Real-world Cardiovascular Outcomes Associated With Degarelix vs Leuprolide for Prostate Cancer Treatment

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Abstract

IMPORTANCE With a growing interest in the use of real-world evidence for regulatory decision-making, it is important to understand whether real-world data can be used to emulate the results of randomized clinical trials.

OBJECTIVE To use electronic health record and administrative claims data to emulate the ongoing PRONOUNCE trial (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease).

DESIGN, SETTING, AND PARTICIPANTS This retrospective, propensity-matched cohort study included adult men with a diagnosis of prostate cancer and cardiovascular disease who initiated either degarelix or leuprolide between December 24, 2008, and June 30, 2019. Participants were commercially insured individuals and Medicare Advantage beneficiaries included in a large US administrative claims database.

EXPOSURES Degarelix or leuprolide.

MAIN OUTCOMES AND MEASURES The primary end point was time to first occurrence of a major adverse cardiovascular event (MACE), defined as death due to any cause, myocardial infarction, or stroke, analogous to the PRONOUNCE trial. Secondary end points were time to death due to any cause, myocardial infarction, stroke, and angina. Cox proportional hazards regression was used to evaluate primary and secondary end points.

RESULTS A total of 32,172 men initiated degarelix or leuprolide for prostate cancer; of them, 9,490 (29.5%) had cardiovascular disease, and 7,800 (24.2%) met the PRONOUNCE trial eligibility criteria and were included in this study. Overall, 165 participants (2.1%) were Asian, 1,390 (17.8%) were Black, 663 (8.5%) were Hispanic, and 5,258 (67.4%) were White. The mean (SD) age was 74.4 (7.4) years. Among 2,226 propensity score–matched patients, no significant difference was observed in the risk of MACE for patients taking degarelix vs those taking leuprolide (10.18 vs 8.60 events per 100 person-years; hazard ratio [HR], 1.18; 95% CI, 0.86-1.61). Degarelix was associated with a higher risk of death from any cause (HR, 1.48; 95% CI, 1.01-2.18) but not of myocardial infarction (HR, 1.16; 95% CI, 0.60-2.25), stroke (HR, 0.92; 95% CI, 0.45-1.85), or angina (HR, 1.36; 95% CI, 0.43-4.27).

CONCLUSIONS AND RELEVANCE In this emulation of a clinical trial of men with cardiovascular disease undergoing treatment for prostate cancer, degarelix was not associated with a lower risk of cardiovascular events than leuprolide. Comparison of these data with PRONOUNCE trial results, when published, will help enhance our understanding of the appropriate role of using real-world data to emulate clinical trials.
Introduction

Prostate cancer is the most common solid organ malignant neoplasm and the second leading cause of cancer death among men in the United States.\(^1\) Androgen deprivation therapy (ADT) is a cornerstone of treatment for many men with prostate cancer\(^2\)\(^-\)\(^4\); however, there is evidence that ADT may increase the risk of cardiovascular morbidity and mortality, especially among patients with preexisting cardiovascular disease.\(^5\)\(^,\)\(^6\) Secondary analyses of multiple randomized clinical trials (RCTs) have suggested that patients treated with degarelix, a gonadotropin-releasing hormone (GnRH) antagonist, may have a lower risk of cardiovascular events than those treated with GnRH agonists, such as leuprolide. Trials have also suggested that relugolix, another GnRH antagonist, is associated with a lower risk of major adverse cardiovascular events (MACEs) compared with leuprolide.\(^7\) However, no prior trials directly comparing degarelix and leuprolide have been published with cardiovascular events as a primary endpoint.\(^8\)\(^-\)\(^10\) As a result, the long-term relationship between ADT and cardiovascular risk, as well as the potential differences between degarelix and leuprolide, remains uncertain.\(^11\)\(^,\)\(^12\) To address this question, a Phase 3b RCT comparing the cardiovascular safety of degarelix and leuprolide among patients with prostate cancer and cardiovascular disease is ongoing (the PRONOUNCE trial [A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease]).\(^13\) 

Real-world data (RWD) are increasingly available to support medical product evaluations, including for regulatory decision-making, to better understand use and associated benefits and risks of treatment. While double-masked RCTs, like PRONOUNCE, are the gold standard to evaluate the efficacy and safety of medical products, they face operational challenges and have important limitations that undermine their generalizability to real-world clinical practice. For instance, RCTs are often expensive, face recruitment and retention difficulties, and take a long time to complete.\(^14\) Furthermore, RCTs often have strict inclusion and exclusion criteria, which can affect the number of participants from racial and ethnic minority groups, who are known to be underrepresented in prostate cancer trials and clinical trials in general.\(^15\)\(^,\)\(^16\) While PRONOUNCE planned to enroll 900 patients when it started in 2016, only 545 patients will have been recruited by estimated study completion in 2021,\(^13\) which may limit the trial’s ability to answer the safety questions of interest.

The noted shortcomings of RCTs have increased interest in rigorously designed observational studies using RWD.\(^16\)\(^,\)\(^17\) While RWD are useful for describing how medications are actually used in clinical practice, including patient demographic characteristics, comorbidities, and concurrent treatments,\(^18\)\(^,\)\(^19\) it remains unclear whether RWD and observational methods can be used to address the same clinical questions evaluated by RCTs and potentially support regulatory decision-making.\(^16\)\(^,\)\(^18\) Many studies have replicated the results of completed RCTs using RWD and observational methods\(^20\)\(^-\)\(^26\); however, such an approach is potentially prone to design, selection, and/or measurement biases, as these analyses are planned after the trials’ results are already known. The ability of routinely collected electronic health record (EHR) or administrative claims data to anticipate the end points of ongoing clinical trials, including emulating the characteristics of enrolled patients and the results of the primary research questions, has not been well examined.

