, the suppression of androgens resulted in notable palliative benefit, while reinjection of androgens exacerbated symptoms. These findings were the basis that led to RCTs that established primary androgen deprivation therapy (ADT) monotherapy as the standard of care in metastatic PCa for decades up until recently.[76-78] ADT is also important as an adjuvant therapy in combination with radiation therapy in locally advanced

PCa.[79] ADT can take two forms, either medically using luteinizing-hormone releasing hormone (LHRH) agonists or surgically through orchiectomy. While both orchiectomy and LHRH agonists accomplish the therapeutic goal of reducing serum testosterone to castrate levels, their specific mechanism of action is different. Surgical removal of the testicles results in nearly immediate reduction of testosterone levels within half a day.[80] Conversely, LHRH agonists exert their action by continuously overstimulating pituitary LHRH receptors which eventually causes desensitization of LHRH pituitary receptors and subsequently shuts down endogenous production of testosterone.[81] Most LHRH agonists achieve castrate levels of testosterone within a month.[82-84] To add to this are another relatively newer class of medical ADT called LHRH antagonists which bind to and directly inhibit LHRH receptors in the pituitary instead of the overstimulation approach taken by agonists.[85] All three forms of ADT (orchiectomy, LHRH agonists, LHRH antagonists) are considered equivalent in terms of cancer control for PCa.[86,87]

Beyond ADT, there are also antiandrogens, which are oral compounds with the ability to bind and inhibit the androgen receptor.[88] Mostly introduced in the 1990s, today they are known as first-generation antiandrogens, and they can classified as steroidal antiandrogens (cyproterone acetate) and non-steroidal antiandrogens (flutamide, nilutamide, bicalutamide). In today's context, they are mostly only used in combination with an LHRH agonist to prevent "testosterone flare" which is the temporary increase in testosterone due to the initial release of luteinizing hormone that can lead to a transient worsening of symptoms from PCa.[89] For this purpose, first-generation antiandrogens can be given during the first 30 days of LHRH agonist therapy.

2.6.4 Metastatic Castration-Sensitive Prostate Cancer

Metastatic castration-sensitive prostate cancer (mCSPC) is essentially metastatic PCa that has not yet been treated with or still responds to ADT.[90] For over half a century, primary ADT alone was the standard of care for mCSPC. While it remains an integral part of disease management to this day, the new standard of care involves combining ADT with other systemic treatments and/or radiation therapy.[91] Since 2016, a slew of RCTs demonstrating the dramatic improvements in overall survival when combining ADT with other modern therapies including docetaxel, abiraterone acetate, enzalutamide, apalutamide, darolutamide.[92-100] Even more recently in 2022, the results of RCTs evaluating the combination of ADT and two additional therapies, a strategy often called "triplet therapy" or "dual intensification", were published.[101,102] In the PEACE-1 trial, the combination of ADT, docetaxel and abiraterone yielded overall survival benefit compared to the combination of ADT and docetaxel.[101] In the ARASENS trial, the combination of ADT, docetaxel and darolutamide demonstrated improved survival relative to the combination of ADT and docetaxel.[102]

2.6.5 Notion of Castration-Resistance

The vast majority of patients will respond strongly to primary ADT, either with a decline of PSA levels, symptom relief, or regression of metastatic disease.[103] Unfortunately, patients eventually develop resistance, also known as castration-resistance. On average, ADT alone provides disease control for a duration ranging from 12 to 36 months of disease control in metastatic patients before the onset of castration-resistance.[58,104,105] Approximately 10% to 20% of PCa patients progress to castration-resistant disease within 5 years of initial diagnosis.[2] According to an analysis in the United Kingdom using primary care data, nearly 30% of patients undergoing ADT

developed CRPC over a 10 year period and estimated an incidence rate of 3.8 CRPC cases per 100 person-years in males diagnosed with PCa.[106]

According to CUA guidelines, the definition of castration-resistant prostate cancer (CRPC) is disease progression despite castrate levels of testosterone (<50 ng/dL).[107] Disease progression includes PSA progression or radiological progression and/or clinical progression. Different urological organizations have slightly different operational definitions of PSA progression (CUA, EAU, AUA, NCCN).[43,90,108] Within the scope of CRPC, two different clinical states can be considered: 1) non-metastatic CRPC (nmCRPC), 2) metastatic CRPC (mCRPC).[90,109] Guidelines recommend that ADT be maintained even past the onset of castration-resistance.[109,110]

2.6.6 Non-Metastatic Castration-Resistant Prostate Cancer

The clinical state of nmCRPC represents patients experiencing PSA progression but without clinically detectable metastatic disease among males treated with ADT.[90,109] It can be considered an "artificial" or "man-made" clinical state as the existence of nmCRPC is attributable to the combination of frequent PSA testing (which has high sensitivity) and the use of conventional imaging technologies (low sensitivity).[111,112]

Previous research identified that nmCRPC patients with a PSA doubling time of less than 10 months are considered at high-risk of developing metastasis.[113] Up until 2018, no treatment was approved for nmCRPC but there are now 3 agents demonstrating improvements in metastasis-free survival and overall survival relative to placebo (enzalutamide, apalutamide, darolutamide) in patients at high risk of metastatic progression.[114-118] Prior to these approvals, in the absence of any treatment demonstrating benefit, only first-generation antiandrogens were offered.

2.6.7 Metastatic Castration-Resistant Prostate Cancer

The clinical disease state of interest across all the works in this thesis is mCRPC. It is considered the final stage of PCa. Broadly speaking, patients with mCRPC are defined as those with detectable metastases on conventional imaging and reached CRPC. A recent study found that 72% of mCPRC cases were initially diagnosed with nonmetastatic PCa whereas 28% were initially diagnosed with de novo metastatic PCa.[119] Within the former, a small percentage (10%) developed mCRPC from nmCRPC. The most frequent site of metastasis in patients with mCRPC is the bone (73%).[120] Also, 43% of patients have bone-only lesions, 21% have a visceral metastasis and a minority (6%) have lymph node metatasis only.[120]

2.6.7.1 Epidemiology of mCRPC

There are currently limited epidemiological reports estimating prevalence and incidence of mCRPC in the literature. Recent studies have shown that the prevalence of mCRPC was estimated from 17 to 62 cases per 100,000 men per year whereas incidence was estimated at 6 cases per 100,000 men per year.[62,121] Data from a study examining trends from 2010-2017 suggests that while the incidence of mCRPC has remained the same over the past decade, the prevalence has increased in the United States.[62] The mean age at the onset of mCRPC ranges from 72-76 years old.[62,122-124] In most studies with descriptions of cohorts of mCRPC patients, at least 50% reached mCRPC at age 70 or older.[62,122,125]

2.6.7.2 Prognosis and Survival in mCRPC

There are a number of established prognostic factors in mCRPC, clinicians should obtain baseline measures for the following: performance status (Karnofsky or ECOG), elevated serum levels of

PSA, elevated testosterone, elevated lactate dehydrogenase, elevated hemoglobin, elevated alkaline phosphatase, as well as the location and number of metastatic sites.[90,126] Visceral metastases are associated with particularly poor prognosis.[120] Additional prognostic factors for survival in mCRPC identified in some studies include PSA doubling time, ISUP grade, presence of pain, skeletal-related event, albumin, etc.[127] Outside of clinical trials, the median survival from the onset of mCRPC ranges from 12 to 23 months.[122,124,125,128,129]

A high level of morbidity is also observed at the mCRPC stage, with skeletal-related events, loco-regional complications, anemia, weight loss, fatigue, hypercoagulability, among others.[109,130] Data from modern RCTs in mCRPC report that approximately one third of patients reported a skeletal-related event, with radiation or surgery to bone being the most common skeletal-related events.[130] However, using real-world data from Canadian cancer centres, 70% reported at least one skeletal-related event (also reported as 85 events per 100 patient-years).[131] Moreover, the occurrence of skeletal-related events leads to clinically significant declines in health-related quality-of-life.[130]

2.6.7.3 Timeline of mCRPC Therapies

The management of mCRPC underwent considerable changes in the 21st century and can be conceptually separated in different eras of innovative breakthroughs. Prior to 2004, no treatment had proven survival benefit in mCRPC, the only options included secondary hormonal treatments with first-generation antiandrogens or ketoconazole. Secondary hormonal manipulation in PCa includes interventions such as: adding a first-generation antiandrogen in patients who were only receiving ADT (leading to combined androgen blockade), as well as withdrawing the first-

generation antiandrogen in those already on combined androgen blockade.[132,133] Unlike in other common solid malignancies, traditional cytotoxic chemotherapies, such as alkylating agents, platinum analogs and antimetabolites, did not demonstrate survival benefits despite numerous trials over the previous decades.[134] In 1996, mitoxantrone was FDA-approved for mCRPC based on palliative response following the results of a small phase III randomized trial, however no survival benefit had been demonstrated in that trial nor in the other trial evaluating mitoxantrone in mCRPC.[135,136] It would take until 2004 for a type of chemotherapy to demonstrate survival benefits, two trials were published that year reporting on the efficacy of docetaxel.[137,138]

The next wave of breakthroughs would come in 2010, with the introduction of another chemotherapy with survival benefits, cabazitaxel.[139] The following years between 2011 and 2014 also saw the addition of abiraterone and enzalutamide, two similar oral agents targeting the androgen receptor axis reported efficacy in multiple indications in mCRPC.[5-8] In 2014, the report of the survival benefits with radium-223, a first-in-class alpha emitting radioligand, was published.[140]

In the 2020s, a third period of breakthroughs came about with the publication of the findings for olaparib and rucaparib, and lutetium-177-PSMA-617.[141-143] Olaparib and rucaparib are of notable interest as they pave the way for a more personalized treatment of advanced PCa. Lutetium-177-PSMA-617, a first prostate-specific membrane antigen (PSMA)-targeted radionuclide. The timeline of mCRPC therapies is illustrated in Figure 2.

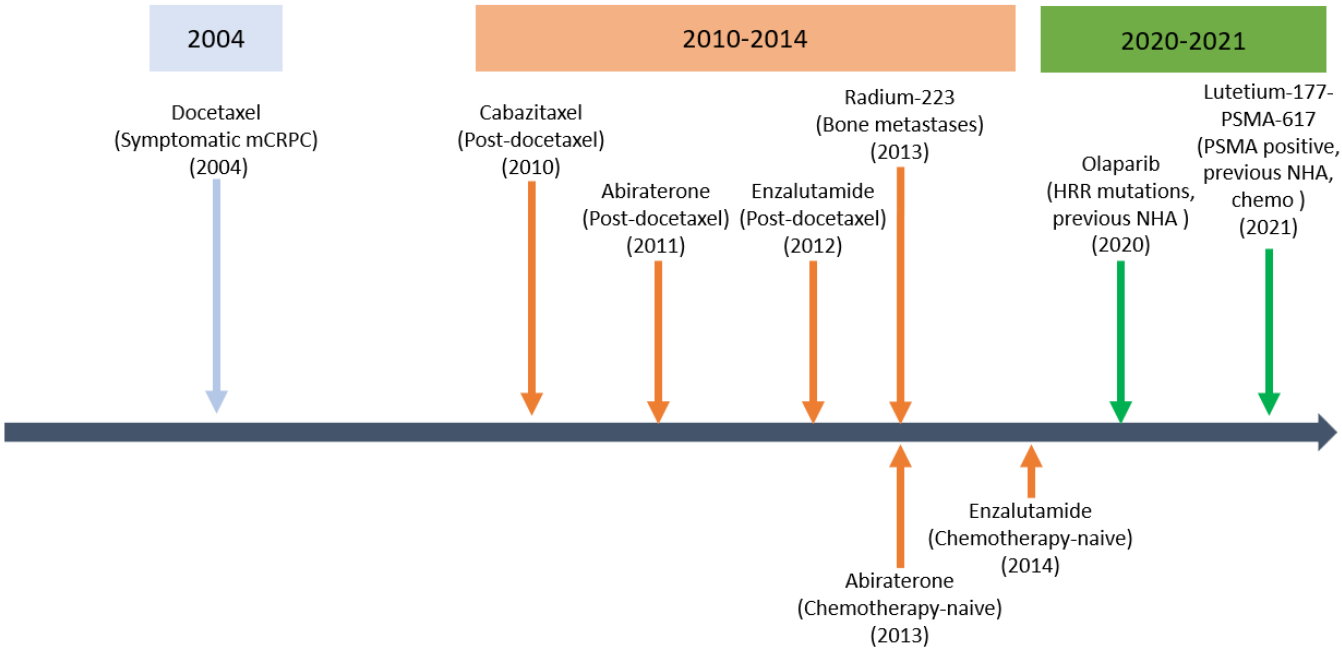

Figure 2. Timeline of mCRPC treatments with survival benefit

2.6.7.4 Treatment Guidelines for mCRPC (modern/today)

As of 2023, with the plethora of therapies available today and the notion that patients may have been exposed to modern therapies in an earlier disease stage (either mCSPC or nmCRPC), the crucial challenge lies in selecting the appropriate agent and determining the optimal sequence of treatments (first-line, second-line, etc.). This will be only a brief description of the 2022 CUA mCRPC guidelines as they do not reflect the study period in the thesis studies, which is the period from 2012 to 2016.[109]

For each line of therapy, the specific agent selected should be based on prior treatment history (avoid choosing a previously used agent or agent with similar mechanism of action), side effect profile, genomic profile, comorbidities, location and extent of disease, and patient preference. Furthermore, despite the high number of therapies approved, mCRPC remains an incurable

disease. As such, enrollment in a clinical trial should always be in consideration at every stage. The CUA mCRPC guidelines are reflected in the following statements:

Four options are available (abiraterone acetate, enzalutamide, docetaxel, olaparib) as first-line therapies. In patients who have not been previously exposed to novel hormonal agents and are asymptomatic or minimally symptomatic, either abiraterone or enzalutamide are recommended. Docetaxel can also be offered.

In patients who are moderately or severely symptomatic and are fit enough to receive chemotherapy, docetaxel is preferred. If patients refuse or are deemed unfit for chemotherapy, either abiraterone or enzalutamide can be considered as well.

In patients who possess homologous recombination repair mutations and were previously treated with either docetaxel or a novel hormonal agent, olaparib is recommended.

When progressing to second-line and beyond, three other therapies become available (cabazitaxel, radium-223, Lu-PSMA-617) in addition to the four options mentioned for the first-line setting.

For patients progressing after docetaxel, cabazitaxel or either novel hormonal agent are recommended. A novel hormonal agent should only be considered if they did not receive one earlier.

For patients who are symptomatic and without visceral metastasis, radium-223 can be recommended if previously treated with a novel hormonal agent or docetaxel.

In patients with PSMA-expressing metastatic lesions and have previously received a taxane chemotherapy and a novel hormonal agent, Lu-PSMA-17 is recommended.

Patients who have limited response to novel hormonal agent, progress with minimal PSA response, or have visceral metastases should consider chemotherapy options earlier.

2.6.7.5 Treatment Guidelines for mCRPC (during study period)

Treatment Options for mCRPC from 2012 to 2016 in Quebec

To better contextualize the thesis projects, a description of the treatment options during the years from 2012 to 2016, and particularly in the province of Quebec, is necessary. To clearly understand the real-world context behind the studies, knowing which treatments that were actually available and publicly covered during the specific study period and in Quebec as well as the clinical practice guidelines during that period is necessary. This is due to the fact that the clinical management of advanced PCa has evolved considerably from 2016 to 2023 which is attributable to the increased number of approved treatments and the results of many RCTs demonstrating the efficacy of several mCRPC-approved treatments in earlier disease states. As such, guidelines from 2023 do not adequately reflect the situation from our study period.

During this period, docetaxel was available and covered for mCRPC since 2004. Although cabazitaxel was approved by Health Canada in 2011, it only obtained public coverage in Quebec in 2016. The specific indication covered in Quebec's public drug plan is for post-docetaxel mCRPC.

While not having survival benefit in mCRPC, mitoxantrone was also publicly covered (since at least 2004).

In terms of the NHAs, abiraterone and enzalutamide were both available and publicly covered. First, abiraterone acetate received Health Canada approval in 2011 and its public drug coverage in Quebec specifically for the indication of post-docetaxel mCRPC in 2012. However, coverage could be provided to patients ineligible for chemotherapy under the "exception patient" measure. Following that, abiraterone also became publicly covered for the indication of chemotherapy-naïve mCRPC in 2014, meaning they must not have been previously treated with docetaxel and are currently either asymptomatic or only mildly symptomatic. Enzalutamide received approvals for the same two indications as abiraterone, and the timing of its Health Canada approvals and Quebec public coverage inclusions resemble that of abiraterone but with a delay of approximately 2 years. Enzalutamide's public coverage for post-docetaxel mCRPC occurred in 2014. Similar to abiraterone in 2012, enzalutamide could also be covered for patients ineligible for chemotherapy under the "exception patient" measure. The coverage for the chemotherapy-naïve mCRPC indication occurred in 2016.

Radium-223 was approved by Health Canada in 2014 for mCRPC with symptomatic bone metastases (without visceral metastases) and received public coverage in Quebec in 2015.

In terms of supportive therapies, zoledronic acid has been available and publicly covered since 2004. For prevention of skeletal-related events in mCRPC, denosumab received public coverage in 2012.

CUA mCRPC Guidelines during the Study Period

In addition to knowing the treatment options during the study period in Quebec, understanding the specific clinical guidelines of the time is also necessary to frame the context of the thesis studies. From 2012 to 2016, the CUA published 2 versions of clinical guidelines for CRPC, in 2013 and 2015.[144,145] The 2013 version represents the earlier part of the study period concerned in the thesis, while the 2015 guidelines expands slightly beyond the 2013 guidelines with the introduction of radium-223. For all intents and purposes, especially regarding the role of the NHAs (abiraterone acetate and enzalutamide) in mCRPC, the 2013 and 2015 guidelines are very similar, with the exception that in the 2013 version, enzalutamide was not yet recommended for chemotherapy-naïve (pre-docetaxel) mCRPC given that the results of the PREVAIL trial were not available at the time of writing.

Regarding the management of mCRPC specifically during those years, it can be distilled down to three typical clinical scenarios: asymptomatic or mildly symptomatic mCRPC, symptomatic mCRPC, and post-docetaxel mCRPC.

For men presenting with no symptoms or mild symptoms, the guidelines recommended as first-line therapy, either NHA (abiraterone acetate or enzalutamide). While docetaxel can be offered, discussions about its use at this juncture (asymptomatic or mildly symptomatic) need to strongly weigh the risk-benefit of chemotherapy and patient preferences. Secondary hormonal manipulation with first-generation antiandrogens could be discussed but is considered as a recommendation with low level of evidence.

For mCRPC patients presenting with symptoms, the guidelines recommended docetaxel as first-line therapy. As an alternative for patients ineligible for chemotherapy, either abiraterone

acetate or enzalutamide could be offered but since the RCTs of both these NHAs in the post-docetaxel setting did not include patients with significant symptoms, this recommendation was only based on expert opinion.

The third clinical scenario in mCRPC that the guidelines covered was post-docetaxel mCRPC, i.e. patients who progressed after docetaxel. In this context, there are multiple options that are backed by RCT-level evidence: abiraterone acetate, enzalutamide, cabazitaxel, and radium-223 (in the 2015 version). A caveat is that radium-223 is only recommended when there are bone metastases without evidence of visceral metastases. Mitoxantrone is also an option in this setting but it only confers palliative benefit. Another option, that is only based on expert opinion, is re-treatment with docetaxel for individuals who previously had good response.

In terms of supportive care, bone-targeted therapies (zoledronic acid and denosumab) were recommended in men with bone metastases for their reduction in skeletal-related events. Both were supported by RCT data. Palliative radiation can be offered for pain relief due to bone metastases.

Summary of CUA mCRPC Guidelines during Study Period

While it may not appear impressive relative to today's therapeutic arsenal, the approval of cabazitaxel, abiraterone acetate, enzalutamide, radium-223 during this period led to a drastic upheaval of mCRPC management compared to what was available before.[146] Relative to today's context, the guidelines were much simpler due to the lesser number of approved therapies but also due to the fact that findings of the RCTs evaluating the efficacy of abiraterone acetate and enzalutamide in earlier disease settings (nmCRPC, mCSPC) had not yet been completed. Since the

optimal sequencing of treatments was unknown, the major element to consider in treatment selection for mCRPC essentially boiled down to the symptomatic burden incurred by disease and whether the patient was previously exposed to docetaxel. Figure 3 below summarizes the CUA mCRPC guidelines from 2013 to 2016.

Although there are more treatments available today and the guidelines have evolved in complexity in response, there are still many unclear aspects of the therapies that were available during that period, especially as it relates to the two first NHAs approved, abiraterone and enzalutamide.

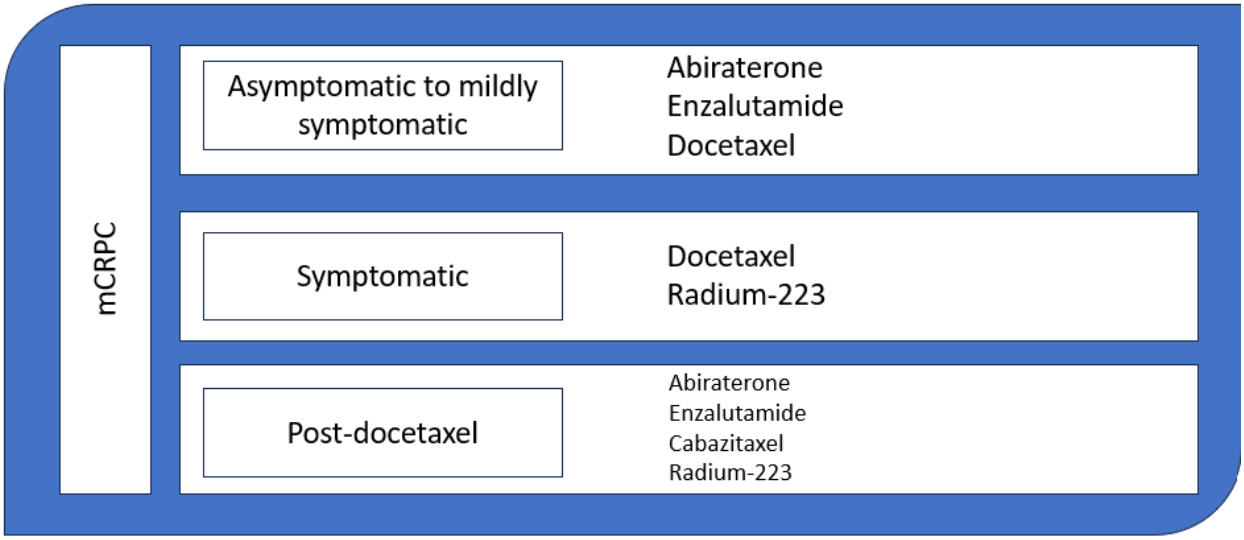

Figure 3. Summary of CUA guidelines for mCRPC during study period

2.6.7.6 Brief Overview of mCRPC Treatments

The treatments for mCRPC which have demonstrated survival benefits in RCTs can be categorized into the following therapeutic classes: taxane chemotherapy, novel hormonal agent (NHA), radiopharmaceutical, and molecular therapy.

Taxane Chemotherapy:

Docetaxel

Docetaxel is a taxane-based chemotherapy that is administered intravenously. It functions by binding to tubulin and disrupting the microtubule assembly process leading to stabilization of the microtubules. This leads to inhibition of cell division and tumor proliferation and ultimately cell death. It was the first treatment demonstrating survival benefits in mCPRC and this was established in two RCTs (TAX 327 and SWOG 9916). In the TAX 327 study, docetaxel plus prednisone was found to result in a modest but statistically significant 1.9-month survival benefit compared to mitoxantrone (a chemotherapy which demonstrated symptom relief but no survival benefit in a previous RCT).[147] The SWOG 9916 found similar results and docetaxel was FDA approved for symptomatic mCRPC.[138] Details from the 2 RCTs are found in Table 2.

Table 2: Docetaxel mCRPC RCTs

Docetaxel			
RCT	Comparison	Indication	Outcomes
SWOG 9916[(138)]	Mitoxantrone	Symptomatic mCRPC	OS: 17.5 vs 15.6 months HR 0.80 (95%CI 0.67, 0.97)
TAX327[(137)]	Mitoxantrone	Symptomatic mCRPC	OS 19.2 vs 16.3 months HR 0.79(95%CI 0.67, 0.93)

Cabazitaxel

Cabazitaxel is a second-generation taxane-based chemotherapy with a similar mechanism of action to docetaxel. It was initially selected for development on the basis of its poorer affinity to P-glycoprotein, giving it an ability to be effective in docetaxel-resistant tumors. In the TROPIC

RCT, which was comprised of men with mCRPC who progressed past docetaxel, cabazitaxel was shown to confer a statistically significant 2.4-month survival benefit compared to mitaxantrone. On the basis of these results, cabazitaxel was approved for use in patients with mCRPC who progressed past docetaxel.[148] Details from the RCT are found in Table 3.

Table 3: Cabazitaxel mCRPC RCTs

Cabazitaxel			
RCT	Comparison	Indication	Outcomes
TROPIC[(139)]	Mitoxantrone	Post-docetaxel mCRPC	OS: 15.1 vs 12.7 months HR 0.70 (95%CI 0.59, 0.83)

Novel Hormonal Agents

Abiraterone acetate

Abiraterone is a non-steroidal androgen synthesis inhibitor, specifically the CYP17 enzyme. Inhibition of CYP17 leads to suppression of gonadal and extragonadal (adrenal and tumour) androgen synthesis.[149] For mCRPC, it was evaluated in the post-docetaxel setting, abiraterone led to an improvement in overall survival of 4.6 months compared to placebo.[150] In another indication for mCRPRC, in the COU-AA-302 RCT, which randomized chemotherapy-naïve patients to either abiraterone or placebo, abiraterone demonstrated an overall survival benefit of 4.4 months.[151] Details from the RCTs are found in Table 4.

Table 4: Abiraterone mCRPC RCTs

Abiraterone			
RCT	Comparison	Indication	Outcomes
COU-AA-301[(5)]	Placebo	Post-docetaxel mCRPC	OS: 15.8 vs 11.2 months HR 0.74 (95%CI 0.64, 0.86)
COU-AA-302[(6)]	Placebo	Chemotherapy-naïve mCRPC	OS 34.7 vs 30.3 months HR 0.81 (95%CI 0.70, 0.93)

Enzalutamide

Enzalutamide is a second-generation non-steroidal antiandrogen which possesses a much higher affinity to the androgen receptor compared to first-generation antiandrogens. Unlike first-generation antiandrogens, enzalutamide does not act as partial agonist, it competitively binds to the androgen receptor, inhibits nuclear translocation and DNA transcription.[152] It has been evaluated in 2 RCTs in mCRPC. In the AFFIRM trial, which randomized patients who progressed on docetaxel to either enzalutamide or placebo, enzalutamide demonstrated a 4.8 month benefit in overall survival.[7] In the PREVAIL trial, which evaluated enzalutamide in chemotherapy-naïve mCRPC patients, enzalutamide yielded an overall survival improvement of 4 months compared to placebo.[153] Details from the RCTs are found in Table 5.

