Cardiovascular Outcomes of α-Blockers vs 5-α Reductase Inhibitors for Benign Prostatic Hyperplasia

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Abstract

IMPORTANCE The most prescribed class of medications for benign prostatic hyperplasia (BPH) is α-blockers (ABs). However, the cardiovascular safety profile of these medications among patients with BPH is not well understood.

OBJECTIVE To compare the safety of ABs vs 5-α reductase inhibitors (5-ARIs) for risk of adverse cardiovascular outcomes.

DESIGN, SETTING, AND PARTICIPANTS This active comparator, new-user cohort study was conducted using insurance claims data from a 20% random sample of Medicare beneficiaries from 2007 to 2019 to evaluate the 1-year risk of adverse cardiovascular outcomes. Males aged 66 to 90 years were indexed into the cohort at new use of an AB or 5-ARI. Twelve months of continuous enrollment and at least 1 diagnosis code for BPH within 12 months prior to initiation were required. Data were analyzed from January 2007 through December 2019.

EXPOSURES Exposure was defined by a qualifying prescription fill for an AB or 5-ARI after at least 12 months without a prescription for these drug classes.

MAIN OUTCOMES AND MEASURES Follow-up began at a qualified refill for the study drug. Primary study outcomes were hospitalization for heart failure (HF), composite major adverse cardiovascular events (MACE; hospitalization for stroke, myocardial infarction, or death), composite MACE or hospitalization for HF, and death. Inverse probability of treatment and censoring-weighted 1-year risks, risk ratios (RRs), and risk differences (RDs) were estimated for each outcome.

RESULTS Among 189,868 older adult males, there were 163,829 patients initiating ABs (mean [SD] age, 74.6 [6.2] years; 579 American Indian or Alaska Native [0.4%], 5890 Asian or Pacific Islander [3.6%], 9179 Black [5.6%], 10,610 Hispanic [6.5%], and 133,510 non-Hispanic White [81.5%]) and 26,039 patients initiating 5-ARIs (mean [SD] age, 75.3 [6.4] years; 76 American Indian or Alaska Native [0.3%], 827 Asian or Pacific Islander [3.2%], 1339 Black [5.1%], 1656 Hispanic [6.4%], and 21,605 non-Hispanic White [83.0%]). ABs compared with 5-ARIs were associated with an increased 1-year risk of MACE (8.95% [95% CI, 8.81%-9.09%] vs 8.32% [95% CI, 7.92%-8.72%]; RR = 1.08 [95% CI, 1.02-1.13]; RD per 1000 individuals = 6.26 [95% CI, 2.15-10.37]), composite MACE and HF (RR = 1.07; [95% CI, 1.03-1.12]; RD per 1000 individuals = 7.40 [95% CI, 2.88-11.93]), and death (RR = 1.07; [95% CI, 1.01-1.14]; RD per 1000 individuals = 3.85 [95% CI, 0.40-7.29]). There was no difference in risk for HF hospitalization alone.

CONCLUSIONS AND RELEVANCE These results suggest that ABs may be associated with an increased risk of adverse cardiovascular outcomes compared with 5-ARIs. If replicated with more
detailed confounder data, these results may have important public health implications given these medications’ widespread use.


Introduction

Cardiovascular diseases and benign prostatic hyperplasia (BPH) are common conditions with shared risk factors among older men.1 The most prescribed class of medications for BPH consists of α-1 blockers (ABs), particularly selective antagonists of the α1-adrenergic receptor (α1-A-AR) subtype.2 Interestingly, the α1-A-AR subtype is expressed in prostate and cardiovascular tissues. Preclinical studies found that the α1-A-AR subtype was associated with cardioprotective outcomes.3,4 Furthermore, the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)5,6 was terminated early because doxazosin (a nonselective AB) was associated with an increased risk of adverse cardiac events, most notably HF, angina, and coronary revascularization. However, previous investigations of the cardiac safety of ABs have produced conflicting results.3,7 Our 2021 study8 found that use of ABs compared with no AB use was associated with an increased risk of mortality among patients undergoing percutaneous coronary intervention for myocardial infarction (MI). This finding highlights the need to investigate AB safety on a broader scale. In this study, we hypothesized that ABs compared with 5-α reductase inhibitors (5-ARIs), the second most prescribed medication class for BPH, would be associated with increased cardiovascular risks among Medicare beneficiaries with BPH.2

Methods

This cohort study was approved by the University of North Carolina at Chapel Hill (UNC-CH) Institutional Review Board, which granted a waiver of informed consent because the risk to patients was no more than minimal. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data Source

This study used insurance claims from a 20% random sample of Medicare beneficiaries in the US (2007-2019). This database contains longitudinal claims on inpatient, outpatient, and prescription drug services and demographic data. We obtained data under a data use agreement with the Centers for Medicare & Medicaid Services as maintained by the UNC-CH Cecil G. Sheps Center for Health Services Research.