In this study, we sought to evaluate whether a large cohort of US patients with commercial insurance could be used to assess the proportion and characteristics of patients in routine practice who met the PRONOUNCE trial inclusion criteria. Furthermore, we applied observational research methods to emulate the PRONOUNCE trial’s anticipated results. This study followed the target trial framework and was conceived and conducted prior to the release of the PRONOUNCE trial results.\(^27\)

Methods

The Mayo Clinic institutional review board exempted this study from review and the requirement for informed consent because it used preexisting, deidentified data. This study was conducted and reported according to the Reporting of Studies Conducted Using Observational Routinely Collected
Study Design and Population
This retrospective cohort study used deidentified administrative claims data from OptumLabs Data Warehouse (OLDW), which includes EHR, medical and pharmacy claims, laboratory results, and enrollment records for commercial and Medicare Advantage enrollees in the United States. OLDW contains longitudinal health information on enrollees, representing a diverse mixture of ages, racial and ethnic groups, and geographical regions across the United States. Inclusion and exclusion criteria for the PRONOUNCE trial were identified from ClinicalTrials.gov and the trial protocol and were adopted and applied to beneficiaries included in OLDW (eAppendix in the Supplement). The cohort included men aged 18 years or older with valid demographic (age and race and ethnicity) data, a history of cardiovascular disease, and a current diagnosis of prostate cancer who initiated degarelix or leuprolide between December 24, 2008 (the Food and Drug Administration [FDA] approval date of degarelix), and June 30, 2019. The date of an individual's first treatment with degarelix or leuprolide was defined as the index date (ie, new-user design). Patients were required to have at least 6 months of continuous enrollment with medical and pharmacy coverage before the index date. Patients were followed up until they experienced an end point of interest, reached the maximum anticipated follow-up of the trial (ie, 336 days) or the end of the study period (July 31, 2019), ended insurance coverage (end of patient enrollment), or died. Variables were defined by the presence of a claim with eligible diagnosis codes, procedure codes, and prescription fills, as detailed in the eAppendix in the Supplement.

End Points
Primary and secondary end points were defined to mirror those of the PRONOUNCE trial. The primary end point was the time from index date to first occurrence of an MACE, a composite end point defined as all-cause death, nonfatal myocardial infarction, or nonfatal stroke (eAppendix in the Supplement). Secondary end points were time from index date to all-cause death, myocardial infarction, stroke, and unstable angina, as separate end points. In the PRONOUNCE protocol, an additional secondary end point was time to cardiovascular-related death. However, in OLDW, we were unable to distinguish causes of death and stable vs unstable angina; therefore, we evaluated all-cause death and any angina. We used previously published and validated diagnosis and procedure codes to determine myocardial infarction, stroke, and angina (eAppendix in the Supplement). Mortality was identified using the mortality data from OLDW, which is based on the Social Security Death Master File, deceased status from EHR data, death as a reason for disenrollment, and death indicated by inpatient discharge status.

Other Variables of Interest
Sociodemographic variables, comorbidities, and prior and concurrent medication use during the baseline 6-month period were recorded (Table 1; eAppendix in the Supplement). In the OLDW database, race is derived from ethnicity. Ethnicity is imputed based on a model run by the data supplier using an individual’s name (first, last, middle) and geographic location and then categorized into 5 race values (ie, Asian, Black, Hispanic, unknown, and White). Race and ethnicity were analyzed so that we could include these data in our propensity score (PS) modeling. When available, laboratory results data were queried for pretreatment prostate-specific antigen (PSA) levels and estimated glomerular filtration rate (eGFR), which were used as matching and subgroup variables, respectively. Laboratory results are available for approximately one-third of patients, conditional on the contracts between commercial laboratory providers and the health plan entities whose patients are represented in OLDW.
| Characteristic                         | Before PS matching | After PS matching |
|---------------------------------------|--------------------|-------------------|
|                                       | Degarelix (n = 1120) | Leuprolide (n = 6680) | Total (N = 7800) | SMD  |
| Age, y                                | 75.0 (7.6)          | 74.3 (7.4)         | 74.4 (7.4)       | 0.10 |
| Median (IQR)                          | 75.5 (70.0-81.0)    | 75.0 (70.0-80.0)   | 75.0 (70.0-80.0) | 0.01 |
| ≤54                                   | <11*               | >60*               |                  | 0.04 |
| 55-64                                 | 113 (10.1)          | 662 (9.9)          | 775 (9.9)        | 0.01 |
| 65-74                                 | >383*              | >2800*             |                  | 0.03 |
| ≥75                                   | 613 (54.7)          | 3545 (53.1)        | 4158 (53.3)      | 0.03 |
| Race and ethnicity                    |                    |                   |                  |     |
| Asian                                 | 24 (2.1)            | 141 (2.1)          | 165 (2.1)        | 0.00 |
| Black                                 | 209 (18.7)          | 1181 (17.7)        | 1390 (17.8)      | 0.03 |
| Hispanic                              | 55 (4.9)            | 608 (9.1)          | 663 (8.5)        | 0.17 |
| White                                 | 783 (69.9)          | 4475 (67.0)        | 5258 (67.4)      | 0.06 |
| Unknown                               | 49 (4.4)            | 275 (4.1)          | 324 (4.2)        | 0.01 |
| Geographic region                     |                    |                   |                  |     |
| Midwest                               | 301 (26.9)          | 1830 (27.4)        | 2131 (27.3)      | 0.01 |
| Northeast                             | 217 (19.4)          | 1063 (15.9)        | 1280 (16.4)      | 0.09 |
| South                                 | >495*              | >3660              |                  | 0.05 |
| West                                  | 96 (8.6)            | 618 (9.3)          | 714 (9.2)        | 0.02 |
| Unknown                               | <11*               | <11*               |                  | 0.01 |
| Serum PSA levelb                      |                    |                   |                  |     |
| No. (%)                               | 440 (35.2)          | 2246 (33.6)        | 2686 (34.4)      | NA  |
| Mean (SD), ng/mL                      | 74.3 (261.2)        | 48.9 (290.7)       | 53.0 (286.1)     | 0.09 |
| Median (IQR), ng/mL                   | 11.6 (6.2-32.4)     | 9.2 (5.1-19.8)     | 9.4 (5.2-21.6)   |     |
| eGFRc                                  |                    |                   |                  |     |
| No. (%)                               | 433 (34.6)          | 2353 (35.2)        | 2786 (35.7)      | NA  |
| Mean (SD), ml/min/1.73 m²             | 66.5 (20.5)         | 68.8 (20.4)        | 68.8 (20.4)      | 0.02 |
| Median (IQR), ml/min/1.73 m²          | 68.3 (52.4-81.9)    | 68.5 (53.1-82.5)   | 68.5 (53.0-82.5) | 0.08 |
| Prostate biopsy within 6 mos of index date, No. (%) | 682 (60.9) | 3635 (54.4) | 4317 (55.3) | 0.13 |
| Baseline comorbidities                |                    |                   |                  |     |
| Coronary artery disease               | 593 (52.9)          | 3424 (51.3)        | 4015 (51.5)      | 0.03 |
| Chronic kidney disease                | 167 (14.9)          | 877 (13.1)         | 1044 (13.4)      | 0.05 |
| Congestive heart failure              | 191 (17.1)          | 1041 (15.6)        | 1232 (15.8)      | 0.04 |
| Cerebrovascular disease               | 159 (14.2)          | 885 (13.2)         | 1044 (13.4)      | 0.03 |
| Peripheral vascular disease           | 326 (29.1)          | 2001 (30.0)        | 2237 (29.8)      | 0.02 |
| Obesityd                              | 71 (6.3)            | 451 (6.8)          | 522 (6.7)        | 0.02 |
| Atrial fibrillation                   | 191 (17.1)          | 1104 (16.5)        | 1295 (16.6)      | 0.01 |
| Sleep apnea                           | 107 (9.6)           | 682 (10.2)         | 789 (10.1)       | 0.02 |
| Hypertension                          | 882 (78.8)          | 5290 (79.2)        | 6172 (79.1)      | 0.01 |
| MI                                     | 119 (10.6)          | 696 (10.4)         | 815 (10.4)       | 0.01 |
| Stroke                                | 60 (5.4)            | 375 (5.6)          | 435 (5.6)        | 0.01 |
| PCI                                    | 81 (7.2)            | 494 (7.4)          | 575 (7.4)        | 0.01 |
| CABG                                  | 97 (8.7)            | 634 (9.5)          | 731 (9.4)        | 0.03 |
| PAD                                    | 232 (20.7)          | 1339 (20.0)        | 1571 (20.1)      | 0.02 |
| Dementia                              | 57 (5.1)            | 271 (4.1)          | 328 (4.2)        | 0.05 |
| COPD                                  | 244 (21.8)          | 1340 (20.1)        | 1584 (20.3)      | 0.04 |
| Peptic ulcer disease                  | 11 (1.0)            | 73 (1.1)           | 84 (1.1)         | 0.01 |
| Mild liver disease                    | 78 (7.0)            | 524 (7.8)          | 602 (7.7)        | 0.03 |
| Diabetes without chronic complication | 414 (37.0)          | 2405 (36.0)        | 2819 (36.1)      | 0.02 |

