

# **Prediction of Findings From the Ongoing PRONOUNCE Trial Using Healthcare Database Analyses**

## **DUPLICATE - PRONOUNCE**

September 9, 2021

NCT04897958

## 1. RCT Details

This section provides a high-level overview of a **published** RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

### 1.1 Title

**Cardiovascular Safety of Degarelix Versus Leuprolide for Advanced Prostate Cancer ([PRONOUNCE Trial](#))**

### 1.2 Intended aim(s)

To compare the incidence of major cardiovascular events (MACE) among advanced prostate cancer subjects treated with degarelix versus leuprolide.

### 1.3 Primary endpoint for replication

Time from randomization to the first confirmed, adjudicated occurrence of a MACE, which is defined as a composite of all-cause death, nonfatal myocardial infarction, or nonfatal stroke through 12 months of ADT treatment.

### 1.4 Required power for primary endpoint and noninferiority margin (if applicable)

Based on prior literature, it was determined that 66 MACE events and 876 subjects would be required to reject a two-sided null hypothesis of equal hazards with 80% power at a 5% type I error rate. A hazard ratio of 0.49 with absolute event rates of 5.1% and 10.2% (degarelix vs leuprolide) were hypothesized.

### 1.5 Secondary endpoint for replication (assay sensitivity) and RCT finding

Secondary cardiovascular objectives: To assess 1) the frequency of MACE components individually (i.e., nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality)

### 1.6 Trial estimate

The trial is ongoing and scheduled to complete in April 2021.

## 2. Person responsible for implementation of replication in Aetion

David Merola, PharmD, SM and Sushama Kattinakere Sreedhara, MBBS, MSPH, implemented the study design in the Aetion Evidence Platform. They are not responsible for the validity of the design and analytic choices. All implementation steps are recorded, and the implementation history is archived in the platform.

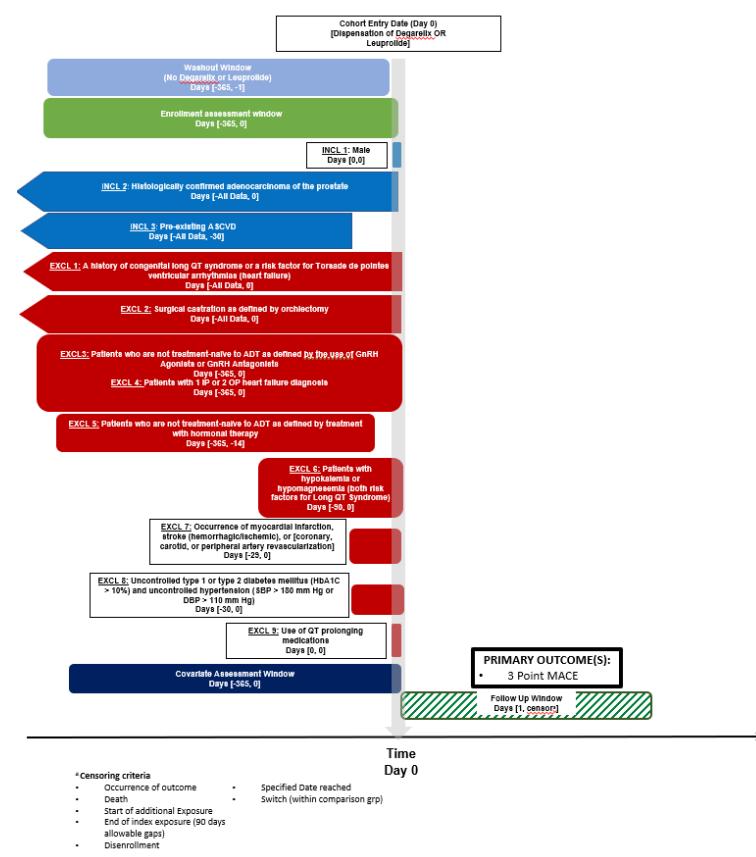
### 3. Data Source(s)

Optum CDM, IBM® MarketScan®, Medicare Diabetes

### 4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Figure 1.



## 5. Cohort Identification

### 5.1 Cohort Summary

An active-comparator, incident-user design will be employed to compare patients that received degarelix vs. leuprolide. Subjects will be selected on the basis of having at least one diagnosis code indicating prostate cancer, male sex, and a history of atherosclerotic cardiovascular disease. Subjects will be excluded if they were not treatment-naïve with respect to prostate cancer, had a record of uncontrolled diabetes or hypertension within 30 days prior to treatment initiation, had a history of long QT syndrome or risk factors thereof (i.e., heart failure, hypokalemia, or medications known to prolong the QT interval), or an acute myocardial infarction, stroke, or revascularization procedure within 30 days prior to treatment initiation. In contrast to the PRONOUNCE trial, patients cannot be required to have had established tumor staging information, angiography-verified stenosis/occlusion of vessels, and a lack of planned cardiac surgery at the time of treatment initiation due to poor capture of this information in administrative data. All patients were required to have continuous enrollment for 365 days prior to cohort entry to ensure incident use of the study drugs.

### 5.2 Important steps for cohort formation

Incident use of the exposure (leuprolide or degarelix) is defined as no use of the exposure drug in the 365 days prior to meeting all eligibility criteria and initiation of exposure.

#### 5.2.1 Eligible cohort entry dates

The degarelix indication for treatment of prostate cancer was approved by the FDA on Dec 24, 2008. Leuprolide was initially approved for the same indication prior to Dec 24, 2008.

- IBM® MarketScan®: Dec 24, 2008 – December 31, 2018 (end of available data)
- Optum CDM: Dec 24, 2008 – June 30, 2020 (end of available data)
- CMS Diabetes: Dec 24, 2008 – Dec 31, 2017 (end of available data)

#### 5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix** and are summarized in the flowcharts below.

### 5.3 Flowchart of the study cohort assembly

For Degarelix vs Leuprolide

	IBM® MarketScan®		Optum CDM		CMS - Diabetes	
	Less Excluded Patients	Remaining Patients	Less Excluded Patients	Remaining Patients	Less Excluded Patients	Remaining Patients
<b>All patients in our database</b>		200,203,908		78,202,636		23,466,175
<b>Patients with Degarelix/Leuprolide [measured between Dec 24, 2008 and Dec 31, 2019.]</b>	-199,937,514	266,394	-78,046,787	155,849	-23,212,628	253,547
<b>Excluded due to insufficient enrollment [-365, 0]</b>	-94,870	171,524	-36,242	119,607	-125,589	127,958
<b>After wash-out for prior use of reference (Leuprolide) [-365, -1]</b>	-106,281	65,243	-77,869	41,738	-96,813	31,145
<b>After wash-out for prior use of exposure (Degarelix) [-365, -1] and Excluded because patient qualified in &gt;1 exposure category</b>	-1,961	63,282	-2,153	39,585	-3,397	27,748
<b>Inclusion only Male gender [-365, 0]</b>	-43,683	19,599	-17,401	22,184	-183	27,565
<b>Inclusion Prostate Cancer [start of all available data, 0]</b>	-784	18,815	-502	21,682	-210	27,355
<b>Inclusion Pre-existing ASCVD [start of all available data, -30]</b>	-14,187	4,628	-15,729	5,953	-16,099	11,256
<b>Exclusion Androgen deprivation therapy (GnRH agonists/antagonists) [-365, 0]</b>	-145	4,483	-106	5,847	-465	10,791
<b>Exclusion Androgen deprivation therapy (hormonal therapy) [-365, -14] and Exclusion Androgen deprivation therapy (Orchiectomy) [start of all available data, 0]</b>	-575	3,908	-748	5,099	-1,768	9,023
<b>Exclusion Uncontrolled Diabetes [-30, 0]</b>	0	3,908	0	5,099	0	9,023
<b>Exclusion Uncontrolled Hypertension [-30, 0]</b>	-28	3,880	-19	5,080	-97	8,926
<b>Exclusion Heart failure [starts of all available data, 0]</b>	-285	3,595	-556	4,524	-1,602	7,324
<b>Exclusion QT syndrome [starts of all available data, 0]</b>	-7	3,588	-9	4,515	-19	7,305

<b>Exclusion Hypokalemia [-90, 0]</b>	-3	3,585	-14	4,501	-37	7,268
<b>Exclusion Hypomagnesemia [-90, 0]</b>	-9	3,576	-7	4,494	-12	7,256
<b>Exclusion QT prolonging medicines [0, 0]</b>	-192	3,384	-191	4,303	-446	6,810
<b>Exclusion Acute MI [-29, 0]</b>	-6	3,378	-9	4,294	-11	6,799
<b>Exclusion Stroke [-29, 0] and Exclusion Revascularization [-29,0]</b>	-9	3,369	-16	4,278	-29	6,770
<b>Final cohort</b>		3,369		4,278		6,770

\*\*Certain exclusion criteria are in collapsed form to maintain compliance with CMS' cell suppression policy\*\*

## 6. Variables

### 6.1 Exposure-related variables:

#### Study drug:

The study exposure of interest is defined by a HCPCS/CPT code or outpatient prescription drug claim indicating degarelix administration or dispensation, respectively. New initiation will be defined by no such records of degarelix in the prior 365 days before treatment initiation (washout period) and fulfillment of study eligibility criteria.

#### Comparator agent:

The comparator is defined by an HCPCS/CPT code or outpatient prescription drug claim indicating leuprolide administration or dispensation, respectively. New initiation will be defined by no such records of leuprolide in the prior 365 days before treatment initiation (washout period) and fulfillment of study eligibility criteria.

### 6.2 Preliminary Covariates:

- Age

The covariate listed above represents only a small subset of the covariate vector that will ultimately be controlled for in the design and analysis. We use the covariate above only for initial feasibility analyses to judge whether there is likely to be sufficient overlap between treatment groups to proceed with the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and the initial power assessment and are listed in Table 1 (**Appendix B**). Gender is not included since the study is already restricted to male subjects.

### 6.3 Outcome variables and study follow-up:

#### 6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in **Appendix**):

- **Primary outcome:** MACE (all-cause death, nonfatal myocardial infarction, or nonfatal stroke through 12 months of primary treatment with leuprolide or degarelix)
- Secondary outcomes:
  - Secondary cardiovascular objectives: To assess 1) the frequency of MACE components individually (i.e., nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality)

#### 6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analyses will be conducted with treatment defined as the index drug on day of cohort entry. An allowable gap of 90 days between records indicating each treatment will qualify as “continuous therapy” with respect to follow-up in the as-treated analysis.

The follow-up will start the day after drug initiation (i.e., cohort entry date), and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest,
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- 365 days
- Switch
- Discontinuation (90 days allowable grace period and risk window)

In the secondary ITT analysis, we will not censor for discontinuation or switching among study drugs

## 7. Initial Feasibility Analysis

Action report name:

For degarelix vs. leuprolide

Optum CDM- <https://bwh-dope.aetion.com/projects/details/1636/rwrs/67085>

IBM® MarketScan®- <https://bwh-dope.aetion.com/projects/details/1323/rwrs/67083>

CMS Diabetes - <https://bwh-dope.aetion.com/projects/details/1637/rwrs/67081>

Date conducted: 03/06/2021

Complete Aetion feasibility analysis using age as the only covariate and the primary endpoint (Section 6.3.1) as the outcome. No measures of association will be computed, nor will incidence rates be stratified by treatment group.