Table 5: Enzalutamide mCRPC RCTs

Enzalutamide			
RCT	Comparison	Indication	Outcomes
AFFIRM[(7)]	Placebo	Post-docetaxel mCRPC	OS: 18.4 vs 13.6 months HR 0.63 (95%CI 0.53, 0.75)
PREVAIL[(8)]	Placebo	Chemotherapy-naïve mCRPC	OS 35.3 vs 31.3months HR 0.77 (95%CI 0.67, 0.88)

Radiopharmaceuticals

Radium-223

Radium-223 is a radioisotope that emits alpha particle radiation.[154] As a calcium mimetic, it specifically targets bone metastases due to its preferential targeting areas of high bone turnover (which correspond to the osteoblastic bone lesions common in PCa).[155] The alpha particles

emitted by radium-223 are powerful but only exert damage over a relatively short range (<100 um), which leads to DNA double-strand breaks in the bone-tumour microenvironment and a return to stabilization of normal bone structure.[156] In the ALSYMPCA RCT, which investigated the efficacy of radium-223 in patients with two or more symptomatic bone lesions, the radium-223 group achieved a 3.6 month survival benefit over placebo.[140] Details from the RCT are found in Table 6.

Table 6: Radium-223 mCRPC RCT

Radium-223			
RCT	Comparison	Indication	Outcomes
ALSYMPCA[(140)]	Placebo	>2 symptomatic bone metastasis No visceral metastasis	OS: 14.9 vs 11.3 months HR 0.70 (95%CI 0.58, 0.83)

Lu-177-PSMA-617

Lu-177-PSMA-617 is a small molecule that binds specifically to PSMA receptors on PCa cells, which enables delivery of beta particle radiation to PSMA-expressing cells adjacent tumor cells which induces DNA damage leading to cell death. A positive diagnostic gallium-68-labeled PSMA PET scan is a prerequisite to select suitable patients. This therapy acquired FDA approval in 2022.[143] Details from the RCT are found in Table 7.

Table 7: Lutetium-177-PSMA-617 mCRPC RCT

Lutetium-177-PSMA-617			
RCT	Comparison	Indication	Outcomes
VISION[(143)]	Standard care	PSMA-positive mCRPC Previous NHA and taxane	OS: 15.3 vs 11.3 months HR 0.62 (95%CI 0.52, 0.74)

Molecular therapy

Olaparib

Homologous recombination repair (HRR) gene mutations are present in up to 30% of metastatic PCa patients.[157] Olaparib is an inhibitor of the enzyme poly ADP-ribose polymerase (PARP), which is involved in DNA repair and play a crucial role in patients with HRR mutations as their cancer cells have an increased reliance on PARP to continue proliferating. As such, PARP inhibitors (PARPi) are particularly effective against these types of cancers given they selectively target PARP. [158] Details from the RCT are found in Table 8.

Table 8: Olaparib mCRPC RCTs

Olaparib			
RCT	Comparison	Indication	Outcomes
PROfound[(141)]	Physician choice (abiraterone or enzalutamide)	BRCA1, BRCA2, or ATM mutation Previous NHA	OS: 19.1 vs 14.7 months HR 0.69 (95%CI 0.50, 0.97)

Supportive therapies

Bone-targeted therapies: Zoledronic acid is an intravenously administered bisphosphonate that inhibits bone resorption and is approved for the prevention of skeletal-related events in mCRPC.[159] Denosumab, a monoclonal antibody that inhibits RANK ligand (RANKL), disrupts oscteoclastic differentiation which leads to reduction in bone resorption.[160] An RCT in mCRPC patients demonstrated the efficacy of denosumab in preventing skeletal-related events compared to zoledronic acid (HR 0.82, 95%CI 0.71, 0.95).[161]

Corticosteroids: An observational report suggests that low dose corticosteroids (prednisone, dexamethasone) may provide PSA response, symptom relief, and radiographic regression in mCRPC patients via suppression of adrenal androgens.[157]

Mitoxantrone: It belongs to the class of anthracenedione agents, exerts its effect as intercalator leading to disruption of DNA synthesis and DNA repair.[162] Palliative improvement demonstrated in mCRPC 2 RCTs, but no improvement in overall survival.[135,136] Can still be offered for palliative relief in mCRPC.

2.7 Evidence Gaps Concerning Abiraterone and Enzalutamide

Although many therapies have been introduced to mCRPC armamentarium in recent years, the NHAs, abiraterone and enzalutamide, are of particular interest. They are the first oral agents that demonstrated overall survival benefits in mCRPC and they are both relatively tolerable compared to chemotherapy, which was the only alternative therapeutic option at the time. As patients with mCRPC are typically older, have many comorbidities and may not be eligible for chemotherapy, the uptake of docetaxel in the real-world has not been high. Previous population-based studies

have found that only about 20-33% of mCRPC patients were treated with chemotherapy.[163-165] It is therefore unsurprising that the NHAs have become the most widely therapies in mCPRC and quickly overtook docetaxel.[4]

Utilization of NHAs and Prescribing Specialty

As the ease of administration (oral) and favorable adverse effect profile of the NHAs are likely contributors to their large and rapid uptake in mCRPC, they also make it accessible to physician specialties other than medical oncologists to prescribe. Contrary to taxane chemotherapy, which had not only a rather limited pool of patients eligible/fit for treatment, the administration of intravenous cytotoxic chemotherapy is typically limited to the practice of medical oncologists. With the advent of oral agents like the NHAs, urologists are presented with the opportunity to continue treating patients instead of referring patients to medical oncologists when they progress to an advanced state such as mCRPC. However, there is limited data reporting on the prescribing patterns of the NHAs in mCRPC, especially as it relates to data on the prescribing specialty.

One study has examined the prescribing trends of NHAs in the United States.[166] Using Medicare Public Use file data, Caram et al examined the number of prescription claims for abiraterone and enzalutamide from 2013 to 2016 at an yearly aggregate level by prescribing specialty (urologist, non-urologist), and prescribing volume (low prescribers, moderate prescribers, high prescribers). Overall, their study examined 367,019 claims for abiraterone and 274,644 claims for enzalutamide. They found that the number of urologists who were moderate-high prescribers of abiraterone increased by 307% during the study period, as opposed to increasing by only 30% for

non-urologists. The number of urologists that were moderate-high prescribers of enzalutamide increased by >3000%, as opposed to non-urologist prescribers which increased by 301%. Although these data clearly suggest an increasing number of prescriptions of NHAs by urologist, there are several limitations to consider as well as many issues related to prescribing patterns that remain unaddressed. Data used in this study was at the provider level and therefore could not adjust for patient-level data. Patient-level data is of particular interest in order to allow for the examination of patient factors (demographic, comorbidities, co-medications, previous treatments, etc.) on the prescribing patterns of NHAs. Additionally, there was no distinction made in the specific mCRPC indication (chemotherapy-naïve vs post-chemotherapy) of the NHAs. Taken altogether, in addition to the lack of data on this issue in Canada, it would be useful to undertake research to better understand how the NHAs are used in clinical practice and to confirm if similar trends in prescribing specialty is occurring in Canada.

Cardiovascular Safety of the NHAs in mCRPC

The NHAs, abiraterone and enzalutamide, possess many similarities. Both exert their effects on the androgen receptor axis, although their specific mechanisms of action differ. In terms of efficacy in mCRPC, they are likely similar given that they demonstrated comparable effects against their placebo arms in their respective phase III RCTs. Despite an overall favorable toxicity profile, the specific adverse effects vary due to their distinct mechanisms of action. For abiraterone, it is frequently associated with fluid retention and hypokalemia, while enzalutamide treatment is characterized by central nervous system (CNS) disorders, hot flashes, and high-grade fatigue. However, concerns about cardiovascular toxicity exist for both agents. Abiraterone,

according to the United States Federal Drug Administration (FDA) prescription labeling, requires closer monitoring in patients with existing cardiovascular disease due to potential mineralocorticoid excess, despite co-administration of prednisone to mitigate such effects.[167] Similarly, the label information for enzalutamide warns of an increased risk of ischemic heart disease and emphasizes the optimization of managing cardiovascular risk factors.[168]

Moreover, a meta-analysis of seven RCTs revealed that both abiraterone and enzalutamide were associated with an elevated risk of cardiovascular toxicity compared to their placebo control arms.[169] Specifically, abiraterone increased the risks of hypertension ([all-grade hypertension: risk ratio 1.79, 95%CI 1.45-2.21], [high-grade hypertension: risk ratio 2.19, 95%CI 1.73-2.78]) and cardiac toxicity ([all-grade cardiac toxicity: risk ratio 1.41, 95%CI 1.21-1.64], [high-grade cardiac toxicity: risk ratio 2.22, 95%CI 1.60-3.27]). Enzalutamide treatment was associated with an increased risk of hypertension ([all-grade hypertension: risk ratio 2.74, 95%CI 2.07-3.63], [high-grade hypertension: risk ratio 2.44, 95%CI 1.64-3.63]) but not cardiac toxicity ([all-grade cardiac toxicity: risk ratio 1.41, 95%CI 0.75-2.63], [high-grade cardiac toxicity: risk ratio 1.32, 95%CI 0.85-2.06]). However, the findings of that study had several limitations. First, it was only using aggregate data from the RCTs, as they did not have access to individual patient-level data. Second, the definition of cardiac toxicity varied across the included studies and could not be standardized in the meta-analysis. Lastly, these data only addressed the cardiotoxicity of the NHAs relative to placebo and could not evaluate the comparison of abiraterone and enzalutamide.

An additional area of uncertainty regarding the cardiotoxicity of the NHAs arises from their application in real-world patients. The RCTs for abiraterone and enzalutamide excluded patients with clinically significant cardiovascular disease or uncontrolled hypertension. This exclusion limits the generalizability of safety findings from the RCTs, and consequently also those of the aforementioned meta-analysis using the aggregate data from the RCTs.[169] Consequently, a knowledge gap persists concerning the cardiovascular safety of abiraterone and enzalutamide in patients treated in routine clinical practice, particularly those with significant comorbidities.

Association between NHA Complications and Prescribing Specialty

Although the NHAs have a favorable tolerability compared to taxane chemotherapy, they are still associated with a wide range of adverse events. As mentioned above, there are some cardiovascular concerns for both NHAs.[167-169] Regarding metabolic complications, abiraterone presents several issues requiring attention, including hepatotoxicity evidenced by an increased frequency of grade 3-4 elevated liver enzymes in documented in the RCTs.[6] Monitoring diabetic patients concurrently receiving treatment is crucial due to potential drug-drug interactions with numerous oral antidiabetics. Co-administration of prednisone with abiraterone can further elevate the risk of hyperglycemia.[170] Infectious complications, particularly upper respiratory tract infections and urinary tract infections, were more commonly reported for abiraterone compared to the placebo group in its randomized trials. Enzalutamide showed a higher prevalence of upper and lower respiratory tract infections. Other general and non-specific complications noted for NHAs include central nervous system disorders, hot flashes, and high-grade fatigue.[167,168] Given this wide range of potential complications, prescribing clinicians must possess proficiency in

identifying and addressing the diverse complications that may arise from treatment with NHAs, as these toxicities often fall beyond the typical scope of practice of a physician's own specialty.

A recent population-based study investigated the outcomes of patients receiving NHAs based on the specialty of the prescribing clinician.[171] Using administrative healthcare claims data from the province of Ontario in Canada, a retrospective cohort of abiraterone and enzalutamide initiators from 2012 to 2017 was assembled. The exposure of interest was prescribing specialty (urologist, medical oncologist, other specialties) of the NHA. Treatment-related toxicity was based on diagnosis codes from hospital admissions and emergency department visits and defined as a composite outcome that included the following type of events: cardiovascular events, fluid-electrolyte imbalances, infections, metabolic complications. All-cause mortality and all-cause hospitalization were also examined as secondary outcomes. Their cohort comprised of 3,405 NHA initiators, and the prescribing specialty grouping were as follows: urologist (23%), medical oncologist (62%), other specialty (10%). The findings in their primary analysis (multivariable regression accounting for prescribing specialty, age, comorbidity score, and some other characteristics) indicated that patients treated by medical oncologists experienced lower risks of treatment-related toxicity (hazard ratio 1.34, 95%CI 1.08-1.69), all-cause hospitalization (hazard ratio 1.16, 95%CI 1.03-1.31), and all-cause mortality (hazard ratio 1.16, 95%CI 1.02-1.33) compared to those treated by urologists. In a sensitivity analysis restricted to patients for whom baseline PSA was available, multivariable regression analyses which included baseline PSA for adjustment led to diluted effect estimates (treatment-related toxicity: hazard ratio 1.18 [95%CI 0.82-1.74], all-cause hospitalization: hazard ratio 1.05 [95%CI 0.85-1.28], all-cause mortality: hazard ratio 0.93 [95%CI 0.82-1.74]). It's noteworthy that the outcome of treatment-related

toxicity was only examined as a composite outcome and no multivariable analyses were undertaken for the various subtypes of complications (only unadjusted frequencies were provided for the various subtypes). Given the extensive array of potential complications linked to NHAs, specific physician specialties may demonstrate better aptitude in managing distinct types of NHA complications due to their training, clinical experience and workflow. This suggests that an analysis that considers the different types of complications associated with NHAs could offer additional insights into the optimal management of patients undergoing NHA treatment.

Summary of Evidence Gaps

Despite the prevalent use of ABI and ENZ in mCRPC, many questions still remain unanswered. There is limited data concerning the utilization of NHAs in the real-world, especially regarding the specific mCRPC indications and prescribing specialty. A knowledge gap concerning the differentiation of abiraterone and enzalutamide is their comparative cardiovascular safety. Although both agents have had certain signals of cardiotoxicity, the data from RCTs may not be applicable to real-world practice. Consequently, the cardiovascular risks of these NHAs in patients outside the realm of clinical trials remains unknown. Finally, with the wide range of potential complications with NHA treatment, managing treatment toxicities can be complex. Given that multiple physician specialties, including urologists and medical oncologists, are likely to partake in the prescribing of NHAs in mCRPC, there needs to be further research examining whether each prescribing specialty is associated with incidence of certain types of complications.

Chapter 3: Utilization trends of novel hormonal agents in metastatic castration-resistant prostate cancer in Quebec

Preface: This descriptive study sought to describe the utilization trends of abiraterone and enzalutamide in patients with mCRPC in the early years after their approval in the province of Quebec in Canada. Over time, there was an increasing proportion of patients who (1) initiated NHAs without prior chemotherapy treatment, (2) NHA prescribing by urologists, and (3) of enzalutamide users. Taken altogether, this implies that the introduction of NHAs has altered the management of mCRPC and urologists quickly adopted NHAs into their practice.

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Utilization trends of novel hormonal agents in metastatic castration-resistant prostate cancer in Quebec

Running title: Utilization trends of novel hormonal agents in mCRPC

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ABSTRACT

Background: The introduction of novel hormonal agents (NHAs) such as abiraterone acetate (ABI) and enzalutamide (ENZ) for metastatic castration-resistant prostate cancer (mCRPC) was an important milestone given their survival benefits, their tolerability and ease of administration relative to taxane chemotherapies. This study sought to describe the utilization trends of ABI and ENZ in patients with mCRPC in the early years after their approval in the province of Quebec in Canada.

Methods: A retrospective population-based cohort was extracted from Quebec public healthcare administrative databases. The cohort included first-time users of NHAs (ABI or ENZ) from 2011-2016. The primary analyses aimed to describe the overall temporal trends (2011-2016) of NHA initiators by chemotherapy status (chemotherapy-naïve versus post-chemotherapy), and prescribing specialty (medical oncology versus urology versus others).

Results: The cohort comprises 2,183 patients, with 1,562 (72%) in the chemotherapy-naïve group and 621 (28%) in the post-chemotherapy group. While the majority of patients were post-chemotherapy NHA initiators in 2012, this proportion decreased over time and accounted for only 13% of NHA initiators by the end of 2016. Medical oncologists were the most frequent prescribers of NHAs (upwards of 60%) throughout 2012 but fell to 45% by the end of 2016. Conversely, the proportion of prescriptions by urologists increased from 22% in 2012 to 42% in 2016.

Conclusion: Over time, there was an increasing proportion of patients who (1) initiated NHAs without prior chemotherapy treatment, (2) NHA prescribing by urologists, and (3) of ENZ users.

Taken altogether, this implies that the introduction of NHAs has altered the management of mCRPC and urologists quickly adopted NHAs into their practice.

Introduction

Prostate cancer (PCa) is the most common noncutaneous maligancy in Canadian men. [1] Most patients are diagnosed at the localized stage and the survival rate is high. [2] However, certain patients will progress to metastatic castration-resistant prostate cancer (mCRPC) which is defined as progression despite castrate levels of testosterone. [3,4] Until 2010, docetaxel chemotherapy was the only treatment with survival benefit in this disease setting. Although it remains an ultimately incurable disease, the treatment landscape for mCRPC has seen significant advances in the past decade. [5] Progress was made with the introduction of the second-generation taxane chemotherapy, cabazitaxel, and further innovation was represented with immunotherapeutic and radiopharmaceutical agents in the form of sipuleucel-T and radium-223, respectively. However, the most important additions have been the novel hormonal agents (NHAs) which include abiraterone acetate (ABI) and enzalutamide (ENZ); their adoption was rapid and in greater magnitude than the other novel mCRPC treatments. [6] This could be attributed to several reasons: both are approved in the pre- and post-docetaxel settings in mCRPC, their ease of delivery (oral administration), and their tolerability compared to taxanes. [5]

In their respective pivotal clinical trials leading to their regulatory approval, ABI and ENZ demonstrated similar survival benefits relative to their placebo control arms. [7-10] While the two have an overall favorable toxicity profile, the adverse effects associated with each is different owing to their specific mechanism of action. Abiraterone acetate is an androgen biosynthesis inhibitor and should be co-administered with prednisone, while ENZ is a second-generation competitive inhibitor of the androgen receptor. [11,12] Adverse effects associated with ABI include liver function abnormalities, fluid retention, and cardiac events. [13] On the other hand, ENZ is

associated with more central nervous system impairments. [14] Increased incidence of hypertension and fatigue are reported with both of these agents. [5]

In the province of Quebec in Canada, ABI was approved for public reimbursement in 2012 for patients with mCRPC previously treated with docetaxel chemotherapy. However, patients ineligible for chemotherapy could still have access to the drug on exceptional medical basis. In 2014, ABI was also approved for patients with mCRPC without prior exposure to docetaxel chemotherapy. For ENZ, its initial approval in the post-docetaxel setting came in 2014 – as with ABI in 2012, patients ineligible for chemotherapy could also have access on exceptional medical basis. The subsequent approval of ENZ in mCRPC patients without prior chemotherapy occurred in 2016.

In this study, we sought to describe the utilization trends of the NHAs and evaluate factors associated with prescribing of ENZ over ABI in the province of Quebec in Canada.

Materials and Methods

Data Sources

As with other Canadian provinces, provincial public healthcare insurance coverage is provided to all its residents for physician visits and medical procedures. This study draws data from public healthcare administrative databases from the province of Quebec, which are administered by the Régie de l'assurance maladie du Québec (RAMQ). The RAMQ provides universal healthcare coverage to residents of the province of Quebec in Canada through the Quebec Health Insurance Plan. This plan covers all physician visits and procedures, and outpatient and inpatient care for

all Quebec residents. The prescription drug insurance plan of the RAMQ (Public Prescription Drug Insurance Plan) provides coverage for individuals aged 65 years and older, welfare recipients, and other residents who do not have access to a private drug insurance plan. The RAMQ databases contain data pertaining to patient basic demographic information, medical services derived from physician billing claims, and prescription drugs dispensed at community pharmacies. Data on hospital admissions was extracted from a complementary source, the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED ECHO) databases.

Study Cohort

This was designed as a retrospective observational study with a cohort comprised of men who initiated an NHA (ABI or ENZ) in the period from January 2011 to December 2016. Patients with no prior history of ADT (luteinizing hormone-releasing hormone agonist or antagonist drugs or orchiectomy) and who were registered to the public drug insurance plan for less than a year prior to NHA initiation were excluded. The index date corresponded to the date of the first prescription of the NHA. It should be noted that although both drugs have gained expanded approval to earlier disease states nowadays, both ABI and ENZ were considered "exception drugs" by the RAMQ that were only approved for mCRPC during the study period in the province of Quebec. This ensures that patients receiving NHAs in the study were for the treatment of mCRPC.

Primary Analyses

The primary analyses aimed to describe the overall temporal trends (2011-2016) of NHA initiators by chemotherapy status (chemotherapy-naïve versus post-chemotherapy), and prescribing specialty (medical oncology versus urology versus others). Patients were considered as post-chemotherapy if physician claims of intravenous chemotherapy administration were identified in the period between ADT initiation and NHA initiation. The prescribing specialty was based on the physician specialty identified in the initial NHA prescription and was obtained in the prescription drug database. The medical oncology grouping includes both medical oncologists and hematologists. Physician specialties other than urology and medical oncology (medical oncologists and hematologists) were grouped as others.

Secondary Analyses

As part of secondary analyses, we sought to describe the trends for each NHA separately in the years when both ABI and ENZ were available (2014 to 2016, referred to hereafter as the ENZ-era). Specifically, we examined the evolution of patterns by chemotherapy status and prescribing specialty within each NHA type.

Patient characteristics

Patient characteristics such as age and region of residence (urban vs rural) were captured at the index date. Characteristics relating to PCa included: prior local PCa treatment (receipt of radical prostatectomy, external beam-radiotherapy, or brachytherapy at any time prior to the index date), time from PCa diagnosis to index date, use of bone-targeted therapy (zoledronic acid or denosumab in the year prior to the index date), chemotherapy status (chemotherapy-naïve vs

post-chemotherapy), and symptomatic indicator (yes vs no). The symptomatic indicator variable is meant to be a proxy of patient symptomatic status and is a composite variable of the any of the following conditions identified in the 3 months prior to the index date: receipt of a urological procedure relating to loco-regional complications of PCa (ex: nephrostomy, ureteral stenting, etc.), receipt of palliative radiotherapy, and use of opiates. All other comorbidities, Charlson comorbidity index, and healthcare utilization metrics (hospitalization and visits to specialist physicians) were measured during the year prior to the index date through diagnosis codes and treatments contained in physician claims, inpatient discharge abstracts, and prescription drug databases.

Statistical Analysis

Descriptive statistics were presented as counts and percentages for categorical variables, and as means with standard deviation for continuous variables. Temporal trends of NHA initiation were observed in tri-monthly intervals (quarters: Q1, Q2, Q3, Q4) over the study years. Temporal trends were evaluated with either the Cochran-Armitage test or the Cochran-Mantel-Haenszel test, whichever was appropriate in a given analysis.

Multivariable logistic regression analyses were performed to identify factors associated with the initiation of ENZ over ABI in the ENZ-era with the main goal of assessing the effect of the prescribing specialty variable when adjusted for other baseline patient characteristics. Two models were fitted, with one model for chemotherapy-naïve patients and the other for post-chemotherapy patients. Results from the multivariable models are presented as odds ratios (OR)

with 95% confidence intervals (95%CI). All analyses were two-sided with the statistical significance level set at $p < 0.05$, and were conducted with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Sensitivity Analyses

To account for potential discrepancies in the initial prescribing physician and subsequent specialties prescribing the NHA for a given patient, we also repeated analyses with an alternative definition for the prescribing specialty. In this alternative definition, the prescribing specialty was defined the specialty accounting for the majority of the NHA prescriptions for a given patient. In another sensitivity analysis, we classified radiation oncologists along with the urologists and repeated the analyses involving prescribing specialties (medical oncologists vs urologists/radiation oncologists vs others).

Results

The study cohort comprises 2,183 patients who initiated an NHA during the study period. These patients filled a total of 29,347 NHA prescription claims and the absolute number of claims increased yearly (2011: 133; 2012: 1,958; 2013: 4,172; 2014: 6,767; 2015: 7,796; 2016: 8,521). Additional descriptive claims-level details can be found in the **appendix Table A1**.

Baseline characteristics

Table 1 displays the baseline characteristics of NHA users stratified by chemotherapy status. Chemotherapy-naïve patients tend to be older and have a greater number of comorbidities relative to post-chemotherapy patients. On the other hand, post-chemotherapy patients have higher proportions for the variables relating to PCa severity (symptomatic indicator, use of bone-targeted therapy), a shorter time from PCa diagnosis to the index date, and higher number of visits to specialists physicians in the year before starting the NHA.

Primary analysis: Overall trends of chemotherapy status and prescribing specialties (2011-2016)

Figure **1A** displays the trend of NHA initiators by chemotherapy status. During the first year of the study, the majority of NHA users were previously treated with chemotherapy but this proportion decreased over time and accounted for only 13% of NHA users in the last quarter of 2016 ($p<0.001$). This decreasing trend of post-chemotherapy NHA initiators (and conversely the increasing trend of chemotherapy-naïve patients) was observed in both the ABI users ($p<0.001$, **appendix Figure A1**) and ENZ users ($p<0.001$, **appendix Figure A2**).

Medical oncologists represented the most frequent prescribers of NHAs (upwards of 60%) throughout 2012 but fell to 45% by the end of 2016 (Figure **1B**). Conversely, the proportion of prescriptions by urologists increased from 22% in 2012 to 42% in 2016 (Figure **1B**).

Secondary analyses: Trends in the ENZ-era (2014-2016)

Figure **2A** displays the trends of NHA type in the ENZ-era. From its first quarter of approval (Q1 of 2014), the proportion of ENZ initiators increased from 10% to 54% at the end of the study period ($p<0.001$).

Regarding ABI initiators in the ENZ-era (Figure **2B**), there was a slight majority of medical oncologists as prescribers (accounting for 49% overall during those years) with urologists ranking second at 36%. For ENZ initiators in the ENZ-era (Figure **2C**), it was the opposite, with a slight majority of urologists as prescribers (accounting for 51% overall during those years) and medical oncologists coming in at second at 39%.

Among post-chemotherapy patients in the ENZ-era (Figure **3A**), medical oncologists were the most frequent prescribing specialty throughout those years (accounting for 73% overall during the ENZ-era). Additionally, ABI was the NHA used by the majority of these patients up until the second quarter of 2016 (**appendix Figure A3**).

Among chemotherapy-naïve patients in the ENZ-era (Figure **3B**), urologists were the top prescribing specialty accounting for 46% of NHA prescribers in the period and medical oncologists ranked second at 40%. These percentages remained relatively stable throughout (temporal trend $p = 0.306$). Regarding the type of NHA used in these patients, the majority of patients were treated by ABI up until the third quarter of 2016 (**appendix Figure A4**).