(continued)
Table 1.Baseline Characteristics Before and After PS Matching (continued)

| Characteristic                          | Before PS matching | After PS matching |
|-----------------------------------------|--------------------|-------------------|
|                                         | Patients, No. (%)  | SMD               |
|                                         | Degarelix (n = 1120) | Leuprolide (n = 6680) |
|                                         | Total (N = 7800)    |                   |
|                                         | SMD                |                   |
|                                         | Degarelix (n = 1113) | Leuprolide (n = 1113) |
|                                         | Total (N = 2226)    |                   |
|                                         | SMD                |                   |
| Diabetes with chronic complication      | 182 (16.3)         | 0.03              |
| Metastatic solid tumor                  | 251 (22.4)         | 0.15              |
| Rheumatic disease                       | 21 (1.9)           | 0.03              |
| Charlson comorbidity score              |                    |                   |
| Mean (SD)                               | 5.5 (3.2)          | 0.00              |
| Median (IQR)                            | 5.0 (3.0-7.0)      | 0.00              |
| Radiotherapy within 6 mos before index date, No. (%) | 19 (1.7)           | 0.09              |
| Use of bicalutamide within 6 mos before index date, No. (%) | 0                  |                    |
| Other baseline medications within       |                    |                   |
| 6 mos before index date                 |                    |                   |
| Statin                                  | 717 (64.0)         | 0.01              |
| Nonstatin lipid-lowering medications    | 170 (15.2)         | 0.00              |
| ACEi                                    | 396 (35.4)         | 0.00              |
| ARB                                     | 215 (19.2)         | 0.00              |
| ACEi and ARB                            | 593 (52.9)         | 0.00              |
| Sacubitril and valsartan                |                    |                   |
| Warfarin                                | 102 (9.1)          | 0.02              |
| DOAC                                    | 70 (6.3)           | 0.02              |
| ß-blockers                              | 581 (51.9)         | 0.00              |
| Loop diuretics                          | 174 (15.5)         | 0.00              |
| Aldosterone antagonist                  | 46 (4.1)           | 0.00              |
| Digoxin                                 | 28 (2.5)           | 0.00              |
| Calcium channel blocker                 | 294 (26.3)         | 0.00              |
| Antiplatelet                            | 214 (19.1)         | 0.00              |
| No. of hospitalizations                 |                    |                   |
| 0                                       | 922 (82.3)         | 0.00              |
| 1                                       | 153 (13.7)         | 0.00              |
| ≥2                                      | 45 (4.0)           | 0.00              |
| No. of ED visits                        |                    |                   |
| 0                                       | 837 (74.7)         | 0.00              |
| 1                                       | 164 (14.6)         | 0.00              |
| ≥2                                      | 119 (10.6)         | 0.00              |
| Year of cohort entry                    |                    |                   |
| 2008                                    | 0                  | 0                 |
| 2009                                    | 0                  | 0.34              |
| 2010                                    | 29 (2.6)           | 0.19              |
| 2011                                    | 61 (5.4)           | 0.08              |
| 2012                                    | 73 (6.5)           | 0.03              |
| 2013                                    | 89 (7.9)           | 0.03              |
| 2014                                    | 95 (8.5)           | 0.05              |
| 2015                                    | 104 (9.3)          | 0.02              |
| 2016                                    | 150 (13.4)         | 0.07              |
| 2017                                    | 196 (17.7)         | 0.06              |
| 2018                                    | 225 (20.1)         | 0.07              |
| 2019                                    | 96 (8.6)           | 0.08              |

(continued)
The full statistical analysis plan is available in the eAppendix in the Supplement. For the primary analyses, we focused on patients in OLWD who would be eligible for the PRONOUNCE trial based on the operational definitions of the inclusion and exclusion criteria. One-to-one matching was used to balance the differences in baseline characteristics between patients who received degarelix vs those who received leuprolide. A PS, representing the probability of receiving degarelix, was estimated using a logistic regression model based on sociodemographic variables, medical history, concurrent medication use, and other patient characteristics presented in Table 1. One-to-one nearest-neighbor caliper matching was used to match patients based on the logit of the PS, using a caliper equal to 0.2 of the SD of the logit of the PS.33 As patients with missing data were excluded during cohort selection, there were no missing data for any of the variables in the PS model expect for PSA level. Patients with and without PSA levels were matched separately.

