In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

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- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
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- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Final Study Report
Control: Non-Interventional.

Title:	5ARI and Prostate Cancer Mortality Study
Phase:	IV
Compound Number:	GSK2285985
Effective Date:	07-SEP-2016
Description:	The primary goal of this study was to compare the risk of prostate cancer mortality among men treated with 5α-reductase inhibitors (5ARI) to those treated with alpha-blockers (AB) in community practice settings. A retrospective matched cohort (N=174,895) and nested case-control study (N=18,311) were conducted in four regions of an integrated healthcare system. Men ages 50 years and older who initiated pharmaceutical treatment for BPH between January 1, 1992 and December 31, 2008 and had at least three consecutive prescriptions were followed through December 31, 2010. After accounting for competing risks, 5ARI use was not associated with prostate cancer mortality when compared to AB use (Adjusted Subdistribution HR: 0.85, 95% CI: 0.72,1.01). Similar results were observed in the case-control study (Adjusted Matched OR: 0.95, 95% CI: 0.78, 1.17). Among men being pharmaceutically treated for benign prostatic hyperplasia in community practice settings, 5ARI use was not associated with an increased risk of prostate cancer specific mortality when compared to AB use. The increased prevalence of high-grade lesions at the time of diagnosis noted in our study and the chemoprevention trials may not result in increased prostate cancer mortality.

Subject: Prostate cancer mortality, BPH treatment, 5ARI

Author(s): [redacted]

Indication Studied: Benign prostatic hyperplasia

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

PASS INFORMATION

Title	5ARI and Prostate Cancer Mortality Study
Version identifier of the final study report	1
Date of last version of the final study report.	03/31/16
EU PAS register number	EUPAS4129
Active substance	**Dutasteride** Pharmacotherapeutic group: testosterone 5 alpha reductase inhibitors, ATC code: G04C B02 **Dutasteride/tamsulosin** Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52
Medicinal product	**Dutasteride** Products registered in the EU: Avodart, Avolve and Duagen **Dutasteride/tamsulosin** Products registered in the EU: Duodart, Combodart and Dutasteride-tamsulosin GSK
Product reference	**Dutasteride** Avodart SE/H/304/001 Avolve SE/H/471/001 Duagen SE/H/305/001 **Dutasteride/tamsulosin** Duodart DE/H/2251/001 Dutasteride-tamsulosin GSK DE/H/2252/001

Procedure number	**Dutasteride** Avodart SE/H/304/001/II/072/G Avolve SE/H/471/001/II/055/G Duagen SE/H/305/001/II/062/G **Dutasteride/tamsulosin** Duodart DE/H/2251/1/II/033/G Dutasteride-tamsulosin DE/H/2252/001/II/023/G
Marketing authorisation holder(s)	UK registration MAH (Avodart and Combodart): GlaxoSmithKline UK Limited 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom
Joint PASS	No
Research question and objectives	This retrospective study assessed the association of benign prostatic hyperplasia (BPH) treatment (5-alpha reductase inhibitors (5ARI) and alpha-blocker medications) with the occurrence of prostate cancer related mortality. This study also assessed a number of secondary endpoints including prostate cancer mortality or metastatic prostate cancer, and all cause mortality.
Country(-ies) of study	US
Author	[redacted] PhD, MPH [redacted]

	[redacted] Office: [redacted] Email: [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	MAH in Reference Member State (RMS): Dutasteride (RMS Sweden): Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom Dutasteride/tamsulosin (RMS Germany): GlaxoSmithKline GmbH & Co. KG Prince Regent Square 9 Munich D-81675 Germany
MAH contact person	Mr. [redacted] Manager, Global Regulatory Affairs GSK Stockley Park West, Iron Bridge Road, Stockley Park, Middlesex. UB111BT. United Kingdom Phone: [redacted] Email: [redacted]

SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study WEUSKOP5723

Name of Project Officer: [redacted]

Title of Project Officer: [redacted]

Signature: [redacted]

Date: 7 - September - 2016

Name of Therapy Area Head: [redacted]

Title of Therapy Area Head: Senior Director, Real World Evidence & Epidemiology [redacted]

Signature: [redacted]

Date: 7 September 2016

[redacted]
Digitally signed by [redacted]
DN: cn [redacted]
o=GSK, ou [redacted]
email [redacted]
c=US
Date: 2016.09.07 08:41:15 -04'00'

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study WEUSKOP5723 was carried out as described in this GlaxoSmithKline Report

Name of Investigator: [redacted]

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 9/7/16

[redacted]
Digitally signed by [redacted]
DN: cn [redacted] o=GSK, ou [redacted] email [redacted] c=US
Date: 2016.09.07 09:35:03 -04'00'

TABLE OF CONTENTS

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1. LIST OF ABBREVIATIONS

AB	Alpha blocker
BPH	Benign Prostatic Hyperplasia
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRN	Cancer Research Network
DCC	Data Coordinating Center
ED	Erectile Dysfunction
CRF	Case Report Form
EMR	Electronic Medical Record
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HEDIS	Healthcare Effectiveness Data and Information Set
HGT	High grade tumors
HR	Hazard Ratio
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
[redacted]	[redacted]
LUTS	Lower Urinary Tract Symptoms
NCI	National Cancer Institute
NDI	National Death Index
NLP	Natural Language Processing
OAB	Overactive Bladder
PSA	Prostate Specific Antigen
PCPT	Prostate Cancer Prevention Trial
REDUCE	Reduction by Dutasteride of Prostate Cancer Events
SAE	Serious Adverse Event
SES	Socioeconomic Status
SHR	Subdistribution Hazard Ratio
SOP	Standard Operating Procedure
UK	United Kingdom
VDW	Virtual Data Warehouse
5ARI	5-alpha reductase inhibitor

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2. RESPONSIBLE PARTIES

INVESTIGATORS

Principal Investigator:

[redacted] PhD, [redacted]

[redacted]

Co- Investigator: [redacted] MD, PhD

Co-Investigator: [redacted] MD

[redacted]

Co- Investigator: [redacted] PhD

Co- Investigator: [redacted] MD

[redacted]

Co- Investigator: [redacted] PhD

[redacted] MD

[redacted]

Co- Investigator: [redacted] PhD

[redacted]

Co-investigator: [redacted] PhD

3. ABSTRACT

Title: 5ARI and Prostate Cancer Mortality Study

Keywords Prostate cancer mortality, BPH treatment, 5ARI

Rationale and background

Results from two clinical trials suggest that the use of 5-alpha reductase inhibitors (5ARI) for benign prostatic hyperplasia (BPH) reduce the risk of prostate cancer. However, in both of these studies, the number of high-grade cancers identified among 5ARI users was increased compared to the placebo group. It remains unknown whether this increase in aggressive disease is associated with an increase in the subsequent risk of prostate cancer death.

Research questions and objectives

The purpose of this study was to evaluate the risk of prostate cancer mortality associated with the use of 5ARIs when compared to the use of alpha-blockers (AB) for treatment of benign prostatic hyperplasia. Secondary objectives included the risk of all-cause mortality, metastatic or prostate cancer mortality as a combined outcome, and the risk of these outcomes associated with long term exposure (2 or more years) and higher doses.

Study design

A retrospective matched cohort and nested case-control study were conducted

Setting

This study identified a cohort of patients in the [redacted] health care systems with long-term follow-up and low attrition rates. Individual patient data from the four participating sites [redacted] and [redacted] was pooled for analysis.

Subjects and study size, including dropouts

Of the 391,107 men who first used BPH medications between 1992 and 2008, men <50 years old (N=54,119) and those who were not members for ≥1 year prior to baseline (N=55,954) were excluded. Men with a diagnosis of prostate cancer prior to drug initiation or within 3 months after initiation or who were taking 1 mg finasteride for alopecia or who had less than 3 consecutive prescriptions for BPH/lower urinary tract symptoms (LUTS) medications were also excluded (N=66,762), leaving 214,272 men eligible for inclusion. These men were then followed via electronic health records from time of their initiation of BPH treatment (earliest date of 1992) through the end of 2010 for death due to prostate cancer. Use of 5ARI and/or alpha-blockers was collected via electronic pharmacy records. Person-time at risk was calculated from the time of 5ARI medication initiation (or index date in AB user) to death due to prostate cancer (event), death due to other causes, loss to follow-up (disenrollment from health plan) or end of

study period. Men who used a 5ARI were matched using risk-set sampling 1:6 to alpha-blocker users on age, race, timing of BPH medication initiation, and prior history of AB use and health plan region. Of the 214,272 eligible men, 73% were successfully matched resulting in an analytic sample of 157,456 men with 174,895 records (18,321 men were matched as both a 5ARI and AB user). Sub-distribution proportional hazards regression was used to estimate the incidence of prostate cancer death comparing 5ARI use to AB use, after adjustment for age, matching factors and other confounding factors and accounting for competing risk of death due to causes other than prostate cancer.

Additionally, a nested case-control study in the unmatched source cohort was conducted. 1671 of the 1684 (99.2%) men who died of prostate cancer in the underlying cohort were defined as case patients and matched 1:10 on age at prostate cancer death, race (African American vs. Other), timing of BPH medication initiation and region to cohort members who did not die of prostate cancer and were alive at the time of the cases' death using risk-set sampling. (N=18,311). Matched odds ratios and 95% confidence intervals were estimated using conditional logistic regression, adjusting for the same covariates as the cohort study except history of AB use, and stratified by cumulative dose and exposure quartiles.

Variables and data sources

All data were abstracted through electronic medical records and historical electronic health plan databases which are comprised in the Virtual Data Warehouse (VDW)and local databases at each study site. These included patient demographics, cancer diagnoses, laboratory data, mortality data, outside medical claims, inpatient and outpatient diagnoses and procedures and pharmacy records. The dates of available data did differ by site and historical databases were used to supplement data available in the VDW. In addition, a National Death Index search was used to capture additional cause of death information as needed.

Results

Prostate cancer was diagnosed in 3.3% of 5ARI users compared to 2.9% of AB users ($p<0.0009$). Among the men diagnosed with prostate cancer who had Gleason scores available (55%), Gleason 8-10 prostate cancer was more common among men who used 5ARI (12%) compared to those who used an AB (9.2%)($p<0.0001$). After multivariable adjustment, 5ARI use was not associated with an increased risk of prostate cancer mortality when compared to taking alpha blockers, taking into account competing risk of death due to other causes (Adjusted SHR: 0.85, 95% CI: 0.72, 1.01; Adjusted MOR: 0.95, 95% CI: 0.78, 1.17).

Discussion

Results from this population-based retrospective cohort study and nested case-control study in general practice settings over 20 years suggest that men who use 5ARIs to treat their BPH are not more likely to die of prostate cancer when compared to men treated with alpha-blockers. While in this study there was an increase in the number of high-

grade tumors diagnosed among 5ARI users, treatment with 5ARIs may not increase the subsequent risk of prostate cancer

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1 Cohort Study	04/15/15	Cohort Report and Analysis	Analyses were updated	Additional exclusion of 924 men put on 5ARI after prostate cancer diagnosis or who were diagnosed with prostate cancer within 3 months of 5ARI initiation; Correction of exclusion error from prior results that accidentally excluded 1266 men who were users for more than 3 consecutive prescriptions
2 Case-control Study	04/15/15	Case-control report and analysis	Analyses were updated	Timing of covariates changed from medication initiation to time of matching (death or index date)
3 All-cause mortality study	9/1/15	All-cause mortality	Analyses were expanded	Analyses were expanded to include time-varying analyses in eligible cohort sample.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	*4/1/13*	*4/1/13*	
End of data collection	*5/1/13*	*4/1/16*	*Additional data pulls were needed for sensitivity analyses*
Registration in the EU PAS register	*6/14/13*	*6/14/13*	
Interim report	*8/31/2013*	*12/4/13*	
Report 1	*11/30/2013*	*4/22/15*	*Reports for the study were generally delayed as a nested case control study was added to confirm the findings from the cohort study*
NLP Validation Report	*1/31/14*	*12/3/14*	
All-cause mortality report	*5/31/14*	*04/9/16*	
Metastatic Report	*11/30/14*	*3/25/16*	
Final report of study results	*5/30/15*	*4/1/16*	

6. RATIONALE AND BACKGROUND

6.1. Background

The potential role of 5-alpha-reductase inhibitors (5ARI) to reduce the risk of prostate cancer by blocking the conversion of testosterone to dihydrotestosterone was the basis for two large randomized controlled trials. The results of the Prostate Cancer Prevention Trial (PCPT) demonstrated that finasteride taken for 7 years compared with placebo reduced the risk of prostate cancer by 25% in men with normal digital rectal exams and prostate-specific antigen (PSA) levels <3.0 ng/ml at baseline. Recent findings from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial again demonstrated that dutasteride, compared to placebo, taken for 4 years significantly reduced the risk of biopsy detectable prostate cancer by 23% in men without prostate cancer at baseline (confirmed by a negative biopsy within 6 months before enrollment) who were at increased risk of developing the disease by virtue of an elevated PSA (2.5-10 ng/ml).

However, there was a greater proportion of high grade tumors (HGT) observed in the 5ARI groups in both studies compared to placebo (Table 1). In PCPT [Thompson , 2003], where biopsies were conducted for cause and an end of study biopsy was offered to participants, tumors of Gleason 7 to 10 were more common in the finasteride group (n =280, 6.4%) than in the placebo group (n =237, 5.1%; P=0.005). (A higher rate of Gleason 8-10 tumors was also observed in PCPT; see Table 1). In REDUCE [Andriole, 2010], where biopsies were protocol mandated at 2 and 4 years as well as conducted for cause, 29 (0.9%) patients were diagnosed with Gleason 8 to 10 tumors in the dutasteride arm, compared with the placebo arm (n =19, 0.6%; p=0.15) over 4 years, with the most pronounced treatment group difference in REDUCE in years 3 and 4 (0.5% versus <0.1%, p=0.003).

In order to answer the question of whether there was a differential risk for HGT (Gleason 8 to 10) among those REDUCE subjects who also had benign prostatic hyperplasia (BPH) at baseline, various post hoc analyses in the REDUCE database have been conducted. The totality of the data resulting from these post hoc analyses is aligned with the overall REDUCE population results and would not suggest a differential risk with dutasteride treatment in those with BPH compared to those with no BPH. Gleason 8 to 10 cancers rates were constant over time in the dutasteride group however an imbalance in Gleason 8 to 10 cancers between dutasteride and placebo was observed in yrs 3 to 4 (higher rates in dutasteride) driving the overall 4 yrs study differences.

However, data from the REDEEM trial, a 3-year study assessing the efficacy and safety of dutasteride in extending the time to progression of prostate cancer, did not show an imbalance in high grade Gleason score tumors at 18 month and 3 year biopsy in the placebo and dutasteride treated groups. There were 2 Gleason score 8 to -10 cancers in the placebo group at 18 months versus 0 in the dutasteride group and 3 versus 2 Gleason score 8 tumors in the placebo and dutasteride treated groups, respectively, at the 3 year biopsy [Fleshner, 2012].

Observational studies have also been conducted examining prostate cancer risk and HGT risk among users of 5ARIs. A cohort of men participating in the screening arm of the

Finnish Prostate Cancer Screening Trial exposed to finasteride or alpha-blockers (tamsulosin and alfuzosin) for the treatment of BPH were followed for the occurrence of prostate cancer. Overall, no significant decreased risk for prostate cancer occurrence was seen in users of finasteride or alpha-blockers in this study, however, the risk of low grade tumors (Gleason 2 to 6) was significantly decreased among finasteride users. In contrast to PCPT, no increased risk of high grade tumors (7 to -10) was found. However, among men using finasteride for ≥4 years, there was an increased risk of high grade (7 to 10) tumors compared to non-users of finasteride and alpha-blockers with a borderline significant p-for-trend across increasing duration of exposure categories (p=0.057) [Murtola, 2016). The current study will allow for an analysis of duration of exposure to extend these findings.

In a recent study by Pinsky et al, prostate cancer survival rates from the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial were used to project prostate cancer mortality based on prostate cancer incidence patterns seen in the REDUCE and PCPT trials. The overall relative risk of prostate cancer mortality comparing treatment to placebo arms was not significantly increased based on projections for patients in the REDUCE or PCPT trials, however mortality rates for those with Gleason scores of 2 to 6 were modestly decreased while mortality rates for those with Gleason scores of 7 and 8 to 10 were modestly increased. These results suggest at most a small increase and potentially a modest decrease in prostate cancer related mortality in the treatment arms of these studies [Pinsky, 2012]. The current study will allow for the real world follow-up of men exposed to these medications over time for the assessment of mortality and will extend these results beyond the framework of hypothetical modeling.

More recently, Azoulay and colleagues evaluated the association between 5ARI use and prostate cancer mortality in men with prostate cancer in the United Kingdom (UK). [Azoulay, 2015]. The results from this study suggest that 5ARIs were not associated with an increased risk of prostate cancer specific or all-cause mortality in men with a new diagnosis of prostate cancer in the UK. Similarly, Preston et al. found that 5ARI use was not associated with lethal prostate cancer in the Health Professional's Follow-up Study, albeit with limited statistical power [Preston, 2014]. Follow-up results from the PCPT suggested that men treated with finasteride were not more likely to die of all causes compared to men randomized to placebo and results from the Finnish Prostate Cancer Screening Trial found no increase in risk of prostate cancer or all-cause mortality associated with 5ARI use in men diagnosed with prostate cancer [Thompson, 2013, Murtola, 2016]. However, these results are difficult to interpret, as prostate cancer is an infrequent cause of death in the overall population, the generalizability of the results are limited by the highly-selected trial populations [Thompson, 2013, Murtola, 2016] and the populations had low exposure rates [Azoulay, 2015, Preston, 2014, Murtola, 2016].

GlaxoSmithKline (GSK) is committed to further investigations to advance the understanding of the benefits and risks of dutasteride. The GSK Avodart™ Team evaluated the appropriateness of an observational study among men who use 5ARIs for symptoms of BPH to measure the risk of incident high grade tumors (HGT) compared to risk in non-users. In consultation with internal and external experts, the team subsequently concluded that such a study would not be feasible: there is no other drug as

a comparator drug that has similar effects on screening, detection, and biology as 5ARIs, resulting in several rate-limiting biases:

- 5ARIs lower PSA levels, potentially differentially affecting prostate cancer screening patterns;
- 5ARIs lower prostate volume, potentially differentially affecting biopsy accuracy;
- 5ARIs are reported to preferentially affect Gleason pattern 3 over pattern 4 and 5 prostate cancer, potentially differentially affecting Gleason score read-out and distribution.

Additionally, based on evidence from REDUCE and PCPT, 5ARIs reduce the risk of prostate cancer occurrence. The outcome of prostate cancer mortality allows for an assessment of whether the relative frequency of high grade tumors among 5ARI versus alpha-blocker users translates into a difference in prostate cancer related mortality. This study assessed the association between 5ARI use and prostate cancer mortality in men treated with BPH medications.

6.2. Rationale

The primary purpose of this study was to assess whether there is an increased risk of prostate cancer mortality associated with the use of 5ARIs in men treated with BPH medications when compared to the use of alpha-blockers in a real-world setting. Since the concern regarding HGTs is their higher aggressiveness potential and risk of poorer disease related outcomes, this study provides evidence as to whether patients who use 5ARIs have a greater likelihood of dying from prostate cancer.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective: Prostate cancer mortality

To assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Secondary Objective: Prostate cancer mortality or metastatic prostate cancer

To assess the risk of prostate cancer mortality or metastatic prostate cancer associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

All-cause mortality

To assess the risk of all-cause mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Long term exposure to BPH medications

To assess the risk of prostate cancer mortality, prostate cancer mortality or metastatic prostate cancer, and all-cause mortality associated with long-term exposure (2 or more years cumulative exposure) to 5ARIs, with or without alpha-blockers, compared to alpha-blockers in the subset of men using long term BPH treatment.

Additional descriptive analyses:

To evaluate the validity of classifying prostate cancer deaths with the developed electronic algorithm as compared with those identified based on cause of death coding.

To evaluate the validity of identifying cases of metastatic prostate cancer with the developed electronic algorithm as compared with those identified based on medical record abstraction.

To describe the occurrence of prostate cancer in men treated with BPH medications and across treatment groups (5ARIs and alpha-blockers).

To describe the occurrence of metastatic prostate cancer in men treated with BPH medications and across treatment groups.

To describe the occurrence of cardiovascular related mortality in men treated with BPH medications and across treatment groups.

To describe PSA testing patterns across treatment groups after treatment initiation and over the course of the study period.

To describe across treatment groups the frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.

To describe across treatment groups Gleason Score and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.

8. RESEARCH METHODS

8.1. Study design

The study used a retrospective cohort design with data from four [redacted] sites collected from electronic health records and data abstracted from paper records from 1992-2010. Men treated with benign prostatic hyperplasia (BPH) medications; 5-alpha reductase inhibitors (5ARIs) (with and without concomitant and/or previous alpha-blocker use) were compared to men treated with alpha-blockers. The main objective of this study was to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications. This study also assessed a number of secondary endpoints including a nested case-control analysis, the combined endpoint of prostate cancer mortality or metastatic prostate cancer, and all-cause mortality, as well as a number of descriptive analyses.

8.2. Study Population and Setting

The primary analysis for this study was a retrospective cohort study from 1992-2010 using data from 4 [redacted] sites: [redacted] and [redacted] This study identified a cohort of patients in the [redacted] health care systems with long-term follow-up and low attrition rates. Individual patient data from the four participating sites [redacted] and [redacted] was pooled and analyzed with [redacted] acting as the central data-coordinating center. [redacted] also performed all data analyses for this study. The inclusion of patient data from multiple sites was to ensure a sufficient number of prostate cancer deaths to obtain a suitably precise and clinically meaningful estimate of risk.

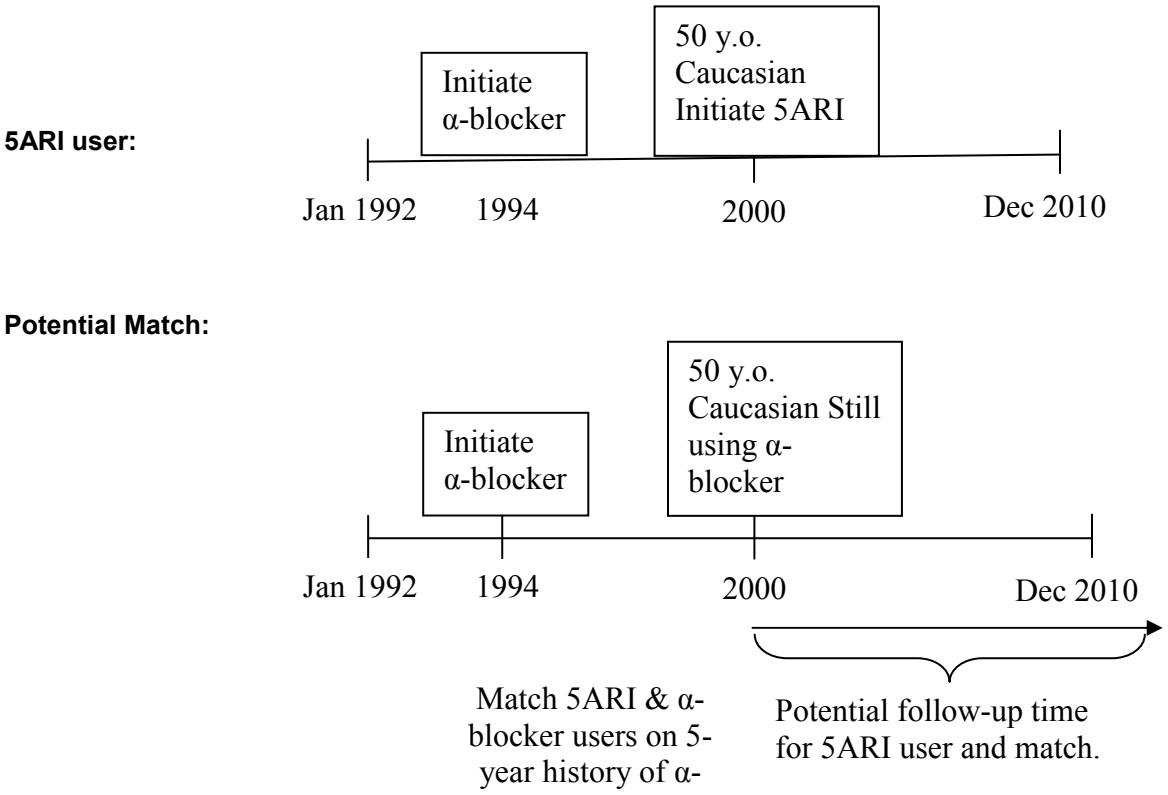
All men age 50 years and older treated with a BPH medication (5ARI and/or alpha-blocker) were eligible for inclusion. Participants were not required to have a BPH diagnosis at the time of their first 5ARI or alpha-blocker prescription as based upon data from a feasibility assessment approximately half of all men received their first recorded BPH diagnosis after initiating treatment. Furthermore, approximately 25% of participants treated with 5ARIs or alpha-blockers did not have a diagnosis code for BPH in their medical record. BPH diagnosis codes were not used in a consistent way historically in the [redacted] data. Men were required to have coverage within the healthcare system for at least 1-year before their first BPH medication prescription. Men with a history of prostate cancer or who developed prostate cancer within <3 months of starting their BPH medication were not eligible for inclusion.

Matching Strategy as Described in Analytic Plan

The ratio of 5ARI users to alpha-blockers users was 1:5.4 in the feasibility study.

5ARI users were selected from the available pool of eligible men and were matched in a ratio of 1:5 or 1:6 with alpha-blocker users to yield an overall matching ratio of 1:5.4. Matching factors included age (±1year), race (African American vs. Other), region, BPH medication initiation year (±1 years) and duration of prior use of alpha-blockers (see the matching diagram below).

5ARI patients initiating BPH treatment with a 5ARI (i.e. having no prior use of alpha-blockers) were matched to alpha-blocker users having the same time (±1 year) of alpha-blocker treatment initiation. Matching was conducted within [redacted] site [redacted] When a suitable match could not be found within a site, matching across sites to maximize the available sample for the study was used.



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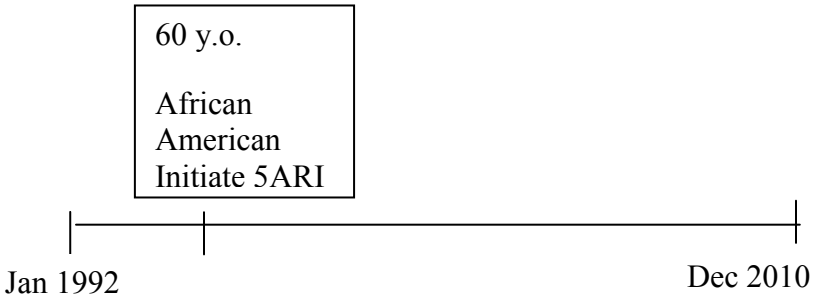
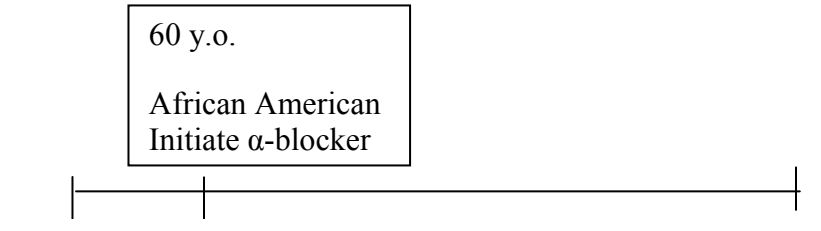


Potential match:



Matching Approach

Potential follow-up time for 5ARI user and match.

Eligible matches for 5ARI users were defined based on their medication exposure at the time of 5ARI initiation. For example, a patient initiating 5ARI medication in 1995 had a pool of potential matches that included all men not previously exposed or currently taking 5ARIs in 1995. Therefore a patient taking an alpha-blocker in 1995 who added a 5ARI in 1999 was an eligible match for the 5ARI user as in 1995 as they have not yet been exposed to 5ARIs. When this alpha-blocker patient initiated 5ARI therapy in 1999, their follow-up time was censored.

The risk-set sampling of "controls" allows for an equal opportunity of the comparison groups to be exposed to 5ARI and does not condition on future use of a 5ARI. In this situation, an alpha-blocker user is eligible to be selected and matched to a 5ARI user up until he starts a 5ARI, at which time he would be matched to another alpha-blocker user.

An existing, widely used SAS macro developed by the Mayo Clinic was used to operationalize the matching. Greedy matching was employed using this macro. [Bergstralh, 1995].

INCLUSION CRITERIA:

- Male
- A new prescription for BPH medication (5ARI and/or alpha-blocker) in 1992 or later that was identified as appropriate treatment for BPH/lower urinary tract symptoms (LUTS) from the [redacted] National Pharmacy guidelines
- Treatment with BPH medication must have been initiated prior to Jan. 1, 2008.
- Age 50 years or older at time of treatment with 5ARI or alpha-blocker.
- At least 1-year of coverage in the healthcare system before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- At least 3 consecutive prescriptions (90 days of supply) for a BPH medication (5ARI and/or alpha-blocker)
    - 5ARI users must have had at least 3 consecutive prescriptions for 5ARI

EXCLUSION CRITERIA:

- Diagnosis of prostate cancer any time before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- Diagnosis of prostate cancer within 3 months after BPH medication initiation(5ARI and/or alpha-blocker)
- Patients treated with finasteride 1mg prior to BPH medication.
- Less than 3 months cumulative exposure or less than 3 consecutive prescriptions, and less than 3 consecutive 5ARI prescriptions among men exposed to 5ARIs.

Exposure was based upon the treatment administered for BPH. The assumption that prescriptions for either a 5ARI or alpha-blocker are in fact for 30 days of supply was checked. The distribution of duration of prescriptions for the drugs included as exposure variables was examined to determine whether or not this inclusion criterion needed to be modified.

We found that using dispense days to define the prescription lengths instead of 3 consecutive dispenses was more accurate because some men had 90 day prescriptions for these drugs, rather than 3, 30 day prescriptions. This allowed us to identify all of the men who may have been using these drugs for shorter than 90 days or 3 30 day prescriptions. The median supply days were 100 days prior to matching, with the 5th percentile at 30 days. We identified 12,103 men who had 1 prescription with the length between 31 days and 90 days, which further confirmed that using dispense days was the best approach. Thus the decision was made to limit the eligible cohort of men to those who had at least 3, 30 day or two 90 day prescriptions of a BPH medication.

Medications

The following medications were included in the analysis and the data were queried using medication name (brand and generic): 5ARI(s): Finasteride (5mg) or Dutasteride

Including Combination Treatment: Jalyn™ (fixed dose combination with tamsulosin), or any combination of 5ARI & alpha-blocker either concurrently or consecutively. Jalyn was not launched until 2010. So, this medication was included to capture any patients who have initiated BPH therapy prior to 2008 and switch to fixed dose combination therapy over the course of the study.

Use of medications indicated for androgenic alopecia (Finasteride 1mg) were identified in the data source to allow for exclusion of patients treated for alopecia before the initiation of treatment for BPH.

Selective alpha 1 blocker (s)/alpha-adrenergic blocking agent(s): Alfuzosin, Doxazosin, Silodosin, Tamsulosin, Terazosin. Prazosin was indicated for BPH treatment according to [redacted] formulary during the study period, but is not currently indicated. We examined the utilization of Prazosin over the study period and determined that patients taking this medication should be included in the analysis as 34.6% of them used Prazosin during the study period.

The full list of medications and corresponding doses are included in the Appendix in Table 18

Exposure Categories

Primary Analysis:

Any 5ARI use including patients with concomitant or consecutive alpha blocker use.

8.2.1. Exposure Duration

Duration of exposure among all 5ARI or alpha blocker users began at the start of the follow up time for each patient and was categorized as: Any exposure, <1 year, 1 to <2 years, or 2 or more years

Cumulative Exposure:

Drug era was defined for each eligible man: When the days of drug supply was available, this info was used to determine whether drug use between two adjacent prescriptions was continuous;

- When the days of drug supply was NOT available, we assumed the average prescription cycle as 30 days.

If the gap between two prescriptions was <=30 d, it was counted as continuous, as one drug era. Otherwise, it was assumed there was a gap, and another drug era was started after the gap.

Duration of one/each drug era (for each drug or drugs): If the adjacent prescription periods did NOT overlap: drug era = From 1st prescription date to "last prescription date + days of drug supply for the last prescription (30 d, if not available)" or the end of observational period, whichever comes first.

If the adjacent prescription periods DO overlap: drug era = From 1st prescription date to "last prescription date + days of drug supply for the last prescription (30 d, if not available)" or the end of observational period, whichever comes first + days of overlap (not double counting any days).

Duration of cumulative exposure = (Duration of exposure for drug era 1) + (Duration of exposure for drug era 2) + (….) + (last drug era)

8.2.2. Outcome definitions

Prostate cancer death

The primary outcome in this study was prostate cancer related mortality. Prostate cancer related mortality was first assessed using cause of death codes from [redacted] electronic health files, state death records, and Social Security Index records.

Standard matching algorithms were used that take into account name, last known address, date of birth and Social Security Numbers (when available) to identify [redacted] members in state death records, and Social Security Index files. The mortality files contain, but are not limited to, the following fields: medical record number, date of death, place of death, and International Classification of Diseases (ICD)-9 and ICD-10 coded underlying cause of death. Underlying cause of death was used for the analyses.

The National Death Index (NDI) mortality data was also used to supplement cause of death information where [redacted] was unable to capture it through their existing systems. NDI is a central computerized index of death record information on file in the state vital statistics offices maintained by the Centers for Disease Control. The NDI includes a national file of identifying death record information compiled from computer files submitted by State vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year. NDI Plus searches provide cause of death codes and are available through 2010 currently (2011 will become available Spring 2013). Three groups of participants were identified and sent to the CDC for a NDI match:

All men (regardless of prostate cancer status) in the sample that died prior to or on 12/31/10 who are missing underlying cause of death info.

All men (regardless of prostate cancer status) in the sample that left [redacted] alive but died on or before 12/31/10 without underlying cause of death.

Men with prostate cancer diagnosis who left [redacted] alive without a death date (up to May 2013) who we do not know are dead. For those men who died after the study end date, these deaths were included in the analysis and they will be censored at the end of the study period (December 31, 2010).

Any deaths determined to be associated with prostate cancer based on information available in NDI will be assigned to the appropriate treatment group based on treatment

information available in [redacted] up until patients left the system. All deaths among men with prostate cancer were divided into 4 groups based on coding from death certificates (underlying cause of death): Cardiovascular disease (CVD) related, Prostate cancer related, other causes likely related to prostate cancer (to be defined based on the [redacted] algorithm and clinical expertise), or deaths not due to the above stated causes of death.

Prostate cancer mortality data for the primary analysis

- Deaths identified via the National Death Index are added into the sample and deaths that occurred after loss to follow-up but before the end of the study period were counted as events.
    - In the matched cohort, 4855 men were sent to the NDI. Of them 3124 were sent for missing cause of death and 1731 were sent because they were lost to follow-up during the study period.
    - 82% of the 4855 were identified in the NDI database and 56% of these were identified as dead with high certainty.
    - We identified a cause of death for 91% of the 3124 that were missing this initially.
    - 10% of those who were lost to follow-up were identified as dead in the NDI database.
    - We therefore gained an additional 117 deaths (regardless of cause) and 56 additional prostate cancer deaths, giving us **1053** prostate cancer deaths after matching.
- Included in the 1053 prostate cancer deaths are 121 deaths that occurred after the men were lost to follow-up but before the end of the study period.

8.2.3. Confounders and effect modifiers

Information on potential confounders was collected in the 1 year pre-treatment initiation period for all outcome analyses. Age, race, and family history of prostate cancer are the only consistent risk factors for prostate cancer incidence and prostate cancer death based on the published literature. While obesity, diet, exercise, and socioeconomic status have been associated with risk of prostate cancer and prostate cancer death, a clear causal relationship between these risk factors and prostate cancer has not been established [Brawley, 2012]. Matching by age and race in the design phase of this study helped to address potential confounding by these important risk factors. It was not possible in this study to control for family history of prostate cancer as this variable was not systematically collected by [redacted] The relative frequency of variables known to be independent risk factors for the outcomes of interest was compared between the 5ARI and alpha-blocker treatment groups. In addition to the adjustment for age, any imbalance in any of the independent risk factors across the two treatment groups were considered for inclusion in the Cox proportional hazards models or as stratification variables.

Pre-treatment covariates

The following pre-treatment variables were summarized based on the 1-year pre-treatment period for all study participants. Pre-treatment variables were considered for inclusion in proportional hazard regression models and as stratification variables based on either their a priori known association with both the exposure and outcome or the association with both in this data.

Race/Ethnicity: Race and ethnicity was collected across sites and based on a race and ethnicity variable that is categorized as: Non-Hispanic White, African American, Asian and Hawaiian/Pacific Islander, Native Alaskan/American Indian, Multiple, and Unknown.

Age at treatment initiation: Age was calculated from date of birth and reflected as age at treatment initiation.

Socioeconomic status (SES): Aggregate SES measures for [redacted] members were calculated via geocoding using 2000 US census estimates at the block, block-group, tract and ZIP level and include income and education.

PSA: PSA was available through our laboratory data in the Virtual Data Warehouse and was measured in ng/mL. Baseline PSA was defined as a PSA one year prior to or within 1 month following BPH medication initiation.

BMI: Body mass index (BMI) was not routinely collected as a vital sign until the implementation of the electronic medical record in each site (mid 2000s) Therefore, only a few years of complete data were available. It was calculated using standard formula and measured in kg/m2.

- Due to the paucity of BMI data, it was only used in sensitivity analyses where the effect of BMI on the association of interest was investigated.

Charlson Comorbidity Index: Charlson comorbidity Index was collected based on ICD-9 codes of the included conditions/complications and a standard algorithm and coding macro were used to derive the score which is usually categorized into (0, 1 or 2+).

CVD Endpoints

• History of cardiovascular disease: ICD-9 410.x-429.x

• History of high blood pressure/hypertension: ICD-9 codes (401.x) and/or dispense of blood pressure medications

• History of diabetes (Healthcare Effectiveness Data and Information Set [HEDIS] definition): dispensing record for insulin or an oral hypoglycemic from the HEDIS list (not including metformin) or any discharge ICD-9 code of 250.xx, 357.2, 362.0, 366.41, 648.0, or hemoglobin A1C >=7.0%.)

• History of hyperlipidemia : Any dispense of statin medications and/or any abnormal lipid profile test: Total cholesterol (>200 mg/dL), HDL (<=40 mg/dL), LDL (>130 mg/dL), Triglycerides (>150 mg/dL)

History of Cancer – Other than Prostate: History of cancer at major sites other than the prostate was determined by cancer and tumor registry records of diagnoses.

Potential confounding factors over the follow-up period:

Additionally information on several variables occurring over the follow-up period were collected including:

- PSA testing patterns after treatment initiation and over the course of the study period.
- The frequency of prostate biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.
- Gleason Score at diagnosis
- Frequency of prostate cancer treatment paradigms (radical prostatectomy, external beam radiation, brachytherapy, cryotherapy, etc.)

Potential effect measure modifiers for consideration:

- Race/ethnicity
- Age
- Socioeconomic status (income)
- Baseline PSA level

8.3. Data Sources

[redacted] **Regional Overviews**

[redacted] is an integrated health care system that provides comprehensive health services in 8 regions nationwide. Data from four of the larger [redacted] sites: [redacted] were used in this study. Taken together, these four sites bring racial, ethnic, and geographic diversity to this study. They serve approximately 3.25 million residents of [redacted] 3.3 residents in [redacted] 535,000 residents in [redacted] and 477,932 residents in the metropolitan [redacted] area. These are the sites with the most extensive experience in identifying and classifying cancer patients and they have the most experience in extracting and analyzing cancer-related treatments, costs and outcomes as they all participate in the National Cancer Institute (NCI) funded Cancer Research Network (CRN). [redacted] and [redacted] are part of the SEER Tumor Registry system and participate in their respective state tumor registries. [redacted] and [redacted] have accredited tumor registries covering their memberships, and participate in their respective state tumor registries. The majority of adult ambulatory cancer care services, including surgery, infused/injected chemotherapy services and radiotherapy are

provided at health plan owned facilities, and all four sites purchase pharmaceutical products under the same national contract and employ similar formularies.

Complete data on chemotherapy (including oral as well as injected and infused agents) was available and extractable at all of the participating sites. [redacted] successfully transitioned to an electronic health record system to support further population and clinical care management at the bedside. The information contained in these electronic records is routinely extracted for research purposes. Thus, information on virtually all aspects of care delivered is captured and retrievable for the proposed research. All of the sites employ the EpicCare® electronic medical record (EMR) system. The EMR systems capture electronically all patient care contacts in the outpatient setting using a controlled medical terminology (based upon ICD-9 and CPT-4 code systems) to document patient assessments, services ordered, and services provided.

Data Availability from Electronic Health Records and Medical Chart

The primary data source for the [redacted] sites was extracted from the Virtual Data Warehouse (VDW). The VDW was originally established by the CRN with funding from NCI for efficient collaboration and pooling of automated data across sites using a standard data formats and definitions. The VDW is virtual in that it is a distributed data system where the health plans retain local control of their data, but a programmer at one site can write a program than can be run at all sites. Using the VDW, standardized automated data on patient characteristics including demographics (age, race, ethnicity, vital status), health plan enrollment, SEER-compatible tumor characteristics (stage and histology), and variables noting the type and date of treatment received (surgery, radiation, chemotherapy, and hormone treatment obtained from tumor registries) can be extracted. In addition, recurrence (local or distal) and date of recurrence are abstracted fields in [redacted] and [redacted] tumor registry files. For [redacted] and [redacted] natural language processing was used to search electronic chart information to find evidence of metastases. Utilization files include automated clinical data associated with inpatient and outpatient encounters, types of procedure and diagnostic codes including International Classification of Diseases (ICD-9) codes for procedures and diagnoses, or HCFA Common Procedure Coding System (HCPCS) codes for procedures. Measures of socioeconomic status are also available via the VDW Census data files where enrollees' residential addresses are mapped to census block data using geocoding software.

Extensive data are available through electronic medical records and historical electronic health plan databases which are comprised in the VDW. Specific to this study, in the VDW, the following was available: cancer diagnoses going back to 1988, outpatient and emergency room diagnoses and procedures from 1994, laboratory data from 1994 on, mortality data from 1988 on, outside claims from 1990 on, inpatient and outpatient diagnoses and procedures from 1994 to current and pharmacy records from 1992 on. The dates of available data in the virtual data warehouse shared across [redacted] sites are shown in the table below. There was the availability to go further back in historical databases across sites and any data that was needed that was not available electronically were abstracted.

Data currently available in the [redacted] Virtual Data Warehouse

Data System	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy	1992-	1995[1]-	1986-	1992-2012
Mortality Underlying cause Multiple causes	 1988-2010 1988-2009	 1966-2010 1966-2009	1990-current[2] 1990-current[2]	1990-2011[2] 1990-2011
Laboratory	1992-	1988-	1993[3]-	1994 *
Tumor Registries	1988-2009	1974-June 2011	1960-	1987-2011
Utilization, Diagnoses and Procedures	1981-	1995[1]-	1994-	1994-2012

[1]Phased in starting in 1991
[2]Based on tumor registry variable identifying men died of prostate cancer
[3]Earlier data available via archived files and paper records.
*At [redacted] Lab procedures are available for 1994 forward. Lab results are available from 2000 forward. PSAs are available back through 1997.

[redacted] Mortality Data

Death information was derived from several sources. Membership files track notices of active members' deaths. This is most complete when the death occurs at a [redacted] facility. Two external sources are used in addition, the state death records and Social Security Index records. Standard matching algorithms were used that take into account name, last known address, date of birth and Social Security Numbers (when available) to identify [redacted] members in these two files. Cause of death codes are assigned by the State mortality registries and follow standard National Center for Health Statistics algorithms. The state death records lag about 14 months for date and underlying cause of death and between two and three years for all causes listed on the death certificate. The mortality files contain, but are not limited to, the following fields: medical record number, date of death, place of death, and ICD-9 coded underlying cause of death.

National Death Index

The National Death Index (NDI) mortality data was used to supplement cause of death information where [redacted] is unable to capture it through their existing systems. NDI is a central computerized index of death record information on file in the state vital statistics offices maintained by the Centers for Disease Control. Working with these state offices, the National Center for Health Statistics established the NDI as a resource to aid epidemiologists and other health and medical investigators with their mortality ascertainment activities. The NDI includes a national file of identifying death record information (beginning with 1979 deaths) compiled from computer files submitted by State vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year. NDI Plus searches provide cause of death codes and are available through 2010 currently (2011 will become available Spring 2013). For known descendants, the CDC charges a flat fee of $5.00 per record for processing, regardless of the number of years processed.

[redacted] submitted a NDI application form to NCHS. After approval, [redacted] submitted the data from all regions which included subjects' names, social security numbers, dates of

birth, and related information to NCHS on diskette or CD-ROM. Once received, the NDI mailed a password protected CD with the match results to [redacted] along with the original CD. Analysts at [redacted] then followed the NDI's suggested algorithm for determining true matches and merged this data with the existing analytic data set from all regions.

Pharmacy Data

Drug exposure data was derived from the Pharmacy Information Management System or PIMS, as similar systems are used in all [redacted] sites. All [redacted] facilities pharmacies are now connected via a central data processing operation to a pharmacy database. Records include the patient's unique medical record number, the drug name and strength, NDC code, the drug class, treatment regimen, date dispensed, prescribing physician and department and days' supply. Information enters the system at the time prescriptions are processed by the pharmacy and virtually 100% of dispensed prescriptions are captured, as it is a "real-time" system used to generate the label attached to packaging (e.g., tube, drug container) provided the patient. Information from PIMS is available in the VDW, but may not go back to 1991 for all sites. Data available in the VDW was supplemented with electronic files (as needed).

Cancer Registries

[redacted] and [redacted] are part of the SEER Tumor Registry system and participate in their respective state tumor registries. [redacted] and [redacted] have accredited tumor registries covering their memberships, and participate in their respective state tumor registries. The cancer registry database in the VDW contains information on patients who were diagnosed at [redacted] hospitals, or who received at least part of their first course of treatment for cancer at a [redacted] hospital, for all reportable cancers. Variables found in the Regional database can be grouped in the following general categories: 1) Patient Identification (name, sex, date of birth [DOB], race, medical record number [MRN], social security number [SSN], etc.); 2) Case Identification (type of case, hospital of diagnosis, date of diagnosis); 3) Tumor Information (site, histology, stage, size, lymph node involvement, markers, etc.); 4) Treatment Methods (types and dates of treatment); and 5) Follow-up (vital status, date of last contact or death, tumor status, and cause of death). In addition, [redacted] collects survival information acquired through an aggressive follow-up program that achieves a more than 95 percent retention rate. Because the [redacted] and [redacted] Cancer Registries report to SEER and the [redacted] and [redacted] tumor registries are certified by the NCI, the registry data are 99% complete for both inpatient and outpatient admissions for the diagnosis of new and prevalent cancers. While cancer diagnosis information is available through both the cancer registry and electronic medical records, information regarding the diagnosis and initial treatment of cancer are pulled from the cancer registry. This is because it is a more complete data source, as cancer diagnoses are not systematically recorded in the electronic charts.

Laboratory data

Laboratory data from all four participating [redacted] sites was available in the VDW going back to at least the mid-1990s for all sites. This system tracks both inpatient and outpatient laboratory orders and results. Records include the patient's unique medical record number, the laboratory test name and procedure codes, date drawn, units,

references ranges, whether the test was abnormal, ordering physician information, and facility information and the lab test results.

8.4. Study size

Sample size considerations

Power calculations done before the start of the study

Assuming a hazard ratio of 1.0, 90% power and a 0.05 two sided alpha we needed approximately 850 deaths to rule out a hazard ratio of 1.25 or higher. This calculation was based on equation 2 in the article by Saville et al [Saville, 2011] and assumes a 1:1 ratio of patients across treatment groups. A 25% increase in risk of prostate cancer is thought to be a signal of concern. While this study is designed to detect any difference (increase or decrease) in risk between 5ARI and alpha-blocker users, given the potential limitations of power in this study, if a difference in risk is not found between the exposure groups, this will not be interpreted to rule out an increased risk of prostate cancer related mortality associated with the use of 5ARIs. If no increased risk is found for 5ARI users compared to alpha-blocker users, this result will add to the body of evidence used to interpret the findings from the REDUCE trial of an increased number of HGTs in the dutasteride arm compared to the placebo arm.

Based on the feasibility assessment using [redacted] data, the allocation of patients across treatment groups (alpha-blocker:5ARI) is expected to be 5.4:1. With this unequal allocation of patients in the exposed and unexposed groups an adjustment was made to the sample size calculation. Using the adjustment suggested by Saville et al with the same assumptions for power, approximately 1,500 prostate cancer related deaths (214 in the 5ARI exposed group and 1,286 in the alpha-blocker only group) are needed to rule out a HR of 1.25 or higher. This calculation assumes a 6:1 allocation of unexposed (alpha-blocker) vs. exposed (5ARI) and equal risk in both exposure groups.

Additionally, sample size calculations have been performed assuming power of 80% and 85%. Under the scenario of 85% power, and a 0.05 two sided-alpha 1262 deaths are needed to rule out a hazard ratio of 1.25. Under the scenario of 80% power, and a 0.05 two sided-alpha approximately 1099 deaths are needed to rule out a hazard ratio of 1.25.

Power	Allocation ratio of 5ARI users to alpha blocker users	Number of prostate cancer related deaths
90	1/5	1314
	1/6	1474
85	1/5	1125
	1/6	1262
80	1/5	980
	1/6	1099

8.5. Data Management

8.5.1. Data transformation (Data handling conventions)

Details are included in Section 8.6 Data Analyses.

8.5.2. Resourcing needs

[redacted] Institutional Involvement

Dr. [redacted] and [redacted] were in charge of overseeing all aspects of this study at [redacted] including the drafting of study documents, data abstraction, analyses and interpretation, development of the cause of death algorithm, chart reviews and validation of the algorithm, preparation of study report and manuscripts and management of the study staff. Our study biostatistician, [redacted] was primarily responsible for the abstraction, programming, transferring and analysis of all data. She worked directly with the site programmers to facilitate the secure data transfers between sites. A data use agreement was executed to facilitate the transfer of data from the three [redacted] sites to [redacted] Data transfers between sites and the Data Coordinating Center used standard encryption software. All file transmissions used 128-bit encryption software (e.g. WinZip v 9.0, Mansfield, CT) and whenever possible, through virtual privacy network (VPN) connections. Identifiable data was maintained within site firewalls. Programming and analytic staff used file transfer protocol (FTP) programs on specific servers that reside in the "DMZ" outside the firewall.

All sites maintained data in a secure manner. Subjects were assigned a random unique number for an identifier and all forms were kept in locked storage cabinets. For electronic records, minimal identifying information was kept in files. Access to these files was password protected and all access logged. There were full back up of study data files made at regular intervals, with copies of complete backup files stored offsite in secure facilities, with updates stored at regular intervals. In addition, final analytic data sets will be archived according to a predefined procedure.

8.6. Data analyses

8.6.1. Essential analyses

Primary analyses

Cohort Study

Matching Iterations and Results

In the first interim version of this Report, a matching attempt was made as outlined in the statistical analytic plan which employed risk-set sampling. However, this left greater than 25% of the 5ARI users unmatched. It was then decided to first relax the drug use year criteria to ± 3 years, which still left 23% of the 5ARI users unmatched (Attempt 1). Next, the age criteria was relaxed to ± 2 years, which still left 24% of 5ARI users unmatched (Attempt 2). Then, a decision was made to drop the drug use year requirement completely as it was felt this was the weakest of the matching criteria. This then left 20% of the cases

unmatched (Attempt 3). Then, the birth year was again relaxed to ± 2 years, with within region matching, which did not result in any more matched 5ARI users (Attempt 4). When across region matching was applied, 18% of 5ARI users were unmatched (Attempt 5). Finally, when the race categories were collapsed comparing African American to all others and within region matching was applied, 19% of the 5ARI users were unmatched (Attempt 6). Finally, when across region matching was used with these same criteria, 16% of the 5ARI users were unmatched. (Attempt 7)

Matching Iteration Results

Attempt 1: Within region match on race, age ± 1year, and drug use year ± 3year

Region	Cases	Unmatched	% of Total	Matched to <6 Controls	% of Total	Fully matched (1:6)	% of Total
[redacted]	1502	247	16	174	12	1081	72
[redacted]	17837	4161	23	554	3	13122	74
[redacted]	2249	631	28	270	12	1348	60
[redacted]	14339	3182	22	717	5	10440	73
Total	35927	8221	23	1715	5	25991	72

Attempt 2: Within region match on race, age ± 2 year, and drug use year ± 1year

Region	Cases	Unmatched	% of Total	Matched to <6 controls	% of Total	Fully matched (1:6)	% of Total
[redacted]	1502	272	18	220	15	1010	67
[redacted]	17837	4296	24	596	3	12945	73
[redacted]	2249	636	28	311	14	1302	58
[redacted]	14339	3528	25	730	5	10081	70
Total	35927	8732	24	1857	5	25338	70

Attempt 3: Within region match on race, age ± 1year, eliminate drug use year

Region	Cases	Unmatched	% of Total	Matched to <6 controls	% of Total	Fully matched (1:6)	% of Total
[redacted]	1502	234	16	108	7	1160	77
[redacted]	17837	3955	22	296	2	13586	76
[redacted]	2249	629	28	163	7	1457	65
[redacted]	14339	2372	17	337	2	11630	81
Total	35927	7190	20	904	3	27833	77

Attempt 4: Within region match on race, age ± 2year, eliminate drug use year

Region	Cases	Unmatched	% of Total	Matched to <6 controls	% of Total	Fully matched (1:6)	% of Total
[redacted]	1502	232	15	79	5	1191	79
[redacted]	17837	3969	22	220	1	13648	77

[redacted]	2249	650	29	115	5	1484	66
[redacted]	14339	2380	17	225	2	11734	82
Total	35927	7231	20	639	2	28057	78

Attempt 5: Across region match on race, age ± 2 year, eliminate drug use year							
	Cases	Unmatched	% of Total	Matched to <6 controls	% of Total	Fully matched (1:6)	% of Total
Total	35927	6491	18	612	2	28824	80

Attempt 6: Within region match on whether race being AF, age ± 2year, eliminate drug use year							
Region	Cases	Unmatched	% of Total	Matched to 6 controls	% of Total	Fully matched (1:6)	% of Total
[redacted]	1502	191	13	50	3	1261	84
[redacted]	17837	3812	21	144	1	13881	78
[redacted]	2249	628	28	89	4	1532	68
[redacted]	14339	2197	15	133	1	12009	84
Total	35927	6828	19	416	1	28683	80

Attempt 7: Across region match on whether race being AF, age ± 2year, eliminate drug use year							
	Cases	Unmatched	% of Total	Matched to 6 controls	% of Total	Fully matched (1:6)	% of Total
Total	35927	5711	16	394	1	29822	83

After these 7 iterations of matching were completed, we investigated which of the matching components was causing men to remain unmatched. After assessing this by looking at the distribution of the matching variables by region, we determined that history of prior alpha blocker (AB) use was the principle issue. The majority of 5ARI users who were not matched had long histories of AB use and there were not enough AB users with similar histories to whom they could be matched successfully. Based on these findings, the study team made the decision to go forward with the following matching criteria, dropping history of AB use as a matching variable:

- Race: African American vs. other
- Age: ± 2 years
- Region: within and then across
- BPH Medication initiation Year (± 2 year)

We next attempted to match on these criteria and not include history of AB use to achieve a higher matching rate. However, we could not use the risk-set matching macro without the history of AB use as it requires a time component. Therefore, to operationalize this

matching, we performed a sequential matching approach, which was presented in the second revisions at a meeting in [redacted] in February.

1. Starting in 2010 and working backwards, matching was done within each year to find eligible controls among the pool of men who were not previously matched the year before.
2. Using this approach, controls were AB users only.

This matching approach performed better among 5ARI users, successfully matching 90% of them, but only 80% of AB users were successfully matched, yielding an overall unmatched rate of 17%. The study team then decided that since this approach did not perform better in terms of successfully matching more men overall and potentially created bias through the use of sequential matching, we would return to using our original a priori risk-set sampling matching approach as outlined in the statistical analysis plan.

Therefore, for this report, men were matched using risk-set sampling as mentioned above and matched on the following factors:

- Race: African American vs. other
- Age: ± 2 years
- Region: within and then across
- BPH Medication Initiation Year (± 2 year)
- History of prior AB use

This matching resulted in successfully matching 73% of the overall cohort, leaving 55,612 men unmatched. Of the 29,944 5ARI users in the overall cohort, 86% of them were successfully matched as 5ARI users. Of the remaining 14% (n=4230) that were not matched as 5ARI users, the majority (96%, n=4075) were matched as AB users prior to the initiation of their 5ARI, leaving only 4% (n=155) who were not matched as either an AB user or 5ARI user.

A sensitivity analysis, using a case-control study was also performed to maximize the number of prostate cancer deaths included since it is a rare outcome and as a source of comparison to the cohort results.

Overall Approach to Primary Statistical Analyses

Continuous variables were compared using two-sample *t*-statistics, variance ratios, and /or standardized differences in percent for each variable. The standardized difference in percent is defined as the mean difference as a percentage of the average standard deviation: $$\frac{100(\bar{x}_c - \bar{x}_t)}{\sqrt{\frac{(s_c^2 + s_t^2)}{2}}}$$

Where for each covariate $\bar{x}_c$ and $\bar{x}_t$ are the sample means in the alpha-blocker and 5ARI groups, respectively, and the s_c^2 and s_t^2 are the corresponding sample variances. The variance ratio is defined as s_c^2 / s_t^2. Significant differences based on the two sample *t*-

statistics, variance ratios that are larger than 1.5 or less than 0.66, or standardized differences larger than 20% would indicate that there is substantial imbalance between the two groups for that variable. Ideally, there would be no significant *t*-statistics, all variance ratios would be between .8 and 1.2 and standardized differences in percent would be less than 10% if the two groups were well balanced (as would be the expectation if they had been randomized).

For categorical/binary variables we compared chi-square statistics and observed proportions by treatment group. Significant differences based on chi-square statistics or large differences in observed proportions suggested that there was an imbalance between the groups on the variables being examined.

Once the 5ARI patients were matched to alpha-blocker patients on the matching variables (age, race, region and duration of prior use of alpha-blockers), the appropriate statistics described above were calculated to confirm that indeed the groups were successfully matched on these characteristics. The success of the matching was further assessed based on whether balance between the treated and control groups was achieved in the matched samples.

Additionally, background characteristics (including cumulative exposure time, follow-up time, follow-up time after cancer diagnosis, and potential pre-treatment initiation confounding factors) were compared between the groups to identify whether there were variables that needed to be considered in the outcome analyses as covariates.

Modeling approach

Person-time calculations

Patients included in the analysis had their survival outcome determined as follows. All patients who died from prostate cancer were considered as events. Patients who died from other causes or who were lost to follow-up (left the [redacted] system) before the end of the study period were coded as censored at the time of death or loss to follow-up. End of follow-up for patients who were alive and were not lost to follow-up or did not die during the study period was the end of study date. In the situation where men died after they had been lost to follow up but before the end of the study period as identified from the National Death Index or Social Security Index matches, they were considered events but their person-time ended at their point of disenrollment. A sensitivity analysis was performed to determine if the inclusion of these deaths changed the association of interest or if the association changed when their follow-up time ended at the time of their death (it did not). Also, because these men did not have complete records up until the time of their death, they were not passed through the cause of death algorithm in the algorithm-based analyses.

- Person-time was calculated from time at which the participant was matched (i.e started a 5ARI prescription and corresponding index date in AB user) up until the time of the event, censoring or end of study period.

Bivariate statistics and comparisons

Next, we examined pre-treatment assignment characteristics such as prior co-morbidities for each treatment group as well as pre-treatment characteristics and prostate cancer related information for those using 5ARI monotherapy and those using 5ARI+alpha-blocker.

Then we examined post-treatment assignment characteristics such as cumulative exposure to the treatment, latency (time since last treatment), and diagnosis of prostate cancer (yes/no).

Among those patients who developed prostate cancer we then descriptively compared patient characteristics between the two exposure groups including the duration of prostate cancer, the prostate cancer stage at diagnosis and Gleason score at diagnosis.

The proportion of prostate cancers diagnosed and the corresponding incidence rates were calculated for all prostate cancers diagnosed during the study period as well as stratified by timing of prostate cancer diagnosis relative to the matching time point.

Survival analysis (taking into account competing risks)

A plot of cumulative incidence was constructed comparing the 5ARI vs. alpha-blocker users for prostate cancer mortality in the context of competing risk of death from other causes.

Crude, age-adjusted and multivariable-adjusted prostate cancer related mortality rates, hazard ratios and sub-distribution hazard ratios were calculated for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose.

Confounding and effect modification

Confounding

- Third variables of interest that were included in the multi-variable adjusted models were chosen based on known a priori confounders (age, race, region, history of AB use, BPH medication initiation year), and variables found to be confounders in this data set.
    - Variables found to be imbalanced after matching across both exposure and outcome categories were included in the multi-variable adjusted models.
    - Backward model selection using Wald chi-square values and corresponding p-values were assessed and the variables which reached a significance level of 0.10 remained in the final model.
    - Both Charlson comorbidity index and the individual comorbidities were eligible for inclusion in the model as they were measuring different aspects of comorbid disease.
- The final models included are adjusted for the following confounders:
    - Matching factors (age, race, region, history of AB use, BPH medication initiation)
    - Charlson index (0,1, 2+)
    - Medical history variables: cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer, use of other medications to treat overactive bladder (OAB) or erectile dysfunction (ED).

Effect Modification

PSA

- Models were stratified by PSA level at time of matching because it was felt that PSA is in the causal pathway by the study team but was an important third variable of interest.
    - Because of the skewed distributions, PSA at matching was log transformed.
    - PSA was missing on 38% of the eligible cohort population prior to matching and 37% after matching, as such, missing values were included as their own category in the PSA stratified analyses.

Lag time

- The data were then stratified using different lag times defined based on the distribution of time from 5ARI initiation (or matched date in AB user) to prostate cancer mortality seen in the data set and crude and multi-variable-adjusted prostate cancer related mortality rates and sub-distribution hazard ratios were calculated for 5ARI and alpha-blocker users.

Other potential effect modifiers

- The crude prostate cancer related mortality rates, hazard ratios and sub-distribution hazard ratios were calculated for 5ARI and alpha-blocker users stratified by pre-treatment characteristics of interest including age, race, PSA level and prior history of AB use to explore whether these variables were modifying the association of interest.

Case-control study

Analytic methods in brief

The distribution of demographic, medical history and prostate cancer characteristics (among those diagnosed) were compared across case and control status, using chi-square tests and two sided Wilcoxon-Mann-Whitney tests where appropriate. Matched odds ratios and 95% confidence intervals were estimated using conditional logistic regression, adjusting for the same covariates as the cohort study except history of AB use, and stratified by cumulative dose and exposure quartiles.

We conducted a number of sensitivity analyses to evaluate the robustness of our findings. Because of secular trends in missingness of PSA and Gleason score, we restricted our study period to 1999 and later when more complete data were available. We also stratified by calendar time and adjusted for calendar time in the adjusted models. We then conducted an analysis stratified by exposure lag time (defined as time from medication initiation to prostate cancer death). All of the sensitivity results yielded comparable results (ANNEX 1).

Secondary objectives

Metastatic "Combination" Outcome Analysis

The primary outcome was metastatic prostate cancer and/or prostate cancer death. This "combination" outcome during the study period was identified via the following methods which combined those identified via coded cause of death as used in the primary analysis (N=1053), those identified as probable prostate cancer death using the Natural Language Processing (NLP) based cause of death algorithm (N=126), and those with evidence of metastatic disease who did not die during the study period (N=424) for a total of 1,603 metastatic prostate cancer and/or prostate cancer death events. The details of the methods of this analysis are described in the appended metastatic report.

All-cause mortality analysis

The primary outcome for this set of analyses was all-cause mortality. Deaths due to any cause during the study period were identified using the same methods as the primary analysis. For this set of analyses, two analytic approaches were employed. First, the association between 5ARI use and all-cause mortality was assessed in the matched cohort sample (as used in the primary analysis), which considered only covariate information at the matched time point (5ARI initiation and corresponding index date for AB user). Second, the analyses were repeated in the eligible cohort (unmatched) and a time-dependent analysis was conducted which allowed for multiple time points of covariate collection. The details of the methods of this analysis are described in the appended all-cause mortality report.

Long term exposure to BPH medications

For all primary and secondary analyses, the association between 5ARI use and prostate cancer mortality as compared to AB use was assessed across levels of increasing

cumulative exposure and dose. Cumulative exposure was defined from the start of matching in the men who only use an AB and from the start of 5ARI in men who either were combo users or who were 5ARI only users. The distribution of cumulative exposure and number of prescriptions was assessed and descriptively compared between cases and controls. Dose response was explored by stratifying by increasing categories of dose. Dose was calculated from the start of matching in the men who only used an AB and from the start of 5ARI in men who either were combo users or who were 5ARI only users.

8.6.2. Exploratory analyses

Multiple exploratory analyses were conducted, assessing the distribution of prostate cancer diagnoses, metastatic disease, PSA testing, prostate biopsy rates and clinical follow-up for metastatic disease including use of bone scans and other imaging. The distribution of these prostate cancer characteristics were categorized in the population overall (both case-control and cohort study sample) and were then compared across exposure status (5ARI vs. AB) using two-sided t-tests and chi-square tests for associations were appropriate.

8.6.3. General considerations for data analyses

Misclassification of prostate cancer death

The definition of prostate cancer death in the first set of the primary analyses included in this report solely utilized the coded cause of death from the death record. As a result, there was a potential that deaths due to prostate cancer are attributed to another cause of death because prostate cancer was not listed as the underlying cause of death on the death certificate. This would have caused an underestimation in the number of prostate cancer deaths potentially, and there is a possibility that this misclassification would be differential across treatment groups. However, the second phase of the analyses utilized our electronic algorithm for assigning prostate cancer death and allowed us to explore whether and how misclassification bias may have occurred. The details of these analyses are presented in the appended metastatic report.

Time-varying nature of the exposure

Using a dichotomous exposure variable for this primary analysis, such that men are classified as either a 5ARI user or AB user does not take into account the complicated time-varying nature of this exposure. Therefore, inferences regarding how change in treatment status over time influences prostate cancer death cannot be drawn from this set of analyses. However, we employed risk-set sampling in this study, which allows men who changed treatment categories over time to contribute person-time at risk to each exposure group, thus in part accounting for the time-varying nature of this exposure.

Bias as a result of matching approach

Due to the complicated matching approach used in this study, a proportion of the men were unable to be matched (27%). As a result, there is the potential that the sample included in this analysis is somehow different from the underlying population from which

the exposed and unexposed subjects arose. However, when explored, the baseline covariates of the unmatched men were not found to be significantly different from those that were matched. In addition, a case-control study was done to maximize the number of cases that were included in the analysis and as a comparison to the cohort results. Table 14 displays the results of the case-control analysis.

Ascertainment of metastatic prostate cancer cases at diagnosis and over the follow-up period

Care was taken to assess any detection bias across treatment groups in the ascertainment of metastatic cancer cases at the time of diagnosis and over the course of the follow-up. At the time of diagnosis we examined the frequency of occurrence of tests to ascertain metastatic prostate cancer across the treatment groups including bone scans, PSA tests, and other relevant tests. Over the course of the follow-up we also documented the frequency of occurrence of these tests for metastatic cancer across the treatment groups as part of the development of the natural language processing algorithm for metastatic prostate cancer (Table 8). This information was used to help further our understanding about any detection bias that might be present in the study.

Additional sources of bias specific to the other analyses performed as part of the study are described in detail in the corresponding appended reports.