Study Cohort

This was an active comparator study comparing new users of ABs vs 5-ARIs for risk of adverse outcomes.9 We constructed a cohort of individuals identified as males who were aged 66 to 90 years at new use; had continuous enrollment in fee-for-service Medicare plans A, B, and D for 12 or more months (with a 45-day gap allowed) prior to new use; and had 1 or more diagnosis codes for BPH at 12 months or less prior to new use (eTable 1 in Supplement 1; eTable 24 in Supplement 2). We excluded patients with chemotherapy within 6 months, hospice care within 12 months, or prostatectomy or prostate cancer at any time prior to new use (eTables 25-27 in Supplement 2).

Exposure Assessment

We identified medications via prescription claims from Medicare part D claims. We considered 2 comparator drug classes (generic or branded): ABs (alfuzosin, doxazosin, tamsulosin, terazosin,
silodosin, and prazosin) and 5-ARIs (finasteride and dutasteride) (eTable 2 in Supplement 1 and eTable 28 in Supplement 2). Medication initiation was defined as a prescription fill after January 1, 2008, without fills 12 months or longer prior. To minimize exposure misclassification due to nonadherence, we required individuals to refill the study drug 30 days or less after finishing their first prescription. We excluded individuals who filled a prescription for the other drug class or experienced an outcome between the first and second fill. Follow-up began at the second prescription fill to ensure equal follow-up across treatment groups (Figure 1).

Outcomes
We identified study outcomes using algorithms with high specificity (93%-98%) or positive predictive value (>95%). Outcomes were hospitalization for heart failure (HF), composite major adverse cardiovascular events (MACE; hospitalization for stroke, MI, or death), composite MACE or HF hospitalization, and death. Hospitalization outcomes were identified from the in-patient record only (eTable 3 in Supplement 1). Death was identified using the Medicare Master Beneficiary Summary File: National Death Index Segment. To ensure comparable outcome identification across the transition from International Classification of Diseases, Ninth Revision (ICD-9) to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes (October 2015), we visually assessed monthly prevalence estimates for each outcome among all Medicare enrollees from 2013 to 2017 (eFigures 1-3 in Supplement 1).

Covariates
Confounders were identified through a directed acyclic graph (eFigure 4 and eTable 4 in Supplement 1). Variables were identified based on claims 12 months or less prior to new use. They included age, race and Hispanic ethnicity, calendar year of new use, acute urinary retention, tobacco use, obesity, coronary heart disease, HF hospitalization, chronic kidney disease, chronic obstructive pulmonary disease (COPD), hypercholesterolemia, MI hospitalization, stroke hospitalization, diabetes, percutaneous coronary intervention, coronary artery bypass graft, atherosclerosis, antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, and diuretics), antidiabetics (dipeptidyl peptidase IV inhibitors, glucagon-like peptide 1 agonists, long-acting insulin, short-acting insulin, sodium-glucose cotransporter-2 inhibitors, sulfonylureas, and thiazolidinediones), other medications (anticoagulants, opioids, nicotine or varenicline, and statins), and components of the Faurot Frailty Index.

Medications were identified using National Drug Codes. Other variables were identified using ICD-9 and ICD-10 diagnosis and procedure codes, Current Procedural Terminology codes, Healthcare

Figure 1. Study Design Diagram With Inclusion and Exclusion Criteria
Common Procedure Coding System codes, and administrative data (eTables 29-65 in Supplement 2). Race and ethnicity were measured as a single ethnoracial variable via beneficiary enrollment file information; we used a classification derived by the Research Triangle Institute. Categories included American Indian or Alaska Native, Asian or Pacific Islander, Black, Hispanic, non-Hispanic White, other (race not within other categories), and unknown. Combined race and ethnicity was included in our analyses as a proxy for processes of marginalization impacting health, not as a biological construct.28

Statistical Analysis
We conducted the observational analogue of an intention-to-treat analysis. Treatment was determined at drug initiation, and patients were retained in that group over follow-up, regardless of treatment changes. Explicitly, we did not censor patients at treatment discontinuation or switching. We thus aimed to estimate the effect of initiating ABs vs 5-ARIs on adverse outcomes; however, because these are nonrandomized, secondary data and we cannot confirm that causal criteria (eg, no confounding) were met, we report associations throughout. For confounding, we calculated propensity scores (PSs) using logistic regression, modeling the probability of treatment with ABs vs 5-ARIs dependent on measured confounders (eTable 5 in Supplement 1). Stabilized inverse probability of treatment weights (IPTWs) were calculated as the marginal probability of a patient’s true treatment divided by the individual’s PS (or 1 minus the patient’s PS among initiators of 5-ARIs).32-34 We assessed covariate balance before and after IPTW using absolute standardized mean differences, with those ≤0.1 indicating adequate balance.