- Report patient characteristics by treatment group
  - Degarelix vs Leuprolide

	Optum CDM			IBM® MarketScan®			CMS - Diabetes		
Variable	Leuprolide - Comparator	Degarelix - Exposure	Difference	Leuprolide - Comparator	Degarelix - Exposure	Difference	Leuprolide - Comparator	Degarelix - Exposure	Difference
Number of patients	3,676	596		2,936	431		5,828	941	
Age									
...mean (sd)	75.71 (7.42)	75.93 (7.66)	-0.22 (-0.88, 0.44)	74.38 (9.05)	74.49 (9.12)	-0.11 (-1.03, 0.82)	76.85 (6.58)	76.94 (6.49)	-0.09 (-0.53, 0.36)
...median [IQR]	76.00 [71.00, 81.00]	76.00 [71.00, 82.00]		75.00 [68.00, 81.00]	75.00 [68.00, 82.00]		76.00 [72.00, 81.00]	77.00 [72.00, 81.87]	

- Report summary parameters of study population **FEASIBILITY- FOR STUDY OUTCOME**
  - For Degarelix vs Leuprolide

FEASIBILITY FOR STUDY OUTCOME			
	Optum CDM	IBM® MarketScan®	CMS - Diabetes
Number of patients in full cohort	4,278	3,369	6,770
Number of patients dropped as incomplete cases	0	0	0
Number of patients that did not begin follow-up	6	2	1
Number of patients in analytic cohort	4,272	3,367	6,769
Number of events	108	43	211
Number of person-years	1,259.68	1,001.03	2,031.94
Number of patients in group: Leuprolide - Comparator	3,676	2,936	5,828
Number of patients in group: Degarelix - Exposure	596	431	941
Risk per 1,000 patients	25.28	12.77	31.17
Rate per 1,000 person-years	85.74	42.96	103.84

- Report median follow-up time by treatment group
  - For Degarelix vs Leuprolide

FOLLOW-UP TIME FOR STUDY OUTCOME			
Median Follow-Up Time (Days) [IQR] – At 90 days gap			
Patient Group	Optum CDM	IBM® MarketScan®	CMS - Diabetes
Overall Patient Population	89 [89, 89]	89 [89, 89]	89 [89, 89]
Referent - Leuprolide	89 [89, 89]	89 [89, 89]	89 [89, 89]
Exposure - Degarelix	82 [33, 132]	68 [31, 126]	67 [32, 124]

- Report reasons for censoring in the overall study population
  - For Degarelix vs Leuprolide

CENSORING REASONS FOR STUDY OUTCOME			
Reasons	Optum CDM	IBM® MarketScan®	CMS - Diabetes
Outcome	108 (2.5%)	43 (1.3%)	211 (3.1%)
Start of an additional exposure	351 (8.2%)	256 (7.6%)	584 (8.6%)
End of index exposure	3,344 (78.3%)	2,674 (79.4%)	5,277 (78.0%)
Maximum follow-up time	118 (2.8%)	94 (2.8%)	205 (3.0%)
Specified date reached	182 (4.3%)	52 (1.5%)	270 (4.0%)
End of patient data	0 (0.0%)	0 (0.0%)	0 (0.0%)
End of patient enrollment	169 (4.0%)	248 (7.4%)	222 (3.3%)

- Report overall risk of the primary outcome.

	Optum CDM	IBM® MarketScan®	CMS - Diabetes	Pooled
Risk per 1,000 patients	25.28	12.77	31.17	25.12

## 8. Initial Power Assessment

Action report name:

- For Degarelix vs Leuprolide
  - Optum CDM- <https://bwh-dope.aetion.com/projects/details/1636/rwrs/67086>
  - IBM® MarketScan®- <https://bwh-dope.aetion.com/projects/details/1323/rwrs/67084>
  - CMS Diabetes - <https://bwh-dope.aetion.com/projects/details/1637/rwrs/67082>

Date conducted:

In order to complete the initial power analysis, a dummy outcome indicating a 90-day gap in database enrollment will be used. This outcome is used to ensure that no information on the comparative risks of the outcomes of interest are available at this stage. A 1:1 PS-matched comparative analysis was performed, including age as the only covariate. Power calculations are based on the formulas

from Chow et al. (2008).

- Stop analyses until feasibility and power are reviewed by primary investigators and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.

- Pooled

<b>Superiority Analysis</b>	
Number of patients matched	3,934
Reference	1,967
Exposed	1,967
Risk per 1,000 patients	25.12
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	98.82208
Power	0.943598201

- Optum CDM

<b>Superiority Analysis</b>	
Number of patients matched	1,192
Reference	596
Exposed	596
Risk per 1,000 patients	25.28
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	30.13376
Power	0.499237002

- IBM® MarketScan®

<b>Superiority Analysis</b>	
Number of patients matched	862
Reference	431
Exposed	431
Risk per 1,000 patients	12.77
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	11.00774
Power	0.21953525

- CMS - Diabetes

<b>Superiority Analysis</b>	
Number of patients matched	1,880
Reference	940
Exposed	940
Risk per 1,000 patients	31.17
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	58.5996
Power	0.779468883

Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	3/17/2021
Reviewed by FDA:	Ken	Date reviewed:	4/3/2021
Reasons for stopping analysis (if required):			

## 9. Balance Assessment

Action report name:

For Degarelix vs. leuprolide

Optum CDM- <https://bwh-dope.aetion.com/projects/details/1636/rwrs/68435>

IBM® MarketScan®- <https://bwh-dope.aetion.com/projects/details/1323/rwrs/68424>

CMS Diabetes - <https://bwh-dope.aetion.com/projects/details/1637/rwrs/68434>

Date conducted: 04/14/2021

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates.

- Provide plot of PS distributions stratified by treatment group.

Note- Please refer to Appendix\_Table1\_PRONOUNCE\_v1 (worksheet named 'PS matching').

- Report covariate balance after matching.

Note- Please refer to Appendix\_Table1\_PRONOUNCE\_v1 (worksheet named 'Table 1').

- Report reasons for censoring by treatment group.

	Overall	Referent	Exposure
Start of an additional exposure	1147 (30.39%)	1 (0.05%)	1146 (60.73%)
End of index exposure	2084 (55.22%)	1645 (87.18%)	439 (23.26%)
Specified date reached	157 (4.16%)	78 (4.13%)	79 (4.19%)
Maximum follow-up reached (365 days)	142 (3.76)	42 (2.23%)	100 (5.30%)
End of patient enrollment	244 (6.46%)	121 (6.41%)	123 (6.52%)

- Report follow-up time by treatment group.

Patient Group	Median Follow-Up Time (Days) [IQR]		
	Optum CDM	IBM® MarketScan®	CMS - Diabetes
Overall Patient Population	89 [64, 116]	89 [55, 118]	89 [61, 109]
Referent	89 [89, 89]	89 [89, 89]	89 [89, 89]
Exposure	82 [33, 140]	67 [31, 126]	68 [33, 125]

## 10. Final Power Assessment

Date conducted: 4/15/2021

Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8.

- Pooled

<b>Superiority Analysis</b>	
Number of patients matched	3,774
Reference	1,887
Exposed	1,887
Risk per 1,000 patients	25.12
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	94.80288
Power	0.93484302

- Optum CDM

<b>Superiority Analysis</b>	
Number of patients matched	1,092
Reference	546
Exposed	546
Risk per 1,000 patients	25.28
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	27.60576
Power	0.465815489

- IBM® MarketScan®

<b>Superiority Analysis</b>	
Number of patients matched	830
Reference	415
Exposed	415
Risk per 1,000 patients	12.77
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	10.5991
Power	0.21311438

- CMS - Diabetes

<b>Superiority Analysis</b>	
Number of patients matched	1,852
Reference	926
Exposed	926
Risk per 1,000 patients	31.17
Desired HR from RCT	0.49
Alpha (2-sided)	0.05
Number of events expected	57.72684
Power	0.773370349

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:		Date reviewed:	
Reviewed by FDA:		Date reviewed:	
Reasons for stopping analysis (if required):			

## 11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns:

Date votes and concerns are summarized:

- If final feasibility and power analyses are reviewed and approved, proceed to the remaining protocol steps.

- All study team and advisory board members that review this protocol should at this stage provide their level of confidence for the success of the RWD study in the [Google Form](#). This form also provides space for reviewers to list any concerns that they feel may contribute to a failure to replicate the findings of the RCT, including differences in study populations, poor measurement of study variables, or residual confounding. All responses will be kept confidential and individual-level results will only be shared with the individual respondent.
- After the deadline for voting has passed, provide the distribution of responses and summarize all concerns here.

## **12. Register study protocol on clinicalTrials.gov**

Date conducted:

- Register the study on [clinicalTrials.gov](#) and upload this document.

## **13. Comparative Analyses**

Action report name:

Date conducted:

13.1 For primary analysis:

13.2 For sensitivity analyses:

## **14. Requested Results**

14.1 Table 1: Baseline characteristics before and after adjustment

Variable	Before adjustment			After adjustment		
	Referent	Exposure	Std. diff.	Referent	Exposure	Std. diff.
Number of patients			-			-
Age categories						
...						

14.2 Table 2: Follow-up time

Patient Group	Median Follow-Up Time (Days) [IQR]
Overall Patient Population	
Referent	
Exposure	

14.3 Table 3: Censoring events

	Overall	Referent	Exposure
Outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
...			

14.4 Table 4: Results from primary analyses;

Analysis	No. exposed events	No. referent events	Exposed rate	Referent rate	HR (95% CI)
Crude					
Analysis 1					
Analysis 2					
...					

HR, Hazard Ratio; CI, Confidence Interval.

14.5 Table 5: Results from secondary analyses;

**15. References**

Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 177

## Appendix A

### Information from Trial

Trial Name: PRONOUNCE <https://www.clinicaltrials.gov/ct2/show/NCT02663908>

NCT: NCT02663908

Therapeutic Area: Oncology

RCT Category: Equivalence/Superiority

Brand Name: Firmagon

Generic Name: Degarelix

Sponsor: Ferring Pharmaceuticals

Year: 2016 - Present

Measurable Endpoint: MACE

Exposure: Degarelix

Comparator: Leuprolide

Population: Men of any age with with advance prostate cancer and predefined CV disease