In Table 2, multivariable regression analyses examining the relationships between initiating ENZ (over ABI) during the ENZ-era confirmed that urologists were likely to prescribe ENZ compared to medical oncologists in both the chemotherapy-naïve setting (Model 1, OR 1.89, 95% 1.38-2.58) and the post-chemotherapy setting (Model 2, OR 3.83, 95%CI 1.76-8.36). Other statistically

significant variables found in the chemotherapy-naïve setting included later years of initiation (OR_{2015} 1.57, 95% 1.06-2.33; OR_{2016} 6.89, 95% 4.81-9.87), age ≥75 (OR 1.38, 95%CI 1.01-1.88), rural residence (OR 1.54; 95%CI 1.13-2.07), prior use of bone-targeted therapy (OR 1.49; 95%CI 1.08-2.03), and ≥ 1 pre-existing one cardiovascular condition (OR 1.54; 95%CI 1.06, 2.25). In the post-chemotherapy model, later year of initiation was a statistically significant variable (OR_{2016} 2.25, 95%CI 1.13-4.47).

Sensitivity Analyses

Given that the initial prescribing specialty concorded with the alternative definition of prescribing specialty (specialty prescribing the majority of the NHA for a given patient) in 94% of patients, analyses repeated with that definition gave quasi-identical results (results not shown). Similarly, the proportion of patients who had their NHA prescribed by radiation oncologists was minimal (2.8%). The repeated analyses with the combined urology/radiation oncology grouping were essentially the same as the original grouping (results not shown).

Discussion

This descriptive study examined the prescribing trends of NHAs in the early years of approval in the province of Quebec in Canada. Over time, there was an increasing proportion of patients who initiated NHAs without prior chemotherapy treatment, of NHA prescribing by urologists, and of ENZ users.

To the best of our knowledge, this is the first report on the utilization patterns of NHAs in mCRPC in Canada. A previous study examining the adoption of ABI and ENZ in the United States corroborates some of our findings. [15] They noted that ENZ had become the most prescribed NHA by 2016, which is similar to our results of ENZ accounting for slightly over 50% of NHA initiators in the latter half of 2016. A Swedish study also noted that more patients were prescribed with ENZ over ABI in 2015-2016. [16]

From one perspective, these results may seem counterintuitive if one expects that ABI should have maintained some dominance as a preferred choice over ENZ given it was approved first. In that line of thought, the two year gap between the introduction of these two agents in the province should have led to some familiarity and physician preference for ABI. Our results suggest this was not the case. To our knowledge, clinical guidelines do not favor either ABI or ENZ in mCRPC. [17-19] Most guidelines recommend that the specific choice of NHA should come down to comorbidities and patient and physician preference as these two drugs, although relatively tolerable, possess different adverse event profiles. The overall rapid adoption of ENZ may also be related to some constraints with ABI: the necessary concomitant use of prednisone, the need for monthly monitoring of blood pressure, potassium and liver function. [13] These constraints could make ENZ a more preferable choice with physicians and patients alike. On a related note, in regression modeling, we identified rural region of residence as a predictor for ENZ over ABI prescription (albeit only for chemotherapy-naïve patients). One possible explanation could be that patients living further away from cancer treatment centers or clinics may prefer the treatment that does not require as much of a stringent monitoring.

Our findings support the notion that urologists are increasingly prescribing NHAs. This was also reflected in previous research, where they specifically noted that the number of moderate-to-high volume ABI-prescribing urologists tripled from 2013-2016 while the corresponding trend in moderate-to-high volume ABI-prescribing non-urologists was a only 30% relative increase. [15] An even more dramatic 3000% growth in moderate-to-high volume ENZ-prescribing urologists was observed during that period. In another study using American data, they found that while the majority of NHA prescriptions originate from medical oncologists, the proportion of prescriptions by urologists has doubled for ABI and tripled for ENZ. [20]

Beyond the increase in urologist prescribing, the aforementioned figures from these two previous studies also suggest a preference for ENZ among urologists. [15,20] This is further confirmed by another study demonstrating that ENZ is more likely prescribed by urologists compared to medical oncologists, which is also consistent with our results. [21] As mentioned earlier, there are several constraints that come with ABI prescribing, and they may present a stronger disincentive to urologists relative to medical oncologists. Compared to a typical medical oncology practice, a typical urology practice may not be as suited to manage frequent monitoring of blood pressure, potassium, liver function as well as potential issues with prednisone treatment.

We found that the proportion of NHA initiators who were not previously treated with chemotherapy increased rapidly. In ABI users, this change happened even before its approval for use in chemotherapy-naïve patients occurred in 2014; in fact, the majority of ABI users were chemotherapy-naïve patients by 2013. For ENZ, the majority of users were chemotherapy-naïve

patients from the onset of approval. These findings suggest that overall more mCRPC patients are receiving life-prolonging treatment. Prior to the advent of NHAs, docetaxel chemotherapy was the only recourse but its uptake was always limited due to the high proportion of mCRPC patients being either too frail for treatment or due to patient preference. [22,23] As the baseline characteristics of our chemotherapy-naïve group show, they are on average nearly 5 years older than the post-chemotherapy patients when initiating an NHA.

Taken altogether, our findings advance the notion that care pathways for mCRPC may have changed with the introduction of NHAs as urologists are increasingly prescribing these life-prolonging treatments. Traditionally, urologists would refer patients with mCRPC to medical oncologists for chemotherapy administration. With the NHAs, urologists have the possibility to be more involved in the management of advanced PCa patients and for longer. This effect may become even sharper with the expanding disease settings where NHAs have shown benefits (metastatic castration-sensitive PCa [mCSPC], non-metastatic CRPC [nmCRPC]) and the approval of more NHAs (apalutamide and darolutamide). This has the potential beneficial implication of better continuity of care for patients as urologists typically have already followed a PCa patient for many years until the point of mCRPC.

Limitations

As these findings only represent the early approval period of NHAs, further follow-up is required to confirm if these patterns persist over time. This limitation is particularly notable for ENZ, as we only captured its initial two years of approval in the provincial drug plan. Furthermore, given

the time frame of this dataset, we could not study the utilization of these NHAs in earlier disease settings (mCSPC, nmCRPC) nor the additional impact of newer NHAs.

While the use of administrative healthcare data allows for a representative portrait of the use of these treatments in clinical practice, several limitations exist with these data. Several clinical- and disease-related variables of interest are not captured in these databases, such as cancer staging, Gleason grading, prostate-specific antigen serum level, metastatic burden, functional status, presence of symptoms, among others. However, we did use proxy variables (symptomatic indicator, use of bone-targeted therapy, time from PCa diagnosis to index date, etc.) to partially remediate this issue in an attempt have some reflection of cancer severity and symptomatic status.

A limitation concerns the identification of chemotherapy regimens. Through physician claims data, we can identify the procedure act of intravenous chemotherapy administration, however the actual chemotherapy regimen used is not available in our datasets. Consequently, we could not identify with certainty if the chemotherapy regimen was docetaxel. However, given the study period, docetaxel was the only chemotherapy with survival benefits in PCa as cabazitaxel was not yet approved in the provincial drug insurance plan. Furthermore, we only considered chemotherapy cycles that were started during the period from ADT initiation to NHA initiation.

Conclusion

The introduction of NHAs in mCRPC represented a critical landmark for patients as they were the first oral drugs offering survival benefit in this disease setting. Although ABI was introduced

earlier than ENZ, the uptake of ENZ was relatively rapid and by the end of the study period, both NHAs were equally used. Along with this rapid adoption of ENZ, the proportion of NHAs prescribed by urologists increased over the years. Over time, the majority of patients who initiated NHAs were chemotherapy-naïve. Finally, our findings also suggest that disease management for advanced PCa may have changed as urologists seem to maintain a more prominent role even in mCRPC. Further research examining how exactly the introduction of NHAs has impacted disease management and referral patterns in advanced PCa may be of interest to clinicians and policy-makers.

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Declaration of Interests

Aprikian A has received honoraria from Abbvie, Astellas Pharma, Bayer, Janssen, Sanofi and TerSera (all unrelated to the study). All other authors have no conflicts of interest to declare.

Author Contributions

J.H. contributed to conceptualization, methodology, software, data analysis and interpretation, manuscript writing and review. A.A. contributed to conceptualization, manuscript review. R.S. contributed to conceptualization, manuscript review. A.D. contributed to conceptualization, methodology, data acquisition, data interpretation, manuscript review, supervision.

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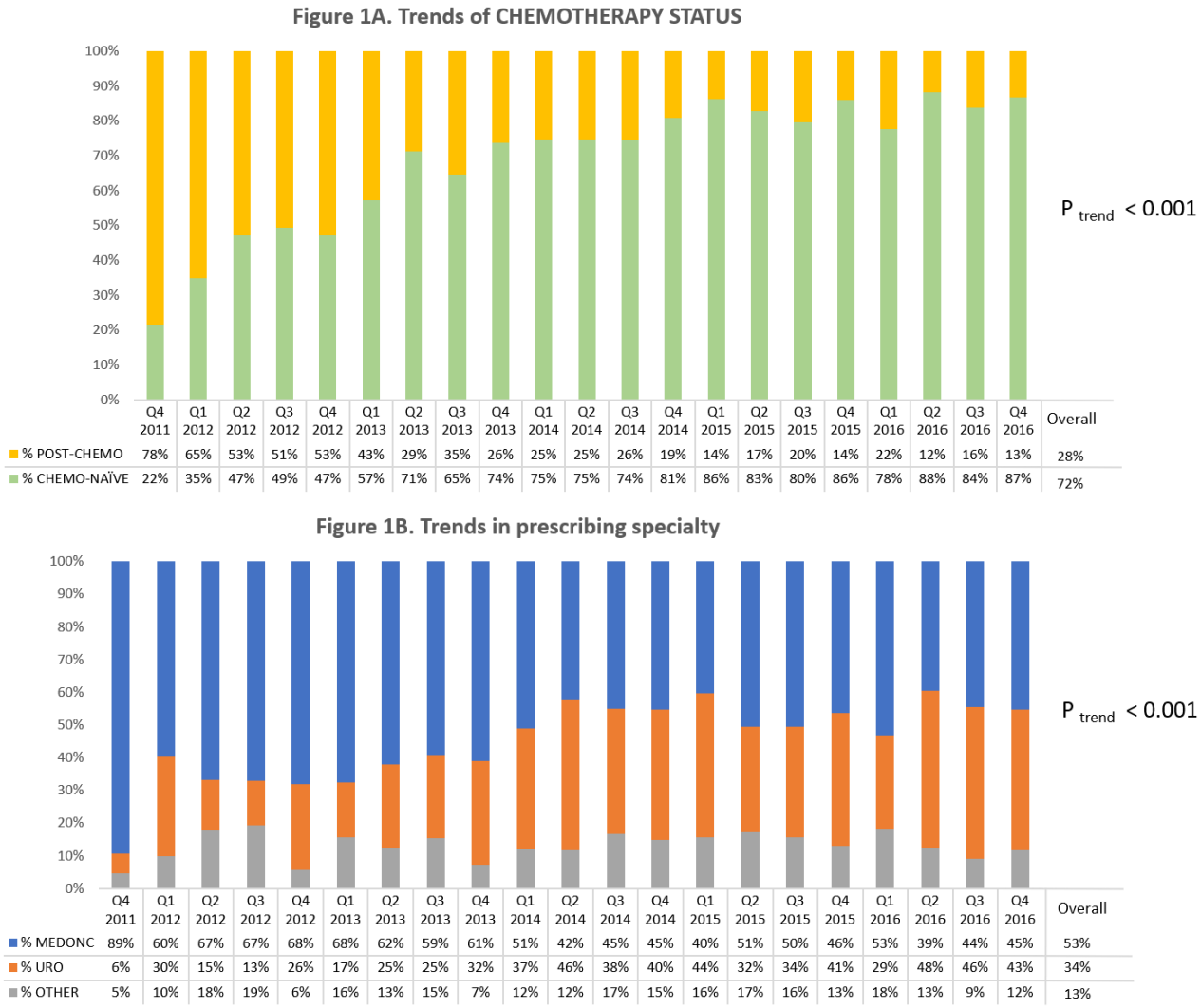
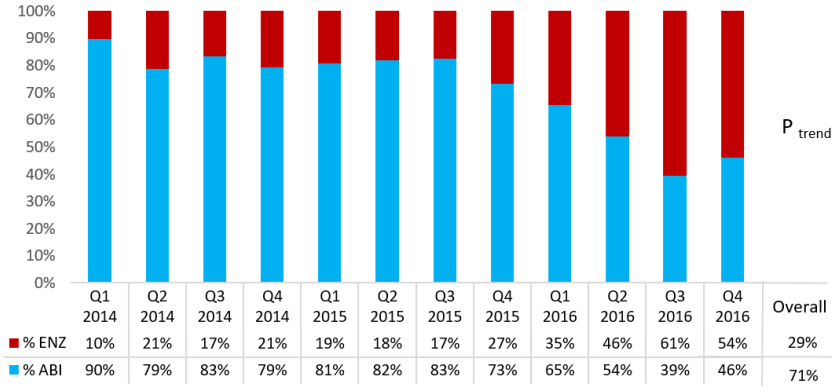
Figure 1. Overall temporal trends in initiation of novel hormonal agents from 2011-2016



Overall temporal trends in initiation of novel hormonal agents from 2011-2016. **(1A)** Stratified by chemotherapy status. **(1B)** Stratified by prescribing specialty.

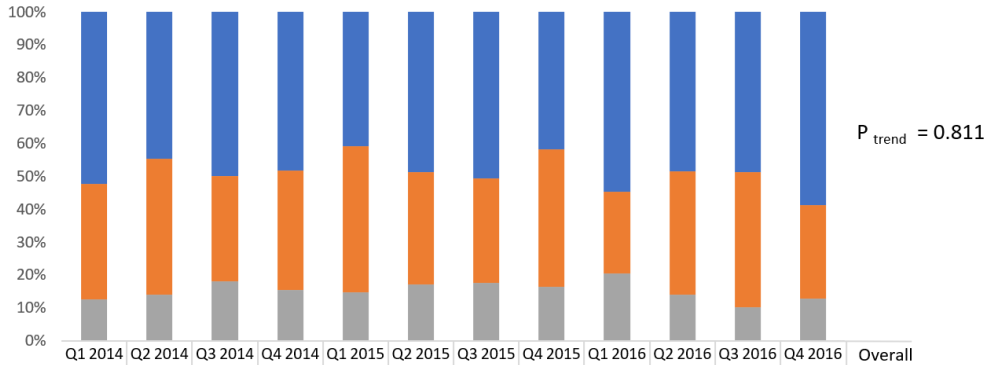
FIGURE 2. Temporal trends of novel hormonal agent (NHA) initiators in ENZ-era

Figure 2A. Trend of NHA Type in ENZ-era



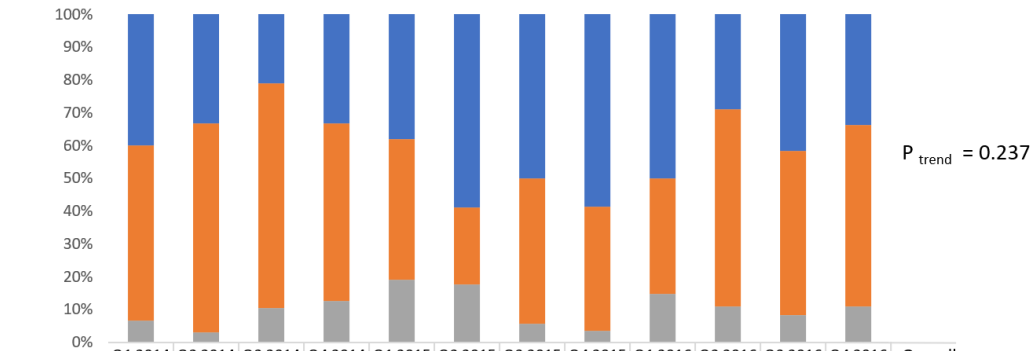
	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Overall
% ENZ	10%	21%	17%	21%	19%	18%	17%	27%	35%	46%	61%	54%	29%
% ABI	90%	79%	83%	79%	81%	82%	83%	73%	65%	54%	39%	46%	71%

FIGURE 2B. Trends of prescribing specialty in ABI users in ENZ-era



	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Overall
% MEDONC	52%	45%	50%	48%	41%	49%	51%	42%	55%	48%	49%	59%	49%
% URO	35%	41%	32%	36%	44%	34%	32%	42%	25%	38%	41%	29%	36%
% OTHER	13%	14%	18%	15%	15%	17%	18%	16%	20%	14%	10%	13%	15%

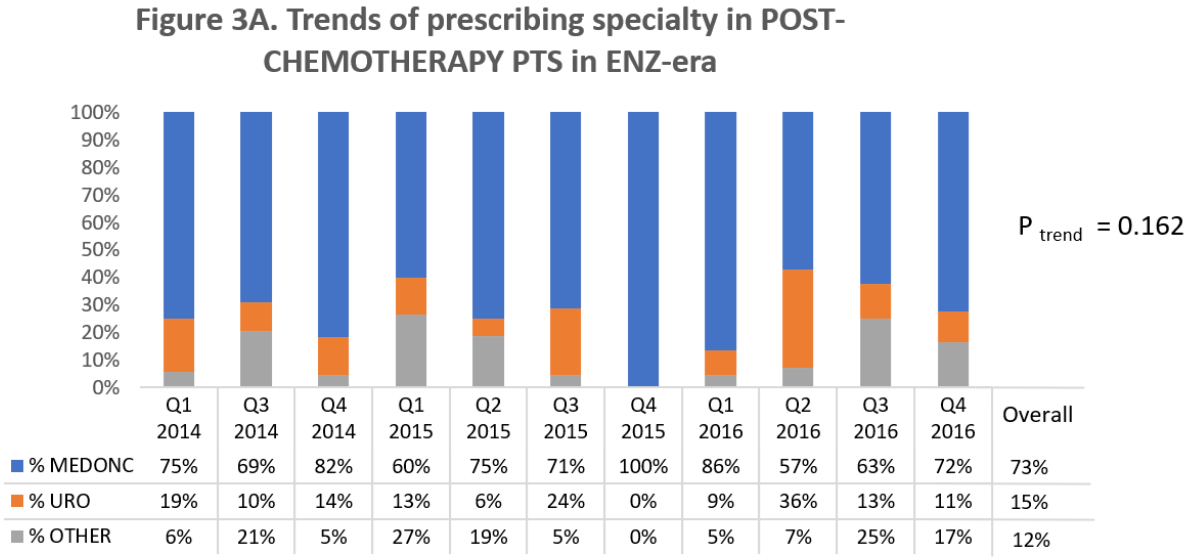
Figure 2C. Trends of prescribing specialty in ENZ users in ENZ-era



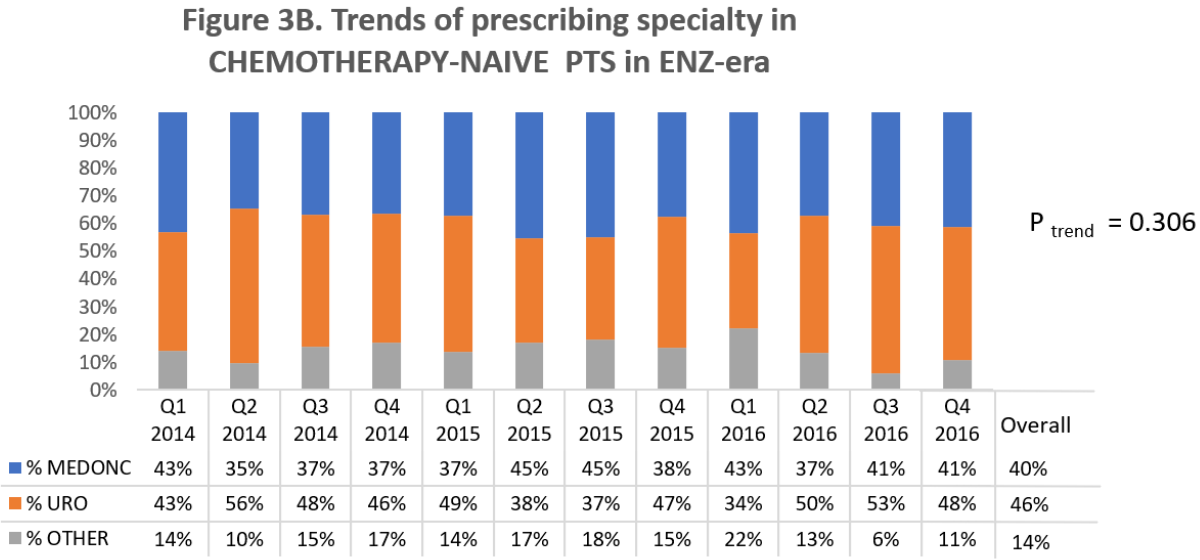
	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Overall
% MEDONC	40%	33%	21%	33%	38%	59%	50%	59%	50%	29%	42%	34%	39%
% URO	53%	64%	68%	54%	43%	24%	44%	38%	35%	60%	50%	55%	51%
% OTHER	7%	3%	11%	13%	19%	18%	6%	3%	15%	11%	8%	11%	10%

Temporal trends of novel hormonal agent (NHA) initiators in ENZ-era (2014-2016). (**2A**) Trends of NHA type. (**2B**) Trends of prescribing specialty in ABI users. (**2C**) Trends of prescribing specialty in ENZ users.

Figure 3. Trends of prescribing specialty of novel hormonal agent (NHA) initiators stratified by chemotherapy status in ENZ-era



	Q1 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Overall
% MEDONC	75%	69%	82%	60%	75%	71%	100%	86%	57%	63%	72%	73%
% URO	19%	10%	14%	13%	6%	24%	0%	9%	36%	13%	11%	15%
% OTHER	6%	21%	5%	27%	19%	5%	0%	5%	7%	25%	17%	12%



	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016	Overall
% MEDONC	43%	35%	37%	37%	37%	45%	45%	38%	43%	37%	41%	41%	40%
% URO	43%	56%	48%	46%	49%	38%	37%	47%	34%	50%	53%	48%	46%
% OTHER	14%	10%	15%	17%	14%	17%	18%	15%	22%	13%	6%	11%	14%

Figure 3. Trends of prescribing specialty of novel hormonal agent (NHA) initiators stratified by chemotherapy status in ENZ-era. (**3A**) Trends of prescribing specialty among post-chemotherapy patients. (**3B**) Trends of prescribing specialty among chemotherapy-naïve patients.

Table 1. Baseline characteristics

	Chemotherapy-naïve (n=1562)	Post-chemotherapy (n=621)
Characteristic		
Age, years; mean (SDev)	78 (8.1)	73 (8.0)
Rural	32.2	33.8
Time from PCa dx to index, years; mean (SDev)	8.1 (5.6)	7.2 (5.1)
Prior local PCa treatment	39.1	43.6
Symptomatic indicator	41.1	52.0
Bone-targeted therapy	34.2	71.0
Charlson index ≥4	6.7	5.6
Hypertension	70.5	67.2
Dyslipidemia	57.2	53.1
Diabetes	22.8	20.6
Coronary artery disease	14.5	14.2
Myocardial infarction	3.1	2.6
Cerebrovascular disease	2.8	1.3
Heart failure	4.9	2.9
Arrhythmia	12.5	9.0
Peripheral artery disease	5.1	4.8
Venous thromboembolism	2.9	4.4
≥ 1 cardiovascular condition	28.1	25.8

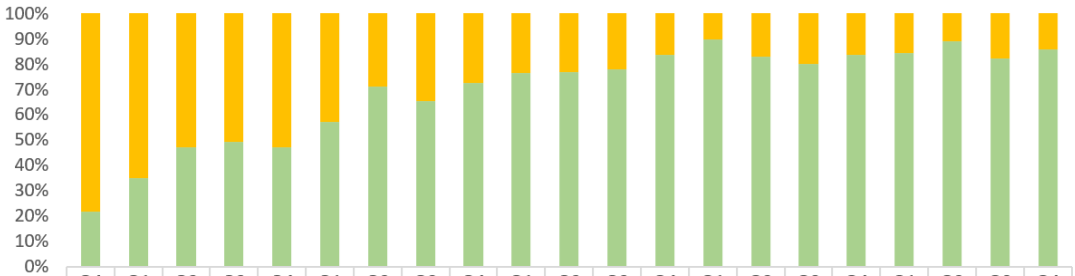
Renal disease	9.9	7.7
Liver disease	1.7	0.7
Nbr SPC visits; mean (SDev)	13.8 (11.6)	22.0 (11.0)
Hospital admission (≥1)	41.8	45.7
Nbr drug classes; mean (SDev)	12.8 (5.2)	14.5 (5.2)
Novel hormonal agent		
ABI	78.8	87.3
ENZ	22.2	12.7
Prescribing specialty		
Medical oncologist	44.5	74.4
Urologist	41.6	14.7
Other	14.0	11.0

All numbers represent percentages unless otherwise noted.

Abbreviations: ASMD = absolute standardized mean difference; Nbr = number; PCa = prostate cancer; SDev = standard deviation; SPC = specialist physician.