Patients were censored only at Medicare Parts A or B disenrollment. To account for this, we calculated stabilized inverse probability of censoring weights (IPCWs),35 using pooled logistic regression to estimate an individual’s probability of not being censored at each quintile of follow-up, dependent on treatment and factors associated with censoring (using the same variables as the PS model). Stabilized IPCWs were estimated as the probability of not being censored, dependent on treatment, divided by an individual’s probability of not being censored, dependent on treatment and factors associated with censoring.

We estimated cumulative incidence, risk ratios (RRs), and risk differences (RDs) from the second prescription fill through 1 year of follow-up using Kaplan-Meier and Aalen-Johansen estimators for mortality and nonmortality outcomes, respectively. Point estimates and CIs were calculated using nonparametric bootstrapping, drawing 500 random samples with replacement. RR and RD estimates and their SDs were calculated as the mean and standard error of point estimates across 500 samples. We calculated 2-sided 95% CIs, which when compared with the null value, indicate 2-sided statistical significance at \( P < .05 \). However, the goal of this study was to estimate effect sizes.36-40 To understand the magnitude of our exposure-outcome association, we calculated the number needed to harm (NNH) as the inverse of the RD estimate for outcomes with 95% CIs that did not overlap with 0. We plotted cumulative incidence curves in the nonbootstrapped sample. Furthermore, we evaluated treatment discontinuation and switching patterns to understand treatment persistence. Analyses were conducted using SAS statistical software version 9.4 (SAS Institute). Data were analyzed from January 2007 through December 2019; follow-up started January 2008.

A Priori Sensitivity Analyses
First, we used asymmetric propensity score trimming to understand the robustness of study results against uncontrolled confounding.41,42 Second, to understand residual confounding by hypertension, we repeated primary analyses considering only the ABs tamsulosin and silodosin, which are not indicated to treat hypertension.43 Third, to investigate our BPH definition, we required patients have 1 or more BPH diagnosis codes within 180 days prior to new use and compared cohort characteristics with those of the original population. Fourth, to assess confounding by BPH severity, we additionally controlled for days since the first-recorded BPH diagnosis code and number of BPH diagnoses during


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the 12-month lookback period. Fifth, to assess potential confounding by being a poor candidate for prostatectomy, we repeated analyses among a population of patients without prior anticoagulant use. Sixth, we limited our study period to start follow-up after October 1, 2015, so that all outcomes would be captured via ICD-10 codes.

Post Hoc Sensitivity Analyses
First, we evaluated hospitalization for injury or poisoning as a negative control outcome (eTable 6 in Supplement 1). Second, we conducted a quantitative bias analysis to investigate residual confounding by misclassified obesity and smoking (eMethods in Supplement 1). Third, we repeated primary analyses among patients with 2 or more outpatient or 1 or more inpatient claims with a BPH diagnosis. Fourth, to investigate exposure-outcome associations among patients with a poor cardiovascular profile, we repeated the primary analysis among patients with 1 or more inpatient hospitalizations for MI, stroke, or HF within 12 months prior to cohort entry. Finally, to investigate confounding by socioeconomic status, we repeated primary analyses additionally controlling for eligibility for Medicaid dual enrollment and the Medicare Part D low-income subsidy.

Results
Among 189,868 older adult males, there were 163,829 initiators of ABs (86.3%; mean [SD] age, 74.6 [6.2] years; 579 American Indian or Alaska Native [0.4%], 5890 Asian or Pacific Islander [3.6%], 9179 Black [5.6%], 10,610 Hispanic [6.5%], and 133,510 non-Hispanic White [81.5%]) and 26,039 initiators of 5-ARIs (13.7%; mean [SD] age, 75.3 [6.4] years; 76 American Indian or Alaska Native [0.3%], 827 Asian or Pacific Islander [3.2%], 1339 Black [5.1%], 1656 Hispanic [6.4%], and 21,605 non-Hispanic White [83.0%]) (Table 1; eFigure 5 in Supplement 1). Tamsulosin was the most frequently filled AB; 141,398 initiators of ABs used a selective-type AB (86.3%) (eFigure 6 in Supplement 1). In the unweighted cohort, initiators of ABs had a higher prevalence than initiators of 5-ARIs of some cardiovascular disease risk factors, such as prior HF hospitalization (12,051 patients [7.4%] vs 1439 patients [5.5%]), prior stroke hospitalization (55,955 patients [3.4%] vs 612 patients [2.9%]), and diabetes (54,347 patients [33.2%] vs 7530 patients [28.9%]). Initiators of 5-ARIs were older with a higher prevalence of hypercholesterolemia than initiators of ABs (81,013 patients [49.4%] vs 14,971 patients [57.5%]). Patients were well-balanced on measured covariates after using IPTWs (eFigures 7 and 8 and eTable 7 in Supplement 1). By 1 year, 96,492 initiators of ABs (58.9%) and 14,383 initiators of 5-ARIs (55.2%) had discontinued treatment, 18,223 initiators of ABs (11.1%) had filled a prescription for a 5-ARI, and 4973 initiators of 5-ARIs (19.1%) had filled a prescription for an AB (eFigure 9, eTable 8, and eTable 9 in Supplement 1).