No. of Patients: TBD

Power: TBD

# Appendix A

PRONOUNCE trial definitions		Implementation in routine care	References/Rationale	Color coding
		TRIAL DETAILS		Criteria
		EXPOSURE vs. COMPARISON	Please see the following Google Drive for further details on any missing information: <a href="https://drive.google.com/open?id=1W0513i8wvY5x0tVcVca8kx4v">https://drive.google.com/open?id=1W0513i8wvY5x0tVcVca8kx4v</a>	
Degarelix 240mg SC q mt x 1 month, Degarelix 80mg SC q mt x 11 months thereafter vs. Degarelix 212.5mg q 3 months x 12 months	Degarelix Arm: Generic name: Degarelix Acetate; HCPCS/CPT: 91155 (inpatient and outpatient) vs. Degarelix Arm: Generic name: Leuprorelin Acetate; HCPCS/CPT: 11950, C1430, 95219, 95218, 95217 (inpatient and outpatient)		ICD-10 codes will be in the document because of direct care definitions and conversion of ICD-10 codes to ICD-10 code sets will be available in the above Google Drive folder listed above. ICD-9 to ICD-10 code conversion was completed using a SAS macro that implements forward/backward mapping based on the CMS ICD-9 to ICD-10 mapping: <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3030610/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3030610/</a>	Can be replicated in claims
		PRIMARY OUTCOME		Using dummy definitions for measuring in claims
		Measured from first day following exposure initiation		Can't be measured in claims
		Death: inpatient death indicated by discharge date		
		Nonfatal MI: ICD-9 diagnosis: 410.xx EXCPT 410.2x		
		ICD-10 diagnosis: I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9		
		ICD-10 procedure: I20.00-I20.09, I20.10-I20.11, I20.12-I20.30, I20.31-I20.40, I20.50-I20.51, I20.60-I20.61, I20.62-I20.67, I20.80-I20.81, I20.91-I20.93, I20.95-I20.97		
		MACE (all-cause death, nonfatal myocardial infarction, nonfatal stroke)	Source: CANVAS trial ( <a href="https://bwh-dept.action.com/measures/details/92945/661/0/basic">https://bwh-dept.action.com/measures/details/92945/661/0/basic</a> )	Can't be measured in claims but not important for the analysis
		EXCLUSION CRITERIA		
1 Histologically confirmed adenocarcinoma of the prostate	Measured from [start of all available data, 0]. Must have both diagnosis code and male gender for inclusion. <b>Malignant Neoplasm of the Prostate</b> ICD-9 diagnosis: 188.0-188.9 ICD-10 diagnosis: C61.0 (inpatient and outpatient) Sex: Male		Male patients with ICD-9 - an exposure provides enough information to confirm diagnosis, as the exposures have very few or no indications outside of advanced PC	
2 Tumor, node, metastasis staging available before treatment start (bone scan and/or CT scan and/or MRI) <12 weeks before study start			Necessitating code for biopsy may exclude subjects with apparent prostate cancer if they were initially diagnosed prior to database enrollment with early stage disease	
3 Investigator judgement to initiate combined ADT therapy with intended duration of 12 months or longer			Lupron is indicated in females for endometriosis. Restricting to males helps ensure indication of interest.	
4 Patients with prostate cancer who developed metastases after local therapy				
5 -Patients with prostate cancer with very high-risk, high-risk, or intermediate risk disease with feature of unfavorable prognosis who will be treated with definitive radiation therapy in combination with at least 12 months of neoadjuvant/adjacent ADT				
		Measured from [start of all available data, 30] on an inpatient or outpatient care setting in any diagnosis position		
		<b>Acute or old MI:</b> ICD-9 diagnosis: 410.xx, 412.xx ICD-10 diagnosis: I21.00-I21.09, I21.10-I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9, I25.2		
		<b>Coronary, Carotid, Iliac, Femoral, Popliteal revascularization (angioplasty/Stent/CABG/vascular bypass/endarterectomy):</b> ICD-9 procedure: "36.67", "36.69", "36.07", "36.09", "36.31", "36.32", "36.33", "36.34", "36.17", "36.10", "36.11", "36.12", "36.13", "36.14", "36.15", "36.16", "36.17", "36.18", "36.2", "36.21", "36.22", "36.23", "36.24", "36.25", "36.26", "36.27", "36.28", "36.29", "36.30", "36.31", "36.32", "36.33", "36.34", "36.35", "36.36", "36.37", "36.38", "36.39", "36.40", "36.41", "36.42", "36.43", "36.44", "36.45", "36.46", "36.47", "36.48", "36.49", "36.50", "36.51", "36.52", "36.53", "36.54", "36.55", "36.56", "36.57", "36.58", "36.59", "36.60", "36.61", "36.62", "36.63", "36.64", "36.65", "36.66", "36.67", "36.68", "36.69", "36.70", "36.71", "36.72", "36.73", "36.74", "36.75", "36.76", "36.77", "36.78", "36.79", "36.80", "36.81", "36.82", "36.83", "36.84", "36.85", "36.86", "36.87", "36.88", "36.89", "36.90", "36.91", "36.92", "36.93", "36.94", "36.95", "36.96", 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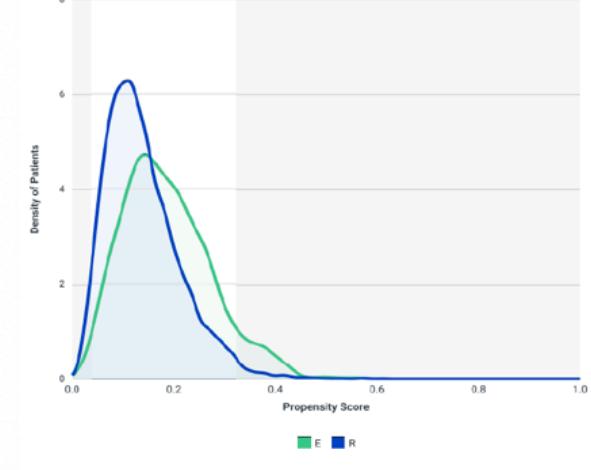
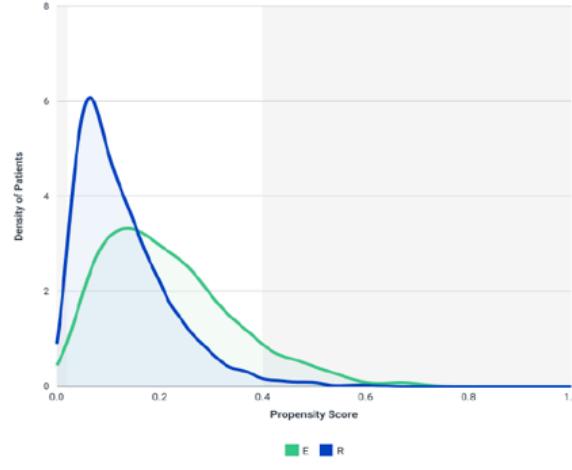
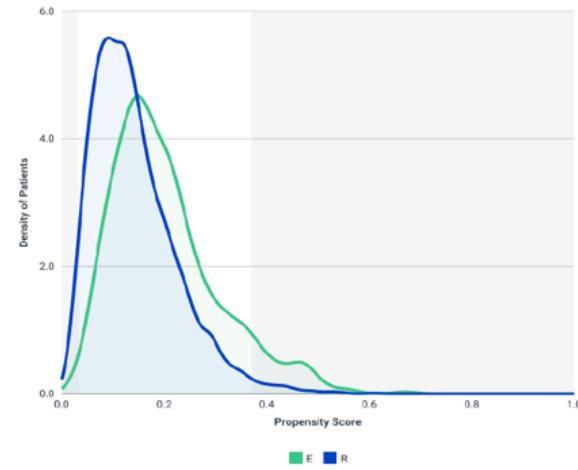
## Appendix A

**Optum****MarketScan****Medicare**

All variables under Table 1 is used in PS matching except Radiation therapies used in Prostate cancer, Chemo therapies used in Prostate cancer and Lithium

All variables under Table 1 is used in PS matching except HIV/AIDS, Radiation therapies used in Prostate cancer, Chemo therapies used in Prostate cancer and Lithium

All variables under Table 1 is used in PS matching except Lithium

**BEFORE PS MATCHING**

**Figure 1:** Pre-matching propensity score overlap

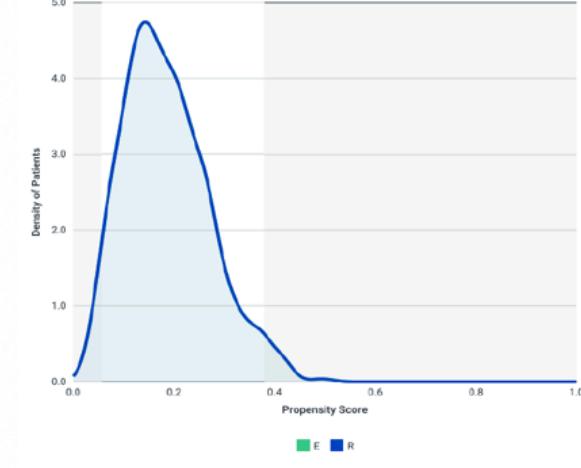
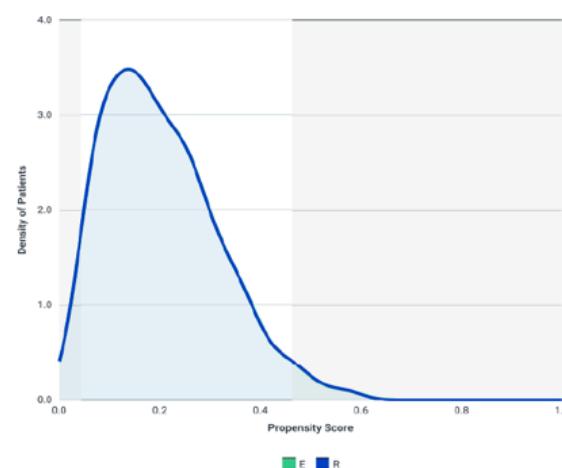
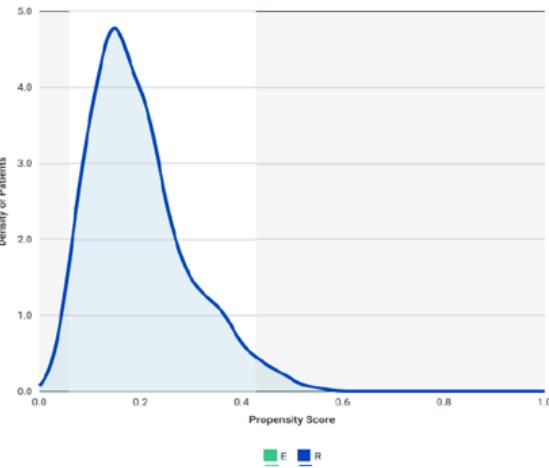
**Figure 1:** Pre-matching propensity score overlap

**Figure 1:** Pre-matching propensity score overlap

The c-statistics for the propensity score model, pre-matching was 0.683. The post-matching c-statistic was 0.62.

The c-statistics for the propensity score model, pre-matching was 0.719. The post-matching c-statistic was 0.625.

The c-statistics for the propensity score model, pre-matching was 0.669. The post-matching c-statistic was 0.597.