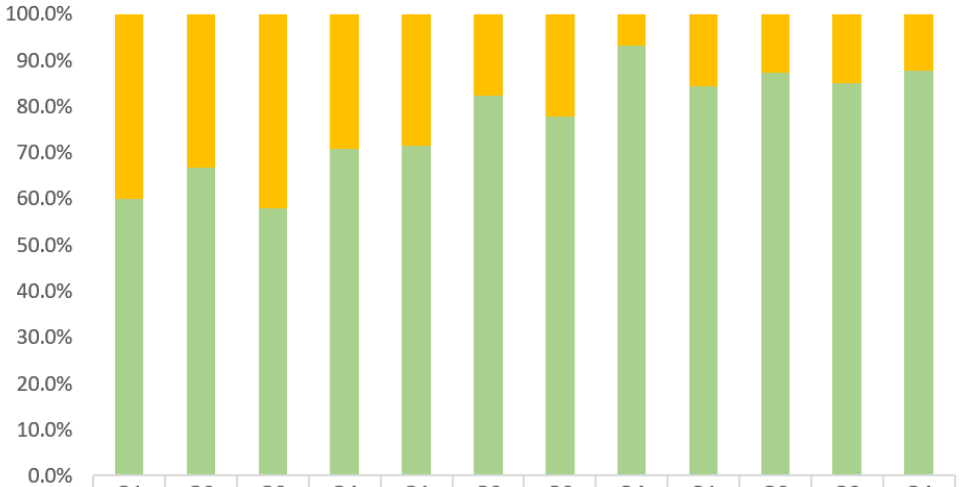
APPENDIX

Figure A1. Trend of CHEMOTHERAPY STATUS in ABI users



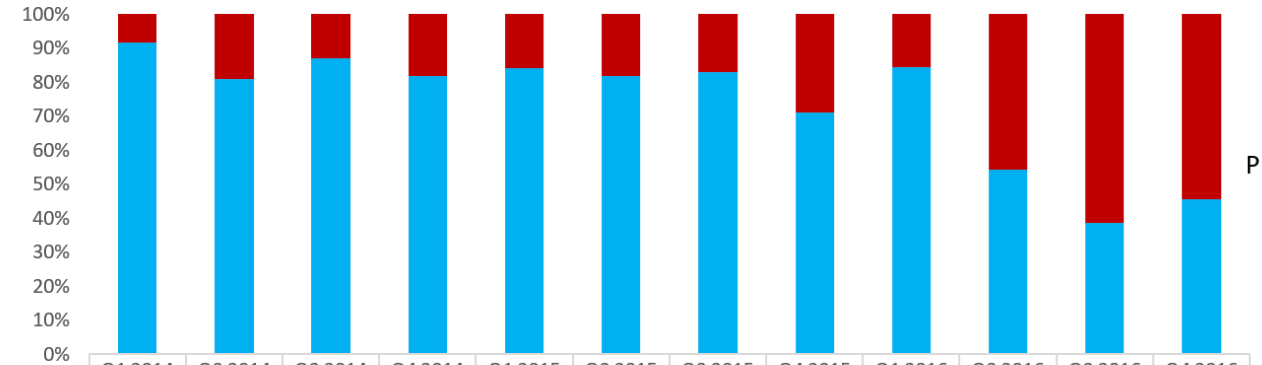
	Q4 2011	Q1 2012	Q2 2012	Q3 2012	Q4 2012	Q1 2013	Q2 2013	Q3 2013	Q4 2013	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016
% POST-CHEMO	78%	65%	53%	51%	53%	43%	29%	35%	28%	23%	23%	22%	16%	10%	17%	20%	16%	16%	11%	18%	14%
% NO-CHEMO	22%	35%	47%	49%	47%	57%	71%	65%	72%	77%	77%	78%	84%	90%	83%	80%	84%	84%	89%	82%	86%

Figure A2. Trend in CHEMOTHERAPY STATUS in ENZ users



	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016
% POST-CHEMO	40.0%	33.3%	42.1%	29.2%	28.6%	17.6%	22.2%	6.9%	15.6%	12.7%	15.0%	12.2%
% CHEMO-NAÏVE	60.0%	66.7%	57.9%	70.8%	71.4%	82.4%	77.8%	93.1%	84.4%	87.3%	85.0%	87.8%

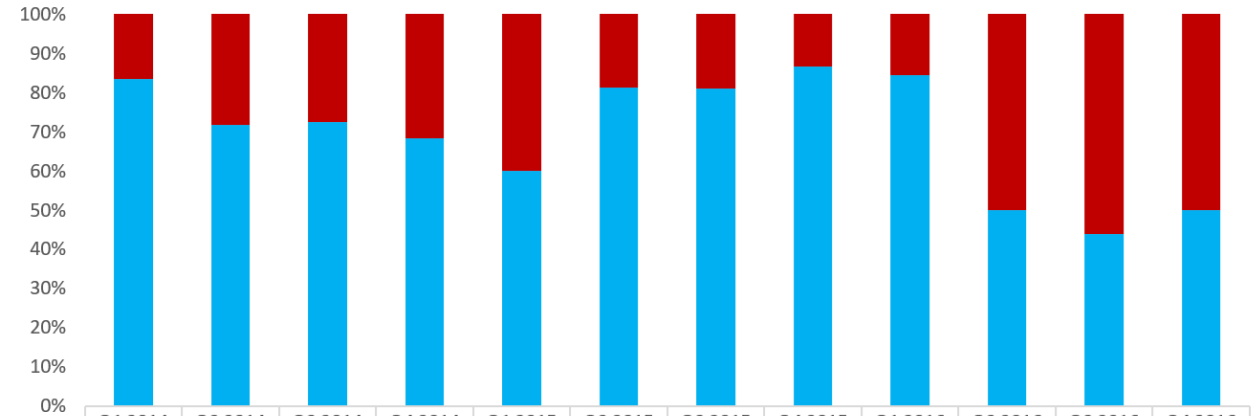
Figure A4. Trends of NHA use in CHEMOTHERAPY-NAIVE PTS in ENZ-era



	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016
% ENZ	8%	19%	13%	18%	16%	18%	17%	29%	16%	46%	61%	55%
% ABI	92%	81%	87%	82%	84%	82%	83%	71%	84%	54%	39%	45%

$P_{trend} < 0.001$

Figure A3. Trends of NHA type in POST-CHEMOTHERAPY PTS in ENZ-era



	Q1 2014	Q2 2014	Q3 2014	Q4 2014	Q1 2015	Q2 2015	Q3 2015	Q4 2015	Q1 2016	Q2 2016	Q3 2016	Q4 2016
% ENZ	17%	28%	28%	32%	40%	19%	19%	13%	16%	50%	56%	50%
% ABI	83%	72%	72%	68%	60%	81%	81%	87%	84%	50%	44%	50%

$P_{trend} = 0.011$

Table A1. Description of Novel Hormonal Agent Prescription Claims

	Year of NHA prescription claim					
	2011	2012	2013	2014	2015	2016
Nbr of NHA claims	133	1958	4172	6767	7796	8521
Nbr of ABI claims	133	1958	3985	5756	6339	6197
Nbr of ENZ claims	0	0	187	1011	1457	2324

Prescribed daily dose (PDD) represented by claim					
ABI			ENZ		
ABI PDD 1000mg	95.2%		ENZ PPD 160mg	94.9%	
ABI PDD 750mg	1.8%		ENZ PPD 120mg	1.8%	
ABI PPD 500mg	0.8%		ENZ PPD 80mg	1.6%	
ABI PPD other	2.1%		ENZ PPD other	1.7%	

Chapter 4: Comparative cardiovascular safety of novel hormonal agents in metastatic castration-resistant prostate cancer using real-world data

Preface: The objective was to assess the comparative cardiovascular safety of abiraterone and enzalutamide in patients with mCRPC in the real-world. Our findings suggest that abiraterone users may be at greater risk of cardiovascular-related hospitalization compared to enzalutamide users, in particular for heart failure. These results provide clinicians with additional insight on the cardiovascular risks of mCRPC patients treated with NHAs in the real-world and further large studies are required to corroborate these findings.

Status: Published

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Comparative cardiovascular safety of novel hormonal agents in metastatic castration-resistant prostate cancer using real-world data

Running title: Cardiovascular safety of abiraterone versus enzalutamide

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Abstract

Background: Novel hormonal agents (NHAs) such as abiraterone acetate (ABI) and enzalutamide (ENZ) are frequently used in metastatic castration-resistant prostate cancer (mCRPC). Despite their overall tolerable risk profile, certain signals of cardiovascular toxicity were reported for these agents in clinical trials but little is known about their incidence in clinical practice. The objective was to assess the comparative cardiovascular safety of ABI and ENZ in patients with mCRPC in the real-world.

Methods: A retrospective population-based cohort was extracted from Quebec public healthcare administrative databases. First-time NHA users between 2011 and 2016 were selected. The primary outcome of interest was cardiovascular-related hospitalization (composite outcome that included acute coronary syndrome, cerebrovascular stroke, heart failure, arrhythmia and others). Inverse probability of treatment weighting (IPTW) with the propensity score was used to adjust for measured baseline characteristics including pre-existing cardiovascular disease.

Results: The cohort comprises 2,183 patients, with 1,773 (81.2%) in the ABI group and 410 (18.8%) in the ENZ group. Crude incidence rates of cardiovascular-related hospitalization were of 9.8 events per 100 person-years (PYs) and of 7.1 events per 100 PYs for the ABI and ENZ groups, respectively. The ABI group was at greater risk of cardiovascular-related hospitalization compared to the ENZ group (IPTW-hazard ratio (HR) 1.82; 95% confidence interval (95%CI) 1.09-3.05). The risk of hospitalization for heart failure was greater in ABI (IPTW-HR 2.88; 95%CI 1.09-7.63).

Conclusions: Our findings suggest that ABI users may be at greater risk of cardiovascular-related hospitalization compared to ENZ users, in particular for heart failure. These results provide clinicians with additional insight on the cardiovascular risks of mCRPC patients treated with NHAs in the real-world and further large studies are required to corroborate these findings.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is the advanced form of prostate cancer where disease progresses in spite of androgen suppression induced by medical or surgical castration. Despite remaining an incurable disease, a number of treatments with demonstrated survival benefits in mCRPC have been approved in the past decade. [1] Two of the most important additions have been the novel hormonal agents (NHA) which include abiraterone acetate (ABI) and enzalutamide (ENZ), both of which were rapidly adopted in this disease setting. [2] While both act on the androgen receptor axis, they each have a distinct mechanism of action. Abiraterone acetate acts by blocking androgen synthesis by inhibition of the cytochrome CYP17. [3] Enzalutamide is a competitive inhibitor of the androgen receptor. [4]

In their respective pivot clinical trials leading to their regulatory approval in mCRPC, ABI and ENZ demonstrated similar survival benefits relative to their placebo control arms. [5-8] While the two have an overall favorable toxicity profile, the adverse effects associated with each is different owing to their specific mechanism of action. [1] Fluid retention and hypokalemia are frequently reported in ABI treatment, whereas central nervous system (CNS) disorders, hot flashes and high-grade fatigue were particularities for ENZ treatment. On the cardiovascular aspect, there has been some concern with both agents. As reflected in the United States Federal Drug Administration (FDA) prescription labelling of ABI, patients with existing cardiovascular disease should be monitored more closely due to potential mineralocorticoid excess despite prednisone co-administration meant to mitigate such effects. [9] Similarly for ENZ, its label warns of the increased risk of ischemic heart disease and calls for the optimization of management of cardiovascular risk factors. [10] In a meta-analysis of seven randomized controlled trials (RCTs), ABI

and ENZ were both associated with increased risk of cardiovascular toxicity relative to their control arms. [11] In particular, the risks of hypertension and cardiac toxicity were increased for ABI, while ENZ treatment increased the risk of hypertension.

Another area of incertitude regarding the cardiotoxicity of NHAs comes from their use in real-world patients given that the randomized studies involving ABI and ENZ in the mCRPC setting specifically excluded patients with clinically significant cardiovascular disease or uncontrolled hypertension. [5-8] The exclusion of such patients limits the generalizability of the safety findings from the RCTs. Consequently, there remains a knowledge gap concerning the cardiovascular safety of ABI and ENZ in patients treated in routine clinical practice who can present with significant comorbidities. The objective of this study was to compare the risk of cardiovascular-related hospitalization in patients with mCRPC treated with ABI and ENZ in a real-world setting.

Methods

Data Source

As with other Canadian provinces, provincial public healthcare insurance coverage is provided to all its residents for physician visits and medical procedures. This study draws data from public healthcare administrative databases from the province of Quebec, which are administered by the Régie de l'assurance maladie du Québec (RAMQ). The RAMQ provides universal healthcare coverage to residents of the province of Quebec in Canada through the Quebec Health Insurance Plan. This plan covers all physician visits and procedures, and outpatient and inpatient care for all Quebec residents. The prescription drug insurance plan of the RAMQ (Public Prescription Drug

Insurance Plan) provides coverage for individuals aged 65 years and older, welfare recipients, and other residents who do not have access to a private drug insurance plan. The RAMQ databases contain data pertaining to patient basic demographic information, medical services derived from physician billing claims, and prescription drugs dispensed at community pharmacies. Data on hospital admissions was extracted from a complementary source, the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED ECHO) databases.

Study Cohort

This was designed as a retrospective observational study with a cohort of men who initiated an NHA in the period from January 2011 to December 2016. Patients with no prior history of androgen deprivation therapy (luteinizing hormone-releasing hormone agonist or antagonist drugs or orchiectomy) and who were registered to the public drug insurance plan for less than a year prior to NHA initiation were excluded. Additionally, patients were required to have a PCa diagnosis code or a PCa-related procedure code (radical prostatectomy, external radiotherapy, brachytherapy, or prostate needle biopsy) at any time prior to initiation. It should be noted that although both drugs have gained expanded approval to earlier disease states nowadays, both ABI and ENZ are considered "exception drugs" by the RAMQ that were only approved for mCRPC during the study period in the province of Quebec. This ensures that patients receiving NHAs in the study were for the treatment of mCRPC. Furthermore, the results of RCTs examining their efficacy in metastatic castration-sensitive prostate cancer (for ABI and ENZ) or nonmetastatic castration-resistant prostate cancer (for ENZ only) were not yet available with the exception of

the STRIVE trial which were published in 2016 and contained a subgroup of patients with nonmetastatic castration-resistant prostate cancer. [12-17]

Exposure Groups

The exposure group was assigned based on the first NHA prescription (ABI or ENZ) received and the index date corresponded to the date of the first prescription of the NHA. Study design is illustrated in eFigure 1. The primary analysis uses the as-treated approach, with patients being followed from the index date until the earliest of the following: 1) study outcome occurrence; 2) death; 3) end of the study period (December 31st, 2016); 4) loss of drug insurance coverage; or 5) 14 days (grace period) after the last drug-exposed day for those who discontinued treatment. For patients who discontinued treatment, the last drug-exposed day is defined as the last drug dispensing date plus days of supply of the drug plus the pharmacokinetic elimination period of the drug. A drug elimination period was included in our analyses given the longer mean terminal elimination half-life of ENZ (6 days) compared to ABI (12 hours). [9, 10] On average, it takes approximately four to five half-lives for a drug to be considered eliminated from the body. [18] Consequently, the drug elimination period was defined as the drug's half-life multiplied by five (ENZ: 30 days; ABI: 3 days).

Study Outcomes

The primary study outcome of interest was cardiovascular-related hospitalization which was defined as a composite of hospitalization admissions with a principal diagnosis for the following causes: acute coronary syndrome (myocardial infarction and unstable angina), cerebrovascular stroke, heart failure, arrhythmia, peripheral arterial disease, venous thromboembolism, and

other cardiac diseases. Each subcomponent of the primary outcome was also evaluated individually as secondary outcomes. Another secondary outcome examined was all-cause hospitalization.

Covariates

A broad range of covariates were selected a priori on the basis that they might be associated with the choice of NHA and be risk factors for the study outcomes. They included patient age, region of residence (metropolitan/rural), prior local prostate cancer treatment (radical prostatectomy, radiation therapy), prior chemotherapy treatment, time from ADT initiation to index date, prior cardiovascular risk factors and disease, Charlson comorbidity score. [19] Particular baseline cardiovascular risk factors and other diseases of interest were hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, arrhythmia, peripheral vascular disease, venous thromboembolism, other cardiac diseases, renal disease and liver disease. Baseline healthcare utilization indicators such as hospital admissions, number of physician visits and number of different drug classes prescribed in the year before the index date were also identified. All comorbidities (including prior cardiovascular risk factors and other diseases) were based on diagnostic codes and treatments identified from inpatient and outpatient claims in the 12-month period preceding the index date unless specified otherwise. Age, number of physician visits, and number of different drug classes were modelled as continuous variables using restricted cubic splines. [20]

Statistical Analysis

Descriptive statistics were presented as counts and percentages for categorical variables, and as means with standard deviation for continuous variables. Crude incidence rates (IR) were reported as number of events per 100 person-years (100PYs) with corresponding 95% confidence intervals (95%CI) based on the Poisson distribution.

Inverse probability of treatment weighting (IPTW) was applied to control for potential baseline confounding. [21] This approach applies weights to the subjects in the original study population and results in the creation of a "pseudo-population" in which treatment assignment is independent of the measured baseline confounders. First, propensity scores were obtained with a multivariable logistic regression model that estimated the predicted probability of initiating ENZ versus ABI given the baseline characteristics mentioned above for each patient. The inverse probability treatment weights were then derived from the propensity scores. To offset potential instability induced by large weights, stabilized weights were obtained by multiplying the inverse probability weights by the marginal probability of receiving the actual treatment received. [22] Balance of baseline characteristics across NHA groups was assessed with absolute standardized differences (ASD), with values greater than 10% being considered evidence of covariate imbalance. [23]

The inverse probability weights were then applied to Cox proportional hazards regression models to estimate cause-specific hazard ratios (HR) with 95%CI for the study outcomes in ENZ users versus ABI users. [24] Evaluation of the proportional hazards assumption was performed with Schoenfeld residuals. Weighted cumulative incidence functions of the study outcomes were also plotted and 12-month risks were extracted. [25] To account for the within-subject heterogeneity

induced by the weighted samples, variances of all weighted analyses were obtained with a robust sandwich-type variance estimator. [26] All analyses were two-sided with the statistical significance level set at $p < 0.05$, and were conducted with SAS software version 9.4 (SAS Institute, Cary, NC).

Subgroup Analyses

Three exploratory subgroup analyses were performed to observe if the effects on the primary outcome differed according to previous chemotherapy use (yes and no), patient age (≥75 years and <75 years), and baseline cardiovascular risk (none and ≥1 risk factor). For the purposes of these subgroup analyses, baseline cardiovascular risk included the presence of any the following in the year before the index date: cardiovascular disease, hypertension, diabetes mellitus, or dyslipidemia. Propensity score models and inverse probability treatment weights were re-estimated for each subgroup to ensure baseline balance between NHA groups for each patient subgroup.

Sensitivity Analyses

A series of sensitivity analyses were performed to assess the robustness of the results from the primary analysis. First, a shorter grace period of 7 days and a longer one of 30 days were explored. Also, the primary analysis was repeated using the subdistribution hazard model instead of the cause-specific hazard model to account for the competing risk of death. [27] Both approaches account for competing risks slightly differently. The cause-specific hazard model is usually more appropriate for research questions of etiological nature and the subdistribution hazard model is more suited for prognostic risk prediction purposes and to estimate incidences in the presence of competing risks. [28] Finally, given that ABI was the only NHA approved for over two years until

ENZ was approved in 2014, it is of interest to conduct a sensitivity analysis that will involve restricting the cohort to patients initiating an NHA in 2014 and beyond.

Results

The study cohort comprises 2,183 patients, of whom 1,773 (81.2%) were in the ABI group and 410 (18.8%) in the ENZ group. Baseline characteristics of the cohort are shown in Table 1. The mean age of patients in the ENZ group was slightly higher (ABI: 76, ENZ: 78). A higher proportion of the ABI group (30.6%) initiated treatment in the post-chemotherapy setting compared to the ENZ group (19.3%). There were more patients in the ENZ group with pre-existing arrythmia (ABI: 10.7%, ENZ: 15.1%), dyslipidemia (ABI: 55.2%, ENZ: 59.5%), heart failure (ABI: 3.9%, ENZ: 5.9%), diabetes (ABI: 21.5%, ENZ: 25.1%), and peripheral arterial disease (ABI:4.7%, ENZ: 6.1%). After IPTW, all baseline characteristics were well-balanced as the ASDs were less than 10% (highest value was 3.26% after weighing compared to 26.42% before weighting). Evaluation of baseline covariate balance with significance testing (p-values) instead of ASDs is shown in eTable 1.

Primary analysis

The crude IR of cardiovascular hospitalizations corresponded to 9.8/100PYs and 7.1/100PYs in the ABI and ENZ group, respectively (Table 2). In weighted analyses, there was a greater risk of cardiovascular-related hospitalization in ABI users compared with ENZ users (HR 1.82; 95%CI 1.09-3.05; p=0.022) (Table 2, Figure 1). For acute coronary syndrome, there was a non-significant HR of 1.76 (95%CI 0.65-4.80; p=0.265) for the ABI group relative to the ENZ group. For cerebrovascular stroke, there was a non-significant HR of 0.54 (95%CI 0.20-1.48; p=0.232) for the ABI group relative to the ENZ group. Regarding heart failure, the risk was nearly tripled in ABI

users compared to ENZ users (HR 2.88; 95%CI 1.09-7.63; p=0.034). With respect to arrhythmia-related hospitalization, the use of ABI was associated with an non-significant HR of 3.01 compared to the use of ENZ (95%CI 0.66-13.73; p=0.152). The occurrence of hospitalizations for peripheral arterial disease, venous thromboembolism and other cardiac diseases were rare in both groups. Patients treated with ABI had a 26% increase in risk of all-cause hospitalization compared to ENZ treated patients (HR 1.26; 95%CI 1.04-1.53; p=0.019). Table 2 further provides the absolute 12-month risks of experiencing the study outcomes provided from weighted analyses. Weighted cumulative incidence curves for the secondary outcomes are shown in eFigure 2.

Subgroup analyses

Figure 2A displays the subgroup analyses. In the pre-chemotherapy subgroup, the effect on cardiovascular-related hospitalization was very similar to the full primary analysis whereas it was slightly dampened in post-chemotherapy patients (HR 1.61; 95%CI 0.42-6.17; p=0.489). A similar pattern was observed when subgrouping by age ≥75 and <75, with a similar effect in the more elderly group (HR 1.92; 95%CI 1.06-3.46; p=0.031) and a minor dilution in the <75 group (HR 1.48; 9%CI 0.44-5.00; p=0.530). In patients with no cardiovascular risk factor at baseline, the HR was 0.89 with a wide 95%CI (0.25-2.55; p=0.697), but in patients with at least one cardiovascular risk factor, a greater risk than observed in the full primary analysis was obtained (HR 2.16; 95%CI 1.21-3.87; p=0.009).

Sensitivity Analyses

The analyses repeated with different grace windows provided similar estimates (Figure 2B). Nearly identical estimates were obtained when using the subdistribution hazard model (HR 1.79; 95%CI 1.06-3.08; p=0.029) instead of the cause-specific hazard model. When restricting the cohort to post-2014 initiators (n=1391), the results were slightly diluted (HR 1.69; 95%CI 0.96-2.89; p=0.067). Results for the secondary outcomes in the post-2014 initiators are shown in eFigure 3.

Discussion

In the current study, we observed a greater risk of cardiovascular-related hospitalization in ABI users compared to ENZ users, in particular for heart failure-related hospitalizations. Regarding the other subcomponents of the composite outcome, the risks were numerically higher, but statistically non-significant, in ABI users versus ENZ users with the exception of cerebrovascular stroke. In sensitivity analyses, the primary results remained fairly similar. Although the confidence interval for the effect in the primary outcome of post-2014 initiators crossed the null value, the effects in most secondary outcomes were stable as well, in particular for hospitalizations related to heart failure.

Our finding concerning greater risks of heart failure-related hospitalization in patients treated by ABI would be in line with its mechanism of action leading to mineralocorticoid excess as cautioned in its prescription label. [9] Mineralocorticoid excess has been shown to be associated with heart failure and arrhythmia. [29, 30] Although we found a large HR for arrhythmia-related hospitalization, the 95%CI is very wide and includes the null value, an imprecision likely brought upon by the low number of events. Conversely to the other subcomponents, our results suggest

that ENZ users may be at greater risk of cerebrovascular stroke compared to ABI users – although this was also not statistically significant. To our knowledge, safety data from the RCTs or observational studies have not mentioned any signal regarding cerebrovascular stroke in ENZ treatment. Having said that, ENZ is known for its capacity to cross the blood-brain barrier and has also been associated with a multitude of adverse events relating to the CNS such as seizures and reduced cognitive function, while ABI has not received such signals. [31] In one population-based study, ENZ users were found to have higher odds of experiencing a CNS event compared to ABI users, but cerebrovascular diseases were not part of the study outcomes evaluated. [32] Future research should consider investigating the different types of cardiovascular-related hospitalizations individually and ensuring a sufficient number of events to gain better precision on effect estimates.

Subgroup analyses were exploratory and given the small size of most subgroups, no hard conclusions concerning treatment heterogeneity can be made. However, the potential augmented risk of ABI relative to ENZ in patients with cardiovascular risk factors could have important ramifications in terms of treatment selection for that patient group and deserves further consideration in future studies.

The current literature is fairly thin on the topic of the risk of cardiovascular adverse effects in real-world patients receiving NHAs. A small number of single-centre studies have reported their experience with NHA users as it pertains to cardiovascular effects. [33-36] Some of these studies report no particular signals of concern, but are limited by a small sample size and a lack of comparison to ENZ. [33, 35, 36] However, one study did find that over a quarter of ABI users had

worsening cardiovascular issues and 8% had an emergency room visit or hospitalization due to treatment-related effects but also lacked an ENZ comparison group. [34]

We did find a larger cohort study examining a tangential issue to ours – the impact of pre-existing cardiovascular disease on short-term outcomes in real-world patients receiving ABI or ENZ. [37] Albeit they evaluated all-cause hospitalizations rather than only cardiovascular-related ones and they used a different analytic approach, our results echo similar trends found in their analyses. Of note, they observed that in chemotherapy-naïve patients with preexisting cardiovascular conditions, ABI was associated with higher hospitalization rates compared to ENZ.

Other studies examining the topic of cardiovascular adverse events of NHAs in the real-world using a different approach from ours were found. [38, 39] Bretagne et al. used disproportionality analyses in pharmacovigilance databases and found that ABI was associated with higher reporting of atrial fibrillation and heart failure compared to ENZ. [38] We found another study conducted also with disproportionality analyses in a pharmacovigilance database that found that ABI was associated with higher odds of being reported for myocardial infarction, arrhythmia, and heart failure but ENZ was not; although this study is currently only available as a conference abstract. [39]

Our results also agree with meta-analyses examining adverse effects reported in RCTs. [11, 40] Although we cannot directly compare our cardiovascular-related hospitalization rates to the safety data from the RCTs due to the lack of granularity available for public viewing, the closest corresponding metric available from the RCTs would be grade ≥3 cardiac adverse events. Patients treated with ABI were reported to be at higher risk of grade ≥3 cardiac events and hypertension

relative to placebo whereas ENZ was found to be associated only with higher risk of grade ≥3 hypertension. [11]

There are several limitations to the present study that should be noted. Given the observational nature of administrative claims data, residual confounding is possible. While we achieved well-balanced groups on measured baseline characteristics of interest with IPTW of the propensity score, we cannot discount the possibility of confounding by variables that are not captured by claims data. Regarding the analysis of the secondary outcomes (the individual subcomponents of the composite outcome of cardiovascular-related hospitalization), the study was likely underpowered to detect statistically significant differences between NHA groups given the low number of events in most individual subcomponents and this resulted in very wide confidence intervals for some effects. The number of patients receiving ENZ overall and the sample size in certain subgroup analyses were rather modest as well. Future studies investigating cardiotoxicity of NHAs should heed well to have larger samples and longer patient follow-up to obtain more precise estimates for the different types of cardiovascular hospitalizations and the differential effects among subgroups. Additionally, our study cohort exclusively evaluated real-world patients in the mCRPC setting, it is unknown if these findings directly translate to their use in earlier disease states such as the metastatic castration-naive state or the nonmetastatic castration-resistant state. Given the protracted treatment duration of NHAs in those disease states, risk of adverse effects is likely greater, although results from a meta-analysis suggests the contrary. This would be an important area of future investigation as the uptake of NHAs is increasing with time.