IPCW-adjusted 1-year risks of primary outcomes were low. Among initiators of ABs and 5-ARIs, 3.90% (95% CI, 3.80% to 4.00%) and 3.29% (95% CI, 3.07% to 3.52%) experienced HF hospitalization, 9.07% (95% CI, 8.93% to 9.21%) and 7.38% (95% CI, 7.04% to 7.72%) experienced MACE, 11.30% (95% CI, 11.14% to 11.45%) and 9.26% (95% CI, 8.89% to 9.63%) experienced composite MACE and HF hospitalization, and 6.11% (95% CI, 5.99% to 6.22%) and 4.95% (95% CI, 4.67% to 5.23%) died, respectively. These risks corresponded to relatively high estimates of RR (range, 1.18 [95% CI, 1.10 to 1.27] for HF hospitalization to 1.23 [95% CI, 1.17 to 1.29] for MACE and 1.23 [95% CI, 1.16 to 1.31] for deaths) and RD per 1000 individuals (range, 6.02 [95% CI, 3.51 to 8.53] for HF hospitalization to 20.38 [95% CI, 16.38 to 24.38] for composite MACE or HF hospitalization) for the AB vs 5-ARI group, but they were attenuated after IPTW. IPTW- and IPCW-adjusted estimates for RR and RD per 1000 individuals for HF hospitalization were 0.99 (95% CI, 0.92 to 1.07) and 0.23 (95% CI, –0.20 to 2.73), respectively, for AB vs 5-ARI groups (Figure 2, Table 2). For MACE, the risk was 8.95% (95% CI, 8.81% to 9.09%) for ABs and 8.32% (95% CI, 7.92% to 8.72%) for 5-ARIs, and the estimated RR and RD per 1000 individuals were 1.08 (95% CI, 1.02 to 1.13) and 6.26 (95% CI, 2.15 to 10.37; NNH = 160 individuals [95% CI, 97 to 466 individuals]), respectively, for AB vs 5-ARI.
Table 1. Distribution of Covariates at Treatment Initiationa