**AFTER PS MATCHING**

**Figure 2:** Post-matching propensity score overlap

**Figure 2:** Post-matching propensity score overlap

**Figure 2:** Post-matching propensity score overlap

Table 1 Unmatched

Variable	UNMATCHED											
	Optum			MarketScan			Medicare			Pooled		
	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff
Number of patients	3,681	597		2,938	431		5,829	941		12,448	1,969	
Year of Cohort Entry Date												
...2008-2009; n (%)	262 (7.1%)	0 (0.0%)		0.39	312 (10.6%)	0 (0.0%)	0.49	353 (6.1%)	0 (0.0%)	0.36	927 (7.4%)	0 (0.0%)
...2010; n (%)	265 (7.2%)	21 (3.5%)		0.16	358 (12.2%)	24 (5.6%)	0.23	427 (7.3%)	37 (3.9%)	0.15	1,050 (8.4%)	82 (4.2%)
...2011; n (%)	263 (7.1%)	25 (4.2%)		0.13	421 (14.3%)	45 (10.4%)	0.12	467 (8.0%)	49 (5.2%)	0.11	1,151 (9.2%)	119 (6.0%)
...2012; n (%)	245 (6.7%)	41 (6.9%)		-0.01	377 (12.8%)	50 (11.6%)	0.04	485 (8.3%)	69 (7.3%)	0.04	1,107 (8.9%)	160 (8.1%)
...2013; n (%)	241 (6.5%)	54 (9.0%)		-0.09	357 (12.2%)	56 (13.0%)	-0.02	757 (13.0%)	121 (12.9%)	0.00	1,355 (10.9%)	231 (11.7%)
...2014; n (%)	247 (6.7%)	38 (6.4%)		0.01	266 (9.1%)	48 (11.1%)	-0.07	888 (15.2%)	177 (18.8%)	-0.10	1,403 (11.3%)	263 (13.4%)
...2015; n (%)	258 (7.0%)	44 (7.4%)		-0.02	257 (8.7%)	66 (15.3%)	-0.20	1,009 (17.3%)	171 (18.2%)	-0.02	1,524 (12.2%)	281 (14.3%)
...2016; n (%)	322 (8.7%)	67 (11.2%)		-0.08	281 (9.6%)	65 (15.1%)	-0.17	784 (13.4%)	148 (15.7%)	-0.07	1,387 (11.1%)	280 (14.2%)
...2017; n (%)	399 (10.8%)	78 (13.1%)		-0.07	193 (6.6%)	50 (11.6%)	-0.17	659 (11.3%)	169 (18.0%)	-0.19	1,251 (10.0%)	297 (15.1%)
...2018; n (%)	435 (11.8%)	86 (14.4%)		-0.08	114 (3.9%)	27 (6.3%)	-0.11	-----	-----		-----	-----
...2019; n (%)	479 (13.0%)	103 (17.3%)		-0.12	-----	-----	-----	-----	-----		-----	-----
...2020; n (%)	265 (7.2%)	40 (6.7%)		0.02	-----	-----	-----	-----	-----		-----	-----
Age												
...mean (sd)	75.71 (7.42)	75.93 (7.65)		-0.03	74.38 (9.05)	74.49 (9.12)	-0.01	76.85 (6.58)	76.94 (6.49)	-0.01	75.93 (7.48)	76.10 (7.49)
...median [IQR]	76.00 [71.00]	76.00 [71.00]		0.00	75.00 [68.00]	75.00 [68.00]	0.00	76.00 [72.00]	77.00 [72.00]	-0.15	75.76 (8.66)	76.26 (8.81)
Region												
...1 - Northeast; n (%)	366 (9.9%)	99 (16.6%)		-0.20	423 (14.4%)	95 (22.0%)	-0.20	1,018 (17.5%)	194 (20.6%)	-0.08	1,807 (14.5%)	388 (19.7%)
...2 - North Central; n (%)	1,037 (28.2%)	143 (24.0%)		0.10	1,176 (40.0%)	150 (34.8%)	0.11	1,482 (25.4%)	225 (23.9%)	0.03	3,695 (29.7%)	518 (26.3%)
...3 - South; n (%)	1,352 (36.7%)	221 (37.0%)		-0.01	914 (31.1%)	137 (31.8%)	-0.02	2,336 (40.1%)	375 (39.9%)	0.00	4,602 (37.0%)	733 (37.2%)
...4 - West; n (%)	925 (25.1%)	131 (21.9%)		0.08	420 (14.3%)	49 (11.4%)	0.09	988 (16.9%)	147 (15.6%)	0.04	2,333 (18.7%)	327 (16.6%)
Race												
...White; n (%)	2,727 (74.1%)	448 (75.0%)		-0.02	-----	-----	4,818 (82.7%)	806 (85.7%)	-0.08	7,545 (60.6%)	1,254 (63.7%)	-0.06
...Asian; n (%)	75 (2.0%)	11 (1.8%)		0.01	-----	-----	N/A	N/A	N/A	N/A	N/A	N/A
...Black; n (%)	346 (9.4%)	62 (10.4%)		-0.03	-----	-----	628 (10.8%)	86 (9.1%)	0.06	974 (7.8%)	148 (7.5%)	0.01
...Hispanic; n (%)	228 (6.2%)	39 (6.5%)		-0.01	-----	-----	N/A	N/A	N/A	N/A	N/A	N/A
...North American Native; n (%)	-----	-----		-----	-----	-----	N/A	N/A	N/A	N/A	N/A	N/A
...Other; n (%)	-----	-----		-----	-----	-----	108 (1.9%)	16 (1.7%)	0.02	108 (1.9%)	16 (1.7%)	0.02
Cardiovascular event prognosticators												
Acute or Old MI; n (%)	1,428 (38.8%)	232 (38.9%)		0.00	713 (24.3%)	97 (22.5%)	0.04	2,039 (35.0%)	354 (37.6%)	-0.05	4,180 (33.6%)	683 (34.7%)
Anxiety; n (%)	228 (6.2%)	37 (6.2%)		0.00	125 (4.3%)	24 (5.6%)	-0.06	399 (6.8%)	58 (6.2%)	0.02	752 (6.0%)	119 (6.0%)
Atrial Fibrillation; n (%)	633 (17.2%)	101 (16.9%)		0.01	387 (13.2%)	73 (16.9%)	-0.10	1,148 (19.7%)	207 (22.0%)	-0.06	2,168 (17.4%)	381 (19.3%)
Coronary Atherosclerosis; n (%)	2,781 (75.6%)	475 (79.6%)		-0.10	2,116 (72.0%)	316 (73.3%)	-0.03	4,790 (82.2%)	776 (82.5%)	-0.01	9,687 (77.8%)	1,567 (79.6%)
Coronary, Carotid, Iliac, Femoral, and Popliteal Revascularization (Angioplasty/Stent/CABG); n (%)	358 (9.7%)	50 (8.4%)		0.05	269 (9.2%)	35 (8.1%)	0.04	611 (10.5%)	71 (7.5%)	0.10	1,238 (9.9%)	156 (7.9%)
Diabetes with Complications; n (%)	1,297 (35.2%)	208 (34.8%)		0.01	357 (12.2%)	63 (14.6%)	-0.07	4,642 (79.6%)	736 (78.2%)	0.03	6,296 (50.6%)	1,007 (51.1%)
Diabetes without Complications; n (%)	747 (20.3%)	131 (21.9%)		-0.04	945 (32.2%)	143 (33.2%)	-0.02	2,203 (37.8%)	355 (37.7%)	0.00	3,895 (31.3%)	629 (31.9%)
DVT; n (%)	150 (4.1%)	27 (4.5%)		-0.02	108 (3.7%)	6 (1.4%)	0.15	257 (4.4%)	43 (4.6%)	-0.01	515 (4.1%)	76 (3.9%)
Edema; n (%)	344 (9.3%)	68 (11.4%)		-0.07	178 (6.1%)	30 (7.0%)	-0.04	721 (12.4%)	138 (14.7%)	-0.07	1,243 (10.0%)	236 (12.0%)
Erectile dysfunction; n (%)	455 (12.4%)	82 (13.7%)		-0.04	265 (9.0%)	44 (10.2%)	-0.04	705 (12.1%)	123 (13.1%)	-0.03	1,425 (11.4%)	249 (12.6%)
Foot ulcer; n (%)	90 (2.4%)	23 (3.9%)		-0.09	52 (1.8%)	10 (2.3%)	-0.04	262 (4.5%)	49 (5.2%)	-0.03	404 (3.2%)	82 (4.2%)
Hyperlipidemia; n (%)	3,088 (83.9%)	511 (85.6%)		-0.05	1,865 (63.5%)	302 (70.1%)	-0.14	5,283 (90.6%)	858 (91.2%)	-0.02	10,236 (82.2%)	1,671 (84.9%)
Hypertension; n (%)	3,188 (86.6%)	522 (87.4%)		-0.02	2,192 (74.6%)	331 (76.8%)	-0.05	5,428 (93.1%)	880 (93.5%)	-0.02	10,808 (86.8%)	1,733 (88.0%)
Intracranial or Retroperitoneal Hemorrhage; n (%)	54 (1.5%)	5 (0.8%)		0.07	20 (0.7%)	5 (1.2%)	-0.05	N/A	N/A	N/A	N/A	N/A
Ischemic Heart Disease; n (%)	3,026 (82.2%)	504 (84.4%)		-0.06	2,250 (76.6%)	333 (77.3%)	-0.02	5,000 (85.8%)	806 (85.7%)	0.00	10,276 (82.6%)	1,643 (83.4%)
Ischemic Stroke; n (%)	644 (17.5%)	119 (19.9%)		-0.06	497 (16.9%)	79 (18.3%)	-0.04	1,510 (25.9%)	232 (24.7%)	0.03	2,651 (21.3%)	430 (21.8%)
Major Trauma; n (%)	196 (5.3%)	30 (5.0%)		0.01	117 (4.0%)	21 (4.9%)	-0.04	410 (7.0%)	56 (6.0%)	0.04	723 (5.8%)	107 (5.4%)
Obesity; n (%)	524 (14.2%)	68 (11.4%)		0.08	252 (8.6%)	47 (10.9%)	-0.08	976 (16.7%)	164 (17.4%)	-0.02	1,752 (14.1%)	279 (14.2%)
Other Disorders of Thyroid Gland; n (%)	112 (3.0%)	18 (3.0%)		0.00	69 (2.3%)	13 (3.0%)	-0.04	262 (4.5%)	38 (4.0%)	0.02	443 (3.6%)	69 (3.5%)
Overweight; n (%)	294 (8.0%)	46 (7.7%)		0.01	83 (2.8%)	13 (3.0%)	-0.01	208 (3.6%)	42 (4.5%)	-0.05	585 (4.7%)	101 (5.1%)
PE; n (%)	59 (1.6%)	10 (1.7%)		-0.01	39 (1.3%)	2 (0.5%)	0.08	99 (1.7%)	14 (1.5%)	0.02	197 (1.6%)	26 (1.3%)
Peripheral Vascular Disease; n (%)	1,234 (33.5%)	205 (34.3%)		-0.02	705 (24.0%)	117 (27.1%)	-0.07	1,798 (30.8%)	277 (29.4%)	0.03	3,737 (30.0%)	599 (30.4%)
Stable Angina; n (%)	490 (13.3%)	83 (13.9%)		-0.02	276 (9.4%)	37 (8.6%)	0.03	769 (13.2%)	115 (12.2%)	0.03	1,535 (12.3%)	235 (11.9%)
Systemic Embolism; n (%)	60 (1.6%)	11 (1.8%)		-0.02	49 (1.7%)	10 (2.3%)	-0.04	N/A	N/A	N/A	N/A	N/A
TIA; n (%)	90 (2.4%)	22 (3.7%)		-0.08	63 (2.1%)	10 (2.3%)	-0.01	266 (4.6%)	36 (3.8%)	0.04	419 (3.4%)	68 (3.5%)
General Health/Mortality Prognosticators												
Abnormal liver function; n (%)	333 (9.0%)	55 (9.2%)		-0.01	189 (6.4%)	28 (6.5%)	0.00	574 (9.8%)	97 (10.3%)	-0.02	1,096 (8.8%)	180 (9.1%)
Alcohol Abuse/Dependence; n (%)	72 (2.0%)	17 (2.8%)		-0.05	33 (1.1%)	5 (1.2%)	-0.01	108 (1.9%)	19 (2.0%)	-0.01	213 (1.7%)	41 (2.1%)
Anemias (Sickle-Cell, G6PD Deficiency, Nutrient Deficiency); n (%)	840 (22.8%)	157 (26.3%)		-0.08	492 (16.7%)	72 (16.7%)	0.00	1,970 (33.8%)	286 (30.4%)	0.07	3,302 (26.5%)	515 (26.2%)
Asthma; n (%)	150 (4.1%)	22 (3.7%)		0.02	106 (3.6%)	22 (5.1%)	-0.07	351 (6.0%)	58 (6.2%)	-0.01	607 (4.9%)	102 (5.2%)
COPD; n (%)	859 (23.3%)	137 (22.9%)		0.01	502 (17.1%)	79 (18.3%)	-0.03	1,421 (24.4%)	223 (23.7%)	0.02	2,782 (22.3%)	439 (22.3%)
Delirium; n (%)	69 (1.9%)	16 (2.7%)		-0.05	50 (1.7%)	5 (1.2%)	0.04	177 (3.0%)	36 (3.8%)	-0.04	296 (2.4%)	57 (2.9%)