8.6.4. Amendments to the statistical analysis plan

N/A

8.7. Quality control and quality assurance

Data Collection and Management

[redacted] contribution included functioning as the data-coordinating center and performing analyses of de-identified data from [redacted] and [redacted] electronic health plan files and the VDW. This included information on exposures, confounders and outcome information as was available in our electronic health plan files. As collaborators, investigators from all the [redacted] sites participated and jointly led the studies, determined analyses and presented data in collaboration with investigators from GlaxoSmithKline. We also provided primary scientific input into the design and conduct of these studies as well as the interpretation, publication and presentation of study results and retained the right to publish results as appropriate. Finally, all of the [redacted] sites conducted these studies in accord with good clinical practices and under the supervision of the local Institutional Review Boards.

Data Coordinating Center (DCC)

The biostatistics and data management expertise was provided by a senior biostatistician at [redacted] who has extensive experience in supervising DCCs for a variety of government and industry-funded projects. Support for the DCC was then provided by our Biostatistics Unit. The Biostatistics Unit provided services including statistical consultation, data

analysis, data extraction and data management to this project. The consultation services also included study design, statistical methods, and sample size calculation.

For this study, [redacted] acted as the DCC and the other participating sites ([redacted] and [redacted] transferred their de-identified data to us for analysis through secure servers. We first developed a Standard Operating Procedure (SOP) to standardize and explain the general process for data management activities at the study sites. Data management activities included system operation and maintenance, security, data specification, programming, systems and data validation, sequencing of operational steps and events, quality assurance / quality control, and data backup. The Data Coordination SOP described the process which [redacted] and the other [redacted] sites used to define pertinent database variables, standardize their definitions and data structure, and merge the variables from the [redacted] and other site's databases into one project dataset at [redacted] These procedures meet applicable FDA regulations (Title 21 CFR Part 11) and International Conference Harmonization (ICH) Good Clinical Practice (GCP) Guidelines by ensuring the authenticity, integrity and confidentiality of electronic records.

The DCC at [redacted] worked with GSK and the other [redacted] sites and core investigators to develop study timelines (e.g., deadlines for IRB approval, development of protocols and analytic plans, development of data dictionary, analysis, etc.).

Data Transfer/Security

A data use agreement was executed to facilitate the transfer of data from the three [redacted] sites to [redacted] Data transfers between sites and the Data Coordinating Center used standard encryption software. All file transmissions used 128-bit encryption software (e.g. WinZip v 9.0, Mansfield, CT) and whenever possible, through virtual privacy network (VPN) connections. Identifiable data was maintained within site firewalls. Programming and analytic staff used file transfer protocol (FTP) programs on specific servers that reside in the "DMZ" outside the firewall.

All sites maintained data in a secure manner. Subjects were assigned a random unique number for an identifier and all forms were kept in locked storage cabinets. For electronic records, minimal identifying information was kept in files. Access to these files was password protected and all access logged. There were full back up of study data files made at regular intervals, with copies of complete backup files stored offsite in secure facilities, with updates stored at regular intervals. In addition, final analytic data sets will be archived according to a predefined procedure.

Chart Abstraction Quality Control and Procedures

Chart abstraction was performed to develop the natural language processing algorithms and further validate the cause of death once the algorithm had been applied. This process entailed four general steps, including the development of the case report form (CRF), locating corresponding electronic records, abstracting and entering the information and developing and carrying out quality control protocols. We outline these steps in more detail below.

Development of the CRF

The generation of a CRF started with the listing of data elements from the investigator, based on the information required by the study protocol. Clinical insights and prior research experience provided the basis for enumerating the items to be collected for case validation, exposure measurements, medical histories, etc.

Once items were assembled into a draft CRF, it was tested for feasibility. This process involved an experienced abstractor pulling several records and abstracting information onto the CRF. This provided insight into the time necessary to collect the information and even more importantly, the availability of the information in the clinical record. This was an iterative process, with input from investigators and abstractors until the CRF was finalized.

The next stage involved the training of the abstractors who were involved in reviewing the records at all 4 [redacted] sites. Records were pulled and abstracted independently by the four abstractors. Once completed, the abstractors compared the gathered information and discussed their approaches to collecting the information. Any discrepancies in specific fields were discussed and an attempt was made to identify the source of discrepancy as well as potential solutions. These included the clarification of definitions, identification of additional locations in which the information can be found within the record and determining a hierarchy of information on which to base the final assessment. Once completed, additional records were pulled and the process repeated. This was done until the abstractors and investigators were comfortable that the process is accurate and reliable.

This important phase of the abstraction process is ongoing through the production phases of data collection. As noted above, it is standard practice to include random assessments of reliability of the abstraction process, preferably within and between abstractors, throughout the study. In addition, routine range and consistency checks are applied early on in the process before analytic files are created. This minimizes the turnaround time to develop the final analytic files. Finally, as part of this process, the progress is monitored through study project management tools. These are critical for reporting progress to leadership as well as maintaining quality.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

This study was reviewed and approved by the IRB in [redacted] and approved by the other participating regions. No patient contact was made as part of this study as only previously collected data was utilized; therefore, informed consent was waived.

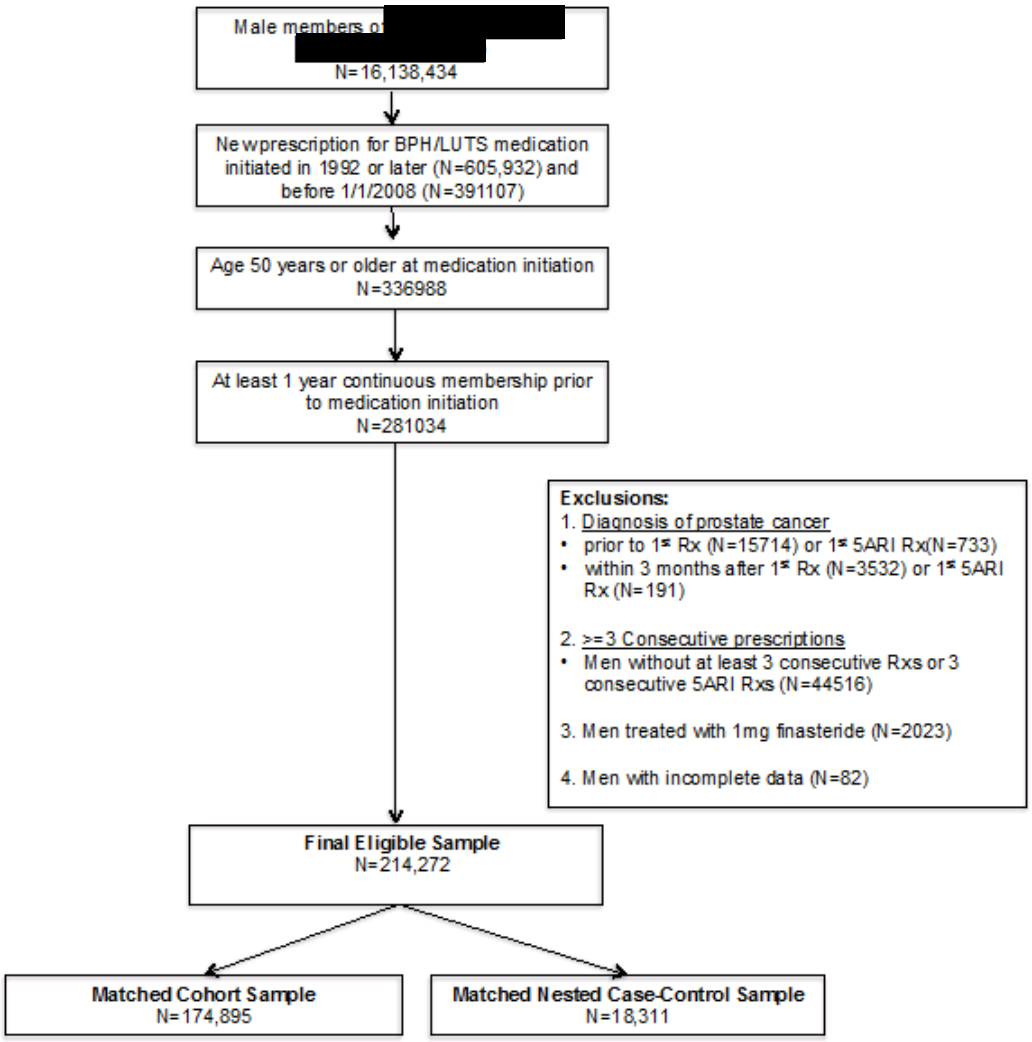
9.2. Subject confidentiality

Data used in this study was de-identified at each [redacted] site before the data was sent to [redacted] the coordinating site, for data analysis. Patients were identified by unique IDs in the data set that were not linked to personal identifiable information. GSK did not have access to the data and received results from [redacted] in aggregate form.

10. RESULTS

10.1. Participants

Figure 1 Inclusion/Exclusion criteria to select study cohort (N=214,272)



10.2. Descriptive data including baseline characteristics

Table 1 Distribution and crude association of demographic and clinical characteristics by drug exposure group before matching (N=214,272)

	Overall (n=214272)	5ARI Users (n=29232)	Alpha-blocker Users (n=185040)	p-value
Characteristic				
Age at BPH Initiation				
Mean (SD)	67.5 (9.5)	68.3 (9.1)	67.4 (9.5)	<0.0001
Median	67.2	68.1	67.0	<0.0001
<60	52729 (24.6%)	6001 (20.5%)	46728(25.3%)	<0.0001
60-69	76907 (35.9%)	10918 (37.4%)	65989 (35.7%)	
70+	84636 (39.5%)	12313 (42.1%)	72323 (39.1%)	
Race				
Non-Hispanic White	156681 (73.1%)	23058 (78.9%)	133623 (72.2%)	<0.0001
African American	17436 (8.1%)	2067 (7.1%)	15369 (8.3%)	
Asian	17210 (8.0%)	2357 (8.1%)	14853 (8.0%)	
Hawaiian, PI, Multiple, Unknown	22945 (10.7%)	1750 (6.0%)	21195 (11.5%)	
Socioeconomic Status				
Missing	5519 (2.6%)	396 (1.4%)	5123 (2.8%)	
Household income, median ($1000)	61.2	63.7	60.9	<0.0001
Household income, mean (SD) ($1000)	65.7 (28.2)	68.4 (29.6)	65.2 (27.9)	<0.0001
Education[1]				
Less than 9th grade	0.08 (0.09), 0.04	0.07 (0.09), 0.04	0.08 (0.09), 0.04	<0.0001
9th – 12 grade	0.10 (0.07), 0.08	0.09 (0.07), 0.08	0.10 (0.07), 0.09	<0.0001
High school graduate	0.21 (0.08), 0.21	0.20 (0.08), 0.20	0.21 (0.08), 0.21	<0.0001
Some college, no degree	0.24 (0.07), 0.25	0.24 (0.07), 0.24	0.24 (0.07), 0.25	<0.0001
Associate degree	0.08 (0.03), 0.07	0.08 (0.03), 0.07	0.08 (0.03), 0.07	0.37
Bachelor degree	0.19 (0.11), 0.18	0.20 (0.10), 0.20	0.19 (0.11), 0.18	<0.0001
Graduate or professional degree	0.11 (0.09), 0.08	0.12 (0.10). 0.09	0.10 (0.09), 0.08	<0.0001
PSA at BPH Initiation				
Missing	80525 (37.6%)	9559 (32.7%)	70966 (38.4%)	<0.0001
.PSA level, mean (SD)	3.7 (18.5)	5.4 (29.1)	3.4 (16.0)	<0.0001
PSA level, median	1.8	3.2	1.7	<0.0001

	Overall (n=214272)	5ARI Users (n=29232)	Alpha-blocker Users (n=185040)	p-value
BMI at BPH Initiation (kg/m²)				
Missing	172750 (80.6%)	23581 (80.7%)	149169 (80.6%)	
<25	9438 (4.4%)	1379 (4.7%)	8059 (4.4%)	0.001
25-30	17298 (8.1%)	2428 (8.3%)	14870 (8.0%)	
≥30	14786 (6.9%)	1844 (6.3%)	12942 (7.0%)	
Charleston Comorbidity Index				
0	136880 (63.9%)	19547 (66.9%)	117333 (63.4%)	<0.0001
1	36822 (17.2%)	4893 (16.7%)	31929 (17.3%)	
2+	40570 (18.9%)	4792 (16.4%)	35778 (19.3%)	
History of cardiovascular disease	42912 (20.0%)	5876 (20.1%)	37036 (20.0%)	0.73
History of high blood pressure	182416 (85.1%)	23342 (79.9%)	159074 (86.0%)	<0.0001
History of hyperlipidemia	125261 (58.5%)	16858 (57.7%)	108403 (58.6%)	0.003
History of diabetes	42513 (19.8%)	4620 (15.8%)	37893 (20.5%)	<0.0001
History of cancer other than prostate	12028 (5.6%)	1665 (5.7%)	10363 (5.6%)	0.51
Use of other medications to treat ED or OAB*	21918 (10.2%)	3100 (10.6%)	18818 (10.2%)	0.02

*PDE5 Inhibitors and/or anticholinergics and antimuscarinic
[1] Geocoded education

Table 1 displays the distribution of pre-treatment characteristics by exposure group prior to matching. Of the 214,272 men prior to matching, 13.6% (29,232) used a 5ARI during follow-up and 86.4% (185,040) used an AB. Men who took 5ARIs were more likely to be older at BPH treatment initiation, Non-Hispanic White, with higher geocoded median household incomes on average when compared to men who used alpha-blockers (all p<0.0001). (Table 1) Men using 5ARIs also had higher PSA levels on average at time of BPH treatment initiation with a median level of 3.2 ng/mL compared to 1.7 ng/mL among AB users (p<0.0001). Men using 5ARIs had lower comorbidity index scores, were less likely to have high blood pressure, and a history of diabetes when compared to AB users (all p<0.0001). However, they were not more likely to have a history of cancer (other than prostate) (p=0.51). (Table 1)

Table 2 Distribution and crude association of exposure, demographic and clinical characteristics and prostate cancer death before matching (N=214,272)

	Overall (n=214272)	Prostate cancer deaths[1] (n=1684)	No prostate cancer death (n=212588)	p-value
Characteristic				
Exposure				
Alpha Blocker only users	185040 (86.4%)	1519 (90.2%)	183521 (86.3%)	<0.0001
5ARI users	29232 (13.6%)	165 (9.8%)	29067(13.7%)	

	Overall (n=214272)	Prostate cancer deaths[1] (n=1684)	No prostate cancer death (n=212588)	p-value
Age at BPH Initiation				
Mean (SD)	67.5 (9.5)	75.0 (8.4)	67.5 (9.4)	<0.0001
Median	67.2	75.9	67.1	<0.0001
<60	52729 (24.6%)	100 (5.9%)	52629 (24.8%)	<0.0001
60-69	76907 (35.9%)	336 (20.0%)	76571 (36.0%)	
70+	84636 (39.5%)	1248 (74.1%)	83388 (39.2%)	
Race				
Non-Hispanic White	156681 (73.1%)	1277 (75.8%)	155404 (73.1%)	<0.0001
African American	17436 (8.1%)	209 (12.4%)	17227 (8.1%)	
Asian	17210 (8.0%)	61 (3.6%)	17149 (8.1%)	
Hawaiian, PI, Multiple, and Unknown	22945 (10.7%)	137 (8.1%)	22808 (10.7%)	
Socioeconomic Status				
Missing	5519 (2.6%)	49 (2.9%)	5470 (2.6%)	
Household income, median ($1000)	61.2	58.4	61.2	
Household income, mean (SD) ($1000)	65.7 (28.2)	63.9 (28.2)	65.7 (28.2)	0.003
Education[2]				
Less than 9th grade	0.08 (0.09), 0.04	0.08 (0.10), 0.04	0.08 (0.09), 0.04	0.27
9th – 12 grade	0.10 (0.07), 0.08	0.11 (0.07), 0.09	0.10 (0.07), 0.09	0.003
High school graduate	0.21 (0.08), 0.21	0.21 (0.08), 0.21	0.21 (0.08), 0.21	0.08
Some college, no degree	0.24 (0.07), 0.25	0.24 (0.07), 0.25	0.24 (0.07), 0.25	0.84
Associate degree	0.08 (0.03), 0.07	0.08 (0.03), 0.07	0.08 (0.03), 0.07	0.22
Bachelor degree	0.19 (0.11), 0.18	0.18 (0.10), 0.17	0.19 (0.11), 0.18	0.008
Graduate or professional degree	0.11 (0.09), 0.08	0.10 (0.09). 0.08	0.11 (0.09), 0.08	0.18
PSA at BPH Initiation				
Missing	80525 (37.6%)	748 (44.4%)	79777 (37.5%)	
.PSA level, mean (SD)	3.7 (18.5)	44.6 (193.5)	3.4 (8.4)	<0.0001
PSA level, median	1.8	7.4	1.8	<0.0001
BMI at BPH Initiation (kg/m^2)				
Missing	172750 (80.6%)	1572 (93.4%)	171178 (80.5%)	
<25	9438 (4.4%)	38 (2.3%)	9400 (4.4%)	<0.0001
25-30	17298 (8.1%)	38 (2.3%)	17260 (8.1%)	
≥30	14786 (6.9%)	36 (2.1%)	14750 (6.9%)	

	Overall (n=214272)	Prostate cancer deaths[1] (n=1684)	No prostate cancer death (n=212588)	p-value
Charleston Comorbidity Index				
0	136880 (63.9%)	1116 (66.3%)	135764 (63.9%)	<0.0001
1	36822 (17.2%)	197 (11.7%)	36625 (17.2%)	
2+	40570 (18.9%)	371 (22.0%)	40199 (18.9%)	
History of cardiovascular disease	42912 (20.0%)	320 (19.0%)	42592 (20.0%)	0.29
History of high blood pressure	182416 (85.1%)	1383 (82.1%)	181033 (85.2%)	0.0005
History of hyperlipidemia	125261 (58.5%)	683 (40.6%)	124578 (58.6%)	<0.0001
History of diabetes	42513 (19.8%)	247 (14.7%)	42266 (19.9%)	<0.0001
History of cancer	12028 (5.6%)	223 (13.2%)	11805 (5.6%)	<0.0001
Use of other medications to treat ED or OAB*	21918 (10.2%)	59 (3.5%)	21859 (10.3%)	<0.0001

[1]This count of prostate cancer deaths is based on underlying cause of death and is not limited to deaths which occur among men with a prostate cancer diagnosis. This count includes the additional deaths identified through the NDI match. Deaths occurring after men were lost to follow-up but occurred before end of study period are also included in this count
[2]Geocoded education

Table 2 displays the distribution of pre-treatment characteristics by prostate cancer death status prior to matching. The proportion of men who died of prostate cancer was low in both groups and 5ARI use was higher among those who did not die of prostate cancer (13.7%) compared to those who did die of prostate cancer (9.8%), (p<0.0001). Men who died from prostate cancer were older at the time of BPH medication initiation (p<0.0001), and more likely to be African American (p<0.0001) compared to men who did not die of prostate cancer. Of the 62% with a PSA level at the time of matching, men who died of prostate cancer had higher median PSA levels (7.4 ng/mL vs. 1.8 ng/mL) (p<0.0001) compared to men who did not die of prostate cancer. Men who died of prostate cancer were less likely to have a history of high blood pressure (p=0.0005), hyperlipidemia (p<0.0001), and diabetes (p<0.0001), compared to men who did not die of prostate cancer. However, men who died of prostate cancer had higher comorbidity index scores and were more likely to have a history of cancer other than prostate compared to men who did not die of prostate cancer (both p<0.0001). (Table 2)

Table 3 Distribution and crude association of exposure, demographic and clinical characteristics and prostate cancer death before matching among unmatched men (includes 5ARI users who were matched as a control but not a case) (N=60,522)

	Overall (n=60522)	5ARI Users (n=3844)	Alpha-blocker Users (n=56678)	p-value
Characteristic				
Age at BPH Initiation				
Mean (SD)	66.2 (10.0)	68.7 (8.4)	66.0 (10.1)	<0.0001
Median	65.0	68.4	64.7	<0.0001
<60	19320 (31.9%)	631 (16.4%)	18689 (33.0%)	<0.0001
60-69	20172 (33.3%)	1548 (40.3%)	18624 (32.9%)	
70+	21030 (34.8%)	1665 (43.3%)	19365 (34.2%)	

	Overall (n=60522)	5ARI Users (n=3844)	Alpha-blocker Users (n=56678)	p-value
Race				
Non-Hispanic White	39248 (64.9%)	3169 (82.4%)	36079 (63.7%)	<0.0001
African American	6062 (10.0%)	182 (4.7%)	5880 (10.4%)	
Asian	4442 (7.3%)	340 (8.8%)	4102 (7.2%)	
Hawaiian, PI, Multiple, and Unknown	10770 (17.8%)	153 (4.0%)	10617 (18.7%)	
Socioeconomic Status				
Missing	2411(4.0%)	19(0.5%)	2392(4.2%)	
Household income, median ($1000)	59.9	64.2	59.5	<0.0001
Household income, mean (SD) ($1000)	64.4 (28.2)	68.7 (29.1)	64.1 (28.1)	<0.0001
Education*				
Less than 9th grade	0.09 (0.10), 0.05	0.07 (0.09), 0.04	0.09 (0.10), 0.05	<0.0001
9th – 12 grade	0.11 (0.07), 0.09	0.09 (0.07), 0.08	0.11 (0.07), 0.09	<0.0001
High school graduate	0.21 (0.08), 0.21	0.20 (0.08), 0.20	0.21 (0.08), 0.21	<0.0001
Some college, no degree	0.24 (0.07), 0.25	0.24 (0.07), 0.24	0.24 (0.07), 0.25	0.11
Associate degree	0.07 (0.03), 0.07	0.08 (0.03), 0.08	0.07 (0.03), 0.07	<0.0001
Bachelor degree	0.18 (0.11), 0.17	0.20 (0.11), 0.20	0.18 (0.11), 0.17	<0.0001
Graduate or professional degree	0.10 (0.09), 0.07	0.12 (0.10). 0.09	0.10 (0.09), 0.07	<0.0001
PSA at BPH Initiation (ng/ML)				
Missing	24719 (40.8%)	1445 (37.6%)	23274 (41.1%)	
.PSA level, mean (SD)	3.9 (24.1)	4.2 (6.4)	3.9 (24.9)	<0.0001
PSA level, median	1.6	2.7	1.5	<0.0001
BMI at BPH Initiation (kg/m^2)				
Missing	50673 (83.7%)	3331 (86.7%)	47342 (83.5%)	
<25	2364 (3.9%)	132 (3.4%)	2232 (3.9%)	<0.0001
25-30	4033 (6.7%)	227 (5.9%)	3806 (6.7%)	
≥30	3452 (5.7%)	154 (4.0%)	3298 (5.8%)	
Charleston Comorbidity Index				
0	40028 (66.1%)	2767 (72.0%)	37261 (65.7%)	<0.0001
1	8999 (14.9%)	578 (15.0%)	8421 (14.9%)	
2+	11495 (19.0%)	499 (13.0%)	10996 (19.4%)	
History of cardiovascular disease	11358 (18.8%)	690 (18.0%)	10668 (18.8%)	0.18
History of high blood pressure	51391 (84.9%)	3065 (79.7%)	48326 (85.3%)	<0.0001
History of hyperlipidemia	32994 (54.5%)	2166 (56.4%)	30828 (54.4%)	0.02
History of diabetes	11729 (19.4%)	536 (13.9%)	11193 (19.8%)	<0.0001

	Overall (n=60522)	5ARI Users (n=3844)	Alpha-blocker Users (n=56678)	p-value
History of cancer	3564 (5.9%)	198 (5.2%)	3366 (5.9%)	0.04
Use of other medications to treat ED or OAB*	5417 (9.0%)	293 (7.6%)	5124 (9.0%)	0.003
*Geocoded education				

Table 3 displays the distribution of pre-treatment characteristics by exposure group for men who were not successfully matched and 5ARI users who were matched as an AB user but not a 5ARI user (N=60,522). The distribution of the demographic characteristics was similar to that displayed in Table 1 among the sample of men who were matched successfully. (Table 3)

Table 4 Distribution and crude association of demographic and clinical characteristics by drug exposure group after matching (N=174,895)*

	Overall (n=174895)	5ARI users (n=25388)	Alpha-blocker users (n=149507)	p-value
Matching Criteria				
BPH initiation calendar year				
1992	3181 (1.8%)	427 (1.7%)	2754 (1.8%)	<0.0001
1993	3176 (1.8%)	434 (1.7%)	2742 (1.8%)	
1994	3295 (1.9%)	448 (1.8%)	2847 (1.9%)	
1995	4166 (2.4%)	584 (2.3%)	3582 (2.4%)	
1996	21843 (12.5%)	3007 (11.8%)	18836 (12.6%)	
1997	9991 (5.7%)	1380 (5.4%)	8611 (5.8%)	
1998	11498 (6.6%)	1718 (6.8%)	9780 (6.5%)	
1999	11971 (6.8%)	1807 (7.1%)	10164 (6.8%)	
2000	11671 (6.7%)	1708 (6.7%)	9963 (6.7%)	
2001	11087 (6.3%)	1546 (6.1%)	9541 (6.4%)	
2002	11651 (6.7%)	1628 (6.4%)	10023 (6.7%)	
2003	12864 (7.4%)	1882 (7.4%)	10982 (7.4%)	
2004	12553 (7.2%)	1735 (6.8%)	10818 (7.2%)	
2005	13761 (7.9%)	1971 (7.8%)	11790 (7.9%)	
2006	17006 (9.7%)	2569 (10.1%)	14437 (9.7%)	
2007	15181 (8.7%)	2544 (10%)	12637 (8.5%)	
Race (matching categories)				
African American	12711 (7.3%)	1885 (7.4%)	10826 (7.2%)	0.30
All other races	162184 (92.7%)	23503 (92.6%)	138681 (92.8%)	
Region				
[redacted]	68700 (39.3%)	9772 (38.5%)	58928 (39.4%)	<0.0001
[redacted]	88580 (50.7%)	13009 (51.2%)	75571 (50.6%)	
[redacted]	9001 (5.2%)	1561 (6.2%)	7440 (5.0%)	
[redacted]	8614 (4.9%)	1046 (4.1%)	7568 (5.1%)	
Exposure and Follow-up				
Cumulative exposure time (years)[1]				
Mean (SD)	1.5 (1.5)	2.2 (2.1)	1.4 (1.4)	<0.0001
Median	1.1	1.5	1.1	<0.0001
Duration of follow-up time from matching time point, for loss of follow up Pca deaths follow up ends at disenrollment (years)[1]				
Mean (SD)	3.1 (2.7)	4.0 (3.1)	3.0 (2.6)	<0.0001
Median	2.4	3.3	2.3	<0.0001
Duration of follow-up time after post-matching prostate cancer diagnosis (years)				
Mean (SD)	3.4 (3.0)	3.2 (3.0)	3.5 (3.0)	0.008

	Overall (n=174895)	5ARI users (n=25388)	Alpha-blocker users (n=149507)	p-value
Median	2.6	2.4	2.7	0.008
At matching Characteristics				
Age				
Mean (SD)	72.4 (9.2)	72.4 (9.3)	72.3 (9.2)	0.16
Median	72.6	72.6	72.5	0.16
<60	17884 (10.2%)	2546 (10.0%)	15338 (10.3%)	0.31
60-69	52980 (30.3%)	7639 (30.1%)	45341 (30.3%)	
70+	104031 (59.5%)	15203 (60.0%)	88828 (59.4%)	
Race				
Non-Hispanic White	134220 (76.7%)	19889 (78.3%)	114331 (76.5%)	<0.0001
African American	12711 (7.3%)	1885 (7.4%)	10826 (7.2%)	
Asian	14636 (8.4%)	2017 (7.9%)	12619 (8.4%)	
HP, IN, MU and UN	13328 (7.6%)	1597 (6.3%)	11731(7.9%)	
PSA				
Missing	65262 (37.3%)	6359 (25.1%)	58903 (39.4%)	
Mean (SD)	4.9 (42.6)	6.6 (30.2)	4.5 (44.8)	<0.0001
Median	2.3	4.1	2.1	<0.0001
0 - 2.5	56985 (32.6%)	6400 (25.2%)	50585 (33.8%)	<0.0001
2.5 – 5.4	17497 (10.0%)	2964 (11.7%)	14533 (9.7%)	
≥4	35151 (20.1%)	9665 (38.1%)	25486 (17.1%)	
Socioeconomic Status				
Missing	3320 (1.9%)	377 (1.5%)	2943 (2.0%)	
Household income, median ($1000)	62.0	63.5	61.8	<0.0001
Household income, mean (SD) ($1000)	66.4 (28.3)	68.3 (29.7)	66.1 (28.0)	<0.0001
Education[2]				
Less than 9th grade	0.07 (0.09), 0.04	0.07 (0.09), 0.04	0.07 (0.09), 0.04	<0.0001
9th – 12 grade	0.10 (0.07), 0.08	0.09 (0.07), 0.08	0.10 (0.07), 0.08	<0.0001
High school graduate	0.21 (0.08), 0.21	0.20 (0.08), 0.20	0.21 (0.08), 0.21	<0.0001
Some college, no degree	0.24 (0.07), 0.25	0.24 (0.07), 0.24	0.24 (0.07), 0.25	<0.0001
Associate degree	0.08 (0.03), 0.08	0.08 (0.03), 0.07	0.08 (0.03), 0.08	0.007
Bachelor degree	0.19 (0.11), 0.19	0.20 (0.11), 0.20	0.19 (0.11), 0.18	<0.0001
Graduate or professional degree	0.11 (0.09), 0.08	0.12 (0.10). 0.09	0.10 (0.09), 0.08	<0.0001
Alpha blocker history (years)				
.Mean (SD)	4.3 (4.1)	4.2 (4.0)	4.4 (4.1)	<0.0001

	Overall (n=174895)	5ARI users (n=25388)	Alpha-blocker users (n=149507)	p-value
Median	3.4	3.2	3.4	<0.0001
BMI (kg/m²)				
Missing	98215 (56.2%)	14244 (56.1%)	83971 (56.2%)	<0.0001
<25	29642 (17.0%)	4352 (17.1%)	25290 (16.9%)	
25-30	26590 (15.2%)	4076 (16.1%)	22514 (15.1%)	
≥30	20448 (11.7%)	2716 (10.7%)	17732 (11.9%)	
Charleston Comorbidity Index				
0	75809 (43.4%)	11633 (45.8%)	64176 (42.9%)	<0.0001
1	34670 (19.8%)	5017 (19.8%)	29653 (19.8%)	
2+	64416 (36.8%)	8738 (34.4%)	55678 (37.2%)	
History of cardiovascular disease	59459 (34.0%)	8992 (35.4%)	50467 (33.8%)	<0.0001
History of high blood pressure	157553 (90.1%)	21289 (83.9%)	136264 (91.1%)	<0.0001
History of hyperlipidemia	117974 (67.5%)	16753 (66.0%)	101221 (67.7%)	<0.0001
History of diabetes	45273 (25.9%)	5554 (21.9%)	39719 (26.6%)	<0.0001
History of cancer	15877 (9.1%)	2473 (9.7%)	13404 (9.0%)	<0.0001
Use of other medications to treat ED or OAB*	23184 (13.3%)	3679 (14.5%)	19505 (13.1%)	<0.0001

*This table is among 174,895 records and therefore includes 18,321 men who were combo therapy users during follow-up and are counted in each column. For those variables that we have multiple measures over time, combo users can have two points of measurement- one at the time of their matching as a control and one at the time of their matching as a case
[1]Cumulative exposure and follow-up times are calculated from time of 5ARI initiation (thus corresponding matching time point for AB user) up until to earliest of date of death, disenrollment or 12/31/2010.
[2] Geocoded education

Table 4 compares demographic and clinical characteristics by exposure group after matching in the 174,895 men in the matched sample. This table includes 174,895 records because the 18,321 AB users who went on to be 5ARI users were matched to another AB user and are counted twice in this table. This makes the bivariate comparisons more similar because of increased comparability between the groups due to the double counting of these men. The distribution of calendar year of initiation of BPH medication was mostly similar across groups, with the proportion of men initiating treatment increasing steadily over time. Race was evenly distributed and not significantly different across exposure group after matching (p=0.30) when the race categories were collapsed into African American vs. other. Regional distributions remained different after matching, with 5ARI users more likely to be in [redacted] and [redacted] and less likely to be in [redacted] or [redacted] compared to AB users (p<0.0001). The median cumulative exposure time after matching was greater among 5ARI users at 1.5 years, compared to 1.1 years for AB users (p<0.0001). Also, duration of follow-up time after matching was longer for the 5ARI users compared to the AB users, with 3.3 years on average compared to 2.3 in the AB users (P<0.0001). The history of prior AB use before matching was comparable across exposure groups, with a median of 3.2 years in the 5ARI group and 3.4 in the AB group (p=<0.0001). (Table 4)

The distributions of characteristics at the time of matching are also displayed in Table 4. Imbalances across exposure groups similar to those displayed in Table 1 remained after

matching. Men who used 5ARIs were still more likely to be non-Hispanic White, had higher geocoded median household income, higher median PSA levels compared to AB users after matching (all $p < 0.0001$). However, after matching, men who used 5ARIs were more likely to have a history of cardiovascular disease and a history of cancer other than prostate compared to AB users (both $p < 0.0001$) (Table 4)

Table 5 Distribution and crude association of demographic and clinical characteristics by outcome group after matching (N=174,895)*

	Overall (n=174895)	Prostate cancer deaths[1] (n=1053)	No prostate cancer death (n=173842)	p-value
Characteristic				
Exposure				
Alpha Blocker users	149507 (85.5%)	895 (85.0%)	148612 (85.5%)	0.65
5ARI users	25388 (14.6%)	158 (15.0%)	25230 (14.5%)	
Age at matching				
Mean (SD)	72.4 (9.2)	79.3 (7.6)	72.3 (9.2)	<0.0001
Median	72.6	80.3	72.5	
<60	17884 (10.2%)	11 (1.0%)	17873 (10.3%)	<0.0001
60-69	52980 (30.3%)	107 (10.2%)	52873 (30.4%)	
70+	104031 (59.5%)	935 (88.8%)	103096 (59.3%)	
Race				
Non-Hispanic White	134220 (76.7%)	848 (80.5%)	133372 (76.7%)	<0.0001
African American	12711 (7.3%)	110 (10.5%)	12601 (7.3%)	
Asian	14636 (8.4%)	39 (3.7%)	14597 (8.4%)	
Hawaiian, PI, Multiple, and Unknown	13328 (7.6%)	56 (5.3%)	13272 (7.6%)	
Socioeconomic Status				
Missing	3320 (1.9%)	29 (2.8%)	3291 (1.9%)	
Household income, median ($1000)	62.0	59.7	62.0	0.005
Household income, mean (SD) ($1000)	66.4 (28.3)	64.5 (29.0)	66.5 (28.3)	0.005
Education				
Less than 9th grade	0.07 (0.09), 0.04	0.07 (0.09), 0.04	0.07 (0.09), 0.04	0.81
9th – 12 grade	0.10 (0.07), 0.08	0.10 (0.07), 0.09	0.10 (0.07), 0.08	0.09
High school graduate	0.21 (0.08), 0.21	0.21 (0.08), 0.21	0.21 (0.08), 0.21	0.07
Some college, no degree	0.24 (0.07), 0.25	0.24 (0.07), 0.25	0.24 (0.07), 0.25	0.92
Associate degree	0.08 (0.03), 0.08	0.08 (0.03), 0.08	0.08 (0.03), 0.08	0.92
Bachelor degree	0.19 (0.11), 0.19	0.19 (0.11), 0.18	0.19 (0.11), 0.19	0.11
Graduate or professional degree	0.11 (0.09), 0.08	0.11 (0.09). 0.08	0.11 (0.09), 0.08	0.39
PSA at matching				
Missing	65262 (37.3%)	328 (31.2%)	64934 (37.4%)	
.PSA level, mean (SD)	4.9 (42.6)	66.9 (294.4)	4.5 (35.0)	<0.0001
PSA level, median	2.3	9.0	2.3	<0.0001
0 – 2.5	56985 (32.6%)	167 (15.9%)	56818 (32.7%)	<0.0001

	Overall (n=174895)	Prostate cancer deaths[1] (n=1053)	No prostate cancer death (n=173842)	p-value
2.5 - 4	17497 (10.0%)	49 (4.7%)	17448 (10.0%)	
≥4	35151 (20.1%)	509 (48.3%)	34642 (19.9%)	
BMI (kg/m²)				
Missing	98215 (56.2%)	825 (78.4%)	97390 (56.0%)	
<25	29642 (17.0%)	89 (8.5%)	29553 (17.0%)	<0.0001
25-30	26590 (15.2%)	80 (7.6%)	26510 (15.3%)	
≥30	20448 (11.7%)	59 (5.6%)	20389 (11.7%)	
Charleston Comorbidity Index				
0	75809 (43.4%)	361 (34.3%)	75448 (43.4%)	<0.0001
1	34670 (19.8%)	124 (11.8%)	34546 (19.9%)	
2+	64416 (36.8%)	568 (53.9%)	63848 (36.7%)	
History of cardiovascular disease	59459 (34.0%)	356 (33.8%)	59103 (34.0%)	0.90
History of high blood pressure	157553 (90.1%)	914 (86.8%)	156639 (90.1%)	0.0003
History of hyperlipidemia	117974 (67.5%)	510 (48.4%)	117464 (67.6%)	<0.0001
History of diabetes	45273 (25.9%)	209 (19.9%)	45064 (25.9%)	<0.0001
History of cancer	15877 (9.1%)	138 (13.1%)	15739 (9.1%)	<0.0001
Use of other medications to treat ED or OAB*	23184 (13.3%)	73 (6.9%)	23111 (13.3%)	<0.0001
Alpha Blocker history (years)[1]				
Mean (SD)	4.3 (4.1)	3.6 (3.8)	4.3 (4.1)	<0.0001
Median	3.4	2.3	3.4	<0.0001

*This table is among 174,895 records and therefore includes 18,321 men who were combo therapy users during follow-up and are counted in each column. For those variables that we have multiple measures over time, combo users can have two points of measurement- one at the time of their matching as a control and one at the time of their matching as a case
[1]AB history is calculated as time on AB prior to initiation of 5ARI or matching.

Table 5 compares the distribution of demographic and clinical characteristics by prostate cancer death status in the matched sample of 174,895 records. The proportion of men who died from prostate cancer was low in both treatment groups and comparable among 5ARI and AB users (p=0.65). Men who died from prostate cancer were older at the time of matching on average (p<0.0001), more likely to be African American (p<0.0001) compared to men who did not die of prostate cancer. Of the 63% of men with a PSA level at the time of matching, men who died of prostate cancer had higher median PSA levels (9.0 ng/mL vs. 2.3 ng/mL) (p<0.0001) compared to men who did not die of prostate cancer and these levels were slightly higher compared to the overall cohort. Men who died of prostate cancer were less likely to have a history of high blood pressure (p=0.0003), hyperlipidemia (p<0.0001), and diabetes (p<0.0001), compared to men who did not die of prostate cancer. However, men who died of prostate cancer had higher comorbidity index scores compared to men who did not die of prostate cancer (p<0.0001). History of AB use after matching was shorter on average in the men who died of prostate cancer, with a median of 2.3 years compared to 3.4 years in those who did not die of prostate cancer (p=<0.0001)(Table 5)

Table 6 Pre-treatment characteristics and prostate cancer related information for those using 5ARIs (monotherapy compared to those using 5ARI+alpha-blocker) (N=25,388)

	Overall (n=25388)	5ARI monotherapy users (n=2115)	5ARI+ monotherapy users (n=23273)	p-value
Demographic Characteristics				
Age at matching				
Mean (SD)	72.4 (9.3)	71.3 (10.7)	72.6 (9.1)	<0.0001
Median	72.6	71.9	72.7	<0.0001
<60	2546 (10.0%)	388 (18.4%)	2158 (9.3%)	<0.0001
60-69	7639 (30.1%)	550 (26.0%)	7089 (30.5%)	
70+	15203 (60.0%)	1177 (55.7%)	14026 (60.3%)	
Race				
Non-Hispanic White	19889 (78.3%)	1634 (77.3%)	18255 (78.4%)	<0.0001
African American	1885 (7.4%)	150 (7.1%)	1735 (7.5%)	
Asian	2017 (7.9%)	139 (6.6%)	1878 (8.1%)	
HP, IN, MU and UN	1597 (6.3%)	192 (9.1%)	1405 (6.0%)	
Socioeconomic Status				
Missing	377 (1.5%)	60 (2.8%)	317 (1.4%)	
Household income, median ($1000)	63.5	62.0	63.7	0.05
Household income, mean (SD) ($1000)	68.3 (29.7)	67.4 (30.9)	68.4 (29.6)	0.05
Education[1]				
Less than 9th grade	0.07 (0.09), 0.04	0.06 (0.08), 0.03	0.07 (0.09), 0.04	0.002
9th – 12 grade	0.09 (0.07), 0.08	0.09 (0.07), 0.07	0.09 (0.07), 0.08	<0.0001
High school graduate	0.20 (0.08), 0.20	0.20 (0.09), 0.19	0.20 (0.08), 0.20	0.002
Some college, no degree	0.24 (0.07), 0.24	0.24 (0.07), 0.24	0.24 (0.07), 0.24	0.36
Associate degree	0.08 (0.03), 0.07	0.07 (0.03), 0.07	0.08 (0.03), 0.07	<0.0001
Bachelor degree	0.20 (0.11), 0.20	0.21 (0.11), 0.21	0.20 (0.11), 0.20	<0.0001
Graduate or professional degree	0.12 (0.10), 0.09	0.13 (0.10). 0.10	0.12 (0.10), 0.09	<0.0001
Clinical Characteristics				
PSA at matching				
Missing	6359 (25.0%)	701 (33.1%)	5658 (24.3%)	
.PSA level, mean (SD)	6.6 (30.2)	10.4 (104.6)	6.3 (10.3)	0.31
PSA level, median	4.1	4.5	4.0	0.31
0 – 2.5	6400 (25.2%)	492 (23.3%)	5908 (25.4%)	<0.0001
2.5 - 4	2964 (11.7%)	160 (7.6%)	2804 (12.1%)	

	Overall (n=25388)	5ARI monotherapy users (n=2115)	5ARI+ monotherapy users (n=23273)	p-value
≥4	9665 (38.1%)	762 (36.0%)	8903 (38.3%)	
BMI (kg/m²)				
Missing	14244 (56.1%)	1509 (71.4%)	12735 (54.7%)	
<25	4352 (17.1%)	208 (9.8%)	4144 (17.8%)	<0.0001
25-30	4076 (16.1%)	234 (11.1%)	3842 (16.5%)	
≥30	2716 (10.7%)	164 (7.8%)	2552 (11.0%)	
Charleston Comorbidity Index				
0	11633 (45.8%)	1171 (55.4%)	10462 (45.0%)	<0.0001
1	5017 (19.8%)	377 (17.8%)	4640 (19.9%)	
2+	8738 (34.4%)	567 (26.8%)	8171 (35.1%)	
History of cardiovascular disease	8992 (35.4%)	631 (29.8%)	8361 (35.9%)	<0.0001
History of high blood pressure	21289 (83.9%)	1255 (59.3%)	20034 (86.1%)	<0.0001
History of hyperlipidemia	16753 (66.0%)	1157 (54.7%)	15596 (67.0%)	<0.0001
History of diabetes	5554 (21.9%)	364 (17.2%)	5190 (22.3%)	<0.0001
History of cancer	2473 (9.7%)	194 (9.2%)	2279 (9.8%)	0.36
Use of other medications to treat ED or OAB*	3679 (14.5%)	235 (11.1%)	3444 (14.8%)	<0.0001
Alpha Blocker history (years)[2]				
Mean (SD)	4.2 (4.0)	0	4.6 (3.9)	<0.0001
Median	3.2	0	3.8	<0.0001
Prostate Cancer Characteristics				
Prostate cancer diagnosed	837 (3.3%)	81 (3.8%)	756 (3.3%)	0.15
Prostate cancer incidence rate (per 1000 person-years)[2]	8.4	8.1	8.5	
Prostate cancer deaths	158 (0.6%)	36 (1.7%)	122 (0.5%)	<0.0001
Prostate cancer mortality rate (per 1000 person-years)[2,3]	1.6	3.5	1.3	

[1] Geocoded education
[2] Person time starts at matching and ends at end of study or Pca diagnosis
[3] Person time for men who were lost to follow-up but died during the study period was calculated up to the date of disenrollment.

Table 6 compares the distributions of the pre-treatment and prostate cancer characteristics among men who used a 5ARI, comparing those who used both a 5ARI and AB to those who only used a 5ARI. Of the 25,388 men who took a 5ARI during follow-up, the vast majority were also exposed to an AB (91.7%). Men who only took a 5ARI were younger at 5ARI initiation compared to combo therapy users (p<0.0001). PSA level at time of 5ARI initiation was comparable between monotherapy and combo therapy users, with a median of 4.5 ng/mL compared to 4.0 ng/mL among the combo therapy users (p=0.31). Approximately 35% of those on combo therapy had a comorbidity index score of 2 or greater compared to 27% of mono therapy users (p<0.0001). Combo users were also more likely to have a history of cardiovascular disease compared to monotherapy users (p<0.0001). (Table 6)

In terms of the prostate cancer characteristics displayed in Table 6, a higher proportion of men were diagnosed with prostate cancer in the 5ARI monotherapy (3.8%) compared to the combo therapy group (3.3%) (p=0.15). However, the incidence rate of prostate cancer was slightly lower in these men, at 8.1/1000 person-years in the monotherapy group compared to 8.5/1000 person-years in the combo therapy group. The proportion of prostate cancer deaths was greater among monotherapy users compared to combo users, with 1.7% occurring in the monotherapy group and 0.5% in the combo therapy group (p<0.0001). However, the prostate cancer mortality rate was higher (3.5/1000 person-years) among monotherapy users compared to combo users (1.3/1000 person-years). (Table 6)

Table 7 Characteristics during follow-up by BPH medication group (N=174,895)

	Overall (n=174895)	5ARI users (n=25388)	Alpha-blocker users (n=149507)	p-value
Post-treatment Characteristics				
Cumulative exposure time (years)*				
Mean (SD)	1.5 (1.5)	2.2 (2.1)	1.4 (1.4)	<0.0001
Median	1.1	1.5	1.1	<0.0001
Cumulative dose (gram)*				
Mean (SD)	2.6 (3.9)	4.1 (4.0)	2.3 (3.8)	<0.0001
Median	1.2	2.9	1.0	<0.0001
Duration of follow-up time (years)*				
Mean (SD)	3.1 (2.7)	4.0 (3.1)	3.0 (2.6)	<0.0001
Median	2.4	3.3	2.3	<0.0001
Patients with ≥1 PSA test	113248 (64.8%)	18801 (74.1%)	94447 (63.2%)	<0.0001
Number of PSA tests				
Mean (SD)	2.2 (3.5)	3.1 (4.2)	2.0 (3.3)	<0.0001
Median	1.0	2.0	1.0	<0.0001
Patients with ≥1 biopsy	14658 (8.4%)	3190 (12.6%)	11468 (7.7%)	<0.0001
Number of Biopsies				
Mean (SD)	0.1 (0.4)	0.2 (0.5)	0.1 (0.4)	<0.0001
Median	0	0	0	<0.0001
Time from last treatment to prostate cancer diagnosed post matching (years)				
Mean (SD)	-0.6 (2.3)	-1.2 (3.0)	-0.5 (2.1)	<0.0001
Median	-0.3	-0.5	-0.2	<0.0001
Prostate cancer incidence rate (per 1000 person- years)[1]	8.4	4.1	9.3	
Prostate cancer diagnosed post-matching	5196 (3.0%)	837 (3.3%)	4359 (2.9%)	0.0009

	Overall (n=174895)	5ARI users (n=25388)	Alpha-blocker users (n=149507)	p-value
Prostate cancer incidence rate (per 1000 person-years)[2]	10.5	4.1	9.3	
Prostate cancer death	1053 (0.6%)	158 (0.6%)	895 (0.6%)	0.65
Prostate cancer mortality rate (per 1000 person-years)[2,3]	1.9	1.6	2.0	

*Cumulative exposure, dose and follow-up time are calculated from time of 5ARI initiation (and matched time point in AB user to the earliest of death, disenrollment or 12/31/2010.
[1]Person-time starts at BPH initiation and ends at end of study or Pca diagnosis
[2]Person time starts at matching and ends at end of study or Pca diagnosis
[3]Person time for men who were lost to follow-up but died during the study period was calculated up to the date of disenrollment.

Table 7 displays the characteristics during follow-up comparing 5ARI users to AB users (N=174,895 records). The median cumulative dose in grams after matching was higher for the 5ARI users at 2.9 grams compared to 1.0 grams for AB users (p<0.0001). Duration of follow-up was also longer on average among 5ARI users compared to AB users, with men who took 5ARIs being followed for an average of 3.3 years compared to men who took ABs being followed for an average 2.3 years post-matching (p<0.0001). The majority of men in this sample had at least 1 PSA test during follow-up, but the number of PSA tests was significantly higher among 5ARI users. Men who used 5ARIs had an average of 2 tests compared to 1 test among AB users during follow-up post matching (p<0.0001). Approximately 12.6% of men who used a 5ARI were biopsied after their 5ARI initiation (matching) compared to 7.7% of men who used an AB (p<0.0001). Almost all of the men (>98%) who were diagnosed with prostate cancer were on treatment for BPH at the time they were diagnosed in both groups. The proportion of men diagnosed with prostate cancer was slightly greater in the 5ARI group (3.3) compared to the AB group (2.9%) (p<0.0009). However,the corresponding incidence rate was greater in the AB group (9.3/1000 person-years) compared to the 5ARI group (4.1/1000 person-years). The proportion of men who died of prostate cancer was comparable between 5ARI users (0.6%) and AB users (0.6%) (p=0.65). The mortality rates were similar at 2.0 per 1000 person-years among AB and 1.6 per 1000 person-years among 5ARI users. (Table 7)

Table 8 Prostate cancer characteristics among men diagnosed with prostate cancer diagnosed post-matching by BPH medication group (N=5,196)

	Overall (n=5196)	5ARI users (n=837)	Alpha-blocker users (n=4359)	p-value
Prostate Cancer Characteristics				
Number of PSA tests				
Mean (SD)	10.2. (8.1)	11.4 (8.8)	9.9 (7.9)	<0.0001
Median	8.0	10.0	8.0	<0.0001
Number of biopsies				
Mean (SD)	1.0 (0.8)	1.0 (1.0)	1.0 (0.8)	0.13
Median	1.0	1.0	1.0	0.13

	Overall (n=5196)	5ARI users (n=837)	Alpha-blocker users (n=4359)	p-value
Age at diagnosis				
Mean (SD)	72.8 (8.5)	75.0 (8.6)	72.4 (8.4)	<0.0001
Median	72.5	75.1	72.0	<0.0001
<60	304 (5.9%)	30 (3.6%)	274 (6.3%)	<0.0001
60-69	1794 (34.5%)	221 (26.4%)	1573 (36.1%)	
70+	3098 (59.6%)	586 (70.0%)	2512 (57.6%)	
Gleason score at diagnosis				
Missing	2313 (44.5%)	365 (43.6%)	1948 (44.7%)	0.02
≤6	1434 (27.6%)	240 (28.7%)	1194 (27.4%)	
7	950 (18.3%)	132 (15.8%)	818 (18.8%)	
8-10	499 (9.6%)	100 (12.0%)	399 (9.2%)	
Stage at prostate cancer diagnosis				
Missing	1173 (22.6%)	171 (20.4%)	1002 (23.0%)	<0.0001
I/II	3472 (66.8%)	547 (65.4%)	2925 (67.1%)	
III/IV	551 (10.6%)	119 (14.2%)	432 (9.9%)	
Bone scan at diagnosis (within 6 months)	1255 (24.2%)	261 (31.2%)	994 (22.8%)	<0.0001
Other tests for metastatic disease at diagnosis (within 6 months)	3274 (63.0%)	518 (61.9%)	2756 (63.2%)	0.46
Prostate cancer primary treatment within 6 months of diagnosis (1 chemo patient not included)				
Surgery	1931 (37.2%)	294 (35.1%)	1637 (37.6%)	0.02
Radiation therapy	835 (16.1%)	115 (13.7%)	720 (16.5%)	
No treatment	2429 (46.8%)	427 (51.0%)	2002 (45.9%)	
Follow –up time after cancer (years)				
Mean (SD)	3.4 (3.0)	3.2 (3.0)	3.5 (3.0)	0.008
Median	2.6	2.4	2.7	0.008
Prostate cancer diagnosed time since last exposure to BPH medication				
Mean (SD)	-0.6 (2.3)	-1.2 (3.0)	-0.5 (2.1)	<0.0001
Median	-0.3	-0.5	-0.2	<0.0001

Table 8 displays characteristics among the 5,196 men diagnosed with prostate cancer in this cohort after matching. The median number of PSA tests was greater among 5ARI users compared to AB users. (p<0.0001). Among the 55% of men with Gleason scores available, the proportion of Gleason 8-10 cancers was greater in the 5ARI group compared to the AB group (12.0% vs. 9.2%) (p=0.02) (Table 8). Men who used a 5ARI were more likely to receive a bone scan compared to AB users (31.2% vs. 22.8%)

(p=<0.0001). 5ARI users were less likely to have treatment for their prostate cancer in the 6 months following diagnosis (p=0.02). The follow-up time after prostate cancer diagnosis was greater among AB users on average compared to 5ARI users (2.7 vs. 2.4 years) (p=0.008). (Table 8)

10.3. Results of essential analyses

Table 9 Crude, age-adjusted and multivariable-adjusted prostate cancer related mortality rates, sub-distribution hazard ratios, and hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Subdist. Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Crude						
Overall (n=174895, 1053 Pca deaths)	0.62	0.60	1.55	2.03	0.81 (0.68,0.96)**	0.72 (0.61,0.86)**
Cumulative exposure						
<6 mos (n=45226, 279 Pca deaths)	0.83	0.59	2.74	2.64	1.1 (0.78,1.56)	1.08 (0.76,1.52)
6 mos-1yr (n=35812, 239 Pca deaths)	0.84	0.64	2.74	2.62	1.11 (0.80,1.55)	1.03 (0.73,1.44)
1 yr-2 yrs (n=45498, 285 Pca deaths)	0.64	0.62	2.02	2.30	0.89 (0.63,1.27)	0.80 (0.57,1.14)
2+ yrs (n=48359, 250 Pca deaths)	0.42	0.54	0.79	1.24	0.60 (0.43,0.83)**	0.52 (0.38,0.73)**
Cumulative dose (gram)						
1st quartile (n=43705, 284 Pca deaths)	1.11	0.65	3.70	2.63	1.43 (0.53,3.83)	1.39 (0.52,3.72)
2nd quartile (n=42735, 277 Pca deaths)	0.81	0.62	2.47	2.24	1.14 (0.83,1.57)	1.07 (0.78,1.46)
3rd quartile (n=44702, 258 Pca deaths)	0.67	0.56	2.23	1.93	1.18 (0.87,1.6)	1.15 (0.84,1.56)
4th quartile (n=43753, 234 Pca deaths)	0.49	0.55	0.95	1.42	0.64 (0.48,0.86)**	0.57 (0.42,0.78)**
Age-adjusted						
Overall (n=174895, 1053 Pca deaths)	0.20	0.23	0.47	0.73	0.82 (0.69,0.97)**	0.70 (0.59,0.83)**
Cumulative exposure						
<6 mos (n=45226, 279 Pca deaths)	0.18	0.28	0.48	1.19	1.07 (0.76,1.51)	1.02 (0.72,1.44)
6 mos-1yr (n=35812, 239 Pca deaths)	0.11	0.27	0.28	1.12	1.06 (0.76,1.48)	0.94 (0.67,1.32)
1 yr-2 yrs (n=45498, 285 Pca deaths)	0.39	0.14	1.19	0.52	0.90 (0.63,1.27)	0.78 (0.55,1.11)
2+ yrs (n=48359, 250 Pca deaths)	0.09	0.32	0.16	0.72	0.63	0.52

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Subdist. Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
					(0.45,0.87)**	(0.38,0.72)**
Cumulative dose (gram)						
1st quartile (n=43705, 284 Pca deaths)	0.04	0.57	0.02	4.66	1.69 (0.63,4.55)	1.68 (0.63,4.50)
2nd quartile (n=42735, 277 Pca deaths)	0.15	0.25	0.38	0.90	1.17 (0.85,1.6)	1.08 (0.79,1.49)
3rd quartile (n=44702, 258 Pca deaths)	0.27	0.17	0.87	0.55	1.14 (0.84,1.55)	1.15 (0.84,1.56)
4th quartile (n=43753, 234 Pca deaths)	0.09	0.30	0.17	0.76	0.62 (0.46,0.83)**	0.52 (0.39,0.71)**
Multi-variable adjusted[1]						
Overall (n=174895)	0.04	0.04	0.12	0.15	0.85 (0.72,1.01)	0.72 (0.61,0.85)**
Cumulative exposure						
<6 mos (n=45226)	0.03	0.02	0.15	0.16	1.07 (0.75,1.51)	1.02 (0.72,1.45)
6 mos-1yr (n=35812)	0.02	0.02	0.01	0.02	1.14 (0.82,1.61)	1.02 (0.72,1.43)
1 yr-2 yrs (n=45498)	0.03	0.03	0.04	0.03	0.93 (0.65,1.33)	0.82 (0.58,1.16)
2+ yrs (n=48359)	0.02	0.02	0.009	0.02	0.66 (0.48,0.92)**	0.53 (0.38,0.74)**
Cumulative dose (gram)						
Q1 (n=43705)	---	---	0.08	0.02	1.62 (0.59,4.44)	1.55 (0.58,4.19)
Q2 (n=42735)	0.06	0.04	0.12	0.06	1.16 (0.84,1.60)	1.07 (0.78,1.48)
Q3 (n=44702)	0.005	0.002	0.002	0.0007	1.27 (0.93,1.74)	1.28 (0.94,1.74)
Q4 (n=43753)	0.004	0.006	0.001	0.005	0.64 (0.47,0.86)**	0.52 (0.38,0.71)**

^Results are from negative binomial regression, with the exception of the sub distributional hazard ratios which were estimated using competing risk proportional hazard regression, and hazard ratios which were estimated using proportional hazard regression.
**P<0.05,
1 Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat overactive bladder or erectile dysfunction.

Table 9 displays the crude, age-adjusted and multi-variable adjusted associations between BPH medication use and risk of prostate cancer mortality overall and stratified by cumulative time of drug exposure and cumulative dose. When the competing risk of death due to other causes was not adjusted for, 5ARI use was not associated with the risk of prostate cancer mortality when compared to AB use (HR: 0.72 95% CI: 0.61, 0.85). After accounting for competing risk of death from other causes and adjusting for age,

race, region, and history of AB use, Charlson, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with prostate cancer mortality (SHR: 0.85, 95% CI: 0.72, 1.01). (Table 9)

When adjusted for competing risks, both cumulative exposure and dose showed similar trends in that men in the highest quartile of dose and with > 2 years cumulative exposure were the least likely to die of prostate cancer if they used a 5ARI compared to an AB (Dose SHR: 0.64, 95%CI: 0.47, 0.86; Cumulative exposure SHR: 0.66, 95%CI: 0.48, 0.92). When not adjusted for competing risks, a decreased risk of prostate cancer death was also associated with 5ARI use among men in the highest quartile of dose and with > 2 years cumulative exposure. (Table 9)

10.4. Other analyses

Table 10 Crude, age-adjusted and multivariable-adjusted prostate cancer related mortality rates, sub-distribution hazard ratios, and hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose*: PSA measured at matching less than 10 ng/ml (n-100,305)*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Subdist. Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Crude						
Overall (n=100305, 388 Pca deaths)	0.30	0.40	0.75	1.34	0.57 (0.42,0.77)**	0.52 (0.39,0.71)**
Cumulative exposure						
<6 mos (n=11493,41 Pca deaths)	0.33	0.37	1.06	1.51	0.73 (0.37,1.44)	0.72 (0.36,1.43)
6 mos-1yr (n=34871,140 Pca deaths)	0.43	0.42	1.39	1.64	0.86 (0.48,1.54)	0.83 (0.46,1.49)
1 yr-2 yrs (n=25758,116 Pca deaths)	0.34	0.47	1.07	1.71	0.61 (0.34,1.11)	0.56 (0.31,1.02)
2+ yrs (n=28183,91 Pca deaths)	0.20	0.36	0.39	0.84	0.42 (0.23,0.75)**	0.38 (0.21,0.68)**
Cumulative dose (gram)						
1st quartile (n=25075,103 Pca deaths)	1.23	0.40	4.12	1.52	2.68 (0.85,8.45)	2.69 (0.85,8.50)
2nd quartile (n=24137,107 Pca deaths)	0.33	0.46	1.00	1.61	0.62 (0.34,1.14)	0.59 (0.32,1.08)
3rd quartile (n=26016,98 Pca deaths)	0.33	0.39	1.09	1.33	0.82 (0.48,1.41)	0.79 (0.46,1.36)
4th quartile (n=25077,80 Pca deaths)	0.23	0.36	0.46	0.93	0.44 (0.26,0.76)**	0.41 (0.23,0.70)**
Age-adjusted						
Overall (n=100305, 388 Pca deaths)	0.12	0.17	0.33	0.54	0.55 (0.41,0.75)**	0.48 (0.36,0.66)**

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Subdist. Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Cumulative exposure						
<6 mos (n=11493,41 Pca deaths)	0.0009	0.001	0.0003	0.0005	0.69 (0.35,1.37)	0.66 (0.33,1.32)
6 mos-1yr (n=34871,140 Pca deaths)	0.09	0.23	0.22	0.96	0.80 (0.45,1.44)	0.75 (0.42,1.36)
1 yr-2 yrs (n=25758,116 Pca deaths)	0.27	0.15	0.85	0.52	0.60 (0.33,1.09)	0.54 (0.30,0.98)**
2+ yrs (n=28183,91 Pca deaths)	0.06	0.24	0.12	0.57	0.42 (0.23,0.75)**	0.36 (0.20,0.65)**
Cumulative dose (gram)						
1st quartile (n=25075,103 Pca deaths)	0.06	0.35	0.03	2.89	2.88 (0.91,9.11)	2.88 (0.91,9.10)
2nd quartile (n=24137,107 Pca deaths)	0.09	0.17	0.17	0.68	0.62 (0.34,1.13)	0.58 (0.32,1.06)
3rd quartile (n=26016,98 Pca deaths)	0.19	0.15	0.60	0.49	0.78 (0.46,1.35)	0.79 (0.46,1.35)
4th quartile (n=25077,80 Pca deaths)	0.06	0.20	0.11	0.54	0.41 (0.24,0.71)**	0.36 (0.21,0.62)**
Multi-variable adjusted						
Overall (n=100305, 388 Pca deaths)	0.009	0.02	0.006	0.02	0.59 (0.43,0.80)**	0.50 (0.37,0.68)**
Cumulative exposure						
<6 mos (n=11493,41 Pca deaths)	9.2E-6	0.00001	0.00006	0.0002	0.71 (0.35,1.42)	0.68 (0.34,1.36)
6 mos-1yr (n=34871,140 Pca deaths)	0.001	0.001	0.0002	0.0006	0.84 (0.47,1.52)	0.79 (0.44,1.45)
1 yr-2 yrs (n=25758,116 Pca deaths)	0.004	0.02	0.001	0.01	0.61 (0.34,1.12)	0.54 (0.29,0.98)**
2+ yrs (n=28183,91 Pca deaths)	0.00007	0.00009	0.0003	0.0003	0.46 (0.26,0.83)**	0.38 (0.21,0.69)**
Cumulative dose (gram)						
1st quartile (n=25075,103 Pca deaths)	---	---	0.0005	0.0001	---	2.69 (0.84,8.59)
2nd quartile (n=24137,107 Pca deaths)	0.001	0.005	0.0002	0.002	0.60 (0.33,1.11)	0.56 (0.30,1.02)
3rd quartile (n=26016,98 Pca deaths)	0.0003	0.0002	0.00003	0.00002	0.85 (0.50,1.45)	0.84 (0.49,1.45)
4th quartile (n=25077,80 Pca deaths)	1.6E-6	1.2E-6	2.1E-6	1.9E-6	---	0.36 (0.20,0.63)**

*Results are from negative binomial regression, with the exception of the sub distributional hazard ratios which were estimated using competing risk proportional hazard regression, and hazard ratios which were estimated using proportional hazard regression.
**P<0.05,
[1] Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB or ED.

Table 11 Crude, age-adjusted and multivariable-adjusted prostate cancer related mortality rates, sub-distribution hazard ratios, and hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose*: PSA measured at matching greater than 10 ng/ml (n=9,761)*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Subdistribution Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Crude						
Overall (n=9328, 337 Pca deaths)	1.74	4.60	4.02	16.70	0.27 (0.20,0.36)**	0.25 (0.18,0.33)**
Cumulative exposure						
<6 mos (n=1218, 60 Pca deaths)	2.84	4.92	9.74	24.38	0.42 (0.24,0.74**)	0.42 (0.24,0.74)**
6 mos-1yr (n=3104, 141 Pca deaths)	2.49	5.78	8.80	24.93	0.36 (0.2,0.65)**	0.35 (0.20,0.64)**
1 yr-2 yrs (n=2115, 73 Pca deaths)	2.28	3.98	6.92	14.46	0.49 (0.28,0.86)**	0.45 (0.25,0.79)**
2+ yrs (n=2891, 63 Pca deaths)	0.95	3.67	1.67	8.42	0.19 (0.11,0.33)**	0.16 (0.09,0.29)**
Cumulative dose (gram)						
1st quartile (n=2276, 118 Pca deaths)	0	5.28	0	23.23	---	---
2nd quartile (n=2332, 87 Pca deaths)	2.42	4.29	7.63	16.37	0.50 (0.29,0.85)**	0.48 (0.28,0.82)**
3r quartile (n=2386, 86 Pca deaths)	2.51	4.44	8.06	15.48	0.52 (0.33,0.82)**	0.52 (0.33,0.82)**
4th quartile (n=2334, 46 Pca deaths)	0.90	3.71	1.55	9.24	0.16 (0.09,0.30)**	0.13 (0.07,0.26)**
Age-adjusted						
Overall (n=9328, 337 Pca deaths)	0.28	2.29	0.56	8.20	0.32 (0.24,0.42)**	0.29 (0.21,0.38)**
Cumulative exposure						
<6 mos (n=1218, 60 Pca deaths)	1.09	3.14	3.06	14.23	0.44 (0.25,0.78)**	0.44 (0.25,0.79)**
6 mos-1yr (n=3104, 141 Pca deaths)	0.0001	0.004	0.0002	0.04	0.37 (0.21,0.67)**	0.35 (0.20,0.64)**
1 yr-2 yrs (n=2115, 73 Pca deaths)	0.0009	0.002	0.003	0.009	0.55 (0.31,0.99)**	0.52 (0.30,0.93)**
2+ yrs (n=2891, 63 Pca deaths)	0.00004	0.003	0.00003	0.01	0.23 (0.13,0.42)**	0.20 (0.11,0.36)**
Cumulative dose (gram)						
1st quartile (n=2276, 118 Pca deaths)	5.0E-9	2.12	5.1E-8	8.20	---	---
2nd quartile (n=2332, 87 Pca deaths)	0.77	2.51	2.16	9.80	0.56 (0.33,0.96)**	0.56 (0.33,0.95)**
3rd quartile (n=2386, 86 Pca deaths)	0.0007	0.002	0.003	0.009	0.56 (0.35,0.90)**	0.60 (0.38,0.96)**
4th quartile (n=2334, 46 Pca deaths)	0.00005	0.004	0.00004	0.02	0.18	0.15

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Subdistribution Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
					(0.10,0.35)**	(0.08,0.30)**
Multi-variable adjusted						
Overall (n=9328, 337 Pca deaths)	0.10	0.42	0.25	2.12	0.37 (0.28,0.50)**	0.33 (0.24,0.44)**
Cumulative exposure						
<6 mos (n=1218, 60 Pca deaths)	0.10	0.12	0.12	0.30	0.48 (0.27,0.86)**	0.49 (0.27,0.87)**
6 mos-1yr (n=3104, 141 Pca deaths)	3.6E-6	0.00005	1.0E-6	0.00004	0.43 (0.23,0.79)**	0.42 (0.23,0.76)**
1 yr-2 yrs (n=2115, 73 Pca deaths)	0.00001	0.00003	0.00005	0.0001	0.64 (0.35,1.18)	0.61 (0.34,1.09)
2+ yrs (n=2891, 63 Pca deaths)	0.00001	0.0003	0.00003	0.0007	0.26 (0.14,0.48)**	0.21 (0.12,0.39)**
Cumulative dose (gram)						
1st quartile (n=2276, 118 Pca deaths)	1.5E-11	0.17	5.6E-12	0.57	---	---
2nd quartile (n=2332, 87 Pca deaths)	0.01	0.02	0.02	0.03	0.63 (0.36,1.10)	0.62 (0.36,1.06)
3rd quartile (n=2386, 86 Pca deaths)	6.3E-7	1.2E-6	9.6E-7	2.7E-6	---	0.73 (0.45,1.19)
4th quartile (n=2334, 46 Pca deaths)	5.4E-8	2.2E-6	6.9E-8	3.3E-6	---	0.16 (0.08,0.31)**

*Results are from negative binomial regression, with the exception of the sub distributional hazard ratios which were estimated using competing risk proportional hazard regression, and hazard ratios which were estimated using proportional hazard regression.
**P<0.05,
[1] Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB or ED.