Table 1. Baseline Characteristics Before and After PS Matching (continued)

| Characteristic | Before PS matching | | | | | After PS matching | | | | |
|----------------|-------------------|---|---|---|---|-------------------|---|---|---|---|
| | Degarelix (n = 1120) | Leuprolide (n = 6680) | Total (N = 7800) | SMD | | Degarelix (n = 1113) | Leuprolide (n = 1113) | Total (N = 2226) | SMD |
| State | | | | | | | | | | |
| Alabama | 34 (3.0) | 170 (2.5) | 204 (2.6) | 0.03 | 34 (3.1) | 31 (2.8) | 65 (2.9) | 0.02 |
| Arizona | 21 (1.9) | 107 (1.6) | 128 (1.6) | 0.02 | 20 (1.8) | 21 (1.9) | 41 (1.8) | 0.01 |
| California | 12 (1.1) | 118 (1.8) | 130 (1.7) | 0.06 | 12 (1.1) | 21 (1.9) | 33 (1.5) | 0.07 |
| Connecticut | 24 (2.1) | 138 (2.1) | 162 (2.1) | 0.01 | 23 (2.1) | 24 (2.2) | 47 (2.1) | 0.01 |
| Florida | 164 (14.6) | 1056 (15.8) | 1220 (15.6) | 0.03 | 164 (14.7) | 157 (14.1) | 321 (14.4) | 0.02 |
| Georgia | 54 (4.8) | 495 (7.4) | 549 (7.0) | 0.11 | 54 (4.9) | 97 (8.7) | 151 (6.8) | 0.15 |
| Illinois | 62 (5.5) | 318 (4.8) | 380 (4.9) | 0.04 | 62 (5.6) | 58 (5.2) | 120 (5.4) | 0.02 |
| Indiana | 39 (3.5) | 177 (2.6) | 216 (2.8) | 0.05 | 39 (3.5) | 34 (3.1) | 73 (3.3) | 0.03 |
| Massachusetts | <11a | >90a | 98 (1.3) | 0.11 | <11a | >11a | >11a | 0.10 |
| Minnesota | 12 (1.1) | 157 (2.4) | 179 (2.2) | 0.10 | 12 (1.1) | 29 (2.6) | 41 (1.8) | 0.11 |
| Missouri | 50 (4.5) | 275 (4.1) | 325 (4.2) | 0.02 | 50 (4.5) | 44 (4.0) | 94 (4.2) | 0.03 |
| North Carolina | >118a | >365a | 498 (6.4) | 0.20 | 124 (11.1) | 54 (4.9) | 178 (8.0) | 0.23 |
| New Jersey | 75 (6.7) | 234 (3.5) | 309 (4.0) | 0.15 | 74 (6.6) | 45 (4.0) | 119 (5.3) | 0.12 |
| New York | 89 (7.9) | 402 (6.0) | 491 (6.3) | 0.08 | 89 (8.0) | 92 (8.3) | 181 (8.1) | 0.01 |
| Ohio | 33 (2.9) | 331 (5.0) | 364 (4.7) | 0.10 | 33 (3.0) | 47 (4.2) | 80 (3.6) | 0.07 |
| Rhode Island | 16 (1.4) | 116 (1.7) | 132 (1.7) | 0.03 | 16 (1.4) | 17 (1.5) | 33 (1.5) | 0.01 |
| South Carolina | 29 (2.6) | 109 (1.6) | 138 (1.8) | 0.07 | 28 (2.5) | 21 (1.9) | 49 (2.2) | 0.04 |
| Tennessee | 16 (1.4) | 133 (2.0) | 149 (1.9) | 0.04 | 16 (1.4) | 22 (2.0) | 38 (1.7) | 0.04 |
| Texas | 28 (2.5) | 533 (8.0) | 561 (7.2) | 0.25 | 28 (2.5) | 66 (5.9) | 94 (4.2) | 0.17 |
| Utah | 15 (1.3) | 143 (2.1) | 158 (2.0) | 0.06 | 15 (1.3) | 21 (1.9) | 36 (1.6) | 0.04 |
| Virginia | <11a | >82a | >90a | 0.07 | <11a | >12a | >20a | 0.08 |
| Wisconsin | 74 (6.6) | 371 (5.6) | 445 (5.7) | 0.04 | 74 (6.6) | 64 (5.8) | 138 (6.2) | 0.04 |
| Other | 137 (12.2) | 744 (11.3) | 881 (11.3) | 0.03 | 135 (12.1) | 118 (10.6) | 253 (11.4) | 0.05 |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DOAC, direct-acting oral anticoagulant; ED, emergency department; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PS, propensity score; PSA prostate-specific antigen; SMD, standardized mean difference.

SI conversion: To convert PSA level to micrograms per liter, multiply by 1.0.
a Cell suppression based on OptumLabs cell size suppression rules. Categories with fewer than 11 individuals are masked to protect patient confidentiality.
b Patients with PSA and without PSA levels were matched separately.
c eGFR was used for the subgroup analyses and not for matching purposes.
d Obesity defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or greater.

Statistical Analysis

Main Analysis

The full statistical analysis plan is available in the eAppendix in the Supplement. For the primary analyses, we focused on patients in OLWD who would be eligible for the PRONOUNCE trial based on the operational definitions of the inclusion and exclusion criteria. One-to-one matching was used to balance the differences in baseline characteristics between patients who received degarelix vs those who received leuprolide. A PS, representing the probability of receiving degarelix, was estimated using a logistic regression model based on sociodemographic variables, medical history, concurrent medication use, and other patient characteristics presented in Table 1. One-to-one nearest-neighborhood caliper matching was used to match patients based on the logit of the PS, using a caliper equal to 0.2 of the SD of the logit of the PS.33 As patients with missing data were excluded during cohort selection, there were no missing data for any of the variables in the PS model expect for PSA level. Patients with and without PSA values were matched separately.
Standardized differences were used to assess the balance of covariates after matching, and a standardized difference 0.1 or smaller was considered acceptable.\textsuperscript{34} Covariates with standardized differences greater than 0.1 were adjusted for in the regression models.