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unweighted cohortb</th>
<th>IPTW cohortb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients initiating treatment, No. (%) (N = 189 868)</td>
<td>Patients initiating treatment, % (95% CI)c (N = 163 829) 5-ARI (n = 26 039) AB</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>73.0 (69.0-79.0)</td>
<td>74.0 (70.0-80.0) 0.117</td>
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<td>Calendar year, median (IQR)</td>
<td>2014.0 (2011.0-2017.0)</td>
<td>2013.0 (2010.0-2016.0) 0.344</td>
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<td>Race and ethnicity</td>
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<td>American Indian or Alaska Native</td>
<td>579 (0.4)</td>
<td>76 (0.3) 0.011</td>
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<td>Asian or Pacific Islander</td>
<td>5890 (3.6)</td>
<td>827 (3.2) 0.023</td>
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<tr>
<td>Black or African American</td>
<td>9179 (5.6)</td>
<td>1339 (5.1) 0.020</td>
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<tr>
<td>Hispanic</td>
<td>10 610 (6.5)</td>
<td>1656 (6.4) 0.005</td>
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<td>Non-Hispanic White</td>
<td>131 510 (81.5)</td>
<td>21 605 (83.0) 0.039</td>
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<tr>
<td>Other</td>
<td>1872 (1.1)</td>
<td>286 (1.1) 0.022</td>
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<tr>
<td>Part D cost share eligibilityd</td>
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<td>Full</td>
<td>4606 (2.5)</td>
<td>591 (2.3) 0.014</td>
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<tr>
<td>Partial</td>
<td>32 281 (19.7)</td>
<td>4080 (15.7) 0.106</td>
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<tr>
<td>Not eligible</td>
<td>127 479 (77.8)</td>
<td>21 368 (82.1) 0.106</td>
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<tr>
<td>Medicaid dual eligibilityd</td>
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<tr>
<td>Full</td>
<td>6692 (4.1)</td>
<td>826 (3.2) 0.049</td>
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<tr>
<td>Partial</td>
<td>24 367 (14.9)</td>
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<tr>
<td>Not eligible</td>
<td>132 770 (81)</td>
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<tr>
<td>Acute urinary retention</td>
<td>36 514 (22.3)</td>
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<td>Coronary heart disease</td>
<td>67 225 (41.0)</td>
<td>10 443 (40.1) 0.019</td>
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<tr>
<td>Hospitalization due to heart failure</td>
<td>12 051 (7.4)</td>
<td>14 971 (57.5) 0.162</td>
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<tr>
<td>Prevalent heart failurec</td>
<td>36 514 (22.3)</td>
<td>4574 (17.6) 0.118</td>
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<td>Chronic kidney disease</td>
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<td>6208 (23.8) 0.125</td>
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<td>COPD</td>
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<td>5385 (20.7) 0.085</td>
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<td>Hypercholesterolemia</td>
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<td>14 971 (57.5) 0.162</td>
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<td>Hospitalization due to MI</td>
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<td>427 (1.6) 0.030</td>
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<td>Hospitalization due to stroke</td>
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<td>612 (2.4) 0.064</td>
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<td>Percutaneous coronary intervention</td>
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<td>437 (1.7) 0.003</td>
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<td>Coronary artery bypass graft surgery</td>
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<td>152 (0.6) 0.049</td>
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<td>Tobacco use</td>
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<td>3671 (14.1) 0.120</td>
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<td>61 533 (37.6)</td>
<td>9258 (35.6) 0.042</td>
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<td>ARB, any use</td>
<td>33 951 (20.7)</td>
<td>5072 (19.5) 0.031</td>
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<td>β-blocker, any use</td>
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<td>Peripheral vasoconstrictor, any use</td>
<td>3029 (1.8)</td>
<td>609 (2.3) 0.034</td>
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<td>Calcium channel blocker, any use</td>
<td>49 928 (26.0)</td>
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<td>Thiazide diuretic, any use</td>
<td>34 827 (18.3)</td>
<td>5250 (20.2) 0.027</td>
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<td>Combination diuretic, any use</td>
<td>18 052 (10.1)</td>
<td>2920 (11.2) 0.006</td>
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<tr>
<td>Potassium sparing diuretic, any use</td>
<td>9191 (5.6)</td>
<td>1391 (5.3) 0.012</td>
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<td>Loop diuretic, any use</td>
<td>25 547 (15.7)</td>
<td>3593 (13.8) 0.051</td>
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<tr>
<td>Other diuretics, any use</td>
<td>3517 (2.1)</td>
<td>453 (1.7) 0.029</td>
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<td>Anticoagulant use</td>
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<tr>
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<td>141 194 (86.2)</td>
<td>22 111 (84.9) 0.036</td>
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<tr>
<td>1 Fill</td>
<td>4223 (2.6)</td>
<td>532 (2.0) 0.036</td>
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<tr>
<td>≥2 Fills</td>
<td>8 412 (11.2)</td>
<td>3396 (13.0) 0.055</td>
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<td>Opioid use</td>
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<tr>
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<td>97 222 (59.3)</td>
<td>17 178 (66.0) 0.137</td>
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<td>1 Fill</td>
<td>26 625 (16.3)</td>
<td>3958 (15.2) 0.029</td>
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<tr>
<td>≥2 Fills</td>
<td>39 822 (24.4)</td>
<td>4903 (18.8) 0.136</td>
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(continued)
For composite MACE or HF hospitalization, the RR was 1.07 (95% CI, 1.03 to 1.12) and the RD per 1000 individuals was 7.40 (95% CI, 2.88 to 11.93; NNH = 136 individuals [95% CI, 84 to 348 individuals]) for AB vs 5-ARI groups. Finally, for mortality, estimates of RR and RD per 1000 individuals were 1.07 (95% CI, 1.01 to 1.14) and 3.85 (95% CI, 0.40 to 7.29; NNH = 260 individuals [95% CI, 138 to 2500 individuals]), respectively, for AB vs 5-ARI groups. These estimates align with 1024 additional MACE, 1204 composite MACE and HF hospitalizations, and 631 deaths over 1 year among initiators of ABs vs 5-ARIs.

Associations were consistent after asymmetric propensity score trimming (eTable 10 in Supplement 1) and after restricting ABs to tamsulosin and silodosin (eTables 11 and 12 in Supplement 1). The population identified when requiring 1 or more BPH diagnoses within 180 days prior to study drug initiation was comparable to the primary cohort (eTable 13 in Supplement 1), as were treatments (eFigure 10 in Supplement 1). Associations were attenuated when additionally controlling for indicators of BPH severity (eTable 14 in Supplement 1). Associations were consistent with primary results after excluding patients with prior anticoagulant use (eTable 15 in Supplement 1). Similarly, results were comparable, although less precise, when restricting to new-use episodes on or after October 1, 2015 (eTable 16 in Supplement 1).

In a post hoc sensitivity analysis evaluating risk of hospitalization for injury or poisoning, we found an RR of 1.06 (95% CI, 0.99 to 1.13) and an RD per 1000 individuals of 2.87 (95% CI, −0.42 to 5.16).