Table 10 and Table 11 display the regression results stratified by PSA level at matching for 63% of the sample of men with PSA levels drawn at the matching time point. PSA level modified the association between 5ARI use and prostate cancer mortality, with a stronger reduction in risk evident among men with PSA levels greater than 10 at 5ARI initiation. Among men with a PSA >10, the use of a 5ARI was associated with a 63% decrease in the risk of prostate cancer mortality when compared to using an AB, after adjustment for age at initiation, medication initiation year, region, race, history of AB use, Charlson score and comorbidities and adjusting for competing risks (SHR: 0.37, 95%CI: 0.28, 0.50). A similar reduction in risk was evident when not adjusting for competing risks as well. (Table 11) Among men with a PSA level below 10 ng/mL at 5ARI initiation, a weaker reduced risk associated with 5ARI use was observed, when adjusting for competing risks (SHR: 0.59, 95%CI: 0.43, 0.80). (Table 10 and Table 11)

Table 12 Crude and adjusted hazard ratios for 5ARI and alpha blocker users overall and stratified by lag time (defined as time from 5ARI initiation/matching to prostate cancer death) among men who died of prostate cancer (N=1053)*

	Hazard Ratio (95% CI)
Crude	
Overall (n=1,053)	0.77 (0.65,0.91)**
Lag Time	
<1year (n=174 (16.5%))	0.75 (0.46,1.22)
1-3 years (n=435 (41.3%))	1.14 (0.87,1.49)
3-6 years (n=295 (28.0%))	1.08 (0.77,1.50)
6-9 years (n=102 (9.7%))	0.92 (0.58,1.46)
9+ years (n=47 (4.5%))	0.87 (0.44,1.70)
Age-Adjusted	
Overall (n=1,053)	0.78 (0.66,0.92)**
Lag Time	
<1year (n=174 (16.5%))	0.76 (0.46,1.24)
1-3 years (n=435 (41.3%))	1.15 (0.88,1.51)
3-6 years (n=295 (28.0%))	1.09 (0.78,1.52)
6-9 years (n=102 (9.7%))	0.95 (0.60,1.51)
9+ years (n=47 (4.5%))	0.92 (0.46,1.82)
Multi-variable adjusted without PSA[1]	
Overall (n=1,053)	0.80 (0.67,0.95)**
Lag Time	
<1year (n=174 (16.5%))	0.69 (0.40,1.21)
1-3 years (n=435 (41.3%))	1.19 (0.90,1.58)
3-6 years (n=295 (28.0%))	1.10 (0.77,1.55)
6-9 years (n=102 (9.7%))	0.95 (0.54,1.68)
9+ years (n=47 (4.5%))	0.99 (0.38,2.62)

Results were estimated using competing risk proportional hazard regression and proportional hazard regression. Results for this sample of men were the same for both modeling approaches.**P<0.05[1] Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB or ED

Table 12 displays the association between 5ARI use and prostate cancer mortality stratified by lag time of use, defined as time of 5ARI initiation/matching to prostate cancer death among the sample of men who died of prostate cancer. While the magnitudes suggested a reduced risk of prostate cancer death among with the shortest lag time (<1 year), and a slightly increased risk of prostate cancer mortality among men who had a lag time of 1-3 years and 3-6 years, none of these results reached statistical significance, most likely due to the small number of events. (Table 12)

Table 13 Crude prostate cancer related mortality rates, crude and adjusted sub-distribution hazard ratios and hazard ratios for 5ARI and alpha-blocker users overall and stratified by pre-treatment characteristics of interest*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Crude Subdist. Hazard Ratio (95% CI)	Adjusted Subdist. Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
	5ARI	**AB**	**5ARI**	**AB**			
Overall (n=174895,1053 Pca deaths)	0.62	0.60	1.55	2.03	0.81 (0.68,0.96)**	0.85 (0.72,1.01)	0.72 (0.61,0.85)**
Age at matching (years)							
<60 (n=17884, 11 Pca deaths)	0.04	0.07	0.09	0.18	0.47 (0.06,3.6)	---	0.46 (0.06,3.70)
60-69 (n=52980, 107 Pca deaths)	0.20	0.20	0.46	0.66	0.68 (0.40,1.17)	0.74 (0.43,1.27)	0.66 (0.38,1.15)
70+ (n=104031, 935 Pca deaths)	0.93	0.89	2.44	3.23	0.83 (0.69,0.99)**	0.86 (0.72,1.03)	0.72 (0.61,0.87)**
Race							
Non-Hispanic White (n=134220, 848 Pca deaths)	0.64	0.63	1.55	2.13	0.78 (0.64,0.94)**	0.82 (0.68,1.00)	0.68 (0.56,0.83)**
African American (n=12711, 110 Pca deaths)	0.90	0.86	2.20	2.52	0.91 (0.54,1.52)	0.93 (0.56,1.6)	0.85 (0.51,1.43)
Asian (n=14636, 39 Pca deaths)	0.15	0.29	0.40	0.97	0.43 (0.13,1.4)	0.49 (0.16,1.49)	0.43 (0.13,1.42)
HP, IN, MU and UN (n=13328, 56 Pca deaths)	0.69	0.38	2.27	1.58	1.49 (0.77,2.88)	---	1.55 (0.77,3.12)
PSA at matching (ng/ml)							
Missing(n=65262, 328 Pca deaths)	0.86	0.46	2.17	1.61	1.41 (1.05,1.88)**	1.37 (1.02,1.83)**	1.10 (0.82,1.48)
0-2.5 (n=56985, 167 Pca deaths)	0.14	0.31	0.37	1.02	0.37 (0.19,0.73)**	0.39 (0.20,0.77)**	0.34 (0.17,0.67)**
2.5-4 (n=17497, 49 Pca deaths)	0.24	0.29	0.59	0.96	0.60 (0.27,1.35)	0.63 (0.28,1.40)	0.54 (0.24,1.21)
>=4 (n=35151, 509 Pca deaths)	0.90	1.66	2.14	5.75	0.40 (0.31,0.50)**	0.48 (0.38,0.60)**	0.42 (0.33,0.53)**
Prior Alpha-blocker history at matching (years)							
0-0.6 (n=43652, 358 Pca deaths)	1.22	0.75	2.23	1.77	1.31 (1.02,1.68)**	1.33 (1.03,1.71)**	1.12 (0.87,1.45)
0.6-3.4 (n=43825, 250 Pca deaths)	0.66	0.56	1.63	1.79	0.98 (0.70,1.37)	1.11 (0.80,1.55)	0.92 (0.66,1.29)
3.4-7.1 (n=43697, 240 Pca deaths)	0.43	0.57	1.17	2.29	0.54 (0.36,0.8)**	0.60 (0.40,0.89)**	0.49 (0.33,0.73)**
>=7.1 (n=43721, 205 Pca deaths)	0.15	0.52	0.53	2.60	0.21 (0.11,0.40)**	0.23 (0.12,0.44)**	0.19 (0.10,0.38)**

Results are from negative binomial regression, with the exception of the sub distributional hazard ratios which were estimated using competing risk proportional hazard regression, and hazard ratios which were estimated using proportional hazard regression. The adjusted models are adjusted for all other factors except the corresponding strata.
**P<0.05

[1]Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB or ED.
--- denotes that models did not converge due to small sample sizes.

Table 13 displays the associations between 5ARI use and prostate cancer death stratified by baseline characteristics that were thought to potentially modify this association. The association of 5ARI use with prostate cancer mortality did not differ significantly across race strata or age at matching. However, there was again heterogeneity across strata for PSA at matching. There was a reduction in risk associated with 5ARI among men with baseline PSA levels in the highest category (>4.0 ng/mL), as 5ARI use was associated with a 53% reduction in the risk of prostate cancer death when compared to AB use (SHR: 0.48, 95%CI: 0.38, 0.60) when adjusted for competing risks. However, a reduced risk of prostate cancer was also evident among men in the lowest PSA category (0-2.5 ng/mL) as well. For men who were missing PSA levels at matching and thus not included in the PSA stratified analyses, men who used 5ARIs were 1.33 times more likely to die of prostate cancer than those using alpha-blockers (SHR: 1.33, 95%CI: 1.03, 1.71). An increasing reduction in risk associated with 5ARI use was seen with increasing levels of history of AB use, as 5ARI users were 77% less likely to die of prostate cancer compared to AB users in the longest category of prior AB use (>7.5 years) (SHR: 0.23, 95%CI: 0.12, 0.44). (Table 13)

Other essential analyses from the case-control, all-cause mortality and combined metastatic prostate cancer mortality reports (full text of the all cause and combined metastatic prostate cancer reports available in ANNEX 1)

Table 14 Multivariable-adjusted matched odds ratios stratified by duration of cumulative exposure, dose and history of AB use from the nested case-control analysis

	Cases N (%) (N=1671)		Controls N (%) N=16,640		Adjusted MOR (95% CI)
	5ARI	AB	5ARI	AB	
Overall	165(9.9)	1506 (90.1)	1746 (10.5)	14894 (89.5)	0.95 (0.78,1.17)
Cumulative exposure					
<6 mos (n=3767)	46 (11.2)	366 (88.8)	370 (11.0)	2985 (89.0)	1.03 (0.61,1.73)
6 mos -1 yr (n=2602)	46 (15.0)	260 (85.0)	339 (14.8)	1957 (85.2)	0.86 (0.46,1.60)
1–2 yr (n=3013)	38 (11.4)	296 (88.6)	390 (14.6)	2289 (85.4)	0.46 (0.21,1.00)
2+ years (n=8929)	35 (5.7)	584 (94.4)	647 (7.8)	7663 (92.2	0.78 (0.50,1.22)
Cumulative dose (gram)					
Q1 (n=4645)	22 (4.5)	469 (95.5)	213 (5.1)	3941 (94.9)	0.71 (0.34,1.49)
Q2 (n=4378)	58 (12.8)	397 (87.3)	455 (11.6)	3468 (88.4)	0.94 (0.55,1.60)
Q3 (n=4736)	65 (15.3)	361 (84.7)	661 (15.3)	3649 (84.7)	0.94 (0.57,1.56)
Q4 (n=4552)	20 (6.7)	279 (93.3)	417 (9.8)	3836 (90.2)	0.62 (0.30,1.29)

[b]Adjusted for age, BPH initiation year, race, region, Charlson score and comorbidities [c]Cumulative exposure was calculated from time of matching (5ARI initiation and matched index date in AB users) in cohort study and from 5ARI initiation among 5ARI users and AB initiation in AB users in case case-control study.

Table 14 displays the main modelling results from the case-control analysis. Overall, a similar proportion of men who died of prostate cancer and their matched controls were exposed to 5ARIs. After adjustment for age, BPH initiation year, race, region, Charlson score and comorbidities, 5ARI use was not associated with prostate cancer mortality when compared to AB use (MOR: 0.95, 95%CI: 0.78, 1.17). When stratified by increasing levels of cumulative exposure and dose, no statistically significant heterogeneity in this association was observed. (Table 14)

Table 15 Multivariable-adjusted all-cause mortality rates, and hazard ratios for all-cause mortality associated with 5ARI and alpha-blocker use overall and stratified by duration of cumulative exposure and cumulative dose in the matched sample* (N=174,895) (see all-cause mortality report in Annex 1)

	No of deaths /No at risk (%)		Mortality Rate Per 1000 p-y		Hazard Ratio[1] (95% CI)
Multi-variable adjusted	**5ARI**	**AB**	**5ARI**	**AB**	
Overall (n=174895, 35266 all-cause deaths)	10.12	11.51	118.34	176.65	0.64 (0.62,0.66)**
Cumulative exposure					
<6 mos (n=21173, 3996 all-cause deaths)	10.43	6.49	551.16	252.81	1.01 (0.79,1.29)
6 mos-1yr (n=59865, 12951 all-cause deaths)	13.82	13.48	130.37	113.27	0.83 (0.79,0.87)**
1-2 yrs (n=45498, 9593 all-cause deaths)	9.48	11.64	47.89	57.03	0.75 (0.70,0.80)**
2+ yrs (n=48359, 8726 all-cause deaths)	6.65	8.08	17.64	23.87	0.54 (0.51,0.57)
Cumulative dose (gram)					
1st quartile (n=43705, 8913 all-cause deaths)	13.13	10.15	244.30	267.29	0.97 (0.76,1.24)
2nd quartile (n=42735, 9852 all-cause deaths)	12.24	11.34	151.17	98.57	0.88 (0.83,0.93)**
3rd quartile (n=44702, 9025 all-cause deaths)	12.11	11.62	83.41	69.25	1.01 (0.95,1.07)
4th quartile (n=43753, 7476 all-cause deaths)	6.68	8.25	18.84	30.94	0.55 (0.52,0.58)**

*Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression. Covariates were collected at the time of matching (or index date). **P<0.05 [1]Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities

Table 15 and Table 16 display the main modelling results from the all-cause mortality analysis. Among the sample of men in the matched sample that was also used for the primary analysis (Table 15), 5ARI use was not associated with an increased risk of all-cause mortality compared to AB use, and may be associated with a reduction in risk (HR: 0.64, 95%CI: 0.62, 0.66). The strongest reduction in risk was evident in the highest cumulative exposure category, with men exposed to 5ARIs great than 2 years having a 50% reduced risk of death compared to AB users exposed for more than 2 years (HR: 0.55, 95%CI: 0.51, 0.57). The results were similar with increasing dose.

Table 16 Multivariable adjusted time varying hazard ratios for all-cause mortality associated with 5ARI and alpha-blocker use overall and stratified by duration of cumulative exposure and cumulative dose in the unmatched cohort (N=214,272)* (See all-cause mortality report in Annex 1)

	No of deaths /No at risk (%)		Mortality Rate Per 1000 p-y		Hazard Ratio[1] (95% CI)
Multi-variable adjusted	**5ARI**	**AB**	**5ARI**	**AB**	
Overall (n=214272, 54423 all-cause deaths)	13.8	22.6	41.4	76.13	0.84 (0.82,0.87)**
Cumulative exposure					
<6 mos (n=1662, 623 all-cause deaths)	16.2	22.1	182.67	292.78	0.99 (0.69,1.40)
6 mos-1yr (n=63640, 17946 all-cause deaths)	19.9	23.7	117.3	120.7	0.88 (0.84,0.92)
1-2 yrs (n=31164, 9623 all-cause deaths)	16.9	25.1	50.7	81.1	0.82 (0.77,0.87)
2+ yrs (n=117806, 26231 all-cause deaths)	11.2	17.3	17.6	29.8	0.99 (0.93,1.04)
Cumulative dose (gram)					
1st quartile (n=57252, 16187 all-cause deaths)	21	23.7	171.3	123	0.95 (0.76,1.20)
2nd quartile (n=53165, 15043 all-cause deaths)	18.7	23.7	72.2	82.7	1.02 (0.96,1.08)
3rd quartile (n=51964, 12558 all-cause deaths)	11.8	18.3	23.1	40.5	1.18 (1.12,1.24)**
4th quartile (n=51891, 10635 all-cause deaths)	8.5	12.6	11.9	20.5	1.05 (0.99,1.11)

Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression. Covariates were adjusted for at two time points, medication initiation at matching (or index date)
**P<0.05
[1]Adjusted for age at BPH, BPH initiation year, race, region, Charlson score and comorbidities.

Table 16 displays the main modelling results from the time-varying all-cause mortality analysis that was performed in the unmatched eligible cohort sample and used two time points of covariate collection (medication initiation and matching (5ARI initiation and index date). For men who were missing the second time point of covariate information, the last value was carried forward. (See all-cause mortality report in ANNEX 1 for details). Among the eligible men in the unmatched cohort (Table 16), 5ARI use was again not associated with an increased risk of all-cause mortality compared to AB use, but may be associated with a reduction in risk (HR: 0.84, 95%CI: 0.82,0.87). The results were different however for increasing cumulative exposure and dose categories, as no significant heterogeneity in the association of 5ARIs and all-cause mortality was evident across strata in this analysis. Multiple other sensitivity analyses were run in both the matched and unmatched cohorts and are presented in the all-cause mortality report in more detail in ANNEX 1.

Table 17 Multivariable-adjusted metastatic or prostate cancer death event rates, and hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose* (see Metastatic Report in Annex 1)

	No of deaths /No at risk (%)		Event Rate Per 1000 p-y		Hazard Ratio[1] (95% CI)
Multi-variable adjusted	**5ARI**	**AB**	**5ARI**	**AB**	
Overall (n=173990, 1603 combo outcome)	0.22	0.29	1.54	2.49	0.66 (0.58,0.76)**
Cumulative exposure					
<6 mos (n=21038, 194 Pca outcomes)	0.005	0.36	0.0017	9.26	0.72 (0.18,2.89)
6 mos-1yr (n=59603, 613 Pca outcomes)	0.29	0.31	1.77	1.99	0.88 (0.71,1.09)
1 to 2 yrs (n=45268, 415 Pca outcomes)	0.11	0.14	0.26	0.31	0.81 (0.61,1.09)
2+ yrs (n=48081, 381 Pca outcomes)	0.05	0.07	0.07	0.11	0.55 (0.42,0.71)**
Cumulative dose (gram)					
1st quartile (n=43492, 438 Pca outcomes)	0.41	0.30	3.20	4.27	0.99 (0.37,2.66)
2nd quartile (n=42568, 412 Pca outcomes	0.31	0.24	2.80	1.45	0.94 (0.72,1.24)
3rd quartile (n=44432, 399 Pca outcomes)	0.20	0.10	0.80	0.35	1.23 (0.96,1.58)
4th quartile (n=43498, 354 Pca outcomes	0.03	0.06	0.03	0.11	0.50 (0.39,0.65)**

*Results are from negative binomial regression, with the exception of hazard ratios which were estimated using proportional hazard regression.
**P<0.05
[1]Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities.

Table 17 presents the modelling results from the combined metastatic prostate cancer and/or prostate cancer death analysis. This analysis also included metastatic disease as an outcome among men who did not die during the study and prostate cancer deaths detected through NLP review of medical records in men who died without prostate cancer as their underlying cause of death. Similar to the results from the primary analysis, and after adjusting for age, race, region, BPH medication initiation year, prior AB history, Charlson, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with an increase in metastatic and/or prostate cancer mortality (HR: 0.66, 95%CI: 0.58, 0.76) when compared to AB use. When stratified by levels of increasing cumulative exposure, the magnitude of the reduced risk of prostate cancer death and/or metastatic disease associated with 5ARI increased. Men who were exposed for greater than 2 years had the greatest reduction in risk associated with 5ARI use (HR: 0.55, 95% CI: 0.42, 0.71).

10.5. Adverse events/adverse reactions

This retrospective cohort study utilized electronic medical records where it was not feasible to make a causality assessment at the individual case level for adverse events/adverse reactions.

11. DISCUSSION

11.1. Interpretations of Results

The results of this large, population-based study in community practice settings suggest that the use of 5ARIs to treat BPH/LUTS is not associated with an increased risk of prostate cancer mortality when compared to AB use. While there was an increase in Gleason 8-10 prostate cancers diagnosed among men treated with 5ARIs (among those for whom we had Gleason scores) in this population, this did not translate into an increased risk of prostate cancer death.

Our findings are in line with those reported by Azoulay and colleagues in a study of men with prostate cancer in the UK [Azoulay, 2015]. Similarly, Preston et al. found that 5ARI use was not associated with lethal prostate cancer in the Health Professional's Follow-up Study, albeit with limited statistical power [Preston, 2014]. Follow-up results from the PCPT suggested that men treated with finasteride were not more likely to die of all causes compared to men randomized to placebo and results from the Finnish Prostate Cancer Screening Trial found no increase in risk of prostate cancer or all-cause mortality associated with 5ARI use in men diagnosed with prostate cancer [Thompson, 2013, Murtola, 2016]. However, these results are difficult to interpret, as prostate cancer is an infrequent cause of death in the overall population, the generalizability of the results are limited by the highly-selected trial populations [Thompson, 2013, Murtola, 2016] and the populations had low exposure rates [Azoulay, 2015, Preston, 2014, Murtola, 2016].

In contrast to these studies which assessed the association between 5ARI use and prostate cancer mortality[Azoulay, 2015, Preston, 2014, Murtola, 2016, the current study specifically addresses the safety of use of 5ARIs relative to a comparator class of drugs (AB), in men treated for BPH/LUTS in real-world community practice settings. In addition, our findings support the suggestion that the increase in Gleason 7-10 prostate cancers diagnosed among 5ARI users in the chemoprevention trials [Andriole, 2010, Thompson, 2003] may be more related to bias rather than biology as previously suggested [FDA, 2015, Andriole, 2007, Goodman, 2006]. The increase in high-grade tumors seen in these trials and other observational studies, including ours, may result from a detection bias [Andriole, 2007, Goodman, 2006, Redman, 2008, Lucia, 2008, Thompson, 2006], through the effect of 5ARIs on improving the sensitivity of prostate specific antigen testing [Thompson, 2006] and decreasing prostate volumes [Cohen, 2007, resulting in the increased detection of higher-grade tumors.

Also, among men who were diagnosed with prostate cancer in our sample, those who used 5ARIs were more likely to be diagnosed with Stage III/IV disease compared to men who used ABs. This stage difference did not translate into an increased risk of prostate cancer death for 5ARI users during the study period and may be more related to detection and surveillance patterns that are different across exposure groups. Men who used 5ARIs were older and were more likely to have bone scans at diagnosis compared to men who used ABs. Men with larger prostate glands, more severe symptoms, and higher PSA levels are also more often treated with 5ARIs in clinical practice and thus followed more

closely [Andriole, 2007, Goodman, 2006, Thompson, 2006]. 5ARIs also reduce PSA levels, which may have delayed diagnosis via PSA screening in these men [Andriole, 2007, Goodman, 2006, Redman, 2008, Lucia, 2008]. These detection and surveillance biases may therefore have resulted in differences in the proportion of metastatic disease at diagnosis across exposure groups in this study.

While this study utilized a large, diverse population in community practice settings, included 19 years of observational data and a large number of men who were exposed to 5ARIs, searched multiple sources for vital status to identify prostate cancer deaths, employed both a cohort and case control design and multiple sensitivity analyses to confirm the robustness of our findings, there are some potential limitations to consider. Missing data in the earlier years of this study, particularly for PSA and Gleason score, limits our ability to conduct stratified analyses. However, the sensitivity analysis restricting our study to dates when more complete data were available found similar results. The number of prostate cancer diagnoses in our study may be underestimated, as only 62% of men who died of prostate cancer had a pathology confirmed diagnosis in the cancer registries. This is likely due to prevalent cancers (diagnosed prior to health plan enrollment) or diagnoses at the time of death. Also, some early cases may have been clinical diagnoses and therefore, excluded from the registries as well. As a result, there are a small proportion of men in our sample (<2%) who initiated their medications after their prevalent or clinical prostate cancer diagnoses. While cohort studies comparing two treatment modalities are subject to immortal time bias, we addressed this bias by matching on exposure in the cohort study so that the follow-up time in both treatment groups began at the same time point (5ARI initiation or index date) rather than date of diagnosis or first dispense in controls, employing risk set sampling of AB users in the ,cohort study and performing a nested case-control analysis [Suissa. 2007]. The average follow-up time after medication initiation in this population and cumulative duration of use was short, mostly due to the advanced age of the cohort and 5ARIs not becoming widely used until later in the study period. However, our study included 543,523 person-years of follow-up, more than previous studies [Azoulay, 2015, Preston, 2014].

11.2. Limitations

Overall potential limitations

Outcome Ascertainment and Measurement

There were changes in how patients were followed and screened for prostate cancer over the study period (1992-2010). These changes may affect the likelihood of detecting prostate cancer, and how diagnosed prostate cancer is treated. In addition, there was differential surveillance for prostate cancer for patients using 5ARIs versus alpha-blockers. Treatment with 5ARIs lowers PSA levels so any increase in PSA while on treatment is a signal for medical intervention or increased surveillance and/or testing. To examine the potential effect of this bias we described the PSA testing patterns and biopsy frequency over the course of the study period. Both PSA tests and bone scans were found to be more common among 5ARI users compared to AB users, whereas the use of biopsies was found to be similar. The greater use of these tests may have resulted in an increased likelihood of men on 5ARI being diagnosed with prostate cancer during the

study period. However, what effect this would have on death due to prostate cancer is unclear. It is possible that the resulting risk of prostate cancer death would be increased by increasing the cause of death attribution to prostate cancer in the presence of a diagnosis. Conversely, there is a potential that the increased surveillance would lead to an earlier diagnosis and curative treatment, and thus may decrease the risk of prostate cancer death. However, the age at diagnosis was higher and the proportion treated within 6 months was lower among 5ARI users in this study.

Person-time at risk calculations in this study began at the time of matching, which corresponded with the initiation of a 5ARI and the corresponding index date in the matched AB user. They therefore, do not reflect the entire history of exposure to AB. This may have introduced bias, however, efforts were made to minimize this bias by adjusting for previous AB use both by matching on it and adjusting for it in the analysis. Also, a sensitivity analysis which defined person-time from the initiation of any BPH medication was performed and the results were found to be similar, suggesting that this bias in this study is minimal.

Defining prostate cancer death based on the underlying or primary coded causes of death from death certificates may result in misclassification. Because men can die of other acute causes that may be due to their prostate cancer and have those reported as their cause of death, it is possible we are underestimating the number of prostate cancer deaths in this population by relying on codes. The use of the electronic algorithm and adjudication to verify prostate cancer death may help minimize any bias that may be due to this misclassification.

Exposure Measurement

There are very few patients using 5ARIs as a monotherapy for the treatment of BPH. Approximately 92% of men who use a 5ARI either previously or concomitantly also used an alpha-blocker. For this reason we matched patients on their timing of BPH medication initiation and prior history of AB use. Also, while the duration of alpha-blocker was not found to be significantly different across exposure groups after matching, it was an a priori identified confounder and therefore was also adjusted for in the models.

Using a dichotomous exposure variable for this first set of analyses, such that men are classified as either a 5ARI user or AB user does not take into account the complicated time-varying nature of this exposure. However, we employed risk-set sampling in this study, which allows men who changed treatment categories over time to contribute person-time at risk to each exposure group, thus in part accounting for the time-varying nature of this exposure.

[redacted] pharmacy data captures fills of prescriptions, therefore we do not know if patients actually took their medications or took them as they were prescribed. This exposure misclassification would most likely not be differential across exposure groups, thus would result in a conservative estimate of the association of interest.

Because this is a retrospective observational study over 20 years of follow up, there are limitations in terms of information available for all patients in the study. The study period

was designed to coincide with the launch of the prescription medications under study. Therefore patients will have varying amounts of medical history available depending upon when they start treatment and meet inclusion criteria for the study. To minimize this bias we are ascertaining information on potential confounders over the one year pre-treatment period for all patients. However, information on co-morbidities and disease duration may not be complete for all patients.

There may be unmeasured confounding due to inherent differences in patients who switch therapy from alpha-blocker to 5ARIs or add 5ARIs to their alpha-blocker treatment versus those who remain on alpha-blocker therapy. These differences may be related to the likelihood of developing and being diagnosed with prostate cancer and also to prostate cancer related mortality. Also, some important confounders such as family history of prostate cancer could not be ascertained for this study. Therefore, there is the potential for residual confounding.

The length of time that men were exposed to the treatments in this study was short, with an average follow-up in the 5ARI group of 4.0 years with a range of 0.1-18.4 years. This therefore limits our ability to determine what the association of interest would have been for men who were exposed to the drug for longer periods of time. Our results suggest that with longer exposure to the 5ARIs, a stronger protective association between 5ARI use and prostate cancer mortality may exist. These results were not statistically significant and therefore our conclusions are limited. But our results support the notion that future studies with longer follow-up should be conducted now that the long-term use of 5ARIs is a standard clinical practice for the treatment of BPH/LUTS.

Prescriber bias (detection bias)

It is possible that the reasons these medications were prescribed differs by exposure group which could result in a prescriber bias being introduced into this study. Men may have been put on their 5ARI after diagnosis of prostate cancer to shrink the volume of the prostate gland rather than for BPH-related LUTS. This would cause the follow-up time among these men to begin after the diagnosis of prostate cancer. To assess this bias, we evaluated the timing of 5ARI prescriptions relative to prostate cancer diagnosis in the sample from [redacted] and found that among the 183 men with a diagnosis of prostate cancer who started a 5ARI ± 90 days around diagnosis, 38.8% began the 5ARI after diagnosis, 9.3% on the day of diagnosis and 51.9% before diagnosis. A random-sample chart review of 20 of the 71 charts of the men who started their 5ARI after diagnosis was performed to determine whether men were put on the 5ARI as a response to prostate cancer diagnosis. There was no evidence in the charts as to why the men initiated therapy.

However, when we stratified our results by timing of prostate cancer diagnosis relative to the initiation of the 5ARI (matching), we found the results did differ. While there was no association between 5ARI use and prostate cancer mortality among men who were diagnosed before they initiated a 5ARI (or index date in AB), there was a 25% increase in risk among men who used a 5ARI compared to AB for men who started the 5ARI (or index date in AB) before they were diagnosed. While it is plausible that men who use a

5ARI are more likely to be diagnosed with aggressive prostate cancer and subsequently die from it, this association may also represent a detection bias in our sample. The use of a 5ARI may trigger closer clinical follow-up, including PSA testing that would diagnose prostate cancer and potentially lead to more work-ups for metastatic cancer (as supported by our data). These men may then be more likely to be diagnosed and presence of this diagnosis in their record would increase the likelihood that their death was then attributed to prostate cancer. For this reason men who were diagnosed with prostate cancer before starting AB or 5ARI therapy were excluded from the study.

Selection biases

Matching was employed in this study to achieve balance of the measured characteristics of men across exposure group, similar to what would be achieved by randomizing in a controlled trial. However, it is possible that the use of matching introduced a selection bias and limited the generalizability of our findings. While there were characteristics found to be unbalanced after matching, adjustment for these characteristics in the models did not significantly change the results, suggesting that the influence of these imbalances on the association of interest is minimal. Furthermore, the demographic characteristics of the matched sample were similar to those of the unmatched overall cohort and the men who were not successfully matched, suggesting the matching did not result in a biased sample. The number of prostate cancer deaths was greater among the 5ARI users in the matched sample compared to the overall cohort, which may have resulted in biasing our association of interest towards the null when it may be protective among the full cohort.

Also, 26% of the sample was unable to be successfully matched in this study and was therefore not included in the analyses. It is possible that those who were successfully matched are different in ways which may influence their risk of prostate cancer death and that may differ across exposure status. This could introduce a selection bias into this sample. However, when we compared the baseline characteristics between those who were matched versus unmatched, only differences in the distribution of comorbidities existed with men in the matched sample having less comorbid conditions on average.

Limited Statistical Power

Because the number of deaths due to prostate cancer was relatively small in the matched sample (N=1053), we have limited statistical power to detect a difference in effect across exposure groups. Previous sample size calculations suggest that we have approximately 80% power to rule out a hazard ratio of 1.25. Conclusions regarding the overall association of 5ARI use with prostate cancer mortality should therefore be made with caution, as our statistical power is limited due to the low number of events in our analytic sample. However, we did perform a nested case control study which had sufficient statistical power, and found very similar results to that of the matched cohort study.

Overall Strengths

[redacted] provides a socio-economically and racially diverse population that is broadly representative of the areas it serves. The availability of comprehensive electronic medical records allows for the collection of laboratory, procedure, diagnosis, utilization

and death data. The retrospective cohort design of this study, which included up to 20 years of follow-up, allowed for direct estimation of the incidence of both prostate cancer diagnoses and death. Detailed exposure information was also available for this cohort, which allowed for estimation of both dose and duration.

[redacted] and [redacted] participate in the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute and [redacted] and [redacted] participate in the NIC funded Cancer Research Network (CRN) making the cancer diagnosis data collected across [redacted] sites high quality. The inclusion of four [redacted] regions also provided a large number of prostate cancer deaths and thus statistical power to detect meaningful differences.

The cause of death ascertainment for this study was comprehensive and more extensive than the methods used in previous studies. We utilized all available sources including local [redacted] sources, state death registries, cancer registries, social security index and national death index matches. Deaths due to prostate cancer were also assessed using a novel, electronic algorithm which utilized both electronic and free text data from the EMR.

Bias due to members being lost to follow-up during the study period was minimized as [redacted] has high retention in members in the age group included in this study. The five year retention for members ages 45-75 is greater than 75% and for members older than 75, is greater than 60%.

The NLP algorithm developed as part of this study to validate prostate cancer related deaths increased the validity of cause of death information in this study beyond the more common method of using cause of death from death certificates.

Generalizability

[redacted] socio-economically and racially diverse population is broadly representative of the areas it serves. Because members are all insured, any influences due to unequal access to care are minimized. The general-practice setting further enhances the generalizability of the study's findings.

12. OTHER INFORMATION

N/A

13. CONCLUSIONS

Results from this study suggest that the use of 5ARIs to treat BPH is not associated with an increased risk of prostate cancer death when compared to the use of alpha-blockers. While there were a higher proportion of high-grade prostate cancers diagnosed in men who used 5ARIs compared to men who used alpha-blockers in the sub-sample where Gleason scores were available, this did not translate to an increased risk of prostate cancer death in this group. In addition, use of 5ARIs was also not associated with increased risk of all-cause mortality, nor was 5ARI use associated with the combined end point of metastatic prostate cancer or prostate cancer death when compared to use of ABs, respectively.

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APPENDICES

Tables and Figures

Table 18 Medications to treat BPH/LUTS included in the study

	GENERIC NAME	BRAND NAME
Alpha-blockers		
	ALFUZOSIN HCL	ALFUZOSIN HCL ER TAB 10MG
	ALFUZOSIN HCL	UROXATRAL TAB 10MG
	DOXAZOSIN MESYLATE	CARDURA 1MG TABLET
	DOXAZOSIN MESYLATE	CARDURA 2MG TABLET
	DOXAZOSIN MESYLATE	CARDURA 4MG TABLET
	DOXAZOSIN MESYLATE	CARDURA 8MG TABLET
	DOXAZOSIN MESYLATE	CARDURA TAB 1MG UD
	DOXAZOSIN MESYLATE	CARDURA TAB 2MG UD
	DOXAZOSIN MESYLATE	CARDURA TAB 4MG UD
	DOXAZOSIN MESYLATE	CARDURA TAB 8MG UD
	DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 1MG
	DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 2MG
	DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 4MG
	DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 8MG
	PRAZOSIN HCL	MINIPRESS 1MG CAPS UD
	PRAZOSIN HCL	MINIPRESS 1MG CAPSULE
	PRAZOSIN HCL	MINIPRESS 1MG CAPSULES
	PRAZOSIN HCL	MINIPRESS 2MG CAPS UD
	PRAZOSIN HCL	MINIPRESS 2MG CAPSULE
	PRAZOSIN HCL	MINIPRESS 5MG CAPS UD
	PRAZOSIN HCL	MINIPRESS 5MG CAPSULE
	PRAZOSIN HCL	MINIPRESS CAP 1MG
	PRAZOSIN HCL	MINIPRESS CAP 1MG UD
	PRAZOSIN HCL	MINIPRESS CAP 2MG
	PRAZOSIN HCL	MINIPRESS CAP 2MG UD
	PRAZOSIN HCL	MINIPRESS CAP 5MG
	PRAZOSIN HCL	MINIPRESS CAP 5MG UD
	PRAZOSIN HCL	PRAZOSIN 1MG CAP
	PRAZOSIN HCL	PRAZOSIN 1MG CAPSULE
	PRAZOSIN HCL	PRAZOSIN 1MG STARTER KIT
	PRAZOSIN HCL	PRAZOSIN 2MG CAP
	PRAZOSIN HCL	PRAZOSIN 2MG CAPSULE
	PRAZOSIN HCL	PRAZOSIN 5MG CAP
	PRAZOSIN HCL	PRAZOSIN 5MG CAPSULE
	PRAZOSIN HCL	PRAZOSIN HCL CAP 1MG
	PRAZOSIN HCL	PRAZOSIN HCL CAP 1MG UD
	PRAZOSIN HCL	PRAZOSIN HCL CAP 2MG
	PRAZOSIN HCL	PRAZOSIN HCL CAP 2MG UD
	PRAZOSIN HCL	PRAZOSIN HCL CAP 5MG
	PRAZOSIN HCL	PRAZOSIN HCL CAP 5MG UD
	PRAZOSIN HCL	PRAZOSIN HCL PINK CAP 2MG U
	PRAZOSIN HCL	PRAZOSIN HCL WHITE CAP 1MG

	GENERIC NAME	BRAND NAME
	SILODOSIN	RAPAFLO CAP 4MG
	SILODOSIN	RAPAFLO CAP 8MG
	TAMSULOSIN HCL	FLOMAX 0.4MG CAP UD
	TAMSULOSIN HCL	FLOMAX CAP 0.4MG
	TAMSULOSIN HCL	TAMSULOSIN HCL CAP 0.4MG
	TAMSULOSIN HCL	TAMSULOSIN HCL CAP 0.4MG UD
	TERAZOSIN HCL	HYTRIN 10MG TABLET
	TERAZOSIN HCL	HYTRIN 1MG TABLET
	TERAZOSIN HCL	HYTRIN 1MG TABS UD
	TERAZOSIN HCL	HYTRIN 2MG TABLET
	TERAZOSIN HCL	HYTRIN 2MG TABS UD
	TERAZOSIN HCL	HYTRIN 5MG TABLET
	TERAZOSIN HCL	HYTRIN 5MG TABS UD
	TERAZOSIN HCL	HYTRIN CAP 10MG
	TERAZOSIN HCL	HYTRIN CAP 10MG UD
	TERAZOSIN HCL	HYTRIN CAP 1MG
	TERAZOSIN HCL	HYTRIN CAP 1MG UD
	TERAZOSIN HCL	HYTRIN CAP 2MG
	TERAZOSIN HCL	HYTRIN CAP 2MG UD
	TERAZOSIN HCL	HYTRIN CAP 5MG
	TERAZOSIN HCL	HYTRIN CAP 5MG UD
	TERAZOSIN HCL	HYTRIN TAB 10MG UD
	TERAZOSIN HCL	HYTRIN TAB 1MG
	TERAZOSIN HCL	HYTRIN TAB 1MG UD
	TERAZOSIN HCL	HYTRIN TAB 2MG
	TERAZOSIN HCL	HYTRIN TAB 2MG UD
	TERAZOSIN HCL	HYTRIN TAB 5MG
	TERAZOSIN HCL	HYTRIN TAB 5MG UD
	TERAZOSIN HCL	TERAZOSIN 1MG CAP
	TERAZOSIN HCL	TERAZOSIN 1MG CAP STARTER K
	TERAZOSIN HCL	TERAZOSIN 1MG CAP STARTER P
	TERAZOSIN HCL	TERAZOSIN 2MG CAP
	TERAZOSIN HCL	TERAZOSIN HCL 2MG CAP
	TERAZOSIN HCL	TERAZOSIN HCL CAP 10MG
	TERAZOSIN HCL	TERAZOSIN HCL CAP 10MG UD
	TERAZOSIN HCL	TERAZOSIN HCL CAP 1MG
	TERAZOSIN HCL	TERAZOSIN HCL CAP 1MG UD
	TERAZOSIN HCL	TERAZOSIN HCL CAP 2MG
	TERAZOSIN HCL	TERAZOSIN HCL CAP 2MG UD
	TERAZOSIN HCL	TERAZOSIN HCL CAP 5MG
	TERAZOSIN HCL	TERAZOSIN HCL CAP 5MG UD
	TERAZOSIN HCL	TERAZOSIN STARTER CARD 1MG/
5-alpha reductase inhibitors		
	DUTASTERIDE	AVODART CAP 0.5MG
	FINASTERIDE	FINASTERIDE TAB 5MG
	FINASTERIDE	PROSCAR 5MG TABLET
	FINASTERIDE	PROSCAR 5MG TABLET
	FINASTERIDE	PROSCAR TAB 5MG
	FINASTERIDE	PROSCAR TAB 5MG UD

	GENERIC NAME	BRAND NAME
	*FINASTERIDE (ALOPECIA)**	*PROPECIA 1MGTABLET*
	*FINASTERIDE (ALOPECIA)**	*PROPECIA PRO-PAK TAB PRO-PA*
	*FINASTERIDE (ALOPECIA)**	*PROPECIA TAB 1MG*
Combination Therapy		
	DUTASTERIDE-TAMSULOSIN HC	JALYN CAP

Table 19 Pre-treatment characteristics and prostate cancer related information for sequential 5ARI users compared to concomitant 5ARI users (N=23273)

	Overall (n=23273)	Sequential Users (n=6380)	Concomitant Users (n=16893)	p-value
Demographic Characteristics				
Age at matching				
Mean (SD)	72.6 (9.1)	72.7 (9.2)	72.5 (9.1)	0.04
Median	72.7	72.8	72.6	0.04
<60	2158 (9.3%)	613 (9.6%)	1545 (9.2%)	0.10
60-69	7089 (30.5%)	1880 (29.5%)	5209 (30.8%)	
70+	14026 (60.3%)	3887 (60.9%)	10139 (60.0%)	
Race				
Non-Hispanic White	18255 (78.4%)	5015 (78.6%)	13240 (78.4%)	0.59
African American	1735 (7.5%)	490 (7.7%)	1245 (7.4%)	
Asian	1878 (8.1%)	508 (8.0%)	1370 (8.1%)	
HP, IN, MU and UN	1405 (6.0%)	367 (5.8%)	1038 (6.1%)	
Socioeconomic Status				
Missing	317 (1.4%)	104 (1.6%)	213 (1.3%)	
Household income, median ($1000)	63.7	63.6	63.7	0.64
Household income, mean (SD) ($1000)	68.4 (29.6)	68.5 (30.3)	68.4 (29.4)	0.64
Education[1]				
Less than 9th grade	0.07 (0.09), 0.04	0.07 (0.09), 0.04	0.07 (0.09), 0.04	0.002
9th – 12 grade	0.09 (0.07), 0.08	0.09 (0.07), 0.07	0.09 (0.07), 0.08	0.0001
High school graduate	0.20 (0.08), 0.20	0.20 (0.08), 0.20	0.20 (0.08), 0.20	0.31
Some college, no degree	0.24 (0.07), 0.24	0.24 (0.07), 0.25	0.24 (0.07), 0.24	0.67
Associate degree	0.08 (0.03), 0.07	0.08 (0.03), 0.07	0.08 (0.03), 0.08	0.06
Bachelor degree	0.20 (0.11), 0.20	0.20 (0.11), 0.20	0.20 (0.11), 0.20	0.04
Graduate or professional degree	0.12 (0.10), 0.09	0.12 (0.10). 0.09	0.12 (0.10), 0.09	0.0001

	Overall (n=23273)	Sequential Users (n=6380)	Concomitant Users (n=16893)	p-value
Clinical Characteristics				
PSA at matching				
Missing	5658 (24.3%)	1776 (27.8%)	3882 (23.0%)	
.PSA level, mean (SD)	6.3 (10.3)	6.3 (13.6)	6.3 (8.8)	<0.0001
PSA level, median	4.0	3.8	4.1	<0.0001
0 – 2.5	5908 (25.4%)	1681 (26.4%)	4227 (25.0%)	<0.0001
2.5 - 4	2804 (12.1%)	683 (10.7%)	2121 (12.6%)	
≥4	8903 (38.3%)	2240 (35.1%)	6663 (39.4%)	
BMI (kg/m^2)				
Missing	12735 (54.7%)	3887 (60.9%)	8848 (52.4%)	
<25	4144 (17.8%)	1032 (16.2%)	3112 (18.4%)	<0.0001
25-30	3842 (16.5%)	907 (14.2%)	2935 (17.4%)	
≥30	2552 (11.0%)	554 (8.7%)	1998 (11.8%)	
Charleston Comorbidity Index				
0	10462 (45.0%)	3126 (49.0%)	7336 (43.4%)	<0.0001
1	4640 (19.9%)	1197 (18.8%)	3443 (20.4%)	
2+	8171 (35.1%)	2057 (32.2%)	6114 (36.2%)	
History of cardiovascular disease	8361(35.9%)	2269(35.6%)	6092(36.1%)	0.48
History of high blood pressure	20034(86.1%)	4772(74.8%)	15262(90.4%)	<0.0001
History of hyperlipidemia	15596(67.0%)	4009(62.8%)	11587(68.6%)	<0.0001
History of diabetes	5190(22.3%)	1263(19.8%)	3927(23.3%)	<0.0001
History of cancer	2279 (9.8%)	637 (10.0%)	1642 (9.7%)	0.55
Use of other medications to treat ED or OAB*	8361(35.9%)	2269(35.6%)	6092(36.1%)	0.48
Alpha Blocker history (years)[1]				
Mean (SD)	4.6 (3.9)	4.0 (3.9)	4.8 (3.9)	<0.0001
Median	3.8	2.9	4.1	<0.0001
Prostate Cancer Characteristics				
Prostate cancer diagnosed	756 (3.3%)	240 (3.8%)	516 (3.1%)	0.007
Prostate cancer incidence rate (per 1000 person-years)[1]	8.5	8.4	8.5	
Prostate cancer deaths	122 (0.5%)	42 (0.7%)	80 (0.5%)	0.08
Prostate cancer mortality rate (per 1000 person-years)[1,2]	1.3	1.4	1.3	

[1]Geocoded education
[2] Person time starts at matching and ends at end of study or Pca diagnosis
[3] Person time for men who were lost to follow-up but died during the study period was calculated up to the date of disenrollment.

Table 20 Pre-treatment characteristics and prostate cancer related information for those using finasteride compared to those dutasteride (N=25,388)

	Overall (n=25388)	Finasteride Users (n=24528)	Dutasteride Users (n=860)	p-value*
Demographic Characteristics				
Age at matching				
Mean (SD)	72.4 (9.3)	72.5 (9.3)	70.6 (9.1)	<0.0001
Median	72.6	72.7	70.6	<0.0001
<60	2546 (10.0)	2426 (9.9)	120 (14.0)	<0.0001
60-69	7639 (30.1)	7344 (29.9)	295 (34.3)	
70+	15203 (59.9)	14758 (60.2)	445 (51.7)	
Race				
Non-Hispanic White	19889 (78.3)	19264 (78.5)	625 (72.7)	<0.0001
African American	1885 (7.4)	1822 (7.4)	63 (7.3)	
Asian	2017 (7.9)	1922 (7.8)	95 (11.1)	
HP, IN, MU and UN	1597 (6.3)	1520 (6.2)	77 (9.0)	
Socioeconomic Status	377 (1.5)	365 (1.5)	12 (1.4)	
Missing				
Household income, median ($1000)	63.5	63.5	65.2	0.02
Household income, mean (SD) ($1000)	68.3 (29.7)	68.2 (29.7)	70.5 (29.9)	0.02
Education				
Less than 9th grade	0.07 (0.09), 0.04	0.07 (0.09), 0.04	0.09 (0.10), 0.04	<0.0001
9th – 12 grade	0.09 (0.07), 0.08	0.09 (0.07), 0.08	0.10 (0.07), 0.08	0.01
High school graduate	0.20 (0.08), 0.20	0.20 (0.08), 0.20	0.20 (0.08), 0.20	0.20
Some college, no degree	0.24 (0.07), 0.24	0.24 (0.07), 0.24	0.23 (0.08), 0.23	<0.0001
Associate degree	0.08 (0.03), 0.07	0.08 (0.03), 0.07	0.07 (0.03), 0.07	0.0003
Bachelor degree	0.20 (0.11), 0.20	0.20 (0.11), 0.20	0.20 (0.11), 0.20	0.49
Graduate or professional degree	0.12 (0.10), 0.09	0.12 (0.10). 0.09	0.12 (0.10), 0.09	0.27
Clinical Characteristics				
PSA at matching				
Missing	6359 (25.1)	6190 (25.2)	169 (19.7)	
.PSA level, mean (SD)	6.6 (30.2)	6.6 (30.7)	5.5 (6.6)	0.09
PSA level, median	4.1	4.1	3.6	0.09
0 – 2.5	6400 (25.2)	6159 (25.1)	241 (28.0)	<0.0001
2.5 - 4	2964 (11.7)	2830 (11.5)	134 (15.6)	
≥4	9665 (38.1)	9349 (38.1)	316 (36.7)	

	Overall (n=25388)	Finasteride Users (n=24528)	Dutasteride Users (n=860)	p-value*
BMI (kg/m²)				
Missing	14244 (56.1%)	13796 (56.3%)	448 (52.1%)	
<25	4352 (17.1%)	4173 (17.0%)	179 (20.8%)	0.02
25-30	4076 (16.1%)	3934 (16.0%)	153 (17.8%)	
≥30	2716 (10.7%)	2625 (10.7%)	91 (10.6%)	
Charleston Comorbidity Index				
0	11633 (45.8%)	11212 (45.7%)	421 (49.0%)	0.14
1	5017 (19.8%)	4864 (19.8%)	153 (17.8%)	
2+	8738 (34.4%)	8452 (34.5%)	286 (33.3%)	
History of cardiovascular disease	8992(35.4%)	8744(35.7%)	248(28.8%)	<0.0001
History of high blood pressure	21289(83.9%)	20589(83.9%)	700(81.4%)	0.05
History of hyperlipidemia	16753(66.0%)	16155(65.9%)	598(69.5%)	0.03
History of diabetes	5554(21.9%)	5357(21.8%)	197(22.9%)	0.46
History of cancer	2473 (9.7%)	2412 (9.8%)	61 (7.1%)	0.008
Use of other medications to treat ED or OAB*	3679(14.5%)	3528(14.4%)	151(17.6%)	0.009
Alpha Blocker history (years)[1]				
Mean (SD)	4.2 (4.0)	4.2 (4.0)	4.5 (3.9)	0..002
Median	3.2	3.2	3.5	0.002
Prostate cancer diagnosed	837 (3.3%)	816 (3.3%)	21 (2.4%)	0.15
Prostate cancer incidence rate (per 1000 person-years)[1]	8.4	8.5	6.6	
Prostate cancer deaths	158 (0.6%)	155 (0.6%)	3 (0.4%)	0.30
Prostate cancer mortality rate (per 1000 person-years)[1,2]	1.6	1.6	0.9	

[1]Person time starts at matching and ends at end of study or Pca diagnosis
[2]Person time for men who were lost to follow-up but died during the study period was calculated up to the date of disenrollment.

Table 21 Characteristics of men missing PSA level vs those who are not missing PSA level at time of matching (5ARI initiation) (N=174,895)

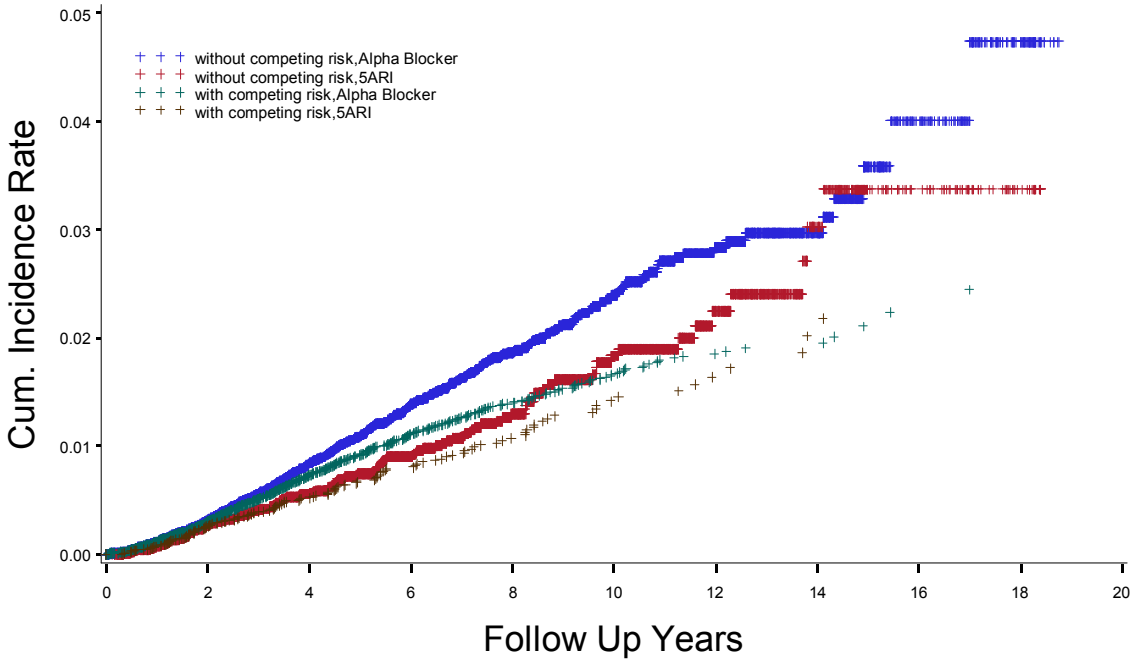
	Overall (n=174895)	Without PSA data at matching (n=85262)	With PSA data at matching (n=109633)	p-value*
Characteristics				
Age at matching				
Mean (SD)	72.4 (9.2)	75.1 (9.7)	70.7 (8.6)	<0.0001
Median	72.6	76.2	70.7	<0.0001
<60	17884(10.2%)	5171(7.9%)	12713(11.6%)	<0.0001
60-69	52980(30.3%)	14243(21.8%)	38737(35.3%)	
70+	104031(59.5%)	45848(70.3%)	58183(53.1%)	

	Overall (n=174895)	Without PSA data at matching (n=85262)	With PSA data at matching (n=109633)	p-value*
Race				
Non-Hispanic White	134220(76.7%)	51352(78.7%)	82868(75.6%)	<0.0001
African American	12711(7.3%)	4267(6.5%)	8444(7.7%)	
Asian	14636(8.4%)	4765(7.3%)	9871(9.0%)	
HP, IN, MU and UN	13328(7.6%)	4878(7.5%)	8450(7.7%)	
Socioeconomic Status				
Missing	3320(1.9%)	3320(1.9%)	3320(1.9%)	
Household income, median ($1000)	62.0	60.4	63.2	<0.0001
Household income, mean (SD) ($1000)	66.4 (28.3)	64.5 (27.3)	67.6 (28.8)	<0.0001
Education				
Less than 9th grade	0.07 (0.09), 0.04	0.08 (0.09), 0.04	0.07 (0.09), 0.04	<0.0001
9th – 12 grade	0.10 (0.07), 0.08	0.10 (0.07), 0.08	0.10 (0.07), 0.08	<0.0001
High school graduate	0.21 (0.08), 0.21	0.21 (0.08), 0.21	0.21 (0.08), 0.20	<0.0001
Some college, no degree	0.24 (0.07), 0.25	0.24 (0.07), 0.25	0.24 (0.07), 0.25	0.0006
Associate degree	0.08 (0.03), 0.08	0.08 (0.03), 0.07	0.08 (0.03), 0.08	<0.0001
Bachelor degree	0.19 (0.11), 0.19	0.19 (0.10), 0.18	0.19 (0.11), 0.19	<0.0001
Graduate or professional degree	0.11 (0.09), 0.08	0.11 (0.09). 0.08	0.11 (0.09), 0.08	<0.0001
BMI (kg/m^2)				
Missing	98215(56.2%)	39585(60.7%)	58630(53.5%)	
<25	29642(17.0%)	10438(16.0%)	19204(17.5%)	<0.0001
25-30	26590(15.2%)	8800(13.5%)	17790(16.2%)	
≥30	20448(11.7%)	6439(9.9%)	14009(12.8%)	
Charleston Comorbidity Index				
0	75809(43.4%)	25474(39.0%)	50335(45.9%)	<0.0001
1	34670(19.8%)	12602(19.3%)	22068(20.1%)	
2+	64416(36.8%)	27186(41.7%)	37230(34.0%)	
History of cardiovascular disease	59459(34.0%)	25925(39.7%)	33534(30.6%)	<0.0001
History of high blood pressure	157553(90.1%)	59041(90.5%)	98512(89.9%)	<0.0001
History of hyperlipidemia	117974(67.5%)	37882(58.1%)	80092(73.1%)	<0.0001
History of diabetes	45273(25.9%)	18819(28.8%)	26454(24.1%)	<0.0001
History of cancer	15877 (9.1%)	6957 (10.7%)	8920 (8.1%)	<0.0001
Use of other medications to treat ED or OAB*	23184(13.3%)	5715(8.8%)	17469(15.9%)	<0.0001

	Overall (n=174895)	Without PSA data at matching (n=85262)	With PSA data at matching (n=109633)	p-value*
Alpha Blocker history (years)[1]				
Mean (SD)	4.3 (4.1)	4.5 (4.1)	4.2 (4.0)	<0.0001
Median	3.4	3.6	3.3	<0.0001

Figure 2 **Prostate cancer-specific mortality cumulative incidence and Kaplan Meier plots comparing men who used 5ARI to men who used AB, with and without adjustment for competing risk of death from other causes (A) and with and without adjustment for age, race, region, BPH medication initiation year and prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB or ED (B).**

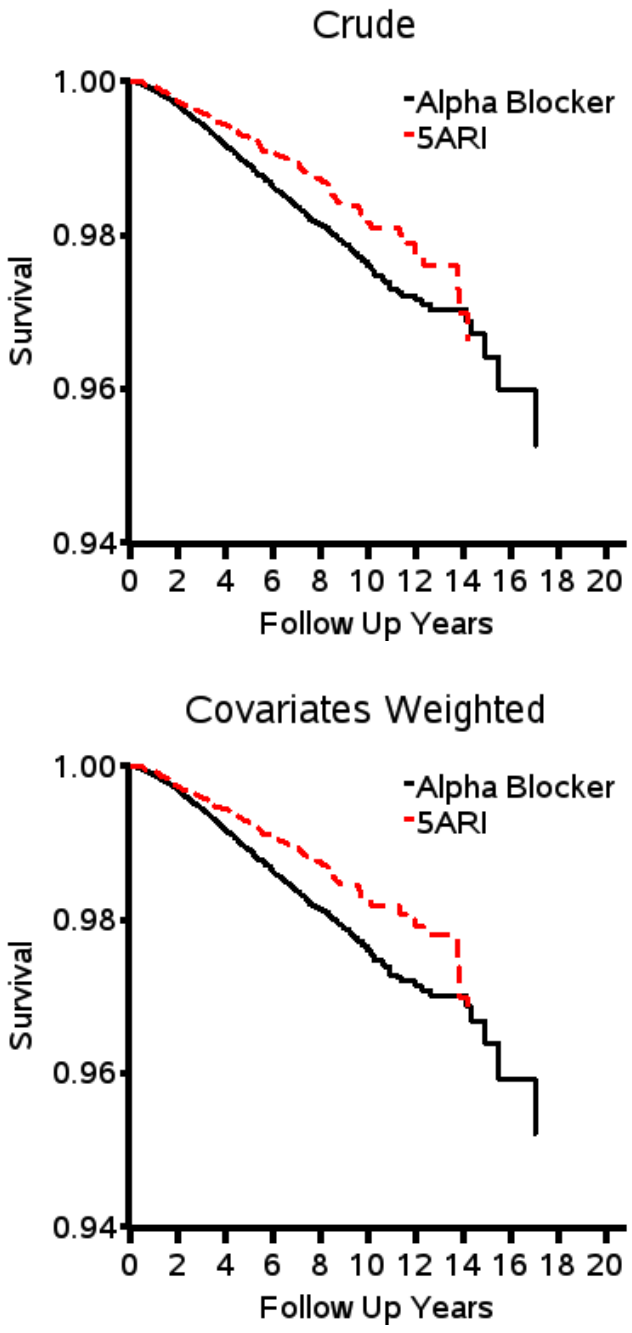
Figure 2A: Cumulative Incidence Functions of Prostate Cancer Mortality



follow up years	0	2	4	6	8	10	12	14	16	18	20
number at risk (AB user)	149507	83345	34918	16338	8494	4296	1861	697	189	63	0
number at risk (5ARI user)	25388	18129	9612	5058	2903	1597	711	290	71	29	0

With competing risk adjustment, Grey's test P=0.006
Without competing risk adjustment, log rank test P=0.0002

Figure 2B: Kaplan-Meier Plots of Prostate Cancer Specific Survival



Prostate cancer specific death Kaplan Meier plots, unadjusted (top, P=0.0002) and weighted (right, P=0.0001) by age, race, region, BPH initiation year, prior Alpha Blocker history, Charlson score and comorbidities.

***Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB or ED.**

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1		03/11/16	All-cause mortality report
2		03/31/16	Metastatic prostate cancer mortality combination analyses report

CONFIDENTIAL

2016N297726_00
WEUSKOP5723

Treatment for Lower Urinary Tract Symptoms and Risk of All-Cause Mortality

Report: All-cause Mortality Analyses

June 28, 2016

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Investigators

Principle Investigator:
[redacted] PhD, [redacted]

[redacted]
Co- Investigator: [redacted] MD, PhD
Co-Investigator: [redacted] MD

[redacted]
Co- Investigator: [redacted] PhD
Co- Investigator: [redacted] MD

[redacted]
Co- Investigator: [redacted] PhD
[redacted] MD

[redacted]
Co- Investigator: [redacted] PhD

[redacted]
Co-investigator: [redacted] PhD

Research Question and Objectives

Background

The recently completed matched retrospective cohort analysis and nested-case control analysis, designed to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, found that 5ARIs did not increase the risk of prostate cancer death. Given the high number of deaths due to other causes and previous literature suggesting that 5ARI use was not associated with all-cause mortality (Thompson 2013), it was of interest to assess the risk of all-cause deaths associated with 5ARI use when compared to AB use in this cohort.

However, given concerns about potential biases resulting from the exclusion of men in the matched sample and to account for the time-varying nature of both the exposure and covariates, we also performed this analysis in the unmatched sample (identified eligible population).

Objective

To assess the risk of all-cause mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Methods

Design

The analysis used the same eligible cohort as defined in the primary analysis of prostate cancer related mortality. Briefly, a retrospective cohort design with data from four [redacted] sites collected from electronic health records and data abstracted from paper records from 1992-2010 was employed. Men treated with benign prostatic hyperplasia (BPH) medications; 5-alpha reductase inhibitors (5ARIs) (with and without concomitant and/or previous alpha-blocker use) were compared to men treated with alpha-blockers.

Setting

A retrospective cohort study from 1992-2010 was conducted using data from 4 [redacted] sites: [redacted] and [redacted] This study identified a cohort of patients in the [redacted] closed health care systems with long-term follow-up and low attrition rates. Individual patient data from the four participating sites ([redacted] and [redacted] were pooled and analyzed with [redacted] acting as the central data-coordinating center. [redacted] performed all data analyses for this study.

Subjects

All men age 50 years and older treated with a BPH medication (5ARI and/or alpha-blocker) were eligible for inclusion. Men were required to have coverage within the healthcare system for at least 1-year before the first BPH medication prescription. Men with a history of prostate cancer or who developed prostate cancer within <3 months of starting their BPH medication were not eligible for inclusion.

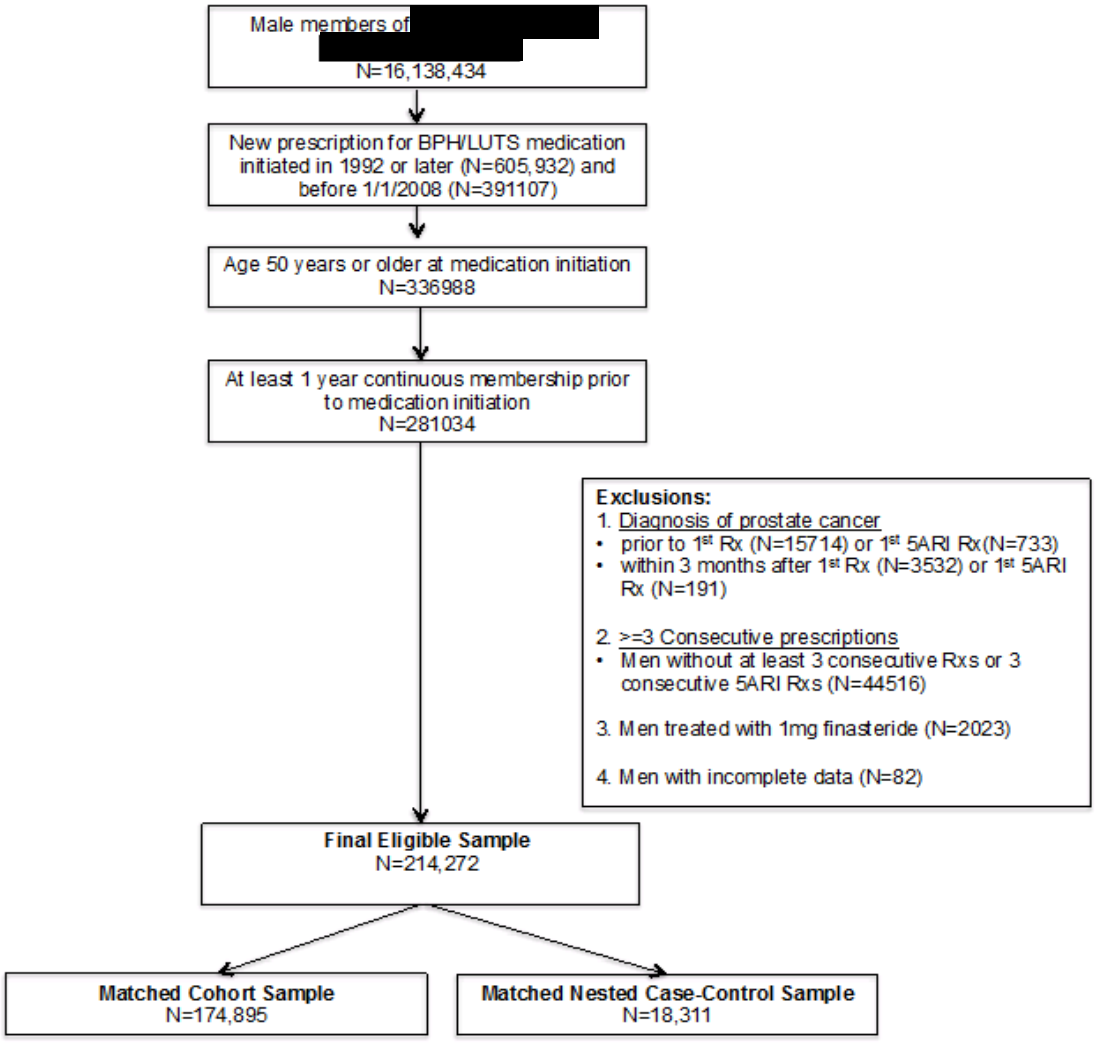
INCLUSION CRITERIA:

- Male
- A new prescription for BPH medication (5ARI and/or alpha-blocker) in 1992 or later that was identified as appropriate treatment for BPH/LUTS from the [redacted] National Pharmacy guidelines
- Treatment with BPH medication must have been initiated prior to Jan. 1, 2008.
- Age 50 years or older at time of treatment with 5ARI or alpha-blocker.
- At least 1-year of coverage in the healthcare system before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- At least 3 consecutive prescriptions (90 days of supply) for a BPH medication (5ARI and/or alpha-blocker)
    - 5ARI users must have had at least 3 consecutive prescriptions for 5ARI.