Cox proportional hazards regression models were used to compare outcomes among patients who received degarelix with those who received leuprolide in the propensity-matched cohort, with robust sandwich estimates to account for the clustering within matched sets.\textsuperscript{35} The proportional hazard assumption was tested on the basis of Schoenfeld residuals.\textsuperscript{36} The Fine and Gray method was used to consider death as a competing risk when assessing nonfatal end points.\textsuperscript{37} All primary analyses compared the assigned treatment groups under the intention-to-treat (ITT) principle.

Subgroup and Sensitivity Analyses

We conducted subgroup (interaction) analyses by age, as outlined in the PRONOUNCE trial protocol. We also conducted subgroup analyses for important demographic and clinical characteristics: race, diabetes, presence of at least 1 prostate biopsy, and kidney function, using receipt of hemodialysis to identify patients with end-stage kidney disease. In addition, for the patients with laboratory data, we generated subgroups of patients with eGFRs of less than and at least 45 mL/min/1.73 m\(^2\).

We then performed several sensitivity analyses to assess the dependence of our results on our cohort definition and statistical approach. First, we repeated our analyses among patients with no previous history or current hormonal management of prostate cancer who failed to meet at least 1 of the cardiovascular inclusion criteria for PRONOUNCE and among patients who met at least 1 of the exclusion criteria. Next, we repeated our analyses excluding all patients who crossed over between the 2 treatments and censoring patients at the point at which they switched. Third, we repeated our primary ITT analyses using inverse probability of treatment weighting (IPTW)—average treatment effect weights—instead of PS matching to evaluate the consistency of our findings. Fourth, we conducted an analysis stratified by adherence to degarelix and leuprolide, ie, patients with proportion of days covered (PDC) of at least 80% and less than 80% until outcome date or the date that a patient switched medications. Lastly, we assessed residual confounding by testing 3 falsification end points, unlikely to be associated with use of degarelix or leuprolide: new diagnoses of chronic obstructive pulmonary disease (COPD), appendicitis, and cholecystitis, after the index date. All sensitivity analyses were considered exploratory.

\(P < .05\) was considered statistically significant for all 2-sided tests. All analyses were performed using SAS version 9.4 (SAS Institute Inc) and Stata version 14.1 (StataCorp).

Results

Patient Characteristics

We identified 103,500 adult men who initiated degarelix or leuprolide between December 24, 2008, and June 30, 2019, of whom 32,172 had valid demographic data, 6 months of continuous enrollment before the index date, and a prostate cancer diagnosis (eFigure in the Supplement). PRONOUNCE trial eligibility criteria were met by 7800 of 32,172 patients (24.2%) (Figure 1; eTable 1 in the Supplement). Their mean (SD) age was 74.4 (7.4) years, and 165 participants (2.1%) were Asian, 1390 (17.8%) were Black, 663 (8.5%) were Hispanic, and 5258 (67.4%) were White. PSA level data were available for 2686 patients (34.4%), with a mean (SD) value of 53.0 (286.1) ng/mL (to convert to micrograms per liter, multiply by 1.0) (Table 1; eTable 2 in the Supplement). After PS matching, primary analyses included 1113 of 1120 patients (99.4%) treated with degarelix and 1113 of 6680 patients (16.7%) treated with leuprolide; these groups were well balanced with SMDs less than 0.10 for all 49 matching characteristics. For 1 year and 3 states, SMDs greater than 0.1 were observed, likely due to the low number of patients across the levels for these characteristics. However, in a sensitivity analysis adjusting for calendar year and state, the results remained the same.
Primary ITT Analyses

Patients who initiated degarelix and leuprolide were observed in the data for a mean (SD) of 9.55 (2.98) months and 9.77 (2.74) months, respectively. No significant difference was observed in the risk of MACE for patients initiated on degarelix vs leuprolide (10.18 vs 8.60 events per 100 person-years; hazard ratio [HR], 1.18; 95% CI, 0.86-1.61; P = .30) (Table 2 and Figure 2). Degarelix was associated with a significantly higher risk of death from any cause (HR, 1.48; 95% CI, 1.01-2.18; P = .046) but not of myocardial infarction (HR, 1.16; 95% CI, 0.60-2.25; P = .66), stroke (HR, 0.92; 95% CI, 0.45-1.85; P = .81), or angina (HR, 1.36; 95% CI, 0.43-4.27; P = .60).

Subgroup and Sensitivity Analyses

There was no evidence of an interaction effect across subgroups for age, race, diabetes, end-stage kidney disease, and baseline eGFR (eTable 3 in the Supplement). Treatment effect sizes for the primary and secondary end points were largely consistent among the 2686 patients with a prostate biopsy and among the 2952 patients who failed to meet the cardiovascular inclusion criteria and hence would be excluded from PRONOUNCE (Table 3; eTable 4 in the Supplement).

We observed considerable crossover from degarelix to leuprolide, with a median (IQR) duration of degarelix exposure of 48 (33-92) days. There were 115 of 722 patients (15.9%) who crossed over within 30 days of initiating degarelix. When excluding patients who crossed over between the 2 treatments (722 who initiated degarelix and 19 who initiated leuprolide) or censoring those at the time of medication switch, degarelix was associated with higher risk of MACE (crossover: HR, 1.58; 95% CI, 1.01-2.47; P = .046; censoring: HR, 1.18; 95% CI, 1.11-2.26; P = .01) and death (crossover: HR, 2.21; 95% CI, 1.24-3.94; P = .01; censoring: HR, 1.95; 95% CI, 1.26-3.03; P = .003) (Table 3).