Conclusion

In summary, findings from this population-based cohort of patients with mCRPC suggest that the risk of cardiovascular-related hospitalization may be higher in ABI users than ENZ users, in particular for heart failure-related hospitalization. Other signals of interest that were uncovered, while not statistically significant, include an elevated hazard ratio for arrhythmia-related hospitalization in ABI users, and possibly a higher risk of cerebrovascular stroke in ENZ users. Future large population-based studies are needed to corroborate these findings. Although the number of approved therapeutic agents for advanced prostate cancer has increased, the number of randomized trials evaluating them in a head-to-head manner remains very limited. In this context, real-world evidence becomes increasingly important in providing information complementary to the RCTs to aid clinicians in making better-informed decisions when selecting a treatment for a particular patient, especially for relatively comparable treatments such as the NHAs.

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Conflict of interest statement

AA has received honoraria from Abbvie, Astellas Pharma, Bayer, Janssen, Sanofi and TerSera (all unrelated to the study).

MV has received honoraria from Astellas Pharma, Bayer, Bristol-Myers Squibb, Ipsen, Jansen, Johnson & Johnson, Pfizer and Sanofi (all unrelated to the study).

JH and AD have no conflicts of interest to declare.

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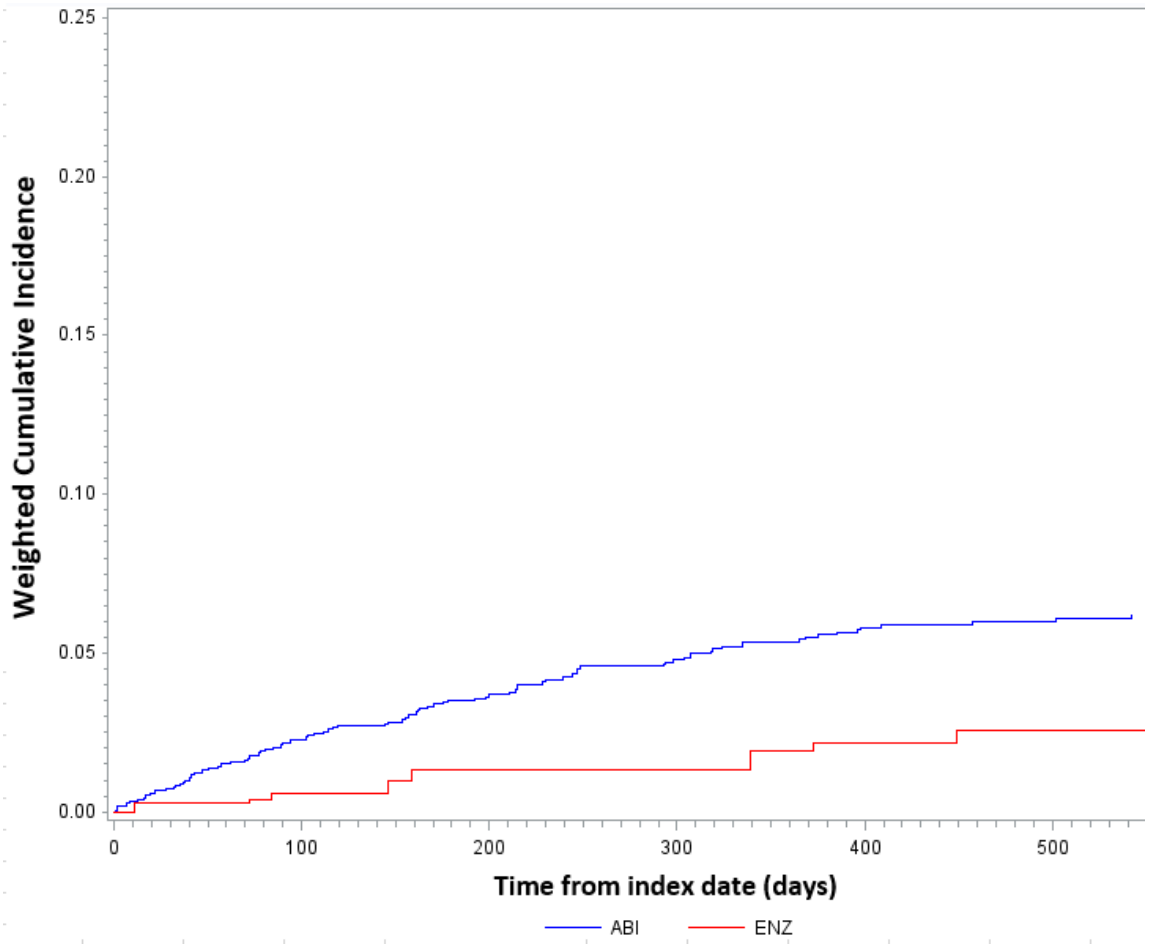


Figure 1. Inverse Probability of Treatment Weighted Cumulative Incidence Curves of Cardiovascular-Related Hospitalization by Novel Hormonal Agent

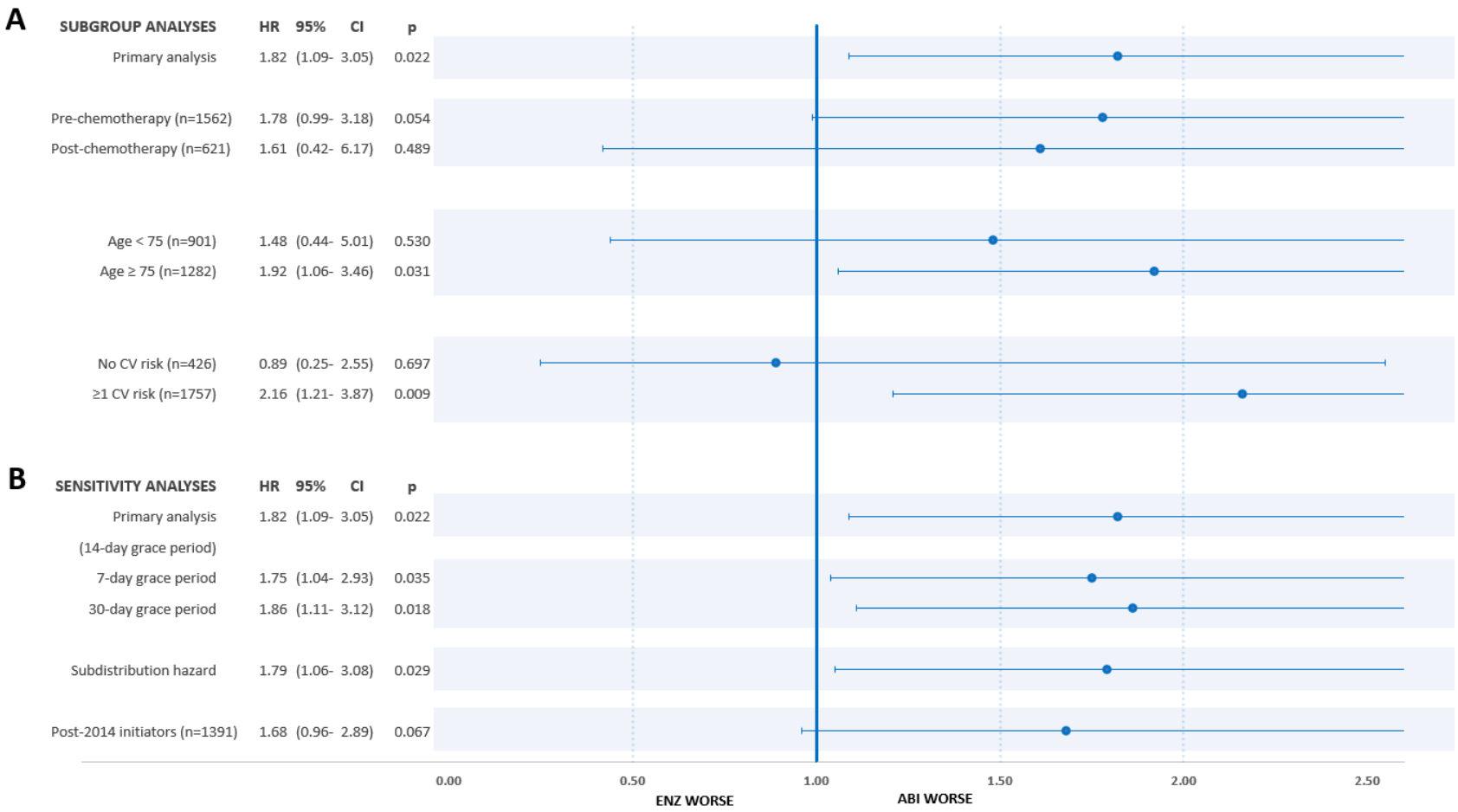


Figure 2. Subgroup analyses and sensitivity analyses for cardiovascular-related hospitalization. A) Subgroup analyses; B) Sensitivity analyses.

Abbreviations: ABI=abiraterone acetate; ENZ=enzalutamide; CV=cardiovascular; HR=hazard ratio; LCL=lower limit of 95% confidence interval; UCL=upper limit of 95% confidence interval.

Table 1. Cohort Baseline Characteristics

	Crude/Unweighted Study Population			IPT-weighted Study Population		
Characteristic	**ABI (n=1773)**	**ENZ (n=410)**	**ASD Before IPTW (%)**	**ABI (n=1772)**	**ENZ (n=412)**	**ASD After IPTW (%)**
Age, years; mean (sdev)	76 (8.3)	78 (8.2)	20.34	76 (8.3)	76 (8.3)	1.29
Rural	31.7	37.1	11.33	32.5	31.0	3.25
Prior local PCa treatment	41.3	36.3	10.16	40.3	40.5	1.41
Time on ADT, months; mean (sdev)	61.2 (51.3)	58.8 (51.7)	5.42	60.8 (51.1)	59.4 (54.6)	2.61
Symptomatic indicator	45.1	40.2	9.87	44.3	44.9	1.15
Post-chemotherapy	30.6	19.3	26.42	28.5	29.0	1.13
Bone-targeted therapy	46.1	38.3	15.93	44.7	44.8	0.36
Charlson index; mean (sdev)	0.92 (1.38)	0.95 (1.43)	1.04	0.93 (1.4)	0.94 (1.4)	0.62
Hypertension	69.4	70.2	1.90	69.6	69.8	0.59
Dyslipidemia	55.2	59.5	8.69	56.0	56.2	0.31
Diabetes	21.5	25.1	8.60	22.2	22.8	1.00
Myocardial infarction	2.9	3.3	2.21	3.0	2.7	1.85
Coronary artery disease	14.6	13.7	2.72	14.4	14.9	0.54
Cerebrovascular disease	2.3	2.7	2.37	2.4	2.6	0.92
Heart failure	3.9	5.9	8.83	4.3	4.1	0.82
Arrhythmia	10.7	15.1	13.35	11.5	12.3	2.01
Peripheral artery disease	4.7	6.1	6.01	5.0	4.5	2.17

Venous thromboembolism	3.4	2.9	2.61	3.3	2.8	2.97
Other cardiac diseases	4.5	5.1	3.12	4.6	4.6	0.05
Renal disease	8.8	11.5	8.84	9.3	8.7	1.43
Liver disease	1.6	0.5	10.81	1.4	1.2	2.08
Nbr ED visits; mean (sdev)	2.4 (3.1)	2.2 (3.1)	6.70	2.4 (3.1)	2.5 (3.2)	0.42
Nbr GP visits; mean (sdev)	3.9 (3.6)	3.9 (3.5)	2.27	3.9 (3.6)	3.9 (3.7)	0.52
Nbr SPC visits; mean (sdev)	16.5 (12.3)	14.4 (10.4)	20.71	16.2 (12.0)	16.7 (13.5)	0.93
Hospital admission (≥1)	43.1	42.2	1.81	42.8	42.2	1.22
Nbr drug classes; mean (sdev)	13.4 (5.2)	12.8 (5.5)	11.76	13.3 (5.2)	13.5 (5.3)	3.26

Note: Data are presented as percentages unless otherwise noted.

Abbreviations: ABI=abiraterone acetate; ENZ=enzalutamide; ASD=absolute standardized difference; IPT=inverse probability of treatment; IPTW=inverse probability of treatment weighting; sdev=standard deviation; PCa=prostate cancer; nbr=number; ED=emergency department; GP=general practitioner; SPC=specialist physician.

Table 2 Risk of Cardiovascular-related Hospitalization for Abiraterone Versus Enzalutamide Users

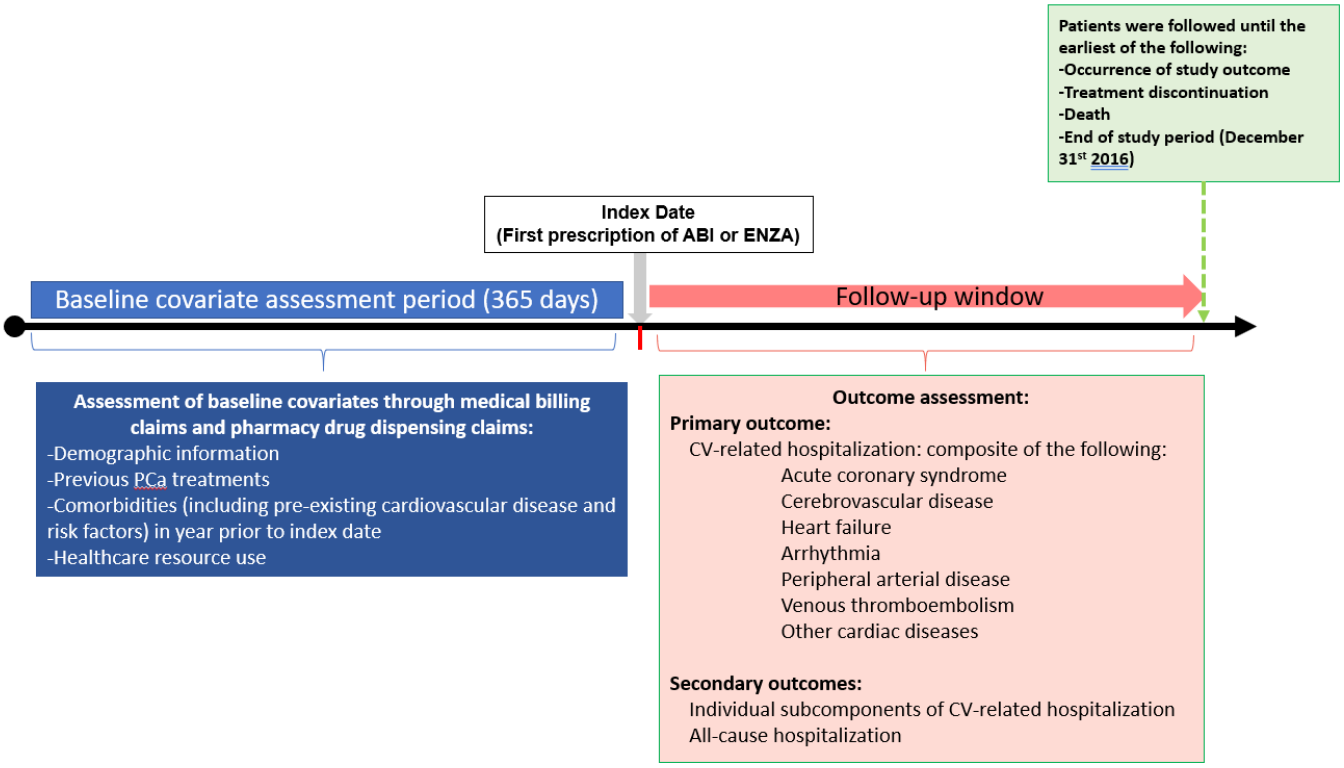
		Events	PYs	Crude incidence rate		Hazard ratio (IPTW)			12-month risk (IPTW)
				IR/100 PYs	95%CI	HR	95%CI	p	
CV-related hospitalization	ENZ	18	252.5	7.1	4.5-11.3		Ref		2.2%
(composite endpoint)	ABI	146	1480.6	9.8	8.4-11.6	1.82	1.09-3.05	0.022	5.4%
Acute Coronary Syndrome	ENZ	5	257.8	1.9	1.6-3.2		Ref		1.3%
	ABI	35	1531.9	2.2	0.8-4.7	1.76	0.65-4.80	0.265	1.6%
Cerebrovascular stroke	ENZ	6	256.4	2.3	1.0-5.2		Ref		1.5%
	ABI	18	1541.9	1.2	0.7-1.9	0.54	0.20-1.48	0.232	1.0%
Heart failure	ENZ	5	258.3	1.9	0.8-4.6		Ref		0.6%
	ABI	49	1530.8	3.2	2.4-4.2	2.88	1.09-7.63	0.034	2.3%
Arrhythmia	ENZ	2	258.1	0.7	0.2-3.1		Ref		0.6%
	ABI	25	1539.0	1.6	1.1-2.4	3.01	0.66-13.73	0.152	1.2%
Peripheral arterial disease	ENZ	0	259.7	0.0	0.0-0.0		Ref		0.0%
	ABI	7	1546.3	0.4	0.2-0.9	NA	NA	NA	0.2%
Venous thromboembolism	ENZ	2	259.5	0.7	0.2-3.1		Ref		0.6%
	ABI	17	1541.3	1.1	0.7-1.8	1.32	0.31-5.61	0.711	0.8%
Other cardiac diseases	ENZ	1	259.5	0.4	0.1-2.7		Ref		0.3%
	ABI	8	1548.2	0.5	0.3-1.0	1.37	0.18-11.20	0.742	0.4%
All-cause hospitalization	ENZ	138	201.9	68.3	57.8-80.7		Ref		40.8%

ABI	912	1137.3	80.2	75.2-85.6	1.26	1.04-1.53	0.019	47.1%

Abbreviations: ABI=abiraterone acetate; ENZ=enzalutamide; PYs=persons-years; 95%CI=95% confidence interval; IPTW=inverse probability of treatment weighted; ND=not available

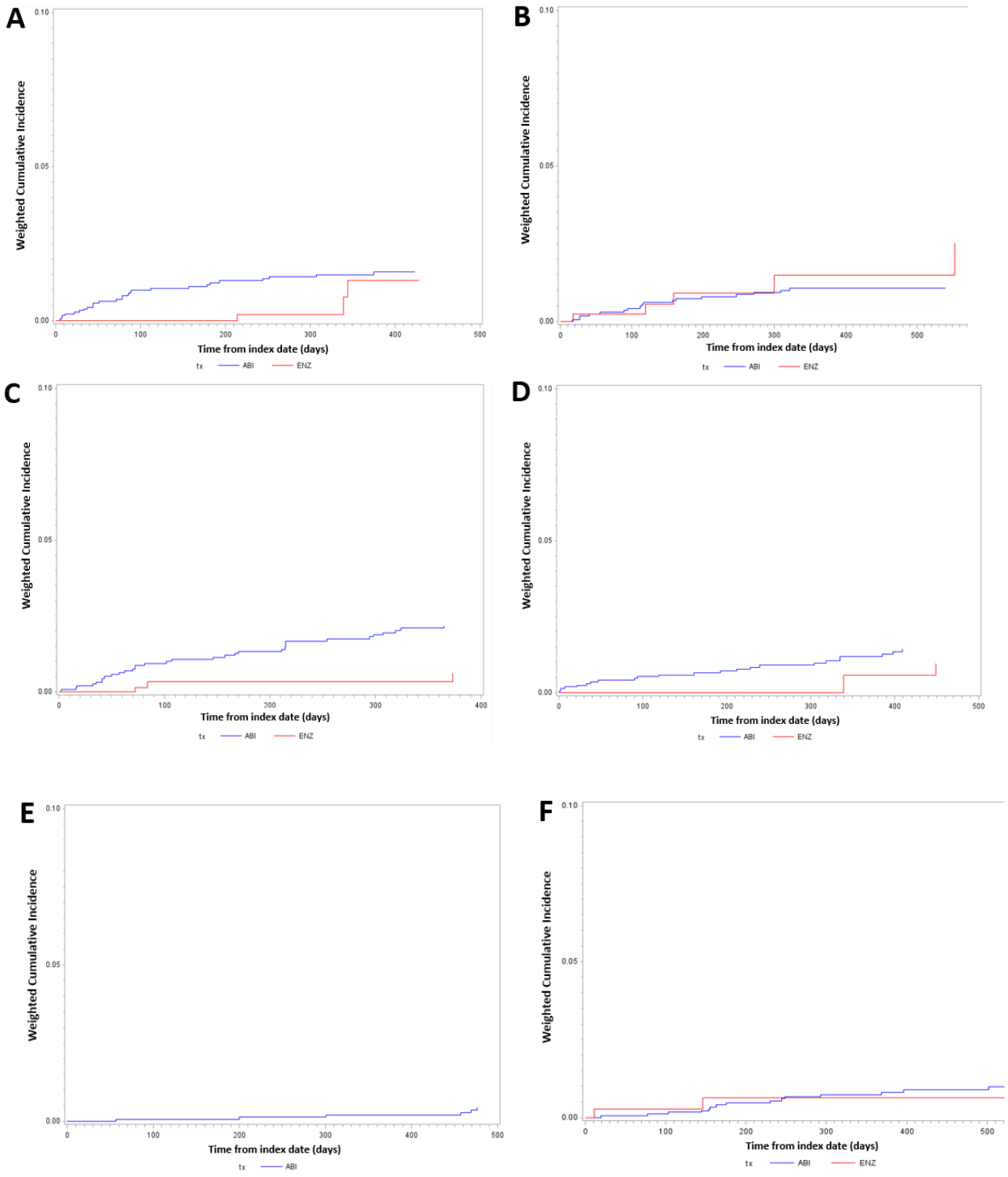
SUPPLEMENTAL CONTENT/APPENDIX

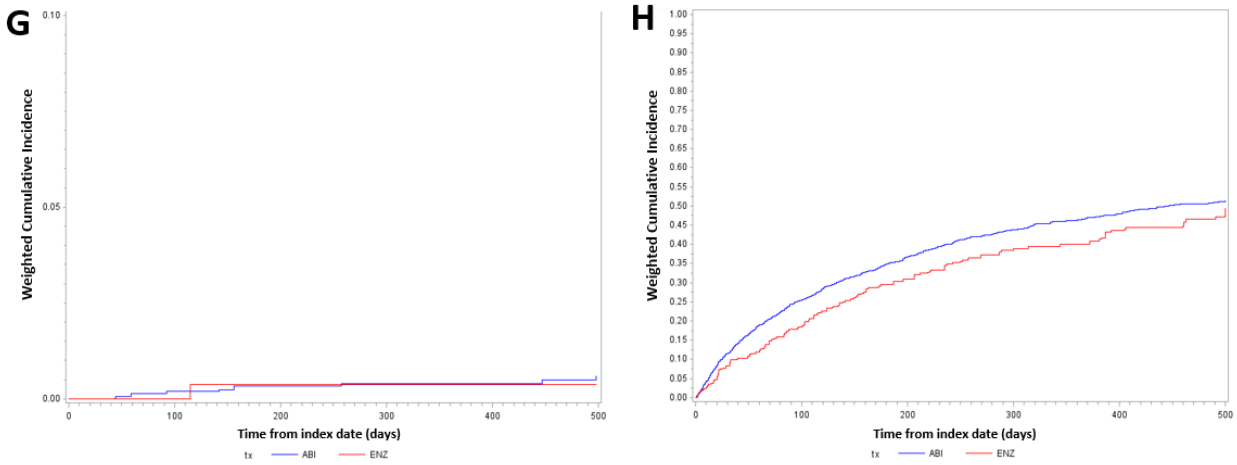
eFigure 1. Study Design



Abbreviations: ABI=abiraterone acetate; ENZ=enzalutamide; CV=cardiovascular.

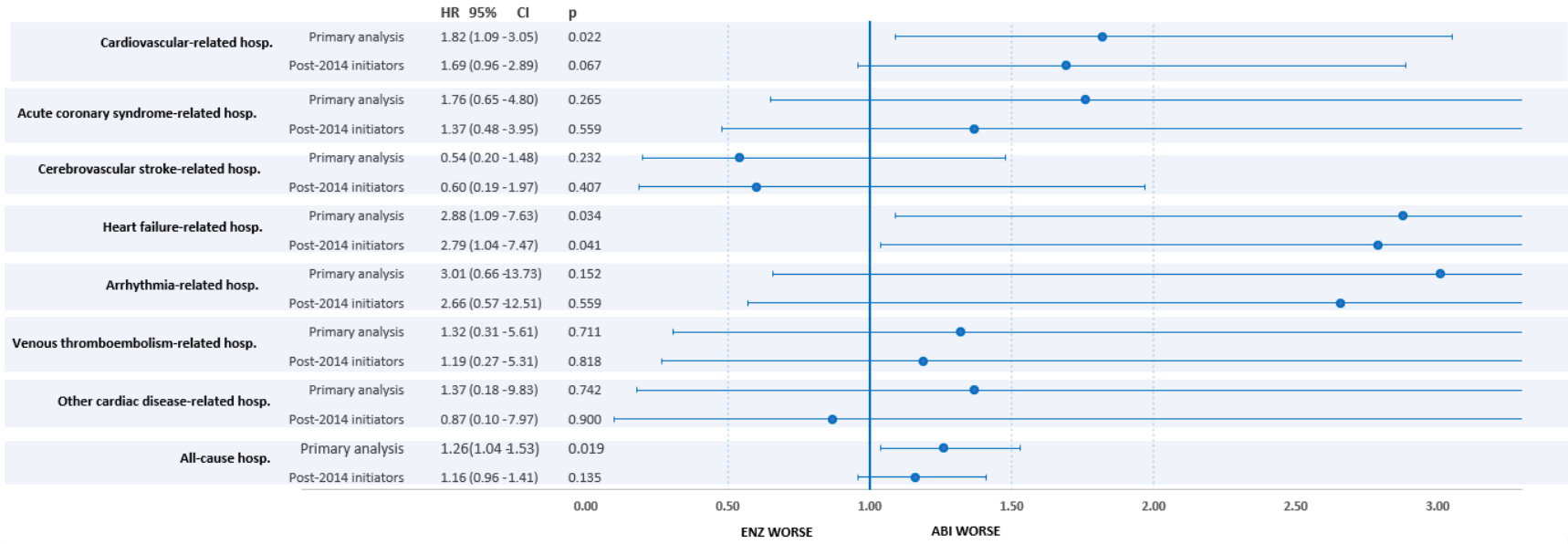
eFigure 2. Inverse Probability of Treatment Weighted Cumulative Incidence of Secondary Outcomes





eFigure 2. Weighted cumulative incidence curves for secondary outcomes stratified by novel hormonal agent**: A)** Hospitalization for acute coronary syndrome; **B)** Hospitalization for cerebrovascular stroke; **C)** Hospitalization for heart failure; **D)** Hospitalization for arrhythmia; **E)** Hospitalization for peripheral arterial disease; **F)** Hospitalization for venous thromboembolism; **G)** Hospitalization for other cardiac diseases; **H)** All-cause hospitalization.

eFigure 3. Sensitivity analysis: Primary and Secondary Outcomes in Post-2014 initiators (n=1391)



Note: No analyses done for peripheral arterial disease-related hospitalization (insufficient events).