EXCLUSION CRITERIA:

- Diagnosis of prostate cancer any time before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- Diagnosis of prostate cancer within 3 months after BPH medication (5ARI and/or alpha-blocker)
- Patients treated with finasteride 1mg prior to BPH medication.
- Less than 3 months cumulative exposure or less than 3 consecutive 5ARI prescriptions among men who used 5ARIs

Flow-chart:



Matching in the Cohort Analysis

Men who initiated a 5ARI were matched using risk-set sampling 1:6 to alpha-blocker users on age at matching (+/- 2 years), race (African American vs. Other), timing of BPH medication initiation (within 2 years), prior history of AB use and health plan region. Of the 214,272 eligible men, 73% were successfully matched resulting in an analytic sample of 157,456 men with 174,895 records (18,321 men were matched as both a 5ARI and AB user). Men were then passively followed via electronic health records through the end of 2010 for death due to prostate cancer (N=1,053) and for this analysis, for death due to all causes (N=35266).

Matching Approach

The all-cause mortality analysis used the same matching approach as the primary analysis, as described below:

Eligible matches for 5ARI users were defined based on their medication exposure at the time of 5ARI initiation. For example, a patient who initiated a 5ARI medication in 1995 had a pool of potential matches that included all men not previously exposed or currently taking 5ARIs in 1995. Therefore a patient on an alpha-blocker in 1995 who added a 5ARI in 1999 was an eligible match for the 5ARI user as in 1995 as they had not yet been exposed to 5ARIs. When this alpha-blocker patient initiated 5ARI therapy in 1999, their follow-up time was censored.

The risk-set sampling of "controls" allowed for an equal opportunity of the comparison groups to be exposed to 5ARI and does not condition on future use of a 5ARI. In this situation, an alpha-blocker user was eligible to be selected and matched to a 5ARI user up until he started a 5ARI, at which time he was matched to another alpha-blocker user.

An existing, widely used SAS macro developed by the Mayo Clinic was used to operationalize the matching. Greedy matching will be employed using this macro. (Bergstrahl and Kosanke 1995).

Exposure

Men who ever had at least 3 consecutive prescriptions for a 5ARI or an alpha-blocker (based on exclusions) were included (without gaps).

- 5ARI exposure was defined as any 5ARI use including patients with concomitant or consecutive alpha blocker use.
  - Trends with increasing time on medications was explored by stratifying by increasing cumulative exposure
    - Cumulative exposure was defined from the start of matching (5ARI initiation or index date in AB user).
    - The distribution of cumulative exposure and number of prescriptions was assessed and descriptively compared between cases and controls.
  - Dose response was explored by stratifying by increasing categories of dose.
    - Dose was calculated from the start of matching (5ARI initiation or matched index date in AB user).

Outcome: All-cause mortality

The primary outcome was all-cause mortality. Deaths due to any cause during the study period were identified via the following methods:

- [redacted] mortality database contains mortality information for [redacted] patients since 1981. Prior to 1988, only deaths occurred in [redacted] hospitals are included. This database combines from various data sources including [redacted] state death files, Social Security Administration (SSA), [redacted] internal systems and Non-[redacted] claims. The information collected by this database include name, date of birth, social security number, address, race, gender, cause of death, date of death and the data source of the death.

- The National Death Index (NDI) mortality data was also used to supplement cause of death information where [redacted] was unable to capture it through their existing systems. NDI is a central computerized index of death record information on file in the state vital statistics offices maintained by the Centers for Disease Control. The NDI includes a national file of identifying death record information compiled from computer files submitted by State vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year. NDI Plus searches provide cause of death codes and are available through 2010 currently (2011 will become available Spring 2013). Three groups of participants were identified and sent to the CDC for a NDI match:
  - All men (regardless of prostate cancer status) in the sample that died prior to or on 12/31/10 who were missing underlying cause of death info.
  - All men (regardless of prostate cancer status) in the sample that left [redacted] alive but died on or before 12/31/10 without underlying cause of death.
  - Men with prostate cancer diagnosis who left [redacted] alive without a death date (up to May 2013) who we did not know were dead. For those men who died after the study end date, these deaths were not included in the analysis and they were censored at the end of the study period (December 31, 2010).

Covariates

- The same covariates as defined in the primary analysis were included in this study (see list below. The timing of collection was at time of matching (5ARI initiation or index date in AB (when data were available).

- Race/ethnicity
  - Race and ethnicity was collected across sites and based on a race and ethnicity variable that is categorized as: Non-Hispanic White, African American, Asian, and Hawaiian/Pacific Islander, Native Alaskan/American Indian, Multiple, Unknown. Race categories were collapsed to be African American vs. Other for matching.
- Age (death/index date)
  - Age was calculated from date of birth and reflected as age at matching (or index).

- BPH initiation calendar year
  - This is the calendar year which the first medication to treat BPH/LUTS was initiated.

- Socioeconomic status (SES)
  - Aggregate SES measures for [redacted] members were calculated via geocoding using 2000 US census estimates at the block, block-group, tract and ZIP level and include income and education.

- PSA
  - PSA was available through our laboratory data in the Virtual Data Warehouse and was measured in ng/mL. Baseline PSA was defined at the time of matching for the matched analysis and BPH initiation for the unmatched analyses.

- BMI
  - BMI was not routinely collected as a vital sign until the implementation of the electronic medical record in each site (mid 2000s) Therefore, only a few years of complete data may be available. It was calculated using a standard formula and measured in kg/m2.
    - Due to the paucity of BMI data, it was only used in sensitivity analyses where the effect of BMI on the association of interest was investigated.

- Charlson Comorbidity Index
  - Charlson comorbidity Index was collected based on ICD-9 codes of the included conditions/complications and a standard algorithm and coding macro were used to derive the score which is usually categorized into (0, 1 or 2+).

- CVD Endpoints
  - History of cardiovascular disease: ICD-9 410.x-429.x
  - History of high blood pressure/hypertension: ICD-9 codes (401.x) *and/or* dispense of blood pressure medications
  - History of diabetes (HEDIS definition): dispensing record for insulin or an oral hypoglycemic from the HEDIS list (not including metformin) *or* any discharge ICD-9 code of 250.xx, 357.2, 362.0, 366.41, 648.0, *or* hemoglobin A1C >= 7.0%.)

- Overactive Bladder and Erectile Dysfunction medications
  - Any medications used to treat either overactive bladder and/or erectile dysfunction including PED-5 inhibitors and anti-cholinergic as identified through [redacted] formulary.

- History of hyperlipidemia : Any dispense of statin medications *and/or* any abnormal lipid profile test:
  - Total cholesterol (>200 mg/dL),
  - HDL (<= 40 mg/dL)
  - LDL (>130 mg/dL),
  - Triglycerides (>150 mg/dL)

- History of Cancer – Other than Prostate
  - History of cancer at major sites other than the prostate was determined by pathology-confirmed diagnoses via the cancer registries.

Potential confounding factors over the follow-up period:

- Additionally information on several variables occurring over the follow-back period were collected including:
  - PSA testing patterns after treatment initiation and over the course of the study period.
  - The frequency of prostate biopsy
  - Gleason Score at diagnosis

- Frequency of prostate cancer treatment paradigms (radical prostatectomy, external beam radiation, brachytherapy, cryotherapy, etc.)

- Confounding factors that occur over the follow-up were not adjusted for in regression analyses, as they may be in the causal path between exposure and outcome. These confounders were instead described by exposure and outcome status.

Potential effect measure modifiers for consideration:

- Race/ethnicity
- Age
- Socioeconomic status (income)
- PSA level at diagnosis (among sample who have a prostate cancer diagnosis)

Statistical Analyses:

For this set of analyses, two analytic approaches were employed. First, the association between 5ARI use and all-cause mortality was assessed in the matched cohort sample (as used in the primary analysis), which considered only covariate information at the matched time point (5ARI initiation and corresponding index date for AB user). Second, the analyses were repeated in the eligible cohort (unmatched) and a time-dependent analysis was conducted which allowed for multiple time points of covariate collection. Both are described in more detail below.

Matched Cohort Analysis

The matched cohort used in this analysis is the same as that used in the primary analysis focused on prostate cancer mortality as the outcome. Briefly, once the 5ARI patients were matched to alpha-blocker patients on the matching variables (birth year, race, BPH initiation calendar year, region and duration of prior use of alpha-blockers), the appropriate statistics were calculated to confirm that indeed the groups were successfully matched on these characteristics. The success of the matching was further assessed based on whether balance between the treated and control groups are achieved in the matched samples. Additionally, background characteristics (including cumulative exposure time, follow-up time, follow-up time after cancer diagnosis, and potential pre-treatment initiation confounding factors) were compared between the groups to identify whether there exist variables that would need to be considered in the outcome analyses as covariates.

The details of this approach are outlined in the Cohort Study Report.

Person-time calculations

Each patient included in the analysis had his survival outcome determined as follows. All patients who died were considered as events. Patients who were lost to follow-up (left the [redacted] system) before the end of the study period were censored at the time of loss to follow-up. End of follow-up for patients who were alive and were not lost to follow-

up or did not die during the study period was at the end of study period. For patients who were lost to follow-up and then later died, they were censored at the time of loss to follow-up for this analysis.

- Person-time (follow up) was calculated from time at which the participant was matched (i.e starts a 5ARI prescription and corresponding index date in AB user) up until the time of the event, censoring or end of study period.

- Cumulative exposure and cumulative dose were defined accordingly (same as primary analysis) and are exposure specific.

Bivariate statistics and comparisons

We examined pre-treatment assignment characteristics such as prior co-morbidities for each treatment group as well as pre-treatment characteristics among those who died during the study period vs. those who did not die. For the bivariate analyses, continuous variables were compared using two-sample *t*-statistics, and categorical variables were compared using chi-square statistics where appropriate (as was done in the primary analysis).

Survival analysis

Crude and covariate adjusted Kaplan Meier plots were constructed comparing the rates of all-cause mortality between 5ARI and alpha-blocker users.

Multivariable-adjusted all cause mortality rates and hazard ratios were estimated using proportional hazard regression, comparing the rate of death due to any cause among 5ARI users vs. alpha-blocker users overall and stratified by duration of cumulative exposure, cumulative dose and clinical characteristics of interest.

Confounding and effect modification

<u>Confounding</u>

- Variables of interest that were included in the multi-variable adjusted models were chosen based on known a priori confounders (age, race, region, history of AB use, BPH medication initiation year), and variables found to be confounders in this data set.
  - Variables found to be imbalanced after matching across both exposure and outcome categories were included in the multi-variable adjusted models.
  - Both Charlson comorbidity index and the individual comorbidities were eligible for inclusion in the model as they were measuring different aspects of comorbid disease.
  - The final models were adjusted for the following confounders:
    - Matching factors (age, race, region, history of AB use, BPH medication initiation calendar year)
    - Charlson index (0,1, 2+)
    - Medical history variables: cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer, use of other medications to treat OAB or ED.

<u>Time-varying Analysis in Unmatched Cohort</u>

- In addition to the analysis in the matched cohort sample, a number of modeling approaches were run in the unmatched eligible cohort. This was done with the goal of confirming the results seen among the matched sample, where various biases were of concern (as described in the cohort report). The unmatched analysis includes the 214,272 men who were eligible to be matched. Person-time (follow up) was calculated from time at which the participant initiated their BPH medication up until the time of the event, censoring or end of study period. Cumulative exposure and cumulative dose were defined accordingly and were exposure specific.

- The unmatched analyses allow for time-varying exposures and covariates in the models. In addition, two time scales were tested (age and calendar) to determine if they produced different results.

Covariate collection, timing and missingness

- Except for 5ARI users who never used an alpha blocker (N=4369) and alpha blocker users who were not matched in the previous prostate cancer mortality analysis (N=56678), two time points were available for covariate collection: (1) initiation of BPH medication "baseline" and (2) the time at which the 5ARI user initiated their 5ARI (matching time point in matched cohort analysis) and the corresponding index date in the AB user the 5ARI man was matched to in subsequent analyses.
  - Because not all men were successfully matched in the matched cohort analysis, 3,844 5ARI users were missing the 2nd covariate time point, as were 56,678 AB users. This was handled in different ways to test the influence of the missingness on our results of interest:
    - Models were run with fixed baseline (BPH initiation) covariate information
    - Missing values were coded as unknown and time-varying covariates were used.
    - Missing values were replaced with the last value carried forward ("baseline" values) and time-varying covariates were used.

Survival Analysis

- Multivariable-adjusted mortality rates and hazard ratios (Cox modeling) were calculated for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure, cumulative dose and clinical characteristics of interest.

- Various sensitivity analyses to account for the time-varying nature of the exposure, the adjustment of covariates at multiple time points and at baseline, and to assess the influence of using different time scales (age vs. calendar) were run and are described below:

  1. Age scale vs. calendar time scale
  2. Fixed baseline covariate adjustment vs. time-varying covariate adjustment
  3. Unknown missing covariate values vs. last value carried forward
  4. Analyses in the sample of men in [redacted] where complete covariate information was available for all time points
     a. Similar sensitivity analyses to those listed above were run in this sample.

- Kaplan Meier curves were not created for the time-varying analysis as current software packages can not readily fit them and their utility conceptually in the setting of time-dependent variables has been long argued in the literature (Simon and Makuch Statistics in Medicine 1984; Klein, Keiding and Copelan, Statistics in Medicine 1994).

- The matched and unmatched, time-varying all-cause mortality analyses were compared to determine whether they differed and if so, to what magnitude. This was done by comparing the HRs from both analyses, as determined a priori. This furthers our understanding about the biases present in the matched cohort analysis.

Results

Note: The descriptive tables by exposure status in the eligible study cohort are included in the report for the primary objective of prostate cancer related mortality

Matched Cohort Sample (N= 174,895) using only covariates at matching

Table 1 Distribution and crude association of demographic and clinical characteristics by outcome group *after* matching (N=174,895), where covariates are defined at the matching time point (5ARI initiation or index date in matched AB user)

	Overall (n=174895)	All deaths (N=35266)	No death (n=139629)	p-value
Characteristic				
Exposure				
Alpha Blocker users	149507(85.5%)	30468(86.4%)	119039(85.3%)	<0.001
5ARI users	25388(14.6%)	4798(13.6%)	20590(14.8%)	
Age at matching				
Mean (SD)	72.4(9.2)	77.9(8.1)	71.0(9.0	
Median	72.6	78.6	70.9	
<60	17884(10.2%)	817(2.3%)	17067(12.2%)	<0.0001
60-69	52980(30.3%)	5126(14.5%)	47854(34.3%)	
70+	104031(59.5%)	29323(83.2%)	74708(53.5%)	
Race				
Non-Hispanic White	134220(76.7%)	29316(83.1%)	104904(75.1%)	<0.0001
African American	12711(7.3%)	2340(6.6%)	10371(7.4%)	
Asian	14636(8.4%)	1959(5.6%)	12677(9.1%)	
Hawaiian, PI, Multiple, and Unknown	13328(7.6%)	1651(4.7%)	11677(8.4%)	
Socioeconomic Status				
Missing	3320(1.9%)	874(2.5%)	2446(1.8%)	
Household income, median ($1000)	66.4(28.3)	63.3(27.1)	67.2(28.5)	<0.0001

Household income, mean (SD) ($1000)	62.0	58.8	62.9	<0.0001
Education*				
Less than 9th grade	0.07(0.09),0.04	0.07(0.09),0.04	0.07(0.09),0.04	0.0002
9th – 12 grade	0.10(0.07),0.08	0.10(0.07),0.08	0.10(0.07),0.08	<.0001
High school graduate	0.21(0.08),0.21	0.21(0.08),0.21	0.21(0.08),0.20	<.0001
Some college, no degree	0.24(0.07),0.25	0.25(0.07),0.25	0.24(0.07),0.25	0.0002
Associate degree	0.08(0.03),0.08	0.08(0.03),0.07	0.08(0.03),0.08	<.0001
Bachelor degree	0.19(0.11),0.19	0.19(0.10),0.18	0.19(0.11),0.19	<.0001
Graduate or professional degree	0.11(0.09),0.08	0.11(0.09),0.08	0.11(0.09),0.08	<.0001
PSA at matching (ng/mL)				
Missing	65262(37.3%)	18657(52.9%)	46605(33.4%)	
.PSA level, mean (SD)	4.9(42.6)	8.2(77.6)	4.3(32.6)	<0.0001
PSA level, median	2.3	2.5	2.3	<0.0001
0 – 2.5	56985 (32.6)	8193 (23.2)	48792 (34.9)	<0.0001
2.5 - 4	17497 (10.0)	2409 (6.8)	15088 (10.8)	
≥4	35151 (20.1)	6007 (17.0)	29144 (20.9)	
BMI (kg/m^2)				
Missing	98215(56.2%)	26259(74.5%)	71956(51.5%)	
<25	29642(17.0%)	3893(11.0%)	25749(18.4%)	<0.0001
25-30	26590(15.2%)	3063(8.7%)	23527(16.9%)	
≥30	20448(11.7%)	2051(5.8%)	18397(13.2%)	
Charleston Comorbidity Index				
0	75809(43.4%)	10864(30.8%)	64945(46.5%)	<0.0001
1	34670(19.8%)	6458(18.3%)	28212(20.2%)	
2+	64416(36.8%)	17944(50.9%)	46472(33.3%)	
History of cardiovascular disease	59459(34.0%)	16696(47.3%)	42763(30.6%)	<0.0001
History of high blood pressure	157553(90.1%)	31712(89.9%)	125841(90.1%)	0.25
History of hyperlipidemia	117974(67.5%)	19610(55.6%)	98364(70.5%)	<0.0001
History of diabetes	45273(25.9%)	10669(30.3%)	34604(24.8%)	<0.0001
History of cancer	15877(9.1%)	5355(15.2%)	10522(7.5%)	<0.0001
Use of other medications to treat ED or OAB*	23184(13.3%)	2186(6.2%)	20998(15.0%)	<0.0001
Alpha Blocker history (years)[1]				
Mean (SD)	4.3(4.1)	3.4(3.7)	4.6(4.1)	<0.0001
Median	3.4	2.1	3.7	<0.0001

*Geocoded education

Table 2 Multivariable-adjusted all-cause mortality rates, and hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose in the matched sample* (N=174,895)

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Crude Hazard Ratio (95% CI)	Age Adjusted Hazard Ratio (95% CI)	Multivar. Hazard Ratio (95% CI)
Multi-variable adjusted	**5ARI**	**AB**	**5ARI**	**AB**			
Overall (n=174895,35266 all-cause deaths)	10.12	11.51	118.34	176.65	0.65 (0.63,0.67)**	0.63 (0.61,0.65)**	0.64 (0.62,0.66)**
Cumulative exposure							
<6 mos (n=21173, 3996 all-cause deaths)	10.43	6.49	551.16	252.81	1.31 (1.02,1.67)**	1.15 (0.90,1.47)	1.01 (0.79,1.29)
6 mos-1yr (n=59865, 12951 all-cause deaths)	13.82	13.48	130.37	113.27	0.88 (0.84,0.92)**	0.83 (0.79,0.87)**	0.83 (0.79,0.87)**
1 yr-2 yrs (n=45498, 9593 all-cause deaths)	9.48	11.64	47.89	57.03	0.72 (0.67,0.76)**	0.70 (0.66,0.75)**	0.75 (0.70,0.80)**
2+ yrs (n=48359, 8726 all-cause deaths)	6.65	8.08	17.64	23.87	0.54 (0.52,0.57)**	0.54 (0.51,0.57)**	0.54 (0.51,0.57)**
Cumulative dose (gram)							
1st quartile (n=43705, 8913 all-cause deaths)	13.13	10.15	244.30	267.29	0.74 (0.58,0.94)**	0.89 (0.70,1.13)	0.97 (0.76,1.24)

2nd quartile (n=42735, 9852 all-cause deaths)	12.24	11.34	151.17	98.57	0.85 (0.81,0.90)**	0.87 (0.82,0.92)**	0.88 (0.83,0.93)**
3rd quartile (n=44702, 9025 all-cause deaths)	12.11	11.62	83.41	69.25	0.98 (0.92,1.03)	0.97 (0.92,1.03)	1.01 (0.95,1.07)
4th quartile (n=43753, 7476 all-cause deaths)	6.68	8.25	18.84	30.94	0.58 (0.55,0.61)**	0.54 (0.51,0.57)**	0.55 (0.52,0.58)**

Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression.
**P<0.05
[1]Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities.

Table 3 Adjusted all-cause mortality rates and adjusted hazard ratios for 5ARI and alpha-blocker users overall and stratified by characteristics of interest in the matched cohort sample* (N=174,895)

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Hazard Ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall (n=174895, 1053 Pca deaths)	10.12	11.51	118.34	176.65	0.64 (0.62,0.66)**
Race					
Non-Hispanic White (n=134220, 29316 all-cause deaths)	10.52	11.77	73.19	112.92	0.63 (0.61,0.65)**
African American (n=12711, 2340 all-cause deaths)	9.06	12.40	72.94	104.4	0.70 (0.62,0.79)**
Asian (n=14636, 1959 all-cause deaths)	7.35	8.85	100.94	141.16	0.61 (0.53,0.70)**
Hawaiian, PI, Multiple, and Unknown (n=13328, 1651 all-cause deaths)	12.15	10.77	135.63	115.81	0.72 (0.61,0.84)**
BMI at BPH Initiation (kg/m²)					
Missing(n=98215, 26259 all cause deaths)	9.57	10.93	109.58	164.78	0.61 (0.59,0.63)**
<25 (n=29642, 3893 all cause deaths)	10.62	11.67	158.31	213.64	0.73 (0.66,0.79)**
25-30 (n=26590, 3063 all cause deaths)	7.27	8.49	62.36	86.68	0.67 (0.61,0.74)**

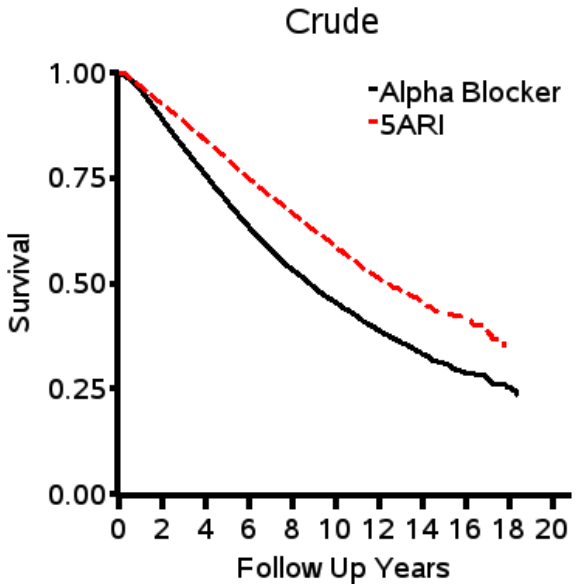
≥30 (n=20448, 2051 all cause deaths)	13.04	15.18	84.52	116.36	0.71 (0.62,0.80)**
Charleston Comorbidity Index					
0 (n=75809, 10864 all cause deaths	6.91	7.57	50.56	61.37	0.62 (0.58,0.65)**
1 (n=34670, 6458 all cause deaths)	9.98	10.98	108.01	145.32	0.61 (0.57,0.66)**
2+ (n=64416, 17944 all cause deaths)	19.51	21.51	314.63	449.42	0.67 (0.65,0.70)**
History of cardiovascular disease (n=59459, 16696 all cause deaths)	14.18	14.58	290.38	409.91	0.67 (0.64,0.70)**
History of high blood pressure (n=157553, 31712 all cause deaths)	10.63	12.23	114.73	167.32	0.63 (0.61,0.65)**
History of hyperlipidemia (n=117974, 19610 all cause deaths)	9.18	10.28	94.09	135.38	0.65 (0.62,0.67)**
History of diabetes (n=45273, 10669 all cause deaths**)**	12.16	14.94	186.56	260.79	0.62 (0.59,0.66)**
History of cancer (n=15877, 5355 all cause deaths)	17.67	17.64	199.54	319.49	0.65 (0.60,0.70)**

[1] Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities. Except the corresponding strata.

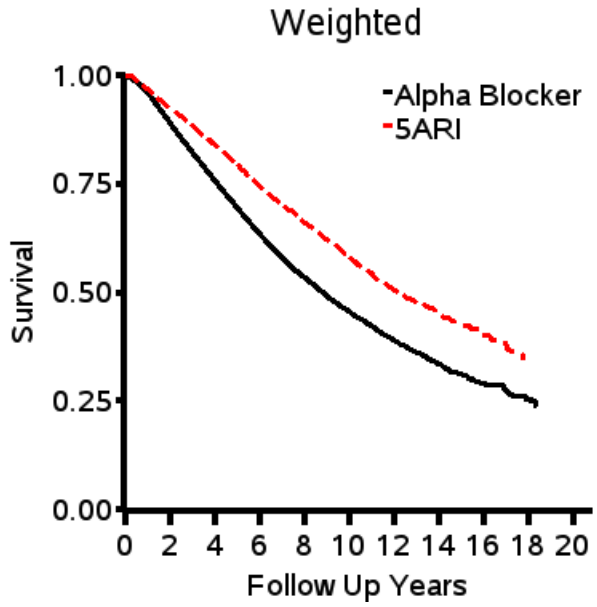
**P<0.05

[*]Results are from negative binomial regression, with the exception of hazard ratios which were estimated using proportional hazard regression.

Figure 1A Kaplan Meier Plots (A) Crude and (B) Covariate weighted (age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities) in the matched cohort sample for the <u>entire study period</u> (N=174,895)



P<0.0001



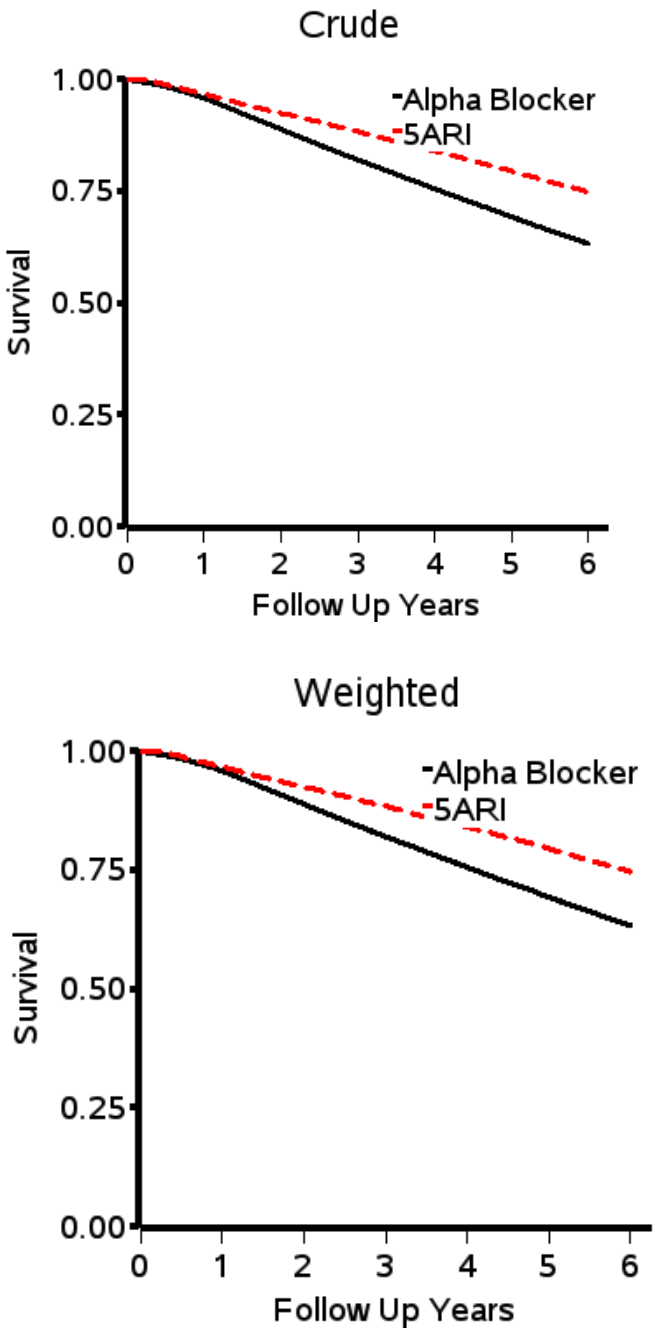
P<0.0001

Number of individuals at risk over time by exposure group

year	0	2	4	6	8	10	12	14	16	18	20

AB	149507	83345	34918	16338	8494	4296	1861	697	189	63	0
5ARI	25388	18129	9612	5058	2903	1597	711	290	71	29	0

Figure 1B: Kaplan Meier Plots (A) Crude and (B) Covariate weighted (age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities) in the matched cohort sample <u>for the first 6 years of the study period</u>



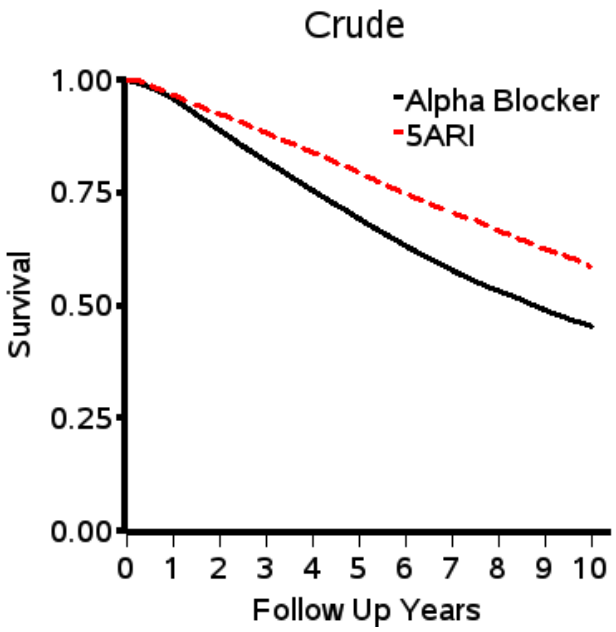
Number at risk at each time interval by exposure group

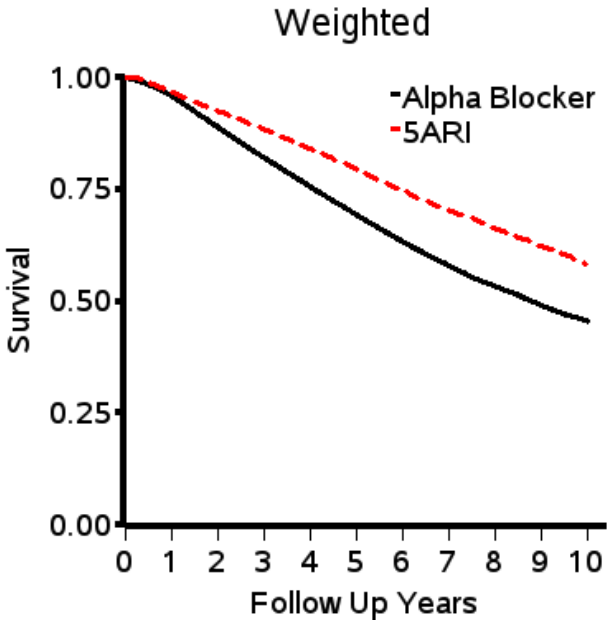
Follow-up year	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6
5ARI	25388	24414	22425	20218	18129	16064	14114	11635	9612	7726	6570	5662	5058
AB	149507	135488	119083	100049	83345	69469	57134	44042	34918	27237	22564	18879	16338

Number of cumulative events at each time interval by exposure

Follow-up year	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6
5ARI	0	302	813	1299	1732	2089	2455	2772	3047	3281	3483	3670	3832
AB	0	2392	5713	9742	13293	16359	18868	20909	22554	23881	24962	25890	26692

Figure 1C: Kaplan Meier Plots (A) Crude and (B) Covariate weighted (age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities) in the matched cohort sample <u>for the first 10 years of the study period</u>





Number at risk

follow up year	0	1	2	3	4	5	6	7	8	9	10
5ARI	25388	22425	18129	14114	9612	6570	5058	4002	2903	2183	1597
AB	149507	119083	83345	57134	34918	22564	16338	12067	8494	6049	4296

Number of cumulative events

follow up year	0	1	2	3	4	5	6	7	8	9	10
5ARI	0	813	1732	2455	3047	3483	3832	4084	4289	4449	4569
AB	0	5713	13293	18868	22554	24962	26692	27935	28785	29380	29764

Unmatched Cohort Analysis with time-varying exposure and covariates (for 5ARI users at BPH initiation and at 5ARI initiation; for AB users at BPH initiation and at matched index date)

Note: The descriptive tables by exposure status in the eligible study cohort are included in the report for the primary objective of prostate cancer related mortality

Table 4 Distribution and crude association of demographic and clinical characteristics at BPH initiation (N=214272)

	Overall (n=214272)	5ARI Users (n=29232)	Alpha-blocker Users (n=185040)	p-value
Characteristic				
Age at BPH Initiation				
Mean (SD)	67.5(9.5)	68.3(9.1)	67.4(9.5)	<0.0001
Median	67.2	68.1	67.0	<0.0001
<60	52729 (24.6%)	6001 (20.5%)	46728(25.3%)	<0.0001
60-69	76907 (35.9%)	10918 (37.4%)	65989 (35.7%)	
70+	84636 (39.5%)	12313 (42.1%)	72323 (39.1%)	
Race				
Non-Hispanic White	156681 (73.1%)	23058 (78.9%)	133623 (72.2%)	<0.0001
African American	17436 (8.1%)	2067 (7.1%)	15369 (8.3%)	
Asian	17210 (8.0%)	2357 (8.1%)	14853 (8.0%)	
Hawaiian, PI, Multiple, and Unknown	22945 (10.7%)	1750 (6.0%)	21195 (11.5%)	
Socioeconomic Status				
Missing	5519 (2.6%)	396 (1.4%)	5123 (2.8%)	
Household income, median ($1000)	65.7(28.2)	68.4(29.6)	65.2(27.9)	<0.0001
Household income, mean (SD) ($1000)	61.2	63.7	60.9	<0.0001
Education*				
Less than 9th grade	0.08(0.09),0.04	0.07(0.09),0.04	0.08(0.09),0.04	<0.0001
9th – 12 grade	0.10(0.07),0.08	0.09(0.07),0.08	0.10(0.07),0.09	<0.0001
High school graduate	0.21(0.08),0.21	0.20(0.08),0.20	0.21(0.08),0.21	<0.0001
Some college, no degree	0.24(0.07),0.25	0.24(0.07),0.24	0.24(0.07),0.25	<0.0001
Associate degree	0.08(0.03),0.07	0.08(0.03),0.07	0.08(0.03),0.07	0.37
Bachelor degree	0.19(0.11),0.18	0.20(0.10),0.20	0.19(0.11),0.18	<0.0001
Graduate or professional degree	0.11(0.09),0.08	0.12(0.10),0.09	0.10(0.09),0.08	<0.0001
PSA at BPH Initiation (ng/ML)				
Missing	80525 (37.6%)	9559 (32.7%)	70966 (38.4%)	
.PSA level, mean (SD)	3.7(18.5)	5.4(29.1)	3.4(16.0)	<0.0001
PSA level, median	1.8	3.2	1.7	<0.0001
BMI at BPH Initiation (kg/m²)				
Missing	172750 (80.6%)	23581 (80.7%)	149169 (80.6%)	
<25	9438 (4.4%)	1379 (4.7%)	8059 (4.4%)	0.001
25-30	17298 (8.1%)	2428(8.3%)	14870 (8.0%)	
≥30	14786 (6.9%)	1844 (6.3%)	12942 (7.0%)	
Charleston Comorbidity Index				

0	136880 (63.9%)	19547 (66.9%)	117333 (63.4%)	<0.0001
1	36822(17.2%)	4893 (16.7%)	31929 (17.3%)	
2+	40570 (18.9%)	4792 (16.4%)	35778 (19.3%)	
History of cardiovascular disease	42912(20.0%)	5876(20.1%)	37036(20.0%)	0.73
History of high blood pressure	182416 (85.1%)	23342 (79.9%)	159074 (86.0%)	<0.0001
History of hyperlipidemia	125261 (58.5%)	16858 (57.7%)	108403(58.6%)	0.003
History of diabetes	42513 (19.8%)	4620 (15.8%)	37893 (20.5%)	<0.0001
History of cancer	12028 (5.6%)	1665 (5.7%)	10363 (5.6%)	0.51
Use of other medications to treat ED or OAB*	21918(10.2%)	3100 (10.6%)	18818 (10.2%)	0.02

*Geocoded education

Table 5 Distribution and crude association of exposure, demographic and clinical characteristics and all cause death in the unmatched sample (N=214,272)

	Overall (n=214272)	**All cause deaths (N=54423)**	**No death (N=159849)**	**p-value**
Characteristic				
Exposure				
Alpha Blocker only users	185040(86.4%)	49221(90.4%)	135819(85.0%)	<0.0001
5ARI users	29232(13.6%)	5202(9.6%)	24030(15.0%)	
Age at BPH Initiation				
Mean (SD)	67.5(9.5)	74.0(8.7)	65.3(8.7)	<0.0001
Median	67.2	74.4	64.8	<0.0001
<60	52729(24.6%)	3750(6.9%)	48979(30.6%)	
60-69	76907(35.9%)	13324(24.5%)	63583(39.8%)	
70+	84636(39.5%)	37349(68.6%)	47287(29.6%)	
Race				
Non-Hispanic White	156681(73.1%)	43293(79.6%)	113388(70.9%)	<0.0001
African American	17436(8.1%)	4311(7.9%)	13125(8.2%)	
Asian	17210(8.0%)	2896(5.3%)	14314(9.0%)	
Hawaiian, PI, Multiple, and Unknown	22945(10.7%)	3923(7.2%)	19022(11.9%)	
Socioeconomic Status				
Missing	5519 (2.6%)	1373(2.5%)	4146(2.6%)	
Household income, median ($1000)	65.7(28.2)	62.7(27.0)	66.7(28.5)	<0.0001
Household income, mean (SD) ($1000)	61.2	58.0	62.1	<0.0001

Education*				
Less than 9th grade	0.08(0.09),0.04	0.08(0.09),0.05	0.08(0.09),0.04	<0.0001
9th – 12 grade	0.10(0.07),0.08	0.10(0.07),0.09	0.10(0.07),0.08	<0.0001
High school graduate	0.21(0.08),0.21	0.22(0.08),0.21	0.21(0.08),0.21	<0.0001
Some college, no degree	0.24(0.07),0.25	0.24(0.07),0.25	0.24(0.07),0.25	0.22
Associate degree	0.08(0.03),0.07	0.07(0.03),0.07	0.08(0.03),0.07	<0.0001
Bachelor degree	0.19(0.11),0.18	0.18(0.10),0.17	0.19(0.11),0.18	<0.0001
Graduate or professional degree	0.11(0.09),0.08	0.10(0.09),0.08	0.11(0.09),0.08	<0.0001
PSA at BPH Initiation (ng/ML)				
Missing	80525(37.6%)	28974(53.2%)	51551(32.2%)	
.PSA level, mean (SD)	3.7(18.5)	5.7(38.3)	3.2(8.8)	<0.0001
PSA level, median	1.8	2.3	1.7	<0.0001
BMI at BPH Initiation (kg/m²)				
Missing	172750(80.6%)	49132(90.3%)	123618(77.3%)	
<25	9438(4.4%)	1846(3.4%)	7592(4.8%)	<0.0001
25-30	17298(8.1%)	1973(3.6%)	15325(9.6%)	
≥30	14786(6.9%)	1472(2.7%)	13314(8.3%)	
Charleston Comorbidity Index				
0	136880(63.9%)	28975(53.2%)	107905(67.5%)	<0.0001
1	36822(17.2%)	9238(17.0%)	27584(17.3%)	
2+	40570(18.9%)	16210(29.8%)	24360(15.2%)	
History of cardiovascular disease	42912(20.0%)	16194(29.8%)	26718(16.7%)	<0.0001
History of high blood pressure	182416(85.1%)	46292(85.1%)	136124(85.2%)	0.58
History of hyperlipidemia	125261(58.5%)	25280(46.5%)	99981(62.6%)	<0.0001
History of diabetes	42513(19.8%)	13431(24.7%)	29082(18.2%)	<0.0001
History of cancer	12028 (5.6%)	5685(10.5%)	6343(4.0%)	<0.0001
Use of other medications to treat ED or OAB*	21918(10.2%)	2576(4.7%)	19342(12.1%)	<0.0001

*Geocoded education

Table 6 Distribution and crude association of demographic and clinical characteristics at BPH initiation (N=210428) among men in the unmatched sample who had complete covariate info at both BPH medication initiation and matching

	Overall (n=210428)	5ARI Users (n=25388)	Alpha-blocker Users (n=185040)	p-value
Characteristic	67.5(9.5),67.1	68.2(9.2),68.0	67.4(9.5),67.0	<0.0001
Age at BPH Initiation				
Mean (SD)	67.5(9.5)	68.2(9.2)	67.4(9.5)	<0.0001
Median	67.1	68.0	67.0	<0.0001
<60	52098(24.8%)	5370(21.2%)	46728(25.3%)	<0.0001
60-69	75359(35.8%)	9370(36.9%)	65989(35.7%)	
70+	82971(39.4%)	10648(41.9%)	72323(39.1%)	
Race				
Non-Hispanic White	153512(73.0%)	19889(78.3%)	133623(72.2%)	<0.0001
African American	17254(8.2%)	1885(7.4%)	15369(8.3%)	
Asian	16870(8.0%)	2017(7.9%)	14853(8.0%)	
Hawaiian, PI, Multiple, and Unknown	22792(10.8%)	1597(6.3%)	21195(11.5%)	
Socioeconomic Status				
Missing	5500 (2.6%)	377(1.5%)	5123(2.8%)	
Household income, median ($1000)	65.6(28.1)	68.3(29.7)	65.2(27.9)	<0.0001
Household income, mean (SD) ($1000)	61.1	63.5	60.9	<0.0001
Education*	0.08(0.09),0.04	0.07(0.09),0.04	0.08(0.09),0.04	<0.0001
Less than 9th grade	0.10(0.07),0.08	0.09(0.07),0.08	0.10(0.07),0.09	<0.0001
9th – 12 grade	0.21(0.08),0.21	0.20(0.08),0.20	0.21(0.08),0.21	<0.0001
High school graduate	0.24(0.07),0.25	0.24(0.07),0.24	0.24(0.07),0.25	<0.0001
Some college, no degree	0.08(0.03),0.07	0.08(0.03),0.07	0.08(0.03),0.07	0.70
Associate degree	0.19(0.11),0.18	0.20(0.11),0.20	0.19(0.11),0.18	<0.0001
Bachelor degree	0.11(0.09),0.08	0.12(0.10),0.09	0.10(0.09),0.08	<0.0001
Graduate or professional degree	0.08(0.09),0.04	0.07(0.09),0.04	0.08(0.09),0.04	<0.0001
PSA at BPH Initiation (ng/ML)				
Missing	79080(37.6%)	8114(32.0%)	70966(38.4%)	
.PSA level, mean (SD)	3.7(18.7)	5.5(30.9)	3.4(16.0)	<0.0001
PSA level, median	1.8	3.2	1.7	<0.0001

BMI at BPH Initiation (kg/m²)				
Missing	169419(80.5%)	20250(79.8%)	149169(80.6%)	
<25	9306(4.4%)	1247(4.9%)	8059(4.4%)	<0.0001
25-30	17071(8.1%)	2201(8.7%)	14870(8.0%)	
≥30	14632(7.0%)	1690(6.7%)	12942(7.0%)	
Charleston Comorbidity Index				
0	134113(63.7%)	16780(66.1%)	117333(63.4%)	<0.0001
1	36244(17.2%)	4315(17.0%)	31929(17.3%)	
2+	40071(19.0%)	4293(16.9%)	35778(19.3%)	
History of cardiovascular disease	42222(20.1%)	5186(20.4%)	37036(20.0%)	0.12
History of high blood pressure	179351(85.2%)	20277(79.9%)	159074(86.0%)	<0.0001
History of hyperlipidemia	123095(58.5%)	14692(57.9%)	108403(58.6%)	0.03
History of diabetes	41977(20.0%)	4084(16.1%)	37893(20.5%)	<0.0001
History of cancer	11830 (5.6%)	1467(5.8%)	10363(5.6%)	0.25
Use of other medications to treat ED or OAB*	21625(10.3%)	2807(11.1%)	18818(10.2%)	<0.0001

Table 7 Multivariable adjusted time varying hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose in the unmatched sample*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Hazard Ratio (95% CI)
Multi-variable adjusted	**5ARI**	**Alpha-blocker**	**5ARI**	**Alpha-blocker**	
Overall (n=100305, 388 Pca deaths)	16.3	25.5	65.5	114.6	0.84 (0.82,0.87)**
Cumulative exposure					
<6 mos (n=1662, 623 all-cause deaths)	18.1	24.5	265.2	376	0.80 (0.49,1.33)
6 mos-1yr (n=63640, 17946 all-cause deaths)	23.7	26.3	198.9	188.3	0.96 (0.90,1.03)
1 yr-2 yrs (n=31164, 9623 all-cause deaths)	22.3	31.9	81.5	124.2	0.92 (0.86,0.99)**
2+ yrs (n=117806, 26231 all-cause deaths)	13.1	19.2	23.5	37.9	0.84 (0.81,0.87)**
Cumulative dose (gram)					
1st quartile (n=57252, 16187 all-cause deaths)	24.5	27	249.6	184.9	0.96 (0.85,1.08)
2nd quartile (n=53165, 15043 all-cause deaths)	24.5	28.6	133	127.2	1.14 (1.07,1.21)**
3rd quartile (n=51964, 12558 all-cause deaths)	16.1	20.9	39.9	54.5	1.11 (1.05,1.17)**
4th quartile (n=51891, 10635 all-cause deaths)	8.8	13.9	13.4	24.6	0.82 (0.78,0.86)**

*Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression. Covariates were adjusted for at two time points, medication initiation at matching (or index date) and last values were carried forward for those missing covariate info at the second time point.
**P<0.05

[1]Adjusted for age at BPH, BPH initiation year, race, region, Charlson score and comorbidities.

Table 8 Multivariable adjusted time varying hazard ratios for 5ARI and alpha-blocker users overall and stratified by characteristics of interest in the unmatched sample *

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Adjusted Hazard Ratio (95% CI)
	5ARI	AB	5ARI	AB	
Overall (n=214272, 54423 all-cause deaths)	16.3	25.5	65.5	114.6	0.84 (0.82,0.87)**
Race					
Non-Hispanic White (n=156681, 43293 all cause deaths)	17.8	26.6	55.3	93.8	0.85 (0.83,0.88)**
African American (n=17436, 4311 all cause deaths)	15.3	27.5	63.8	111	0.78 (0.69,0.87)**
Asian (n=17210, 2896 all cause deaths)	9.9	20.6	41.7	99.7	0.80 (0.70,0.92)**
HP, IN, MU and UN (n=22945, 3923 all cause deaths)	15.4	19.2	55.6	97.5	0.84 (0.72,0.98)**
BMI at BPH Initiation (kg/m^2)					
Missing (n=172750, 49132 all cause deaths)	15.8	24.8	65.5	118.9	0.83 (0.80,0.86)**
<25 (n=9438, 1846 all cause deaths)	10	15.8	41.5	78.1	0.87 (0.75,1.00)
25-30 (n=17298, 1973 all cause deaths)	8.3	14.9	36.4	69.9	0.96 (0.83,1.11)
≥30 (n=14786, 1472 all cause deaths)	11.1	17.7	48.3	91.5	0.94 (0.79,1.10)
Charleston Comorbidity Index					
0 (n=136880, 28975 all cause deaths)	13.8	22.7	45.3	88.6	0.83 (0.80,0.86)**
1 (n=36822, 9238 all cause deaths)	13.9	20.3	66.1	96.3	0.85 (0.79,0.91)**
2+ (n=40570, 16210 all cause deaths)	25.5	36.8	147.5	234.1	0.96 (0.91,1.01)
History of cardiovascular disease (n=42912, 16194 all cause deaths)	20.9	29.4	102.3	164.9	0.91 (0.87,0.96)**
History of high blood pressure (n=182416, 46292 all cause deaths)	17.5	27.4	62.1	110.8	0.84 (0.81,0.87)**

History of hyperlipidemia (n=125261, 25280 all cause deaths)	15.1	23.4	47	89.9	0.87 (0.83,0.90)**
History of diabetes (n=42513, 13431 all cause deaths)	17.8	27.9	72.6	140.2	0.85 (0.80,0.91)**
History of cancer (n=12028, 5685 all cause deaths)	25.1	36	141.2	233.5	0.90 (0.82,0.98)**

*Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression. Covariates were adjusted for at two time points, medication initiation at matching (or index date) and last values were carried forward for men missing the second covariate time point.
**P<0.05
[1]Adjusted for age at BPH, BPH initiation year, race, region, Charlson score and comorbidities.

Analysis with time-varying exposure and covariates (for 5ARI users at BPH initiation and at 5ARI initiation; for AB users at BPH initiation and at matched index date) in sample of men who were included in the matched cohort analysis (N=157,426)

Table 9 Multivariable adjusted time varying hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose in the subsample of men who were previously included in the matched analysis (N=157,426)*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Hazard Ratio[1] (95% CI)
Multivariable adjusted	**5ARI**	**Alpha-blocker**	**5ARI**	**Alpha-blocker**	
Overall (n=157426, 36657 all-cause deaths)	14.8	20.5	46.1	56.4	0.96 (0.93,0.99)**
Cumulative exposure					

<6 mos (n=339,113 all-cause deaths)	12.3	27.5	97.5	299.6	1.26 (0.74,2.15)
6 mos-1yr (n=24641,6955 all-cause deaths)	18.1	19.3	92.4	77.6	1.22 (1.13,1.32)**
1 yr-2 yrs (n=23757,6991 all-cause deaths)	19.1	26.6	64.5	88.2	0.99 (0.92,1.07)
2+ yrs (n=108689,22598 all-cause deaths)	12.2	17	20.3	29.8	0.88 (0.84,0.91)**
Cumulative dose (gram)					
1st quartile (n=22221,6287 all-cause deaths)	20.4	21.1	143.9	78.3	1.24 (1.09,1.41)**
2nd quartile (n=40047,10557 all-cause deaths)	21.5	23.9	93.4	77.1	1.27 (1.19,1.35)**
3rd quartile (n=45803,10255 all-cause deaths)	14.5	18.2	32.4	40.6	1.17 (1.11,1.24)**
4th quartile (n=49355,9558 all-cause deaths)	8.5	12.8	12.1	20.5	0.84 (0.80,0.89)**

*Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression. Covariates were adjusted for at two time points, medication initiation at matching (or index date) and last values were carried forward for men missing the second covariate time point.

**P<0.05

[1]Adjusted for age at BPH, BPH initiation year, race, region, Charlson score and comorbidities.

Table 10 Multivariable adjusted time varying hazard ratios for 5ARI and alpha-blocker users overall and stratified by characteristics of interest in the sample of men previously included in the matched analysis (N=157,426)*

	No of deaths/ No at risk (%)		Mortality rate Per 1000 p-y		Hazard Ratio (95% CI)
	5ARI	AB	5ARI	AB	
Overall (n=157426,36657 all cause deaths)	14.8	20.5	46.1	56.4	0.96 (0.93,0.99)**
Race					
Non-Hispanic White (n=120450, 30437 all cause deaths)	16.3	21.8	39.6	49.6	0.97 (0.93,1.00)
African American (n=11553, 2398 all cause deaths)	14.5	21.4	44.4	47.4	0.97 (0.85,1.09)
Asian (n=13099, 2029 all cause deaths)	8.1	13.9	29.4	47.9	0.91 (0.79,1.05)
HP, IN, MU and UN (n=12324, 1793 all cause deaths)	13.6	16.6	29.5	39.1	1.02 (0.85,1.22)
BMI at BPH Initiation (kg/m²)					
Missing (n=125353, 32720 all cause deaths)	14.1	19.6	44.1	54.2	0.95 (0.92,0.98)**
<25 (n=7166, 1312 all cause deaths)	9.1	13.6	30	47.1	0.95 (0.81,1.11)
25-30 (n=13442, 1488 all cause deaths)	7.1	11.4	30.5	51.7	1.08 (0.93,1.26)
≥30 (n=11465, 1137 all cause deaths)	9.1	13	34.3	48.7	1.04 (0.87,1.24)

Charleston Comorbidity Index					
0 (n=99573, 19348 all cause deaths)	11.3	16.6	26.7	37.1	0.93 (0.89,0.97)**
1 (n=28369, 6734 all cause deaths)	13	16.7	51	56.5	0.92 (0.85,0.99)**
2+ (n=29484, 10575 all cause deaths)	23.5	30.2	97	107.7	1.12 (1.05,1.19)**
History of cardiovascular disease (n=32148, 10967 all cause deaths)	19.5	24.9	69.4	81.4	1.05 (1.00,1.11)
History of high blood pressure (n=133945, 30976 all cause deaths)	16.2	22.3	45.8	58	0.96 (0.93,0.99)**
History of hyperlipidemia (n=94311, 17466 all cause deaths)	14.1	19.1	37.1	49.7	0.99 (0.95,1.04)
History of diabetes (n=31280, 8883 all cause deaths)	16.4	22.9	55	73.3	0.98 (0.92,1.06)
History of cancer (n=8638, 3588 all cause deaths)	21.8	27.5	84.4	94.4	1.06 (0.96,1.17)

*Results are from negative binomial regression, with the exception of the hazard ratios which were estimated using proportional hazard regression. Covariates were adjusted for at two time points, medication initiation at matching (or index date) and last values were carried forward for men missing the second covariate time point.

**P<0.05

[1]Adjusted for age at BPH, BPH initiation year, race, region, Charlson score and comorbidities

Table 11 Summary table of multivariable hazard ratios for each analysis and sensitivity analysis

	Time-scale	Exposure	Covariate Adjustment	2nd time point covariate missingness approach	Adjusted Hazard Ratio (95% CI)
Matched Sample N=174,895					
Fixed exposure; fixed covariates at matching	Calendar	Fixed	Fixed at matching time point	n/a	0.64 (0.62,0.66)
Time-varying #6 in sub-sample included in matched analyses	Calendar	Time-varying	Time varying (both 5ARI and AB): BPH initiation and matching time point	Last value carried forward (BPH initiation)	0.96 (0.93, 0.99)**
Unmatched Cohort N=214,272					
Time-varying crude	Age: not stratified on birth cohort	Time-varying	None	n/a	1.08 (1.06,1.11)

Time-varying #1	Calendar	Time-varying	Time varying (both 5ARI and AB): BPH initiation and matching time point	Last value carried forward (BPH initiation)	0.84 (0.82,0.87)
Time-varying #2	Calendar	Time-varying	Time varying (5ARI) 5ARI: BPH initiation and matching; AB: fixed at BPH initiation	Coded as unknown	0.77 (0.75,0.79)
Time-varying #3	Age; stratified by birth cohort	Time-varying	Time varying (5ARI) 5ARI: BPH initiation and matching; AB: fixed at BPH initiation	Coded as unknown	0.76 (0.75,0.78)
Time-varying #4	Calendar	Time-varying	Fixed at BPH initiation	n/a	0.89 (0.87,0.92)
Time-varying #5	Age; stratified on birth cohort	Time-varying	Fixed at BPH initiation	n/a	0.89 (0.86,0.92)
[redacted] **unmatched sample only N-=91,751**					
[redacted] time-varying #1	Age; stratified on birth cohort	Time-varying	Time varying (5ARI) 5ARI: BPH initiation and matching; AB: fixed at BPH initiation	Re-pull 2nd time point so no missing	0.72 (0.69, 0.75)
[redacted] time-varying #2	calendar	Time-varying	Time varying (5ARI) 5ARI: BPH initiation and matching; AB: fixed at BPH initiation	Re-pull 2nd time point so no missing	0.71 (0.68, 0.74)
[redacted] time-varying #3	Calendar	Time-varying	Time varying (5ARI) 5ARI: BPH initiation and matching; AB: fixed at BPH	Coded as unknown	0.74 (0.71,0.77)

			initiation		
[redacted] time-varying #4	Calendar	Time-varying	Time varying (5ARI) 5ARI: BPH initiation and matching; AB: fixed at BPH initiation	Last value carried forward	0.75 (0.72,0.78)
[redacted] time-varying #5	Calendar	Time-varying	Fixed at BPH initiation	n/a	0.97 (0.93, 1.00)

Table 12 Proportion of men who died due to cardiovascular disease* by exposures status in both cohort samples

Matched sample	Overall	5ARI users (N=25388)	AB users (N=149507)	p-value
CVD cause of death				
Eligible Sample (N=214,272)	24834 (11.6%)	2419 (8.3%)	22415 (12.1%)	<0.0001
Matched Sample (N=174,895)	17759 (10.2%)	2174 (8.6%)	15585 (10.4%)	<0.0001
All Deaths Eligible Sample (N=79,530)	24816 (31.2%)	2419 (28.2%)	22397 (31.6%)	<0.0001
All Deaths Matched Sample (N=35266)	12320 (34.9%)	1674 (34.9%)	10646 (34.9%)	0.94

* CVD-related deaths were determined using the National Center for Health Statistics definition of CVD death, using the corresponding ICD-9 and ICD-10 codes.

Results

Key findings from matched cohort analysis

Table 1 displays the distribution of pre-treatment characteristics by death status after matching in the matched cohort sample. The proportion of men who died of all-causes was significantly different across exposure groups, as 18.9% of 5ARI users died compared to 20.3% of AB users (p<0.0001). Men who died were older at the time of matching on average (p<0.0001), and more likely to be Caucasian (p<0.0001) compared to men who did not die during follow-up. Of those with a PSA level at the time of matching, men who died had slightly higher median PSA levels (2.5 ng/mL vs. 2.3 ng/mL) (p<0.0001) compared to men who did not die. Men who died were more likely to have a higher Charlson index score, history of cardiovascular disease (p<0.0001), diabetes (p<0.0001), and cancer other than prostate (p<0.0001), compared to men who did not die. (Table 1)

Table 2 displays the crude, age-adjusted and multivariable adjusted all cause-mortality rates and hazard ratios comparing the risk of death among 5ARI users to AB users overall and stratified by cumulative time of drug exposure and cumulative dose. After adjusting for age, race, region, BPH medication initiation year, prior AB history, Charlson, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with an increase in all-cause mortality (HR: 0.64; 95% CI: 0.62, 0.66) when compared to AB use. When stratified by level of cumulative exposure, the magnitude of the reduced risk of death associated with 5ARI increased across increasing exposure categories. Men who were exposed for greater than 2 years had the greatest reduction in risk associated with 5ARI use (HR: 0.54, 0.51, 0.57). Also, among men who were exposed to the highest doses, 5ARI was also associated with a reduced risk of mortality when compared to ABs. (HR: 0.55, 95%CI: 0.52, 0.58.)

Table 3 displays the multivariable adjusted -mortality rates and hazard ratios comparing the risk of death among 5ARI users to AB users overall and stratified by characteristics of interest. The association between 5ARI use and all-cause mortality was strikingly homogenous when stratified by race, BMI, Charlson and comorbidities. (Table 3).

Figure 1**A-C** display the unweighted and weighted Kaplan Meier plots in the matched cohort sample. The cumulative probability of survival across the study period was significantly greater for 5ARI users when compared to AB users, both in the unweighted and weighted plots. (both p<0.0001). The difference was consistent across the study period (Figure 1A), and in the first 6 (Figure 1B) and 10 years (Figure 1C).

Unmatched cohort analysis

Table 4 displays the distribution of characteristics at BPH initiation by exposure status in the unmatched cohort sample for all men, which includes those who do not have complete covariate information at both time points. Thus, this table also includes the men who were missing the second covariate time point data in whom we carried the last value forward. Men who used 5ARI were older at the time of their medication initiation on average (p<0.0001), and more likely to be Caucasian (p<0.0001) compared to men who used AB. Of those with a PSA level at the time of initiation, men who used a 5ARI had higher median PSA levels (3.2 ng/mL vs. 1.7 ng/mL) (p<0.0001) compared to men who used AB. 5ARI users were more likely to have a lower Charlson index score (p<0.001). The proportion of men with a history of cardiovascular disease, and cancer other than prostate was not significantly different across exposure groups (Table 4).

Table 5 displays the distribution of characteristics at BPH treatment initiation by death status in the unmatched cohort sample. The proportion of men who died of all-causes was significantly different across exposure groups, as 29.3% of 5ARI users died compared to 38.3% of AB users (p<0.0001). Men who died were older at the time of their medication initiation on average (p<0.0001), and more likely to be Caucasian (p<0.0001) compared to men who did not die during follow-up. Of those with a PSA level at the time of initiation, men who died had slightly higher median PSA levels (2.2 ng/mL vs. 1.7 ng/mL) (p<0.0001) compared to men who did not die. Men who died were more likely to have a higher Charlson index score, history of cardiovascular disease (p<0.0001), diabetes (p<0.0001), and cancer other than prostate (p<0.0001), compared to men who did not die. (Table 5)

Table 6 displays the distribution of characteristics at BPH initiation by exposure status in the unmatched cohort sample for men who have complete covariate information at both time points (initiation for AB users and initiation and matching for 5ARI users) to determine if those who were missing the second time point were very different (as displayed in Table 4). The results were very similar to those presented in Table 4.

Table 7 displays the multivariable adjusted -mortality rates and hazard ratios comparing the risk of death among 5ARI users to AB users overall and stratified by cumulative time of drug exposure and cumulative dose in the unmatched sample where both the exposure and covariates were allowed to be time-varying. This meant using two time points of covariate collection for both AB and 5ARI users, BPH initiation and matching time point in the previous matched analysis, and carrying the last value forward for men who were missing the second covariate time point. After adjusting for age, race, region, BPH medication initiation year, Charlson index, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with an increase in all-cause mortality (HR: 0.84 95%CI: 0.82,0.87) when compared to AB use. Little heterogeneity in the association between 5ARI use and mortality was seen when stratified by increasing levels of cumulative exposure or dose.

Table 8 displays the multivariable adjusted -mortality rates and hazard ratios comparing the risk of death among 5ARI users to AB users overall and stratified by characteristics of interest in the unmatched sample. The association between 5ARI use and all-cause mortality was strikingly homogenous when stratified by race, BMI, Charlson and comorbidities (Table 8).

Sensitivity Results

Table 9 and Table 10 display the results of a sensitivity analysis that employed similar time-varying methods for the covariates and exposure as was done in the unmatched analyses, but was done in the sub-sample of men who were included in the matched cohort sample and analysis. This meant using two time points of covariate collection for both AB and 5ARI users, BPH initiation and matching time point in the previous matched analysis. After adjusting for age, race, region, BPH medication initiation year, Charlson index, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with an increase in all-cause mortality (HR: 0.96 95%CI: 0.93,0.99) when compared to AB use. There was heterogeneity in the association between 5ARI use and mortality when stratified by increasing levels of cumulative exposure or dose. Men exposed less than 1 year had an increased risk of death due to 5ARI use when compared to AB use, but this risk was attenuated with exposure intervals of greater than 1 year. Also, while an increased risk of death among 5ARI users was seen in those exposed to the first three quartiles of dose, those exposed to the highest doses, this risk was attenuated. (Table 8) The association between 5ARI use and all-cause mortality was homogenous when stratified by race and BMI, but among men with 2 or more comorbidities, 5ARI use was associated with an increased risk of mortality compared o AB use (HR: 1.12, 95%CI: 1.05, 1.19) (Table 7).

Table 11 displays the results of a number of sensitivity analyses that were performed in the unmatched and matched cohort samples. In time-varying analysis #2, 5ARI users had two time points of collection of the covariates but only baseline covariates (at BPH medication initiation) were used for AB users. This was done because the second time point of collection (the matching time point's index date) is an arbitrary date for AB users and conditional on the start date of 5ARI of their matched pair. To assess this selection bias, we ran the model without this second time point available in the AB user. 5ARI men who were not matched and had missing covariates at the 2nd time point were coded as unknown. After adjusting for age, race, region, BPH medication initiation year, Charlson, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with an increase in all-cause mortality (HR: 0.77: 95%CI: 0.75, 0.79) when compared to AB use. Similar results were seen when this same model was run using age as the time scale and stratifying by birth cohort to account for any calendar effects. (HR: 0.76, 95%CI: 0.75, 0.78). (Time varying #3, Table 10).

Two models were run allowing for time-varying exposures but fixing the covariate information at BPH initiation for both exposure groups. When using calendar time as the time scale, 5ARI use was again not associated with an increase in all-

cause mortality (HR: 0.89; 95% CI: 0.87, 0.92) when compared to AB use. Similar results were seen when age was used as the time scale (HR: 0.89; 95% CI: 0.86, 0.92). (Time varying #4 and Time-varying #5, Table 11).

Table 11 also displays the results of similar sensitivity analyses that were performed on the sample of the population in [redacted] because they had complete covariate information at both time points of interest. In the first set of models, 5ARI users had two time points of collection of the covariates but only baseline covariates (at BPH medication initiation) were used for AB users. This was done because the second time point of collection (the matching time point's index date) is an arbitrary date for AB users and conditional on the start date of 5ARI of their matched pair. To assess this selection bias, we ran the model without this second time point available in the AB user. We re-pulled covariate information for 5ARI men who were not matched and had missing covariates at the 2nd time point so that they had complete information in this analysis. When using calendar time as the time scale, 5ARI use was again not associated with an increase in all-cause mortality (HR: 0.71; 95% CI: 0.68, 0.74) when compared to AB use. Similar results were seen when age was used as the time scale (HR: 0.72; 95% CI: 0.69, 0.75). [redacted] time-varying #2 and 1, Table 10). Similarly, for the 5ARI users who were missing the second covariate information, when the missingness was coded as unknown and the last value was carried forward, the results were again similar [redacted] Time-varying #3 and 4, Table 10). Finally, when a model was run where the covariates were fixed at baseline, 5ARI were again not associated with an increase in the risk of death compared to AB users (HR: 0.97; 95%CI: 0.93, 1.00).

We also assessed the proportion of men who died from cardiovascular disease in both samples and compared these proportions across exposure group as presented in **Table 12**. Overall, 10.2% of the matched cohort and 11.6% of the unmatched cohort died of cardiovascular related causes. In Both samples, the proportion of men who died from CVD-related causes was greater among AB users when compared to 5ARI users (both p<0.0001). In the matched sample, 10.4% of the AB users and 8.6% of the 5ARI users died of CVD causes and in the unmatched sample, it was 12.1% and 8.3%, respectively. Overall, 31.2% of the deaths that occurred in the eligible unmatched sample were due to CVD, and 34.9% of the deaths that occurred in the matched sample were due to CVD. The proportion of all deaths that were due to CVD was greater among the AB users (31.6%) compared to the 5ARI users 28.2%) in the unmatched eligible sample (p<0.0001), but was equivalent in the matched sample (34.9%, p=0.94) (Table 12)

Discussion

Comparison between matched and unmatched all-cause mortality results-Summary
In general, regardless of the approach used, all of the results suggest that 5ARIs are not associated with an increased risk of mortality when compared to ABs. However, differences in the results were seen when comparing the matched cohort analysis to the time-varying unmatched cohort analysis. The strongest magnitude of association was seen in the matched cohort analysis when the covariates were only collected at and adjusted for at one time point, the time of matching (5ARI initiation or index date in matched AB user). However, in the unmatched cohort analysis when the exposure was time-varying but the covariates were fixed at BPH initiation, the association of interest moved more towards the null. This may in part be due to the fact that timing of BPH medication initiation occurs before the 5ARI initiation time point (used for matching) in most men. To further explore the differences in the results between samples, a subsequent time-varying analysis was run on the subsample of men included in the matched cohort analysis. These results were close to the null and more similar to the results from the unmatched time-varying analyses.