### Table 1. Distribution of Covariates at Treatment Initiation

<table>
<thead>
<tr>
<th>Covariate</th>
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<th>IPTW cohortb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients initiating treatment, No. (%)</td>
<td>AB (n = 183 829)</td>
<td>5-ARI (n = 26 039)</td>
</tr>
<tr>
<td>(N = 189 868)</td>
<td>Absolute SMD</td>
<td></td>
</tr>
<tr>
<td>Nicotine or varenicline, any use</td>
<td>0.008</td>
<td></td>
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<tr>
<td>Statin, any use</td>
<td>0.054</td>
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<tr>
<td>Diabetes</td>
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<td>DPP-4i</td>
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<td>≥2 fills</td>
<td>0.041</td>
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<td>SGLT-2i, any Fill</td>
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<tr>
<td>Sulfonlureas, any Fill</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>T2D, any fill</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Atherosclerosis or peripheral vascular disease</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>0.141</td>
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</table>

Abbreviations: 5-ARI, α-reductase inhibitor initiator; AB, α-blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; IPTW, inverse probability of treatment weight; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; MI, myocardial infarction; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; SMD, standardized mean difference; TZD, thiazolidinedione.

a Distribution is given in the primary cohort after trimming nonoverlapping regions of the propensity score distributions across 2 treatment groups. Results are presented before and after applying IPTWs.

b Patients who experienced heart failure or a major adverse cardiovascular event between their first and second prescription fill are included. The sum of the standardized weight among the AB treatment group was 163 840, and the sum among the 5-ARI group was 26 009.

c CIs were calculated using the proc surveymeans procedure in SAS statistical software using bootstrapping (with 250 resamples) to account for interdependence caused by the use of IPTWs.

d These variables were not included in the primary propensity score model.

e Identified as 2 or more outpatient or 1 or more inpatient claims with a diagnosis code for heart failure in any position.

For composite MACE or HF hospitalization, the RR was 1.07 (95% CI, 1.03 to 1.12) and the RD per 1000 individuals was 7.40 (95% CI, 2.88 to 11.93; NNH = 136 individuals [95% CI, 84 to 348 individuals]) for AB vs 5-ARI groups. Finally, for mortality, estimates of RR and RD per 1000 individuals were 1.07 (95% CI, 1.01 to 1.14) and 3.85 (95% CI, 0.40 to 7.29; NNH = 260 individuals [95% CI, 138 to 2500 individuals]), respectively, for AB vs 5-ARI groups. These estimates align with 1024 additional MACE, 1204 composite MACE and HF hospitalizations, and 631 deaths over 1 year among initiators of ABs vs 5-ARIs.

Associations were consistent after asymmetric propensity score trimming (eTable 10 in Supplement 1) and after restricting ABs to tamsulosin and silodosin (eTables 11 and 12 in Supplement 1). The population identified when requiring 1 or more BPH diagnosis codes within 180 days prior to study drug initiation was comparable to the primary cohort (eTable 13 in Supplement 1), as were treatments (eFigure 10 in Supplement 1). Associations were attenuated when additionally controlling for indicators of BPH severity (eTable 14 in Supplement 1). Associations were consistent with primary results after excluding patients with prior anticoagulant use (eTable 15 in Supplement 1). Similarly, results were comparable, although less precise, when restricting to new-use episodes on or after October 1, 2015 (eTable 16 in Supplement 1).

In a post hoc sensitivity analysis evaluating risk of hospitalization for injury or poisoning, we found an RR of 1.06 (95% CI, 0.99 to 1.13) and an RD per 1000 individuals of 2.87 (95% CI, −0.42 to 5.16).
6.16) for AB vs 5-ARI groups (eTable 17 in Supplement 1). Estimates from the quantitative bias analysis for misclassified smoking were attenuated from primary results for composite MACE and HF hospitalization (RR range, 0.94 to 1.03 for AB vs 5-ARI groups), although comparable when adjusted for misclassified obesity (RR range, 1.07 to 1.11 for AB vs 5-ARI groups) (eTable 18 in Supplement 1).

Outcomes were A, hospitalization for heart failure (HF), B, major adverse cardiovascular events (MACE), C, composite MACE or hospitalization for HF, and D, all-cause mortality. 5-ARI indicates 5α-reductase inhibitor; AB, α-blocker.