Table 2. End Points in 2226 Propensity-Matched Patients

| End point              | Degarelix (n = 1113) | Leuprolide (n = 1113) | Hazard ratio (95% CI) | P value |
|-----------------------|----------------------|-----------------------|-----------------------|---------|
|                       | Events, No. | Person-years | Event rate per 100 person-years | Events, No. | Person-years | Event rate per 100 person-years |                     |
| Primary end point     |           |             |                               |           |             |                               |                     |
| MACE<sup>a</sup>      | 88        | 864.65      | 10.18                          | 73        | 849.15      | 8.60                          | 1.18 (0.86-1.61)   | .30                 |
| Secondary end points  |           |             |                               |           |             |                               |                     |
| Death                 | 65        | 875.05      | 7.43                           | 43        | 861.81      | 4.99                          | 1.48 (1.01-2.18)   | .046                |
| Myocardial infarction | 19        | 869.63      | 2.18                           | 16        | 855.18      | 1.87                          | 1.16 (0.60-2.25)   | .66                 |
| Stroke                | 15        | 869.75      | 1.72                           | 16        | 855.78      | 1.87                          | 0.92 (0.45-1.85)   | .81                 |
| Angina<sup>b</sup>    | <11       | NA          | NA                             | <11       | NA          | NA                            | 1.36 (0.43-4.27)   | .60                 |

Abbreviations: MACE, major adverse cardiovascular event; NA, not applicable.

<sup>a</sup> MACE was defined as a composite end point of death from any cause, myocardial infarction, or stroke.

<sup>b</sup> Cell suppression based on OptumLabs cell size suppression rules. Categories with fewer than 11 individuals are masked to protect patient confidentiality.
were no statistically significant associations between degarelix and myocardial infarction, stroke, and angina. The results of the IPTW analyses for MACE and death were consistent with the primary analyses.

No statistically significant differences between degarelix and leuprolide were observed across end points when patients were stratified by PDC of at least 80% vs less than 80%. There were also no significant associations between degarelix and any of the falsification end points of COPD, appendicitis, and cholecystitis (eTable 5 in the Supplement).

Figure 2. Cumulative Incidence of Major Adverse Cardiovascular Event (MACE), Death, Stroke, Myocardial Infarction, and Angina in the Overall Cohort

MACE was a composite end point defined as death from any cause, nonfatal myocardial infarction, or nonfatal stroke.
In a cohort of US patients with commercial insurance or Medicare Advantage and established cardiovascular disease initiating ADT for prostate cancer treatment, we emulated the forthcoming analyses.

### Table 3. End Points in Sensitivity Analyses

| Outcome                              | Degarelix                  | Leuprolide                | Hazard ratio (95% CI) | P value |
|--------------------------------------|-----------------------------|---------------------------|-----------------------|---------|
| Patients who failed to meet the cardiovascular inclusion criteria |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 2952 (112) 2297.82 4.87    | 2952 (92) 2293.01 4.01    | 1.21 (0.92-1.60)      | .17     |
| Death                                | 2952 (83) 2310.67 3.59      | 2952 (54) 2308.80 2.34     | 1.53 (1.09-2.16)      | .02     |
| Myocardial infarction                | 2952 (12) 2307.05 0.52      | 2952 (23) 2301.27 1.00     | 0.52 (0.26-1.04)      | .06     |
| Stroke                               | 2952 (27) 2301.10 1.17      | 2952 (27) 2300.51 1.17     | 0.99 (0.58-1.70)      | .98     |
| Angina                               | 2952 (<11<sup>b</sup>) NA  | 2952 (<11<sup>b</sup>) NA  | 0.66 (0.19-2.34)      | .52     |
| Patients who met the cardiovascular exclusion criteria |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 96 (<11<sup>b</sup>) NA  | 96 (12) NA NA             | 0.64 (0.27-1.56)      | .33     |
| Death                                | 96 (<11<sup>b</sup>) NA  | 96 (<11<sup>b</sup>) NA  | 0.83 (0.29-2.44)      | .74     |
| Myocardial infarction                | 96 (<11<sup>b</sup>) NA  | 96 (<11<sup>b</sup>) NA  | 3.02 (0.32-28.87)     | .34     |
| Stroke                               | 96 (<11<sup>b</sup>) NA  | 96 (<11<sup>b</sup>) NA  | 0.39 (0.08-2.00)      | .26     |
| Angina                               | 96 (<11<sup>b</sup>) NA  | 96 (<11<sup>b</sup>) NA  | NA NA                 |         |
| Patients who crossed over between 2 treatments censored when they switched |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 1113 (52) 431.30 12.06     | 1113 (72) 847.11 8.50      | 1.58 (1.11-2.26)      | .01     |
| Death                                | 1113 (35) 436.55 8.02       | 1113 (42) 859.76 4.89      | 1.95 (1.26-3.03)      | .003    |
| Myocardial infarction                | 1113 (13) 433.96 3.00       | 1113 (16) 853.14 1.88      | 1.57 (0.74-3.35)      | .24     |
| Stroke                               | 1113 (<11<sup>b</sup>) NA | 1113 (16) NA NA           | 1.10 (0.48-2.53)      | .81     |
| Angina                               | 1113 (<11<sup>b</sup>) NA | 1113 (<11<sup>b</sup>) NA | 1.45 (0.39-5.43)      | .58     |
| Patients who crossed over between treatments excluded |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 398 (47) 289.85 16.22      | 398 (32) 310.44 10.31     | 1.58 (1.01-2.47)      | .046    |
| Death                                | 398 (35) 294.34 11.89       | 398 (17) 310.92 5.40       | 2.21 (1.24-3.94)      | .01     |
| Myocardial infarction                | 398 (<11<sup>b</sup>) NA | 398 (14) 310.58 4.51       | 0.66 (0.28-1.52)      | .33     |
| Stroke                               | 398 (<11<sup>b</sup>) NA | 398 (<11<sup>b</sup>) NA | 1.67 (0.55-5.11)      | .37     |
| Angina                               | 398 (<11<sup>b</sup>) NA | 398 (<11<sup>b</sup>) NA | 0.51 (0.09-2.79)      | .44     |
| IPTW instead of propensity-score matching |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 1120 (593) 6194.59 9.58    | 6680 (531) 6135.66 8.65    | 1.10 (0.86-1.41)      | .43     |
| Death                                | 1120 (460) 6252.48 7.36     | 6680 (304) 6231.80 4.87    | 1.50 (1.13-2.01)      | .01     |
| Myocardial infarction                | 1120 (132) 6218.51 2.13     | 6680 (139) 6180.94 2.24    | 0.94 (0.56-1.58)      | .82     |
| Stroke                               | 1120 (89) 6225.89 1.43      | 6680 (128) 6187.43 2.06    | 0.69 (0.38-1.24)      | .21     |
| Angina                               | 1120 (44) 6235.09 0.71      | 6680 (42) 6214.76 0.68     | 1.03 (0.44-2.42)      | .95     |
| PDC ≥80%                             |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 690 (50) 523.12 9.56       | 690 (52) 494.69 10.51     | 0.90 (0.61-1.33)      | .61     |
| Death                                | 690 (36) 530.74 6.78       | 690 (31) 505.73 6.13       | 1.09 (0.68-1.77)      | .71     |
| Myocardial infarction                | 690 (13) 526.60 2.47       | 690 (15) 498.44 3.01       | 0.83 (0.39-1.74)      | .62     |
| Stroke                               | 690 (<11<sup>b</sup>) NA | 690 (<11<sup>b</sup>) NA | 1.07 (0.41-2.78)      | .89     |
| Angina                               | 690 (<11<sup>b</sup>) NA | 690 (<11<sup>b</sup>) NA | 2.84 (0.58-13.99)     | .20     |
| PDC <80%                             |                             |                           |                       |         |
| MACE<sup>a</sup>                     | 417 (38) 336.90 11.28      | 417 (25) 352.12 7.10       | 1.60 (0.97-2.64)      | .07     |
| Death                                | 417 (29) 339.69 8.54       | 417 (19) 353.18 5.38       | 1.60 (0.90-2.85)      | .11     |
| Myocardial infarction                | 417 (<11<sup>b</sup>) NA | 417 (<11<sup>b</sup>) NA | 3.10 (0.63-15.60)     | .16     |
| Stroke                               | 417 (<11<sup>b</sup>) NA | 417 (<11<sup>b</sup>) NA | 1.02 (0.33-3.17)      | .97     |
| Angina                               | 417 (<11<sup>b</sup>) NA | 417 (<11<sup>b</sup>) NA | 0.34 (0.04-3.32)      | .36     |