Varying the time scale between using calendar time and age with birth cohort adjustment did not yield different results in the unmatched cohort analysis. The hazard ratios moved more when we altered the adjustment of the covariates, either by allowing them to vary over time (with two time points) in both exposure groups or just for men who used 5ARIs. When we only allowed 5ARI users to have two time points of covariate collection and used only covariate information at AB initiation among AB users, the results were more similar to that of the matched cohort study. However, when we allowed both groups to have two time points of covariates and carried the last value forward for those who were missing the second time point, we saw the association move more towards the null.

Because a proportion of men were unable to be matched in the matched cohort study, we did not pull their data from the other sites for the second time point. As a result, some of them are missing the 2nd time point of covariate info. To account for this, we ran the same sensitivity analyses in the [redacted] sample where we had complete information on all men at both time points. In doing this, the results largely did not change, which suggests that any bias related to the missing values used in the unmatched cohort sample is minimal.

It is also feasible that the differences in the calculations of person-time in the matched and unmatched cohorts may be contributing to the difference in the results seen in these two samples. In the matched cohort, person-time is calculated from 5ARI initiation or the corresponding index time point among AB users until death, loss to follow-up or the end of the study. This truncates the person time in both exposure groups. In the unmatched cohort, we calculated person time from first initiation of either a 5ARI or AB, thus the amount of person time contributed to each exposure group is longer. In prior sensitivity analyses, we found that the majority of men who were ultimately not matched and included in the matched sample were longer-term AB users. Therefore, because these men were unable to be matched and thus are not included in the matched sample, their person-time was truncated to a larger extent than the 5ARI users. As a result, it is possible that this greater decrease in person-time among the AB users resulted in an artificially higher rate of death among AB users. This then biases the hazard ratio away from the null, making it look as though 5ARIs are associated with a stronger reduction in risk of death due to all causes in the matched sample when compared to the results from the unmatched sample.

Comparison to other studies
Overall, our results are similar to those reported by Thompson et al in the New England Journal of Medicine and Azoulay and colleagues in JAMA Oncology which both found that 5ARIs were not associated with an increased risk of mortality. However, in both of our analyses, the probability of survival was lower than that reported by Thompson et al. in the

PCPT follow-up study, which found a 78% probability of survival at 15 years in both the finasteride and placebo groups. When compared to the study by Azoulay et al., which used only a baseline assessment of 5ARI exposure, the magnitude of association was also very similar to our findings. It should be noted, however, the comparison group was not AB users, but rather those not exposed to 5ARIs (Azoulay) and placebo (PCPT).

Potential Limitations
In addition to the biases noted in the Cohort Report that are potentially present in the matched cohort analysis, there are additional potential limitations to consider specific to these analyses. First, the time point of the second covariate data collection is conditional on men being matched in the matched cohort analysis. While this corresponds to the initiation of the 5ARI in the 5ARI group, it is the index (matched) date in the AB, and therefore not clinically meaningful. The availability of data at the second time point is therefore conditional on whether or not the men were successfully matched, which potentially creates a selection bias. As many long term AB users were unable to be matched, it is possible that the death rate among the group successfully matched is different from those who were unable to be matched and are missing this second covariate time point.

Second, because men who were not matched are missing the second time point in all of the sites except SCAL, it is possible this missingness is influencing our results. However, we performed multiple sensitivity analyses to assess this bias and found the results were very similar when run in the SCAL sample with full covariate data and when the missingness was treated using various techniques in the full sample. This suggests that this missing data has minimal influence on the main association of interest.

Finally, the crude mortality rates between the matched and unmatched samples are quite different, with the rate among 5ARI users being slightly higher in the matched sample, and the rate among AB users being lower in the matched sample when compared to the unmatched sample. This difference may be the result of a selection bias associated with the matching approach used, particularly as it relates to the calculations of person-time as described above. As a result, we also performed multiple additional analyses in the unmatched sample as a source of comparison.

Conclusions

In both the matched cohort analyses and the time-varying analyses in the unmatched cohort, 5ARIs were not associated with an increased risk of mortality when compared to use Abs in men treated for symptoms of benign prostatic hyperplasia.

APPENDIX

Table 13 Follow-up in the unmatched and matched samples

Unmatched	5ARI	AB
Person-time (per 1000 pys)	251,041.9	1,240,700.0
N died all causes	5202	49221
N lost to follow-up	2615	43723
N censored at end of study	21415	92096
Matched sample	**5ARI**	**AB**
Person-time (per 1000 pys)	101,854.3	506,274.3
N died all causes	5146	31511
N lost to follow-up	2606	21914
N censored at end of study	21312	74937

Table 14A-B Model building estimates (B) and corresponding output (C) for the unmatched sample (Time-varying analysis #1) and fully adjusted model stratified by BPH medication initiation year

Time varying exposure models	HR (95% CI)
Unadjusted	1.17 (1.14,1.21)**
Age adjusted only	0.98 (0.96,1.01)**
Race adjusted only	1.16 (1.12,1.19)**
Region adjusted only	1.16 (1.13, 1.20)**
BPH initiation year adjusted only	1.10 (1.06,1.13)**
Charlson comorbidity adjusted only	1.12(1.09,1.15)**
Cancer history adjusted only	1.13 (1.10,1.17)**
Cardiovascular disease adjusted only	1.07 (1.04,1.10)**
Hypertension adjusted only	1.21 (1.17,1.24)**
Hyperlipidemia adjusted only	1.16 (1.13,1.19)**
Diabetes adjusted only	1.20 (1.16,1.23)**
Other meds adjusted only	1.18 (1.14,1.21)**
Fully adjusted	0.84 (0.82,0.87)**
Strata: age at BPH category <60, fully adjusted	0.84 (0.74,0.97)**
Strata: age at BPH category [60,70), fully adjusted	0.80 (0.75,0.85)**

Strata: age at BPH category >=70, fully adjusted	0.91 (0.88,0.94)**
Strata: BPH initiation year 1992-1995, fully adjusted	0.80 (0.74,0.87)**
Strata: BPH initiation year 1996-1999, fully adjusted	0.82 (0.78,0.85)**
Strata: BPH initiation year 2000-2003, fully adjusted	0.85 (0.80,0.90)**
Strata: BPH initiation year 2004-2007, fully adjusted	0.96 (0.90.1.03)

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
exposure		1	-0.17289	0.01505	1.007	131.9245	<.0001	0.841	0.817	0.866	
age_at_BPH		1	0.085630	.0005770	1.039	22023.0998	<.0001	1.089	1.088	1.091	
ENTRYYR		1	-0.12391	0.00139	1.020	7993.3054	<.0001	0.883	0.881	0.886	ENTRYYR
REGION	[redacted]	1	-0.18519	0.01852	0.952	99.9842	<.0001	0.831	0.801	0.862	REGION [redacted]
REGION	[redacted]	1	-0.09331	0.00980	1.012	90.7548	<.0001	0.911	0.894	0.929	REGION
REGION	[redacted]	1	-0.05353	0.02061	1.026	6.7484	0.0094	0.948	0.910	0.987	REGION [redacted]
RACE	2	1	0.06650	0.01690	1.036	15.4892	<.0001	1.069	1.034	1.105	RACE 2
RACE	3	1	-0.23081	0.01948	0.997	140.3826	<.0001	0.794	0.764	0.825	RACE 3
RACE	4	1	0.33432	0.01743	0.961	367.8096	<.0001	1.397	1.350	1.446	RACE 4
charlson	1	1	0.44571	0.01367	0.999	1062.8564	<.0001	1.562	1.520	1.604	charlson 1
charlson	2+	1	1.05536	0.01306	1.026	6529.8189	<.0001	2.873	2.800	2.947	charlson 2+
cardio	1	1	0.34764	0.01071	1.021	1053.2488	<.0001	1.416	1.386	1.446	cardio 1
hyperten	1	1	0.20463	0.01432	0.996	204.1235	<.0001	1.227	1.193	1.262	hyperten 1
hyperlip	1	1	-0.31326	0.01014	1.029	955.2469	<.0001	0.731	0.717	0.746	hyperlip 1
diabetes	1	1	0.19805	0.01138	1.048	302.9262	<.0001	1.219	1.192	1.247	diabetes 1
oth_med	1	1	-0.22617	0.01936	0.996	136.4141	<.0001	0.798	0.768	0.828	oth_med 1
cancer_hist	1	1	0.37256	0.01434	1.097	674.7284	<.0001	1.451	1.411	1.493	cancer_hist 1

Type 3 Tests

Effect	DF	Wald Chi-Square	Pr > ChiSq
exposure	1	131.9245	<.0001
age_at_BPH	1	22023.0998	<.0001
ENTRYYR	1	7993.3054	<.0001
REGION	3	153.1050	<.0001
RACE	3	552.3994	<.0001

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
charlson	2	6680.8083	<.0001
cardio	1	1053.2488	<.0001
hyperten	1	204.1235	<.0001
hyperlip	1	955.2469	<.0001
diabetes	1	302.9262	<.0001
oth_med	1	136.4141	<.0001
cancer_hist	1	674.7284	<.0001

Table 15A-B Model building estimates (D) and corresponding output (E) for the matched sample as presented in Table 2 above.

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
matched_case	1	833.3166	<.0001
age_at_matching	1	11169.5910	<.0001
REGION	3	72.6819	<.0001
RACE	3	167.3597	<.0001
ENTRYYR	1	1521.0434	<.0001
yr_AB_history	1	1169.1316	<.0001
charlson_score	2	3477.6609	<.0001
cardio_fg	1	709.9902	<.0001
hyperten_fg	1	55.2602	<.0001
hyperlip_fg	1	499.4179	<.0001
can_his	1	427.7957	<.0001
diabetes_fg	1	141.7503	<.0001
oth_med_fg	1	178.3747	<.0001

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
matched_case		1	-0.45235	0.01567	833.3166	<.0001	0.636	0.617	0.656
age_at_matching		1	0.07392	0.0006994	11169.5910	<.0001	1.077	1.075	1.078
REGION	[redacted]	1	-0.02994	0.02885	1.0768	0.2994	0.971	0.917	1.027
REGION		1	-0.01260	0.01194	1.1140	0.2912	0.987	0.965	1.011
REGION		1	-0.19529	0.02348	69.1788	<.0001	0.823	0.786	0.861
RACE	2	1	-0.16008	0.02174	54.2304	<.0001	0.852	0.817	0.889
RACE	3	1	-0.21788	0.02353	85.7418	<.0001	0.804	0.768	0.842
RACE	4	1	0.13488	0.02613	26.6445	<.0001	1.144	1.087	1.205
ENTRYYR		1	-0.06880	0.00176	1521.0434	<.0001	0.934	0.930	0.937
yr_AB_history		1	-0.06231	0.00182	1169.1316	<.0001	0.940	0.936	0.943
charlson_score	1	1	0.36405	0.01669	475.6911	<.0001	1.439	1.393	1.487
charlson_score	2+	1	0.89952	0.01559	3330.9621	<.0001	2.458	2.384	2.535
cardio_fg		1	0.32685	0.01227	709.9902	<.0001	1.387	1.354	1.420
hyperten_fg		1	0.13997	0.01883	55.2602	<.0001	1.150	1.109	1.193
hyperlip_fg		1	-0.27433	0.01228	499.4179	<.0001	0.760	0.742	0.779
can_his		1	0.31902	0.01542	427.7957	<.0001	1.376	1.335	1.418
diabetes_fg		1	0.15634	0.01313	141.7503	<.0001	1.169	1.140	1.200
oth_med_fg		1	-0.30046	0.02250	178.3747	<.0001	0.740	0.709	0.774

CONFIDENTIAL 2016N297726_00
WEUSKOP5723

Treatment for Lower Urinary Tract Symptoms and Risk of Metastatic Prostate Cancer or Prostate Cancer Mortality

Report: Metastatic Combination Analysis

July 26, 2016

Investigators

Principle Investigator:
[redacted] PhD, [redacted]

[redacted]
Co- Investigator: [redacted] MD, PhD
Co-Investigator: [redacted] MD

[redacted]
Co- Investigator: [redacted] PhD
Co- Investigator: [redacted] MD

[redacted]
Co- Investigator: [redacted] PhD
[redacted] MD

[redacted]
Co- Investigator: [redacted] PhD

[redacted]
Co-investigator: [redacted] PhD

Research Question and Objectives

Background

The recently completed matched retrospective cohort analysis and nested-case control analysis, designed to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, found that 5ARIs did not increase the risk of prostate cancer death. However, men who were exposed to 5ARIs were more often diagnosed with late stage disease (stage III-IV) when compared to men exposed to alpha-blockers. Also, through our development of the natural language based cause of death algorithm (see NLP development report), we identified additional men who most likely died of prostate cancer but were not coded as such (and therefore not included in the primary analysis). Therefore, in order to incorporate these additional deaths (considered probable prostate cancer deaths) and further explore the association of 5ARIs with metastatic disease, we repeated the primary analyses with additional cases of both metastatic disease (among men who did not die during the study period) and probable prostate cancer deaths included as a comparison to the results from our primary analysis.

Objective

To assess the risk of a combined outcome of metastatic prostate cancer or prostate cancer death associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Methods

Design

This analysis was conducted in the same cohort of men utilized for the primary analysis of prostate cancer related mortality based on death records. Briefly, this study used data from four [redacted] sites collected from electronic health records and abstracted from paper records from 1992-2010. Men treated with benign prostatic hyperplasia (BPH) medications; 5-alpha reductase inhibitors (5ARIs) (with and without concomitant and/or previous alpha-blocker use) were compared to men treated with alpha-blockers.

Subjects

All men age 50 years and older treated with a BPH medication (5ARI and/or alpha-blocker) were eligible for inclusion. Participants were not required to have a BPH diagnosis at the time of their first 5ARI or alpha-blocker prescription as based upon data from the feasibility report approximately half of all men received their first recorded BPH diagnosis after initiating treatment. Furthermore, approximately 25% of participants treated with 5ARIs or alpha-

blockers did not have a diagnosis code for BPH in their medical record. BPH diagnosis codes were not used in a consistent way historically in the [redacted] data. Men were required to have coverage within the healthcare system for at least 1-year before the first BPH medication prescription. Men with a history of prostate cancer or who developed prostate cancer within <3 months of starting their BPH medication were not eligible for inclusion.

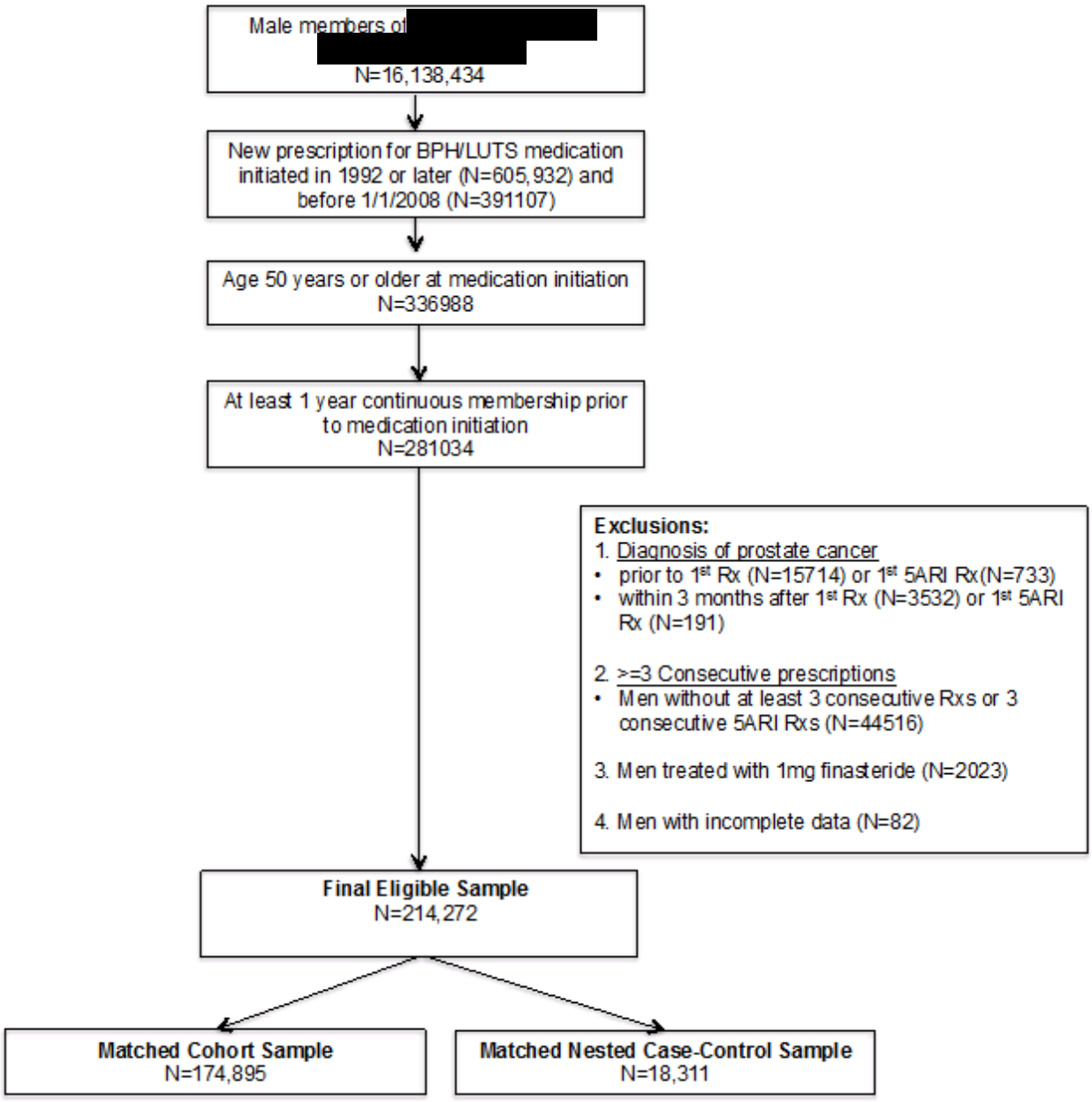
INCLUSION CRITERIA:

- Male
- A new prescription for BPH medication (5ARI and/or alpha-blocker) in 1992 or later that was identified as appropriate treatment for BPH/LUTS from the [redacted] National Pharmacy guidelines
- Treatment with BPH medication must have been initiated prior to Jan. 1, 2008.
- Age 50 years or older at time of treatment with 5ARI or alpha-blocker.
- At least 1-year of coverage in the healthcare system before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- At least 3 consecutive prescriptions (90 days of supply) for a BPH medication (5ARI and/or alpha-blocker)
    - 5ARI users must have had at least 3 consecutive prescriptions for 5ARI.

EXCLUSION CRITERIA:

- Diagnosis of prostate cancer any time before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- Diagnosis of prostate cancer within 3 months after BPH medication initiation (5ARI and/or alpha-blocker)
- Patients treated with finasteride 1mg prior to BPH medication.
- Less than 3 months cumulative exposure or less than 3 consecutive 5ARI prescriptions among men who used 5ARIs

Flow-chart:



Matching in the Cohort Analysis

Men who initiated a 5ARI were matched using risk-set sampling 1:6 to alpha-blocker users on age at matching (+/- 2 years), race (African American vs. Other), timing of BPH medication initiation (within 2 years), prior history of AB use and health plan region. Of the 214,272 eligible men, 73% were successfully matched resulting in an analytic sample of

157,456 men with 174,895 records (18,321 men were matched as both a 5ARI and AB user). Men were then passively followed via electronic health records through the end of 2010 for death due to prostate cancer (N=1,053)

Matching Approach

As was done in the matched cohort analysis, this analysis used the following matching approach:

Eligible matches for 5ARI users were defined based on their medication exposure at the time of 5ARI initiation. For example, a patient initiating 5ARI medication in 1995 had a pool of potential matches that included all men not previously exposed or currently taking 5ARIs in 1995. Therefore a patient taking an alpha-blocker in 1995 who added a 5ARI in 1999 would be an eligible match for the 5ARI user as in 1995 as they had not yet been exposed to 5ARIs. When this alpha-blocker patient initiated 5ARI therapy in 1999, their follow-up time was censored.

The risk-set sampling of "controls" allowed for an equal opportunity of the comparison groups to be exposed to 5ARI and did not condition on future use of a 5ARI. In this situation, an alpha-blocker user was eligible to be selected and matched to a 5ARI user up until he started a 5ARI, at which time he was matched to another alpha-blocker user.

An existing, widely used SAS macro developed by the Mayo Clinic was used to operationalize the matching. Greedy matching will be employed using this macro. (Bergstrahl and Kosanke 1995).

Exposure

Men who ever had at least 3 consecutive prescriptions for a 5ARI or an alpha-blocker (based on exclusions) were included (without gaps).

- A man's exposure status was defined at the time he was selected for matching. All exposure history up until the time of matching was used to define prior AB use.
  - Trends with increasing time on medications were explored by stratifying by increasing cumulative exposure
    - Cumulative exposure was defined from the start of matching in the men who only use an AB and from the start of 5ARI in men who either are combo users or who are 5ARI only users.
  - Dose response was explored by stratifying by increasing categories of dose
    - Dose was calculated in 5ARI users from the date of 5ARI initiation (matching time point) until earliest date of metastases, death, loss to follow-up or end of study (2010). Among AB users, dose was calculated from their index date (matched date) until the earliest date of either 5ARI use, metastases, death, loss to follow-up or end of study (2010).

Outcome: Metastatic prostate cancer and/or prostate cancer death

The primary outcome was metastatic prostate cancer or prostate cancer death. This "combination" outcome during the study period was identified via the following methods which combined those identified via coded cause of death as used in the primary analysis, those identified as probable prostate cancer death using the NLP-based cause of death algorithm, and those with evidence of metastatic disease who did not die during the study period for a total of 1,603 metastatic prostate cancer or prostate cancer death events. **(Figure 1)**

Deaths due to prostate cancer in primary analysis N=1053

- [redacted] mortality database contains mortality information for [redacted] patients since 1981. Prior to 1988, only deaths occurred in [redacted] hospitals are included. This database combines from various data sources including [redacted] state death files, Social Security Administration (SSA), [redacted] internal systems and Non-[redacted] claims. The information collected by this database include name, date of birth, social security number, address, race, gender, cause of death, date of death and the data source of the death.

- The National Death Index (NDI) mortality data was also used to supplement cause of death information where [redacted] is unable to capture it through their existing systems. NDI is a central computerized index of death record information on file in the state vital statistics offices maintained by the Centers for Disease Control. The NDI includes a national file of identifying death record information compiled from computer files submitted by State vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year. NDI Plus searches provide cause of death codes and are available through 2010 currently (2011 will become available Spring 2013). Three groups of participants were identified and sent to the CDC for a NDI match:
  - All men (regardless of prostate cancer status) in the sample that died prior to or on 12/31/10 who are missing underlying cause of death info.
  - All men (regardless of prostate cancer status) in the sample that left [redacted] alive but died on or before 12/31/10 without underlying cause of death.
  - Men with prostate cancer diagnosis who left [redacted] alive without a death date (up to May 2013) who we do not know are dead. For those men who died after the study end date, these deaths will not be included in the analysis and they were censored at the end of the study period (December 31, 2010).

Probable Prostate Cancer Death identified via NLP algorithm N=126

Men who died during the study period who had a diagnosis of prostate cancer but did not have a coded cause of death (ICD-9) that was prostate cancer were run through our previously developed cause of death algorithm (N=752)(see cause of death algorithm in Appendix). Natural language processing was used to search the pathology, radiology and clinic notes of each man to identify the presence of metastatic disease and combined with coded information from the EMR to confirm that the death was most likely due to prostate cancer.

The development of the NLP components for the cause of death algorithm was completed in the fall of 2014. The resulting accuracy statistics are listed below in the table. After developing each algorithm component separately, we achieved perfect sensitivity and for the majority of items, excellent specificity. The only exception was component 2K, which identified a mention of bone, back, arm or leg pain in conjunction with metastatic disease in the same clinic note. We were only able to achieve a SP of 67% for this item, such that there were a number of false positives. (Table 1)

Table 1 Summary of Component development and accuracy statistics

Component	Accuracy	Sensitivity	Specificity
Pathology Reports			
2A. Adenocarcinoma	98.5%	94.1%	99.2%
Radiology Reports			

2H. Bone Scan	99.3%	100.0%	98.5%
2J. Lesions on imaging	99.0%	100.0%	99.2%
Clinic Notes			
2I. Lymph node or distant spread	91.0%	100.0%	92.6%
2K and 3C. Pain in clinic note	73.5%	100.0%	67.0%

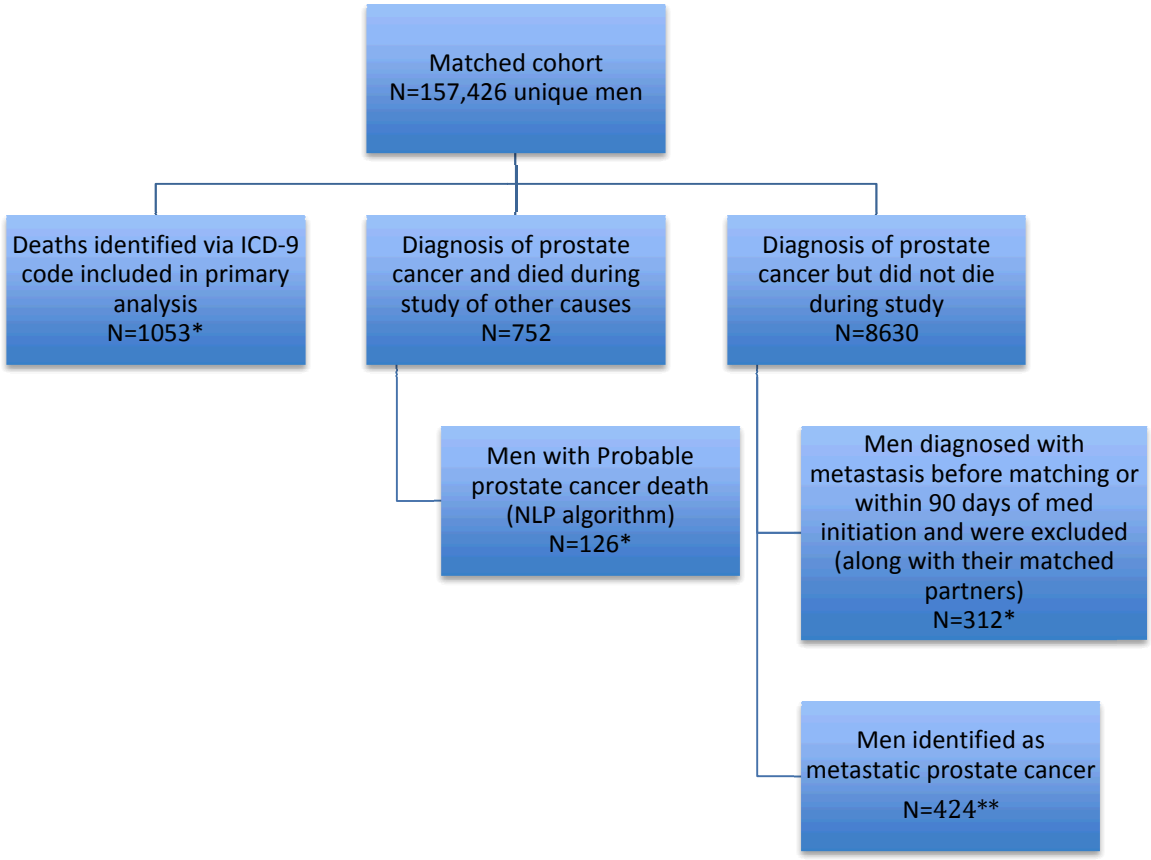
Using this algorithm, we identified **126 men** who were probable prostate cancer deaths as they had significant evidence in their charts that they had metastatic disease soon before their death.

Metastatic prostate cancer among men who did not die N=424

For the remaining 8,630 men who did not die during the study but had a diagnosis of prostate cancer, we further determined whether their cancer was metastatic. As we did not have radiology, pathology or clinic notes on these men from all of the [redacted] sites included in this study, we used the coded electronic components from the metastatic part of the cause of death algorithm which we had complete data on, and applied the following definition to ascertain metastatic disease. The coded components were divided into major and minor components based on their accuracy in identifying metastatic disease during the cause of death algorithm development process. Major components were further discussed by the investigator and clinical team as those which were most clinically meaningful in determining the presence of metastatic disease. PSA and ICD-9 codes were the components that most accurately identified metastatic disease as part of the cause of death algorithm (appendix). Because men who have biochemical recurrence and not metastatic disease may have both increasing visits to oncology and also use ADT as a salvage therapy, these components were classified as minor as they result in a number of false positives when defining metastatic disease. As a result, the investigator team decided that these "minor" components should contribute less to the definition of metastatic disease. Therefore, the "major" components were considered necessary in the definition of metastatic disease as follows:

- All men who have both major components (ICD-9 196.x-199.x and PSA > 100 or Rising PSA (*quadruple in 1 year or baseline PSA >10*)) are positive for metastatic disease.
    - The distribution of all of the coded components considered is included in the Appendix.
- If men had only one of these major components, then they also needed to have at least 1 of the minor criteria to be positive (Use of ADT as secondary treatment or orchiectomy (*6 months after initial PCa diagnosis*) or Increasing visits to oncology (the oncologist or the radiation oncologist for pain or for palliative radiation for pain) (*6 months after initial PCa diagnosis, at least 2 visits per year*)
- If men don't have either an ICD-9 code or high or rapidly rising PSA, then they are negative for metastatic disease.

Figure 1 Outcome Definition Flow Chart



**Combination outcome includes 1053 Definite prostate cancer death + 126 Probable prostate cancer deaths + 424 metastatic prostate cancer cases = 1603 metastatic and/or prostate cancer death

*There were 312 men diagnosed with metastatic prostate cancer in the AB group who developed metastases long after their first AB prescription and were thus not excluded in the primary analysis. We further excluded them here along with their matched partners because the development of metastases occurred prior to their matching date or within 90 days.

Covariates

- The same covariates as defined in the primary analysis were included in this study (see list below), with the timing of collection at the time of matching (5ARI initiation or index date in AB.

- Race/ethnicity
  - Race and ethnicity was collected across sites and based on a race and ethnicity variable that was categorized as: Non-Hispanic White, African American, Asian, and Hawaiian/Pacific Islander, Native Alaskan/American Indian, Multiple, Unknown. Race categories were collapsed to be African American vs. Other for matching.

- Age (death/index date)
  - Age was calculated from date of birth and reflected as age at matching (or index).

- BPH initiation calendar year
  - This is the calendar year which the first medication to treat BPH/LUTS was initiated.

- Socioeconomic status (SES)
  - Aggregate SES measures for [redacted] members were calculated via geocoding using 2000 US census estimates at the block, block-group, tract and ZIP level and include income and education.

- PSA
  - PSA was available through our laboratory data in the Virtual Data Warehouse and was measured in ng/mL. Baseline PSA was defined at the time of matching.

- BMI
  - BMI was not routinely collected as a vital sign until the implementation of the electronic medical record in each site (mid 2000s) Therefore, only a few years of complete data were available. BMI was calculated using standard formula and measured in kg/m2.
  - Due to the paucity of BMI data, it was only be used in sensitivity analyses where the effect of BMI on the association of interest was investigated.

- Charlson Comorbidity Index
  - Charlson comorbidity Index was collected based on ICD-9 codes of the included conditions/complications and a standard algorithm and coding macro was used to derive the score which was categorized into (0, 1 or 2+)

- CVD Endpoints
  - History of cardiovascular disease: ICD-9 410.x-429.x
  - History of high blood pressure/hypertension: ICD-9 codes (401.x) *and/or* dispense of blood pressure medications

- History of diabetes (HEDIS definition): dispensing record for insulin or an oral hypoglycemic from the HEDIS list (not including metformin) *or* any discharge ICD-9 code of 250.xx, 357.2, 362.0, 366.41, 648.0, *or* hemoglobin A1C >= 7.0%.)

- Overactive Bladder and Erectile Dysfunction medications
  - Any medications used to treat either overactive bladder and/or erectile dysfunction including PED-5 inhibitors and anti-cholinergic as identified through [redacted] formulary.

- History of hyperlipidemia : Any dispense of statin medications *and/or* any abnormal lipid profile test:
  - Total cholesterol (>200 mg/dL),
  - HDL (<= 40 mg/dL)
  - LDL (>130 mg/dL),
  - Triglycerides (>150 mg/dL)

- History of Cancer – Other than Prostate
  - History of cancer at major sites other than the prostate was determined by pathology-confirmed diagnoses via the cancer registries.

Potential confounding factors over the follow-up period:

- Additionally information on several variables occurring over the follow-up period was collected including:
  - PSA testing patterns after treatment initiation and over the course of the study period.
  - The frequency of biopsy
  - Gleason Score at diagnosis
  - Frequency of prostate cancer treatment paradigms (radical prostatectomy, external beam radiation, brachytherapy, cryotherapy, etc.)

- Confounding factors that occur over the follow-up were not adjusted for in regression analyses, as they may have been in the causal path between exposure and outcome. These confounders were instead described by exposure status.

Potential effect measure modifiers for consideration:

- Race/ethnicity
- Age
- Socioeconomic status (income)
- PSA level at diagnosis (among sample who have a prostate cancer diagnosis)

Statistical Analyses:

The matched cohort used in this analysis is similar to that used in the primary analysis focused on prostate cancer mortality as the outcome, except that 312 men and their matched partners were further excluded due to the timing of metastatic disease diagnosis. Briefly, once the 5ARI patients were matched to alpha-blocker patients on the matching variables (birth year, race, BPH initiation calendar year, region and duration of prior use of alpha-blockers), the

appropriate statistics were calculated to confirm that indeed the groups were successfully matched on these characteristics. The success of the matching was further assessed based on whether balance between the treated and control groups was achieved in the matched samples. Additionally, background characteristics (including cumulative exposure time, follow-up time, follow-up time after cancer diagnosis, and potential pre-treatment initiation confounding factors) were compared between the groups to identify whether there were variables that would need to be considered in the outcome analyses as covariates. The details of this approach are outlined in the Cohort Study Report.

Person-time calculations

Each patient included in the analysis has his survival outcome determined as follows. All patients who died or developed metastatic disease were considered as events. Patients who were lost to follow-up (left the [redacted] system) before the end of the study period but later died before the end of the study were included as outcomes, but their person-time was truncated at the date of loss to follow-up. End of follow-up for patients who were alive and were not lost to follow-up or did not die or develop metastatic disease during the study period was at the end of study period.

- Person-time (follow up) was calculated from time at which the participant was matched (i.e started a 5ARI prescription and corresponding index date in AB user) up until the time of the event, censoring, or end of the study period. Cumulative exposure and cumulative dose were defined accordingly (same as primary analysis) and were exposure specific.

Bivariate statistics and comparisons

Next, we examined pre-treatment assignment characteristics such as prior co-morbidities for each treatment group as well as pre-treatment characteristics among those who died from prostate cancer or developed metastatic disease during the study period vs. those who did not. We also compared these characteristics across metastatic status (among men who did not die) and probable prostate cancer status. For the bivariate analyses, continuous variables were compared using two-sample *t*-statistics, and categorical variables were compared using chi-square statistics where appropriate (as was done in the primary analysis).

Survival analysis

Multivariable-adjusted mortality rates and hazard ratios were estimated using proportional hazard regression, comparing the rate of metastatic disease or death due to prostate cancer among 5ARI users vs. alpha-blocker users overall and stratified by duration of cumulative exposure, cumulative dose and clinical characteristics of interest.

- Adjustment for competing risks in this context was not done because we inherently are ignoring the competing risk nature of the two outcomes (metastases and death) when we combined them into a combination outcome. Therefore, in this setting, adjustment for competing risks was not felt to be appropriate.

Confounding and effect modification

<u>Confounding</u>

- Third variables of interest that are included in the multi-variable adjusted models were chosen based on known a priori confounders (age, race, region, history of AB use, BPH medication initiation year), and variables found to be confounders in this data set.

- Variables found to be imbalanced after matching across both exposure and outcome categories were included in the multi-variable adjusted models.
- Both Charlson comorbidity index and the individual comorbidities were eligible for inclusion in the model as they are measuring different aspects of comorbid disease.
- The final models were adjusted for the following confounders:
  - Matching factors (age, race, region, history of AB use, BPH medication initiation calendar year)
  - Charlson index (0,1, 2+)
  - Medical history variables: cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer, use of other medications to treat OAB or ED.

COMBINED OUTCOME RESULTS

Note: The baseline characteristics of the eligible population are presented in the primary analysis report (matched cohort report).

Table 2 Demographic and Clinical Characteristics* by Combination Outcome Status (combined definition of prostate cancer death, probable prostate cancer death or metastatic prostate cancer)

	Overall (n=173,990)	Metastatic disease and/or Prostate Cancer Death (n=1,603)	No metastatic disease and/or prostate cancer death (n=172,387)	p-value
Characteristic				
Exposure				
Alpha Blocker users	148911 (85.6%)	1375 (85.8%)	147536 (85.6%)	0.83
5ARI users	25079 (14.4%)	228 (14.2%)	24851 (14.4%)	
Age at matching				
Mean (SD)	72.3 (9.2)	77.3 (8.5)	72.3 (9.2)	<0.0001
Median	72.5	78.1	72.5	<0.0001
<60	17876 (10.3%)	42 (2.6%)	17834 (10.4%)	<0.0001
60-69	52791 (30.3%)	271 (16.9%)	52520 (30.5%)	
70+	103323 (59.4%)	1290 (80.5%)	102033 (59.2%)	
Race				
Non-Hispanic White	133557 (76.8%)	1276 (79.6%)	132281 (76.7%)	<0.0001
African American	12558 (7.2%)	188 (11.7%)	12370 (7.2%)	

Asian	14580 (8.4%)	66 (4.1%)	14514 (8.4%)	
Hawaiian, PI, Multiple, and Unknown	13295 (7.6%)	73 (4.6%)	13222 (7.7%)	
Socioeconomic Status				
Missing	3315 (1.9%)	38 (2.4%)	3277 (1.9%)	
Household income, median ($1000)	62.0	61.3	62.0	0.06
Household income, mean (SD) ($1000)	66.4 (28.2)	65.6 (29.3)	66.5 (28.3)	0.06
Education**				
Less than 9th grade	0.07(0.09),0.04	0.07(0.09),0.04	0.07(0.09),0.04	0.17
9th – 12 grade	0.10(0.07),0.08	0.10(0.07),0.08	0.10(0.09),0.08	0.65
High school graduate	0.21(0.08),0.21	0.21(0.08),0.21	0.21(0.08),0.21	0.95
Some college, no degree	0.24(0.07),0.25	0.24(0.07),0.25	0.24(0.07),0.25	0.78
Associate degree	0.08(0.03),0.08	0.08(0.03),0.07	0.08(0.03),0.08	0.33
Bachelor degree	0.19(0.11),0.19	0.19(0.11),0.18	0.19(0.11),0.19	0.71
Graduate or professional degree	0.11(0.09),0.08	0.11(0.10),0.09	0.11(0.09),0.08	0.56
PSA at matching (ng/mL)				
Missing	65049 (37.4%)	480 (29.9%)	64569 (37.5%)	
.PSA level, mean (SD)	4.7 (39.3)	52.7 (281.3)	4.2 (26.7)	<0.0001
PSA level, median	2.3	6.9	2.3	<0.0001
0 – 2.5	56693 (32.6%)	286 (17.8%)	56407 (32.7%)	<0.0001
2.5 - 4	17409 (10.0%)	98 (6.1%)	17311 (10.0%)	
≥4	34839 (20.0%)	739 (46.1%)	34100 (19.8%)	
BMI (kg/m^2)				
Missing	87639 (56.1%)	1228 (76.6%)	96411 (55.9%)	
<25	29475 (16.9%)	140 (8.7%)	29335 (17.0%)	<0.0001
25-30	26489 (15.2%)	136 (8.5%)	26353 (15.3%)	
≥30	20387 (11.7%)	99 (6.2%)	20288 (11.8%)	
Charleston Comorbidity Index				
0	75525 (43.4%)	609 (38.0%)	74916 (43.5%)	<0.0001
1	34537 (19.9%)	186 (11.6%)	34351 (19.9%)	
2+	63928 (36.7%)	808 (50.4%)	63120 (36.6%)	
History of cardiovascular disease	59111(34.0%)	531 (33.1%)	58580 (34.0%)	0.47
History of high blood pressure	156720 (90.1%)	1383 (86.3%)	155337 (90.1%)	<.0001
History of hyperlipidemia	117368 (67.5%)	863 (53.8%)	116505 (67.6%)	<.0001
History of diabetes	45069 (25.9%)	319 (19.9%)	44750 (26.0%)	<.0001
History of cancer	15779 (9.1%)	177 (11.0%)	15602 (9.1%)	0.006
Use of other medications to treat ED or OAB*	23043 (13.2%)	136 (8.5%)	22907 (13.3%)	<.0001
Alpha Blocker history (years)[1]				

Mean (SD)	4.3 (4.1)	3.7 (2.3)	4.3 (4.1)	<0.0001
Median	3.4	2.3	3.4	<0.0001

***Characteristics were defined at the time of matching (5ARI initiation) or the index date in AB users**

****Geocoded education**

Table 3 Demographic and Clinical Characteristics* by Probable Prostate Cancer Status (N=770 records run through the cause of death algorithm)

	Overall (n=770)	Probable prostate cancer (n=127)	No probable prostate cancer (n=643)	p-value
Characteristic				
Exposure				
Alpha Blocker users	719 (93.4%)	117 (92.1%)	602 (93.6%)	0.54
5ARI users	51 (6.6%)	10 (7.9%)	41 (6.4%)	
Age at matching				
Mean (SD)	78.3 (7.6)	79.4 (7.5)	78.1 (7.6)	0.10
Median	78.8	79.8	78.6	0.10
<60	5 (0.7%)	0 (0)	5 (0.8%)	0.56
60-69	115 (14.9%)	16 (12.6%)	99 (15.4%)	
70+	650 (84.4%)	111 (87.4%)	539 (83.8%)	
Race				
Non-Hispanic White	629 (81.7%)	107 (84.3%)	522 (81.2%)	0.71
African American	94 (12.2%)	15 (11.8%)	79 (12.3%)	

Asian	35 (4.6%)	4 (3.2%)	31 (4.8%)	
Hawaiian, PI, Multiple, and Unknown	12 (1.6%)	1 (0.8%)	11 (1.7%)	
Socioeconomic Status				
Missing	14 (1.8%)	0 (0)	14 (2.2%)	
Household income, median ($1000)	64.2 (28.3)	64.9 (28.6)	64.1 (28.3)	0.74
Household income, mean (SD) ($1000)	59.3	63.3	58.9	0.74
Education**				
Less than 9th grade	0.07(0.09),0.04	0.07(0.08),0.04	0.07(0.09),0.04	0.28
9th – 12 grade	0.10(0.07),0.09	0.09(0.07),0.08	0.10(0.07),0.09	0.19
High school graduate	0.21(0.09),0.21	0.22(0.10),0.21	0.21(0.08),0.21	0.88
Some college, no degree	0.24(0.07),0.24	0.24(0.07),0.24	0.24(0.07),0.25	0.57
Associate degree	0.08(0.03),0.07	0.07(0.03),0.07	0.08(0.03),0.07	0.84
Bachelor degree	0.19(0.10),0.18	0.19(0.11),0.18	0.19(0.10),0.18	0.91
Graduate or professional degree	0.11(0.09),0.08	0.11(0.10),0.08	0.11(0.09),0.08	0.75
PSA at matching (ng/mL)				
Missing	218 (28.3%)	40 (31.5%)	178 (27.7%)	
.PSA level, mean (SD)	20.3 (214.5)	75.4 (536.5)	10.0 (24.8)	0.31
PSA level, median	4.6	4.9	4.6	0.31
0 – 2.5	215 (27.9%)	34 (26.8%)	181 (28.2%)	0.83
2.5 - 4	43 (5.6%)	6 (4.7%)	37 (5.8%)	
≥4	294 (38.2%)	47 (37.0%)	247 (38.4%)	
BMI (kg/m^2)				
Missing	595 (77.3%)	81 (63.8%)	514 (79.9%)	
<25	75 (9.7%)	20 (15.8%)	55 (8.6%)	0.001
25-30	69 (9.0%)	19 (15.0%)	50 (7.8%)	
≥30	31 (4.0%)	7 (5.5%)	24 (3.7%)	
Charleston Comorbidity Index				
0	238 (30.9%)	34 (26.8%)	204 (31.7%)	0.46
1	98 (12.7%)	19 *15.0%)	79 (12.3%)	
2+	434 (56.4%)	74 (58.3%)	360 (56.0%)	
History of cardiovascular disease	380 (49.4%)	69 (54.3%)	311 (48.4%)	0.22
History of high blood pressure	694 (90.1%)	119 (93.7%)	575 (89.4%)	0.14
History of hyperlipidemia	444 (57.7%)	78 (61.4%)	366 (56.9%)	0.35
History of diabetes	215 (27.9%)	33 (26.0%)	182 (28.3%)	0.59
History of cancer	65 (8.4%)	11 (8.7%)	54 (8.4%)	0.92
Use of other medications to treat ED or OAB*	45 (5.8%)	3 (2.4%)	42 (6.5%)	0.07
Alpha Blocker history (years)[1]				

Mean (SD)	4.6 (4.1)	4.7 (4.0)	4.6 (4.1)	0.76
Median	3.9	3.9	3.9	0.76

***Characteristics were defined at the time of matching (5ARI initiation) or the index date in AB users**

****Geocoded education**

Table 4 Multivariable-adjusted metastatic or prostate cancer death event rates, and hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose*

	No of deaths/ No at risk (%)		Event rate Per 1000 p-y		Adjusted Hazard Ratio (95% CI)
Multi-variable adjusted	**5ARI**	**AB**	**5ARI**	**AB**	
Overall (n=173990, 1603 combo outcome)	0.22	0.29	1.54	2.49	0.66 (0.58,0.76)**
Cumulative exposure					
<6 mos (n=21038, 194 Pca outcomes)	0.005	0.36	0.0017	9.26	0.72 (0.18,2.89)
6 mos-1yr (n=59603, 613 Pca outcomes)	0.29	0.31	1.77	1.99	0.88 (0.71,1.09)
1 yr-2 yrs (n=45268, 415 Pca outcomes)	0.11	0.14	0.26	0.31	0.81 (0.61,1.09)

2+ yrs (n=48081, 381 Pca outcomes)	0.05	0.07	0.07	0.11	0.55 (0.42,0.71)**
Cumulative dose (gram)					
1st quartile (n=43492, 438 Pca outcomes)	0.41	0.30	3.20	4.27	0.99 (0.37,2.66)
2nd quartile (n=42568, 412 Pca outcomes)	0.31	0.24	2.80	1.45	0.94 (0.72,1.24)
3rd quartile (n=44432, 399 Pca outcomes)	0.20	0.10	0.80	0.35	1.23 (0.96,1.58)
4th quartile (n=43498, 354 Pca outcomes)	0.03	0.06	0.03	0.11	0.50 (0.39,0.65)**

*Results are from negative binomial regression, with the exception of hazard ratios which were estimated using proportional hazard regression.

**P<0.05

[1]Adjusted for age, BPH initiation year, race, region, prior AB history, Charlson score and comorbidities.

METASTATIC PROSTATE CANCER RESULTS N=424

Table 5 Algorithm Components by metastatic prostate cancer status (among men who did not die of prostate cancer but had a diagnosis of prostate cancer)

Algorithm Components	No metastatic prostate cancer	Metastatic prostate cancer

	(N=8264)*	(N=424)*
2. Does subject have evidence of metastatic prostate cancer?		
B. Code for metastatic disease (196.x-199.x)	530 (6.4%)	306 (72.2%)
C. High or Rapidly Rising PSA	686 (8.3%)	318 (75.0%)
F. Use of ADT or orchiectomy as secondary treatment	80 (1.0%)	11 (2.6%)
G. Increasing visits to oncology	1691 (20.5%)	292 (68.9%)

Note: counts reflect number of records in matched sample, they do not reflect number of unique patients.

Algorithm Components	No metastatic prostate cancer (N=7889)	Metastatic prostate cancer (N=424)
2. Does subject have evidence of metastatic prostate cancer?		
B. Code for metastatic disease (196.x-199.x)	482 (6.1%)	306 (72.2%)
C. High or Rapidly Rising PSA	621 (7.9%)	318 (75.0%)
F. Use of ADT or orchiectomy as secondary treatment	78 (1.0%)	11 (2.6%)
G. Increasing visits to oncology	1633 (20.7%)	292 (68.9%)

Note: counts reflect number of unique patients.

Table 6 Demographic and Clinical Characteristics* by Metastatic Prostate Cancer Status among men with a diagnosis of prostate cancer who did not die during the study period (N=8688)

	Overall (n=8668)	Metastatic prostate cancer (n=424)	No metastatic prostate cancer (n=8264)	p-value
Characteristic				
Exposure				
Alpha Blocker users	8008 (92.2%)	364 (85.9%)	7644 (92.5%)	<0.001
5ARI users	680 (7.8%)	60 (14.2%)	620 (7.5%)	
Age at matching				
Mean (SD)	71.9 (8.2)	71.8 (8.3)	71.9 (8.2)	0.64
Median	72.0	71.5	72.0	0.64
<60	679 (7.8%)	31 (7.3%)	648 (7.8%)	0.84
60-69	2934 (33.8%)	148 (34.9%)	2786 (33.7%)	
70+	5075 (58.4%)	245 (57.8%)	4830 (58.5%)	
Race				
Non-Hispanic White	6670 (76.8%)	322 (75.9%)	6348 (76.8%)	0.23
African American	1083 (12.5%)	63 (14.9%)	1020 (12.3%)	
Asian	632 (7.3%)	23 (5.4%)	609 (7.4%)	
Hawaiian, PI, Multiple, and Unknown	303 (3.5%)	16 (3.8%)	287 (3.5%)	
Socioeconomic Status				
Missing	123 (1.4%)	9 (2.1%)	114 (1.4%)	
Household income, median ($1000)	63.1	54.6	63.1	0.58
Household income, mean (SD) ($1000)	67.1 (28.4)	68.3 (30.2)	67.1 (28.4)	0.58
Education**				
Less than 9th grade	0.07(0.09),0.04	0.07(0.09),0.03	0.07(0.09),0.04	0.42
9th – 12 grade	0.09(0.07),0.08	0.09(0.07),0.07	0.09(0.07),0.08	0.45
High school graduate	0.20(0.08),0.2	0.20(0.08),0.19	0.21(0.08),0.21	0.01
Some college, no degree	0.24(0.07),0.25	0.24(0.07),0.25	0.24(0.07),0.25	0.80
Associate degree	0.08(0.03),0.08	0.07(0.03),0.07	0.08(0.03),0.08	0.07
Bachelor degree	0.20(0.11),0.19	0.20(0.11),0.20	0.20(0.10),0.19	0.17
Graduate or professional degree	0.11(0.09),0.09	0.12(0.10),0.09	0.11(0.09),0.09	0.10
PSA at matching (ng/mL)				
Missing	1500 (17.3%)	112 (26.4%)	1388 (16.8%)	
.PSA level, mean (SD)	6.1 (19.7)	13.3 (44.4)	5.8 (17.7)	<0.0001
PSA level, median	3.5	5.1	3.5	<0.0001
0 – 2.5	2898 (33.4%)	85 (20.1%)	2813 (34.0%)	<0.0001
2.5 - 4	999 (11.5%)	43 (10.1%)	956 (11.6%)	
≥4	3291 (37.9%)	184 (43.4%)	3107 (37.6%)	
BMI (kg/m^2)				
Missing	4865 (56.0%)	323 (76.2%)	4542 (55.0%)	

<25	1318 (15.2%)	31 (7.3%)	1287 (15.6%)	<0.0001
25-30	1452 (16.7%)	37 (8.7%)	1415 (17.1%)	
≥30	1053 (12.1%)	33 (7.8%)	1020 (12.3%)	
Charleston Comorbidity Index				
0	3290 (37.9%)	214 (50.5%)	3076 (37.2%)	<0.0001
1	1118 (12.9%)	43 (10.1%)	1075 (13.0%)	
2+	4280 (49.3%)	167 (39.4%)	4113 (49.8%)	
History of cardiovascular disease	2497 (28.7%)	107 (25.2)	2390 (28.9)	0.10
History of high blood pressure	7707 (88.7%)	351 (82.8)	7356 (89.0)	<0.0001
History of hyperlipidemia	5894 (67.8%)	276 (65.1)	5618 (68.0)	0.21
History of diabetes	1854 (21.3%)	77 (18.2)	1777 (21.5)	0.10
History of cancer	642 (7.4%)	28 (6.6)	614 (7.4)	0.53
Use of other medications to treat ED or OAB*	1415 (16.3%)	60 (14.2)	1355 (16.4)	0.22
Alpha Blocker history (years)[1]				
Mean (SD)	5.4 (4.5)	3.6 (3.9)	5.5 (4.5)	<0.0001
Median	4.9	1.9	5.0	<0.0001

Note: counts reflect number of records in matched sample, they do not reflect number of unique patients.

***Characteristics were defined at the time of matching (5ARI initiation) or the index date in AB users**

****Geocoded education**

Table 7 Characteristics by exposure status, among men with metastatic cancer (N=424)*

	Overall (n=424)	5ARI (n=60)	AB (n=364)	p-value
Characteristic				
Age at matching				
Mean (SD)	71.8 (8.3)	74.0 (8.8)	71.5 (8.2)	0.03
Median	71.5	75.0	71.1	0.03
<60	31 (7.3%)	2 (3.3%)	29 (8.0%)	0.16
60-69	148 (34.9%)	17 (28.3%)	131 (36.0%)	
70+	245 (57.8%)	41 (68.3%)	204 (56.0%)	
Race				
Non-Hispanic White	322 (75.9%)	45 (75%)	277 (76.1%)	0.96
African American	63 (14.9%)	9 (15%)	54 (14.8%)	
Asian	23 (5.4%)	3 (5%)	20 (5.5%)	
Hawaiian, PI, Multiple, and Unknown	16 (3.8%)	3 (5%)	13 (3.6%)	
Socioeconomic Status				
Missing	9 (2.1)	0 (0)	9 (2.5%)	
Household income, median ($1000)	64.6	65.5	64.4	0.68
Household income, mean (SD) ($1000)	68.3 (30.2)	70.4 (32.7)	67.9 (29.8)	0.68
Education**				
Less than 9th grade	0.07(0.09), 0.03	0.04(0.04), 0.03	0.07(0.09), 0.04	0.09
9th – 12 grade	0.09(0.07), 0.07	0.09(0.07), 0.08	0.10(0.07), 0.07	0.49
High school graduate	0.20(0.08), 0.19	0.20(0.10), 0.18	0.20(0.08), 0.19	0.63
Some college, no degree	0.24(0.07), 0.25	0.25(0.07), 0.25	0.24(0.07), 0.25	0.60
Associate degree	0.07(0.03), 0.07	0.08(0.03), 0.07	0.07(0.03), 0.07	0.42
Bachelor degree	0.20(0.11), 0.2	0.21(0.12), 0.21	0.20(0.11), 0.19	0.43
Graduate or professional degree	0.12(0.10), 0.09	0.13(0.11), 0.11	0.12(0.10), 0.09	0.56
PSA at matching (ng/mL)				
Missing	112 (26.4%)	13 (21.7%)	99 (27.2%)	
.PSA level, mean (SD)	13.3 (44.4)	15.3 (18.1)	12.9 (47.6)	<0.0001
PSA level, median	5.1	10.1	4.7	<0.0001
0 – 2.5	85 (20.1%)	7 (11.7%)	78 (21.4%)	0.006
2.5 - 4	43 (10.1%)	2 (3.3%)	41 (11.3%)	
≥4	184 (43.4%)	38 (63.3%)	146 (40.1%)	

BMI (kg/m²)				
Missing	323 (76.2%)	44 (73.3%)	279 (76.7%)	
<25	31 (7.3%)	8 (13.3%)	23 (6.3%)	
25-30	37 (8.7%)	3 (5.0%)	34 (9.3%)	0.20
≥30	33 (7.8%)	5 (8.3%)	28 (7.7%)	
Charleston Comorbidity Index				
0	214 (50.5%)	35 (58.3%)	179 (49.2%)	
1	43 (10.1%)	11 (18.3%)	32 (8.8%)	0.007
2+	167 *(39.4%)	14 (23.3%)	153 (42.0%)	
History of cardiovascular disease	107 (25.2%)	19 (31.7%)	88 (24.2%)	0.22
History of high blood pressure	351 (82.8%)	48 (80%)	303 (83.2%)	0.54
History of hyperlipidemia	276 (65.1%)	35 (58.3%)	241 (66.2%)	0.24
History of diabetes	77 (18.2%)	10 (16.7%)	67 (18.4%)	0.75
History of cancer	28 (6.6%)	6 (10.0%)	22 (6.0%)	0.25
Use of other medications to treat ED or OAB*	60 (14.2%)	7 (11.7%)	53 (14.6%)	0.55
Alpha Blocker history (years)[1]				
Mean (SD)	3.6 (3.9)	3.2 (3.7)	3.6 (3.9)	0.13
Median	1.9	1.3	2.1	0.13
Follow up characteristics				
Cumulative exposure time (years)				
Mean (SD)	1.32 (1.34)	1.78 (1.57)	1.24 (1.28)	0.003
Median	0.87	1.22	0.82	0.003
Cumulative dose (gram)				
Mean (SD)	2.22 (3.62)	3.35 (3.00)	2.04 (3.69)	<0.0001
Median	1.00	2.14	0.80	<0.0001
Duration of follow-up time (years)				
Mean (SD)	3.26 (2.65)	3.78 (2.75)	3.17 (2.63)	0.06
Median	2.49	3.11	2.38	0.06
Patients with ≥1 PSA test	410 (96.7%)	59 (98.3%)	351 (96.4%)	0.70
Number of biopsies				
Mean (SD)	1.28 (0.56)	1.27 (0.55)	1.29 (0.56)	0.82
Median	1.0	1.0	1.0	0.82
Time from last treatment to prostate cancer diagnosis (years)**				

Mean (SD)	-1.80 (3.25)	-1.44 (3.29)	-0.88 (2.65)	0.02
Median	-0.58	-1.09	-0.48	0.02
Time from last treatment to prostate cancer diagnosis among men diagnosed after matching[1] (years)				
Mean (SD)	-0.98 (2.78)	-1.44 (3.29)	-0.88 (2.65)	0.02
Median	-0.58	-1.09	-0.48	0.02
Prostate cancer diagnosed	424 (100%)	60 (100%)	364 (100%)	--
Metastatic incidence rate (per 1000 person-years)	306.8	264.8	315.1	--
Prostate cancer death	0 (0)	0 (0)	0 (0)	--

*Identified among the 8688 men who had a prostate cancer diagnosis but did not die during the study period.
**Geocoded education
[1] Negative numbers here reflect that men were on treatment at the time of their diagnosis.

Results

Key findings from combination outcome results

Table 1 displays the distribution of characteristics (collected at matching) by combination outcome status after matching. The proportion of men who died of prostate cancer and/or developed metastatic disease was not significantly different across exposure groups (p= 0.83). Men who died or had metastatic disease were older at the time of matching on average (p<0.0001), and more likely to be African American (p<0.0001) compared to men who did not die or have metastatic disease during follow-up. Of those with a PSA level at the time of matching, men who died or had metastatic disease had higher median PSA levels (6.9 ng/mL vs. 2.3 ng/mL) (p<0.0001) compared to men who did not die or have metastatic disease. Men who died or had metastatic disease were more likely to have a higher Charlson index score, and cancer other than prostate (p=0.006), compared to men who did not die from prostate cancer or have metastatic disease. (Table 1)

Table 2 displays the baseline demographic and clinical characteristics by probable prostate cancer status as identified using the cause of death algorithm. Of the 770 men with prostate cancer who died (but did not have prostate cancer as a primary cause of death), 127 men were identified as probable prostate cancer deaths. The distribution of the demographic and medical history variables was comparable when comparing probable prostate cancer deaths to those who were not identified as such.

Table 3 displays the multivariable adjusted mortality rates and hazard ratios comparing the risk of death due to prostate cancer or risk of metastatic disease among 5ARI users to AB users overall and stratified by cumulative exposure and dose. After adjusting for age, race, region, BPH medication initiation year, prior AB history, Charlson, comorbidities, and use of other medications to treat OAB or ED, 5ARI use was not associated with an increase metastatic disease or prostate cancer mortality (HR: 0.66, 95%CI: 0.58, 0.76) when compared to AB use. When stratified by levels of increasing cumulative exposure, the magnitude of the reduced risk of prostate cancer death and/or metastatic disease associated with 5ARI increased, particularly among those exposed to the highest exposure category. Men who were exposed for greater than 2 years had the greatest reduction in risk associated with 5ARI use (HR: 0.55, 95%CI: 0.42, 0.71).

Metastatic prostate cancer sensitivity analyses

Table 4 displays the algorithm components used to define metastatic disease in men who were still alive during the study. Of the 424 men who were defined as having metastatic prostate cancer, 72.2% had an ICD-9 code for metastases, 77.50% had high or rapidly rising PSA levels, 2.6% used ADT or orchiectomy as salvage therapy and 68.9% had increasing visits to oncology. Of the men defined as not having metastatic prostate cancer according to the algorithm, 6.1% had ICD-9 codes, 7.9% had high or rapidly rising PSA, and 20.7% had increasing visits to oncology.

Table 5 displays the distribution of clinical characteristics by metastatic prostate cancer status. A greater proportion of men developed metastatic disease among the 5ARI users (8.8%) vs. the AB users (4.5%) (p<0.001). Men with metastatic disease had higher median PSA levels (5.1 ng/mL vs. 3.5) (p<0.0001). Men with metastatic disease had lower Charlson comorbidity index scores, and were less likely to have a history of high blood pressure when compared to men without metastatic disease (both p<0.001). The median length of AB use prior to matching was lower among men with metastatic prostate cancer compared to men without metastatic prostate cancer (1.9 vs. 5 years) (P<0.0001).

Table 6 displays the clinical characteristics by exposure status among men with metastatic prostate cancer. Among men with metastatic prostate cancer, those who were 5ARI users were older at matching (p=0.03), had higher median PSA levels (10.1 vs. 4.7) (p<0.0001) lower Charlson index scores (p=0.007), higher median cumulative exposure times (1.22 vs. 0.82 years) (p=0.003), and were exposed to higher median doses (2.14 vs. 0.8 g) (p<0.0001) compared to AB users. 5ARI users and AB users had the same number of prostate biopsies on average (1.0) (p=0.82). The incidence rate of metastatic disease was lower among 5ARI users compared to AB users (264.8 vs. 315.1 per 1000 person-years).

Discussion

Summary of results

In summary, 5ARI use was not associated with an increased risk of metastatic disease or prostate cancer death (when combined as one outcome) when compared to AB use. Results from the primary analysis suggested that among men who were diagnosed with prostate cancer in our sample, those who used 5ARIs were more likely to be diagnosed with Stage III/IV disease compared to men who used ABs. This stage difference did not translate into an increased risk of prostate cancer death for 5ARI users in the primary analysis. The increased proportion of men diagnosed with metastatic disease may be more related to detection and surveillance patterns that are different across exposure groups. Men who used 5ARIs were older and were more likely to have bone scans at diagnosis compared to men who used ABs. Men with larger prostate glands, more severe symptoms, and higher PSA levels are also more often treated with 5ARIs in clinical practice and thus followed more closely (Andriole et al. 2007, Goodman et al. 2006, Thompson et al. 2006). 5ARIs also reduce PSA levels, which may have delayed diagnosis via PSA screening in these men (Andriole et al. 2007, Goodman et al. 2006, Redman et al. 2008, Lucia et al. 2008). These detection and surveillance biases may therefore result in differences in the proportion of metastatic disease at diagnosis across exposure groups in this study.

Potential Limitations

In addition to the biases noted in the Cohort Report that are potentially present in the matched cohort analysis, there are additional potential limitations to consider specific to these analyses. The natural language processing was not available to scan the pathology, radiology, and clinic notes of all men in this sample, particularly those who did not die during the study period. As a result, only coded electronic data from the medical records was used to define metastatic disease for this subset of men. It is possible the variables that were used (ICD-9 metastatic code, PSA level and increasing oncology visits) may have missed some cases of metastatic disease. However, we do not believe this would be differential across exposure group, and most likely resulted in a conservative estimate of the incidence of metastatic disease among men who were still alive during the study period.

Conclusions

In these analyses, which also incorporated metastatic disease as part of the outcome of interest, 5ARIs were not associated with an increased risk of metastatic disease or prostate cancer mortality when compared to use of ABs. These results were similar to the findings from the primary analyses.

APPENDIX

Table 8 Exploration of metastatic components that do not require NLP to build the metastatic definition for the men who did not die during the study period but had a diagnosis of prostate cancer.

Metastatic Disease	ICD-9 code for metastases	High or Rising PSA	Increasing oncology visits	ADT/Orchietomy as salvage therapy	Evidence of 2nd primary tumor in cancer registry	N
Positive	+	-	+	-	-	238
Positive	-	+	+	-	-	180
Positive	+	+	-	-	-	165
Positive	+	+	+	-	-	114
Positive	+	-	-	+	-	12
Positive	-	+	-	+	-	9
Positive	+	+	+	+	-	8
Positive	+	+	-	+	-	5
Positive	+	-	+	+	-	4
Positive	-	+	+	+	-	2
Negative	-	-	-	-	-	5086
Negative	-	-	+	-	-	1430
Negative	-	+	-	-	-	552
Negative	+	-	-	-	-	335
Negative	-	-	-	-	+	136
Negative	-	-	+	-	+	91
Negative	+	-	+	-	+	69
Negative	-	-	-	+	-	61
Negative	+	-	-	-	+	49
Negative	-	+	-	-	+	23
Negative	-	+	+	-	+	16
Negative	+	+	+	-	+	14

Negative	+	+	-	-	+	14
Negative	-	-	+	+	-	11
Negative	-	-	+	+	+	2
Negative	+	+	-	+	+	1
Negative	+	-	-	+	+	1
Negative	-	+	-	+	+	1
Negative	-	-	-	+	+	1

*(+) denotes a positive component and (-) denotes a negative component. Components are not mutually exclusive. Number of positives includes 312 who were ultimately excluded due to timing of metastatic disease development.