Table 1 Unmatched

Dementia; n (%)	101 (2.7%)	18 (3.0%)	-0.02	56 (1.9%)	10 (2.3%)	-0.03	222 (3.8%)	31 (3.3%)	0.03	379 (3.0%)	59 (3.0%)	0.00
Depression; n (%)	318 (8.6%)	48 (8.0%)	0.02	157 (5.3%)	25 (5.8%)	-0.02	561 (9.6%)	77 (8.2%)	0.05	1,036 (8.3%)	150 (7.6%)	0.03
Falls; n (%)	229 (6.2%)	42 (7.0%)	-0.03	68 (2.3%)	13 (3.0%)	-0.04	351 (6.0%)	72 (7.7%)	-0.07	648 (5.2%)	127 (6.4%)	-0.05
Fractures; n (%)	226 (6.1%)	32 (5.4%)	0.03	147 (5.0%)	22 (5.1%)	0.00	341 (5.9%)	47 (5.0%)	0.04	714 (5.7%)	101 (5.1%)	0.03
HIV/AIDS; n (%)	6 (0.2%)	2 (0.3%)	-0.02	1 (0.0%)	0 (0.0%)		N/A	N/A	N/A	N/A	N/A	N/A
Organ Transplant; n (%)	16 (0.4%)	5 (0.8%)	-0.05	20 (0.7%)	4 (0.9%)	-0.02	N/A	N/A	N/A	N/A	N/A	N/A
Osteoporosis; n (%)	201 (5.5%)	27 (4.5%)	0.05	134 (4.6%)	14 (3.2%)	0.07	399 (6.8%)	56 (6.0%)	0.03	734 (5.9%)	97 (4.9%)	0.04
Peptic Ulcer Disease; n (%)	892 (24.2%)	154 (25.8%)	-0.04	437 (14.9%)	80 (18.6%)	-0.10	1,593 (27.3%)	259 (27.5%)	0.00	2,922 (23.5%)	493 (25.0%)	-0.04
Pneumonia; n (%)	72 (2.0%)	17 (2.8%)	-0.05	134 (4.6%)	17 (3.9%)	0.03	108 (1.9%)	19 (2.0%)	-0.01	314 (2.5%)	53 (2.7%)	-0.01
Renal Failure; n (%)	775 (21.1%)	142 (23.8%)	-0.06	393 (13.4%)	57 (13.2%)	0.01	1,467 (25.2%)	252 (26.8%)	-0.04	2,635 (21.2%)	451 (22.9%)	-0.04
Renal Failure (CKD Stage 4 or higher); n (%)	128 (3.5%)	20 (3.4%)	0.01	95 (3.2%)	12 (2.8%)	0.02	311 (5.3%)	50 (5.3%)	0.00	534 (4.3%)	82 (4.2%)	0.00
Sleep Apnea; n (%)	432 (11.7%)	57 (9.5%)	0.07	317 (10.8%)	44 (10.2%)	0.02	741 (12.7%)	109 (11.6%)	0.03	1,490 (12.0%)	210 (10.7%)	0.04
Sleep Disorder; n (%)	295 (8.0%)	29 (4.9%)	0.13	307 (10.4%)	39 (9.0%)	0.05	760 (13.0%)	104 (11.1%)	0.06	1,362 (10.9%)	172 (8.7%)	0.07
Smoking; n (%)	1,015 (27.6%)	194 (32.5%)	-0.11	352 (12.0%)	71 (16.5%)	-0.13	1,758 (30.2%)	296 (31.5%)	-0.03	3,125 (25.1%)	561 (28.5%)	-0.08
Frailty Score: Empirical Version 365 days (ICD-9 and ICD-10) v2												
...mean (sd)	0.17 (0.05)	0.17 (0.05)	0.00	0.16 (0.05)	0.16 (0.05)	0.00	0.20 (0.06)	0.19 (0.06)	0.17	0.18 (0.05)	0.18 (0.06)	0.00
...median [IQR]	0.16 [0.13, 0.16]	0.16 [0.13, 0.16]	0.00	0.15 [0.13, 0.15]	0.15 [0.13, 0.15]	0.00	0.19 [0.16, 0.18]	0.15 [0.15, 0.17]	0.17	0.17 (0.06)	0.17 (0.06)	0.00
<b>Healthcare utilization</b>												
Any hospitalization; n (%)	905 (24.6%)	155 (26.0%)	-0.03	786 (26.8%)	95 (22.0%)	0.11	1,691 (29.0%)	250 (26.6%)	0.05	3,382 (27.2%)	500 (25.4%)	0.04
Bone mineral density; n (%)	162 (4.4%)	23 (3.9%)	0.03	78 (2.7%)	10 (2.3%)	0.03	245 (4.2%)	43 (4.6%)	-0.02	485 (3.9%)	76 (3.9%)	0.00
BUN tests; n (%)	502 (13.6%)	89 (14.9%)	-0.04	281 (9.6%)	48 (11.1%)	-0.05	1,511 (19.7%)	184 (19.6%)	0.00	1,934 (15.5%)	321 (16.3%)	-0.02
Cardiologist visit												
0	1,492 (40.5%)	205 (34.3%)	0.13	1,317 (44.8%)	193 (44.8%)	0.00	1,338 (23.0%)	195 (20.7%)	0.06	4,147 (33.3%)	593 (30.1%)	0.07
1-2	1,101 (29.9%)	175 (29.3%)	0.01	744 (25.3%)	115 (26.7%)	-0.03	1,920 (32.9%)	325 (34.5%)	-0.03	3,765 (30.2%)	615 (31.2%)	-0.02
3-5	665 (18.1%)	146 (24.5%)	-0.16	536 (18.2%)	76 (17.6%)	0.02	1,567 (26.9%)	254 (27.0%)	0.00	2,768 (22.2%)	476 (24.2%)	-0.05
>=6	423 (11.5%)	71 (11.9%)	-0.01	341 (11.6%)	47 (10.9%)	0.02	1,004 (17.2%)	167 (17.7%)	-0.01	1,768 (14.2%)	285 (14.5%)	-0.01
Colonoscopy; n (%)	412 (11.2%)	69 (11.6%)	-0.01	330 (11.2%)	43 (10.0%)	0.04	632 (10.8%)	109 (11.6%)	-0.03	1,374 (11.0%)	221 (11.2%)	-0.01
Endocrinologist Visit; n (%)	178 (4.8%)	20 (3.4%)	0.07	83 (2.8%)	15 (3.5%)	-0.04	563 (9.7%)	93 (9.9%)	-0.01	824 (6.6%)	128 (6.5%)	0.00
Fecal occult blood (FOB) test; n (%)	300 (8.1%)	52 (8.7%)	-0.02	127 (4.3%)	20 (4.6%)	-0.01	401 (6.9%)	64 (6.8%)	0.00	828 (6.7%)	136 (6.9%)	-0.01
Flu vaccine; n (%)	1,333 (36.2%)	218 (36.5%)	-0.01	588 (20.0%)	82 (19.0%)	0.03	3,495 (60.0%)	617 (65.6%)	-0.12	5,416 (43.5%)	917 (46.6%)	-0.06
Glucose test strips; n (%)	86 (2.3%)	14 (2.3%)	0.00	45 (1.5%)	8 (1.9%)	-0.03	357 (6.1%)	63 (6.7%)	-0.02	488 (3.9%)	85 (4.3%)	-0.02
Glucose tests; n (%)	578 (15.7%)	101 (16.9%)	-0.03	336 (11.4%)	59 (13.7%)	-0.07	1,837 (31.5%)	276 (29.3%)	0.05	2,751 (22.1%)	436 (22.1%)	0.00
HbA1c tests; n (%)	1,554 (42.2%)	280 (46.9%)	-0.09	570 (19.4%)	97 (22.5%)	-0.08	4,510 (77.4%)	724 (76.9%)	0.01	6,634 (53.3%)	1,101 (55.9%)	-0.05
<b>Imaging/Diagnostics Used in Prostate Cancer</b>												
0	1,717 (46.6%)	197 (33.0%)	0.28	1,366 (46.5%)	132 (30.6%)	0.33	2,879 (49.4%)	355 (37.7%)	0.24	5,962 (47.9%)	684 (34.7%)	0.27
1-3	1,620 (44.0%)	323 (54.1%)	-0.20	1,243 (42.3%)	217 (50.3%)	-0.16	2,248 (38.6%)	438 (46.5%)	-0.16	5,111 (41.1%)	978 (49.7%)	-0.17
>=4	344 (9.3%)	77 (12.9%)	-0.11	329 (11.2%)	82 (19.0%)	-0.22	702 (12.0%)	148 (15.7%)	-0.11	1,375 (11.0%)	307 (15.6%)	-0.14
Internal Medicine/Family Medicine Visits; n (%)	3,489 (94.8%)	568 (95.1%)	-0.01	2,513 (85.5%)	377 (87.5%)	-0.06	5,219 (89.5%)	838 (89.1%)	0.01	11,221 (90.1%)	1,783 (90.6%)	-0.02
Lipid tests; n (%)	2,689 (73.1%)	439 (73.5%)	-0.01	1,011 (34.4%)	152 (35.3%)	-0.02	5,013 (86.0%)	789 (83.8%)	0.06	8,713 (70.0%)	1,380 (70.1%)	0.00
Microalbuminuria tests; n (%)	921 (25.0%)	150 (25.1%)	0.00	404 (13.8%)	72 (16.7%)	-0.08	2,428 (41.7%)	425 (45.2%)	-0.07	3,753 (30.1%)	647 (32.9%)	-0.06
<b>Number of different/distinct medication prescriptions</b>												
...mean (sd)	8.01 (6.17)	8.27 (6.02)	-0.04	10.22 (5.52)	10.55 (5.10)	-0.06	11.92 (5.24)	11.69 (4.90)	0.05	10.36 (5.60)	10.40 (5.31)	-0.01
...median [IQR]	8.00 [3.00, 12]	8.00 [4.00, 12]	0.00	9.00 [6.00, 13]	10.00 [7.00, 11]	-0.19	11.00 [8.00, 11]	11.00 [8.00, 11]	0.00	9.64 (6.20)	9.87 (5.91)	-0.04
<b>Office Visits (outpatient setting only)</b>												
...mean (sd)	12.48 (6.80)	12.44 (6.38)	0.01	12.31 (7.03)	12.46 (6.32)	-0.02	14.62 (7.67)	14.29 (6.95)	0.05	13.44 (7.27)	13.33 (6.65)	0.02
...median [IQR]	11.00 [8.00, 11]	11.00 [8.00, 15.00]	0.00	11.00 [8.00, 11]	11.00 [8.00, 11]	0.00	13.00 [9.00, 11]	13.00 [9.00, 11]	0.00	11.94 (8.02)	11.96 (7.38)	0.00
<b>Oncology Specialist Visit</b>												
0	2,571 (69.8%)	409 (68.5%)	0.03	2,668 (90.8%)	390 (90.5%)	0.01	3,246 (55.7%)	552 (58.7%)	-0.06	8,485 (68.2%)	1,351 (68.6%)	-0.01
1-5	455 (12.4%)	77 (12.9%)	-0.02	112 (3.8%)	16 (3.7%)	0.01	1,059 (18.2%)	185 (19.7%)	-0.04	1,626 (13.1%)	278 (14.1%)	-0.03
>=6	655 (17.8%)	111 (18.6%)	-0.02	158 (5.4%)	25 (5.8%)	-0.02	1,524 (26.1%)	204 (21.7%)	0.10	2,337 (18.8%)	340 (17.3%)	0.04
Pneumonia vaccine; n (%)	958 (26.0%)	183 (30.7%)	-0.10	276 (9.4%)	49 (11.4%)	-0.07	1,445 (24.8%)	281 (29.9%)	-0.11	2,679 (21.5%)	513 (26.1%)	-0.11
<b>Prostate cancer prognosticators</b>												
Radiation Therapies Used in Prostate Cancer; n (%)	18 (0.5%)	1 (0.2%)	0.05	7 (0.2%)	0 (0.0%)	0.06	N/A	N/A	N/A	N/A	N/A	N/A
PSA Test												
...mean (sd)	2.42 (1.78)	2.40 (1.74)	0.01	1.19 (3.39)	1.00 (1.51)	0.12	2.59 (1.58)	2.41 (1.43)	0.12	2.21 (2.20)	2.10 (1.55)	0.06
...median [IQR]	2.00 [1.00, 3]	2.00 [1.00, 3]	0.00	0.00 [0.00, 2]	0.00 [0.00, 2]	0.00	2.00 [2.00, 3]	2.00 [1.00, 3]	-1.33	1.53 (2.74)	1.56 (1.73)	-0.01
Prostatectomy; n (%)	146 (4.0%)	18 (3.0%)	0.05	117 (4.0%)	11 (2.6%)	0.08	132 (2.3%)	22 (2.3%)	0.00	395 (3.2%)	51 (2.6%)	0.04
Prostate exam for DRE												
...mean (sd)	1.19 (3.27)	1.18 (2.90)	0.00	0.31 (1.48)	0.31 (1.42)	0.17	0.38 (0.81)	0.42 (0.82)	-0.05			
...median [IQR]	0.00 [0.00, 0]	0.00 [0.00, 0]	0.00	0.00 [0.00, 0]	0.00 [0.00, 0]	0.17	0.00 [0.00, 0]	0.00 [0.00, 1]	0.00			
<b>Prostate Cancer Comorbidity Index (PCCI)</b>												
...mean (sd)	35.65 (6.07)	36.68 (6.34)	-0.17	33.34 (4.90)	34.65 (5.37)	-0.02	36.36 (6.00)	36.99 (6.37)	-0.10	35.44 (5.78)	36.38 (6.16)	-0.16
...median [IQR]	35.00 [31.00, 36.00]	32.00 [32.00, 36.00]	0.00	33.00 [30.00, 34.00]	30.00 [30.00, 34.00]	-0.02	35.00 [32.00, 36.00]	33.00 [33.00, 36.00]	-0.16	34.53 (6.24)	35.56 (6.74)	-0.16
<b>Medications</b>												
ACE inhibitors; n (%)	1,263 (34.3%)	190 (31.8%)	0.05	1,161 (39.5%)	181 (42.0%)	-0.05	2,704 (46.4%)	461 (49.0%)	-0.05	5,128 (41.2%)	832 (42.3%)	-0.02