Table 2. Association of Treatment With Study Outcomesa

<table>
<thead>
<tr>
<th>Study outcome</th>
<th>Non-IPTW estimates</th>
<th>IPTW estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk, % (95% CI)</td>
<td>Risk, % (95% CI)</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>S-ARI</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>3.90 (3.80 to 4.00)</td>
<td>3.29 (3.17 to 3.52)</td>
</tr>
<tr>
<td>MACE outcomes</td>
<td>9.07 (8.93 to 9.21)</td>
<td>7.38 (7.04 to 7.72)</td>
</tr>
<tr>
<td>Composite MACE or hospitalization for HF</td>
<td>11.30 (11.14 to 11.45)</td>
<td>9.26 (8.89 to 9.63)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>6.11 (5.99 to 6.22)</td>
<td>4.95 (4.67 to 5.23)</td>
</tr>
</tbody>
</table>

Abbreviations: S-ARI, 5α-reductase inhibitor; AB, α-blocker; HF, heart failure; IPTW, inverse probability of treatment weight; MACE, major adverse cardiovascular event; RD, risk difference; RR, risk ratio.

*a Results are among the primary study population after trimming nonoverlapping regions of the propensity score distributions comparing initiators of ABs vs S-ARIs. Results are presented with and without IPTWs; all results incorporate inverse probability of censoring weights.
Results were consistent among a population with 2 or more outpatient or 1 or more inpatient claims with a BPH diagnosis code (eTables 19 and 20 in Supplement 1). Estimates among patients with prior hospitalization for HF, MI, or stroke were too imprecise for meaningful conclusions (eTables 21 and 22 in Supplement 1). Finally, controlling for socioeconomic status yielded generally consistent results (eTable 23 in Supplement 1).

Discussion

In this large cohort study of Medicare beneficiaries with BPH, we found that initiation of ABs compared with 5-ARIs was associated with an increased risk of death, MACE, and composite MACE and HF hospitalization. We did not identify an increased risk for HF hospitalization alone. IPCW-adjusted risks of these outcomes were low. To our knowledge, this is the largest study assessing cardiovascular risk in patients taking ABs and the first to focus on mortality and MACE among patients with BPH.

Residual confounding could contribute to these results. However, even a small difference in cardiovascular outcomes associated with ABs vs 5-ARIs would have substantial public health implications given how widely ABs are prescribed for BPH. Per our NNH estimate, for every 136 individuals (95% CI, 84-348 individuals) with BPH treated with ABs over 5-ARIs, we would expect 1 additional MACE or HF hospitalization within 1 year after initiation. To provide perspective, 163,829 individuals in our 20% Medicare sample (86.3%) were prescribed ABs over 5-ARIs. When this number is divided by the NNH of 136 individuals, this is potentially associated with 1205 additional events over 1 year. The importance of these findings may also be amplified because most patients with BPH require long-term medical therapy; thus, the risk of AB exposure could be cumulative. Furthermore, more than 5 million people filled a prescription for tamsulosin alone in the US in 2020, underscoring the potential magnitude of outcomes associated with these medications.

Our findings regarding HF potentially contrast with those of ALLHAT, wherein a 2-fold risk of incident HF led to discontinuation of the nonselective AB group. Initial hypotheses regarding adverse effects of doxazosin pointed to less effective blood pressure control in this population compared with individuals receiving chlorthalidone. However, further analyses did not support this. Apparent differences between the 2 studies also could arise from ALLHAT’s examination of hospital and home-treated HF, whereas we considered only HF hospitalization. Furthermore, our cohort’s mean age was approximately 7 years older than that of participants in ALLHAT and included only male patients with an established diagnosis of BPH, whereas ALLHAT included male and female participants.

Our finding that ABs were not associated with HF hospitalization risk may also appear to contrast with an RR of 1.10 among users of ABs compared with those using 5-ARIs reported by Lusty et al. However, the Ontario study focused on new diagnosis of HF, whereas we studied HF hospitalization. Furthermore, they indexed patients into the study at the time of BPH diagnosis, introducing potential selection bias that our approach avoids. A meta-analysis of randomized trials among patients with indications for ABs by Sousa et al found that patients receiving ABs compared with those in active or placebo control groups had increased risk of acute HF (odds ratio = 1.78 [95% CI, 1.46-2.16]). They found no association with mortality (odds ratio = 1.10 [95% CI, 0.84-1.42]), although they did not analyze outcomes with respect to a relevant comparator group as we have done with patients taking 5-ARIs.

In contemporary practice, the most prescribed ABs for BPH are α-1A subtype-selective antagonists that have minimal impact on blood pressure. We found that increased risks of adverse cardiovascular outcomes were maintained when the exposure was limited to subtype-selective ABs in sensitivity analyses. This finding was unsurprising given that 141,398 ABs (86.3%) prescribed in our study were subtype selective. Collectively, these data align with the concept that activation of endogenous cardiac α1-A-ARs is cardioprotective, as demonstrated in preclinical studies.
Strengths and Limitations

This study has important strengths. Our source population was Medicare beneficiaries enrolled in Parts A and B fee-for-service plans. Given that approximately 54% of Medicare beneficiaries were enrolled in these plans in 2019, our study represents a substantial percentage of US adults aged 65 years or older. Moreover, we adhered to prespecified analyses and used rigorous methodology, such as IPTWs and IPCWs to account for systematic bias. We conducted a new-user, active comparator cohort study that minimized confounding by indication and avoided immortal time bias. Furthermore, we conducted an observational analog of the intention-to-treat analysis, minimizing bias due to informative censoring. Finally, our choice of active comparator is clinically relevant: ABs and 5-ARIs are first-line treatments for BPH, but adverse cardiac outcomes are hypothesized only with ABs. This choice ensured that our study addressed a pertinent clinical question and so may provide valuable insights into the safety of medications commonly prescribed for BPH management.