CAUSE OF DEATH ALGORITHM

1. What is the coded cause of death? Review all cause of death codes (both underlying and immediate)			**Source**
A. Is the underlying or primary cause prostate cancer?	YES NO	If yes, **Definite PCa death**. STOP HERE. If no, go to b.	Mortality data/NDI
B. Is the cause of death stated to be one of the other significant causes of death? Pneumonia Pulmonary emboli Urosepsis Septic shock Anoxic brain damage Renal failure Failure to thrive Multi-organ failure Cerebrovascular Disease Suicide Disseminated Intravascular Coagulation	YES NO	If yes, go to 2. If "no", go to C	Mortality data/NDI
C. Is the cause of death stated to be cardiovascular disease?	YES NO	If yes, go to 2. If no, STOP HERE.	Mortality data/NDI
2. Does subject have metastatic prostate cancer?			
A. Adenocarcinoma found in biopsy of a metastatic lesion in absence of other primary	YES NO	If yes, **Probable PCa death. STOP HERE.**	NLP pathology reports

adenocarcinoma?		If no, go to B.	
B. Does patient have a code for metastatic disease (196.x-199.x)	YES NO	If yes, go to H. If no, go to C.	EMR
C. PSA > 100 or Rising PSA (*quadruple in 1 year or baseline PSA >10*)	YES NO	If yes, go to H. If no, go to D.	Lab
D. Elevated acid phosphatase level (*5-10 times upper limit of normal*)?	YES NO	If yes, go to H. If no, go to E.	Lab
E. Increasing narcotic requirements (in conjunction with mention of metastatic disease in same note)?	YES NO	If yes, go to H. If no, go to F.	Pharmacy Clinical Notes
F. Use of ADT as secondary treatment or orchiectomy (*6 months after initial PCa diagnosis*)?[1]	YES NO	If yes, go to H. If no, go to G.	Pharmacy
G. Increasing visits to oncology (the oncologist or the radiation oncologist for pain or for palliative radiation for pain) (*6 months after initial PCa diagnosis, at least 2 visits per year*)	YES NO	If yes, go to H. If no, go to H.	Utilization
H. abnormal bone scan finding suspicious for metastatic cancer or spinal cord compression)?	YES NO	If yes, go to L. If no, go to I.	NLP radiology reports
I. Evidence of metastatic disease to lymph nodes or distant organs?	YES NO	If yes, go to L. If no, go to J.	NLP clinic notes
J. Presence of lesion on non-NM bone imaging?	YES NO	If yes, go to L. If no, go to K.	NLP radiology reports
K. Complaint of bone, back, leg pain in conjunction with mention of metastatic disease in same note (Spinal cord compression)?	YES NO	If yes, go to L. If no, go to 3.	NLP clinic notes
L. Evidence of second primary tumor in breast, lung or kidney, multiple myeloma, osteosarcoma, bone marrow cancer?	YES NO	If yes, STOP HERE. **If no, Probable PCa death**.	Cancer registries
3. Does subject have evidence of progressive and debilitating disease during the *interval immediately preceding death*? (6 months)			
A. pathological fractures (ICD-9: 733.1x)	YES NO	**If yes, Possible PCa death.** If no, go to B.	Diagnoses
B. requiring blood transfusions (not related to surgery or trauma) (ICD9: 99.0x)	YES NO	**If yes, Possible PCa death.** If no, go to C.	Diagnoses/Procedures
C. pain (any) in conjunction with mention of metastatic cancer in same note.	YES NO	**If yes, Possible PCa death.** If no, go to D.	NLP-clinic notes
D. increasing narcotic requirements (with mention of metastatic cancer in same note)	YES NO	**If yes, Possible PCa death.** If no, go to E.	Pharmacy data

E. renal failure due to ureteral obstruction (new-onset failure with no history of CKD)	YES NO	**If yes, Possible PCa death.** If no, go to F.	EMR Diagnoses
F. enrolled in hospice (with mention of metastatic cancer in same note)	YES NO	**If yes, Possible PCa death.** If no, go to 4.	EMR
4. Did subject have condition related to prostate cancer *interval immediately preceding death*? (3 months)			
a. Sepsis/Septic Shock b. pulmonary emboli c. pneumonia d. failure to thrive e. multi-organ failure f. cerebrovascular disease (stroke, TIA) g. anoxic brain damage h. DIC	YES NO	**If yes, Possible PCa death.** *If no, death was not due to prostate cancer. STOP HERE*	Inpatient, outpatient diagnoses
Was death due to prostate cancer?	**Definite Probable Possible**		

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Division: Worldwide Development
Retention Category: GRS019
Information Type: Worldwide Epidemiology Study Protocol

Title:	5ARI and Prostate Cancer Mortality Study

Compound Number: GI198745

Development Phase IV

Effective Date: 11-15-2012

Description: This retrospective cohort study will assess the association of benign prostatic hyperplasia (BPH) treatment (5-alpha reductase inhibitors (5ARI) and alpha-blocker medications) with the occurrence of prostate cancer related mortality. This study will also assess a number of secondary endpoints including prostate cancer mortality or metastatic prostate cancer, and all cause mortality.

Subject: Prostate cancer mortality, BPH treatment, 5ARI.

Author(s):

[redacted]

SPONSOR SIGNATORY:

[redacted]	**Date**
[redacted] Director Worldwide Epidemiology	**Date**
[redacted] Interim VP Worldwide Epidemiology	**Date**

SPONSOR INFORMATION PAGE

Worldwide Epidemiology
WEUSKOP5723

GlaxoSmithKline
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: [redacted]

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Required Standard Wording:

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

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LIST OF ABBREVIATIONS

AE	Adverse Event
GSK	GlaxoSmithKline
HGT	High grade tumors
BPH	Benign prostatic hyperplasia
5ARI	5-alpha reductase inhibitor
AUR	Acute urinary retention
PSA	Prostate-specific antigen
PCPT	Prostate Cancer Prevention Trial
REDUCE	Reduction by Dutasteride of Prostate Cancer Events
[redacted]	[redacted]

Trademark Information

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PROTOCOL SUMMARY

Rationale

The potential role of 5-alpha-reductase inhibitors (5ARI) to reduce the risk of prostate cancer by blocking the conversion of testosterone to dihydrotestosterone was the basis for two large randomized controlled trials. The results of the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial demonstrated that finasteride and dutasteride, respectively, significantly reduce the risk of prostate cancer compared to placebo. However, there was a greater proportion of high grade tumors (HGT) observed in the 5ARI groups in both studies compared to placebo. In REDUCE (Andriole et al., 2011), 29 (0.9%) patients were diagnosed with Gleason 8-10 tumors in the dutasteride arm, compared with the placebo arm (n = 19, 0.6%; p = 0.15) over 4 years, with the most pronounced treatment group difference in REDUCE in years 3 and 4 (0.5% versus <0.1%, p = 0.003).

GSK is committed to further investigations to advance the understanding of the benefits and risks of dutasteride. Over the past several months, the GSK AVODART™ Team has evaluated the appropriateness of an observational study among men who use 5ARIs for symptoms of benign prostatic hyperplasia (BPH) to measure the risk of incident HGTs compared to risk in non-users. In consultation with internal and external experts, the team subsequently concluded that such a study would not be feasible: there is no other drug as a comparator drug that has similar effects on screening, detection, and biology as 5ARIs, resulting in several rate-limiting biases:

- 5ARIs lower PSA levels, potentially differentially affecting prostate cancer screening patterns;
- 5ARIs lower prostate volume, potentially differentially affecting biopsy accuracy;
- 5ARIs are reported to preferentially affect Gleason pattern 3 over pattern 4 and 5 prostate cancer, potentially differentially affecting Gleason score read-out and distribution.

Since the concern regarding HGTs is their higher agressiveness potential and risk of poorer disease related outcomes, this study will provide evidence as to whether patients who use 5ARIs have a greater likelihood of dying from prostate cancer. The outcome of prostate cancer mortality allows for an assessment of whether the relative frequency of high grade tumors among 5ARI versus alpha-blocker users translates into a difference in prostate cancer related mortality. This study will assess the association between 5ARI use with or without alpha-blockers and prostate cancer mortality in men treated with BPH medications.

Objective(s)

Primary Objective:

Prostate cancer mortality

1. To assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Secondary Objectives:

Prostate cancer mortality or metastatic prostate cancer

2. To assess the risk of prostate cancer mortality or metastatic prostate cancer associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

All cause mortality

3. To assess the risk of all cause mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Long term exposure to BPH medications

4. To assess the risk of prostate cancer mortality, prostate cancer mortality or metastatic prostate cancer, and all cause mortality associated with long-term exposure (2 or more years cumulative exposure) to 5ARIs, with or without alpha-blockers, compared to alpha-blockers in the subset of men using long term BPH treatment.

Additional descriptive analyses:

5. To evaluate the validity of classifying prostate cancer deaths with the developed electronic algorithm as compared to those identified based on cause of death coding and physician chart abstraction (see section 4.3: outcome definitions for further details).

6. To evaluate the validity of identifying cases of metastatic prostate cancer with the developed electronic algorithm as compared to those identified based on medical record abstraction.

7. To describe the occurrence of prostate cancer in men treated with BPH medications and across treatment groups (5ARIs and alpha-blockers).

8. To describe the occurrence of metastatic prostate cancer in men treated with BPH medications and across treatment groups.

9. To describe the occurrence of cardiovascular related mortality in men treated with BPH medications and across treatment groups.

10. To describe PSA testing patterns across treatment groups after treatment initiation and over the course of the study period.

11. To describe across treatment groups the frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.

12. To describe across treatment groups Gleason Score and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.

Study Design

A retrospective cohort study from 1992-2010 will be conducted using data from 4 [redacted] sites: [redacted] and [redacted] Men treated with BPH medications, 5ARIs (with and without concomitant and/or previous alpha-blocker use) will be compared to men treated with alpha-blockers. A matched design will be used with each man treated with 5ARIs being matched with 5 or 6 men treated with alpha-blockers. Men 50 years or older at the time of their first prescription for a study defined BPH medication, initiating treatment between 1992 and 2008 with at least 1-year of coverage in the healthcare system before the first prescription for BPH medication and at least 3 consecutive prescriptions (90 days of supply) for a BPH medication will be eligible for inclusion in the study. Men with a diagnosis of prostate cancer any time before the first prescription for BPH medication, having a diagnosis of prostate cancer within 3 months after initiation of their first BPH medication, and those treated with finasteride 1mg prior to their BPH medication will be excluded from the study. 5ARI initiators will be matched to alpha-blocker users in a ratio of 1:5 or 1:6 to yield an overall matching ratio of 1:5.4. Matching factors include age (+/- 1 year), timing of BPH treatment initiation (+/- 1 year), race, and duration of prior use of alpha-blockers. Based on the feasibility study from [redacted] we expect there to be approximately 284,000 men treated with BPH medications meeting eligibility criteria for inclusion in the study sample.

Study Endpoints/Assessments

The following outcomes will be assessed: prostate cancer mortality, prostate cancer mortality or metastatic cancer, and all cause mortality.

1. INTRODUCTION

Avodart (dutasteride), launched in 2003, is approved in over 90 countries as a monotherapy or in combination with tamsulosin to treat the symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate and, in some countries, to reduce the risk of acute urinary retention (AUR) and BPH-related surgery. Dutasteride has been extensively studied in clinical trials involving 7,500 men with BPH. The total estimated post-marketing exposure to Dutasteride from product launch through March 2012 is 8.9 million patient years. The estimated exposure to Combodart/Duodart/Jalyn from product launch through March 2012 is 461,627 patient years.

1.1. Background

The potential role of 5-alpha-reductase inhibitors (5ARI) to reduce the risk of prostate cancer by blocking the conversion of testosterone to dihydrotestosterone was the basis for two large randomized controlled trials. The results of the Prostate Cancer Prevention Trial (PCPT) demonstrated that finasteride taken for 7 years compared with placebo reduced the risk of prostate cancer by 25% in men with normal digital rectal exams (DRE) and prostate-specific antigen (PSA) levels < 3.0 ng/ml at baseline. Recent findings from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial again demonstrated that dutasteride, compared to placebo, taken for 4 years significantly reduced the risk of biopsy detectable prostate cancer by 23% in men without prostate cancer at baseline (confirmed by a negative biopsy within 6 months before enrollment) who were at increased risk of developing the disease by virtue of an elevated PSA (2.5-10 ng/ml).

However, there was a greater proportion of high grade tumors (HGT) observed in the 5ARI groups in both studies compared to placebo (Table 1). In PCPT (Thompson et al., 2003), where biopsies were conducted for cause and an end of study biopsy was offered to participants, tumors of Gleason 7-10 were more common in the finasteride group (n = 280, 6.4%) than in the placebo group (n = 237, 5.1%; P=0.005). (A higher rate of Gleason 8-10 tumors was also observed in PCPT; see Table 1). In REDUCE (Andriole et al., 2010), where biopsies were protocol mandated at 2 and 4 years as well as conducted for cause, 29 (0.9%) patients were diagnosed with Gleason 8-10 tumors in the dutasteride arm, compared with the placebo arm (n = 19, 0.6%; p = 0.15) over 4 years, with the most pronounced treatment group difference in REDUCE in years 3 and 4 (0.5% versus <0.1%, p = 0.003).

Table 1. Results from the two randomized control trials: PCPT and REDUCE: 5ARI use and risk of HGT

PCPT*	(7 years)		Gleason 7-10***	Gleason 8-10***
		Finasteride (n=4368)	280 (6.4%)	90 (2.1%)
		Placebo (n=4692)	237 (5.1%)	53 (1.1%)
		P	0.005	Not reported
REDUCE**	(4 years)	Dutasteride (n=3298)	220 (6.7%)	29 (0.9%)
		Placebo (n=3406)	233 (6.8%)	19 (0.6%)
		P	0.81	0.15
	Years 1-2	Dutasteride (n=3239)	144 (4.4%)	17 (0.5%)
		Placebo (n=3345)	175 (5.2%)	18 (0.5%)
		P	0.15	1.00
	Years 3-4	Dutasteride (n=2446)	76 (3.1%)	12 (0.5%)
		Placebo (n=2342)	58 (2.5%)	1 (<0.1%)
		P	0.19	0.003****

*N=number of men evaluated with for cause biopsies or end of study biopsy.
**N=number of men receiving study mandated biopsies at years 2 and 4 or for cause biopsies.
***N=count of Gleason score 7-10 and 8-10 tumors among men biopsied. Percentages= percent 7-10 and 8-10 Gleason score tumors among men receiving biopsies based on PCPT and REDUCE study definitions for biopsied populations.
****p-value not adjusted for multiple comparisons.

In order to answer the question of whether there was a differential risk for HGT (Gleason 8-10) among those REDUCE subjects who also had BPH at baseline, various post hoc analyses in the REDUCE database have been conducted. The totality of the data resulting from these post hoc analyses is aligned with the overall REDUCE population results and would not suggest a differential risk with dutasteride treatment in those with BPH compared to those with no BPH. Gleason 8-10 cancers rates were constant over

time in the dutasteride group however an imbalance in Gleason 8-10 cancers between dutasteride and placebo was observed in yrs 3-4 (higher rates in dutasteride) driving the overall 4 yrs study differences.

However, data from the REDEEM trial, a 3-year study assessing the efficacy and safety of dutasteride in extending the time to progression of prostate cancer, did not show an imbalance in high grade Gleason score tumors at 18 month and 3 year biopsy in the placebo and dutasteride treated groups. There were 2 Gleason score 8-10 cancers in the placebo group at 18 months versus 0 in the dutasteride group and 3 versus 2 Gleason score 8 tumors in the placebo and dutasteride treated groups, respectively, at the final biopsy (Fleshner et al, 2012, GSK dutasteride white paper).

Observational studies have also been conducted examining prostate cancer risk and HGT risk among users of 5ARIs. A cohort of men participating in the screening arm of the Finnish Prostate Cancer Screening Trial exposed to finasteride or alpha-blockers (tamsulosin and alfuzosin) for the treatment of BPH were followed for the occurrence of prostate cancer. Overall no significant decreased risk for prostate cancer occurrence was seen in users of finasteride or alpha-blockers in this study, however, the risk of low grade tumors (Gleason 2-6) was significantly decreased among finasteride users. In contrast to PCPT no increased risk of high grade tumors (7-10) was found. However, among men using finasteride for $\geq$ 4 years there was an increased risk of high grade (7-10) tumors compared to non-users of finasteride and alpha-blockers with a borderline significant p-for-trend across increasing duration of exposure categories (p=0.057) (Murtola et al, 2009). The current study will allow for an analysis of duration of exposure to extend these findings.

In a recent study by Pinsky et al prostate cancer survival rates from the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial were used to project prostate cancer mortality based on prostate cancer incidence patterns seen in the REDUCE and PCPT trials. The overall relative risk of prostate cancer mortality comparing treatment to placebo arms was not significantly increased based on projections for patients in the REDUCE or PCPT trials, however mortality rates for those with Gleason scores of 2-6 were modestly decreased while mortality rates for those with Gleason scores of 7 and 8-10 were modestly increased. These results suggest at most a small increase and potentially a modest decrease in prostate cancer related mortality in the treatment arms of these studies (Pinsky et al, 2012). The current study will allow for the real world follow-up of men exposed to these medications over time for the assessment of mortality and will extend these results beyond the framework of hypothetical modelling.

GSK reviews the safety and performance of all its medicines on a continuous basis. Following the decision of the Oncology Drug Advisory Committee in early December 2010 not to recommend the use of dutasteride for prostate cancer prevention, GSK announced in March 2011 that it will no longer pursue global approval (marketing authorisation) for the use of Avodart for this indication. http://www.gsk.com/media/pressreleases/2011/2011_pressrelease_10043.htm. GSK has since added new safety information to the Avodart label concerning the risk of high grade prostate cancer and effects on PSA monitoring.

GSK is committed to further investigations to advance the understanding of the benefits and risks of dutasteride. Over the past several months, the GSK Avodart Team has evaluated the appropriateness of an observational study among men who use 5ARIs for symptoms of BPH to measure the risk of incident high grade tumors (HGT) compared to risk in non-users. In consultation with internal and external experts, the team subsequently concluded that such a study would not be feasible: there is no other drug as a comparator drug that has similar effects on screening, detection, and biology as 5ARIs, resulting in several rate-limiting biases:

- 5ARIs lower PSA levels, potentially differentially affecting prostate cancer screening patterns;
- 5ARIs lower prostate volume, potentially differentially affecting biopsy accuracy;
- 5ARIs are reported to preferentially affect Gleason pattern 3 over pattern 4 and 5 prostate cancer, potentially differentially affecting Gleason score read-out and distribution.

Additionally, based on evidence from REDUCE and PCPT, 5ARIs reduce the risk of prostate cancer occurrence. The outcome of prostate cancer mortality allows for an assessment of whether the relative frequency of high grade tumors among 5ARI versus alpha-blocker users translates into a difference in prostate cancer related mortality. This study will assess the association between 5ARI use and prostate cancer mortality in men treated with BPH medications.

1.2. Rationale

The primary purpose of this study is to assess whether there is an increased risk of prostate cancer mortality associated with the use of 5ARIs in men treated with BPH medications when compared to the use of alpha-blockers in a real-world setting. Since the concern regarding HGTs is their higher agressiveness potential and risk of poorer disease related outcomes, this study will provide evidence as to whether patients who use 5ARIs have a greater likelihood of dying from prostate cancer. Based on a feasibility assessment performed by [redacted] (see section 4.2, study design) there are very few users of dutasteride in the target study population (4% of 5ARI users). We will therefore pool dutasteride and finasteride into one exposure group and consider a class effect in this study. The study will support the ongoing team efforts regarding the assessment of both the benefits and risks of 5ARIs.

2. OBJECTIVE(S)

Primary Objective:

Prostate cancer mortality

1. To assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Secondary Objectives:

Prostate cancer mortality or metastatic prostate cancer

2. To assess the risk of prostate cancer mortality or metastatic prostate cancer associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

All cause mortality

3. To assess the risk of all cause mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Long term exposure to BPH medications

4. To assess the risk of prostate cancer mortality, prostate cancer mortality or metastatic prostate cancer, and all cause mortality associated with long-term exposure (2 or more years cumulative exposure) to 5ARIs, with or without alpha-blockers,
compared to alpha-blockers in the subset of men using long term BPH treatment.

Additional descriptive analyses:

5. To evaluate the validity of classifying prostate cancer deaths with the developed electronic algorithm as compared to those identified based on cause of death coding and physician chart abstraction (see section 4.3: outcome definitions for further details).

6. To evaluate the validity of identifying cases of metastatic prostate cancer with the developed electronic algorithm as compared to those identified based on medical record abstraction.

7. To describe the occurrence of prostate cancer in men treated with BPH medications and across treatment groups (5ARIs and alpha-blockers).

8. To describe the occurrence of metastatic prostate cancer in men treated with BPH medications and across treatment groups.

9. To describe the occurrence of cardiovascular related mortality in men treated with BPH medications and across treatment groups.

10. To describe PSA testing patterns across treatment groups after treatment initiation and over the course of the study period.

11. To describe across treatment groups the frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.

12. To describe across treatment groups Gleason Score and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.

3. TARGET AUDIENCE

Global safety board, Avodart project team, External scientific community.

4. METHODOLOGY

The proposed study will use a retrospective cohort design with data collected from electronic health records.

Data Source

This study will identify a cohort of patients in the [redacted] closed health care systems with long-term follow-up and low attrition rates. Individual patient data from the four participating sites [redacted] and [redacted] will be pooled and analyzed with [redacted] acting as the central data-coordinating center. [redacted] will also perform all data analyses for this study. The inclusion of patient data from multiple sites is to ensure a sufficient number of prostate cancer deaths to obtain a suitably precise and clinically meaningful estimate of risk.

[redacted] Regional Overviews

[redacted] is an integrated health care system that provides comprehensive health services in 8 regions nationwide. Data from four of the larger [redacted] sites: [redacted] will be used in this study. Taken together, these four sites bring racial, ethnic, and geographic diversity to this study. They serve approximately 3.25 million residents of [redacted] 3.3 residents in [redacted] 535,000 residents in [redacted] and 477,932 residents in the metropolitan [redacted] area. These are the sites with the most extensive experience in identifying and classifying cancer patients and they have the most experience in extracting and analyzing cancer-related treatments, costs and outcomes as they all participate in the NCI funded Cancer Research Network (CRN). [redacted] and [redacted] are part of the SEER Tumor Registry system and participate in their respective state tumor registries. [redacted] and [redacted] have accredited tumor registries covering their memberships, and participate in their respective state tumor registries. The majority of adult ambulatory cancer care services, including surgery, infused/injected chemotherapy services and radiotherapy are provided at health plan owned facilities, and all four sites purchase pharmaceutical products under the same national contract and employ similar formularies.
Complete data on chemotherapy (including oral as well as injected and infused agents) is available and extractable at all of the participating sites. [redacted] has successfully transitioned to an electronic health record system to support further population and clinical care management at the bedside. The information contained in these electronic records is routinely extracted for research purposes. Thus, information on virtually all aspects of care delivered is captured and retrievable for the proposed research. All of the sites employ the EpicCare® electronic medical record (EMR) system. The EMR systems capture electronically all patient care contacts in the outpatient setting using a controlled medical terminology (based upon ICD-9 and CPT-4 code systems) to document patient assessments, services ordered, and services provided.

Data Availability from Electronic Health Records and Medical Charts

The primary data source for the [redacted] sites will be extracted from the Virtual Data Warehouse (VDW). (See section 7, Study Management, for details on data identification and protection of personally identifiable information). The VDW was originally established by the CRN with funding from NCI for efficient collaboration and pooling of automated data across sites using a standard data formats and definitions. The VDW is virtual in that it is a distributed data system where the health plans retain local control of their data, but a programmer at one site can write a program than can be run at all sites. Using the VDW, standardized automated data on patient characteristics including demographics (age, race, ethnicity, vital status), health plan enrollment, SEER-compatible tumor characteristics (stage and histology), and variables noting the type and date of treatment received (surgery, radiation, chemotherapy, and hormone treatment obtained from tumor registries) can be extracted. In addition, recurrence (local or distal) and date of recurrence are abstracted fields in [redacted] and [redacted] tumor registry files. For [redacted] and [redacted] natural language processing will be used to search electronic chart

information to find evidence of metastases (see Outcome definition section). Utilization files include automated clinical data associated with inpatient and outpatient encounters, types of procedure and diagnostic codes including International Classification of Diseases (ICD-9) codes for procedures and diagnoses, or HCFA Common Procedure Coding System (HCPCS) codes for procedures. Measures of socioeconomic status are also available via the VDW Census data files where enrollees' residential addresses are mapped to census block data using geocoding software.

Extensive data are available through electronic medical records and historical electronic health plan databases which are comprised in the VDW. Specific to this proposal, in the VDW, the following is available: cancer diagnoses going back to 1988, outpatient and emergency room diagnoses and procedures from 1994, laboratory data from 1994 on, mortality data from 1988 on, outside claims from 1990 on, inpatient and outpatient diagnoses and procedures from 1994 to current and pharmacy records from 1992 on. The dates of available data in the virtual data warehouse shared across [redacted] sites are shown in the table below. There is the availability to go further back in historical databases across sites and any data that is needed that is not available electronically can be found in paper medical charts through abstraction as outlined below. Diagnoses are also routinely verified by abstracting a random sample of medical charts and comparing them to electronic medical records.

Data currently available in the [redacted] Virtual Data Warehouse

Data System	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy	1992-	1995[1]-	1986-	1992-2012
Mortality			1990-current[2]	1990-2011[2]
Underlying cause	1988-2010	1966-2010		
Multiple causes	1988-2009	1966-2009	1990-current[2]	1990-2011
Laboratory	1992-	1988-	1993[3]-	1994 *
Tumor Registries	1988-2009	1974-June 2011	1960-	1987-2011
Utilization, Diagnoses and Procedures	1981-	1995[1]-	1994-	1994-2012

[1]Phased in starting in 1991
[2]Based on tumor registry variable identifying men died of prostate cancer
[3]Earlier data available via archived files and paper records.
*At [redacted] Lab procedures are available for 1994 forward. Lab results are available from 2000 forward. PSAs are available back through 1997. However, there is a capability to get older values from archived files and paper records.

[redacted] ***Mortality Data***

Death information is derived from several sources. Membership files track notices of active members' deaths. This is most complete when the death occurs at a [redacted] facility. Two external sources are used in addition, the state death records and Social Security Index records. Standard matching algorithms are used that take into account name, last known address, date of birth and Social Security Numbers (when available) to identify [redacted] members in these two files. Cause of death codes are assigned by the State mortality registries and follow standard National Center for Health Statistics algorithms. The state death records lag about 14 months for date and underlying cause of death and between two and three years for all causes listed on the death certificate. The mortality files contain, but are not limited to, the following fields: medical record number, date of death, place of death, and ICD-9 coded underlying cause of death.

National Death Index

The National Death Index (NDI) mortality data will be used to supplement cause of death information where [redacted] is unable to capture it through their existing systems. NDI is a central computerized index of death record information on file in the state vital statistics offices maintained by the Centers for Disease Control. Working with these state offices, the National Center for Health Statistics established the NDI as a resource to aid epidemiologists and other health and medical investigators with their mortality ascertainment activities. The NDI includes a national file of identifying death record information (beginning with 1979 deaths) compiled from computer files submitted by State vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year. NDI Plus searches provide cause of death codes and are available through 2010 currently (2011 will become available Spring 2013). For known descendants, the CDC charges a flat fee of $5.00 per record for processing, regardless of the number of years processed.

[redacted] will first submit a NDI application form to NCHS. CDC states that applicants should allow about 2 months for their applications to be reviewed and approved. Once approved, [redacted] will submit the data from all regions which will include subjects' names, social security numbers, dates of birth, and related information to NCHS on diskette or CD-ROM. Once received, the NDI will mail a password protected CD with the match results to [redacted] along with the original CD. Analysts at [redacted] will then follow the NDI's suggested algorithm for determining true matches and merge this data with the existing analytic data set from all regions.

Based on estimates from the pilot study in [redacted] it is expected that 30% of the study eligible population will die during the study. Of these men who died, 25% will not have cause of death information and will need to be matched through the NDI. So, approximately 7% of the overall eligible population will be matched. Because [redacted] and [redacted] are similar in population size, if an assumption is made that a similar eligible population will be identified in each region, approximately 18000 men will need to be sent to NDI match from these regions (9000 per region). Applying these numbers to the population sizes of [redacted] and [redacted] it is expected that 1500 deaths will need to be validated

from each of those regions through NDI. So in total, an estimated maximum of **21,000** records will need to be sent to the CDC for cause of death information.

Pharmacy Data

Drug exposure data will be derived from the Pharmacy Information Management System or PIMS, as similar systems are used in all [redacted] sites. All [redacted] facilities pharmacies are now connected via a central data processing operation to a pharmacy database. Records include the patient's unique medical record number, the drug name and strength, NDC code, the drug class, treatment regimen, date dispensed, prescribing physician and department and days' supply. Information enters the system at the time prescriptions are processed by the pharmacy and virtually 100% of dispensed prescriptions are captured, as it is a "real-time" system used to generate the label attached to packaging (e.g., tube, drug container) provided the patient. Information from PIMS is available in the VDW, but may not go back to 1991 for all sites. So data available in the VDW will be supplemented with electronic files (and potentially paper records).

Cancer Registries

[redacted] and [redacted] are part of the SEER Tumor Registry system and participate in their respective state tumor registries. [redacted] and [redacted] have accredited tumor registries covering their memberships, and participate in their respective state tumor registries. The cancer registry database in the VDW contains information on patients who were diagnosed at [redacted] hospitals, or who received at least part of their first course of treatment for cancer at a [redacted] hospital, for all reportable cancers. Variables found in the Regional database can be grouped in the following general categories: 1) Patient Identification (name, sex, DOB, race, MRN, SSN, etc.); 2) Case Identification (type of case, hospital of diagnosis, date of diagnosis); 3) Tumor Information (site, histology, stage, size, lymph node involvement, markers, etc.); 4) Treatment Methods (types and dates of treatment); and 5) Follow-up (vital status, date of last contact or death, tumor status, and cause of death). In addition, [redacted] collects survival information acquired through an aggressive follow-up program that achieves a more than 95 percent retention rate. Because the [redacted] and [redacted] Cancer Registries report to SEER and the [redacted] and [redacted] tumor registries are certified by the NCI, the registry data are 99% complete for both inpatient and outpatient admissions for the diagnosis of new and prevalent cancers. While cancer diagnosis information is available through both the cancer registry and electronic medical records, information regarding the diagnosis and initial treatment of cancer are pulled from the cancer registry. This is because it is a more complete data source, as cancer diagnoses are not systematically recorded in the electronic charts.

Laboratory data

Laboratory data from all four participating [redacted] sites is available in the VDW going back to at least the mid-1990s for all sites. This system tracks both inpatient and outpatient laboratory orders and results. Records include the patient's unique medical record number, the laboratory test name and procedure codes, date drawn, units, references ranges, whether the test was abnormal, ordering physician information, and facility information and the lab test results.

4.1 Study Population

All men age 50 years and older treated with a BPH medication (5ARI and/or alpha-blocker) will be eligible for inclusion. Men using alpha-blocker medications were selected as the comparison group for this study as alpha-blockers are the most common treatment for BPH and men with BPH or lower urinary tract symptoms that are untreated for their condition are likely to be very different from those with severe enough symptoms to seek medical care and take medication. Furthermore, there is no published literature to suggest that alpha-blockers are associated with the risk of prostate cancer occurrence. Participants are not required to have a BPH diagnosis at the time of their first 5ARI or alpha-blocker prescription as based upon data from the feasibility report approximately half of all men received their first recorded BPH diagnosis after initiating treatment. Furthermore, approximately 25% of participants treated with 5ARIs or alpha-blockers did not have a diagnosis code for BPH in their medical record. BPH diagnosis codes were not used in a consistent way historically in the [redacted] data. Sensitivity analyses will be conducted in the analysis phase of the study to examine the effects of BPH diagnosis on the exposure disease relationship. Men should have coverage within the healthcare system for at least 1-year before the first BPH medication prescription. Men with a history of prostate cancer or who develop prostate cancer within <3 months of starting their first BPH medication are not eligible for inclusion.

INCLUSION CRITERIA:

- Male
- A new prescription for BPH medication (5ARI and/or alpha-blocker) in 1992 or later that is identified as appropriate treatment for BPH/LUTS from the [redacted] National Pharmacy guidelines (see section 4.4 Exposure definition).
- Treatment with BPH medication must be initiated prior to Jan1, 2008.
- Age 50 years or older at time of treatment with 5ARI or alpha-blocker.
- At least 1-year of coverage in the healthcare system before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- At least 3 consecutive prescriptions (90 days of supply) for a BPH medication (5ARI and/or alpha-blocker).

EXCLUSION CRITERIA:

- Diagnosis of prostate cancer any time before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- Diagnosis of prostate cancer within 3 months after first BPH medication (5ARI and/or alpha-blocker)
- Patients treated with finasteride 1mg prior to BPH medication. Finasteride 1mg is the dose approved for androgenic alopecia and as the target population for this study is men with treated BPH, we will exclude all men treated with the 1mg dose. Patients treated with 1mg Finasteride will be characterized in terms of which study exposure group they would have transitioned into (5ARI or alpha-blocker) had they been included in the study population, and basic baseline demographic factors.

4.2 Study Design

The study will use a retrospective cohort design with data from four [redacted] sites collected from electronic health records and data abstracted from paper records from 1992-2010.
[redacted] conducted a feasibility study using data from their site only (see Appendix 1). The following inclusion criteria were used in the feasibility study:

- Male
- A new prescription for BPH medication (5ARI and/or alpha-blockers) in 1992 to 2008.
- Prescription for a BPH medication identified as appropriate treatment for BPH/LUTS from the [redacted] National Pharmacy guidelines.Treatment with BPH medication initiated prior to Jan1, 2008.
- Age 50 years or older at time of treatment with 5ARI or alpha-blocker.
- At least 1-year of coverage in the healthcare system before the first prescription for BPH medication (5ARI and/or alpha-blocker).
- No history of prostate cancer diagnosis before first prescription for BPH medication.

The feasibility study identified 123,503 men in [redacted] exposed to BPH medications and meeting the inclusion criteria; 104,272 men were exposed to alpha-blockers only, 1,619 to 5ARIs only, and 17,612 to combination therapy. Among combination therapy users, the vast majority (92%) used an alpha-blocker and then switched to or added a 5ARI over the course of the study period. As most 5ARI patients have a history of alpha-blocker use or are currently using alpha-blockers, the 5ARI exposure group in this study will include combination therapy users and prior use of alpha-blockers will be a matching factor (see Data analysis section 4.9). Additional

exploratory analyses will be conducted among those using 5ARIs and alpha-blockers concurrently versus those using 5ARIs only (see section 4.9.2 exploratory analyses).

Among those using 5ARI medications in the feasibility study, 96% were exposed to finasteride, with only 4% exposed to dutasteride. Therefore we will combine dutasteride and finasteride users in this study and consider the class effect of 5ARI medications. The ratio of 5ARI users to alpha-blockers users was 1:5.4 in the feasibility study. Assuming that this same ratio will be maintained in the overall study sample, we will match 5ARI:alpha-blocker patients in a 1:5.4 ratio.

Cohort Selection

5ARI users will be selected from the available pool of eligible men and will be matched in a ratio of 1:5 or 1:6 with alpha-blocker users to yield an overall matching ratio of 1:5.4. Matching factors include age (+/- 1 year), timing (calendar year) of BPH treatment initiation (+/- 1 year), race, and duration of prior use of alpha-blockers (see Appendix 2: matching diagram). The purpose of matching on prior use of alpha-blockers is to control for potential confounding factors associated with being treated for BPH and accessing the medical care system such as increased screening and treatment for medical conditions. Additionally, matching on prior use of alpha-blockers will help to control for the use of alpha-blockers in the 5ARI exposure group.

5ARI patients initiating BPH treatment with a 5ARI (i.e. having no prior use of alpha-blockers) will be matched to alpha-blocker users having the same date (+/- 1 year) of alpha-blocker treatment initiation. Categories for the prior use of alpha blockers will be defined based on the distribution of the number of years of alpha-blocker use in the [redacted] data. One year strata for history of alpha-blocker use will be used if the number of available matches across strata is sufficient. Matching will be conducted within [redacted] site [redacted] When a suitable match cannot be found within a study site consideration will be given to matching across sites to maximize the available sample for the study. Additionally, if it is difficult to find matches for particular participants, matching criteria may be relaxed to allow for inclusion of all eligible 5ARI men. For example, matching on year of initiation of treatment may be relaxed to (+/- 2 years) to allow for more possible matches.

Two approaches for matching will be explored:

1. Eligible matches for 5ARI users will be defined based on their medication exposure at the time (+/- 1 year) of 5ARI initiation. For example, a patient initiating 5ARI medication in 1995 would have a pool of potential matches that includes all men not previously exposed or currently taking 5ARIs in 1995. Therefore a patient taking an alpha-blocker in 1995 who adds a 5ARI in 1999 would be an eligible match for the 5ARI user as in 1995 they have not yet been exposed to 5ARIs. When this alpha-blocker patient initiates 5ARI therapy in 1999, their follow-up time will be censored.

2. A group of patients exposed to alpha-blockers only over their duration of follow-up will be defined and will serve as potential matches to patients exposed to 5ARI medications.

Matching approach #2 will allow for a cleaner comparison group and for longer duration of follow-up time to be included for alpha-blocker users as follow-up time will not be truncated due to initiation of a 5ARI. However, this approach could introduce bias due to the selection of patients based on post-treatment initiation information. Based on the feasibility study, it is expected that approximately 92% of patients will use alpha-blockers only and 8% will use 5ARIs with or without alpha-blockers. So, there is a low probability that 5ARI users will be matched to alpha-blocker users who eventually start therapy with a 5ARI. Therefore both approaches should yield similar patient groups and we will examine the characteristics of the resulting patient groups under matching schemes #1 and #2.

Follow-up time for each matched group begins at the date of first prescription of a 5ARI medication. For prostate cancer mortality, and all cause mortality, follow-up ends with death, loss to follow-up or the end of the study (defined as last available date in the database, December 2010). For prostate cancer mortality or metastatic prostate cancer follow-up ends with death, occurrence of metastatic prostate cancer, loss to follow-up or the end of the study (defined as last available date in the database, December 2010). Additionally, under matching scenario 1, for alpha-blocker users who are matched to 5ARI users and initiate therapy with a 5ARI, their follow-up time will be censored at the date when they add or switch to a 5ARI medication.

4.3 Outcome definitions

Metastatic Prostate Cancer:
Metastatic Prostate Cancer at the time of diagnosis will be identified using data recorded in the cancer registries. The occurrence of metastatic prostate cancer over the course of the study period will be ascertained using an algorithm to be developed jointly by GSK and [redacted] Based on previous [redacted] studies, the ICD-9 code for metastatic cancer (196.x,197.x, 198.x and 199.x) is underutilized and therefore lacks the sensitivity needed to comprehensively capture cases of metastatic cancer. Using electronic medical records a partly natural language processing algorithm (see natural language processing section below) will be developed. Information from available electronic medical records (procedure codes and results, patient medications, and lab values) including medical chart notes will be included in the algorithm. This information will be used along with the ICD-9 code for metastatic cancer to identify newly occurring cases of metastatic cancer. (see section 4.5 for additional discussion concerning detection bias and metastatic prostate cancer).

Prostate Cancer Mortality:

Summary of the overall process of identification and validation of prostate cancer related deaths

Prostate Cancer deaths will be identified among men with a diagnosis of prostate cancer. First, cause of death codes from state death information or NDI death records will be reviewed for any mention of prostate cancer, CVD, or other causes thought to be related to prostate cancer, as a cause of death. Many previous investigations have relied solely on cause of death information from death certificates to determine whether deaths are related to prostate cancer (Eifler et al, 2012, Abdollah et al, 2012, Jorgensen et al 2012, Kim et al 2012, Scosyrev et al, 2012). The agreement between prostate cancer related cause of death information from death certificates compared to the gold standard of physician chart review has been found to fall in the range of 87% to 97% (Albertsen et al, 2000, Penson et al, 2001). In this study an electronic algorithm will be used to improve the accuracy of the determination of cause of death from death certificates.

Once deaths based on cause of death codes from death certificates have been identified, an algorithm developed by [redacted] that will be adapted for use in this study, will be applied to validate the cause of death as related to prostate cancer based on death certificate coding (see natural language processing and cause of death classification sections below). Algorithms have been used in cancer screening clinical trials to aid in determining cause of death. In the Prostate, Lung, Colorectal, and Ovarian cancer screening trial (PLCO), an algorithm was used to determine which deaths were likely due to cancer and required further review by physicians, and the adjudication committee then determined the cause of death based upon clinical judgement (Miller et al, 2000). In the European Randomized Screening for Prostate Cancer trial (ERSPC), physicians reviewed information abstracted from patient medical records and using pre-determined decision points defined in a cause of death algorithm, classified deaths as related or not related to prostate cancer. Adjudication by a committee of three reviewers was then used to determine final cause of death (De Koning et al, 2003). In this study we will use an electronic algorithm with pre-defined decision points to classify cause of death among men with prostate cancer. A random stratified sample chart review will then be performed to further validate cause of death as determined by the algorithm. (see Appendix 3 flow diagram).

[redacted] *algorithm*

Dr. [redacted] and Dr. [redacted] investigators at [redacted] have developed an algorithm for determining the cause of death among prostate cancer patients. This algorithm was developed for use in a multi-site study using data on cause of death from the [redacted] tumor registries. Dr. [redacted] has reviewed the charts of prostate cancer patients for several past studies and this algorithm was developed based on her expertise and is a documentation of the process she used to determine cause of death. Additionally, as part of the development of the algorithm, all participating sites sent a list of the causes of death listed for all patients who died and had prostate cancer. This list was reviewed by Dr. [redacted] and causes of death deemed to be potentially misclassified and likely due to prostate cancer and not the recorded cause of death, were included in question 2 b. of the algorithm (see Appendix 4). Charts were reviewed for all patients from the time of cancer diagnosis until death for the necessary elements included

in the algorithm. For patients included in the [redacted] tumor registry, who die, chart review is performed routinely to determine cause of death and there is a variable available in the tumor registry electronic data indicating whether or not a patient's death is due to cancer. The algorithm correctly captured 98% of the cases identified as prostate cancer deaths by this tumor registry variable. This algorithm will be reviewed by [redacted] and the study sponsor and changes may be made to the algorithm in an attempt to improve its ability to classify deaths correctly. The revised algorithm will be tested with deaths known to be related to prostate cancer identified from the [redacted] registry, to ensure that the elements included in the algorithm are sufficient to capture prostate cancer related deaths. Many of the data elements needed for this algorithm can be abstracted from electronic medical records. For the remaining algorithm items for which review of the notes or free text section of electronic medical records would be required, natural language processing will be used.

Natural Language Processing

Approximately 85% of the world's data are unstructured. With the rapid development of computer, internet, and EMR system, the amount of unstructured data are being created at an increasing speed. [redacted] EPIC based EMR system's user-friendly design allows the caregivers to dictate and/or enter free text easily. Those unstructured free text fields contains a plethora of rich information on a patient's status and granular detail of their current therapy(ies).

Natural language processing (NLP) is a field of computer science and linguistics that aims to understand human (natural) languages and facilitate the interaction between human and computer. NLP is a multidisciplinary technology and typically uses statistically based machine learning technology to learn the patterns of human languages. One way NLP is utilized is to identify and extract valuable information from the unstructured 'free text'. Compared to human chart review of medical records, NLP is more efficient and the results are consistent; it can also match and surpass the accuracy of human chart review (Denny et al, 2012).

In [redacted] Research and Evaluation Department, NLP has successfully been used on a series of research projects across different disease areas, such as identifying potential lung cancer patients based on the radiology reports and comparing these results with ICD/CPT codes (Danforth et al, 2012), patient identification and extraction of their related disease characteristics for prostate and breast cancer patients.

For this study, we will utilize NLP in two ways: 1) To help in determining among men with prostate cancer who died, whether their deaths were attributable to prostate cancer and 2) to aid in identifying men with metastatic prostate cancer. We will leverage clinical information including (but not limited to) pathology reports, radiology reports, and clinical notes, to find pre-specified free-text information based on a modified version of the [redacted] algorithm mentioned above.

Classification of cause of death among men with prostate cancer

All deaths among men with prostate cancer will be divided into 3 groups based on coding from death certificates (see Appendix 3):

1) CVD related
2) Prostate cancer related
3) Other causes likely related to prostate cancer (to be defined based on the [redacted] algorithm and clinical expertise).

These groups will be defined using underlying cause of death only, and using underlying and contributing causes.
The modified [redacted] algorithm, using variables from the EMR and natural language processing (see Appendix 4 for a list of potential variables), will then be applied to a subset of the data and will be tested and validated using random sample chart review in [redacted] before being applied to each region to identify potential prostate cancer deaths. As part of this process, the algorithm will be applied to known cases of metastatic disease and deaths known to be related to prostate cancer (based on physician chart review) to ensure that the algorithm can detect these cases. The testing and validation of the algorithm will utilize clinical input from the clinician-investigators, including urologists, epidemiologists, and oncologists as well as NLP specialized programmers, and as needed, chart review to determine whether further tailoring of the algorithm is required. These processes may be repeated as necessary until an agreed upon level of validity of the algorithm is reached (see section 4.9.1 essential analyses). If a suitable sensitivity and specificity is not reached, discussions with GSK and [redacted] investigators regarding other alternatives or iterations needed will take place. Also, a sub-sample chart review within each region's cases will be performed to check for any systematic differences in the algorithm's performance across regions that may arise from within region variability in the reporting of metastatic disease. There will be an assessment of the concordance of the classification of deaths using coding from death certificates alone versus the algorithm.

Once validated, the algorithm will be applied to all deaths among men diagnosed with prostate cancer in all regions to identify men who died from prostate cancer. Based on the results of the algorithm, men will then be categorized as follows:

- Men who died of prostate cancer
- Men who died of cardiovascular disease:
    - Likely due to prostate cancer
    - Not likely due to prostate cancer
- Men who died of other causes:
    - Likely due to prostate cancer
    - Not likely due to prostate cancer

Validation of the electronic algorithm with chart review

Further validation of the cause of death algorithm will be performed on a random sample of 200 records. A case report form will be created including relevant information from patients medical histories to be defined by GSK and [redacted] and chart review by two trained abstractors will be performed to validate the cause of death. A random sample, stratified as follows will be performed:

- Prostate cancer deaths (as identified by algorithm)
- Cardiovascular deaths (as identified by algorithm)
- Other significant deaths (causes of death thought to be potentially related to prostate cancer such as cerebrovascular disease, suicide, etc.) Exact list of causes of death is to be determined.

A panel of clinicians, including the two urologists and the medical oncologist who are [redacted] co-investigators on this study, will adjudicate the cause of death by reviewing the available information on the case report forms abstracted from the stratified random sample chart review and applying clinical judgment to determine if the death was due to prostate cancer. Death information and supporting documentation will be sent to each clinician and blinded to treatment status. Including clinicians from three different sites allows for further insight into any regional differences that may be present in the medical record data. Each reviewer will then assign the cause of death into the three categories as used with the algorithm:

- Men who died of prostate cancer
- Men who died of cardiovascular disease:
    - Likely due to prostate cancer
    - Not likely due to prostate cancer
- Men who died of other causes:
    - Likely due to prostate cancer
    - Not likely due to prostate cancer

The results from the adjudication will then be compared to the cause of death algorithm based on electronic and NLP data and the concordance and discordance will be quantified. The kappa statistic, sensitivity and specificity will be calculated, using the adjudication review panel as the gold standard. In instances where the algorithm and reviewer do not agree or the reviewers do not agree with each other, the case will be discussed among the panel until a consensus is reached regarding the cause of death. The cases will be discussed via teleconference and the majority decision will be used to determine final cause of death.

Detailed documentation concerning the development and validation of the algorithm will be maintained and shared with the study sponsor.

All-Cause Mortality:

All cause mortality in the overall study cohort and among men with prostate cancer will be defined as any death regardless of cause. Death information is derived from several sources. Membership files track notices of active members' deaths. This is most complete when the death occurs at a [redacted] facility. Two external sources are used in addition, the state death records and Social Security Index. In addition, an NDI match will be performed on members who are known to be deceased but are lacking cause of death information. Membership files and the external sources listed above will be searched to identify all deaths occurring in the study cohort.

4.4 Exposure definitions

Exposure will be based upon the treatment administered for BPH. Patients must have at least 3 consecutive prescriptions (90 days of supply) for either a 5ARI or alpha-blocker product to be considered exposed. The following medications will be included in the analysis and the data will be queried using medication name (brand and generic):

EXPOSURES:

- 5 ARI(s): **Finasteride (5mg) or Dutasteride**
    - **Including** Combination Treatment: **Jalyn (fixed dose combination with tamsulosin)**, or any combination of 5ARI & alpha-blocker either concurrently or consecutively. Jalyn was not launched until 2010. So, this medication will be included to capture any patients who have initiated BPH therapy prior to 2008 and switch to fixed dose combination therapy over the course of the study.
    - **Use of medications indicated for androgenic alopecia (Finasteride 1mg) will be identified in the data source to allow for exclusion of patients treated for alopecia.**
- Selective alpha 1 blocker (s)/alpha-adrenergic blocking agent(s): **Alfuzosin, Doxazosin, , Silodosin, Tamulosin, Terazosin.** Prazosin was indicated for BPH treatment according to [redacted] formulary during the study period, but is not currently indicated. We will examine the utilization of Prazosin over the study period and determine whether patients taking this medication should be excluded from the analysis.

Alpha-Blockers		5-alpha reductase inhibitors		Combination therapy
GENERIC NAME	BRAND NAME	GENERIC NAME	BRAND NAME	DUTASTERIDE-TAMSULOSIN HC CAP
ALFUZOSIN HCL ER TAB 10MG	ALFUZOSIN HCL	DUTASTERIDE 0.5MG	AVODART CAP	JALYN
ALFUZOSIN HCL 10MG	UROXATRAL TAB	FINASTERIDE 5MG	FINASTERIDE TAB	
DOXAZOSIN MESYLATE TABLET	CARDURA 1MG	FINASTERIDE TABLET	PROSCAR 5MG	
DOXAZOSIN MESYLATE TABLET	CARDURA 2MG	FINASTERIDE	PROSCAR TAB 5MG	
DOXAZOSIN MESYLATE TABLET	CARDURA 4MG	FINASTERIDE UD	PROSCAR TAB 5MG	
DOXAZOSIN MESYLATE TABLET	CARDURA 8MG	*FINASTERIDE (ALOPECIA)**	*PROPECIA 1MG TABLET*	
DOXAZOSIN MESYLATE 1MG UD	CARDURA TAB	*FINASTERIDE (ALOPECIA)**	*PROPECIA PRO-PAK*	
DOXAZOSIN MESYLATE 2MG UD	CARDURA TAB	*FINASTERIDE (ALOPECIA)**	*PROPECIA TAB 1MG*	
DOXAZOSIN MESYLATE 4MG UD	CARDURA TAB			
DOXAZOSIN MESYLATE 8MG UD	CARDURA TAB			
DOXAZOSIN MESYLATE MESYLATE TAB 1MG	DOXAZOSIN			
DOXAZOSIN MESYLATE	DOXAZOSIN			

MESYLATE TAB 2MG			
DOXAZOSIN MESYLATE MESYLATE TAB 4MG	DOXAZOSIN		
DOXAZOSIN MESYLATE MESYLATE TAB 8MG	DOXAZOSIN		
PRAZOSIN HCL CAPS UD	MINIPRESS 1MG		
PRAZOSIN HCL CAPSULE	MINIPRESS 1MG		
PRAZOSIN HCL CAPSULES	MINIPRESS 1MG		
PRAZOSIN HCL CAPS UD	MINIPRESS 2MG		
PRAZOSIN HCL CAPSULE	MINIPRESS 2MG		
PRAZOSIN HCL CAPS UD	MINIPRESS 5MG		
PRAZOSIN HCL CAPSULE	MINIPRESS 5MG		
PRAZOSIN HCL 1MG	MINIPRESS CAP		
PRAZOSIN HCL 1MG UD	MINIPRESS CAP		
PRAZOSIN HCL 2MG	MINIPRESS CAP		
PRAZOSIN HCL 2MG UD	MINIPRESS CAP		
PRAZOSIN HCL 5MG	MINIPRESS CAP		
PRAZOSIN HCL 5MG UD	MINIPRESS CAP		
PRAZOSIN HCL CAP	PRAZOSIN 1MG		
PRAZOSIN HCL CAPSULE	PRAZOSIN 1MG		
PRAZOSIN HCL STARTER KIT	PRAZOSIN 1MG		
PRAZOSIN HCL CAP	PRAZOSIN 2MG		
PRAZOSIN HCL CAPSULE	PRAZOSIN 2MG		
PRAZOSIN HCL CAP	PRAZOSIN 5MG		
PRAZOSIN HCL CAPSULE	PRAZOSIN 5MG		
PRAZOSIN HCL CAP 1MG	PRAZOSIN HCL		
PRAZOSIN HCL CAP 1MG UD	PRAZOSIN HCL		
PRAZOSIN HCL CAP 2MG	PRAZOSIN HCL		
PRAZOSIN HCL CAP 2MG UD	PRAZOSIN HCL		
PRAZOSIN HCL CAP 5MG	PRAZOSIN HCL		
PRAZOSIN HCL CAP 5MG UD	PRAZOSIN HCL		
PRAZOSIN HCL PINK CAP 2MG U	PRAZOSIN HCL		
PRAZOSIN HCL WHITE CAP 1MG	PRAZOSIN HCL		
SILODOSIN 4MG	RAPAFLO CAP		
SILODOSIN	RAPAFLO CAP		

8MG			
TAMSULOSIN HCL CAP UD	FLOMAX 0.4MG		
TAMSULOSIN HCL 0.4MG	FLOMAX CAP		
TAMSULOSIN HCL CAP 0.4MG	TAMSULOSIN HCL		
TAMSULOSIN HCL CAP 0.4MG UD	TERAZOSIN HCL		
TERAZOSIN HCL TABLET	HYTRIN 1MG		
TERAZOSIN HCL TABS UD	HYTRIN 1MG		
TERAZOSIN HCL TABLET	HYTRIN 2MG		
TERAZOSIN HCL TABS UD	HYTRIN 2MG		
TERAZOSIN HCL TABLET	HYTRIN 5MG		
TERAZOSIN HCL TABS UD	HYTRIN 5MG		
TERAZOSIN HCL 10MG	HYTRIN CAP		
TERAZOSIN HCL 10MG UD	HYTRIN CAP		
TERAZOSIN HCL	HYTRIN CAP 1MG		
TERAZOSIN HCL UD	HYTRIN CAP 1MG		
TERAZOSIN HCL	HYTRIN CAP 2MG		
TERAZOSIN HCL UD	HYTRIN CAP 2MG		
TERAZOSIN HCL	HYTRIN CAP 5MG		
TERAZOSIN HCL UD	HYTRIN CAP 5MG		
TERAZOSIN HCL UD	HYTRIN TAB 10MG		
TERAZOSIN HCL	HYTRIN TAB 1MG		
TERAZOSIN HCL UD	HYTRIN TAB 1MG		
TERAZOSIN HCL	HYTRIN TAB 2MG		
TERAZOSIN HCL UD	HYTRIN TAB 2MG		
TERAZOSIN HCL	HYTRIN TAB 5MG		
TERAZOSIN HCL UD	HYTRIN TAB 5MG		
TERAZOSIN HCL CAP	TERAZOSIN 1MG		
TERAZOSIN HCL CAP STARTER K	TERAZOSIN 1MG		
TERAZOSIN HCL CAP STARTER P	TERAZOSIN 1MG		
TERAZOSIN HCL CAP	TERAZOSIN 2MG		
TERAZOSIN HCL 2MG CAP	TERAZOSIN HCL		
TERAZOSIN HCL CAP 10MG	TERAZOSIN HCL		
TERAZOSIN HCL CAP 10MG UD 1	TERAZOSIN HCL		
TERAZOSIN HCL CAP 1MG	TERAZOSIN HCL		
TERAZOSIN HCL CAP 1MG UD	TERAZOSIN HCL		
TERAZOSIN HCL	TERAZOSIN HCL		

CAP 2MG TERAZOSIN HCL CAP 2MG UD TERAZOSIN HCL CAP 5MG TERAZOSIN HCL CAP 5MG UD TERAZOSIN HCL STARTER CARD 1MG/	TERAZOSIN HCL TERAZOSIN HCL TERAZOSIN HCL TERAZOSIN		

*Drugs for male-pattern baldness will also be collected in order to separate out later

EXPOSURE CATEGORIES:

1) Any 5ARI use (at least 3 prescriptions (90 day supply)) including patients with concomitant or consecutive alpha blocker use.
2) Alpha-blocker users (at least 3 prescriptions (90 day supply)).

DURATION OF EXPOSURE

Duration of exposure among all 5ARI or alpha blocker users with at least 3 consecutive prescriptions (90 days supply) will begin at the start of the follow up time for each patient and will be categorized as:

1) Any exposure
2) < 1 year
3) 1 - <2 years
4) 2 or more years

Cumulative Exposure:

Define **drug era** for each eligible man:

- When the days of drug supply is available, use this info to determine whether drug use between two adjacent prescriptions are continuous;
- When the days of drug supply is NOT available, assume average prescription cycle as 30 d *(This was learned to be the case from previous projects – the median gap between any two adjacent prescriptions was 30 d. This assumption will be confirmed in the [redacted] data before analysis begins).*
- If the gap between two prescriptions is <= 30 d, count it as continuous, as one drug era. Otherwise, assume there was a gap, and start another drug era after the gap.

Duration of one/each drug era (for each drug or drugs)

- If the adjacent prescription periods do NOT overlap: drug era = From 1st prescription date to "last prescription date + days of drug supply for the last prescription (30 d, if not available)" or the end of observational period, whichever comes first.
- If the adjacent prescription periods DO overlap: drug era = From 1st prescription date to "last prescription date + days of drug supply for the last prescription (30 d, if not available)" or the end of observational period, whichever comes first + days of overlap.

Duration of cumulative exposure = Duration of exposure for drug era 1 + Duration of exposure for drug era 2 +…. + last drug era

4.5 Other Variables (Including potential Confounders and effect modifiers)

Variable definitions for descriptive analyses:

Prostate cancer:
Prostate cancer diagnosis will be identified in all participating [redacted] sites through the tumor registries. These registries contain information on patients who were diagnosed at [redacted] hospitals, or who received at least part of their first course of treatment for cancer at a [redacted] hospital, for all reportable cancers. These diagnoses are based on the established and validated methods that SEER uses (based on ICD-03 codes) by cancer site. C619 identifies prostate cancer as the primary site. Detailed information regarding the SEER coding and staging methodology can be found at:http://seer.cancer.gov/tools/codingmanuals/.

Cardiovascular related mortality:
Cardiovascular related mortality is defined as deaths due to cardiovascular-related causes as coded by State mortality registries or NDI. The state registries follow the National Center for Health Statistics algorithm for assigning CVD death. Detailed instructions regarding the NCHS methods for cause of death determination can be found at: http://www.cdc.gov/nchs/nvss/instruction_manuals.htm. All deaths that occur among men with prostate cancer that have cardiovascular disease mentioned will be captured and these deaths will similarly be validated using the [redacted] algorithm. Cardiovascular deaths

will be captured as a mutually exclusive category from prostate cancer related deaths. Therefore care will be taken in determining cause of death in patients with advanced prostate cancer whose underlying cause of death is listed as cardiovascular disease based on state death certificate information. Additionally, all deaths among the overall cohort where cardiovascular disease is listed as the underlying cause of death will be identified as part of descriptive analyses when assessing all cause mortality.

PSA testing patterns:

Laboratory data from all four participating [redacted] sites is available in the VDW going back to at least the mid-1990s for all sites. This system tracks both inpatient and outpatient laboratory orders and results. Records include the patient's unique medical record number, the laboratory test name and procedure codes, date drawn, units, references ranges, whether the test was abnormal, ordering physician information, and facility information and the lab test results. [redacted] has rich PSA testing data for the study period. In the past 3 years alone in [redacted] we have approximately 25,000 men per year over the age of 50 who have received at least one PSA test, and we have administered almost 1 million PSA tests in this time period. PSA tests for all 4 [redacted] sites are currently housed within the VDW and have gone through quality assurance checks for previous studies. CPT codes which apply for finding PSA tests are 84152-84154.

Biopsies:

Prostate biopsies will be identified within each region according to either CPT or internal [redacted] codes. Care will be taken with the change in coding practices over time within region. Potential CPT codes that will be used include 55700, 55705 and 55706.

Gleason Scores:

Gleason scores are only available in more recent years from the cancer registry (approximately 2007 forward depending on region). Gleason scores are however, available using natural language processing from the pathology reports of both biopsy specimens and surgical specimens, when available. Changes in Gleason score definition over time will be taken into account when abstracting the data. The primary and secondary patterns are added together to create a score. Primary pattern is doubled when there is no secondary pattern. Tertiary pattern is not used to determine Gleason score.

Prostate cancer treatment paradigms:

Prostate cancer treatment will be identified through the cancer and tumor registries at each site. The registries contain information on surgical, chemotherapy, hormone therapy, brachytherapy, external beam radiation and active surveillance treatment choices. These are based on codes for treatment as outlined by SEER. This is the most reliable source of treatment information within the [redacted] system.

Confounders and effect measure modifiers

Information on potential confounders will be collected in the 1 year pre-treatment initiation period for all outcome analyses. Age, race, and family history of prostate cancer are the only consistent risk factors for prostate cancer incidence and prostate cancer death based on the published literature. While obesity, diet, exercise, and socioeconomic status have been associated with risk of prostate cancer and prostate cancer death, a clear causal relationship between these risk factors and prostate cancer has not been established (Brawley, 2012). Matching by age and race in the design phase of this study will help to address potential confounding by these important risk factors. It is not possible in this study to control for family history of prostate cancer as this variable is not systematically collected by [redacted] The relative frequency of variables know to be independent risk factors for the outcomes of interest will be compared between the 5ARI and alpha-blocker treatment groups. If an imbalance is found in any of the independent risk factors across the two treatment groups, these variables will be considered for inclusion in the Cox proportional hazards models or as stratification variables.

Potential confounding factors:

Prostate cancer mortality, prostate cancer mortality or metastatic prostate cancer occurrence:

Potential confounding factors at baseline:

- Race/Ethnicity
  - Race and ethnicity is collected across sites and based on a race and ethnicity variable that is categorized as: Non-Hispanic Whites, African Americans, Hispanic, Asian/Pacific Islander, Other and Missing.

- Age
  - Age is routinely collected and calculated from date of birth.

- Socioeconomic status (SES)
  - Aggregate SES measures for [redacted] members were calculated via geocoding in 2002 using 2000 US census estimates at the block, block-group, tract and ZIP level and include race, income and education.

- PSA
  - PSA is available through our laboratory data in the VDW and is measured in ng/mL.

- BMI
    - BMI was not routinely collected as a vital sign until the implementation of the electronic medical record in each site. Therefore, only a few years of complete data may be available. It is calculated using standard formula and measured in kg/m2.

- Smoking status
    - Smoking status information also was collected as part of patient's history during office visits starting with the implementation of the electronic medical record system (mid-2000s). Information on tobacco use (ever, former, never), pack-years, type of tobacco product used (cigarettes, chewing, pipe, cigar) is available.

- Charlson Comorbidity Index
    - Charlson comorbidity Index is collected based on ICD-9 codes of the included conditions/complications and a standard algorithm and coding macro are used to derive the score which is usually categorized into (0, 1 or 2+).

- CV endpoints
    - Data from diagnosis, lab, and pharmacy are available to define any of these endpoints.
        - History of cardiovascular disease
        - History of high blood pressure
        - History of diabetes
        - History of hyperlipidemia

- History of cancer other than prostate
    - History of cancer other than the prostate will be determined through the cancer registry and tumor registries at each site. A standard SEER coding system is used to identify cancer diagnosis, diagnosis date and site.

Potential confounding factors over the follow-up period:

Additionally information on several variables occurring over the follow-up period will be collected including:

- PSA testing patterns after treatment initiation and over the course of the study period.
- The frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.
- Gleason Score at diagnosis and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.

- Frequency of prostate cancer treatment paradigms (radical prostatectomy, external beam radiation, brachytherapy, cryotherapy, etc.).

Imbalances in these variables across treatment groups will be examined as they may help to explain some of the association between the exposure groups and occurrence of prostate cancer mortality and metastases.

Potential effect measure modifiers for consideration:

Race/ethnicity

Age

SES

Additional considerations for ascertainment of metastatic prostate cancer cases at diagnosis and over the follow-up period

Care will be taken to assess any detection bias across treatment groups in the ascertainment of metastatic cancer cases at the time of diagnosis and over the course of the follow-up. At the time of diagnosis we will examine the frequency of occurrence of tests to ascertain metastatic prostate cancer across the treatment groups including bone scans, PSA tests, and other relevant tests. Over the course of the follow-up we will also document the frequency of occurrence of these tests for metastatic cancer across the treatment groups as part of the development of the natural language processing algorithm for metastatic prostate cancer. This information can be used to help to quantify any detection bias that might be present in the study and potentially help to control for this bias in the analysis phase of the study.

All cause mortality:

Potential confounding factors at baseline:

- Age
- Race/Ethnicity
- SES
- BMI
- Smoking status
- Charlson Comorbidity Index
- History of cancer other than prostate
- Other medications patients may be taking during the study period (to be determined as part of the statistical analysis plan using data from [redacted]

4.6 Adverse drug experience/event measures

Information on adverse events will not be collected in this retrospective analysis. Adverse events will be reported according to SOP-BMD-3003 Safety Reporting from Epidemiology Studies and Analyses of Epidemiology Databases.

4.7 Data collection and management

We will use data from four [redacted] sites: [redacted] and [redacted] The majority of the data is available electronically. Data for some variables will be abstracted from paper based medical records (see section 4.1 Data source). [redacted] will serve as the coordinating site for the study with all other sites sending de-identified data to the [redacted] site for compilation into one large data set. [redacted] will also act as a central IRB with all other study sites ceding IRB authority so that one central IRB approval for the study will be obtained.

4.8 Validation procedures

See outcome definitions (section 4.3)

4.9 Data analysis

Assessment of the success of matching and description of the sample

The first step for these analyses is to identify and quantify the amount of imbalance that existed between the two groups prior to matching. This involves calculating a series of statistics that identify which baseline characteristics are different between the treated and control groups. We now describe the statistics that we will examine for continuous and categorical variables.

Continuous variables will be compared using two-sample *t*-statistics, variance ratios, and /or standardized differences in percent for each variable. The standardized difference in percent is defined as the mean difference as a percentage of the average standard deviation:

$$\frac{100(\bar{x}_c - \bar{x}_t)}{\sqrt{\frac{(s_c^2 + s_t^2)}{2}}}$$

Where for each covariate $\bar{x}_c$ and $\bar{x}_t$ are the sample means in the alpha-blocker and 5ARI groups, respectively, and the s_c^2 and s_t^2 are the corresponding sample variances. The variance ratio is defined as s_c^2 / s_t^2.

Significant differences based on the two sample *t*-statistics, variance ratios that are larger than 1.5 or standardized differences larger than 20% would indicate that there is substantial imbalance between the two groups for that variable. Ideally, there would be no significant *t*-statistics, all variance ratios would be between .8 and 1.2 and standardized differences in percent would be less than 10% if the two groups were well balanced (as would be the expectation if they had been randomized).

For categorical/binary variables we will compare chi-square statistics and observed proportions by treatment group. Significant differences based on chi-square statistics or large differences in observed proportions would suggest that there is an imbalance between the groups on the variables being examined.

The next step is to compare the matched “treated” (5ARI) and “control” (alpha-blocker) patients on the four matching variables (age, timing of treatment initiation, race, and duration of prior use of alpha-blockers) to confirm that indeed the groups were successfully matched on these characteristics. The success of the matching will be assessed based on whether balance between the treated and control groups is achieved in the matched samples.

Next, background characteristics (including cumulative exposure time, follow-up time, follow-up time after cancer diagnosis, and potential pre-treatment initiation confounding

factors) will be compared between the groups to identify whether there exist variables that would need to be considered in the outcome analyses as covariates

4.9.1 Essential analyses

Primary analysis (prostate cancer mortality)

Once the cohort has been selected and the groups are confirmed to have been adequately matched on age, date of treatment initiation, race, and duration of prior use of alpha-blocker, then the outcome analyses will be performed. As described above, descriptive statistics will be summarized overall and according to treatment group for age at first prescription, race, cumulative exposure time, follow-up time, other co-morbid conditions, and clinical variables of interest. Each patient included in the analysis will have their survival outcome determined as follows. All patients who die from prostate cancer will be considered as events. Patients who die from other causes or who are lost to follow-up (leave the [redacted] system) will be coded as censored at the time of death or loss to follow-up. We will search the NDI for deaths occurring within 2 years of patients leaving [redacted] Any deaths determined to be associated with prostate cancer based on information available in NDI will be assigned to the appropriate treatment group based on treatment information available in [redacted] up until patients left the system. Patients who are alive at their last follow-up visit will be censored at that time.

An initial Kaplan Meier curve will be estimated comparing the 5ARI vs alpha-blocker users for prostate cancer mortality without any additional adjustments. Additionally, a plot of cumulative incidence, adjusting for competing risks of death, will be constructed allowing for the investigation of the effect of competing risks on the Kaplan-Meier probability estimates.

Next, we will examine pre-treatment assignment characteristics such as prior co-morbidities (if available) for each treatment group. Then we will examine post-treatment assignment characteristics such as cumulative exposure to the treatment, latency (time since last treatment), and diagnosis of prostate cancer (yes/no). Among those patients who develop prostate cancer we will then compare between the two groups the duration of prostate cancer, the prostate cancer stage at diagnosis and Gleason score at diagnosis.