Abbreviations: IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular event; NA, not applicable; PDC, proportion of days covered.  
<sup>a</sup> MACE was defined as a composite end point of death from any cause, myocardial infarction, or stroke.  
<sup>b</sup> Cell suppression based on OptumLabs cell size suppression rules. Categories with fewer than 11 individuals are masked to protect patient confidentiality.
PRONOUNCE trial to examine cardiovascular risk of prostate cancer treatment. Using these RWD, we determined that only one-quarter of real-world patients who initiated these medications met the trial’s narrow inclusion and exclusion criteria. Among the men who did, we found no significant difference in the risk of MACE between patients taking degarelix vs those taking leuprolide. While we did observe degarelix to be associated with a significantly higher risk of death from any cause, which was consistent across a range of sensitivity analyses, there were no statistically significant differences between degarelix and leuprolide for myocardial infarction, stroke, or angina. Comparison of the patient characteristics and end points reported here with the PRONOUNCE trial results, upon their publication, will help to further enhance our understanding of the appropriate role of using RWD to emulate randomized clinical trials.

In contrast to previous studies, our findings do not support the hypothesis that degarelix is associated with a lower cardiovascular risk than leuprolide.7-12,38 Notably, no previous trial was designed with cardiovascular morbidity as the primary end point. Although degarelix was associated with an unexpectedly higher risk of MACE in the secondary analyses, this appears to be driven by the higher risk of all-cause mortality, as there was no difference in rates of MACE components, including myocardial infarction and stroke. It is likely that residual confounding due to patient and prescriber behaviors could have contributed to the observed findings, especially the increased risk of all-cause mortality, in ways that would not occur in an RCT. In particular, preferential use of degarelix for patients with more cardiovascular comorbidity and higher disease burden could not be risk-adjusted for using claims data. It is also possible that the inclusion of all-cause mortality in the MACE end point could have biased our results toward the null. Although we analyzed the components of MACE separately and matched the cohort on several cardiovascular baseline comorbidities, the presence of metastatic disease, and PSA levels, we could not account for all characteristics, and PSA data were not available for approximately two-thirds of patients. Overall, the impact of residual confounding on the direction and strength of the observed associations is unclear, and we await the results of the PRONOUNCE trial to ascertain whether the observations made here align with the trial’s enrolled patient population, outcome event rates, and inferences.

Our experience highlights several important considerations related to the interventions, eligibility criteria, end points, follow-up, and statistical analyses in designing RWD studies to emulate RCTs. First, emulation requires studying existing therapeutics and is not appropriate for novel drugs or therapies. Indeed, only 15% of US-based clinical trials published in high-impact journals in 2017 could have been evaluated using RWD.18 Second, adequate observational data are necessary to emulate trial eligibility criteria and evaluate end points. While we were able to emulate the major PRONOUNCE eligibility criteria, certain variables were not found in EHR data (eg, ankle-brachial pressure index).18 Similarly, precise emulation of end points—such as cancer-specific death or differentiation between fatal and nonfatal cardiovascular events—was not possible with claims data. Third, although we had adequate follow-up to emulate the PRONOUNCE trial, as our median follow-up period was 8 months vs 11 months for the trial, future studies should carefully consider the availability of enrollment dates to assess follow-up. For instance, emulation studies relying on EHR data would not have enrollment dates. Lastly, our experience demonstrates the analytical complexities of conducting emulation studies and implementing the ITT framework, particularly when patients cross over between interventions. These challenges emphasize the importance of sensitivity analyses to evaluate the consistency of results and conclusions.27 As the FDA continues to invest in the use of RWD to simulate evidence from clinical trials,16 it will be necessary for investigators to follow best practices when it comes to trial emulation (eg, the target trial framework).27 Moreover, it will be critical to compare concordant and discordant results between RCTs and RWD emulations, with a focus on understanding potential differences between patient characteristics and study results and identifying the best RWD structures, epidemiologic methods, and study characteristics suitable for emulation.

The methodologic approach applied here has a number of strengths, including some clear advantages over a traditional RCT and, if validated, may represent an ideal approach to help answer
certain questions for existing therapies. First, our sample reflects actual clinical use of degarelix and leuprolide across a large cohort of patients over a 10-year period, and results are therefore generalizable to contemporary clinical practice. In particular, emulating RCTs using RWD can allow for the examination of benefits and risks in a broader population than any given clinical trial. Second, this emulation took approximately 1 year to design and conduct, a fraction of the time and cost of a traditional RCT. Third, evidence suggests that many of the clinical end points that we evaluated (ie, myocardial infarction, stroke, and death) are well captured in claims data. The available data allowed us to match patients on 49 different patient variables including comorbidities, procedures, and medications, and we anticipate the potential for even more refined risk adjustment in the future as the quality of claims data capture improves.