It is important to acknowledge several limitations in our study. First, like other studies using insurance claims data, this study is susceptible to variable misclassification. In sensitivity analyses, we found that our results were robust against poorly classified obesity but that if smoking operated as a confounder beyond what we have captured, residual confounding may explain our results. However, many studies have found that a large majority of individuals with COPD currently or previously smoked. Given that we controlled for COPD, there may be less residual confounding than this sensitivity analysis suggested. Second, despite substantial effort to control for confounding, some confounding may persist. Our results were consistent across multiple sensitivity analyses (e.g., asymmetric PS trimming), although when controlling for indicators of BPH severity, for example, we found attenuated point estimates. Given the sizes of our association estimates, a post hoc negative control outcome analysis was uninformative (eAppendix in Supplement 1). Third, we evaluated only 1 year of follow-up; we were concerned about our ability to capture reasons for treatment changes (e.g., BPH symptom severity), and treatment changes were common. Furthermore, we did not consider medication dosing given that clinicians often instruct patients to take a different number of the same pill dosage according to their BPH symptoms, which cannot be captured in claims. Fourth, this study may not be generalizable to all patients with BPH. We excluded beneficiaries enrolled in Medicare Advantage plans, required 2 or more medication fills, and included claims only through 2019. These limitations should not impact our study's internal validity; however, any differences in the distribution of variables that modify the effect of ABs vs 5-ARIs on cardiovascular outcomes (i.e., effect measure modifiers) will impact the transportability of our results to other populations.

Conclusions

This cohort study is the largest study of the association of ABs with cardiovascular events to date, to our knowledge. We found that new prescription of ABs compared with 5-ARIs was associated with a higher risk of all-cause mortality and MACE among patients with BPH. Although we present the most extensive analysis, to our knowledge, of the cardiovascular safety of ABs heretofore, further investigation with more detailed clinical data is warranted to guide ongoing clinical practice.
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Author Contributions: Ms Latour and Ms Olawore 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. Dr Zhang and Ms Latour contributed equally to this work.

Concept and design: Zhang, Latour, Pate, Friedlander, Jonsson Funk, Jensen.

Acquisition, analysis, or interpretation of data: Zhang, Latour, Olawore, Pate, Friedlander, Stürmer, Jensen.

Drafting of the manuscript: Zhang, Latour, Jensen.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Zhang, Latour, Olawore.

Obtained funding: Jensen.

Administrative, technical, or material support: Zhang, Latour, Olawore, Pate, Friedlander, Stürmer.

Supervision: Zhang, Jonsson Funk, Jensen.

Conflict of Interest Disclosures: Dr Latour reported receiving consulting fees from Target RWE and Amgen, Inc outside the submitted work. Dr Pate reported receiving grants from the National Institute on Aging and National Center for Advancing Translational Sciences during the conduct of the study. Dr Stürmer reported receiving stock from Novartis, Roche, and Novo Nordisk outside the submitted work and salary support as director of comparative effectiveness research, North Carolina Translational and Clinical Sciences Institute, the University of North Carolina (UNC) Clinical and Translational Science Award, from the Center for Pharmacoepidemiology (current members: GSK, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim, Astellas, and Sarepta), from pharmaceutical companies (Novo Nordisk), and from a generous contribution from Dr Nancy A. Dreyer to the Department of Epidemiology, UNC at Chapel Hill. Dr. Stürmer reported owning stock in Novartis, Roche, and Novo Nordisk. Dr Jonsson Funk reported receiving salary support as director of the Center for Pharmacoepidemiology housed in the Department of Epidemiology through collaborative agreements with AbbVie, Astellas, Boehringer Ingelheim, GSK, Sarepta, Takeda, and UCB Biosciences and being a member of the Scientific Steering Committee for a postapproval safety study of an unrelated drug class funded by GSK invoiced by and paid to UNC Chapel Hill and a member of the Epidemiology and Clinical Advisory Board for Epidvian. Dr Jensen reported having a patent for US 11,213,514 B2 issued for an α-1 adrenergic receptor agonist therapy. No other disclosures were reported.

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Data Sharing Statement: See Supplement 3.

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