Abbreviations: ABI=abiraterone acetate; ENZ=enzalutamide; hosp.=hospitalization; HR=hazard ratio; CI=confidence interval.

eTable 1. Cohort Baseline Characteristics (p-values instead of absolute standardized differences)

	Crude/Unweighted Study Population			IPT-weighted Study Population
Characteristic	**ABI (n=1773)**	**ENZ(n=410)**	**P-value**	**P-value**
Age, years; mean (sdev)	76 (8.3)	78 (8.2)	<0.001	0.807
Rural	31.7	37.1	0.037	0.754
Prior local PCa treatment	41.3	36.3	0.066	0.958
Time on ADT, months; mean (sdev)	61.2 (51.3)	58.8 (51.7)	0.393	0.855
Symptomatic indicator	45.1	40.2	0.073	0.814
Post-chemotherapy	30.6	19.3	<0.001	0.835
Bone-targeted therapy	46.1	38.3	0.004	0.994
Charlson index; mean (sdev)	0.92 (1.38)	0.95 (1.43)	0.847	0.892
Hypertension	69.4	70.2	0.730	0.923
Dyslipidemia	55.2	59.5	0.114	0.964
Diabetes	21.5	25.1	0.111	0.807
Myocardial infarction	2.9	3.3	0.764	0.740
Coronary artery disease	14.6	13.7	0.622	0.838
Cerebrovascular disease	2.3	2.7	0.656	0.811
Heart failure	3.9	5.9	0.086	0.844
Arrhythmia	10.7	15.1	0.012	0.732

Peripheral artery disease	4.7	6.1	0.255	0.791
Venous thromboembolism	3.4	2.9	0.640	0.689
Other cardiac diseases	4.5	5.1	0.561	0.959
Renal disease	8.8	11.5	0.094	0.788
Liver disease	1.6	0.5	0.087	0.763
Nbr ED visits; mean (sdev)	2.4 (3.1)	2.2 (3.1)	0.219	0.766
Nbr GP visits; mean (sdev)	3.9 (3.6)	3.9 (3.5)	0.688	0.921
Nbr SPC visits; mean (sdev)	16.5 (12.3)	14.4 (10.4)	<0.001	0.645
Hospital admission (≥1)	43.1	42.2	0.741	0.824
Nbr drug classes; mean (sdev)	13.4 (5.2)	12.8 (5.5)	0.025	0.682

Note: Data are presented as percentages unless otherwise noted.

Abbreviations: ABI=abiraterone acetate; ENZ=enzalutamide; ASD=absolute standardized difference; IPT=inverse probability of treatment; IPTW=inverse probability of treatment weighting; sdev=standard deviation; PCa=prostate cancer; nbr=number; ED=emergency department; GP=general practitioner; SPC=specialist physician.

Chapter 5: Association between prescribing specialty and treatment-related complications in patients using novel hormonal agents for metastatic castration-resistant prostate cancer: an observational study

Preface: The objective was to assess the association between the incidence of NHA-related complications and prescribing specialty in mCRPC patients treated with NHAs. We found no differences across prescribing specialties for overall NHA-related complications, all-cause mortality and all-cause hospitalization but subtype-specific associations were identified. Relative to the Medical Oncology group, the Urology group was associated with a higher risk of cardiovascular complications but a lower risk of infectious complications. These results highlight the complexity of the management of mCRPC with NHA treatment and further studies are required to corroborate these findings.

Status: submission upcoming

Association between prescribing specialty and treatment-related complications in patients using novel hormonal agents for metastatic castration-resistant prostate cancer: an observational study

Running title: Treatment complications in novel hormonal agent users by prescribing specialty

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Abstract

Background: Novel hormonal agents (NHAs) such as abiraterone acetate (ABI) and enzalutamide (ENZ) are frequently used in metastatic castration-resistant prostate cancer (mCRPC). While mCRPC treatment has been traditionally administered by medical oncologists, urologists have also adopted the use of NHAs. Complications from treatment with NHAs vary widely in scope, from cardiovascular to infectious. Data comparing the incidence of overall and subtypes of NHA-related complications by prescribing specialty is limited. The objective was to assess the association between the incidence of NHA-related complications and prescribing specialty in mCRPC patients treated with NHAs.

Methods: A retrospective population-based cohort was extracted from Quebec public healthcare administrative databases. First-time NHA users between 2011 and 2016 were selected and grouped by the prescribing specialty (medical oncology (MO) vs urology (URO) vs other (OTH)). Outcomes of interest were overall NHA-related complications and its subtypes: cardiovascular, metabolic, infectious and general/non-specific. Secondary outcomes included all-cause mortality and all-cause hospitalization. The overlap weighting (OLW) method was used to adjust for measured baseline characteristics.

Results: The cohort comprised 2,183 patients, with 1,157 (53.0%) in the MO group, 740 (33.9%) in the URO group, and 286 (13.1%) in the OTH group. Crude incidence rates of overall NHA-related complications were of 15.9 events/100 person-years (100PYs), 14.2 events/100PYs, 21.7 events/100PYs for the MO, URO and OTH groups, respectively. For overall NHA-related complications, the URO group (OLW-hazard ratio (HR): 0.97, 95%CI 0.72-1.31) and OTH group (OLW-HR 1.05, 95%CI 0.70-1.54) were not different compared to the MO group. While the URO

group was associated with a greater incidence of cardiovascular complications compared to the MO group (OLW-HR 1.85, 95%CI 1.04-3.28), it was also at lower risk of infectious complications (OLW-HR 0.66, 95%CI 0.43-0.98). Neither all-cause mortality (OLW-HR_{URO} 1.08, 95%CI 0.93-1.24; OLW-HR_{OTH} 1.12, 95%CI 0.94-1.33) nor all-cause hospitalization (OLW-HR_{URO} 1.11, 95%CI 0.90-1.34; OLW-HR_{OTH} 1.10, 95%CI 0.94-1.28) was associated with prescribing specialty.

Conclusions: We found no differences across prescribing specialties for overall NHA-related complications, all-cause mortality and all-cause hospitalization but subtype-specific associations were identified. Relative to the MO group, the URO group was associated with a higher risk of cardiovascular complications but a lower risk of infectious complications. These results highlight the complexity of the management of mCRPC with NHA treatment and further studies are required to corroborate these findings.

Introduction

Castration-resistant prostate cancer (CRPC) is broadly defined as the progression of prostate cancer despite castrate levels of testosterone. [1] The prognosis for men with metastatic CRPC (mCRPC) is particularly poor with an estimated median overall survival in the range of 18 to 40 months, depending on the timing of the onset of clinically detectable metastases and castration-resistance. [2-4] Although the treatment landscape for mCRPC has evolved dramatically in the past decade, options were limited in this setting for a very long time with only palliative treatments available until docetaxel chemotherapy was shown to have survival benefit in 2004. [5, 6] Further breakthroughs came in the early 2010s with cabazitaxel chemotherapy, sipuleucel-T, abiraterone acetate (ABI), enzalutamide (ENZ), and radium-223. [7] Even more recently, olaparib, rucaparib, and lutetium Lu-177 vipivotide tetraxetan have been FDA-approved for select patient groups. [8, 9]

Of all these innovative treatments, ABI and ENZ, which are broadly referred to as novel hormonal agents (NHAs), are the most widely used and were adopted quickly in clinical practice. [10] The NHAs act on the androgen receptor axis, but they each have a distinct mechanism of action which leads to a particular safety profile for each agent. [11] Abiraterone acetate acts by blocking androgen synthesis by inhibition of the cytochrome CYP17. [12] Enzalutamide is a competitive inhibitor of the androgen receptor. [13] Despite their tolerability relative to chemotherapy, both drugs are associated with a wide range of adverse events that can be complex to manage.

Cardiovascular complications have been noted for both ABI and ENZ, [14] albeit they are likely more important for ABI than for ENZ. [15, 16] Due to the inhibition of CYP17, treatment with ABI is associated with higher risk of hypokalemia and fluid retention, which potentially lead to more substantial cardiovascular issues such as arrhythmia and heart failure. [17] Indeed, safety findings

from the initial pivotal randomized clinical trials of ABI in mCRPC had already included signals concerning heart failure and arrhythmia. [14, 18] Consequently, prescription labelling for ABI mentions the necessary regular monitoring of blood pressure, serum potassium, and symptoms of fluid retention. [18] For ENZ, the initial pivotal trials in the mCRPC setting did not identify any cardiovascular signal, however, ischemic heart disease was identified as a potential risk in later randomized trials in the metastatic hormone-sensitive setting. [19, 20]

In terms of metabolic complications, ABI has several issues that demand attention. Hepatotoxicity was identified in the randomized trials as a signal of concern as there was an increased frequency of grade 3-4 elevated liver enzymes in the ABI arms. [21] Adrenal insufficiency is also another signal of interest given its mechanism of action on CYP17, albeit it is rare. Careful monitoring of patients concurrently receiving diabetes treatment is warranted due to the potential drug-drug interactions between ABI and numerous oral antidiabetics. [22] Additionally, prednisone, which must be co-administrated with ABI, can increase the risk of hyperglycemia. [23]

Infectious complications, in particular upper respiratory tract infections and urinary tract infections, were more frequently reported for ABI compared to the placebo group in its randomized trials. Upper and lower respiratory tract infections were more prevalent for ENZ. Other general and non-specific complications noted for the NHAs include central nervous system (CNS) disorders, hot flashes and high-grade fatigue were particularities for ENZ treatment.

Over any other physician specialty, urologists are substantially involved in prostate cancer care throughout the entire course of disease. They account for the most of the care provided to patients with prostate cancer, especially for localized disease. [24] In contrast, medical oncologists

start to have a greater role as the disease becomes more advanced, when it requires systemic treatment and general symptom palliation. Consequently, in the past, many patients reaching mCRPC were referred to medical oncologists for administration of docetaxel chemotherapy or management of symptom palliation. However, with the introduction of oral drugs such as ABI and ENZ that can be prescribed by all specialties, urologists have rapidly adopted them in their clinical practice. [25-27]

Given all the various types of potential complications from treatment with the NHAs, prescribing clinicians must be proficient at recognizing and treating these toxicities that may be outside of their usual scope of practice. A recent study examined the outcomes of patients treated with NHAs by prescribing specialty and found that patients treated by urologists had lower risks of treatment-related toxicity, all-cause hospitalization, and all-cause mortality compared to patients treated by medical oncologists. [28] However, treatment-related toxicity was analyzed as a composite outcome that included all the various different subtypes of complications associated with NHA treatment. Given the wide range of potential complications from treatment with the NHAs, certain specialties may be better suited at managing particular aspects of NHA toxicity than others due to their training background, experience, and clinical workflow. As such, analysis of the subtypes of NHA-related complications may provide further insight into the management of patients treated with NHAs. The aim of this study was to evaluate the association between prescribing specialty and the incidence of overall NHA-related complications, as well as the different subtypes of NHA-related complications, in mCRPC patients treated with NHAs.

Methods

Data Source

This study was conducted with data from the public healthcare administrative databases in the province of Quebec, which are administered by the Régie de l'assurance maladie du Québec (RAMQ). In Canada, public healthcare insurance coverage is provided to all its residents and is administrated at the provincial level. The RAMQ provides universal healthcare coverage to residents in the province of Quebec through the Quebec Health Insurance Plan. This plan covers all physician visits and procedures, and outpatient and inpatient care for all Quebec residents. The prescription drug insurance plan of the RAMQ (Public Prescription Drug Insurance Plan) provides coverage for individuals aged 65 years and older, welfare recipients, and other residents who do not have access to a private drug insurance plan. The RAMQ databases contain data pertaining to patient basic demographic information, medical services derived from physician billing claims, and prescription drugs dispensed at community pharmacies. Data on hospital admissions was extracted from a complementary source, the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED ECHO) databases. These databases have been used previously for research purposes in numerous therapeutic areas and are well-validated.

Study Cohort

A retrospective observational cohort of men who initiated an NHA in the period from January 2011 to December 2016 was constructed from the RAMQ population. Patients with no prior history of androgen deprivation therapy (luteinizing hormone-releasing hormone agonist or

antagonist drugs or orchiectomy) and who were registered to the public drug insurance plan for less than a year prior to NHA initiation were excluded. Additionally, patients were required to have a PCa diagnosis code or a PCa-related procedure code (radical prostatectomy, external radiotherapy, brachytherapy, or prostate needle biopsy) at any time prior to initiation. It should be noted that although both drugs have gained expanded approval to earlier disease states nowadays, both ABI and ENZ are considered "exception drugs" by the RAMQ that were only approved for mCRPC during the study period in the province of Quebec. This ensures that patients receiving NHAs in the study were for the treatment of mCRPC. Furthermore, the results of RCTs examining their efficacy in metastatic castration-sensitive prostate cancer (for ABI and ENZ) or nonmetastatic castration-resistant prostate cancer (for ENZ only) were not yet available, making it further unlikely the NHAs prescribed during the study period were used in settings earlier than mCRPC. [19, 29-33]

Exposure Groups

The exposure group was assigned based on the prescribing specialty of the first NHA prescription (ABI or ENZ) received and the index date corresponded to the date of the first prescription of the NHA. Prescribing specialty was grouped as follows: medical oncology (MO), urology (URO), and other specialty (OTH). The MO group includes both medical oncology and hematology. The primary analysis uses the as-treated approach, with patients being followed from the index date until the earliest of the following: 1) occurrence of the outcome; 2) death; 3) end of the study period (December 31st, 2016); 4) loss of drug insurance coverage; or 5) 14 days (grace period) after the last drug-exposed day. The last drug-exposed day is defined as the last drug dispensing

date plus days of supply of the drug plus the pharmacokinetic elimination period of the drug. A drug elimination period was included in our analyses given the longer mean terminal elimination half-life of ENZ (6 days) compared to ABI (12 hours). [18, 20] On average, it takes approximately four to five half-lives for a drug to be considered eliminated from the body. [34] Consequently, the drug elimination period was defined as the drug's half-life multiplied by five (ENZ: 30 days; ABI: 3 days).

Study Outcomes

The co-primary study outcomes of interest were overall NHA-related complication which was defined as a composite of hospitalization admissions with a principal diagnosis for the following subtypes: cardiovascular, metabolic, infectious, and general/non-specific. These were identified from the safety findings from the randomized trials and previous research. [35] The subtypes of overall NHA-related complications were also considered as co-primary outcomes. Specifically, cardiovascular complications included acute ischemic coronary events (myocardial infarction and unstable angina), heart failure, and arrhythmia. Metabolic complications included admissions due to diabetes, liver disease, and adrenal insufficiency. Infectious complications related specifically to upper and lower respiratory tract infections, and urinary tract infections. The general/non-specific category comprised of ICD codes relating to joint pain, malaise, fatigue, diarrhea . All-cause mortality and all-cause hospitalization were examined as secondary outcomes.

Covariates

A broad range of covariates were selected a priori on the basis that they may be confounders and risk factors for the study outcomes. Patient characteristics such as age and region of residence

(urban vs rural) were captured at the index date. Characteristics relating to PCa included: type of NHA (ABI or ENZ), prior local PCa treatment (receipt of radical prostatectomy, external beam-radiotherapy, or brachytherapy at any time prior to the index date), time from PCa diagnosis to index date, use of bone-targeted therapy (zoledronic acid or denosumab in the year prior to the index date), chemotherapy status (chemotherapy-naïve or post-chemotherapy), and symptomatic indicator (yes vs no). Regarding chemotherapy status, patients were considered as post-chemotherapy if physician claims of intravenous chemotherapy administration were identified in the period between ADT initiation and NHA initiation. The symptomatic indicator variable is meant to be a proxy of patient symptomatic status and is a composite variable of the any of the following conditions identified in the 3 months prior to the index date: receipt of a urological procedure relating to loco-regional complications of PCa (ex: nephrostomy, ureteral stenting, etc.), receipt of palliative radiotherapy, and use of opiates. Baseline comorbidities (including Charlson comorbidity score) included hypertension, diabetes, dyslipidemia, coronary artery disease, heart failure, arrhythmia, peripheral vascular disease, venous thromboembolism, other cardiac diseases, renal disease, liver disease. [36] Baseline healthcare utilization indicators such as hospital admissions, number of physician visits and number of different drug classes prescribed in the year before the index date were also identified. All comorbidities (including prior cardiovascular risk factors and other diseases) were based on diagnostic codes and treatments identified from inpatient and outpatient claims in the 12-month period preceding the index date unless specified otherwise.

Statistical Analysis

Descriptive statistics were presented as counts and percentages for categorical variables, and as means with standard deviation for continuous variables. Crude incidence rates (IR) were reported as number of events per 100 person-years (100PYs) with corresponding 95% confidence intervals (95%CI) based on the Poisson distribution.

Overlap weighting (OLW) was applied to control for potential baseline confounding. [37] This approach applies weights to the subjects in the original study population and results in the creation of a "pseudo-population" in which treatment assignment is independent of the measured baseline confounders. While similar to inverse probability of treatment weighting, OW focuses specifically on the "overlap region", conceptually representing the patients who have the most clinical equipoise. First, propensity scores were obtained with a multivariable logistic regression model that estimated the predicted probability of the prescribing specialty given the baseline characteristics mentioned above for each patient. The overlap weights were then derived from the propensity scores. Balance of baseline characteristics across prescribing specialty groups was assessed with absolute standardized differences (ASD), with values greater than 10% being considered evidence of covariate imbalance. [38]

The overlap weights were then applied to Cox proportional hazards regression models to estimate cause-specific hazard ratios (HR) with 95%CIs for the study outcomes across the prescribing specialty groups (with MO as the reference group throughout the analyses). [39] The proportional hazards assumption was assessed using log-minus-log plots and Schoenfeld residuals. To account for the within-subject heterogeneity induced by the weighted samples, variances of all weighted analyses were obtained with a robust sandwich-type variance

estimator.[40] Weighted cumulative incidence functions of the study outcomes were also plotted. All analyses were two-sided with the statistical significance level set at $p < 0.05$, and were conducted with SAS software version 9.4 (SAS Institute, Cary, NC).

Subgroup Analyses

Four exploratory subgroup analyses were performed to observe if the effects on the co-primary outcomes differed according to chemotherapy status (chemotherapy-naïve and post-chemotherapy), NHA type (ABI and ENZ), and time period (pre- and post-2014). The rationale for exploring the pre- and post-2014 periods is due to the increasing proportion of urologists as NHA prescribers which was especially notable from 2014 onwards.[26] Propensity score models and overlap weights were re-estimated for each subgroup to ensure baseline balance between prescribing specialty groups for each patient subgroup.

Sensitivity Analyses

A series of sensitivity analyses were performed to assess the robustness of the results from the primary analysis. First, a shorter grace period of 7 days and a longer one of 30 days were explored. Also, the primary analysis was repeated using the subdistribution hazard model instead of the cause-specific hazard model.[41] Both approaches account for the competing risk of dying before the occurrence of a study outcome but each is suitable for particular contexts. The cause-specific hazard model is more appropriate for research questions of etiological nature and the subdistribution hazard model is more suited for prognostic risk prediction purposes and to estimate incidences in the presence of competing risks.[42] To explore the potential differences

due to analytical methods for the control of confounding, analyses using inverse probability of treatment weighting, rather than overlap weighting, were conducted as well.

Results

The study cohort comprises 2,183 patients, of whom 1,157 (53.0%) belonged to the MO group, 740 (33.8%) in the URO group, and 286 (13.1%) in the OTH group. Baseline characteristics of the cohort are shown in Table 1. The mean age of patients is slightly higher in the URO group (MO: 76.0, URO: 76.7, OTH: 75.9). Nearly half (47.9%) of the patients in the OTH group resided in rural areas, whereas the corresponding figure was lower for the MO (27.5%) and URO (34.6%) groups. A higher proportion of the MO (86.4%) and OTH (85.3%) groups initiated received ABI compared to URO group (71.5%). The ONC group (30.9%) also had the highest proportion in terms initiating the NHA in the post-chemotherapy setting compared to the URO group (12.3%) and OTH group (23.8%). For the variables relating to disease severity and symptomatic status, the proportion in the URO group (37.8%) was the lowest, compared to the other two groups (URO: 46.9%, OTH: 49.7%). A slightly higher percentage of the patients in the URO (44.0%) and OTH (43.4%) group had a time from ADT initiation to the index date less than 36 months.

The URO group (60.4%) had the highest proportion of patients with a Charlson score of 0. In terms of individual comorbidities, the OTH group generally had the greatest percetanges. After overlap weighting, all baseline characteristics were well-balanced as the ASDs were less than 0.010 (highest value was 0.039 after weighing compared to 0.670 before weighting). Evaluation of baseline covariate balance with significance testing (p-values) instead of ASDs is shown in eTable 1.

Primary analysis

The crude IR of overall NHA-related complications corresponded to 15.9/100PYs (95%CI 13.5-18.7), 14.2/100PYs (11.4-17.7), and 21.7/100PYs (16.1-29.3) for the MO, URO, and OTH groups, respectively (Figure 1). In weighted analyses, there were no differences for the URO group (HR 0.97, 95%CI 0.72-1.31, *p* = 0.843) and the OTH group (HR 1.05, 95%CI 0.70-1.54, *p* = 0.822) as compared to the MO group (Figure 1). The weighted cumulative incidence curve is displayed in Figure 2.

For the weighted analysis of cardiovascular complications (Figure 2), an increased risk for the URO group was observed (HR 1.85, 95%CI 1.04-3.28, *p* = 0.035), and the HR for the OTH group was 1.57 (95%CI 0.72-1.54, *p* =0.822). Concerning metabolic complications, the weighted HRs for the URO and OTH group were 1.17 (95%CI 0.42-3.29, *p* = 0.768) and 1.43 (95%CI 0.38-5.45, *p* = 0.599), respectively. Regarding the weighted analyses of infectious complications, the risk was reduced in the URO group (HR 0.66. 95%CI 0.43-0.98, *p* = 0.041) but not for the OTH group (HR 0.97, 95%CI 0.61-1.55, *p* = 0.912). With respect to general/non-specific complications, no difference between the URO group and the MO group was identified (HR 0.62, 95%CI 0.04-8.64, *p* = 0.725) and the analysis was not performed for the OTH group due to lack of events.

For the weighted analyses of all-cause mortality, no differences were found for the URO group (HR 1.08, 95%CI 0.93-1.24, *p* = 0.285) and the OTH group (HR 1.12, 9%%CI 0.94-1.33, *p* = 0.198). The occurrence of all-cause hospitalizations was similar across the groups as well with weighted HRs of 1.11 (95%CI 0.90-1.34, *p* = 0.353) and 1.10 (95%CI 0.94-1.28, *p* = 0.224) for the URO and OTH group, respectively.

Subgroup analyses

Table 2 displays the subgroup analyses. Across all the explored subgroups, similar results were obtained for overall NHA-related complications, all-cause mortality, and all-cause hospitalization. For cardiovascular complications, the direction of effects across all subgroups also suggested a higher risk for the URO group, with the exception of the post-chemotherapy subgroup (HR 0.59, 95%CI 0.08-4.45, p = 0.612) which was accompanied by a very wide 95%CI. Compared to the primary analysis, slightly higher point estimates for the URO group were obtained in the pre-2014, ABI, and chemotherapy-naïve subgroups. With the exception of the ENZ subgroup (HR 1.08), point estimates for the URO group across subgroups were all suggestive of a lower risk regarding infectious complications.

Sensitivity Analyses

The sensitivity analyses varying the durations of the grace windows led to similar results (Table 3). Similar estimates were obtained when using the subdistribution hazard model (HR 1.79, 95%CI 0.94-3.34, p = 0.092) but confidence intervals were wider. When using inverse probability of treatment weights instead of overlap weights, the results were similar but also were not as precise.

Discussion

In the current study, we observed no differences in the risk of NHA-related complications by prescribing specialty when considering them as an overall composite. However, when evaluating the subtypes of NHA-related complications individually, we found that the URO group was associated with a greater risk of cardiovascular complications, but a lower risk of infectious

complications compared to the MO group. Notably, no differences across the specialties were found for all-cause mortality and all-cause hospitalization. Across an array of sensitivity analyses, the point estimates remained relatively similar.

To our knowledge, only one other study has reported on the outcomes of NHA-treated mCRPC patients by prescribing specialty. [28] They also used Canadian data, but from the province of Ontario, and restricted their cohort to chemotherapy-naïve patients only. Regarding their adjusted analyses evaluating the association between outcomes and prescribing specialty, they found a higher risk of all-cause mortality, all-cause hospitalization, and toxicity-related hospital visits for medical oncologist-treated patients compared to urologist-treated patients. However, in their sensitivity analyses restricted to the subset of patients for whom baseline prostate-specific antigen serum level was available for statistical adjustment, all of the aforementioned effects were diluted to the null and they found no difference across the prescribing specialties. In this manner, our results for the outcome of overall NHA-related complication, all-cause hospitalization and all-cause mortality are in line with their sensitivity analyses. However, since they did not extend their adjusted analyses to the different subtypes of NHA-related complications, we could not compare our adjusted/weighted subtype-specific findings, only their crude incidence. It should be noted that their outcome definition of complications included either emergency department visit or an hospitalization admission.

Our reported crude incidence rates for the subtypes of NHA-related complications are similar to those reported in other population-based cohorts in the mCRPC setting. While not directly comparable to the figures in the study by Woon et al, as mentioned above, since they defined

complications as either emergency department visits or hospitalization, our results are in a relatively similar range. [28] Moreover, they also found that infectious complications ranked first in terms of frequency followed by cardiovascular complications. However, our incidences for arrhythmia- and heart failure-related complications are substantially lower compared to those reported in a French cohort. [43]

There was a limited number of events for the subtypes of metabolic complications and general/nonspecific complications. Although this led to estimated effects with very wide confidence intervals in the weighted analyses, the crude incidence rates did not suggest a difference between the URO and MO groups. On the other hand, the OTH group's crude incidence rate for metabolic complications is nearly triple that of the URO and MO groups. Additionally, a slightly elevated point estimate for the HR of the OTH group remained even in the weighted analysis but the large level of imprecision does not allow for any firm conclusions.

The effects were relatively similar across the explored subgroups, and especially stable for the outcomes of overall NHA-related complications, all-cause hospitalization and all-cause mortality. While some effects seem to have large discrepancies from those observed in the primary analysis for the subtypes of complications, caution is warranted in overinterpreting those results. Given the very limited number of events and restricted size of certain subgroups, most notably the ENZ subgroup and post-chemo subgroup, instability in their estimates and wide confidence intervals are to be expected.