**Table 1 Unmatched**

Anti-arrhythmics; n (%)	54 (1.5%)	12 (2.0%)	-0.04	55 (1.9%)	5 (1.2%)	0.06	136 (2.3%)	20 (2.1%)	0.01	245 (2.0%)	37 (1.9%)	0.01
Anti-diabetic Drugs; n (%)	747 (20.3%)	131 (21.9%)	-0.04	752 (25.6%)	118 (27.4%)	-0.04	3,789 (65.0%)	582 (61.8%)	0.07	5,288 (42.5%)	831 (42.2%)	0.01
Chemotherapies Used in Prostate Cancer; n (%)	18 (0.5%)	1 (0.2%)	0.05	10 (0.3%)	0 (0.0%)	0.08	N/A	N/A	N/A	N/A	N/A	N/A
Metformin; n (%)	486 (13.2%)	87 (14.6%)	-0.04	388 (13.2%)	68 (15.8%)	-0.07	2,144 (36.8%)	346 (36.8%)	0.00	3,018 (24.2%)	501 (25.4%)	-0.03
Use of anticonvulsants; n (%)	354 (9.6%)	52 (8.7%)	0.03	293 (10.0%)	44 (10.2%)	-0.01	901 (15.5%)	138 (14.7%)	0.02	1,548 (12.4%)	234 (11.9%)	0.02
Use of antidepressants; n (%)	426 (11.6%)	70 (11.7%)	0.00	379 (12.9%)	58 (13.5%)	-0.02	1,015 (17.4%)	144 (15.3%)	0.06	1,820 (14.6%)	272 (13.8%)	0.02
Use of Antiparkinsonian Meds; n (%)	51 (1.4%)	13 (2.2%)	-0.06	69 (2.3%)	7 (1.6%)	0.05	207 (3.6%)	18 (1.9%)	0.10	327 (2.6%)	38 (1.9%)	0.05
Use of antiplatelet agents; n (%)	985 (26.8%)	161 (27.0%)	0.00	1,135 (38.6%)	162 (37.6%)	0.02	2,276 (39.0%)	356 (37.8%)	0.02	4,396 (35.3%)	679 (34.5%)	0.02
Use of antipsychotics; n (%)	25 (0.7%)	7 (1.2%)	-0.05	35 (1.2%)	8 (1.9%)	-0.06	N/A	N/A	N/A	N/A	N/A	N/A
Use of anxiolytics/hypnotics; n (%)	137 (3.7%)	25 (4.2%)	-0.03	176 (6.0%)	25 (5.8%)	0.01	428 (7.3%)	62 (6.6%)	0.03	741 (6.0%)	112 (5.7%)	0.01
Use of ARBs; n (%)	573 (15.6%)	100 (16.8%)	-0.03	627 (21.3%)	88 (20.4%)	0.02	1,403 (24.1%)	230 (24.4%)	-0.01	2,603 (20.9%)	418 (21.2%)	-0.01
Use of Benzos; n (%)	355 (9.6%)	60 (10.1%)	-0.02	409 (13.9%)	45 (10.4%)	0.11	594 (10.2%)	108 (11.5%)	-0.04	1,358 (10.9%)	213 (10.8%)	0.00
Use of beta blockers; n (%)	1,806 (49.1%)	305 (51.1%)	-0.04	1,879 (64.0%)	286 (66.4%)	-0.05	3,987 (68.4%)	689 (73.2%)	-0.11	7,672 (61.6%)	1,280 (65.0%)	-0.07
Use of bisphosphonate; n (%)	105 (2.9%)	9 (1.5%)	0.10	82 (2.8%)	5 (1.2%)	0.11	175 (3.0%)	18 (1.9%)	0.07	362 (2.9%)	32 (1.6%)	0.09
Use of calcium channel blockers; n (%)	837 (22.7%)	154 (25.8%)	-0.07	889 (30.3%)	113 (26.2%)	0.09	1,955 (33.5%)	294 (31.2%)	0.05	3,681 (29.6%)	561 (28.5%)	0.02
Use of COPD/asthma meds; n (%)	468 (12.7%)	82 (13.7%)	-0.03	513 (17.5%)	89 (20.6%)	-0.08	1,128 (19.4%)	166 (17.6%)	0.05	2,109 (16.9%)	337 (17.1%)	-0.01
Use of Dementia Meds; n (%)	30 (0.8%)	10 (1.7%)	-0.08	63 (2.1%)	8 (1.9%)	0.01	153 (2.6%)	19 (2.0%)	0.04	246 (2.0%)	37 (1.9%)	0.01
Use of digoxin; n (%)	53 (1.4%)	12 (2.0%)	-0.05	93 (3.2%)	12 (2.8%)	0.02	211 (3.6%)	43 (4.6%)	-0.05	357 (2.9%)	67 (3.4%)	-0.03
Use of heparin and other low-molecular weight heparins; n (%)	40 (1.1%)	8 (1.3%)	-0.02	62 (2.1%)	7 (1.6%)	0.04	107 (1.8%)	25 (2.7%)	-0.06	209 (1.7%)	40 (2.0%)	-0.02
Use of insulin; n (%)	214 (5.8%)	34 (5.7%)	0.00	223 (7.6%)	34 (7.9%)	-0.01	1,154 (19.8%)	186 (19.8%)	0.00	1,591 (12.8%)	254 (12.9%)	0.00
Use of Lithium; n (%)	6 (0.2%)	0 (0.0%)	0.06	2 (0.1%)	0 (0.0%)	0.04	N/A	N/A	N/A	N/A	N/A	N/A
Use of Loop Diuretics; n (%)	338 (9.2%)	59 (9.9%)	-0.02	395 (13.4%)	61 (14.2%)	-0.02	1,199 (20.6%)	197 (20.9%)	-0.01	1,932 (15.5%)	317 (16.1%)	-0.02
Use of nitrates; n (%)	524 (14.2%)	75 (12.6%)	0.05	630 (21.4%)	82 (19.0%)	0.06	1,348 (23.1%)	205 (21.8%)	0.03	2,502 (20.1%)	362 (18.4%)	0.04
Use of NSAIDs; n (%)	405 (11.0%)	74 (12.4%)	-0.04	402 (13.7%)	57 (13.2%)	0.01	1,015 (17.4%)	132 (14.0%)	0.09	1,822 (14.6%)	263 (13.4%)	0.03
Use of opioids; n (%)	1,034 (28.1%)	173 (29.0%)	-0.02	1,087 (37.0%)	171 (39.7%)	-0.06	2,338 (40.1%)	369 (39.2%)	0.02	4,459 (35.8%)	713 (36.2%)	-0.01
Use of oral antiocoagulants (Dabigatran, Rivaroxaban, Apixaban, Warfarin); n (%)	326 (8.9%)	52 (8.7%)	0.01	350 (11.9%)	53 (12.3%)	-0.01	822 (14.1%)	147 (15.6%)	-0.04	1,498 (12.0%)	252 (12.8%)	-0.02
Use of oral corticosteroids; n (%)	700 (19.0%)	134 (22.4%)	-0.08	710 (24.2%)	103 (23.9%)	0.01	1,538 (26.4%)	252 (26.8%)	-0.01	2,948 (23.7%)	489 (24.8%)	-0.03
Use of other antiplatelet agents; n (%)	33 (0.9%)	8 (1.3%)	-0.04	50 (1.7%)	3 (0.7%)	0.09	N/A	N/A	N/A	N/A	N/A	N/A
Use of other diuretics; n (%)	100 (2.7%)	16 (2.7%)	0.00	122 (4.2%)	22 (5.1%)	-0.04	289 (5.0%)	52 (5.5%)	-0.02	511 (4.1%)	90 (4.6%)	-0.02
Use of other hypertension drugs; n (%)	274 (7.4%)	49 (8.2%)	-0.03	266 (9.1%)	32 (7.4%)	0.06	661 (11.3%)	91 (9.7%)	0.05	1,201 (9.6%)	172 (8.7%)	0.03
Use of other lipid-lowering drugs; n (%)	329 (8.9%)	45 (7.5%)	0.05	477 (16.2%)	55 (12.8%)	0.10	910 (15.6%)	135 (14.3%)	0.04	1,716 (13.8%)	235 (11.9%)	0.06
Use of statins; n (%)	2,231 (60.6%)	374 (62.6%)	-0.04	2,230 (75.9%)	342 (79.4%)	-0.08	4,610 (79.1%)	766 (81.4%)	-0.06	9,071 (72.9%)	1,482 (75.3%)	-0.05
Use of thiazide; n (%)	321 (8.7%)	46 (7.7%)	0.04	315 (10.7%)	45 (10.4%)	0.01	730 (12.5%)	113 (12.0%)	0.02	1,366 (11.0%)	204 (10.4%)	0.02