Limitations
Despite the potential advantages of emulating RCTs using RWD, we acknowledge a number of limitations to this approach. First, despite PS matching and statistical adjustment, observational studies are subject to residual confounding. Second, we were unable to operationalize every component of certain inclusion and exclusion criterion and end points, as outlined previously. However, the sensitivity analyses and falsification end points provide some reassurance that there is no strong evidence for substantial residual confounding. Third, reliance on billing codes may have led to misclassification of medical history and end points. Fourth, we included patients who initiated additional androgen agents within 6 months after starting ADT, which could have affected the incidence of cardiovascular adverse events. However, meaningful confounding seems unlikely, as fewer than 10% of patients had additional hormonal agents after the index date. Fifth, we found evidence that relatively few patients started on degarelix without switching over to leuprolide in clinical practice and that exposure to degarelix was relatively short, which may bias our findings toward the null and adds an additional layer of complexity that would not have occurred in an RCT. While crossover likely occurred for patient convenience due to the less frequent dosing interval of leuprolide, it may have also occurred due to progressive disease, and thus, it may portend a greater risk of mortality, thereby influencing the primary MACE outcome. However, our findings were broadly consistent after excluding all patients who crossed over between the 2 treatments and censoring patients at the point at which they switched, increasing our confidence in the reported results. Sixth, our evaluation included patients who initiated degarelix or leuprolide between 2008 and 2019. However, since the PRONOUNCE Trial started in 2016, it will be necessary to ensure that the baseline characteristics between the real-world cohort and the trial population are similar before formally comparing the findings.

Conclusions
In this emulated clinical trial of men with commercial insurance or Medicare Advantage in the United States who had cardiovascular disease and initiated ADT for prostate cancer, degarelix was not associated with a lower risk of cardiovascular events vs leuprolide, in contrast to prior reports. We observed frequent crossover between medications and missing data on disease characteristics in our cohort, which may have contributed to residual confounding and highlights some of the challenges of using RWD to emulate RCTs. The population included in this study as well as the findings should be compared with those of the PRONOUNCE trial, once available, to assess the fidelity of results from this real-world observational study with reported trial end points and to deepen our understanding of the optimal role of using RWD to emulate RCTs.
ARTICLE INFORMATION

Accepted for Publication: August 20, 2021.

Published: October 22, 2021. doi:10.1001/jamanetworkopen.2021.30587

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Author Contributions: Drs Deng and Lyon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Wallach, Deng, Herrin, Polley, Yao.

Obtained funding: Shah, Ross.

Administrative, technical, or material support: Berkowitz, Quinto, Crown, Noseworthy, Shah.

Supervision: Noseworthy, Ross, Lyon.

Conflict of Interest Disclosures: Dr Wallach reported receiving research support through the Collaboration for Research Integrity and Transparency (CRIT) at Yale University from the Laura and John Arnold Foundation and through the Yale–Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI) program (U01FD005938) and being supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under award KO1AA028258. Dr McCoy reported receiving support from the National Institute of Health National Institute of Diabetes and Digestive and Kidney Diseases under grant K23DK114497 and, in the past 36 months, receiving support from an AARP Quality Measure Innovation Grant, the Mayo Clinic Center for Health Equity and Community Engagement Research, and the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery. Dr Dhruva reported being funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health (K24HL138046), the National Evaluation System for Health Technology (NEST), the Greenwall Foundation, and Arnold Ventures. Dr Herrin reported working under contract to the Centers for Medicare & Medicaid Services on the development and evaluations of measures of health care quality. Dr Noseworthy reported receiving personal fees from Optum during the conduct of the study. Dr. Shah reported receiving support through the Mayo Clinic from the Food and Drug Administration to establish the Yale-Mayo Clinic CERSI program (U01FD005938); the Centers of Medicare & Medicaid Innovation under the Transforming Clinical Practice Initiative; the Agency for Healthcare Research and Quality (R01HS025164, R01HS025402, R03HS025517, and K23HS026379); the National Heart, Lung, and Blood Institute of the US National Institutes of Health (R56HL130496, R01HL131535, and R01HL151662); the National Science Foundation; and the Patient-Centered Outcomes Research Institute to develop a clinical data research network (LHSNet). Dr Ross reported that in the past 36 months, he has received support through Yale University from the Laura and John Arnold Foundation for CRIT at Yale, from Medtronic, Inc, and the Food and Drug Administration to develop
methods for postmarket surveillance of medical devices (U01FD004585) and the Centers of Medicare & Medicaid Services to develop and maintain performance measures that are used for public reporting (HHSM-500-2013-13018I); Dr Ross reported currently receiving research support through Yale University from Johnson & Johnson to develop methods for clinical trial data sharing; from the Medical Device Innovation Consortium as part of NEST, from the Food and Drug Administration for the Yale–Mayo Clinic CERSI program (U01FD005938); from the Agency for Healthcare Research and Quality (RO1HS022882); from the National Heart, Lung, and Blood Institute of the National Institutes of Health (RO1HS021664, RO1HL144644); and from the Laura and John Arnold Foundation to establish the Good Pharma Scorecard at Bioethics International.

Funding/Support: This publication is supported by the US Food and Drug Administration (FDA) of the US Department of Health and Human Services (HHS) as part of a financial assistance award U01FD005938 totaling $250,000 with 100% funded by FDA/HHS.

Role of the Funder/Sponsor: The FDA was involved in the design and conduct of the study, collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the US government.

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**SUPPLEMENT.**

eAppendix. Study Protocol
eFigure. Initial Cohort for PRONOUNCE
eTable 1. Summary of Inclusion and Exclusion Criteria for PRONOUNCE Trial, Overall Cohort Population and Postcohort Development
eTable 2. Use of Hormonal Management of Prostate Cancer and First-Generation Antiandrogen Agents Within 6 Months After Index Date and Baseline Characteristics Among Patients With and Without Prostate-Specific Antigen Levels
eTable 3. Subgroup Analyses for the Primary Intention-to-Treat Propensity Score-Matched Analyses
eTable 4. Outcomes in Additional Subgroup Analyses
eTable 5. Falsification Analyses