Even prior to the introduction of the NHAs, urologists have had a significant amount of experience prescribing certain systemic therapies in the PCa patient population, specifically

androgen deprivation therapy and first-generation anti-androgens. Notably, the majority of ADT-treated patients (over 75%) receive their ADT prescriptions from urologists. [44] Furthermore, urologists are well-aware of the cardiotoxic signals associated with androgen deprivation therapy and have emitted numerous clinical recommendations and review articles addressing them in both multi-specialty collaborations and urology-specific initiatives. [45-47] Consequently, our results indicating a higher incidence of cardiovascular complications in the URO group compared to the MO group may be due to the particular challenges that the NHAs present, especially with regards to ABI. Routine clinical monitoring for ABI treatment includes monthly surveillance of blood pressure, serum potassium, fluid retention, the two latter are not part of the routine monitoring for androgen deprivation therapy or part of the typical workflow for a urology practice. On the other hand, these aspects of clinical monitoring are comparatively more familiar to a medical oncologist given their training background in internal medicine. Furthermore, it has been suggested that, compared to medical oncologists, urologists may prefer to prescribe ENZ over ABI, independent of patient-level variables. [26, 48] A possible explanation for this pattern could be that the aforementioned issues with the routine clinical monitoring with ABI may prove to be a greater disincentive to urologists than medical oncologists whereas management of ENZ is not as stringent/complex.

Conversely, we also found that the risk of infectious complications was lower in the URO group compared to the MO group. While this subtype included both respiratory tract infections and urinary tract infections, the latter was most prevalent and likely drove this effect. Compared to medical oncologists, urologists likely have more subject matter expertise, greater exposure to, and a workflow more conducive to identifying, managing and treating urinary tract issues,

including infections, given their specialized training background and work environment. This could potentially allow them to manage urinary tract infections before they worsen and require hospitalization. While not pertaining directly to this topic, prior literature indicates that urologists are more likely to have guideline-

concordant management of urinary tract infections compared to other specialties. [49, 50]

The management of treatment-related morbidity is particularly salient in the context of an incurable disease such as mCRPC. While it is reassuring that we found no difference in all-cause mortality, all-cause hospitalization, and even overall NHA-related complications across prescribing specialties, the associations we identified between prescribing specialty and the incidence of certain subtypes of NHA-related complications suggest possible improvements to the management of patients with mCRPC receiving treatment with NHAs. Although multidisciplinary teams to manage patients with PCa has often been promoted, prior studies have shown that a substantial proportion patients with metastatic PCa are consulting urologists only. [51] Although the aforementioned studies used data prior to the introduction of the NHAs (pre-2010). In other advanced cancers, some research suggest that multidisciplinary teams have an impact in terms of outcomes. [52, 53]

The study contains several limitations that should be noted. As with any observational study with non-randomized exposure groups, residual confounding is possible. Although the overlap weighting method provides great balance across groups, it can only do so for variables that are captured by the data available. We cannot rule out the possibility of confounding by variables that are not captured by administrative healthcare claims data. Of particular concern is the

inability to capture prognostic mCRPC variables, such as metastatic volume and sites, performance status, and other markers with prognostic value. We did attempt to partly remediate for this by including variables such as the symptomatic indicator variable (use of palliative radiation, opioids, or treatment with urological procedure in 3 months before NHA initiation), time from ADT to index date, prior use of bone-targeted therapy which are meant to be a reflection of symptomatic burden and disease severity.

Detailed information on physician-level and institutional-level variables were also not available in this dataset but may be of interest such as physician sub-specialized training, type of institution, previous experience with advanced PCa management, among others. Although difficult to obtain, inclusion of these variables could help further clarify the association between prescribing specialty and specific types of safety outcomes.

Moreover, our study cohort exclusively evaluated the use ABI and ENZ for the treatment of mCRPC, nowadays both are used in earlier disease states (metastatic castration-naive prostate cancer, nonmetastatic castration-resistant prostate cancer). As such, it is unknown whether the associations we identified extend to their use in these states.

Conclusion

Overall, our findings emphasize the reality that management of mCRPC is complex. In this cohort, prescribing specialty was not associated with the risk of overall NHA-related complications, all-cause mortality, or all-cause hospitalization but was associated with certain subtypes of NHA-related complications. Specifically, patients with urologist prescribers were associated with a higher incidence of cardiovascular complications but lower incidence of infectious complications,

compared to patients with medical oncologist prescribers. Additional population-based studies are needed to further explore these associations. While the NHAs are more tolerable compared to chemotherapy agents such as docetaxel and cabazitaxel, clinicians should not underestimate their potential for serious complications. Clinical guidelines covering mCRPC management may need additional emphasis on adequate monitoring and management of NHA-related complications. Furthermore, strategies to enhance the opportunity and process for multidisciplinary care between medical oncologists, urologists and other specialists can potentially play a role in optimizing patient monitoring and minimize the risk of complications in patients receiving NHAs.

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Conflict of interest statement

AA has received honoraria from Abbvie, Astellas Pharma, Bayer, Janssen, Sanofi and TerSera (all unrelated to the study).

JH and AD have no conflicts of interest to declare.

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Figure 1. Crude incidence rate and overlap-weighted hazard ratios for primary and secondary outcomes

Outcome	Crude IR		HR	95%CI	*p*
	IR/100PYs	95%CI			
Overall NHA complication					
URO	14.2	11.4-17.7	0.97	0.72-1.31	0.843
OTH	21.7	16.1-29.3	1.05	0.7-1.54	0.822
MO	15.9	13.5-18.7	1.00	Ref	
Cardiovascular complication					
URO	6.4	4.6-8.8	1.85	1.04-3.28	0.035
OTH	5.9	3.3-10.5	1.57	0.72-3.41	0.252
MO	4.8	3.6-6.4	1.00	Ref	
Metabolic complication					
URO	1.2	0.6-2.5	1.17	0.42-3.29	0.768
OTH	2.9	1.3-6.4	1.43	0.38-5.45	0.599
MO	1.3	0.8-2.3	1.00	Ref	
Infectious complication					
URO	7.7	5.8-10.4	0.66	0.43-0.98	0.041
OTH	13.3	9.1-19.4	0.97	0.61-1.55	0.912
MO	9.9	8.1-12.1	1.00	Ref	
General/non-specific complication					
URO	0.2	0.0-1.2	0.62	0.04-8.64	0.725
OTH	0.0	-		NA	
MO	0.2	0.0-0.8	1.00	Ref	
All-cause mortality					
URO	41.6	37.6-46.1	1.08	0.93-1.24	0.285
OTH	56.1	48.6-64.7	1.12	0.94-1.33	0.198
MO	49.7	46.3-53.4	1.00	Ref	
All-cause hospitalization					
URO	76.1	68.5-84.6	1.11	0.90-1.34	0.353
OTH	97.7	83.0-114.9	1.10	0.94-1.28	0.224
MO	75.9	69.9-82.4	1.00	Ref	

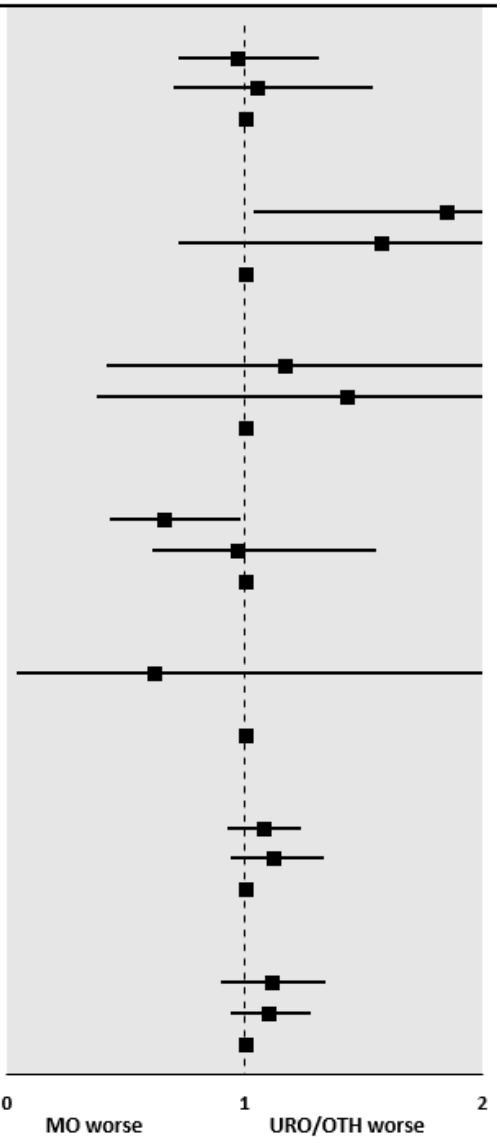
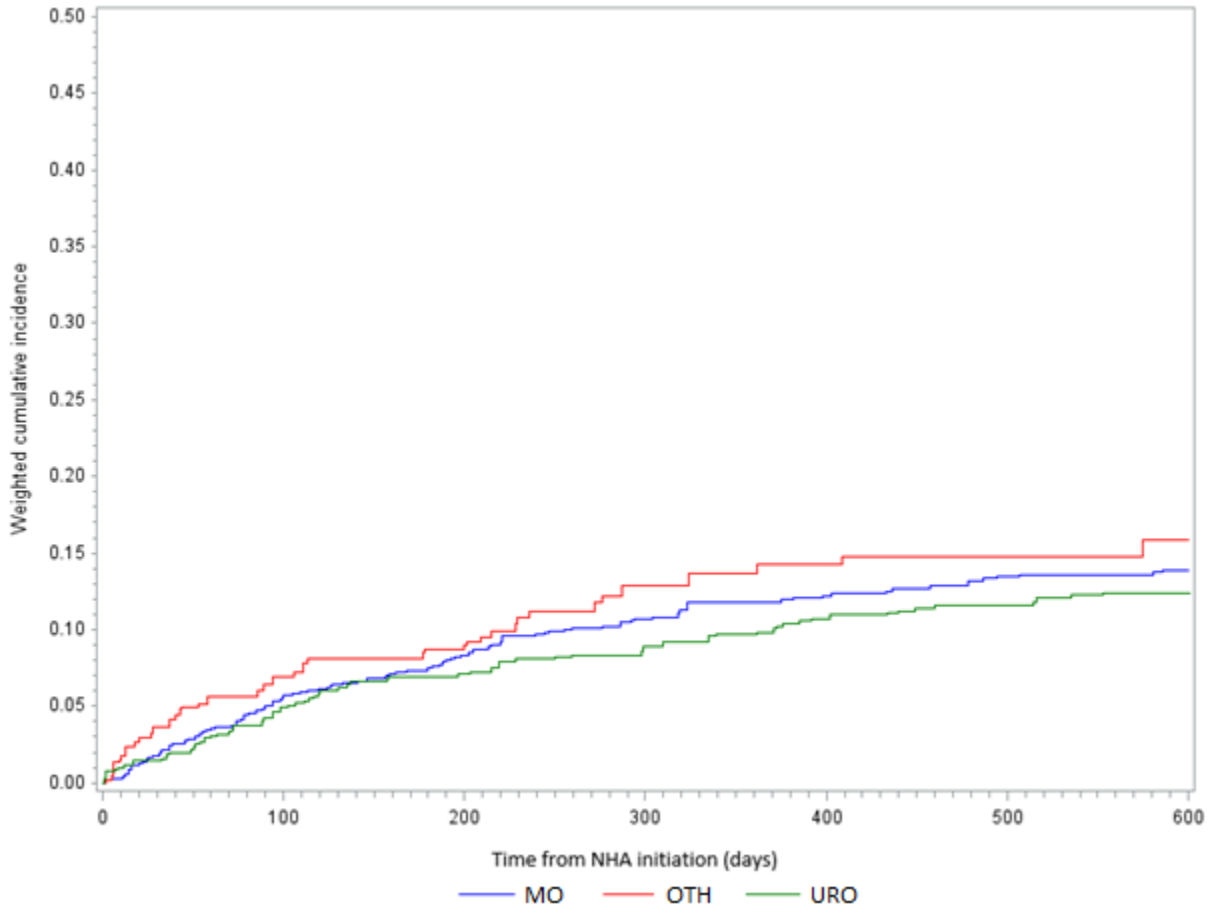


Figure 1. The table component displays the crude IRs (per 100 PYs) and overlap-weighted HRs for the study outcomes. The shaded right side area of the figure depicts the overlap-weighted HRs as a forest plot in which the vertical dashed line represents an HR of 1.00.

Abbreviations: 95%CI = 95% confidence interval; HR = hazard ratio; IR = incidence rate; MO = medical oncology; NHA = novel hormonal agent; OTH = other; PYs = person-years; Ref = reference; URO = urology.

Figure 2. Overlap-weighted Cumulative Incidence Curves of Overall NHA-related Complication by Prescribing Specialty



Abbreviations: MO = medical oncology; NHA = novel hormonal agent; OTH = other; URO = urology.

Table 1. Cohort Baseline Characteristics

	Crude/Unweighted Study Population					Weighted (OLW) Study Population				
Characteristic	**MO (n=1157)**	**URO (n=740)**	**OTH (n=286)**	**ASD Before OLW[1]**	**ASD Before OLW[2]**	**MO**	**URO**	**OTH**	**ASD After OLW[1]**	**ASD After OLW[2]**
Age, years; mean (sdev)	76.0 (8.3)	76.7 (8.4)	75.9 (8.2)	0.089	0.010	76.1 (2.9)	76.0 (3.8)	75.9 (5.8)	0.015	0.017
Rural	27.7%	34.6%	47.9%	0.140	0.412	39.6%	38.7%	40.0%	0.018	0.008
NHA										
Enzalutamide	13.6%	28.5%	14.7%	0.396	0.030	16.1%	17.3%	18.2%	0.031	0.034
Abiraterone acetate	86.4%	71.5%	85.3%			83.9%	82.7%	81.8%		
Post-chemotherapy	39.9%	12.3%	23.8%	0.670	0.392	21.9%	22.1%	21.2%	0.005	0.018
Years from PCa dx; mean (sdev)	7.6 (5.4)	8.4 (5.5)	7.8 (5.6)	0.145	0.040	8.0 (1.9)	8.1 (2.5)	8.1 (4.0)	0.022	0.017
Time on ADT < 36 months	44.0%	40.1%	43.4%	0.078	0.013	41.7%	41.8%	42.1%	0.003	0.009
Symptomatic indicator	46.9%	37.8%	49.7%	0.183	0.055	45.1%	45.7%	44.4%	0.012	0.014
Palliative radiation	7.2%	4.7%	9.1%	0.085	0.048	10.5%	10.5%	10.3%	0.030	0.005
Opioid prescription	39.8%	29.6%	42.3%	0.210	0.053	37.1%	37.7%	36.7%	0.014	0.007
Urological procedure	10.5%	10.8%	12.2%	0.009	0.177	9.0%	9.9%	8.3%	0.001	0.024
Bone-targeted therapy	59.6%	41.6%	49.0%	0.359	0.212	50.2%	48.3%	46.2%	0.038	0.080
Prior local PCa treatment	40.7%	39.9%	40.2%	0.017	0.010	41.8%	41.0%	41.7%	0.016	0.001
Charlson score 0	56.2%	60.4%	51.8%	0.085	0.089	55.4%	56.8%	55.1%	0.029	0.005
Charlson score 1	17.6%	16.2%	19.2%	0.034	0.043	18.6%	18.8%	19.7%	0.005	0.027
Charlson score 2	14.3%	11.8%	10.1%	0.080	0.132	11.4%	10.9%	10.8%	0.018	0.022

Charlson score 3+	12.0%	11.6%	18.9%	0.011	0.197	14.6%	13.5%	14.4%	0.031	0.004
Hypertension	68.5%	69.3%	74.5%	0.019	0.134	71.4%	71.9%	71.5%	0.011	0.003
Dyslipidemia	53.9%	58.1%	59.1%	0.084	0.104	56.9%	56.7%	57.9%	0.006	0.018
Diabetes	22.4%	20.4%	25.9%	0.047	0.083	23.2%	23.0%	22.6%	0.006	0.016
Myocardial infarction	2.7%	2.8%	4.2%	0.009	0.084	3.5%	3.5%	3.2%	0.001	0.014
Coronary artery disease	13.5%	15.0%	16.8%	0.042	0.092	15.8%	15.1%	15.0%	0.019	0.020
Cerebrovascular disease	2.3%	2.2%	3.2%	0.010	0.049	3.1%	2.5%	2.9%	0.032	0.009
Heart failure	4.7%	3.8%	4.2%	0.046	0.024	4.2%	3.9%	3.6%	0.015	0.029
Arrhythmia	11.1%	11.4%	13.6%	0.009	0.079	12.0%	12.1%	11.7%	0.004	0.009
Peripheral artery disease	4.9%	5.3%	4.6%	0.016	0.018	4.9%	4.8%	4.6%	0.006	0.014
Venous thromboembolism	3.0%	3.1%	4.9%	0.004	0.100	3.6%	3.5%	3.8%	0.005	0.012
No cardiovascular disease	20.5%	19.5%	15.7%	0.027	0.123	18.4%	18.2%	18.4%	0.007	0.000
Renal disease	7.9%	10.0%	13.3%	0.069	0.175	11.7%	10.4%	10.3%	0.042	0.043
Liver disease	1.1%	1.8%	1.4%	0.056	0.024	1.1%	1.4%	1.4%	0.026	0.024
Hospital admission (≥1)	57.3%	60.8%	46.5%	0.070	0.217	53.3%	54.2%	54.0%	0.017	0.013
Nbr ED visits GE 2	50.4%	43.5%	56.3%	0.138	0.118	51.1%	50.3%	50.9%	0.015	0.003
Nbr drug classes	32.3%	37.0%	25.9%	0.102	0.140	30.5%	30.9%	31.4%	0.009	0.021
Nbr drug classes	57.7%	55.0%	61.2%	0.056	0.070	59.4%	59.2%	59.6%	0.003	0.004
Nbr drug classes	9.9%	8.0%	12.9%	0.066	0.101	10.2%	9.9%	9.0%	0.008	0.040
ACEi	45.3%	44.2%	46.9%	0.022	0.031	45.2%	45.9%	45.8%	0.013	0.012
Anticoagulants	13.2%	17.3%	14.0%	0.119	0.022	13.3%	14.0%	13.6%	0.022	0.008
Statins	52.4%	57.0%	57.0%	0.094	0.093	55.2%	55.2%	56.6%	0.000	0.028

Year of NHA initiation										
2012	22.0%	9.6%	14.7%	0.353	0.208	14.6%	15.9%	13.3%	0.035	0.039
2013	22.7%	14.7%	18.2%	0.210	0.119	17.7%	17.7%	17.6%	0.001	0.003
2014	20.8%	28.8%	24.8%	0.183	0.092	25.7%	24.0%	26.1%	0.039	0.009
2015	16.7%	21.2%	22.0%	0.111	0.131	20.8%	21.3%	21.4%	0.011	0.015
2016	17.7%	25.7%	20.3%	0.194	0.063	21.2%	21.2%	21.7%	0.001	0.012

Note: Data are presented as percentages unless otherwise noted.

[1]ASD for MO vs URO; [2]ASD for MO vs OTH

Abbreviations: ADT = Androgen deprivation therapy; ASD = absolute standardized difference; Dx = diagnosis; ED = emergency department; MO = medical oncology; nbr = number; PCa = prostate cancer; OLW = overlap weighting; OTH = other; sdev = standard deviation; URO = urology

Table 2. Subgroup analyses of the risk of NHA-related complications by prescribing specialty

		Time period of NHA initiation						NHA type						Chemotherapy status					
		Pre-2014 (n=792)			Post-2014 (n=1391)			ABI (n=1773)			ENZ (n=410)			Chemo-naïve (n=1562)			Post-chemo (n=621)		
		Hazard ratio (weighted)			Hazard ratio (weighted)			Hazard ratio (weighted)			Hazard ratio (weighted)			Hazard ratio (weighted)			Hazard ratio (weighted)		
		HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*
Overall NHA-related complication (composite endpoint)	MO		Ref			Ref			Ref			Ref			Ref			Ref	
	URO	1.05	0.60-1.85	0.858	0.92	0.63-1.36	0.681	0.99	0.71-1.38	0.942	1.54	0.48-4.91	0.523	0.94	0.67-1.33	0.739	0.97	0.41-2.26	0.934
	OTH	1.30	0.73-2.30	0.376	0.90	0.53-1.55	0.710	1.13	0.76-1.67	0.550	-	-	-	1.01	0.65-1.57	0.980	1.14	0.47-2.75	0.767
Cardiovascular complication	MO		Ref			Ref			Ref			Ref			Ref			Ref	
	URO	2.13	0.90-5.01	0.085	1.73	0.76-3.98	0.195	1.91	1.04-3.51	0.037	4.26	0.48-37.5	0.196	1.91	0.98-3.70	0.055	0.59	0.08-4.45	0.612
	OTH	2.21	0.84-5.84	0.110	1.12	0.31-4.12	0.864	1.56	0.71-3.43	0.269	-	-	-	1.52	0.62-3.73	0.365	0.36	0.07-1.83	0.218
Metabolic complication	MO		Ref			Ref			Ref			Ref			Ref			Ref	
	URO	1.58	0.35-7.26	0.555	0.98	0.25-3.78	0.973	0.93	0.31-2.84	0.899	-	-	-	1.03	0.34-3.13	0.961	1.88	0.17-21.2	0.610
	OTH	0.26	0.03-2.15	0.211	3.98	1.11-14.3	0.035	1.54	0.45-5.23	0.493	-	-	-	1.39	0.33-5.79	0.654	4.25	0.39-46.5	0.236
Infectious complication	MO		Ref			Ref			Ref			Ref			Ref			Ref	
	URO	0.49	0.23-1.04	0.062	0.71	0.45-1.15	0.170	0.71	0.47-1.06	0.105	1.08	0.32-3.69	0.901	0.70	0.46-1.06	0.093	0.60	0.19-1.88	0.380
	OTH	1.21	0.61-2.39	0.581	0.83	0.44-1.50	0.499	0.94	0.59-1.49	0.796	-	-	-	0.89	0.53-1.51	0.670	1.07	0.36-3.15	0.902
All-cause mortality	MO		Ref			Ref			Ref			Ref			Ref			Ref	
	URO	1.14	0.92-1.42	0.223	1.03	0.85-1.26	0.761	1.09	0.94-1.27	0.260	1.71	0.96-3.02	0.065	1.08	0.92-1.28	0.354	1.08	0.81-1.42	0.614
	OTH	1.10	0.86-1.41	0.440	1.19	0.93-1.54	0.162	1.05	0.87-1.26	0.607	0.80	0.46-1.37	0.415	1.12	0.90-1.37	0.334	1.10	0.81-1.52	0.531
All-cause hospitalization	MO		Ref			Ref			Ref			Ref			Ref			Ref	
	URO	1.15	0.87-1.52	0.326	1.02	0.84-1.25	0.813	1.11	0.94-1.32	0.210	0.90	0.53-1.55	0.705	1.10	0.92-1.31	0.295	1.03	0.72-1.49	0.644
	OTH	1.07	0.76-1.49	0.708	1.15	0.89-1.49	0.285	1.07	0.86-1.32	0.562	1.29	0.68-2.49	0.451	1.12	0.88-1.41	0.361	1.11	0.71-1.73	0.858

Abbreviations: 95%CI = 95% confidence interval; ABI = abiraterone acetate; ENZ = enzalutamide; HR = hazard ratio; IPTW = inverse probability of treatment weighting; NHA = novel hormonal agent; MO = medical oncology; OTH = other; Ref = reference; URO = urology.

Table 3. Sensitivity analyses of the risk of NHA-related complications by prescribing specialty

		No grace period			30-day grace period			IPTW			Subdistribution hazard		
		Hazard ratio (weighted)			Hazard ratio (weighted)			Hazard ratio (weighted)			Hazard ratio (weighted)		
		HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*
Overall NHA-related complication (composite endpoint)	MO		Ref			Ref			Ref			Ref	
	URO	0.97	0.71-1.33	0.852	1.01	0.75-1.35	0.967	1.01	0.74-1.38	0.959	0.90	0.58-1.62	0.759
	OTH	1.04	0.69-1.55	0.860	1.03	0.71-1.51	0.866	0.99	0.67-1.48	0.971	0.96	0.51-1.80	0.899
Cardiovascular complication	MO		Ref			Ref			Ref			Ref	
	URO	1.80	0.99-3.25	0.051	1.86	1.05-3.29	0.033	1.62	0.91-2.91	0.109	1.79	0.94-3.34	0.092
	OTH	1.65	0.76-3.61	0.207	1.78	0.84-3.74	0.130	1.43	0.68-3.06	0.360	1.37	0.67-2.83	0.550
Metabolic complication	MO		Ref			Ref			Ref			Ref	
	URO	1.04	0.35-3.10	0.938	1.36	0.51-3.60	0.538	1.49	0.35-5.41	0.649	1.30	0.13-5.24	0.834
	OTH	1.42	0.37-5.36	0.609	1.36	0.36-5.10	0.648	1.38	0.44-5.04	0.521	1.09	0.27-6.21	0.859
Infectious complication	MO		Ref			Ref			Ref			Ref	
	URO	0.69	0.47-1.03	0.068	0.72	0.50-1.03	0.074	0.74	0.51-1.08	0.114	0.64	0.36-1.10	0.159
	OTH	0.92	0.57-1.49	0.743	0.93	0.60-1.45	0.759	0.96	0.60-1.54	0.874	0.88	0.42-1.79	0.704
General/Non-specific complication	MO		Ref			Ref			Ref			Ref	
	URO	0.63	0.04-8.87	0.731	0.63	0.05-8.66	0.726	0.55	0.05-6.68	0.639	0.57	0.01-373.5	0.866
	OTH	-	-	-	-	-	-	-	-	-	-	-	-
All-cause mortality	MO		Ref			Ref			Ref			Ref	
	URO		NA			NA		1.10	0.96-1.26	0.179		NA	

	OTH		NA			NA		1.15	0.97-1.37	0.120		NA	
	MO		Ref			Ref			Ref			Ref	
All-cause hospitalization	URO	1.09	0.93-1.27	0.272	1.10	0.95-1.29	0.203	1.13	0.96-1.32	0.131	1.08	0.81-1.44	0.582
	OTH	1.12	0.92-1.36	0.287	1.12	0.92-1.36	0.282	1.08	0.87-1.33	0.505	1.02	0.84-1.24	0.311

Abbreviations: 95%CI = 95% confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; NHA = novel hormonal agent; MO = medical oncology; OTH = other; Ref = reference; URO = urology.