Table 1 Matched

Variable	MATCHED												Pooled		
	Optum			MarketScan			Medicare			Pooled					
Variable	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff	Leuprolide	Degarelix	St. Diff
Number of patients	546	546		415	415		926	926		1,887	1,887				
Year of Cohort Entry Date															
...2008-2009; n (%)															
...2010; n (%)	18 (3.3%)	20 (3.7%)	-0.02	28 (6.7%)	24 (5.8%)	-0.04	46 (5.0%)	37 (4.0%)	-0.05	92 (4.9%)	81 (4.3%)	-0.03			
...2011; n (%)	26 (4.8%)	23 (4.2%)	-0.03	42 (10.1%)	45 (10.8%)	-0.02	53 (5.7%)	49 (5.3%)	-0.02	121 (6.4%)	117 (6.2%)	-0.01			
...2012; n (%)	42 (7.7%)	40 (7.3%)	-0.02	44 (10.6%)	50 (12.0%)	-0.04	92 (9.9%)	69 (7.5%)	-0.08	178 (9.4%)	159 (8.4%)	-0.04			
...2013; n (%)	50 (9.2%)	50 (9.2%)		61 (14.7%)	56 (13.5%)	-0.03	116 (12.5%)	121 (13.1%)	-0.02	227 (12.0%)	227 (12.0%)				
...2014; n (%)	39 (7.1%)	35 (6.4%)	-0.03	42 (10.1%)	46 (11.1%)	-0.03	143 (15.4%)	170 (18.4%)	-0.08	224 (11.9%)	251 (13.3%)	-0.04			
...2015; n (%)	39 (7.1%)	42 (7.7%)	-0.02	58 (14.0%)	60 (14.5%)	-0.01	182 (19.7%)	171 (18.5%)	-0.03	279 (14.8%)	273 (14.5%)	-0.01			
...2016; n (%)	67 (12.3%)	62 (11.4%)	-0.03	63 (15.2%)	63 (15.2%)	0.00	130 (14.0%)	144 (15.6%)	-0.05	260 (13.8%)	269 (14.3%)	-0.01			
...2017; n (%)	65 (11.9%)	74 (13.6%)	-0.05	53 (12.8%)	47 (11.3%)	-0.05	164 (17.7%)	165 (17.8%)	0.00	282 (14.9%)	286 (15.2%)	-0.01			
...2018; n (%)	72 (13.2%)	76 (13.9%)	-0.02	24 (5.8%)	24 (5.8%)	0.00									
...2019; n (%)	89 (16.3%)	91 (16.7%)	-0.01												
...2020; n (%)	39 (7.1%)	33 (6.0%)	0.04												
Age															
...mean (sd)	76.19 (6.92)	76.04 (7.59)	0.02	74.65 (9.34)	74.49 (9.17)	0.02	76.99 (6.56)	77.02 (6.47)	0.00	76.24 (6.74)	76.18 (6.87)	0.01			
...median (IQR)	77.00 [72.00, 81.00]	76.00 [71.00, 82.00]	0.14	75.00 [67.00, 82.00]	75.00 [68.00, 82.00]	0.00	76.00 [72.00, 82.00]	77.00 [72.00, 82.00]	-0.15	76.07 [7.36]	76.27 [7.46]	-0.03			
Region															
...1 - Northeast; n (%)	86 (15.8%)	85 (15.6%)	0.01	94 (22.7%)	82 (23.2%)	0.01	194 (21.0%)	199 (20.4%)	0.01	274 (19.8%)	266 (19.4%)	0.01			
...2 - North Central; n (%)	131 (24.0%)	132 (24.0%)	0.00	145 (34.9%)	144 (34.7%)	0.00	208 (22.5%)	223 (24.1%)	-0.04	484 (25.6%)	498 (26.4%)	-0.02			
...3 - South; n (%)	209 (38.3%)	205 (37.5%)	0.02	139 (33.5%)	130 (31.3%)	0.05	273 (40.3%)	368 (39.7%)	0.01	721 (38.2%)	703 (37.3%)	0.02			
...4 - West; n (%)	120 (22.0%)	125 (22.9%)	-0.02	37 (8.9%)	49 (11.8%)	-0.10	151 (16.3%)	146 (15.8%)	0.01	308 (16.3%)	320 (17.0%)	-0.02			
Race															
...White; n (%)	437 (80.0%)	438 (80.2%)	-0.01				796 (86.0%)	803 (86.7%)	-0.02	1,233 (65.3%)	1,241 (65.8%)	-0.01			
...Asian; n (%)	8 (0.5%)	11 (2.0%)	0.04				N/A	N/A	N/A	N/A	N/A	N/A			
...Black; n (%)	66 (12.1%)	61 (11.5%)	0.03				93 (10.0%)	85 (9.2%)	0.03	159 (8.4%)	146 (7.7%)	0.03			
...Hispanic; n (%)	35 (6.4%)	36 (6.6%)	-0.01				N/A	N/A	N/A	N/A	N/A	N/A			
...North American Native; n (%)	—	—					N/A	N/A	N/A	N/A	N/A	N/A			
...Other; n (%)	—	—					18 (1.9%)	16 (1.7%)	0.02	18 (1.9%)	16 (1.7%)	0.02			
Cardiovascular event prognosticators															
Acute or Old MI; n (%)	204 (37.4%)	212 (38.8%)	-0.03	97 (23.4%)	94 (22.7%)	0.02	357 (39.6%)	348 (37.6%)	0.02	658 (34.9%)	654 (34.7%)	0.00			
Anxiety; n (%)	32 (5.9%)	33 (6.0%)	0.00	20 (4.8%)	22 (5.3%)	-0.02	60 (5.5%)	57 (6.2%)	0.01	112 (5.9%)	112 (5.9%)	0.00			
Atrial Fibrillation; n (%)	84 (15.4%)	80 (16.5%)	-0.03	62 (14.9%)	70 (16.9%)	-0.05	187 (20.2%)	206 (22.2%)	-0.05	335 (17.6%)	366 (19.4%)	-0.05			
Coronary Atherosclerosis; n (%)	436 (79.9%)	432 (79.1%)	0.02	305 (73.5%)	302 (72.8%)	0.02	764 (82.5%)	752 (82.3%)	0.01	1,505 (79.8%)	1,496 (79.3%)	0.01			
Coronary, Carotid, Iliac, Femoral, and Popliteal Revascularization (Angioplasty/Stent/CABG); n (%)	30 (5.5%)	43 (7.9%)	-0.10	40 (9.5%)	52 (7.7%)	-0.08	63 (6.8%)	70 (7.5%)	-0.03	133 (7.1%)	145 (7.7%)	-0.03			
Diabetes with Complications; n (%)	181 (33.2%)	186 (34.1%)	-0.02	62 (14.3%)	58 (14.0%)	0.00	745 (80.5%)	724 (78.2%)	-0.06	988 (52.4%)	968 (51.3%)	-0.02			
Diabetes without Complications; n (%)	98 (17.9%)	116 (21.2%)	-0.08	149 (35.9%)	134 (32.3%)	0.05	340 (36.7%)	351 (37.9%)	-0.02	587 (31.1%)	601 (31.8%)	-0.02			
DVT; n (%)	24 (4.4%)	23 (4.2%)	0.01	7 (1.7%)	6 (1.4%)	0.02	45 (4.9%)	42 (4.5%)	0.02	76 (4.0%)	71 (3.8%)	0.03			
Edema; n (%)	60 (11.0%)	60 (11.0%)	0.00	30 (7.2%)	28 (6.7%)	0.02	136 (14.7%)	135 (14.6%)	0.00	226 (12.0%)	223 (11.8%)	0.01			
Erectile dysfunction; n (%)	76 (14.5%)	77 (14.1%)	-0.01	39 (9.4%)	42 (10.1%)	-0.02	121 (13.1%)	121 (13.1%)	0.00	239 (12.7%)	240 (12.7%)	0.00			
Foot ulcer; n (%)	12 (2.2%)	18 (3.3%)	-0.07	9 (2.2%)	10 (2.4%)	-0.01	48 (5.2%)	48 (5.2%)	0.00	69 (3.7%)	76 (4.0%)	-0.02			
Hyperlipidemia; n (%)	467 (84.1%)	467 (85.5%)	0.04	300 (72.3%)	290 (69.9%)	0.05	837 (90.4%)	843 (91.0%)	-0.02	1,596 (84.6%)	1,600 (84.8%)	-0.01			
Hypertension; n (%)	477 (87.4%)	475 (87.7%)	-0.02	313 (75.4%)	318 (76.5%)	-0.03	862 (93.1%)	867 (93.6%)	-0.02	1,652 (87.5%)	1,664 (88.2%)	-0.02			
Intracranial or Retroperitoneal Hemorrhage; n (%)	7 (0.3%)	5 (0.5%)	0.04	4 (1.0%)	3 (0.7%)	0.03	121 (3.1%)	17 (1.8%)	-0.04	23 (1.1%)	25 (1.3%)	-0.03			
Ischemic Heart Disease; n (%)	461 (84.4%)	457 (83.7%)	0.02	325 (78.3%)	319 (76.9%)	0.03	795 (85.9%)	791 (85.4%)	0.01	1,581 (83.8%)	1,587 (83.0%)	0.02			
Ischemic Stroke; n (%)	101 (18.5%)	103 (18.5%)	0.00	77 (18.6%)	76 (18.3%)	0.01	228 (24.6%)	229 (24.7%)	0.00	406 (21.5%)	406 (21.5%)	0.00			
Major Trauma; n (%)	21 (3.8%)	27 (4.9%)	-0.05	22 (5.3%)	18 (4.3%)	0.05	657 (70.7%)	55 (5.9%)	0.04	108 (5.7%)	100 (5.3%)	0.02			
Obesity; n (%)	66 (12.1%)	59 (10.8%)	0.04	55 (13.3%)	45 (10.8%)	0.08	147 (15.9%)	159 (17.2%)	-0.03	268 (14.2%)	263 (13.9%)	0.03			
Other Disorders of Thyroid Gland; n (%)	12 (2.2%)	16 (2.9%)	-0.04	16 (3.9%)	13 (3.1%)	0.04	34 (3.7%)	38 (4.1%)	-0.02	62 (3.3%)	67 (3.6%)	-0.02			
Overweight; n (%)	38 (7.0%)	40 (7.3%)	-0.01	20 (4.2%)	13 (3.1%)	-0.04	41 (4.4%)	42 (4.5%)	0.00	89 (4.7%)	95 (5.0%)	-0.03			
PE; n (%)	10 (1.8%)	8 (1.5%)	0.02	21 (0.5%)	20 (0.5%)	0.00	103 (11.1%)	97 (10.5%)	0.02	191 (10.1%)	177 (9.4%)	0.02			
Peripheral Vascular Disease; n (%)	191 (35.0%)	185 (33.9%)	0.02	109 (26.3%)	111 (26.7%)	-0.01	284 (30.7%)	272 (29.4%)	0.03	584 (30.9%)	568 (30.1%)	0.02			
Stable Angina; n (%)	62 (11.4%)	75 (13.7%)	-0.07	38 (9.2%)	34 (8.2%)	0.04	107 (11.6%)	112 (12.1%)	-0.02	207 (11.0%)	221 (11.7%)	-0.02			
Systemic Embolism; n (%)	9 (1.6%)	8 (1.5%)	0.01	9 (2.2%)	9 (2.2%)	0.00	N/A	N/A	N/A	N/A	N/A	N/A			
TIA; n (%)	19 (3.5%)	19 (3.5%)	0.00	8 (1.9%)	10 (2.4%)	-0.03	35 (3.8%)	36 (3.9%)	-0.01	62 (3.3%)	65 (3.4%)	-0.01			
General Health/Mortality Prognosticators															
Abnormal liver function; n (%)	57 (10.4%)	63 (9.7%)	0.02	31 (7.5%)	27 (6.5%)	0.04	103 (11.1%)	97 (10.5%)	0.02	191 (10.1%)	177 (9.4%)	0.02			
Alcohol Abuse/Dependence; n (%)	19 (3.5%)	15 (2.7%)	0.05	5 (1.2%)	5 (1.2%)	0.00	181 (19.5%)	68 (16.4%)	0.08	282 (30.5%)	280 (30.2%)	0.01			
Anemias (Sickle-Cell, G6PD Deficiency, Nutrient Deficiency); n (%)	129 (23.6%)	141 (25.8%)	-0.05	81 (19.5%)	68 (16.4%)	0.02	81 (26.1%)	54 (5.8%)	0.01	492 (26.1%)	489 (25.9%)	0.00			
Asthma; n (%)	23 (4.2%)	21 (3.8%)	0.02	21 (5.1%)	21 (5.1%)	0.00	60 (6.5%)	58 (6.3%)	0.01	104 (5.5%)	100 (5.3%)	0.01			
COPD; n (%)	127 (23.3%)	125 (22.9%)	0.01	84 (20.2%)	74 (17.8%)	0.06	236 (25.5%)	221 (23.9%)	0.04	447 (23.7%)	420 (22.3%)	0.03			
Delirium; n (%)	15 (2.7%)	14 (2.6%)	0.01	4 (1.0%)	4 (1.0%)	0.00	34 (3.7%)	34 (3.7%)	0.00	63 (2.8%)	52 (2.8%)	0.00			
Dementia; n (%)	17 (3.1%)	18 (3.3%)	-0.01	11 (2.7%)	9 (2.2%)	0.03	24 (2.6%)	30 (3.2%)	-0.04	52 (2.8%)	57 (3.0%)	-0.01			
Depression; n (%)	49 (9.0%)	45 (8.2%)	0.03	23 (5.9%)	22 (5.3%)	0.01	72 (7.8%)	76 (8.2%)	-0.01	144 (7.6%)	143 (7.6%)	0.00			
Falls; n (%)	31 (5.7%)	38 (7.0%)	-0.05	10 (2.4%)	10 (2.4%)	0.00	60 (6.5%)	71 (7.7%)	-0.05	101 (5.4%)	119 (6.3%)	-0.04			
Fractures; n (%)	35 (6.4%)	29 (5.3%)	0.05	22 (5.3%)	21 (5.1%)	0.01	44 (4.8%)	45 (4.9%)	0.00	101 (5.4%)	95 (5.0%)	0.02			
HIV/AIDS; n (%)	0 (0.0%)	2 (0.4%)	-0.09	0 (0.0%)	0 (0.0%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A			
Organ Transplant; n (%)	1 (0.2%)	3 (0.5%)	-0.05	4 (1.0%)	4 (1.0%)	0.00	N/A	N/A	N/A	N/A	N/A	N/A			
Osteoporosis; n (%)	29 (5.3%)	23 (4.2%)	0.05	14 (3.4%)	12 (2.9%)	0.03	48 (5.2%)	54 (5.8%)	-0.03	91 (4.8%)	89 (4.7%)	0.00			
Peptic Ulcer Disease; n (%)	142 (26.0%)	141 (25.8%)	0.00	73 (17.6%)	72 (17.3%)	0.01	249 (26.9%)	254 (27.4%)							