To better understand the pattern of changes in absolute mortality rates and hazard ratios, by duration of exposure, the data will then be stratified by duration of 5ARI/alpha-blocker exposure: any exposure >3months, < 1 year, 1 - <2 years, 2+ years and the crude mortality rates and hazard ratio will be estimated within strata of exposure. Given power limitations due to the likely number of deaths across exposure duration strata, the data will be pooled for use in regression analyses.

The data will then be stratified using different lag times to be defined based on the distribution of time from BPH treatment initiation to prostate cancer mortality seen in the

data set. The distribution of time from treatment initiation to death in the cohort will be examined.

Additionally, the mortality rates for those using 5ARIs only and those using 5ARIs with an alpha-blocker will be examined separately. Given the likely small size of patients using 5ARIs alone without alpha-blockers these groups will likely be combined in the analysis, however, combining groups assumes that the mortality rate among patients exposed to 5ARIs only is equivalent to that of patients using 5ARIs with an alpha-blocker.

Next, the data will be pooled across exposure and lag time strata and Cox proportional hazard regression models will be fit in the overall data set to compare prostate cancer mortality between groups while adjusting for the pre-treatment characteristics identified above. Of interest will be testing whether there are any potential interactions among the pre-treatment patient characteristics and the treatments (5ARI vs alpha-blocker) and if such interactions are found, this may suggest that the Cox proportional hazards models may need to be fit stratified by the characteristics of interest. Post-treatment characteristics will not be adjusted for in the primary analysis as they may be treatment effects or in the causal path between the exposures and the outcome of prostate cancer mortality. If large imbalances exist in post-treatment variables of interest, stratified analyses may be considered.

An issue that we will confront in analyses is that the outcome of interest is prostate cancer mortality, yet the groups will be selected for analysis prior to the diagnosis of prostate cancer and in fact many patients may not develop prostate cancer at all during this study. Therefore, although the primary outcome of interest is prostate cancer mortality, prostate cancer diagnosis will be examined descriptively across treatment groups.

Secondary analyses:

A similar approach in terms of classifying follow-up time, constructing Kaplan Meier curves, examination of pre- post-treatment assignment characteristics, and stratification by exposure duration and lag time, as detailed above for the primary analysis for prostate cancer related mortality, will be used for the following analyses:

- Prostate cancer mortality or metastatic prostate cancer occurrence
- All cause mortality
- Long terms users of BPH medications

Among users of 5ARIs and alpha-blockers, who use these medications for 2 years or more, the association between 5ARI exposure and prostate cancer related mortality will be estimated.

Cox proportional hazard regression models will then be fit adjusting for imbalances in pre-treatment assignment characteristics. Characteristics that are balanced between the groups may also be included in regression models to increase precision in the treatment effect estimates.

Descriptive analyses:

Prostate cancer

The percent of patients diagnosed with cancer and the incidence rate per 1,000 person years of prostate cancer will be calculated, overall and by treatment group. The data will then be stratified and the incidence of prostate cancer by duration of 5ARI/alpha-blocker exposure will be estimated: any exposure, >3months, < 1 year, 1 - <2 years, 2 or more years. The stage and grade distribution of patients diagnosed with prostate cancer will be determined, overall and by treatment group.

Additionally, information on several variables occurring over the follow-up period will be collected, including:

- BPH related surgery and hospitalizations
  - BPH surgeries will be captured using CPT codes and [redacted] internal codes for older data. Procedures for BPH included most commonly in our system include: transurethral resection of the prostate (TURP) (CPT: 52601, 52612, 52614) and visual laser ablation of the prostate (VLAP) (CPT: 52647 and 52648). However, we will also collect information on: transurethral needle ablation (TUNA) (CPT: 53850 and 53852), high-intensity focused ultrasound (HIFU) (53850), Prostatectomy for benign disease (55801, 55821, 55831).
  - Hospitalizations due to BPH will be captured by abstracting the discharge codes for any inpatient stay and determining whether BPH was one of the conditions coded. The ICD-9 diagnosis code for BPH (600.x) will be used as well as internal [redacted] codes for older data where the ICD-9 code for BPH was not reliably assigned.

- PSA testing patterns after BPH treatment initiation and before cancer diagnosis occurring over the course of the study period..
- Frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy, after BPH treatment initiation and before cancer diagnosis..

Imbalances in these variables across treatment groups will be examined as they may help to describe potential detection bias in the diagnosis of prostate cancer

Metastatic prostate cancer
The percent of patients with metastatic prostate cancer and the incidence rate per 1,000 person years of metastatic prostate cancer will be calculated overall and by treatment group among patients who do not die during the study period. The data will then be stratified and the incidence of metastatic prostate cancer by duration of 5ARI/alpha-blocker exposure will be estimated: any exposure, >3months, < 1 year, 1 - <2 years, 2 or more years. The occurrence of metastatic disease by stage and grade at initial diagnosis will also be examined.

Cardiovascular related mortality
The percent of deaths overall and by treatment group, among men with prostate cancer, due to cardiovascular disease will be estimated as part of the validation process for prostate cancer related deaths. Additionally, the percent of deaths in the overall cohort due to cardiovascular disease will be estimated, overall and by treatment group.

Validation of prostate cancer mortality and metastatic prostate cancer algorithms
The sensitivity, specificity, positive and negative predictive values for the prostate cancer mortality and metastatic prostate cancer algorithms will be assessed in comparison to medical record abstraction. GSK and [redacted] will agree on an adequate level of sensitivity, specificity and predictive value for the algorithms based on the results from the validation process. If numerous iterations of NLP algorithm application and medical chart abstraction cannot produce an adequate level of validity for the algorithms, chart abstraction may need to be used for a larger sample of medical records and GSK and [redacted] will determine how best to proceed and how this will impact the scope of work and timelines for the study.

[redacted] will have 2 abstractors responsible for abstracting medical records, reviewing, and determining the cause of death (or metastatic disease status) for patients included in the validation studies. A third [redacted] person will be responsible for adjudicating cause of death (or metastatic disease status) when disagreements arise between abstractors. The kappa statistic will be calculated for agreement between abstractors.

PSA testing patterns across treatment groups after treatment initiation and over the course of the study period
The percent of patients with a PSA test and the mean and median number of PSA tests over the follow-up will be estimated overall and by treatment group.

Frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy

The percent of patients with a biopsy and the mean and median number of biopsies over the follow-up will be estimated overall and by treatment group. Similarly the mean and median number of cores per biopsy and number of positive cores per biopsy will be estimated.

The percent of patients with a negative biopsy in the 1-year pre-baseline period will be calculated overall and by treatment group. Additionally, the percent of patients with a negative biopsy within their entire [redacted] medical history pre-baseline will be calculated overall and by treatment group. A biopsy is usually performed in response to a signal related to the possible presence of prostate cancer such as increasing PSA or detection of a lump during digital rectal examination. History of negative biopsy will be collected as a way to describe the prostate cancer risk among patients in the sample before the start of the study period.

Gleason Score and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies

The distribution of Gleason score at prostate cancer diagnosis will be determined overall and by treatment group. Changes in Gleason score definition over time will be taken into account when abstracting the data. Among those patients who have a radical prostatectomy, Gleason scores will again be determined and any reclassification of Gleason score from initial diagnosis biopsy based on a radical prostatectomy biopsy will be noted.

4.9.2 Exploratory analyses

Primary analysis:

- Sensitivity analyses will be conducted including the following:

- The data will be stratified by cumulative dose of 5ARI medication and the association between 5ARI exposure and prostate cancer related mortality will be estimated within each stratum. Categories for cumulative dose will be defined based on the distribution of cumulative dose in the data and independently from outcome status. Preliminary categories will be defined as part of the development of the statistical analysis plan.

- After examining the treatment data independently from the mortality data we will define groups of patients based on gaps in their exposure history and will conduct sensitivity analyses to examine how the exposure-disease relationship might vary based on these groups. For example, participants with > 9 month gaps between drug eras and a maximum duration of drug era of 3 months over the course of follow-up might constitute one group while those with cumulative exposure of >2 years with <3 months of time between drug eras (time off of treatment) over the course of the study period may constitute another. In this way, we will examine the validity of the assumption that exposure time can be summed across treatment eras without accounting for gaps in treatment (main study analysis).

- The data will be stratified by time since the end of BPH treatment to prostate cancer related mortality (< 1 year, 1- <2years, 2 to 3 years, 3+ years) to see how the main association differs within each of these groups.

- When patients drop out of the [redacted] system they will be censored at the time they leave the system for the primary analysis of prostate cancer mortality. The NDI will be searched for deaths occurring within the study period among men who dropped out of [redacted] Any deaths determined to be associated with prostate cancer based on information available in NDI will be assigned to the appropriate treatment group based on treatment information available in [redacted] up until patients left the system. A sensitivity analysis will be conducted including these deaths to see if the primary association differs with the inclusion of these additional cases.

- Deaths due to prostate cancer occurring in the first year after treatment initiation will be excluded from the analysis as it is not biologically plausible that BPH treatments could cause prostate cancer and subsequent death within the first year of treatment exposure.

- Men with a history of cancer other than prostate will be excluded from the analysis to see how the main association differs when this groups is excluded.

- Men without a BPH diagnosis will be excluded from the analysis to see how the main association differs when this groups is excluded.

- A subgroup of men will be defined who had an increase in their PSA level. Some of the men will have received a 5ARI in response to their PSA increase and some will not. 5ARI patients will be matched to alpha-blocker patients and we will examine prostate cancer mortality in these groups. This analysis will allow us to examine the effect of 5ARI initiation when it is triggered by PSA increases..

- We will stratify 5ARI exposed patients into 2 groups: those using 5ARIs as monotherapy and those using 5ARIs concurrently with alpha-blockers. We will examine descriptively whether there are any differences between patients using these different treatment regimens with respect to prostate cancer mortality.

- If the results from stratified analyses indicate heterogeneity across strata of post-treatment characteristics of interest (PSA testing patterns after treatment initiation and over the course of the study period, frequency of biopsy, the number of cores per biopsy, the number of positive cores per biopsy, and frequency of prostate cancer treatment paradigms), marginal structural models (Hernan et al, 2000) may be used to explore the potential effects of post-treatment characteristics on the relationship between BPH medication use and prostate cancer related mortality.

Secondary analyses:

Prostate cancer mortality or metastatic prostate cancer occurrence, all cause mortality

Depending upon the results from the exploratory analyses for the primary outcome of prostate cancer related mortality we will consider repeating some of the exploratory analyses listed above, as appropriate, among long term users of BPH treatment and for the outcomes of:

- prostate cancer mortality or metastatic prostate cancer occurrence

- all cause mortality

Descriptive analyses:

Prostate cancer

- We will stratify the data by cumulative dose of 5ARI medication and estimate the incidence of prostate cancer overall and within each stratum. Categories for cumulative dose will be defined based on the distribution of cumulative dose in the data and independently from outcome status.

  We will stratify the data using different latency periods to be defined based on the distribution of time from BPH treatment exposure to detection of cancer seen in the data set.

4.9.3 General considerations for data analyses

Matching on pre-treatment characteristics, considered major potential confounders based on the literature and expert opinion, will be conducted to minimize potential confounding by these covariates. Additionally, covariate adjustment and stratification will be used in the analysis phase of the study to adjust for imbalances in baseline characteristics between exposure groups.

4.9.4 Data handling conventions

N/A

5. SAMPLE SIZE AND POWER/PRECISION CALCULATIONS

Assuming a hazard ratio of 1.0, 90% power and a 0.05 two sided alpha we would need approximately 850 deaths to rule out a hazard ratio of 1.25 or higher. This calculation is based on equation 2 in the article by Saville et al (Saville et al, 2011) and assumes a 1:1 ratio of patients across treatment groups. A 25% increase in risk of prostate cancer is thought to be a signal of concern. While this study is designed to detect any difference (increase or decrease) in risk between 5ARI and alpha-blocker users, given the potential limitations of power in this study, if a difference in risk is not found between the exposure groups, this will not be interpreted to rule out an increased risk of prostate cancer related mortality associated with the use of 5ARIs. If no increased risk is found for 5ARI users compared to alpha-blocker users, this result will add to the body of evidence used to interpret the findings from the REDUCE trial of an increased number of HGTs in the dutasteride arm compared to the placebo arm. Further consideration for the possible results from the analysis (e.g. a hazard ratio of 1.15 with a confidence interval not including 1) and how they will be interpreted will be included in the statistical analysis plan.

Based on the feasibility assessment using [redacted] data, the allocation of patients across treatment groups (alpha-blocker:5ARI) is expected to be 5.4:1. With this unequal allocation of patients in the exposed and unexposed groups an adjustment must be made to the sample size calculation. Using the adjustment suggested by Saville et al with the same assumptions for power, 1,500 prostate cancer related deaths (214 in the 5ARI exposed group and 1,286 in the alpha-blocker only group) are needed to rule out a HR of 1.25 or higher. This calculation assumes a 6:1 allocation of unexposed (alpha-blocker) vs. exposed (5ARI) and equal risk in both exposure groups.

The target of 1,500 deaths should be reached by pooling data across four [redacted] sites. 846 deaths were observed in the feasibility study. Roughly the same number of deaths from [redacted] can be expected and about 15% of this amount from [redacted] and [redacted] yielding an estimated total number of deaths of 1,946. When these prostate cancer related deaths are validated it is estimated that up to 25% of them will be reclassified as non-prostate cancer related which will yield approximately 1,500 prostate cancer related deaths.

Based on feasibility data from [redacted] we expect there to be approximately 284,000 men eligible for inclusion in the study. As mentioned above, there were 846 prostate cancer related deaths observed in the feasibility study resulting from a population of 123,503 men yielding an event rate of 0.7% (846/123,503). Dividing the expected number of deaths, 1500, by the event rate results in a target sample size of 218,977 men. If we assume that the ratio of alpha-blocker:5ARI users will be the same in the overall study sample (5.4:1) as in the feasibility study, then we would expect to have 34,215 5ARI users and 184,762 alpha-blocker users in our study.

There will be a pool of approximately 249,785 alpha-blocker users from which 184,762 matches will be selected for the 5ARI users in this study. As 74% of the available matches will need to be included in the study sample to meet the target sample size of

218,977 men, there may be some difficulties in finding 5 to 6 appropriate matches for each 5ARI patient. Therefore some deaths among alpha-blocker users may not be included in the study. To address this potential issue matching criteria may be relaxed to increase the windows for age, timing of treatment initiation, and duration of alpha-blocker (e.g. from ± 1 year to ± 2 years).

Additionally, sample size calculations have been performed assuming power of 80% and 85%. Under the scenario of 85% power, and a 0.05 two sided-alpha we would need approximately 1262 deaths to rule out a hazard ratio of 1.25. Under the scenario of 80% power, and a 0.05 two sided-alpha we would need approximately 1099 deaths to rule out a hazard ratio of 1.25.

Power	Allocation ratio of 5ARI users to alpha blocker users	Number of prostate cancer related deaths
90	1/5	1314
	1/6	1474
85	1/5	1125
	1/6	1262
80	1/5	980
	1/6	1099

6. STUDY LIMITATIONS

Limitations

- There were changes in how patients are followed and screened for prostate cancer over the study period (1992-2008). These changes may affect the likelihood of detecting prostate cancer, and how diagnosed prostate cancer is treated. To help minimize this bias we are matching patients on calendar time of treatment initiation and will describe the frequency of use of different cancer treatment paradigms across the treatment groups

- Based on the feasibility study from [redacted] there are very few patients using 5ARIs only for the treatment of BPH. Most patients use an alpha-blocker and then switch to or add 5ARI therapy. For this reason we are matching patients on their duration of alpha-blocker use at the time that the index patient (5ARI user) initiates treatment. Matching on prior use of alpha-blockers will help to control for the use of alpha-blockers in the 5ARI exposure group.

- There may be inherent differences in patients who switch therapy from alpha-blocker to 5ARIs or add 5ARIs to their alpha-blocker treatment versus those who remain on alpha-blocker only therapy. These differences may be related to the likelihood of developing and being diagnosed with prostate cancer and also to prostate cancer related mortality. We will attempt to control for some of the potential differences between study groups by matching in the design phase of the study, and by controlling for confounding through regression analysis and stratification in the analysis phase of the study.

- There is likely to be differential surveillance for prostate cancer for patients using 5ARIs versus alpha-blockers. Treatment with 5ARIs lowers PSA levels so any increase in PSA while on treatment is a signal for medical intervention or increased surveillance and/or testing. To examine the potential effect of this bias we will describe PSA testing patterns and biopsy frequency over the course of the study period.

- The primary endpoint in this analysis is the occurrence of mortality due to prostate cancer. There may be a long duration of follow-up time between a patient's diagnosis of prostate cancer and occurrence of prostate cancer related death with many potential events occurring. For example, patients may be treated differently for their cancer across exposure groups and treatment modality may affect the likelihood of prostate cancer mortality. Adjusting for variables that occur once a patient has started treatment may bias the mortality ratio across exposure groups as it is difficult to disentangle the effects of various potential causal factors in this observational study. Therefore we will likely not control for variables occurring after the index date or beginning of time at risk for the outcome. We will attempt to balance all potential confounders of interest at the index date and will consider all events occurring after the index date to be part of

the treatment effect. We will describe some events including type of prostate cancer treatment and if these variables are unbalanced across treatment groups we will consider different methods for controlling for the imbalances.

- [redacted] pharmacy data captures fills of prescriptions, but we will not know if patients actually took their medications or took them as they were prescribed. There is no reason to think that this exposure misclassification would be differential across exposure groups.

- We will be developing two algorithms based on natural language processing to identify metastatic prostate cancer cases and deaths due to prostate cancer. These algorithms will misclassify some deaths and cases of metastatic cancer and we will minimize this bias by validating the algorithms with medical record abstraction. Misclassification of these outcomes should be independent of exposure status as those classifying the outcomes will be blinded to the exposure status of the patients.

- [redacted] data represents patients with commercial insurance and those enrolled in a [redacted] Medicare plan. Several regions within the US are represented within the study, but the study population will not be representative of the US population with respect to insurance coverage or distribution of race/ethnicity. Therefore the results from the study may not be generalizable to all US men with treated BPH.

- Some important confounders such as family history of prostate cancer are not systematically collected and will therefore not be adjusted for in the analysis.

- As this is a retrospective observational study there are limitations in terms of information available for all patients in the study. The study period was designed to coincide with the launch of the prescription medications under study. Therefore patients will have varying amounts of medical history available depending upon when they start treatment and meet inclusion criteria for the study. To minimize this bias we are ascertaining information on potential confounders over the one year pre-treatment period for all patients. However, information on co-morbidities and disease duration may not be complete for all patients.

Strengths

- Pooling data across 4 [redacted] sites allows for a large study population representing many person years of exposure to BPH medications.

- [redacted] data contains information from electronic medical records including lab values and procedure results which will be necessary for this study. Additionally patients can be linked to state or national death record information. Information from patient medical records can be abstracted to validate cause of death information from death certificates.

- [redacted] and [redacted] participate in the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute and [redacted] and [redacted] participate in the NIC funded Cancer Research Network (CRN) therefore the cancer diagnosis data collected across [redacted] sites must meet the quality standards to be included as part of SEER and CRN.

- There is a low turn over in [redacted] data compared to commercial claims data. Based on the feasibility study using [redacted] data approximately 4% of patients were lost to follow-up due to disenrollment over the study period of 1992 to 2008.

- Over 90% of patients who turn 65 years of age and are eligible for Medicare and are currently enrolled in [redacted] plans choose to remain in [redacted] and enrol in one of their Medicare plans. As our study population in 50 years and over this is a major strength of the [redacted] data in answering our study question related to mortality as few patients are lost to follow up.

- The NLP algorithm developed as part of this study to validate prostate cancer related deaths will increase the validity of cause of death information in this study beyond the more common method of using cause of death from death certificates.

7. STUDY MANAGEMENT

7.1 Ethical approval and subject consent

This study will be reviewed and approved by the IRB in [redacted] and approved by the other participating regions. No patient contact will be made as part of this study as only previously collected data will be utilized.

7.2 Subject confidentiality

Data used in this study will be de-identified at each [redacted] site before the data is sent to [redacted] the coordinating site, for data analysis. Patients are identified by unique IDs in the data set that will not be linked to personal identifiable information. GSK will not have access to the data and will receive results from [redacted] in aggregate form.

7.3 Reporting of adverse drug events

Reporting will be carried out according to SOP-BMD-3003 Safety Reporting from Epidemiology Studies and Analyses of Epidemiology Databases.

7.4 Study closure/uninterpretability of results

N/A

7.5 Study milestones

Date	Objective and Tasks to Complete	Deliverables
Start Date: December 2012		
Months 0-3	Protocol development, data analysis plan, obtain IRB approval, obtain IRB ceding or approvals from other regions and get data use agreements in place.	Protocol and data analysis plan; IRB documentation
Months 3-7	Data abstraction for NDI match and primary objectives in all regions, build analytic datasets and transfer data to [redacted] for analyses.	Interim Progress Report (including mortality counts); data to [redacted]
Months 4-7	NDI Match (CDC)	
4-16	Develop and validate natural language processing algorithms for cause of death and metastatic disease ([redacted] Other sites send report and text data for NLP to [redacted] Validate algorithm with each region's data (chart review as needed)	Interim NLP Progress Report; NLP data sent to [redacted]
Months 7-10	Primary analysis of mortality objectives (based on crude coded death categorization)	Report #1
Month 10-12	Apply cause of death algorithm; Random sample validation of prostate cancer deaths (chart review in each region)	Validation report
Months 12-16	Analysis and reporting of Primary objective (using validated death data)	Report #2
Months 16-22	Analysis and reporting of Secondary Objectives	Report #3
Months 22-28	Analysis and reporting of additional exploratory objectives	Final report
End Date: April 2015		

7.6 Study advisory committee

N/A

7.7 Study reporting and publications

The results from this study will be submitted to a peer reviewed journal within 18 months of the completion of data analysis per GSK policy POL-GSKF-408.

7.8 Resourcing needs

N/A

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9. TABLES

A selection of key tables for this study is presented below. The inclusion of additional tables will be considered as the analysis plan is developed for the study.

Table 2: Pre-treatment characteristics by exposure group after matching (5ARI and alpha-blocker)

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)	p-value
Characteristic				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%)				
<60				
60-69				
70+				
Race (%)				
Non-Hispanic White				
African American				
Hispanic				
Asian/Pacific Islander				
Other				
Missing				
SES				
PSA level (mean (sd), median				
Prostate volume				
BMI (kg/m2) (%)				
<25 mg/kg2				

<=25 mg/kg2 <30 mg/kg2				
>=30 mg/kg2				
Smoking status				
Charlson Comorbidity index (%)				
0				
1				
2+				
History of cardiovascular disease				
History of high blood pressure				
History of hyperlipidemia				
History of diabetes				
History of cancer				
Use of other medications				

Table 3: Post-treatment characteristics by exposure group

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)	p-value
Characteristic				
Cumulative exposure time, years (mean (sd), median)				
Cumulative dose				
Duration of follow-up time, years (mean (sd), median)				
Patients with >=1 PSA test (%)				
Number of PSA tests (mean (sd), median)*				
Patients with >=1 biopsy (%)				
Number of Biopsies (mean (sd), median)				
Number of cores/biopsy** (mean(sd), median)				
Number of positive cores/biopsy (mean(sd), median)				
Prostate cancer diagnosis (%)				
Prostate cancer incidence rate, /1,000 person-years				

***Patients without PSA tests not included in percentages.**

****Patients without biopsies not included in percentages.**

Table 4: Characteristics of men developing prostate cancer over the follow-up period by exposure group.

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)
Characteristic			
Number of PSA tests (mean (sd), median)			
Number of Biopsies (mean (sd), median)			
Number of cores/biopsy (mean(sd), median)			
Number of positive cores/biopsy (mean(sd), median)			
Age at diagnosis (mean (sd), median)			
Age at diagnosis (%)			
<60			
60-69			
70+			
Gleason score at diagnosis(n (%))			
<=6			

7			
7-10			
8-10			
Radical prostatectomy (n(%))			
Reclassification of Gleason score at prostatectomy (%same, % upgrade, % downgrade))			
<=6			
7			
7-10			
8-10			
Stage at diagnosis			
I			
II			
III			
IV			
Bone scan at diagnosis (%)			
Positive bone scans (%)			
Other tests for metastatic disease at diagnosis (%)			
Positive tests (%)			
Prostate cancer treatment within 6 months of diagnosis (%)			

Surgery			
Hormonal therapy			
Chemotherapy			
Immunotherapy			
Radiation therapy			
Other therapy			
Follow-up time after cancer diagnosis, years (mean (sd, median)			
Time since last exposure to BPH medication			

Table 5: Progression to metastatic disease by stage and grade at diagnosis

	Incidence rate of metastatic disease		
	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)
Patient Stratum			
Gleason score at diagnosis (%)			
<=6			
7			
8			
9			
10			
Stage at diagnosis			
I			
II			
III			

Table 6: Pre-treatment characteristics after matching, prostate cancer incidence, and prostate cancer mortality by 5ARI user type

	Overall (n= _)	5ARI monotherapy users (n= _)	5ARI+Alpha-blocker users (n= _)
Characteristic			
Age at treatment initiation (mean (sd), median)			
Age at treatment initiation (%)			
<60			
60-69			
70+			
Race (%)			
Non-Hispanic White			
African American			
Hispanic			
Asian/Pacific Islander			
Other			
Missing			
SES			
PSA level (mean (sd), median			
Prostate volume			
BMI (kg/m2) (%)			
<25 mg/kg2			

<=25 mg/kg2 <30 mg/kg2			
>=30 mg/kg2			
Smoking status			
Charlson Comorbidity index (%)			
0			
1			
2+			
History of cardiovascular disease			
History of high blood pressure			
History of hyperlipidemia			
History of diabetes			
History of cancer			
Use of other medications			
Prostate cancer diagnosis (%)			
Prostate cancer incidence rate, /1,000 person-years			
Prostate cancer deaths (%)			
Prostate cancer mortality rate, /1,000 person-years			

Table 7: Crude and adjusted prostate cancer related mortality rates and hazard ratios stratified by characteristics of interest.

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Overall						
Cumulative exposure						
➢ 3 months						
< 1year						
1 year-<2 years						
2+ years						
Cumulative dose						
1st quartile						
2nd quartile						
3rd quartile						
4th quartile						

Table 8: **Crude and adjusted prostate cancer mortality or metastatic cancer rates and hazard ratios stratified by characteristics of interest.**

	No of events/ No at risk		Event rate/ 1,000 p-y		Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Overall						
Cumulative exposure						
➢ 3 months						
< 1year						
1 year-<2 years						
2+ years						
Cumulative dose						
1st quartile						
2nd quartile						
3rd quartile						
4th quartile						

Table 9: Crude and adjusted all cause mortality rates and hazard ratios stratified by characteristics of interest.

	No of events/ No at risk		Mortality rate/ 1,000 p-y		Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Overall						
Cumulative exposure						
➢ 3 months						
< 1year						
1 year-<2 years						
2+ years						
Cumulative dose						
1st quartile						
2nd quartile						
3rd quartile						
4th quartile						

Table 10: **Crude and adjusted prostate cancer mortality rates and hazard ratios stratified by pre-treatment characteristics of interest.**

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Overall						
Baseline characteristics						
Race (%)						
Non-Hispanic White						
African American						
Hispanic						
Asian/Pacific Islander						
Other						
Missing						
SES						
BMI (kg/m2) (%)						
<25 mg/kg2						
<=25 mg/kg2 <30 mg/kg2						
>=30 mg/kg2						
Smoking status						
Charlson Comorbidity index (%)						
0						

1						
2+						
History of cardiovascular disease						
History of high blood pressure						
History of hyperlipidemia						
History of diabetes						
History of cancer						

Table 11: Crude and adjusted prostate cancer mortality or metastatic cancer rates and hazard ratios stratified by pre-treatment characteristics of interest.

	No of events/ No at risk		Event rate/ 1,000 p-y		Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Overall						
Baseline characteristics						
Race (%)						
Non-Hispanic White						
African American						
Hispanic						
Asian/Pacific Islander						
Other						
Missing						
SES						
BMI (kg/m2) (%)						
<25 mg/kg2						
<=25 mg/kg2 <30 mg/kg2						
>=30 mg/kg2						
Smoking status						
Charlson Comorbidity index (%)						
0						
1						

2+						
History of cardiovascular disease						
History of high blood pressure						
History of hyperlipidemia						
History of diabetes						
History of cancer						

Table 12: Crude and adjusted all cause mortality rates and hazard ratios stratified by characteristics of interest.

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker		
Overall						
Baseline characteristics						
Race (%)						
Non-Hispanic White						
African American						
Hispanic						
Asian/Pacific Islander						
Other						
Missing						
SES						
BMI (kg/m2) (%)						
<25 mg/kg2						
<=25 mg/kg2 <30 mg/kg2						
>=30 mg/kg2						
Smoking status						
Charlson Comorbidity index (%)						
0						
1						

2+						
History of cardiovascular disease						
History of high blood pressure						
History of hyperlipidemia						
History of diabetes						
History of cancer						

10. FIGURES

Kaplan Meier curves for prostate cancer related mortality, prostate cancer related mortality or metastatic prostate cancer, all cause mortality, metastatic prostate cancer, and prostate cancer comparing 5ARI and alpha-blocker users will be constructed.

11. APPENDICES

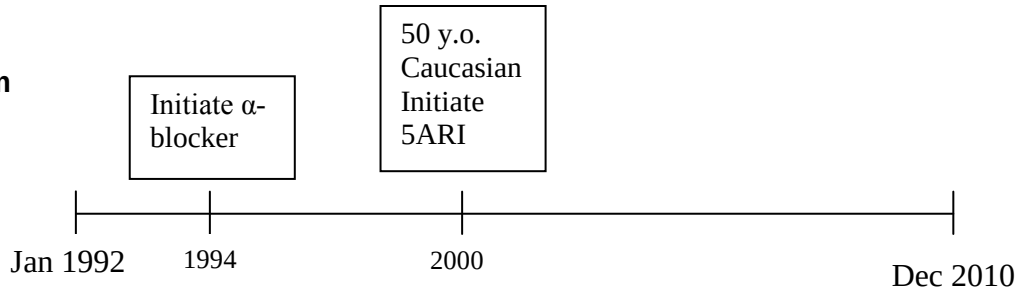
Appendix 1: Main table from feasibility study

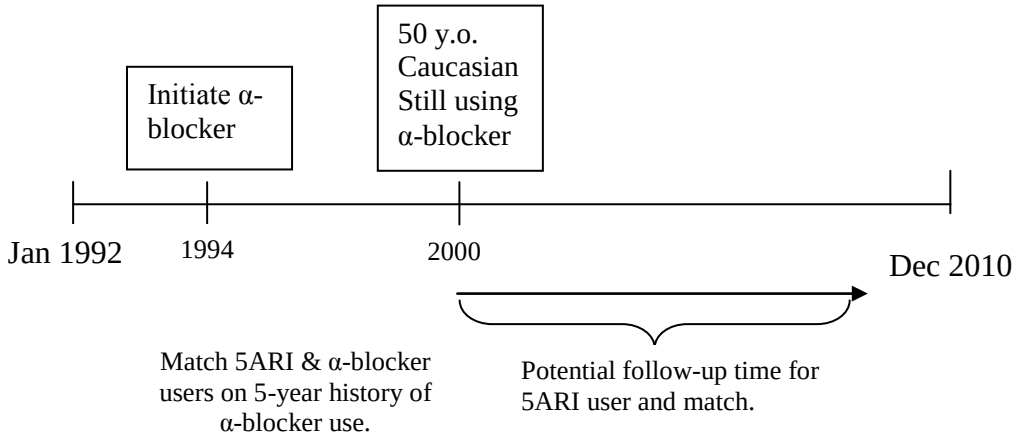
	α-blocker Only (N=104,272)	5ARI Only (N=1,619)	Combination Therapy (N=17,612)
BPH diagnoses			
Number of patients with BPH diagnosis	75,133	917	17,199
Median age at BPH diagnosis	67.7	68.3	68.1
Time from BPH diagnosis to first Rx (in months, % were based on BPH diagnosed)			
0 (first Rx before diagnosis)	37673 (50.1)	233 (25.4)	9547 (55.5)
0-3	24653 (32.8)	258 (28.1)	4509 (26.2)
3-6	923 (1.2)	26 (2.8)	207 (1.2)
6-12	1517 (2.0)	42 (4.6)	388 (2.3)
12+	10367 (13.8)	358 (39.0)	2548 (14.8)
Median (range)	0 (0,319)	1 (0,324)	0 (0,307)
BPH Treatment			
Median age at first medication Rx	65.7	64.2	66.3
Number of patients with follow-up time[2] (years)	N=104187	N=1619	N=17611
< 1	8158 (7.8)	156 (9.6)	235 (1.3)
1-2	6786 (6.5)	145 (9.0)	246 (1.4)
2-4	17712 (17.0)	436 (26.9)	1822 (10.4)
4-6	20339 (19.5)	442 (27.3)	3226 (18.3)
6-10	25686 (24.7)	248 (15.3)	4692 (26.6)
10+	25506 (24.5)	192 (11.9)	7390 (42.0)
Median (range)	5.9 (0, 20.0)	4.2 (0, 18.8)	8.7 (0, 20.0)
Number of patients with cumulative duration of medication supply, (%)[3]			
< 6 months	14543 (14.0)	269 (16.6)	92 (0.5)
6-12 months	9856 (9.5)	184 (11.4)	251 (1.4)
1-2 years	11662 (11.2)	219 (13.5)	483 (2.7)
2-4 years	12156 (11.7)	220 (13.6)	918 (5.2)
4+ years	56055 (53.8)	727 (44.9)	15868 (90.1)
Median (in years, range)	4.9 (0, 2382.5)	3.2 (0, 355.6)	38.8 (0.1, 2627.6)
PSA			
Total number of PSA tests	571671	8346	141740
Total number of PSAs with value	570760	8327	141494
Number of Patients with at least 1 PSA test, (%)[3]	95791 (91.9)	1413 (87.3)	17002 (96.5)
Median Number of PSAs	5	4	7
Median number (min, p25, p75, max) of PSA tests by year of initiation of BPH medication			
1st year post initiation	1 (1, 1, 2, 20)	1 (1, 1, 1, 5)	1 (1, 1, 2, 16)
2nd year post initiation	1 (1, 1, 1, 18)	1 (1, 1, 1, 6)	1 (1, 1, 2, 13)
3rd year post initiation	1 (1, 1, 1, 21)	1 (1, 1, 1, 8)	1 (1, 1, 2, 15)
4th year post initiation	1 (1, 1, 1, 40)	1 (1, 1, 1, 10)	1 (1, 1, 2, 15)
5th year post initiation	1 (1, 1, 1, 14)	1 (1, 1, 1, 5)	1 (1, 1, 2, 16)

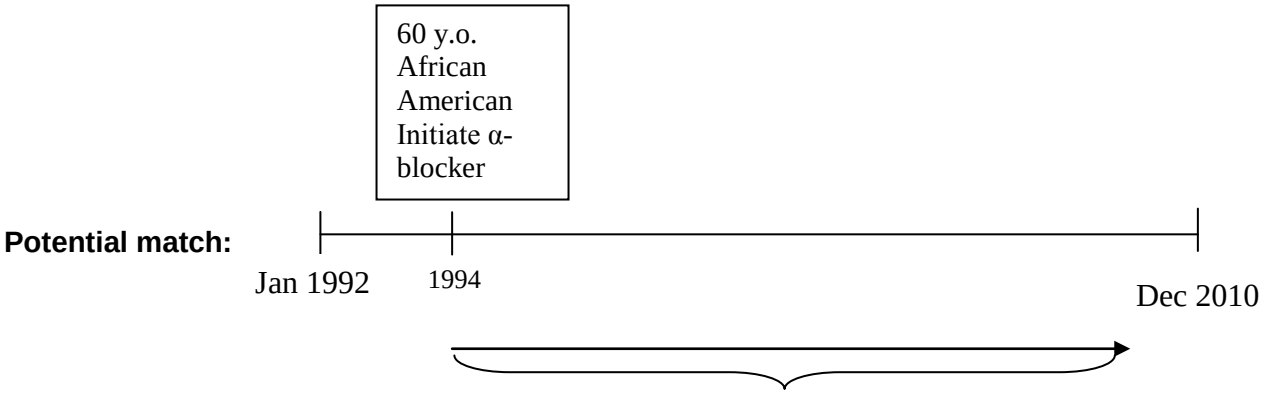
Prostate Cancer	N (%) or median (SE)	N (%) or median (SE)	N (%) or median (SE)
Number of men with prostate cancer, (%)[3]	7856 (7.5)	50 (3.1)	1185 (6.7)
Age at diagnosis	69.7 (0.1)	70.4 (1.4)	72.6 (0.2)
Time since first medication prescription (in years)	2.4 (0)	1.0 (0.4)	4.3 (0.1)
Time since BPH diagnosis (in years)	1.2 (0.1)	2.0 (1.1)	2.7 (0.1)
Gleason Score[4] (sum of both primary and secondary) at diagnosis	N=3267	N=28	N=665
≤6	1621 (49.6)	13 (46.4)	386 (58.0)
7	1064 (32.6)	12 (42.9)	158 (23.8)
8	255 (7.8)	0 (0)	52 (7.8)
9	296 (9.1)	3 (10.7)	61 (9.2)
10	31 (0.9)	0 (0)	8 (1.2)
Cancer stage at diagnosis[5]	N=5579	N=37	N=972
I	46 (0.8)	0 (0)	17 (1.8)
II	4840 (86.8)	29 (78.4)	856 (88.1)
III	301 (5.4)	2 (5.4)	30 (3.1)
IV	392 (7.0)	6 (16.2)	69 (7.1)
Prostate cancer treatment within 6 months of diagnosis, (%)[3]			
Surgery	2078 (26.5)	18 (36.0)	261 (22.0)
Hormonal Therapy	1484 (18.9)	9 (18.0)	246 (20.8)
Chemotherapy	15 (0.2)	1 (2.0)	4 (0.3)
Immunotherapy	2 (0.03)	0 (0)	0 (0)
Radiation Therapy	869 (11.1)	6 (12.0)	116 (9.8)
Other Therapy	5 (0.06)	0 ()	1 (0.1)
Prostate Cancer Mortality	**N (%) or median (range)**	**N (%) or median (range)**	**N (%) or median (range)**
Total number of deaths, (%)[3]	749 (0.7)	10 (0.6)	87 (0.5)
Age at death, median (range)	80.7 (51.1, 97.6)	81.2 (57.4, 93.8)	80.9 (59.5, 100.5)
Time since first medication prescription (in years), median (range)	5.6 (0.1, 17.1)	3 (0.5, 14.9)	5.8 (0.7, 17.3)
Time since BPH diagnosis (in years)	3.5 (0.0,28.7)	1.9 (0.5,26.4)	4.3 (0.6,27.1)
Time since prostate cancer diagnosis (in years)[6]	N=608 2.9 (0, 16.5)	N=6 1.1 (0.4, 6.0)	N=71 1.8 (0, 15.1)
Lost to Follow-Up[7]	**N (%)**	**N (%)**	**N (%)**
Number of patients lost to follow-up	26689 (25.6)	298 (18.4)	2393 (13.6)

Appendix 2

Matching diagram



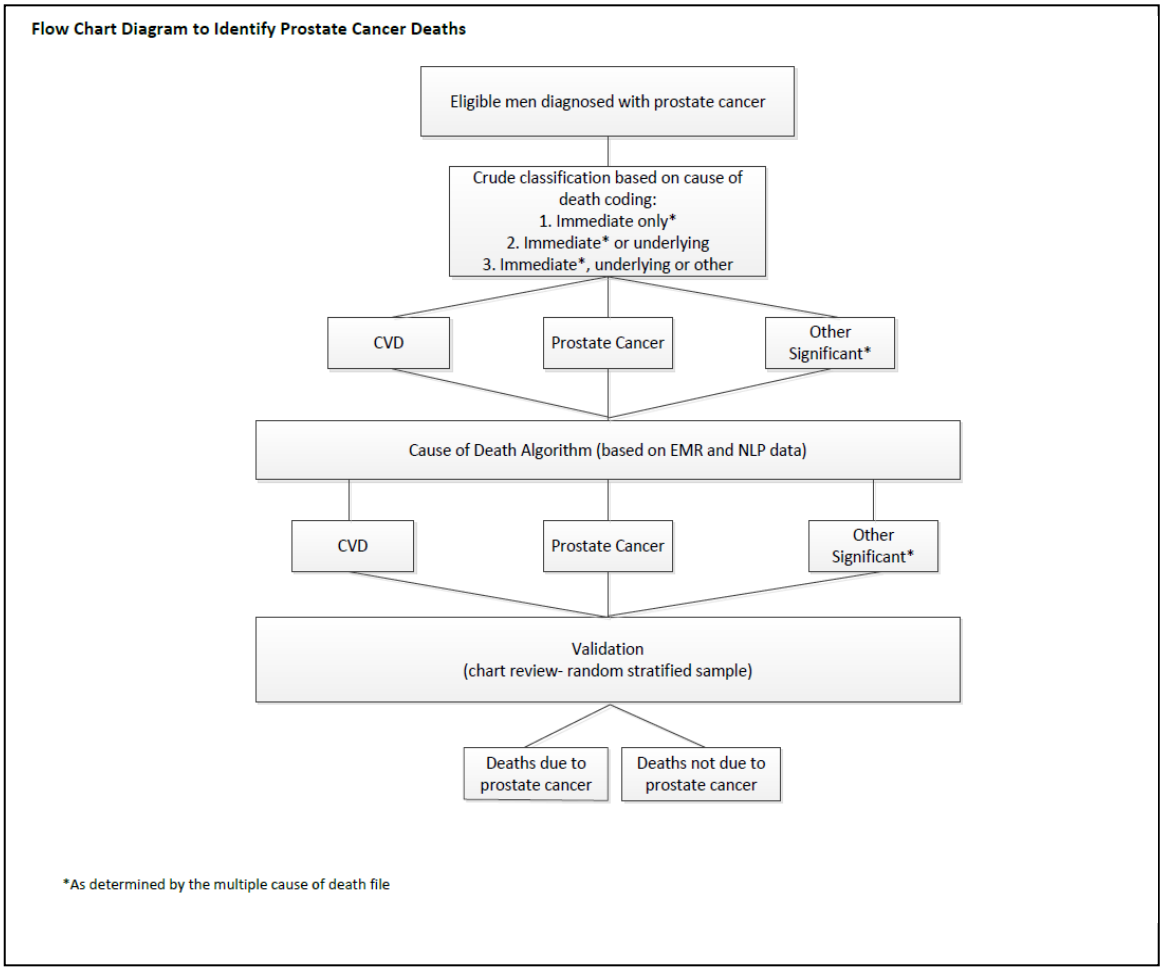




Potential follow-up time for 5ARI user and match.

Appendix 3

Prostate cancer death validation process flow chart



Appendix 4

DETERMINING CAUSE OF DEATH ALGORITHM ID_____

1. Does subject have adenocarcinoma of the prostate?			Data Source
a. Is there a pathology report of a prostate biopsy that shows adenocarcinoma?	YES NO	If yes, go to 2.	NLP-pathology reports
b. Is there a PSA level > 10?	YES NO	If yes, go to 2.	Lab data
c. Is there an acid phosphatase level greater than normal?	YES NO	If yes, go to 2.	Lab data
d. Is there a DRE which the examiner states is very suspicious for cancer?	YES NO	If yes AND e yes, go to 2.	NLP- clinic notes
e. Is there a report of an abnormal bone scan that is suspicious for metastatic cancer?	YES NO	If yes AND d yes, go to 2.	NLP- radiology reports
If a through c are no AND either d or e is no, death was not due to prostate cancer. STOP HERE			
2. Is there another clear-cut cause of death? Starting with the date of death and working backwards in the record, review all clinical data including outpatient clinic visits, hospital summaries, hospice notes, telephone calls, etc.			
a. Is there a clear statement that the cause of death is something other than prostate cancer?	YES NO	If yes, go to b. If no, go to 3.	Mortality data
b. Is the cause of death stated to be one of the	YES NO	If no, then the death was not due to prostate	Mortality data

following? Pneumonia Pulmonary emboli Urosepsis Septic shock Anoxic brain damage Renal failure Failure to thrive Multi-organ failure Unknown		cancer. STOP HERE. If yes, go to 3.	
3. Does subject have evidence of metastatic disease?			
a. bone scan that is abnormal and suggestive of metastatic disease	YES NO	If yes, go to 4.	NLP- radiology reports
b. PSA level >100	YES NO	If yes, go to 4.	Lab data
c. elevated acid phosphatase level?	YES NO	If yes, go to 4.	Lab data
d. prostate cancer found in biopsy of a metastatic lesion	YES NO	If yes, go to 4.	NLP-pathology reports
e. evidence of metastatic disease to lymph nodes or distant organs and no other known primary site of cancer besides prostate cancer	YES NO	If yes, go to 4.	NLP- clinic notes
f. blastic lesion on bone x-rays	YES NO	If yes, go to 4.	NLP- radiology

If the answers to a through f are all no, go to 5.			
4. Does subject have evidence of progressive and debilitating disease during the interval immediately preceding death?			
a. rising PSA	YES NO	If yes, PC death.	Lab data
b. worsening bone scan	YES NO	If yes, PC death.	NLP-radiology
c. pathological fractures	YES NO	If yes, PC death.	EMR-Diagnoses
d. requiring blood transfusions	YES NO	If yes, PC death.	EMR- Diagnoses
e. increasing pain	YES NO	If yes, PC death.	NLP-clinic notes
f. increasing narcotic requirements	YES NO	If yes, PC death.	Pharmacy data
h. renal failure due to ureteral obstruction	YES NO	If yes, PC death.	EMR Diagnoses
g. enrolled in hospice	YES NO	If yes, PC death.	EMR
If all of a through g are no, go to 5.			
5. Did subject die of a cause related to prostate cancer? Starting with the date of death and working backwards in the record, review all outpatient clinic notes and hospital summaries.			

a. urosepsis due to outlet obstruction from locally-advance prostate cancer	YES NO	If yes, PC death.	EMR- Diagnoses
b. pulmonary emboli	YES NO	If yes, PC death.	EMR- Diagnoses
c. post-operative complications of prostate surgery (1) infection (2) bleeding (3) pulmonary emboli (4) urosepsis as a post-operative complication of prostate ca. surgery	YES NO	If yes, PC death.	Diagnoses
If all are no, death was not due to prostate cancer. STOP HERE			
Was death due to prostate cancer?	YES NO		

Protocol Amendment for WEUSKOP5723: 5ARI and Prostate Cancer Mortality Study

The primary analysis for WEUSKOP5723 has been completed. The objective of this analysis was to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

As background, the rationale for this study was to further explore a safety issue arising in a GSK clinical trial of dutasteride, a 5-alpha-reductase inhibitor (5ARI). The potential role of 5ARIs to reduce the risk of prostate cancer by blocking the conversion of testosterone to dihydrotestosterone was the basis for two large randomized controlled trials. The results of the Prostate Cancer Prevention Trial (PCPT), conducted by Merck, and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, conducted by GSK, demonstrated that finasteride (also a 5ARI) and dutasteride, respectively, significantly reduce the risk of prostate cancer compared to placebo. However, there was a greater proportion of high grade tumors (HGT) observed in the 5ARI groups in both studies compared to placebo. In REDUCE (Andriole et al., 2011), 29 (0.9%) patients were diagnosed with Gleason 8-10 tumors in the dutasteride arm, compared with the placebo arm (n = 19, 0.6%; p = 0.15) over 4 years, with the most pronounced treatment group difference in REDUCE in years 3 and 4 (0.5% versus <0.1%, p = 0.003).

The GSK AVODART™ Team evaluated the appropriateness of an observational study among men who use 5ARIs for symptoms of benign prostatic hyperplasia (BPH) to measure the risk of incident HGTs compared to risk in non-users. In consultation with internal and external experts, the team subsequently concluded that such a study would not be feasible: there is no other drug as a comparator drug that has similar effects on screening, detection, and biology as 5ARIs, resulting in several biases:

- 5ARIs lower PSA levels, potentially differentially affecting prostate cancer screening patterns in that men on 5ARIs may receive closer monitoring of their PSA levels and therefore may be more likely to be diagnosed with prostate cancer;
- 5ARIs lower prostate volume, potentially differentially affecting biopsy accuracy (having a smaller prostate may increase the likelihood of having a tumor diagnosed);
- 5ARIs are reported to preferentially affect Gleason pattern 3 over pattern 4 and 5 prostate cancer, potentially differentially affecting Gleason score read-out and distribution.

The concern regarding HGTs is their higher aggressiveness potential and risk of poorer disease related outcomes, and this study was therefore designed to provides evidence as to whether patients who use 5ARIs have a greater likelihood of dying from prostate cancer. The outcome of prostate cancer mortality allows for an assessment of whether the relative frequency of high grade tumors among 5ARI versus alpha-blocker users translates into a difference in prostate cancer related mortality. This study assessed the association between 5ARI use, with or without alpha-blockers, and prostate cancer mortality in men treated with BPH medications.

The cohort study described above only included 1,092 prostate cancer related deaths. There were a total of 1,740 prostate cancer related deaths occurring in the overall eligible cohort. A large number of prostate cancer related deaths (648) were not included in the cohort study as suitable matches could not be found for all eligible patients. Given concerns about potential biases resulting from the exclusion of these 648 prostate cancer related deaths, a nested case control study will be conducted within the study cohort to maximize the number of prostate cancer deaths included in the analysis.

This protocol amendment describes a nested case control study within the cohort of patients selected for the cohort study with the goal of maximizing the number of prostate cancer related deaths included in the analysis.

I have included below a portion of the abstract from the draft final report for the cohort study for further context concerning the design of the cohort study:

Rationale and background: Results from two clinical trials suggest that the use of 5-alpha reductase inhibitors (5ARI) for benign prostatic hyperplasia (BPH) reduces the risk of prostate cancer. However, in both of these studies, the number of high-grade cancers identified among 5ARI users was increased compared to the placebo group. It remains unknown whether this increase in aggressive disease translates to an increase in the subsequent risk of prostate cancer death.

Purpose: Therefore, the purpose of this study is to evaluate the risk of prostate cancer mortality associated with the use of 5ARIs when compared to the use of alpha-blockers (AB) for treatment of benign prostatic hyperplasia.

Study Design/Setting/Subjects: A retrospective matched cohort study of 158,318 male members of 4 managed care organization health plans that initiated BPH treatment between 1992 and 2008. Of the 391,107 men who first used BPH medications between 1992 and 2008, men less than 50 years old (N=54,119) and those who were not members for at least 1 year prior to baseline (N=55,954) were excluded. Men with a diagnosis of prostate cancer prior to drug initiation or within 3 months after initiation or who were taking 1 mg finasteride for alopecia or who had less than 3 consecutive prescriptions for BPH/LUTS medications were also excluded (N=67,104), leaving 213,930 men eligible for inclusion. Men who used a 5ARI were matched using risk-set sampling 1:6 to alpha-blocker users on age, race, timing of BPH medication initiation, prior history of AB use and health plan region. Of the 213,390 eligible men, 74% were successfully matched resulting in an analytic sample of 158,318 men with 176,265 records. Men were then passively followed via electronic health records through the end of 2010 for death due to prostate cancer (N=1,092), as identified via state death records, social security index and national death index matches. Use of 5ARI and/or alpha-blockers was collected via electronic pharmacy records.

Analysis: Person-time at risk was calculated from the time of 5ARI medication initiation (or index date in AB user) to death due to prostate cancer (event), death due to other causes, loss to follow-up

(disenrollment from health plan) or end of study period. Subdistribution proportional hazards regression was used (Fine and Gray 1999) to estimate the incidence of prostate cancer death comparing 5ARI use to AB use, after adjustment for age, race, region, medication initiation year, history of AB use, Charlson score, history of cardiovascular disease, high blood pressure, hyperlipidemia, diabetes, other cancer and use of other medications to treat OAB [over-active bladder] or ED [erectile dysfunction] and accounting for competing risk of death due to other causes.

Nested Case-Control Study

Background

The recently completed matched retrospective cohort study, designed to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications, included 1,092 prostate cancer related deaths. There were a total of 1,740 prostate cancer related deaths occurring in the overall eligible cohort (n=213,930). A large number of prostate cancer related deaths (648) were not included in the cohort study as suitable matches could not be found for all eligible patients treated with the two medications of interest.

Given concerns about potential biases resulting from the exclusion of these 648 prostate cancer related deaths, a nested case control study will be conducted within the study cohort to maximize the number of prostate cancer deaths included in the analysis.

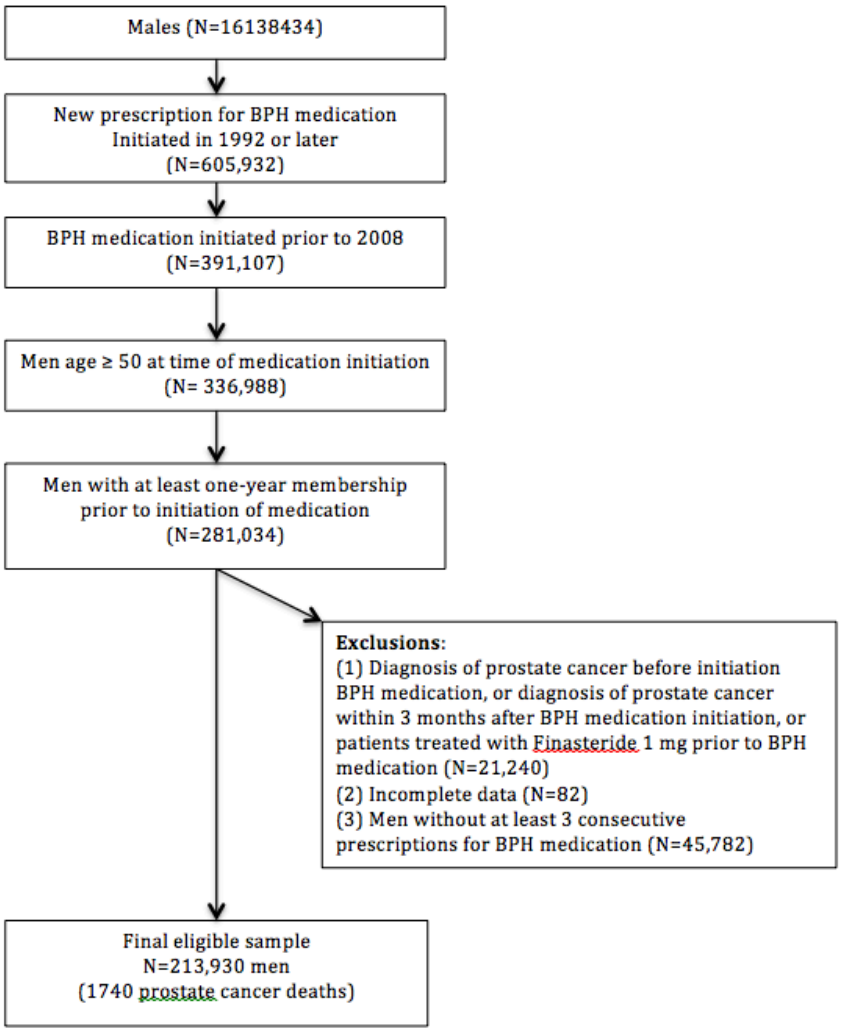
Objective

The nested case control study has the same goal as the cohort study, namely, to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

Sample:

- 213,930 men in the cohort after exclusions but prior to exposure matching (insert revised flow chart)

Flow-chart:



Methods:

- Matching
    - Match each of the 1,740 men who died of prostate cancer (based on underlying COD) (Cases) to 10 men who were sampled from the risk set as not a prostate cancer death (controls) to maximize the number of prostate cancer deaths successfully matched as cases.
        - Matching window of +/- 1 year will first be attempted and expanded as needed

- Allowing for a variable number of controls will also be explored to try and maximize the sample included in this analysis. This will be balanced against making sure that we do not lose any cases due to unsuccessful matching.

- Match men on following characteristics:
  - Age at prostate cancer death
  - Race (African American vs. Other)
  - Region
    - Within and across region matching will be explored as needed

- Use density (risk-set) sampling to match controls such that they are alive at the time the case is selected
  - As long as controls are alive on the first day of the sampling window, they are eligible to be picked as a control (regardless if they go on to die during window of other causes)
  - A man who is selected as a control is eligible to later become a case and his exposure status will be assessed at each matching time point.

- Exposure

  - Men who ever had at least 3 consecutive prescriptions for a 5ARI or an alpha-blocker (based on exclusions) will be included (without gaps).
    - 5ARI exposure will be defined as men who have ever taken a 5ARI and compared to AB. For men who switch back to an AB after the 5ARI, they would still be defined as 5ARI exposed.
    - A man's exposure status will be defined at the time he is selected for matching. All exposure history up until the time of matching will be used to define the man as a 5ARI or alpha-blocker user.

  - Trends with increasing time on medications will be explored by stratifying by increasing cumulative exposure
    - Cumulative exposure will be defined from the start of AB in the men who only use an AB and from the start of 5ARI in men who either are combo users or who are 5ARI only users.
    - The distribution of cumulative exposure and number of prescriptions will be assessed and descriptively compared between cases and controls.

  - Dose response will be explored by stratifying by increasing categories of dose
    - Dose will be calculated from the start of AB in the men who only use an AB and from the start of 5ARI in men who either are combo users or who are 5ARI only users.

  - Recency and latency will also be assessed, similar to how it was done in the cohort analysis.
    - <u>Latency:</u> We will stratify the data using different latency periods to be defined based on the distribution of time from BPH treatment exposure to detection of cancer seen in the data set.

- Recency: 98% of men died while taking one of the medications so recency would only be assessed in a 2% sample of men who were not on medications at the time of their death.

Covariates

- The same covariates as defined in the primary analysis will be included in this study (see list below), but the timing of collection will now be at time of initiation of first BPH medication (prostate cancer death or index date in controls)
    - PSA will be the only covariate defined at the time of diagnosis among the sample of men who have a diagnosis.

i. Race/ethnicity

Race and ethnicity is collected across sites and based on a race and ethnicity variable that is categorized as: Non-Hispanic White, African American, Asian and Hawaiian/Pacific Islander, Native Alaskan/American Indian, Multiple, and Unknown. Race categories will be collapsed to be African American vs. Other for matching.

ii. Age at matching (death/index date)

Age will be calculated from date of birth and reflected as age at treatment initiation.

iii. Socioeconomic status (SES)

Aggregate SES measures for [redacted] members were calculated via geocoding using 2000 US census estimates at the block, block-group, tract and ZIP level and include income and education.

iv. PSA

PSA is available through our laboratory data in the Virtual Data Warehouse and is measured in ng/mL. Baseline PSA is defined at the time of prostate cancer diagnosis for the subset of men who have a diagnosis during our study period.

v. BMI

BMI was not routinely collected as a vital sign until the implementation of the electronic medical record in each site (mid 2000s) Therefore, only a few years of complete data may be available. It is calculated using standard formula and measured in kg/m2.

Due to the paucity of BMI data, it will only be used in sensitivity analyses where the effect of BMI on the association of interest will be investigated.

vi. Charlson Comorbidity Index

Charlson comorbidity Index is collected based on ICD-9 codes of the included conditions/complications and a standard algorithm and coding macro are used to derive the score which is usually categorized into (0, 1 or 2+).

vii. CVD Endpoints

- History of cardiovascular disease: ICD-9 410.x-429.x
- History of high blood pressure/hypertension: ICD-9 codes (401.x) *and/or* dispense of blood pressure medications
- History of diabetes (HEDIS definition): dispensing record for insulin or an oral hypoglycemic from the HEDIS list (not including metformin) *or* any discharge ICD-9 code of 250.xx, 357.2, 362.0, 366.41, 648.0, *or* hemoglobin A1C >= 7.0%.)

viii. Overactive Bladder and Erectile Dysfunction medications

- Any medications used to treat either overactive bladder and/or erectile dysfunction including PED-5 inhibitors and anti-cholinergic as identified through [redacted] formulary.

- History of hyperlipidemia : Any dispense of statin medications *and/or* any abnormal lipid profile test:

  Total cholesterol (>200 mg/dL),

  HDL (<= 40 mg/dL)

  LDL (>130 mg/dL),

  Triglycerides (>150 mg/dL)

ix. History of Cancer – Other than Prostate

History of cancer at major sites other than the prostate will be determined by icd9 codes.

Potential confounding factors over the follow-back period:

Additionally information on several variables occurring over the follow-back period will be collected including:

- PSA testing patterns after treatment initiation and over the course of the study period.
- The frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.
- Gleason Score at diagnosis and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.
- Frequency of prostate cancer treatment paradigms (radical prostatectomy, external beam radiation, brachytherapy, cryotherapy, etc.)

Confounding factors that occur over the follow-up will not be adjusted for in regression analyses, as they may be in the causal path between exposure and outcome. These confounders will be described by exposure and case-control status.

Potential effect measure modifiers for consideration:

- Race/ethnicity
- Age
- Socioeconomic status (income)
- PSA level at diagnosis (among sample who have a prostate cancer diagnosis)

Power calculations:

, A 5ARI exposure incidence of 14% and the number of estimated outcomes (cases) (N=1740 prostate cancer deaths) to be included were drawn from the underlying eligible cohort identified in the cohort study. The statistical power was then estimated for varying magnitudes of odds ratios and for increasing ratios of matching (1:4 through 1:20 were explored. The statistical power was found to be near to maximimum at a 1:10 ratio, which will give us 87% power to rule out an odds ratio of 1.25, as was used in the cohort analyses power calculations.

Odds Ratio	Power
0.80	0.81
0.90	0.27
1.10	0.27
1.20	0.71
1.25	0.87

Statistical Analysis:

- **Distribution of demographic, medical history and prostate cancer charactateristcs (among those diagnosed) will be compared across case and control groups**
    - **For categorical variables, differences in the distribution across case/control status will be assessed using chi-square tests for association.**
    - **For continuous variables, differences in the distribution across case/control status will be assessed using two sided t-tests.**

- Matched analysis using conditional logistic regression
    - Adjustment for factors found to be imbalanced by case/control groups and a priori identified confounders (see covariate section above). Sensitivity analysis breaking pairs and using unconditional logistic regression as a comparison.

- Stratified analyses by PSA (in sample with data), Gleason score (in sample with data), timing of prostate cancer diagnosis, history of AB use, drug dose and duration.

Sensitivity analyses

The following sensitivity analyses will be run to further our understanding about the biases that may be present in the initial retrospective cohort analysis as well as this case-control analysis.

- Run case-control sensitivity analyses where we define cases as follows:

1. 1092 deaths that were in the matched cohort sample
    a. This will allow for a more direct comparison with the retrospective cohort results.

2. 648 deaths that were in the case-control study but not in the matched cohort study
    a. This will allow us to understand the bias that may have resulted from excluding these deaths in the cohort study

Interpretation of study results:

The overall case-control results and those from the above sensitivity analyses will be compared to those of the retrospective cohort analysis to determine whether they differ and if so, to what magnitude. This will be done by comparing the odds ratio from the case-control analyses (including sensitivity results) to the HRs from the cohort analysis, as the rare disease assumption is met and risk-set sampling was employed to ensure comparability of the results. This will allow us to further our understanding about the biases present in the cohort analysis and/or confirm our results from that analysis.

Table 1A: Distribution and crude association of exposure, demographic and clinical characteristics and prostate cancer death *before* matching*

	Overall (n=213930)	Prostate cancer deaths[1]	No prostate cancer death	p-value
Characteristic				
Exposure Alpha Blocker only Any 5ARI use (≥ 3 scripts)				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Asian Hawaiian, PI, Multiple, Unknown				
Socioeconomic Status Missing (%) Median household income ($1000) (mean (sd), median) Education Less than 9th grade 9th-12th grade High school graduate Some college, no degree Associate degree Bachelor degree Graduate or professional degree				
History of AB use (years (mean, (SD), median)				
PSA at treatment initiation (ng/mL) Missing (%) (mean (sd), median)				
BMI at treatment initiation (kg/m2) (%) Missing (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1				

2+				
History of cardiovascular disease (Yes)				
History of high blood pressure (Yes)				
History of hyperlipidemia (Yes)				
History of diabetes (Yes)				
History of cancer (Yes)				
Use of other medications to treat ED or OAB[2] (Yes)				

*Characteristics are defined at the start of first BPH medication.

Table 1B: Distribution and crude association of demographic and clinical characteristics by drug exposure group *before* matching*

	Overall (n=213930)	5ARI users	Alpha-blocker users	p-value
Characteristic				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Asian HP,IN,MU and UN				
SES Missing (%) Median household income ($1000) (mean (sd), median) Education Less than 9th grade 9th-12th grade High school graduate Some college, no degree Associate degree Bachelor degree Graduate or professional degree				
PSA at treatment initiation Missing (%) PSA level (mean (sd), median)				
BMI at treatment initiation (kg/m2) (%) Missing <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Yes)				
History of high blood pressure (Yes)				
History of hyperlipidemia (Yes)				
History of diabetes (Yes)				
History of cancer (Yes)				
Use of other medications to treat ED or OAB (Yes)[1]				

*Characteristics are defined at the of start of first BPH medication..

Table 1C: Distribution and crude association of exposure, demographic and clinical characteristics and prostate cancer death *before* matching among unmatched men*

	Overall (n=)	Cases (Prostate Cancer Death)	Controls	p-value
Characteristic				
Age at matching (mean (sd), median)				
Age at matching (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Asian Hawaiian, PI, Multiple, Unknown				
Socioeconomic Status Missing (%) Median household income ($1000) (mean (sd), median) Education Less than 9th grade 9th-12th grade High school graduate Some college, no degree Associate degree Bachelor degree Graduate or professional degree				
PSA at diagnosis (ng/mL) Missing (%) (mean (sd), median)				
BMI at treatment initiation (kg/m2) (%) Missing (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Yes)				
History of high blood pressure (Yes)				
History of hyperlipidemia (Yes)				
History of diabetes (Yes)				
History of cancer (Yes)				
Use of other medications to treat ED or OAB[1] (Yes)				

*Characteristics in this table are defined at the time of first BPH treatment initiation.. The exception is PSA which is defined at the time of diagnosis for men with a prostate cancer diagnosis during follow-up.

Table 2A: Distribution and crude association of demographic and clinical characteristics by case/control status *after* matching

	Overall (n=176265)	Cases (prostate cancer deaths)	Controls	p-value
Characteristic				
BPH initiation calendar year (%) 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007				
Exposure Alpha Blocker users 5ARI users				
Age at matching (mean (sd), median)				
Age at matching (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Asian Hawaiian, PI, Multiple, Unknown				
Socioeconomic Status Missing (%) **Median household income ($1000)** (mean (sd), median) **Education** Less than 9th grade 9th-12th grade High school graduate Some college, no degree Associate degree				

Bachelor degree Graduate or professional degree				
PSA at diagnosis Missing (%) **PSA level (ng/mL)** (mean (sd), median)				
PSA % 0-2.5 2.5-4 >=4				
BMI (kg/m2) (%) Missing (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Yes)				
History of high blood pressure (Yes)				
History of hyperlipidemia (Yes)				
History of diabetes (Yes)				
History of cancer (Yes)				
Use of other medications to treat ED or OAB2 (Yes)				
Alpha Blocker history (years) [1] (mean (sd), median)				

*Characteristics in this table are defined at the time first BPH medication initiation. The exception is PSA which is defined at the time of diagnosis for men with a prostate cancer diagnosis during follow-up and the matching factors.