APPENDIX

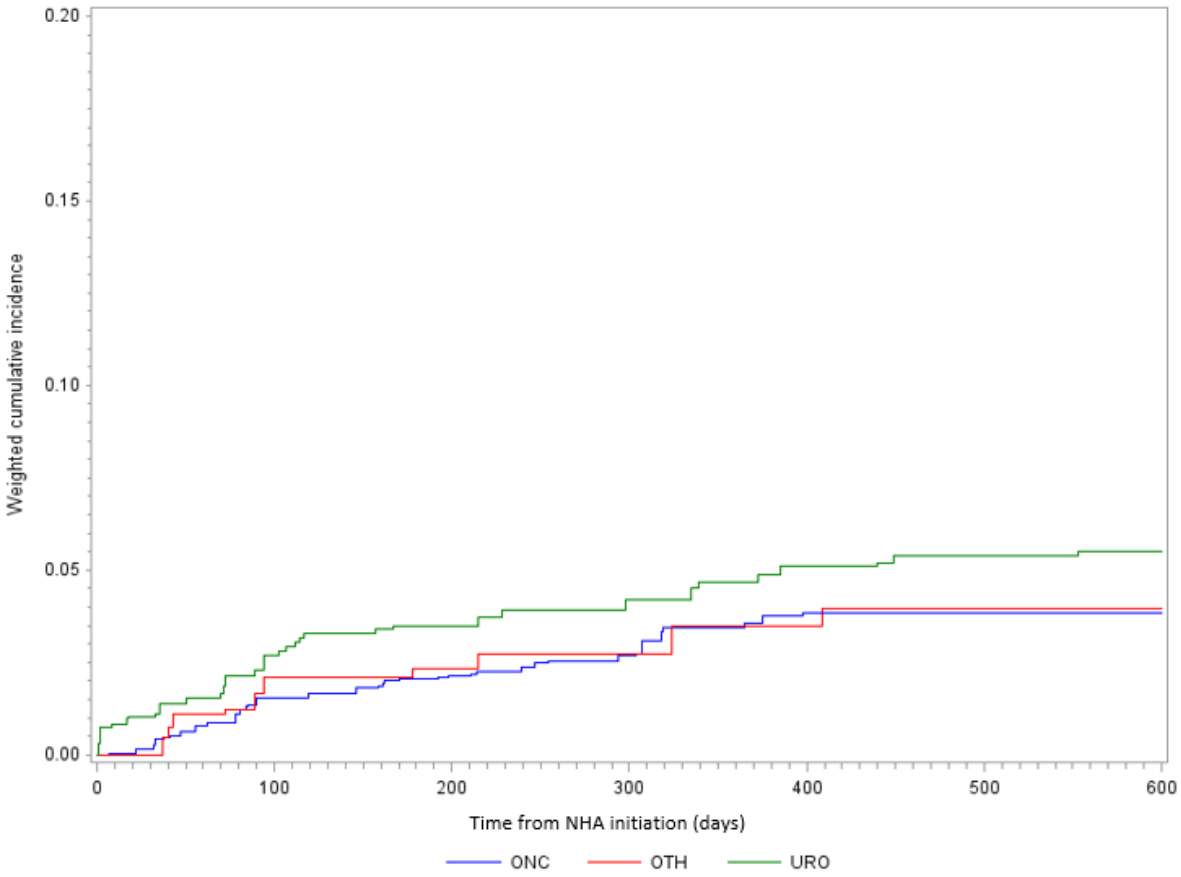


Figure A1. Overlap-weighted cumulative incidence curve of cardiovascular complications by prescribing specialty

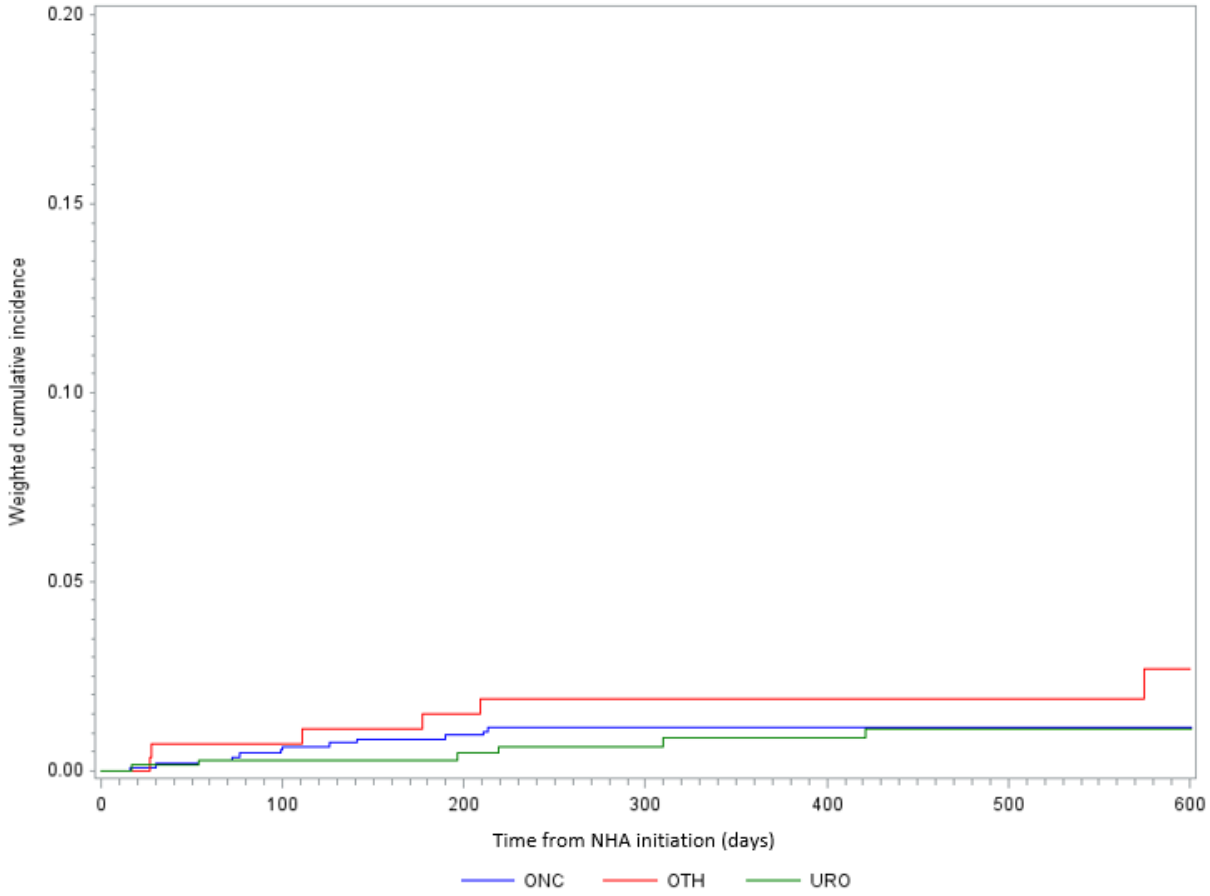


Figure A2. Overlap-weighted cumulative incidence curve of metabolic complications by prescribing specialty

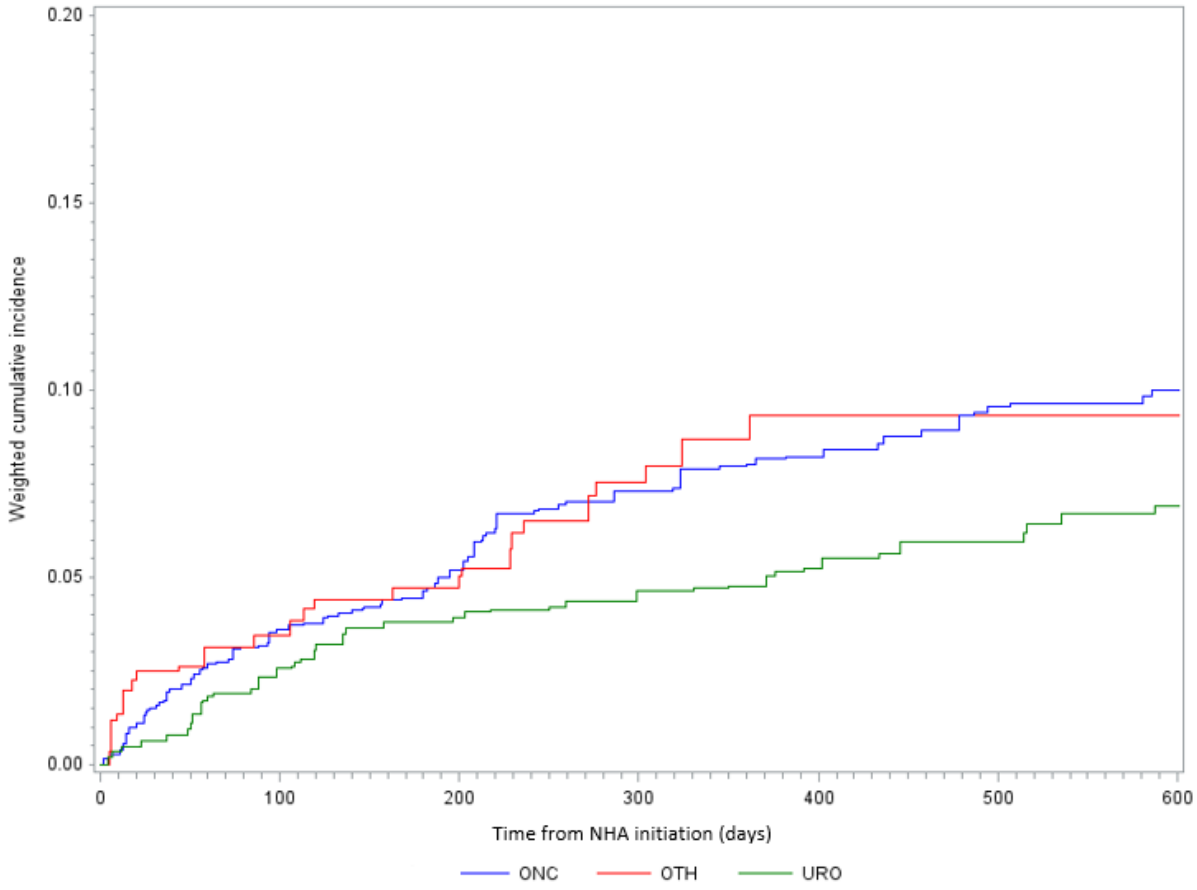


Figure A3. Overlap-weighted cumulative incidence curve of infectious complications by prescribing specialty

Chapter 6: Discussion and Conclusions

6.1 Summary of Findings

The overarching aim of this thesis was to generate real-world evidence concerning current knowledge gaps regarding abiraterone and enzalutamide in mCRPC by examining the use and outcomes of these NHAs in the real-world. While several studies have examined the utilization of NHAs in mCRPC in clinical practice, most of these studies are set in the United States and Europe, there were few studies evaluating practice in Canada and none in the province of Quebec. Furthermore, no study had thoroughly described the utilization by prescribing specialty. Data on the incidence of cardiovascular complications of abiraterone and enzalutamide in the real-world were also limited due not only the exclusion of patients with history of significant cardiovascular disease at baseline in the large phase III RCTs, but also the limited comparative (randomized and observational) cardiovascular safety data of these two agents. Finally, there remains limited data concerning the incidence of treatment-related complications in patients receiving NHAs for mCRPC by prescribing specialty. To generate the real-world evidence concerning these knowledge gaps, a study population consisting of first-time users of abiraterone and enzalutamide from 2011 to 2016 was extracted using administrative healthcare data from the province of Quebec in Canada. This study population served as the basis of three real-world studies that sought to address the three thesis objectives.

In the first manuscript, the primary analyses sought to characterize the temporal patterns (2011-2016) of individuals initiating NHAs, categorized by their chemotherapy history (chemotherapy-naïve or post-chemotherapy) and the specialty of the prescribing physician (medical oncology,

urology, or other specialties). Among the cohort of 2,183 first-time users of NHAs for mCPRC, 1,562 (72%) were in the chemotherapy-naïve group and 621 (28%) were in the post-chemotherapy group. While most patients were post-chemotherapy NHA initiators in 2012, this proportion decreased over time and accounted for only 13% of NHA initiators by the end of 2016. Medical oncologists were the most frequent prescribers of NHAs (upwards of 60%) throughout 2012 but fell to 45% by the end of 2016. Conversely, the proportion of prescriptions by urologists increased from 22% in 2012 to 42% in 2016. From its availability in the first quarter of 2014, the proportion of enzalutamide initiators increased from 10% to 54% by the end of the study period. In multivariable regression analyses examining the relationships between initiating enzalutamide (over abiraterone) confirmed that urologists were likely to prescribe enzalutamide compared to medical oncologists in both the chemotherapy-naïve setting (OR 1.89, 95% 1.38-2.58) and the post-chemotherapy setting (OR 3.83, 95%CI 1.76-8.36). Previous studies in the United States and Sweden examining the adoption of NHAs in the United States corroborates our finding that enzalutamide initiators slightly exceeded abiraterone initiators by 2016.[166,172] This suggests a relatively quick adoption of enzalutamide which could be partly attributed to the constraints with abiraterone (need for concomitant use of prednisone, monthly monitoring of blood pressure, potassium and liver function). In summary, these findings suggests that the introduction of NHAs may have changed that the care pathways for mCRPC as urologists are increasingly prescribing the NHAs. In eras prior to the introduction of NHAs, urologists would refer patients with mCRPC to medical oncologists for chemotherapy administration but urologists now have the possibility to be more involved in the management of advanced PCa patients and for longer.

In the second manuscript, the objective was to assess the comparative cardiovascular safety of abiraterone and enzalutamide in patients with mCRPC in the real-world. First-time NHA users of abiraterone and enzalutamide between 2011 and 2016 were compared. The primary outcome of interest was cardiovascular-related hospitalization (composite outcome that included acute coronary syndrome, cerebrovascular stroke, heart failure, arrhythmia and others). Among the cohort of 2,183 patients, 1,773 (81.2%) were abiraterone initiators and 410 (18.8%) were enzalutamide initiators. Abiraterone initiators were at greater risk of cardiovascular-related hospitalization compared to enzalutamide initiators (HR 1.82; 95% confidence interval (95%CI) 1.09-3.05). When analyzing the individual subcomponents of the cardiovascular-related hospitalization, the risk of hospitalization for heart failure was greater in abiraterone initiators (HR 2.88; 95%CI 1.09-7.63) compared to enzalutamide users. Regarding the other subcomponents of the composite outcome, the risks were numerically higher, but statistically non-significant, in abiraterone initiators versus enzalutamide initiators except for cerebrovascular stroke. The greater risk of heart failure-related hospitalization in patients treated with abiraterone would be in line with what is known about its mechanism of action, as inhibition of CYP17 enzyme leads to secondary mineralocorticoid excess leading.[173-175] The potential greater cardiovascular risk in abiraterone users, especially in those with cardiovascular risk factors at baseline (subgroup analysis: HR 2.16; 95%CI 1.21-3.87) could have important ramifications in terms of treatment selection for that patient group and additional population-based studies with greater sample sizes and number of events are needed to corroborate these findings.

In the third manuscript, the objective was to assess the association between the incidence of NHA-related complications and prescribing specialty in mCRPC patients treated with NHAs. First-time NHA users were grouped by their prescribing specialty (medical oncology (MO) vs urology (URO) vs other (OTH)). Outcomes of interest were overall NHA-related complications and its subtypes: cardiovascular, metabolic, infectious and general/non-specific. Secondary outcomes included all-cause mortality and all-cause hospitalization. Among the cohort of 2,183 patients, 1,157 (53.0%) were in the MO group, 740 (33.9%) were in the URO group, and 286 (13.1%) were in the OTH group. For overall NHA-related complications, the URO group (HR 0.97, 95%CI 0.72-1.31) and OTH group (HR 1.05, 95%CI 0.70-1.54) were not different compared to the MO group. While the URO group was associated with a greater incidence of cardiovascular complications compared to the MO group (HR 1.85, 95%CI 1.04-3.28), it was also at lower risk of infectious complications (HR 0.66, 95%CI 0.43-0.98). Neither all-cause mortality (HR_{URO} 1.08, 95%CI 0.93-1.24; HR_{OTH} 1.12, 95%CI 0.94-1.33) nor all-cause hospitalization (HR_{URO} 1.11, 95%CI 0.90-1.34; HR_{OTH} 1.10, 95%CI 0.94-1.28) was associated with prescribing specialty. These results suggest that when examining NHA-related complications by prescribing specialty, it is important to specify which type of complications as the risks may be quite different. The greater incidence of cardiovascular complications in the URO group compared to the MO group may be due to the particular challenges that the NHAs present, especially with regards to abiraterone which require routine monitoring of blood pressure, serum potassium, fluid retention. These aspects of clinical management may be comparatively more familiar to a medical oncologist given their training background in internal medicine. In contrast, the lower incidence of infectious complications, mostly driven by urinary tract infections, observed in patients treated by URO, may be explained

by the urologists' expertise in managing urinary tract issues. Taken altogether, the results demonstrate the need for greater awareness in mCRPC clinical guidelines regarding management of NHA-related complications and drives the call to further promote multidisciplinary care in order to optimize patient outcomes.

6.2 Limitations

As with all observational studies performed with secondary data, biases can lead to misleading results. This section will briefly summarize the main methodological limitations that may have impacted the study findings across the thesis projects.

While administrative healthcare claims data allow for the study of large populations, adjustment of large sets of variables, and longitudinal follow-up of patients, they are not generated for research purposes and may lack certain variables of interest. For the thesis studies, data on potential confounders and risk factors that are not captured in claims data include: performance status, symptomatic status, metastatic site and volume, laboratory test results (PSA, Gleason grade, alkaline phosphatase, lactate dehydrogenase, etc.), among others. Regarding the assessment of comorbidities, they are limited with respect to the clinical detail that can be ascertained as they are derived from diagnosis codes and medications, and not directly extracted from medical records. Consequently, concerns of unmeasured and residual confounding will always remain. Having said that, we tried to mitigate this by including variables that could serve as proxies to the confounders and risk factors not captured directly in claims data. For example, we derived a series of variables identified in the 90 days before NHA initiation to approximate symptomatic status: use of palliative radiotherapy, treatment with urological procedures, use of

opioids. Additionally, variables such as time from ADT to NHA initiation, prior use of bone-targeted therapy and prior local treatment may also reflect cancer severity.

In the second and third manuscript, patients were censored upon treatment discontinuation (as-treated exposure definition). While this exposure definition is widely used in pharmacoepidemiologic studies, it may be prone to informative censoring – a form of selection bias which can occur if there is differential loss to follow up across exposure groups. To address this bias, analytic methods such as inverse probability of censoring weighting may be used. However, given the similar rates of loss to follow-up across groups, as well as the minimal percentage of treatment switching, informative censoring was thought to not likely be of concern and sensitivity analysis using inverse probability of censoring weighting was not pursued.

As with all studies evaluating drug effects using administrative healthcare claims data, prescription drug claims do not necessarily correspond to actual intake of the drug by patients and the days supply data may not reflect the actual number of days on treatment. Consequently, there is potential for treatment exposure misclassification – a form of information bias. Given the therapeutic context of advanced cancer and the life-prolonging benefits of NHAs, patient adherence is expected to be high. Nonetheless, in both the second and third manuscript, several sensitivity analyses varying the grace periods were performed to address this potential limitation. Furthermore, given the significantly longer half-life of enzalutamide compared to abiraterone, a drug elimination period was added on top of the grace period to account for potential exposure misclassification.

6.3 Implications of Findings

The results of the first manuscript show that the proportion of NHA initiators who are chemotherapy-naïve increased rapidly through the years. In abiraterone users, this change happened even before its approval for coverage for use in chemotherapy-naïve patients occurred in 2014 and must have occurred through the exception patient measure. For enzalutamide, the majority of users were chemotherapy-naïve patients from the onset of approval. These findings suggest that overall more mCRPC patients are receiving life-prolonging treatment. Prior to the advent of NHAs, docetaxel chemotherapy was the only option with survival benefit but its uptake was always limited due to the high proportion of mCRPC patients being either too frail for treatment or due to patient preference.[163,164] Given the greater tolerability and ease of administration (oral) relative to chemotherapy, this is perhaps not too surprising. Furthermore, our results potentially indicate that the introduction of NHAs appears to have led to an increasing number of patients with mCRPC being managed by urologists. This may be ideal since it can provide better continuity in care as most PCa patients are managed by urologists in earlier disease stages.[176] Moreover, having urologists more involved in the management of mCRPC can be beneficial as it could lead to increased opportunities for multidisciplinary care. Additionally, the need to further emphasize multidisciplinary aspects of treatment management in mCRPC is highlighted by the third manuscript. As the results allude to, the management of NHA-related complications is complex, and patients would likely benefit from the involvement of multiple specialists in their care. Notably, multiple aspects of PCa care have received calls for increased multidisciplinary care, clinical guidelines and various leading physicians covering the entire spectrum of PCa from diagnosis, management and treatment of localized disease, and up to the

final mCRPC state, have frequently mentioned the importance of multidisciplinary decision-making.[44,109,177-179] Numerous studies have also shown a multitude of benefits that multidisciplinary teams in PCa can confer, including increased adoption of innovative treatments, impacting clinical decision-making, increased adherence to clinical guidelines, and potentially improving outcomes.[180-185]

The second manuscript provided data on the cardiovascular safety of the abiraterone and enzalutamide, which remains lacking in the literature especially in a comparative manner in the real-world. Within the scope of mCRPC, this topic is particularly relevant as both agents are relatively similar: orally administered, target the androgen receptor axis, demonstrated similar efficacy versus their control groups in their respective phase III RCTs and approved for the same indications in mcRPC (chemotherapy-naïve and post-docetaxel). Although both are considered tolerable, they do possess distinct adverse effect profiles. Current guidelines recommend that treatment selection between these two should be based on patient preference and comorbidities. This means that any additional data that can help differentiate the two agents can assist clinicians and patients in making better-informed decisions. Our results suggest that abiraterone users may be at higher risk of cardiovascular complications, especially as it relates to heart failure. While this was insinuated in the RCT data, as the frequency of cardiac failure adverse events was greater in the abiraterone groups than the placebo groups, the generalizability of the RCT data was questionable due to their exclusion of patients with clinically significant cardiovascular disease. The data in our work relates to users in actual clinical practice who may have history of significant cardiovascular disease, multiple comorbidities, multiple medications, and who generally have less healthy status relative to RCT patients.

6.4 Future Directions

While the works in this thesis provide some additional real-world evidence about the use and outcomes of patients treated with NHAs for mCRPC, there remains much that is unanswered. The sample size of the study cohort is relatively modest, and the studies were likely underpowered to adequately assess the risk of certain outcomes, in particular the individual subcomponents of the composite outcomes in manuscript 2. The sparse number of events in certain outcomes led to wide imprecision in analyses and makes the interpretation of certain results difficult to interpet. Larger observational studies are required to not only confirm our findings and also to provide greater precision in areas our studies could not.

A second point of consideration for future research in these areas is to examine the use and outcomes of NHAs beyond mCRPC. Abiraterone and enzalutamide are now approved for earlier disease stages, including mCSPC (abiraterone and enzalutamide) and nmCRPC (enzalutamide only). It is unknown if our findings are generalizable to these stages. Additionally, there are now two newer NHAs (apalutamide, darolutamide). Given the dearth of randomized head-to-head data between NHAs, there is ample opportunity to use real-world data to evaluate their outcomes, especially as it relates to safety.

Related to the previous point, another issue to consider in future research is the significant changes not only in mCRPC management, but advanced PCa management in recent years. As the review section in the Background chapter described, the approved treatments and clinical guidelines have undergone major changes, especially for the nmCRPC and mCSPC states. For several of the currently approved therapies for mCRPC, namely docetaxel, abiraterone acetate and enzalutamide, they were evaluated in phase III studies in an environment that is very

different from today – most notably, the standard of care and clinical practice are very different today. Specifically, the phase III trials for docetaxel (TAX 327 and SWOG 9916) were conducted in the early 2000s, when no treatment offered survival benefit.[137,138] Only mitoxantrone chemotherapy was approved for palliative relief and it served as the comparator arm in those trials. Regarding abiraterone acetate and enzalutamide, their clinical development programs ran nearly in parallel in the late 2000s and they both received their first mCRPC FDA approvals at around the same time (abiraterone acetate in 2011, enzalutamide in 2012). Both were evaluated in an environment where docetaxel was the only treatment available and their phase III trials reflect that. Abiraterone acetate was evaluated in the pre-docetaxel mCRPC setting (COU-AA-302) and the post-docetaxel mCRPC setting (COU-AA-301).[5,6] Similarly, enzalutamide was evaluated in the pre-docetaxel mCRPC setting (PREVAIL) and the post-docetaxel mCRPC setting (AFFIRM).[7,8] Ultimately, a common issue of concern for all these three therapies is that the efficacy shown in mCRPC during their respective phase III RCTs may not apply anymore in today's clinical environment. Patients presenting with mCRPC today may have been treated with docetaxel and/or a novel hormonal agent in mCSPC or nmCRPC given these are part of the standard of care today. A similar concern extends to cabazitaxel in post-docetaxel mCRPC as its pivot phase III trial (TROPIC) also occurred in the late 2000s.[148] All three thesis studies were conducted using a study population initiating NHAs from 2011 to 2016, before the release of results indicating the efficacy of abiraterone or enzalutamide in earlier disease states. It would be of interest to evaluate the effectiveness of abiraterone and enzalutamide in mCRPC for patients progressing through advanced PCa in today's environment, with the high probability that would they have been exposed to an NHA earlier in either nmCRPC or mCSPC. This type of

research is another opportunity for real-world data to provide complementary insight since new RCTs evaluating these previously approved treatments again in mCRPC are likely to be undertaken. That is, of course, provided that fit-for-use data sources, appropriate study designs and rigorous methods are employed to conduct the research.

6.5 Conclusion

Overall, this thesis provides additional data to understand how the NHAs, abiraterone and enzalutamide, are being used for mCRPC in clinical practice in Quebec and their outcomes. The evidence generated by this work demonstrate that the majority of NHA initiators during the period from 2011 to 2016 were chemotherapy-naïve, urologists were increasingly prescribing NHAs and they had a preference for prescribing enzalutamide over abiraterone. The comparative cardiovascular safety of the NHAs was evaluated and abiraterone initiators were at greater risk of cardiovascular-related hospitalization, in particular for heart failure-related hospitalization. Although no difference in NHA-related complications was found between patients treated by urologists and those treated by medical oncologists, there was a higher risk of cardiovascular-related complications. Conversely, those treated by urologists were at lower risk of infectious-related complications compared to those treated by medical oncologists. Given the numerous similarities between the two and their prevalent use in mCRPC, additional research outlining potential differences between the two is essential. In this context, with the aim to complement the knowledge gaps left unanswered by RCTs, using real-world data to generate evidence can help clinicians guide treatment choice and optimize the use of the NHAs.

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