**Table 1 Matched**

Flu vaccine; n (%)	222 (40.7%)	204 (37.4%)	0.07	84 (20.2%)	79 (19.0%)	0.03	599 (64.7%)	605 (65.3%)	-0.01	805 (48.0%)	888 (47.1%)	0.02
Glucose test strips; n (%)	6 (1.1%)	12 (2.2%)	-0.09	8 (1.9%)	8 (1.9%)	-0.06	59 (6.4%)	63 (6.8%)	-0.02	73 (3.3%)	83 (4.4%)	-0.03
Glucose tests; n (%)	74 (13.6%)	91 (16.7%)	-0.09	73 (17.6%)	54 (13.0%)	0.13	268 (28.9%)	271 (29.3%)	-0.01	415 (22.0%)	416 (22.0%)	0.00
HbA1c tests; n (%)	246 (45.1%)	249 (45.6%)	-0.01	101 (24.3%)	92 (22.2%)	0.05	712 (76.9%)	712 (76.9%)	0.00	1,059 (56.1%)	1,053 (55.8%)	0.01
<b>Imaging/Diagnostics Used in Prostate Cancer</b>												
0	177 (32.4%)	183 (33.2%)	-0.02	128 (30.8%)	132 (31.8%)	-0.02	332 (35.9%)	348 (37.6%)	-0.04	637 (33.8%)	661 (35.0%)	-0.03
1-3	304 (55.7%)	296 (54.2%)	0.03	209 (50.4%)	208 (50.1%)	0.01	449 (48.5%)	433 (46.8%)	0.03	962 (51.0%)	937 (49.7%)	0.03
>4	65 (11.9%)	69 (12.6%)	-0.02	78 (18.3%)	75 (18.1%)	-0.02	145 (15.7%)	145 (15.7%)	0.00	288 (15.3%)	289 (15.3%)	0.00
Internal Medicine/Family Medicine Visits; n (%)	512 (93.8%)	521 (95.4%)	-0.07	368 (88.7%)	364 (87.7%)	0.03	827 (89.3%)	824 (89.0%)	0.01	1,707 (90.5%)	1,709 (90.6%)	0.00
Lipid tests; n (%)	407 (74.5%)	402 (73.6%)	0.02	151 (36.4%)	146 (35.2%)	0.03	770 (83.2%)	775 (83.7%)	-0.01	1,328 (70.4%)	1,323 (70.1%)	0.01
Microalbuminuria tests; n (%)	129 (23.6%)	138 (25.3%)	-0.04	70 (16.9%)	66 (15.9%)	0.03	423 (45.7%)	419 (45.2%)	0.01	622 (33.0%)	623 (33.0%)	0.00
<b>Number of different/distinct medication prescriptions</b>												
-mean (sd)	8.05 (5.80)	8.22 (6.03)	-0.03	10.77 (5.60)	10.45 (5.00)	0.06	11.62 (4.86)	11.67 (4.91)	-0.01	10.40 (4.84)	10.40 (4.79)	0.00
-median (IQR)	8.00 [4.00, 12.00]	8.04 [4.00, 12.00]	0.00	10.00 [7.00, 14.00]	10.00 [7.00, 13.00]	0.00	11.00 [8.00, 15.00]	11.00 [8.00, 15.00]	0.00	9.91 [5.31]	9.91 [5.28]	0.00
<b>Office Visits (outpatient setting only)</b>												
-mean (sd)	12.19 (6.15)	12.35 (6.28)	-0.03	13.06 (6.91)	12.48 (6.36)	0.09	13.78 (6.87)	14.30 (6.98)	-0.08	13.16 (5.92)	13.34 (5.86)	-0.03
-median (IQR)	11.00 [8.00, 15.00]	11.00 [8.00, 15.00]	0.00	12.00 [8.00, 16.00]	11.00 [8.00, 16.00]	0.15	13.00 [9.00, 17.00]	13.00 [9.00, 18.00]	0.00	12.20 (6.68)	11.98 (6.65)	0.03
<b>Oncology Specialist Visit</b>												
0	370 (67.8%)	370 (67.8%)	0.00	368 (88.7%)	375 (90.4%)	-0.06	565 (61.0%)	546 (59.0%)	0.04	1,303 (69.1%)	1,291 (68.4%)	0.02
1-5	73 (13.4%)	72 (13.2%)	0.01	18 (4.3%)	16 (3.9%)	0.02	166 (17.9%)	181 (19.5%)	-0.04	257 (13.6%)	269 (14.3%)	0.02
>6	103 (18.9%)	104 (19.0%)	0.00	29 (7.0%)	24 (5.8%)	0.05	195 (21.1%)	199 (21.5%)	-0.01	322 (17.3%)	227 (17.3%)	0.00
Pneumonia vaccine; n (%)	174 (31.9%)	174 (31.9%)	0.05	45 (10.8%)	48 (11.6%)	-0.02	257 (27.8%)	275 (29.7%)	-0.04	476 (25.2%)	497 (26.3%)	-0.03
<b>Prostate cancer prognosticators</b>												
Radiation Therapies Used in Prostate Cancer; n (%)	3 (0.5%)	1 (0.2%)	0.05	1 (0.2%)	0 (0.0%)	0.06	N/A	N/A	N/A	N/A	N/A	N/A
PSA Test	-	-	-	-	-	-	-	-	-	-	-	-
-mean (sd)	2.38 (1.80)	2.41 (1.75)	-0.02	0.94 (1.45)	1.01 (1.53)	-0.05	2.33 (1.40)	2.40 (1.42)	-0.05	2.04 (1.40)	2.10 (1.41)	0.00
-median (IQR)	2.00 [1.00, 3.00]	2.01 [1.00, 3.25]	0.00	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.00	1.56 [1.54]	1.56 [1.55]	0.00
Prostatectomy; n (%)	14 (2.6%)	17 (3.1%)	-0.03	16 (3.9%)	11 (2.7%)	-0.24	52 (2.4%)	21 (2.3%)	-0.22	52 (2.8%)	49 (2.6%)	0.01
Prostate exam for DRE	-	-	-	-	-	-	-	-	-	-	-	-
-mean (sd)	1.27 (2.39)	1.17 (2.84)	0.03	0.33 (1.24)	0.30 (1.42)	0.07	0.45 (0.90)	0.42 (0.82)	0.03	0.66 (1.94)	0.61 (1.77)	0.00
-median (IQR)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00	0.00 [1.98]	0.00 [1.76]	0.00
<b>Prostate Cancer Comorbidity Index (PCI)</b>												
mean (sd)	36.39 (6.41)	36.50 (6.31)	-0.02	34.75 (5.72)	34.42 (5.19)	0.06	37.00 (6.38)	36.59 (6.21)	0.00	36.33 (5.55)	36.28 (5.35)	0.00
median (IQR)	35.00 [32.00, 40.00]	35.00 [32.00, 40.00]	0.00	34.00 [30.00, 38.00]	34.00 [30.00, 37.00]	0.00	36.00 [32.00, 41.00]	36.00 [33.00, 41.00]	0.00	35.27 (6.25)	35.27 (6.03)	0.00
<b>Medications</b>												
ACE Inhibitors; n (%)	179 (32.8%)	178 (32.6%)	0.00	162 (39.0%)	173 (41.7%)	-0.06	146 (48.2%)	153 (48.9%)	-0.04	787 (41.7%)	804 (42.5%)	-0.02
Anti-arrhythmics; n (%)	9 (1.6%)	11 (2.0%)	0.03	7 (1.7%)	5 (1.7%)	0.04	11 (1.2%)	19 (2.1%)	-0.07	27 (1.4%)	35 (1.9%)	-0.04
Anti-diabetic Drugs; n (%)	141 (21.2%)	140 (20.9%)	0.01	114 (24.7%)	114 (26.7%)	0.01	132 (26.2%)	134 (26.0%)	0.02	312 (43.0%)	299 (42.3%)	0.03
Chemotherapies Used in Prostate Cancer; n (%)	3 (0.5%)	1 (0.2%)	0.05	1 (0.2%)	0 (0.0%)	0.06	N/A	N/A	N/A	N/A	N/A	N/A
Metformin; n (%)	73 (13.4%)	77 (14.1%)	-0.02	76 (18.3%)	62 (14.9%)	0.09	320 (34.6%)	341 (36.8%)	-0.05	469 (24.9%)	480 (25.4%)	-0.03
Use of anticoagulants; n (%)	46 (8.4%)	49 (9.0%)	-0.02	44 (10.6%)	41 (9.9%)	0.02	128 (13.8%)	135 (14.6%)	-0.02	218 (11.6%)	225 (11.9%)	-0.03
Use of antidepressants; n (%)	67 (12.3%)	64 (11.7%)	0.02	46 (11.3%)	53 (12.8%)	-0.05	144 (15.6%)	142 (15.3%)	0.01	257 (13.6%)	259 (13.7%)	0.00
Use of anti-parkinsonian Meds; n (%)	10 (1.8%)	10 (1.8%)	0.00	6 (1.4%)	7 (1.7%)	-0.02	20 (2.2%)	18 (1.9%)	0.02	36 (1.9%)	35 (1.9%)	0.00
Use of antiplatelet agents; n (%)	143 (26.2%)	142 (26.0%)	0.00	164 (39.5%)	153 (36.9%)	0.05	358 (38.7%)	348 (37.6%)	0.02	665 (35.2%)	643 (34.1%)	0.02
Use of antipsychotics; n (%)	6 (1.1%)	6 (1.1%)	0.00	4 (1.0%)	7 (1.7%)	-0.06	N/A	N/A	N/A	N/A	N/A	N/A
Use of anxiety/tx/hypnotics; n (%)	24 (4.4%)	23 (4.2%)	0.01	22 (5.3%)	24 (5.8%)	-0.02	57 (6.2%)	62 (6.7%)	-0.02	103 (5.5%)	109 (5.8%)	-0.03
Use of ARBs; n (%)	81 (14.8%)	87 (15.9%)	-0.03	90 (21.7%)	86 (20.7%)	0.02	248 (26.8%)	228 (24.6%)	0.05	319 (22.2%)	401 (21.3%)	0.02
Use of Benzos; n (%)	51 (9.3%)	54 (9.9%)	-0.02	48 (11.6%)	44 (10.6%)	0.03	98 (10.6%)	103 (11.1%)	-0.02	197 (10.4%)	201 (10.7%)	-0.03
Use of beta blockers; n (%)	273 (50.0%)	278 (50.9%)	-0.02	268 (64.6%)	276 (65.5%)	-0.04	668 (72.1%)	675 (72.9%)	-0.02	1,009 (64.1%)	1,229 (65.1%)	-0.02
Use of bisphosphonate; n (%)	12 (2.2%)	9 (1.6%)	0.04	11 (2.7%)	5 (1.2%)	0.11	181 (1.9%)	18 (1.9%)	0.00	412 (2.4%)	321 (1.7%)	0.04
Use of calcium channel blockers; n (%)	144 (26.4%)	144 (26.4%)	0.00	110 (26.5%)	108 (26.0%)	0.01	288 (31.1%)	291 (31.4%)	-0.01	542 (28.7%)	543 (28.8%)	0.00
Use of COPD/asthma meds; n (%)	75 (13.7%)	78 (14.3%)	-0.02	93 (22.4%)	82 (19.8%)	0.06	172 (18.6%)	163 (17.6%)	0.03	340 (18.0%)	323 (17.1%)	0.02
Use of Dementia Meds; n (%)	6 (1.1%)	8 (1.5%)	-0.04	11 (2.7%)	8 (1.9%)	0.05	20 (2.2%)	19 (2.1%)	0.01	37 (2.0%)	35 (1.9%)	0.03
Use of digoxin; n (%)	9 (1.6%)	10 (1.8%)	-0.02	11 (2.7%)	12 (2.9%)	-0.01	31 (3.3%)	43 (4.6%)	-0.07	51 (2.7%)	65 (3.4%)	-0.04
Use of heparin and other low-molecular weight heparins; n (%)	4 (0.7%)	6 (1.1%)	-0.04	9 (2.2%)	6 (1.4%)	0.06	26 (2.8%)	25 (2.7%)	0.01	39 (2.1%)	37 (2.0%)	0.03
Use of Insulin; n (%)	23 (4.2%)	28 (5.1%)	-0.04	30 (7.2%)	32 (7.7%)	-0.02	174 (18.8%)	184 (19.9%)	-0.03	227 (12.0%)	244 (12.9%)	-0.03
Use of Lithium; n (%)	1 (0.2%)	0 (0.0%)	0.06	0 (0.0%)	0 (0.0%)	0.06	N/A	N/A	N/A	N/A	N/A	N/A
Use of Loop Diuretics; n (%)	45 (8.2%)	52 (9.5%)	-0.05	51 (12.3%)	58 (14.0%)	-0.05	186 (20.1%)	195 (21.1%)	-0.02	282 (14.9%)	305 (16.2%)	-0.04
Use of nitrates; n (%)	74 (13.6%)	69 (12.6%)	0.03	74 (17.8%)	77 (18.6%)	-0.02	198 (21.4%)	201 (21.7%)	-0.01	346 (18.3%)	347 (18.4%)	0.00
Use of NSAIDs; n (%)	71 (13.0%)	69 (12.6%)	0.01	62 (14.9%)	57 (13.7%)	0.03	141 (15.2%)	128 (13.8%)	0.04	274 (14.5%)	254 (13.5%)	0.03
Use of opioid; n (%)	169 (31.0%)	159 (29.1%)	0.04	158 (38.1%)	162 (39.0%)	-0.02	376 (40.6%)	361 (39.0%)	0.03	703 (37.3%)	682 (36.1%)	0.02
Use of oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban, Warfarin); n (%)	46 (8.4%)	46 (8.4%)	0.00	51 (12.3%)	51 (12.3%)	0.06	138 (14.9%)	147 (15.9%)	-0.03	235 (12.5%)	244 (12.9%)	-0.03
Use of oral corticosteroids; n (%)	126 (23.1%)	124 (22.7%)	0.01	110 (26.5%)	100 (24.1%)	0.06	277 (29.9%)	246 (26.6%)	0.07	513 (27.2%)	470 (24.9%)	0.05
Use of other antiplatelet agents; n (%)	8 (1.5%)	5 (0.9%)	0.06	4 (1.0%)	3 (0.7%)	0.03	N/A	N/A	N/A	N/A	N/A	N/A
Use of other diuretics; n (%)	16 (2.9%)	16 (2.9%)	0.00	29 (7.0%)	21 (5.1%)	0.08	48 (5.2%)	51 (5.5%)	-0.01	93 (4.9%)	88 (4.7%)	0.03
Use of other hypertension drugs; n (%)	44 (8.1%)	47 (8.6%)	-0.02	28 (6.7%)	31 (7.5%)	-0.03	96 (10.4%)	90 (9.7%)	0.02	168 (8.9%)	168 (8.9%)	0.00
Use of other lipid-lowering drugs; n (%)	37 (6.8%)	41 (7.5%)	-0.03	45 (10.8%)	51 (12.3%)	-0.05	131 (14.1%)	132 (14.3%)	-0.01	213 (11.3%)	224 (11.9%)	-0.02
Use of statins; n (%)	347 (63.6%)	341 (62.5%)	0.02	324 (78.1%)	327 (78.8%)	-0.02	743 (80.2%)	752 (81.2%)	-0.03	1,414 (74.9%)	1,420 (75.3%)	-0.03
Use of thiazide; n (%)	42 (7.7%)	41 (7.5%)	0.01	40 (9.6%)	43 (10.4%)	-0.03	106 (11.4%)	112 (12.1%)	-0.02	188 (10.0%)	196 (10.4%)	-0.03