Table 2B: Distribution and crude association of demographic and clinical characteristics by drug exposure group *after* matching

	Overall (n=176265)	5ARI users	Alpha-blocker users	p-value
Matching Criteria				
BPH initiation calendar year (%) 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007				
Race (matching categories) African American All other races				
Region [redacted]				
Exposure and Follow-up				
Cumulative exposure time, years (mean (sd), median)[1]				
Follow-up time (years), from drug initiation to matching/index				
At-matching Characteristics				
Age (mean (sd), median)				

Age (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Asian HP,IN,MU and UN				
PSA Missing (%) PSA level (mean (sd), median)				
PSA (%) 0-2.5 2.5-4 >=4				
SES Missing (%) Median household income ($1000) (mean (sd), median) Education Less than 9th grade 9th-12th grade High school graduate Some college, no degree Associate degree Bachelor degree Graduate or professional degree				
Alpha Blocker history (years) (mean (sd), median)				
BMI (kg/m2) (%) Missing (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Yes)				
History of high blood pressure (Yes)				
History of hyperlipidemia (Yes)				

History of diabetes (Yes)				
History of cancer (Yes)				
Use of other medications to treat ED or OAB2 (Yes)				

Table 3: Characteristics during follow-up by case/control status

	Overall	Cases	Controls	p-value
Characteristics				
Cumulative exposure time, years (mean (sd), median) AB users 5ARI users				
Cumulative dose (gram)[2] AB users 5ARI users				
Duration of follow-up time, years (mean (sd), median) AB users 5ARI users				
Patients with ≥1 PSA test (%)				
Number of PSA tests (mean (sd), median)				
Patients with >=1 biopsy (%)				
Number of Biopsies (mean (sd), median)				
Prostate cancer diagnoses (%) Overall AB users 5ARI users				
Follow-up time in those diagnosed with prostate cancer pre 5ARI initiation, years (mean (sd), median)				
Follow-up time in those diagnosed post-5ARI initiation, years (mean (sd), median)				
Follow-up time (initiation to death or index date), years (mean (sd), median)				
Age at diagnosis (%) <60 60-69 70+				
Gleason score at diagnosis (n (%)) Missing <=6 7 8-10				
Stage at prostate cancer diagnosis Missing I				

II III IV				
Bone scan at diagnosis (%) (within 6 months)				
Other tests for metastatic disease at diagnosis (%) (within 6 months)				
Prostate cancer primary treatment within 6 months of diagnosis (%)[2] Surgery Radiation therapy None				
Follow-up time after cancer, years (mean (sd, median)				
Prostate cancer diagnosed time since last exposure to BPH medication				

Table 4: Characteristics of men missing PSA level vs those who are not missing PSA level at time of prostate cancer diagnosis

	Overall	Without PSA data at matching	With PSA data at matching	p-value
Characteristic				
Age at matching (mean (sd), median)				
Age at matching (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Asian Hawaiian, PI, Multiple, Unknown				
Socioeconomic Status Missing (%) **Median household income ($1000)** (mean (sd), median) **Education** Less than 9th grade 9th-12th grade High school graduate Some college, no degree Associate degree Bachelor degree Graduate or professional degree				
BMI (kg/m2) (%) Missing (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Yes)				
History of high blood pressure (Yes)				
History of hyperlipidemia (Yes)				
History of diabetes (Yes)				
History of cancer (Yes)				

Use of other medications to treat ED or OAB2 (Yes)				
Alpha Blocker history (years) [1] (mean (sd), median)				

Table 5: Crude and multivariable-adjusted matched odds ratios (MORs) comparing odds of prostate cancer death among 5ARI users compared to AB users and stratified by third variables of interest.

	Cases N (%)		Controls N (%)		Crude MOR (95% CI)	Adjusted MOR (95% CI)
	5ARI	AB	5ARI	AB		
Overall						
Cumulative exposure[1] 3 mo-<1 yr 1-<2 yrs 2+ years						
Cumulative dose (gram)[1] Q1 Q2 Q3 Q4						
Latency < 1 yr 1-3yr 3-6 yr 6-9 yr 9+ yr						
PSA at matching >10 <10						
History of AB use Q1 Q2 Q3 Q4						
Age at matching <60 60-69 70+						
Race Non-Hispanic White African American Asian Other (HP, IN, MU and UN)						

[redacted]

Treatment for Lower Urinary Tract Symptoms and Prostate Cancer Mortality

Analytic Plan

Table of Contents

[redacted]

[redacted]

I. Study Description

The study will use a retrospective cohort design with data from four [redacted] sites collected from electronic health records and data abstracted from paper records from 1992-2010. Men treated with benign prostatic hyperplasia (BPH) medications, 5-alpha reductase inhibitors (5ARIs) (with and without concomitant and/or previous alpha-blocker use) will be compared to men treated with alpha-blockers. The main objective of this study is to assess the risk of prostate cancer mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.. This study will also assess a number of secondary endpoints including the combined endpoint of prostate cancer mortality or metastatic prostate cancer, and all-cause mortality, as well as a number of descriptive analyses.

II. Sample size considerations

A. Power calculations:

1. Assuming a hazard ratio of 1.0, 90% power and a 0.05 two sided alpha we would need approximately 850 deaths to rule out a hazard ratio of 1.25 or higher. This calculation is based on equation 2 in the article by Saville et al (Saville et al, 2011) and assumes a 1:1 ratio of patients across treatment groups. A 25% increase in risk of prostate cancer is thought to be a signal of concern. While this study is designed to detect any difference (increase or decrease) in risk between 5ARI and alpha-blocker users, given the potential limitations of power in this study, if a difference in risk is not found between the exposure groups, this will not be interpreted to rule out an increased risk of prostate cancer related mortality associated with the use of 5ARIs. If no increased risk is found for 5ARI users compared to alpha-blocker users, this result will add to the body of evidence used to interpret the findings from the REDUCE trial of an increased number of HGTs in the dutasteride arm compared to the placebo arm. A recent analysis of long term follow-up data from the PCPT found no increased risk of all-cause mortality for men exposed to finasteride versus placebo (adjusted HR: 1.03 (0.98,1.09)) and all-cause mortality among men diagnosed with prostate cancer (adjusted HR: 0.93 (0.78,1.12)) (Thompson et al, 2013). This study will extend the findings from Thompson et al by examining the risk of prostate cancer related mortality among men exposed to 5ARIs.

[redacted]

[redacted]

2. Based on the feasibility assessment using [redacted] data, the allocation of patients across treatment groups (alpha-blocker:5ARI) is expected to be 5.4:1. With this unequal allocation of patients in the exposed and unexposed groups an adjustment must be made to the sample size calculation. Using the adjustment suggested by Saville et al with the same assumptions for power, approximately 1,500 prostate cancer related deaths (214 in the 5ARI exposed group and 1,286 in the alpha-blocker only group) are needed to rule out a HR of 1.25 or higher. This calculation assumes a 6:1 allocation of unexposed (alpha-blocker) vs. exposed (5ARI) and equal risk in both exposure groups.

3. The target of 1,500 deaths should be reached by pooling data across four [redacted] sites. 846 deaths were observed in the feasibility study. Roughly the same number of deaths from [redacted] can be expected and about 15% of this amount from [redacted] and [redacted] yielding an estimated total number of deaths of 1,946. When these prostate cancer related deaths are validated it is estimated that up to 25% of them will be reclassified as non-prostate cancer related which will yield approximately 1,500 prostate cancer related deaths.

4. Based on feasibility data from [redacted] we expect there to be approximately 284,000 men eligible for inclusion in the study. As mentioned above, there were 846 prostate cancer related deaths observed in the feasibility study resulting from a population of 123,503 men yielding an event rate of 0.7% (846/123,503). Dividing the expected number of deaths, 1500, by the event rate results in a target sample size of 218,977 men. If we assume that the ratio of alpha-blocker:5ARI users will be the same in the overall study sample (5.4:1) as in the feasibility study, then we would expect to have 34,215 5ARI users and 184,762 alpha-blocker users in our study.

5. There will be a pool of approximately 249,785 alpha-blocker users from which 184,762 matches will be selected for the 5ARI users in this study. As 74% of the available matches will need to be included in the study sample to meet the target sample size of 218,977 men, there may be some difficulties in finding 5 to 6 appropriate matches for each 5ARI patient. Therefore some deaths among alpha-blocker users may not be included in the study. To address this potential issue matching criteria may be relaxed to increase the windows for age, timing of treatment initiation, and duration of alpha-blocker (e.g. from ± 1 year to ± 2 years). Also, propensity score matching may be considered as an alternative if a suitable number of matches can't be identified.

[redacted]

[redacted]

6. Additionally, sample size calculations have been performed assuming power of 80% and 85%. Under the scenario of 85% power, and a 0.05 two sided-alpha we would need approximately 1262 deaths to rule out a hazard ratio of 1.25. Under the scenario of 80% power, and a 0.05 two sided-alpha we would need approximately 1099 deaths to rule out a hazard ratio of 1.25.

Power	Allocation ratio of 5ARI users to alpha blocker users	Number of prostate cancer related deaths
90	1/5	1314
	1/6	1474
85	1/5	1125
	1/6	1262
80	1/5	980
	1/6	1099

[redacted]

[redacted]

III. Pre-treatment variable definitions

A. The following pre-treatment variables will be summarized based on the 1-year pre-treatment period for all study participants. Pre-treatment variables will be considered for inclusion in Cox proportional hazard regression models and as stratification variables in the analysis phase of the study. Additionally, age and race/ethnicity will be used as matching factors in this study.

1. Race/Ethnicity

   Race and ethnicity is collected across sites and based on a race and ethnicity variable that is categorized as: Non-Hispanic Whites, African Americans, Hispanic, Asian/Pacific Islander, Other and Missing.

2. Age

   Age will be calculated from date of birth.

3. Socioeconomic status (SES)

   Aggregate SES measures for [redacted] members were calculated via geocoding using 2000 US census estimates at the block, block-group, tract and ZIP level and include income and education.

4. PSA

   PSA is available through our laboratory data in the Virtual Data Warehouse and is measured in ng/mL.

5. BMI

   BMI was not routinely collected as a vital sign until the implementation of the electronic medical record in each site (mid 2000s) Therefore, only a few years of complete data may be available. It is calculated using standard formula and measured in kg/m2.

      Because of the high level of missingness of BMI, it will only be used in sensitivity analyses where the effect of BMI on the association of interest will be investigated.

6. Charlson Comorbidity Index

[redacted]

[redacted]

Charlson comorbidity Index is collected based on ICD-9 codes of the included conditions/complications and a standard algorithm and coding macro are used to derive the score which is usually categorized into (0, 1 or 2+).

7. CV endpoints

Data from diagnosis, lab, and pharmacy are available to define any of these endpoints.

- History of cardiovascular disease
    - ICD-9 410.x-429.x
- History of high blood pressure/hypertension
    - ICD-9 codes (401.x) *and/or*
    - Dispense of blood pressure medications
- History of diabetes (HEDIS definition)
    - dispensing record for insulin or an oral hypoglycemic from the HEDIS list (not including metformin) *or*
    - any discharge ICD-9 code of 250.xx, 357.2, 362.0, 366.41, 648.0, *or*
    - hemoglobin A1C >= 7.0%.
- History of hyperlipidemia
    - Any dispense of statin medications *and/or*
    - Any abnormal lipid profile test:
        - Total cholesterol (>200 mg/dL),
        - HDL (<= 40 mg/dL)
        - LDL (>130 mg/dL),
        - Triglycerides (>150 mg/dL)

[redacted]

8. History of cancer other than prostate

History of cancer at major sites other than the prostate will be determined by icd9 codes.

IV. Cohort Selection

A. Inclusion/Exclusion Criteria

1. INCLUSION CRITERIA:
    - Male
    - A new prescription for BPH medication (5ARI and/or alpha-blocker) in 1992 or later that is identified as appropriate treatment for BPH/LUTS from the [redacted] National Pharmacy guidelines.(i.e exclude men with a previous Rx for BPH/LUTS prior to 1992)
    - Treatment with BPH medication must be initiated prior to Jan1, 2008.
    - Age 50 years or older at time of treatment with 5ARI or alpha-blocker.
    - At least 1-year of coverage in the healthcare system before the first prescription for BPH medication (5ARI and/or alpha-blocker).
    - At least 3 consecutive prescriptions (90 days of supply) for a BPH medication (5ARI and/or alpha-blocker). (To be applied once all regions data are compiled)
        - Concomitant and consecutive 5ARI users are also required to have at least 3 months cumulative exposure or at least 3 consecutive 5ARI prescriptions.
        -

2. EXCLUSION CRITERIA:
    - Diagnosis of prostate cancer any time before prescription for BPH medication (5ARI and/or alpha-blocker).
        - In combination users (5ARI+ alpha-blocker) or consecutive users who initiate with an alpha-blocker and subsequently switch to a 5ARI, diagnosis of prostate cancer cannot have occurred before initiation of 5ARI treatment .
    - Diagnosis of prostate cancer within 3 months after BPH medication (5ARI and/or alpha-blocker)
        - In combination users (5ARI+ alpha-blocker) or consecutive users who initiate with an alpha-blocker and subsequently switch to a 5ARI,

[redacted]

diagnosis of prostate cancer cannot have occurred within 3 months after initiation of 5ARI treatment .

- Patients treated with finasteride 1mg prior to BPH medication. Finasteride 1mg is the dose approved for androgenic alopecia and as the target population for this study is men with treated BPH, we will exclude all men treated with the 1mg dose. Patients treated with 1mg Finasteride will be characterized in terms of which study exposure group they would have transitioned into (5ARI or alpha-blocker) had they been included in the study population, and basic baseline demographic factors.

[redacted]

[redacted]

V. Exposures

A. Definitions

1. Exposure will be based upon the treatment administered for BPH. Patients must have at least 3 consecutive prescriptions (90 days of supply) for either a 5ARI or alpha-blocker product to be considered exposed.

2. The assumption that prescriptions for either a 5ARI or alpha-blocker are in fact for 30 days of supply will be checked. The distribution of duration of prescriptions for the drugs included as exposure variables will be examined to determine whether or not this inclusion criteria will need to be modified.

3. The following medications will be included in the analysis and the data will be queried using medication name (brand and generic):5 ARI(s): **Finasteride (5mg) or Dutasteride**

   a) **Including** Combination Treatment: **Jalyn (fixed dose combination with tamsulosin)**, or any combination of 5ARI & alpha-blocker either concurrently or consecutively. Jalyn was not launched until 2010. So, this medication will be included to capture any patients who have initiated BPH therapy prior to 2008 and switch to fixed dose combination therapy over the course of the study.

   b) Use of medications indicated for androgenic alopecia (Finasteride 1mg) will be identified in the data source to allow for exclusion of patients treated for alopecia.

4. Selective alpha 1 blocker (s)/alpha-adrenergic blocking agent(s): **Alfuzosin, Doxazosin, , Silodosin, Tamsulosin, Terazosin.** Prazosin was indicated for BPH treatment according to [redacted] formulary during the study period, but is not currently indicated. We will examine the utilization of Prazosin over the study period and determine whether patients taking this medication should be excluded from the analysis.

[redacted]

[redacted]

Alpha-Blockers	
GENERIC NAME	BRAND NAME
ALFUZOSIN HCL	ALFUZOSIN HCL ER TAB 10MG
ALFUZOSIN HCL	UROXATRAL TAB 10MG
DOXAZOSIN MESYLATE	CARDURA 1MG TABLET
DOXAZOSIN MESYLATE	CARDURA 2MG TABLET
DOXAZOSIN MESYLATE	CARDURA 4MG TABLET
DOXAZOSIN MESYLATE	CARDURA 8MG TABLET
DOXAZOSIN MESYLATE	CARDURA TAB 1MG UD
DOXAZOSIN MESYLATE	CARDURA TAB 2MG UD
DOXAZOSIN MESYLATE	CARDURA TAB 4MG UD
DOXAZOSIN MESYLATE	CARDURA TAB 8MG UD
DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 1MG
DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 2MG
DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 4MG
DOXAZOSIN MESYLATE	DOXAZOSIN MESYLATE TAB 8MG
PRAZOSIN HCL	MINIPRESS 1MG CAPS UD
PRAZOSIN HCL	MINIPRESS 1MG CAPSULE
PRAZOSIN HCL	MINIPRESS 1MG CAPSULES
PRAZOSIN HCL	MINIPRESS 2MG CAPS UD
PRAZOSIN HCL	MINIPRESS 2MG CAPSULE
PRAZOSIN HCL	MINIPRESS 5MG CAPS UD
PRAZOSIN HCL	MINIPRESS 5MG CAPSULE
PRAZOSIN HCL	MINIPRESS CAP 1MG
PRAZOSIN HCL	MINIPRESS CAP 1MG UD
PRAZOSIN HCL	MINIPRESS CAP 2MG
PRAZOSIN HCL	MINIPRESS CAP 2MG UD
PRAZOSIN HCL	MINIPRESS CAP 5MG
PRAZOSIN HCL	MINIPRESS CAP 5MG UD
PRAZOSIN HCL	PRAZOSIN 1MG CAP
PRAZOSIN HCL	PRAZOSIN 1MG CAPSULE
PRAZOSIN HCL	PRAZOSIN 1MG STARTER KIT
PRAZOSIN HCL	PRAZOSIN 2MG CAP
PRAZOSIN HCL	PRAZOSIN 2MG CAPSULE
PRAZOSIN HCL	PRAZOSIN 5MG CAP
PRAZOSIN HCL	PRAZOSIN 5MG CAPSULE
PRAZOSIN HCL	PRAZOSIN HCL CAP 1MG
PRAZOSIN HCL	PRAZOSIN HCL CAP 1MG UD
PRAZOSIN HCL	PRAZOSIN HCL CAP 2MG
PRAZOSIN HCL	PRAZOSIN HCL CAP 2MG UD
PRAZOSIN HCL	PRAZOSIN HCL CAP 5MG
PRAZOSIN HCL	PRAZOSIN HCL CAP 5MG UD
PRAZOSIN HCL	PRAZOSIN HCL PINK CAP 2MG U
PRAZOSIN HCL	PRAZOSIN HCL WHITE CAP 1MG
SILODOSIN	RAPAFLO CAP 4MG
SILODOSIN	RAPAFLO CAP 8MG
TAMSULOSIN HCL	FLOMAX 0.4MG CAP UD
TAMSULOSIN HCL	FLOMAX CAP 0.4MG
TAMSULOSIN HCL	TAMSULOSIN HCL CAP 0.4MG
TAMSULOSIN HCL	TAMSULOSIN HCL CAP 0.4MG UD
TERAZOSIN HCL	HYTRIN 10MG TABLET
TERAZOSIN HCL	HYTRIN 1MG TABLET
TERAZOSIN HCL	HYTRIN 1MG TABS UD
TERAZOSIN HCL	HYTRIN 2MG TABLET
TERAZOSIN HCL	HYTRIN 2MG TABS UD
TERAZOSIN HCL	HYTRIN 5MG TABLET
TERAZOSIN HCL	HYTRIN 5MG TABS UD
TERAZOSIN HCL	HYTRIN CAP 10MG
TERAZOSIN HCL	HYTRIN CAP 10MG UD
TERAZOSIN HCL	HYTRIN CAP 1MG

5-alpha reductase inhibitors	
GENERIC NAME	BRAND NAME
DUTASTERIDE	AVODART CAP 0.5MG
FINASTERIDE	FINASTERIDE TAB 5MG
FINASTERIDE	PROSCAR 5MG TABLET
FINASTERIDE	PROSCAR TAB 5MG
FINASTERIDE	PROSCAR TAB 5MG UD
*FINASTERIDE (ALOPECIA)**	*PROPECIA 1MGTABLET*
*FINASTERIDE (ALOPECIA)**	*PROPECIA PRO-PAK TAB PRO-PA*
*FINASTERIDE (ALOPECIA)**	*PROPECIA TAB 1MG*

Combination therapy	
GENERIC NAME	B
DUTASTERIDE-TAMSULOSIN HC	J

[redacted]

[redacted]

TERAZOSIN HCL	HYTRIN CAP 1MG UD
TERAZOSIN HCL	HYTRIN CAP 2MG
TERAZOSIN HCL	HYTRIN CAP 2MG UD
TERAZOSIN HCL	HYTRIN CAP 5MG
TERAZOSIN HCL	HYTRIN CAP 5MG UD
TERAZOSIN HCL	HYTRIN TAB 10MG UD
TERAZOSIN HCL	HYTRIN TAB 1MG
TERAZOSIN HCL	HYTRIN TAB 1MG UD
TERAZOSIN HCL	HYTRIN TAB 2MG
TERAZOSIN HCL	HYTRIN TAB 2MG UD
TERAZOSIN HCL	HYTRIN TAB 5MG
TERAZOSIN HCL	HYTRIN TAB 5MG UD
TERAZOSIN HCL	TERAZOSIN 1MG CAP
TERAZOSIN HCL	TERAZOSIN 1MG CAP STARTER K
TERAZOSIN HCL	TERAZOSIN 1MG CAP STARTER P
TERAZOSIN HCL	TERAZOSIN 2MG CAP
TERAZOSIN HCL	TERAZOSIN HCL 2MG CAP
TERAZOSIN HCL	TERAZOSIN HCL CAP 10MG
TERAZOSIN HCL	TERAZOSIN HCL CAP 10MG UD
TERAZOSIN HCL	TERAZOSIN HCL CAP 1MG
TERAZOSIN HCL	TERAZOSIN HCL CAP 1MG UD
TERAZOSIN HCL	TERAZOSIN HCL CAP 2MG
TERAZOSIN HCL	TERAZOSIN HCL CAP 2MG UD
TERAZOSIN HCL	TERAZOSIN HCL CAP 5MG
TERAZOSIN HCL	TERAZOSIN HCL CAP 5MG UD
TERAZOSIN HCL	TERAZOSIN STARTER CARD 1MG/

B. Categories:

1. Primary Analysis:

a) Any 5ARI use (at least 3 prescriptions (90 day supply)) including patients with concomitant or consecutive alpha blocker use.

b) Alpha-blocker users only (?)(at least 3 prescriptions (90 day supply)).

C. Outputs/deliverables

1. Tables describing the distribution of the duration of prescriptions for 5ARI and alpha-blocker products included in the study. A flow chart of cohort selection based on inclusion/exclusion criteria. Tables characterizing men excluded from the study based on their use of Finasteride 1mg prior to BPH medication

[redacted]

[redacted]

D. Exposure Duration

1. Duration of exposure among all 5ARI or alpha blocker users with at least 3 consecutive prescriptions (90 days supply) will begin at the start of the follow up time for each patient and will be categorized as:

   a) Any exposure

   b) < 1 year

   c) 1 - <2 years

   2 or more years

2. Follow-up time begins for each 5ARI user once they have met the inclusion criteria for having at least 3 consecutive prescriptions for a 5ARI. For alpha-blocker users matched to the 5ARI patients, follow-up time begins once they have met the inclusion criteria for having at least 3 consecutive prescriptions for an alpha-blocker within the timeframe of the 5ARI user to which they are matched (see **section VI Matching**).

3. **Cumulative Exposure:**

   a) Define drug era for each eligible man:

      (1) When the days of drug supply is available, use this info to determine whether drug use between two adjacent prescriptions are continuous;

      (2) When the days of drug supply is NOT available, assume average prescription cycle as 30 d (This was learned to be the case from previous projects – the median gap between any two adjacent prescriptions was 30 d. This assumption will be confirmed in the [redacted] data before analysis begins).

      (3) If the gap between two prescriptions is <= 30 d, count it as continuous, as one drug era. Otherwise, assume there was a gap, and start another drug era after the gap.

For men exposed to 5ARIs, cumulative exposure will reflect their time exposed to a 5ARI and concomitant or consecutive exposure to an alpha-blocker medication will not be included in the cumulative exposure time calculation. A second variable, cumulative exposure to medications, will also be calculated for men exposed to 5ARIs. Cumulative exposure to medications will reflect all time on 5ARI and alpha-blocker medications and will not double count overlapping periods of concomitant use of these medications. All primary analyses of cumulative exposure

[redacted]

will use the exposure variable based on exposure to 5ARIs only and the cumulative exposure to medications variable will serve as a potential exposure variable for sensitivity analyses.

b) Duration of one/each drug era (for each drug or drugs)

(1) If the adjacent prescription periods do NOT overlap: drug era = From 1st prescription date to "last prescription date + days of drug supply for the last prescription (30 d, if not available)" or the end of observational period, whichever comes first.

(2) If the adjacent prescription periods DO overlap: drug era = From 1st prescription date to "last prescription date + days of drug supply for the last prescription (30 d, if not available)" or the end of observational period, whichever comes first.

c) Duration of cumulative exposure = Duration of exposure for drug era 1 + Duration of exposure for drug era 2 +…. + last drug era

4. **Outputs/deliverables**: Shell tables describing the duration of cumulative exposure for patients to 5ARI and alpha-blocker medications.

[redacted]

VI. Matching

A. Matching Strategy

1. The ratio of 5ARI users to alpha-blockers users was 1:5.4 in the feasibility study. Assuming that this same ratio will be maintained in the overall study sample, we will match 5ARI:alpha-blocker patients in a 1:5.4 ratio.

2. 5ARI users will be selected from the available pool of eligible men and will be matched in a ratio of 1:5 or 1:6 with alpha-blocker users to yield an overall matching ratio of 1:5.4. Matching factors include age (+/- 1 year), timing (calendar year) of BPH treatment initiation (+/- 1 year), race, and duration of prior use of alpha-blockers (see the matching diagram below).

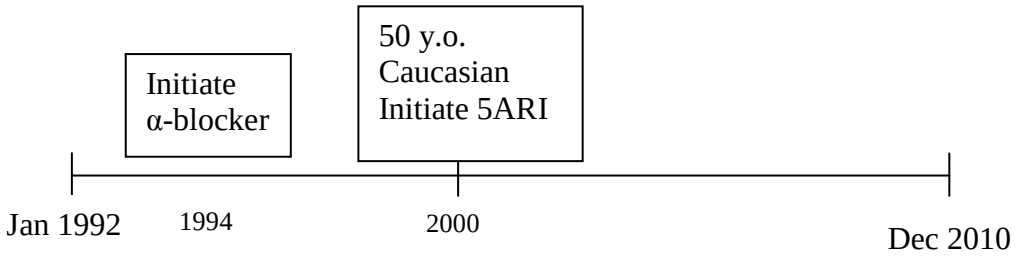
3. 5ARI patients initiating BPH treatment with a 5ARI (i.e. having no prior use of alpha-blockers) will be matched to alpha-blocker users having the same date (+/- 1 year) of alpha-blocker treatment initiation. Categories for the prior use of alpha blockers will be defined based on the distribution of the number of years of alpha-blocker use in the data. One year strata for history of alpha-blocker use will be used if the number of available matches across strata is sufficient. Matching will be conducted within [redacted] site [redacted] When a suitable match cannot be found within a study site consideration will be given to matching across sites to maximize the available sample for the study. Additionally, if it is difficult to find matches for particular participants, matching criteria may be relaxed to allow for inclusion of all eligible 5ARI men. For example, matching on year of initiation of treatment may be relaxed to (+/- 2 years) to allow for more possible matches. Also, propensity score matching may be considered as an alternative if a suitable number of matches can't be identified.

4. The current categories for race are Non-Hispanic Whites, African Americans, Hispanic, Asian/Pacific Islander, Other and Missing. It is likely that some of these categories will need to be collapsed to allow for the identification of a sufficient number of matches. The number of patients within strata of matching factors will be examined and decisions about the combination of race categories will be discussed with the study team. Men missing race will be matched to other men who are missing race as needed.

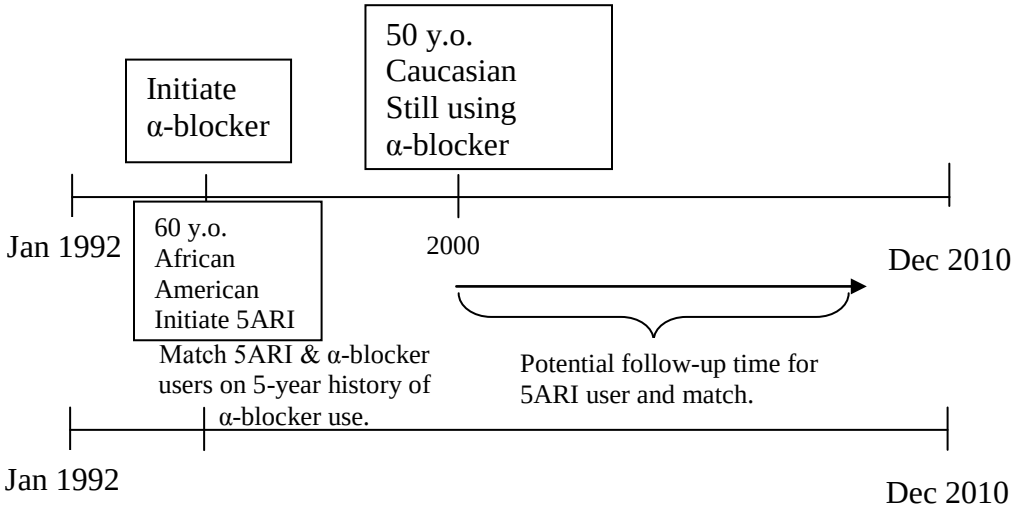
[redacted]

[redacted]

5ARI user:

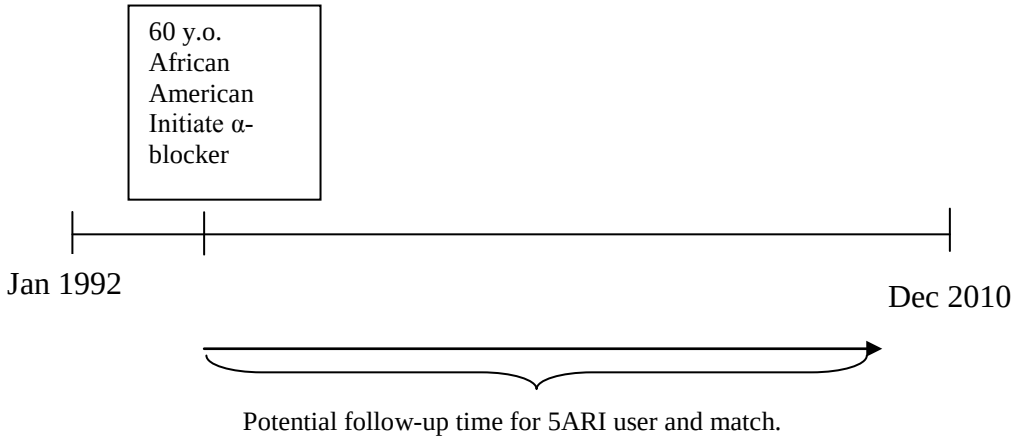


Potential match:



New 5ARI user:

Potential match:



[redacted]

B. Matching Approaches

1. Two approaches for matching will be explored:

   a) Eligible matches for 5ARI users will be defined based on their medication exposure at the time (+/- 1 year) of 5ARI initiation. For example, a patient initiating 5ARI medication in 1995 would have a pool of potential matches that includes all men not previously exposed or currently taking 5ARIs in 1995. Therefore a patient taking an alpha-blocker in 1995 who adds a 5ARI in 1999 would be an eligible match for the 5ARI user as in 1995 as they have not yet been exposed to 5ARIs. When this alpha-blocker patient initiates 5ARI therapy in 1999, their follow-up time will be censored.

      (1) The risk-set sampling of "controls" allows for an equal opportunity of the comparison groups to be exposed to 5ARI and does not condition on future use of a 5ARI. In this situation, an AB users is eligible to be selected and matched to a 5ARI user up until he starts a 5ARI, at which time he would be matched to another AB user. This approach will be used for the main analysis.

   b) As a sensitivity analysis, a group of patients exposed to alpha-blockers only (never take a 5ARI) over their duration of follow-up will be defined and will serve as potential matches to patients exposed to 5ARI medications.

2. Based on the feasibility study, it is expected that approximately 92% of patients will use alpha-blockers only and 8% will use 5ARIs with or without alpha-blockers. So, there is a low probability that 5ARI users will be matched to alpha-blocker users who eventually start therapy with a 5ARI. Therefore both approaches should yield similar patient groups and we will examine the characteristics of the resulting patient groups under matching schemes #1 and #2.

3. A table (**Table 1**) will be filled out before matching comparing the baseline characteristics of the 5ARI and alpha-blocker groups. A series of statistics that identify which baseline characteristics are different between the 5ARI and alpha-blocker user groups will be calculated.

4. An existing, widely used SAS macro developed by the Mayo Clinic has the ability to do both types of matching (see Bergstrahl and Kosanke 1995 reference).

[redacted]

VII. Statistical Analyses

A. Overall Approach

1. Continuous variables will be compared using two-sample *t*-statistics, variance ratios, and /or standardized differences in percent for each variable. The standardized difference in percent is defined as the mean difference as a percentage of the average standard deviation:

$$\frac{100(\bar{x}_c - \bar{x}_t)}{\sqrt{\frac{(s_c^2 + s_t^2)}{2}}}$$

[redacted]

2. Where for each covariate $\bar{x}_c$ and $\bar{x}_t$ are the sample means in the alpha-blocker and 5ARI groups, respectively, and the s_c^2 and s_t^2 are the corresponding sample variances. The variance ratio is defined as s_c^2 / s_t^2.

3. Significant differences based on the two sample *t*-statistics, variance ratios that are larger than 1.5 or less than 0.66, or standardized differences larger than 20% would indicate that there is substantial imbalance between the two groups for that variable. Ideally, there would be no significant *t*-statistics, all variance ratios would be between .8 and 1.2 and standardized differences in percent would be less than 10% if the two groups were well balanced (as would be the expectation if they had been randomized).

4. For categorical/binary variables we will compare chi-square statistics and observed proportions by treatment group. Significant differences based on chi-square statistics or large differences in observed proportions would suggest that there is an imbalance between the groups on the variables being examined.

5. Once the 5ARI patients have been matched to alpha-blocker patients on the four matching variables (age, timing of treatment initiation, race, and duration of prior use of alpha-blockers), using both matching approaches, **Table 2** below will be filled in twice (once for each matching approach) and the appropriate statistics described above will be calculated to confirm that indeed the groups were successfully matched on these characteristics. The success of the matching will be assessed based on whether balance between the treated and control groups is achieved in the matched samples. The two matching approaches will be compared and a decision will be made regarding which approach to use for the study analyses.

6. Additionally, background characteristics (including cumulative exposure time, follow-up time, follow-up time after cancer diagnosis, and potential pre-treatment initiation confounding factors) will be compared between the groups to identify whether there exist variables that would need to be considered in the outcome analyses as covariates.

7. **Outputs/deliverables:**

   a) Shell tables or other summary describing the count of available 5ARI and alpha-blocker users across strata of the matching factors. Team discussion regarding final definitions of matching variables and matching strata.

   b) Tables 1 and 2 completed and results from associated statistical tests. Discussion of the matching approach and team decision regarding which approach to use for the study analyses.

[redacted]

VIII. Definition and analysis plan for the primary outcome

A. Step 1: prostate cancer related mortality based on death certificates

1. Once the cohort has been selected and the groups are confirmed to have been adequately matched on age, date of treatment initiation, race, and duration of prior use of alpha-blocker, then the outcome analyses will be performed.

2. Prostate Cancer deaths will be identified among men with a diagnosis of prostate cancer. The primary outcome in this study is prostate cancer related mortality. Prostate cancer related mortality will first be assessed using cause of death codes from [redacted] electronic health files, state death records, and Social Security Index records.

3. Standard matching algorithms are used that take into account name, last known address, date of birth and Social Security Numbers (when available) to identify [redacted] members in state death records, and Social Security Index files. The mortality files contain, but are not limited to, the following fields: medical record number, date of death, place of death, and ICD-9 and ICD-10 coded underlying cause of death. Underlying cause of death will be used for the analyses. Sensitivity analyses will be done around the inclusion of other (contributing/multiple) causes of death

4. The National Death Index (NDI) mortality data will also be used to supplement cause of death information where [redacted] is unable to capture it through their existing systems. NDI is a central computerized index of death record information on file in the state vital statistics offices maintained by the Centers for Disease Control. The NDI includes a national file of identifying death record information compiled from computer files submitted by State vital statistics offices. Death records are added to the NDI file annually, approximately 12 months after the end of a particular calendar year. NDI Plus searches provide cause of death codes and are available through 2010 currently (2011 will become available Spring 2013). Three groups of participants will be identified and sent to the CDC for a NDI match:

   a) All men (regardless of PCa status) in the sample that died prior to or on 12/31/10 who are missing underlying cause of death info.

   b) All men (regardless of PCa status) in the sample that left [redacted] alive but died on or before 12/31/10 without underlying cause of death.

   c) Men with prostate cancer diagnosis who left [redacted] alive without a death date (up to May 2013) who we do not know are dead. For those men who died after the study end date, these deaths will not be included in the analysis and they will be censored at the end of the study period (December 31, 2010).

[redacted]

5. Any deaths determined to be associated with prostate cancer based on information available in NDI will be assigned to the appropriate treatment group based on treatment information available in [redacted] up until patients left the system. All deaths among men with prostate cancer will be divided into 4 groups based on coding from death certificates (underlying cause of death):

   a) CVD related

   b) Prostate cancer related

   c) Other causes likely related to prostate cancer (to be defined based on the [redacted] algorithm and clinical expertise)

   d) Deaths not due to the above stated causes of death

6. Each patient included in the analysis will have their survival outcome determined as follows. All patients who die from prostate cancer will be considered as events. Patients who die from other causes or who are lost to follow-up (leave the [redacted] system) before the end of the study period will be coded as censored at the time of death or loss to follow-up. End of follow-up for patients who are alive and were not lost to follow-up or did not die during the study period will be the end of study date. In the situation where men die after they have been lost to follow up, they will be censored at the time of their death and a sensitivity analysis will be performed to determine if the inclusion of these deaths changes the association of interest. However, because these men will not have complete records up until the time of their death, they will not be passed through the cause of death algorithm in the algorithm-based analyses. Person-time will be calculated from time at which person meets inclusion/exclusion criteria to the time of the event, censoring or end of study period.

   a) Primary analyses will use prostate cancer related deaths as the outcome. Sensitivity analyses will assess whether the inclusion of other causes likely related to prostate cancer change the association of interest.

7. A plot of cumulative incidence will be constructed comparing the 5ARI vs alpha-blocker users for prostate cancer mortality in the context of competing risk of death from other causes (based on methods of Anderson et. al 1995).

8. Next, we will examine pre-treatment assignment characteristics such as prior co-morbidities for each treatment group (**Table 2**) as well as pre-treatment characteristics and prostate cancer related information for those using 5ARI monotherapy and those using 5ARI+alpha-blocker (**Table 3**).

9. Then we will examine post-treatment assignment characteristics such as cumulative exposure to the treatment, latency (time since last treatment), and diagnosis of prostate cancer (yes/no) (**Table 4**).

10. Among those patients who develop prostate cancer we will then descriptively compare patient characteristics between the two exposure groups including the duration of prostate cancer, the prostate cancer stage at diagnosis and Gleason score at diagnosis (**Table 5**).

11. Crude prostate cancer related mortality rates and subdistribution hazard ratios will be calculated for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose (**Table 6**). Given power limitations due to the likely number of deaths across exposure duration strata, the data will be pooled for use in adjusted proportional subdistribution hazards regression analyses.

    a) The data will then be stratified using different lag times to be defined based on the distribution of time from BPH treatment initiation to prostate cancer mortality seen in the data set and crude prostate cancer related mortality rates and subdistribution hazard ratios will be calculated for 5ARI and alpha-blocker users (**Table 7**). Given power limitations due to the likely number of deaths across lag time strata, the data will be pooled for use in adjusted regression analyses. Finally, the crude prostate cancer related mortality rates and subdistribution hazard ratios will be calculated for 5ARI and alpha-blocker users by pre-treatment characteristics of interest (**Table 8**). Given power limitations due to the likely number of deaths across pre-treatment characteristic strata, the data will be pooled for use in adjusted regression analyses.

12. **All-cause mortality rates**

    a) Objective: To assess the risk of all-cause mortality associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

    b) Outcomes

        (1) The distribution of deaths from all causes overall and by treatment group will be estimated.

    c) Statistical Analysis

        (1) Cox regression models will also be carried out as well as Kaplan-Meier graphs with all-cause mortality as the outcome. The same methods for assessing confounding and modification will be used. (as described above).

[redacted]

(2) A similar approach in terms of classifying follow-up time, constructing Kaplan Meier curves, examination of pre- post-treatment assignment characteristics, and stratification by exposure duration and lag time, as detailed above for the primary analysis for prostate cancer related mortality, will be used to determine the association with all-cause mortality. (**Tables 9 and 10**)

d) Exploratory Analyses

(1) Depending upon the results from the exploratory analyses for the primary outcome of prostate cancer related mortality we will consider repeating some of the exploratory analyses listed in the primary analyses.

13. **Regression analyses**

a) Competing risk analysis

(1) Competing risks need to be accounted for because a participant dying of another cause precludes them from dying of prostate cancer. Therefore, the goal of this analysis is to directly model the cumulative incidence of prostate cancer mortality. We will modify the risk set to allow subjects to stay in the risk set even after the competing risk occurs, but with a reducing time dependent weight which takes into account the conditional probability of being under follow up had the competing event not occurred. (According to the method described in Fine and Gray 1999)

(2) Proportional subdistribution hazard regression models will be fit in the overall data set to compare prostate cancer related mortality between treatment groups while adjusting for pre-treatment characteristics. Of interest will be testing whether there are any potential interactions among the pre-treatment patient characteristics and the treatments (5ARI vs alpha-blocker) and if such interactions are found, this may suggest that the proportional subdistribution hazards models may need to be fit stratified by the characteristics of interest.

b) Potential confounders will be included as covariates and the adjusted regression estimates will be compared to the unadjusted estimates to assess the impact of the confounding. Final multivariate regression models will include confounders with which adjustments lead to more than 10% change in the regression coefficient of the association of interest. Effect modification will be assessed via the inclusion of interaction terms and assessed for statistical significance when appropriate. The ultimate goal of the model building will be to fit the most parsimonious model possible.

[redacted]

c) Model Fit will be assessed for nested models using the likelihood ratio test and among non-nested models, we will rely on information criteria to pick the best fit model.

d) Model building will be done so that scientifically sound and/or statistically significant characteristics from table 2 would be put into a main effect adjusted model. Stepwise variable selection will then be performed, either based on statistical significance or by manually picking the characteristics with large impact or higher significance. The model of best fit would then be selected based on either fit statistics or the criteria listed above.

14. **Outputs/deliverables**

a) Tables 3-10 completed, team discussion of potential stratification by pre and post-treatment initiation variables, outputs from proportional subdistribution hazard models as well as Cox models, and cause specific cumulative incidence graph as well as Kaplan Meier plots.

[redacted]

B. Step 2: prostate cancer related mortality based on cause of death algorithm

1. Once deaths based on underlying cause of death codes from death certificates have been identified, an electronic algorithm developed by [redacted] that will be adapted for use in this study, will be applied to validate the cause of death as related to prostate cancer based on death certificate coding among men with prostate cancer.

2. Many of the data elements needed for this algorithm can be abstracted from electronic medical records. For the remaining algorithm items for which review of the notes or free text section of electronic medical records would be required, natural language processing will be used.

3. The modified [redacted] algorithm will be applied to a subset of the data and will be tested and validated using random sample chart review in [redacted] before being applied to each region to identify potential prostate cancer deaths. As part of this process, the algorithm will be applied to known cases of metastatic disease and deaths known to be related to prostate cancer (based on physician chart review) to ensure that the algorithm can detect these cases. The testing and validation of the algorithm will utilize clinical input from the clinician-investigators, including urologists, epidemiologists, and oncologists as well as NLP specialized programmers, and as needed, chart review to determine whether further tailoring of the algorithm is required.

4. These processes may be repeated as necessary until an agreed upon level of validity of the algorithm is reached. If a suitable sensitivity and specificity (to be agreed upon by [redacted] and GSK investigators) is not reached, discussions with GSK and [redacted] investigators regarding other alternatives or iterations needed will take place.

5. A sub-sample chart review within each region's cases will be performed to check for any systematic differences in the algorithm's performance across regions that may arise from within region variability in the reporting of metastatic disease. There will be an assessment of the concordance of the classification of deaths using coding from death certificates alone versus the algorithm.

6. Once validated, the algorithm will be applied to all deaths among men diagnosed with prostate cancer in all regions to identify men who died from prostate cancer. Based on the results of the algorithm, men will then be categorized as follows:

[redacted]

a) Men who died of prostate cancer

b) Men who died of cardiovascular disease:

(1) Likely due to prostate cancer

(2) Not likely due to prostate cancer

c) Men who died of other causes:

(1) Likely due to prostate cancer

(2) Not likely due to prostate cancer

7. For men who die after they are lost from the [redacted] system, they will be censored at the time of their death for the main analyses and at the time they are lost for sensitivity analyses. For the main analyses, therefore, we will not put these men through the cause of death algorithm as they will not have complete algorithm information (from medical records) up until the point of their death.

8. **Validation of the electronic algorithm with chart review**

a) Further validation of the cause of death algorithm will be performed on a random sample of 200 records. A case report form will be created including relevant information from patients medical histories to be defined by GSK and [redacted] and chart review by two trained abstractors will be performed to validate the cause of death. A random sample, stratified as follows will be performed:

(1) Prostate cancer deaths (as identified by algorithm)

(2) Cardiovascular deaths (as identified by algorithm)

(3) Other significant deaths (causes of death thought to be potentially related to prostate cancer such as cerebrovascular disease, suicide, etc.) Exact list of causes of death is to be determined.

[redacted]

9. **Clinical Adjudication**

a) A panel of clinicians, including the two urologists and the medical oncologist who are [redacted] co-investigators on this study, will adjudicate the cause of death by reviewing the available information on the case report forms abstracted from the stratified random sample chart review and applying clinical judgment to determine if the death was due to prostate cancer. Death information and supporting documentation will be sent to each clinician and blinded to treatment status. Including clinicians from three different sites allows for further insight into any regional differences that may be present in the medical record data. Each reviewer will then assign the cause of death into the three categories as used with the algorithm:

(1) Men who died of prostate cancer

(2) Men who died of cardiovascular disease:

- Likely due to prostate cancer
- Not likely due to prostate cancer

(3) Men who died of other causes:

- Likely due to prostate cancer
- Not likely due to prostate cancer

b) The results from the adjudication will then be compared to the cause of death algorithm based on electronic and NLP data and the concordance and discordance will be quantified. The kappa statistic, sensitivity and specificity will be calculated, using the adjudication review panel as the gold standard. In instances where the algorithm and reviewer do not agree or the reviewers do not agree with each other, the case will be discussed among the panel until a consensus is reached regarding the cause of death. The cases will be discussed via teleconference and the majority decision will be used to determine the final cause of death.

[redacted]

10. **Regression Analysis**

a) The analyses for **Tables 6-8** will be repeated for the second step of the primary analysis, prostate cancer related mortality based on the cause of death algorithm.

b) Proportional subdistribution hazard regression models will also be repeated for prostate cancer related mortality based on the cause of death algorithm as well as cumulative incidence graph. The same methods for assessing confounding and modification will be used. Cause specific cumulative incidence graph would be plotted (as described above).

11. **Outputs/deliverables:**

a) Validation report, Tables 6-8 completed, outputs from regression models and cause specific cumulative incidence graphs, Validation report will include flow charts of natural language processing algorithms used for each individual NLP component in the death algorithm. In addition, the report will also include NLP statistics on % of positive/negative NLP hits. We will also include statistics on agreement (kappa, other correlation coefficients when appropriate) between death algorithm and chart review, and clinician adjudication.

IX. Exploratory analyses for the primary outcome, prostate cancer related mortality based on the death certificates and the validated NLP algorithm

A. Once the cause of death algorithm has been validated and applied to the data, a number of sensitivity analyses will be conducted including the following:

1. After examining the BPH treatment data independently from the mortality data we will define groups of patients based on gaps in their exposure history and will conduct sensitivity analyses to examine how the exposure-disease relationship might vary based on these groups. For example, participants with > 9 month gaps between drug eras and a maximum duration of drug era of 3 months over the course of follow-up might constitute one group while those with cumulative exposure of >2 years with <3 months of time between drug eras (time off of treatment) over the course of the study period may constitute another. In this way, we will examine the validity of the assumption that exposure time can be summed across treatment eras without accounting for gaps in treatment (main study analysis).

3. The data will be stratified by time since the end of BPH treatment to prostate cancer related mortality (< 1 year, 1- <2years, 2 to 3 years, 3+ years) to see how the main association differs within each of these groups. The NDI will be searched for deaths occurring within the study period among men who dropped out of [redacted] Any deaths determined to be associated with prostate cancer based on information available in NDI will be assigned to the appropriate treatment group based on treatment information available in [redacted] up until patients left the system. These deaths will be included in the main analysis. A sensitivity analysis will be conducted excluding these deaths to see if the primary association differs with the inclusion of these additional cases.

4. Deaths due to prostate cancer occurring in the first year after treatment initiation will be excluded from the analysis as it is not biologically plausible that BPH treatments could cause prostate cancer and subsequent death within the first year of treatment exposure.

5. Deaths due to prostate cancer that occur in the first 6 months will also be assessed to determine if a 6 month window is more appropriate for exclusion.

6. Men with a history of cancer other than prostate will be excluded from the analysis to see how the main association differs when this groups is excluded.

7. Men without a BPH diagnosis will be excluded from the analysis to see how the main association differs when this groups is excluded.

8. A subgroup of men will be defined who had an increase in their PSA level. Some of the men will have received a 5ARI in response to their PSA increase and some will not. 5ARI patients will be matched to alpha-blocker patients and we will examine prostate cancer related mortality in these groups. This analysis will allow us to examine the effect of 5ARI initiation when it is triggered by PSA increases.

9. We will stratify 5ARI exposed patients into 2 groups: those using 5ARIs as monotherapy and those using 5ARIs concurrently or consecutively with alpha-blockers. We will examine descriptively whether there are any differences between patients using these different treatment regimens with respect to prostate cancer mortality.

10. If the results from stratified analyses indicate heterogeneity across strata of post-treatment characteristics of interest (PSA testing patterns after treatment initiation and over the course of the study period, frequency of biopsy, the number of cores per biopsy, the number of positive cores per biopsy, and frequency of prostate cancer treatment paradigms), marginal structural models may be used to explore the potential effects of post-treatment characteristics on the relationship between BPH medication use and prostate cancer related mortality.

[redacted]

11. **Post-treatment characteristics**

a) These will not be adjusted for in the primary analysis as they may be treatment effects or in the causal path between the exposures and the outcome of prostate cancer related mortality. Stratification by post-treatment variables will be considered. Post-treatment characteristics include:

(1) PSA testing patterns after treatment initiation and over the course of the study period.

(2) The frequency of biopsy, the number of cores per biopsy, and the number of positive cores per biopsy.

(3) Gleason Score at diagnosis and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.

(4) Frequency of prostate cancer treatment paradigms (radical prostatectomy, external beam radiation, brachytherapy, cryotherapy, etc.).

b) If large imbalances (as determined by descriptive statistics and comparison tests showing statistically significant differences) exist in post-treatment variables of interest, stratified analyses may be considered.

[redacted]

[redacted]

X. TABLES FOR PRIMARY ANALYSES

A. Table 1: Pre-treatment demographic and clinical characteristics by BPH medication group before matching

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)	p-value
Characteristic				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing				
SES				
PSA level (mean (sd), median				
Prostate volume				
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Y/N)				
History of high blood pressure (Y/N)				
History of hyperlipidemia (Y/N)				
History of diabetes (Y/N)				
History of cancer				

[redacted]

[redacted]

(Y/N)				
Use of other medications to treat ED or OAB (Y/N) (PDE5I and/or anticholinergics and antimuscarinics)				

*p-values from chi-square tests, 2 sided t-tests and fisher's exact tests where appropriate

B. Table 2: Pre-treatment demographic and clinical characteristics by BPH medication group after matching (to be completed for both matching schemes)

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)	p-value
Characteristic				
Cumulative exposure time, years (mean (sd), median)				
Duration of follow-up time, years (mean (sd), median)				
Duration of follow-up time after prostate cancer diagnosis, years (mean (sd), median)				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing				
SES				
PSA level (mean (sd), median				
Prostate volume				

[redacted]

[redacted]

BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Smoking status				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Y/N)				
History of high blood pressure (Y/N)				
History of hyperlipidemia (Y/N)				
History of diabetes (Y/N)				
History of cancer (Y/N)				
Use of other medications (Y/N)				

*When using risk-set sampling, a man can be eligible and chosen as a AB user and later selected as a 5ARI user if he starts using 5-ARI during the study period. As such, these men will be represented in both the 5ARI and AB column of this table and double counted.

C. Table 3: Pre-treatment characteristics and prostate cancer related information for those using 5ARI monotherapy compared to those using 5ARI+alpha-blocker (also do for dutasteride vs. finasteride users)

	Overall (n= _)	5ARI monotherapy users (n= _)	5ARI+Alpha-blocker users (n= _)	p-value*
Characteristic				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				

[redacted]

[redacted]

Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing				
SES				
PSA level (mean (sd), median				
Prostate volume				
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Smoking status				
CharIson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Y/N)				
History of high blood pressure (Y/N)				
History of hyperlipidemia (Y/N)				
History of diabetes (Y/N)				
History of cancer (Y/N)				
Use of other medications (Y/N)				
Prostate cancer diagnosis (%)				
Prostate cancer incidence rate, /1,000 person-years				
Prostate cancer deaths (%)				
Prostate cancer mortality rate, /1,000 person-years				

*p-value will only be calculated if number of 5ARI only users is sufficient to do so.

[redacted]

[redacted]

D. Table 3b: Pre-treatment characteristics and prostate cancer related information for those using Finasteride compared to those Dutasteride (as feasible given the limited N of Dutasteride users in [redacted])

	Overall (n= _)	Finasteride users (n= _)	Dutasteride users (n= _)	p-value*
Characteristic				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing				
SES				
PSA level (mean (sd), median				
Prostate volume				
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Smoking status				
Charlson Comorbidity index (%) 0 1 2+				
History of cardiovascular disease (Y/N)				
History of high blood pressure (Y/N)				
History of hyperlipidemia (Y/N)				
History of diabetes (Y/N)				
History of cancer (Y/N)				

[redacted]

[redacted]

Use of other medications (Y/N)				
Prostate cancer diagnosis (%)				
Prostate cancer incidence rate, /1,000 person-years				
Prostate cancer deaths (%)				
Prostate cancer mortality rate, /1,000 person-years				

E. Table 4: Post-treatment assignment characteristics by BPH medication group

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)	p-value
Characteristic				
Cumulative exposure time, years (mean (sd), median)				
Cumulative dose				
Duration of follow-up time, years (mean (sd), median)				
Patients with >=1 PSA test (%)				
Number of PSA tests (mean (sd), median)*				
Patients with >=1 biopsy (%)				
Number of Biopsies (mean (sd), median)				
Number of cores/biopsy** (mean(sd), median)				
Number of positive cores/biopsy (mean(sd), median)				
Time from last treatment to prostate cancer diagnosis, years				

[redacted]

[redacted]

(mean (sd), median)				
Prostate cancer diagnosis (%)				
Prostate cancer incidence rate, /1,000 person-years				

***based on availability of the biopsy core data (to be determined) as it may require NLP techniques to abstract**

F. Table 5: Prostate cancer characteristics among men diagnosed with prostate cancer by BPH medication group

	Overall (n= _)	5ARI users (n= _)	Alpha-blocker users (n= _)	p-value
Characteristic				
Number of PSA tests (mean (sd), median)				
Number of Biopsies (mean (sd), median)				
Number of cores/biopsy (mean(sd), median)				
Number of positive cores/biopsy (mean(sd), median)				
Age at diagnosis (mean (sd), median)				
Age at diagnosis (%) <60 60-69 70+				
Gleason score at diagnosis(n (%)) <=6 7 7-10 8-10				
Radical prostatectomy (n(%)) (CPT codes: 55866, 55812-55845)				
Stage at diagnosis I				

[redacted]

[redacted]

II III IV				
Bone scan at diagnosis (%) (within 6 months)				
Positive bone scans (%)				
Other tests for metastatic disease at diagnosis (%) within 6 months				
Positive tests (%)				
Prostate cancer treatment within 6 months of diagnosis (%) Surgery Hormonal therapy Chemotherapy Immunotherapy Radiation therapy Other therapy				
Follow-up time after cancer diagnosis, years (mean (sd, median)				
Time since last exposure to BPH medication				

G. Table 6: Crude and adjusted prostate cancer related mortality rates and subdistribution hazard ratios for 5ARI and alpha-blocker users overall and stratified by duration of cumulative exposure and cumulative dose

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Crude Subdistribution Hazard ratio (95% CI)
CRUDE	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Cumulative exposure >3 months 3 months-1year 1 year-<2 years 2+ years					
Cumulative dose 1st quartile 2nd quartile					

[redacted]

[redacted]

3rd quartile 4th quartile					
Adjusted	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Cumulative exposure >3 months 3 months-1year 1 year-<2 years 2+ years					
Cumulative dose 1st quartile 2nd quartile 3rd quartile 4th quartile					

H. Table 7: Crude and adjusted prostate cancer related mortality rates and subdistribution hazard ratios for 5ARI and alpha-blocker users overall and stratified by lag time (TBD)

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Subdistribution Hazard ratio (95% CI)
CRUDE	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Lag Time					
ADJUSTED	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Lag Time					

[redacted]

[redacted]

I. Table 8*: Crude prostate cancer related mortality rates and subdistribution hazard ratios for 5ARI and alpha-blocker users overall and stratified by pre-treatment characteristics of interest

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Crude Subdistribution Hazard ratio (95% CI)
CRUDE	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing					
SES					
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2					
Charlson Comorbidity index (%) 0 1 2+					
History of cardiovascular disease (Y/N)					
History of high blood pressure (Y/N)					
History of hyperlipidemia (Y/N)					
History of diabetes (Y/N)					
History of cancer (Y/N)					

*Based on findings from this table, adjusted models will be fit to control for covariates when appropriate.

[redacted]

[redacted]

A. Table 9: Crude and adjusted all-cause mortality rates and hazard ratios stratified by characteristics of interest.

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Hazard ratio (95% CI)
CRUDE	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Cumulative exposure >3 months 3 months-1year 1 year-<2 years 2+ years					
Cumulative dose 1st quartile 2nd quartile 3rd quartile 4th quartile					
Adjusted	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Cumulative exposure >3 months 3 months-1year 1 year-<2 years 2+ years					
Cumulative dose 1st quartile 2nd quartile 3rd quartile 4th quartile					

[redacted]

[redacted]

B. Table 10*: Crude all-cause mortality rates and hazard ratios stratified by characteristics of interest.

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing					
SES					
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2					
Charlson Comorbidity index (%) 0 1 2+					
History of cardiovascular disease (Y/N)					
History of high blood pressure (Y/N)					
History of hyperlipidemia (Y/N)					
History of diabetes (Y/N)					
History of cancer (Y/N)					

*Based on findings from this table, adjusted models will be fit to control for covariates when appropriate.

[redacted]

[redacted]

XI. Secondary Analyses

A. Secondary Aims

1. Combined endpoint of prostate cancer mortality or metastatic prostate cancer

   a) To assess the risk of prostate cancer mortality or metastatic prostate cancer associated with use of 5ARIs, with or without alpha-blockers, compared to alpha-blockers in men treated with BPH medications.

2. Long term exposure to BPH medications

   a) To assess the risk of prostate cancer mortalityassociated with long-term exposure (2 or more years cumulative exposure) to 5ARIs, with or without alpha-blockers, compared to alpha-blockers alone in the subset of men using long term BPH treatment.

B. Approach

1. Combined endpoint of prostate cancer mortality or metastatic disease

   a) Outcomes

      (1) Events will be defined as men who died from prostate cancer (as defined through the cause of death algorithm) or who developed metastatic disease (as defined by part 2 and 3 of the cause of death algorithm).

   b) Statistical Analysis

      (1) The percent of patients with metastatic prostate cancer and the incidence rate per 1,000 person years of metastatic prostate cancer will be calculated overall and by treatment group among patients who do not die during the study period. The data will then be stratified and the incidence of metastatic prostate cancer by duration of 5ARI/alpha-blocker exposure will be estimated: any exposure, >3months, 3 months- 1 year, 1 - <2 years, 2 or more years. The occurrence of metastatic disease by stage and grade at initial diagnosis will also be examined. (**Table 11**)

[redacted]

[redacted]

(2) A similar approach in terms of classifying follow-up time, constructing Kaplan Meier curves, examination of pre- post-treatment assignment characteristics, and stratification by exposure duration and lag time, as detailed above for the primary analysis for prostate cancer related mortality, will be used to determine the association with the combined endpoint of prostate cancer mortality or metastatic disease.

(3) Proportional subdistribution hazard regression models will also be repeated as well as Kaplan-Meier and cumulative incidence graphs. The same methods for assessing confounding and modification will be used. (**Tables 12 and 13**)

c) Exploratory Analyses

(1) Depending upon the results from the exploratory analyses for the primary outcome of prostate cancer related mortality we will consider repeating some of the exploratory analyses listed in the primary analyses.

d) Outputs/deliverables

(1) Tables 11-13 completed, team discussion of potential stratification by pre and post-treatment initiation variables, outputs from subdistribution regression models, and cause specific cumulative incidence graphs

2. Long-term exposure to BPH medications

a) Outcomes

(1) Outcomes for this analysis will be the same as the primary analysis (prostate cancer mortality)

b) Exposures

(1) Among users of 5ARIs and alpha-blockers, who use these medications for 2 years or more, the association between 5ARI exposure and prostate cancer related mortality will be estimated.

c) Statistical Analyses

(1) Proportional subdistribution hazard regression models will also be repeated as well as cumulative incidence graphs with prostate cancer mortality as the outcome. The same methods for assessing confounding and modification will be used. (**Tables 14 and 15**)

[redacted]

d) Exploratory Analyses

(1) Depending upon the results from the exploratory analyses for the primary outcome of prostate cancer related mortality we will consider repeating some of the exploratory analyses listed in the primary analyses.

e) Outputs/Deliverables

(1) Tables 14 and 15 completed, team discussion of potential stratification by pre and post-treatment initiation variables, outputs from regression models, and cause specific cumulative incidence graphs

XII. Descriptive Analyses

A. Descriptive Analyses Aims

1. To evaluate the validity of classifying prostate cancer deaths with the developed electronic algorithm as compared to those identified based on cause of death coding

2. To evaluate the validity of identifying cases of metastatic prostate cancer with the developed electronic algorithm as compared to those identified based on medical record abstraction.

3. To describe the occurrence of cardiovascular related mortality in men treated with BPH medications and across treatment groups.

4. To describe across treatment groups Gleason Score and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies.

B. Approach

1. Cardiovascular related mortality

a) The percent of deaths overall and by treatment group, among men with prostate cancer, due to cardiovascular disease will be estimated as part of the validation process for prostate cancer related deaths. Additionally, the percent of deaths in the overall cohort due to cardiovascular disease will be estimated, overall and by treatment group.

2. Validation of prostate cancer mortality and metastatic prostate cancer algorithms

a) The sensitivity, specificity, positive and negative predictive values for the prostate cancer mortality and metastatic prostate cancer algorithms will be assessed in comparison to medical record abstraction. GSK and [redacted] will agree on an adequate level of sensitivity, specificity and predictive value for the algorithms based on the results from the validation process. If numerous iterations of NLP algorithm application and medical chart abstraction cannot produce an adequate level of validity for the algorithms, chart abstraction may need to be used for a larger sample of medical records and GSK and [redacted] will determine how best to proceed and how this will impact the scope of work and timelines for the study.

b) [redacted] will have 2 abstractors responsible for abstracting medical records, reviewing, and determining the cause of death (or metastatic disease status) for patients included in the validation studies. A third [redacted] person will be responsible for adjudicating cause of death (or metastatic disease status) when disagreements arise between abstractors. The kappa statistic will be calculated for agreement between abstractors.

3. Gleason Score and reclassification of Gleason Score between initial diagnosis biopsy and radical prostatectomy biopsy among those receiving radical prostatectomies

a) The distribution of Gleason score at prostate cancer diagnosis will be determined overall and by treatment group. Changes in Gleason score definition over time will be taken into account when abstracting the data. Among those patients who have a radical prostatectomy, Gleason scores will again be determined and any reclassification of Gleason score from initial diagnosis biopsy based on a radical prostatectomy biopsy will be noted.

[redacted]

XIII. Tables for Secondary Analyses

A. Table 11: Baseline Demographic and Clinical Characteristics by Metastatic Prostate Cancer Status

	Overall (n= _)	No Metastatic Prostate Cancer (n= _)	Metastatic Prostate Cancer (n= _)	Incidence Rate (per 1000 person-years)	p-value
Characteristic					
Age at treatment initiation (mean (sd), median)					
Age at treatment initiation (%) <60 60-69 70+					
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing					
SES					
PSA level (mean (sd), median					
Prostate volume					
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2					
Charlson Comorbidity index (%) 0 1 2+					
History of cardiovascular disease (Y/N)					
History of high blood pressure (Y/N)					
History of hyperlipidemia (Y/N)					
History of diabetes					

[redacted]

[redacted]

(Y/N)					
History of cancer (Y/N)					
Stage at metastatic prostate cancer Diagnosis I II III IV					
Gleason Score at metastatic prostate cancer diagnosis <=6 7 7-10					

B. Table 12*: Crude and adjusted prostate cancer mortality or metastatic cancer rates and subdistribution hazard ratios stratified by characteristics of interest.

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Subdistribution Hazard ratio (95% CI)
CRUDE	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Cumulative exposure >3 months 3 months-1year 1 year-<2 years 2+ years					
Cumulative dose 1st quartile 2nd quartile 3rd quartile 4th quartile					
Adjusted	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Cumulative exposure					

[redacted]

[redacted]

>3 months 3 months-1year 1 year-<2 years 2+ years					
Cumulative dose 1st quartile 2nd quartile 3rd quartile 4th quartile					

C. Table 13*: Crudeprostate cancer mortality or metastatic cancer rates and subdistribution hazard ratios stratified by pre-treatment characteristics of interest.

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Subdistribution Hazard ratio (95% CI)
	5ARI	Alpha-blocker	5ARI	Alpha-blocker	
Overall					
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing					
SES					
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2					
Charlson Comorbidity index (%) 0 1 2+					
History of cardiovascular disease (Y/N)					
History of high					

[redacted]

[redacted]

blood pressure (Y/N)					
History of hyperlipidemia (Y/N)					
History of diabetes (Y/N)					
History of cancer (Y/N)					

*Based on findings from this table, adjusted models will be fit to control for covariates when appropriate.

D. Table 14: Distribution of length of BPH medication use by demographic and clinical characteristics of interest.

	Overall (n= _)	Short Term Users (< 2 years)	Long Term Users (2+ years)	p-value
Characteristic				
Age at treatment initiation (mean (sd), median)				
Age at treatment initiation (%) <60 60-69 70+				
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander Other Missing				
SES				
PSA level (mean (sd), median				
Prostate volume				
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2				
Charlson Comorbidity index				

[redacted]

[redacted]

(%) 0 1 2+				
History of cardiovascular disease (Y/N)				
History of high blood pressure (Y/N)				
History of hyperlipidemia (Y/N)				
History of diabetes (Y/N)				
History of cancer (Y/N)				
Stage at prostate cancer Diagnosis I II III IV				
Gleason Score at prostate cancer diagnosis <=6 7 7-10				

E. Table 15*: Crude prostate cancer mortality rates and subdistribution hazard ratios stratified by characteristics of interest comparing short term vs. long term BPH medication users

	No of deaths/ No at risk		Mortality rate/ 1,000 p-y		Subdistribution Hazard ratio (95% CI)
	Short-term	Long-term	Short-term	Long- term	
Overall					
Race (%) Non-Hispanic White African American Hispanic Asian/Pacific Islander					

[redacted]

[redacted]

Other Missing					
SES					
BMI (kg/m2) (%) <25 kg/m2 25-30 kg/m2 ≥30 kg/m2					
Charlson Comorbidity index (%) 0 1 2+					
History of cardiovascular disease (Y/N)					
History of high blood pressure (Y/N)					
History of hyperlipidemia (Y/N)					
History of diabetes (Y/N)					
History of cancer (Y/N)					

*Based on findings from this table, adjusted models will be fit to control for covariates when appropriate.

[redacted]