Hypertension

ORIGINAL ARTICLE

Comparative Safety and Effectiveness of Aldosterone Antagonists Versus Beta-Blockers as Fourth Agents in Patients With Apparent Resistant Hypertension

Raj Desai, Haesuk Park, Joshua D. Brown, Rajesh Mohandas, Carl J. Pepine, Steven M. Smith

BACKGROUND: Limited evidence exists regarding long-term effectiveness and safety of aldosterone antagonists (AAs) versus beta blockers (BBs) as fourth-line antihypertensive agents in patients with resistant hypertension (RH). We evaluated the comparative effectiveness and safety of aldosterone AA versus BB.

METHODS: We conducted a real-world retrospective cohort study using IBM MarketScan commercial claims and Medicare Supplemental claims (2007–2019). Patients with RH entered the cohort (ie, index date) when they newly initiated either AA or BB. The effectiveness outcome was major adverse cardiovascular events. Safety outcomes were hyperkalemia, gynecomastia, and kidney function deterioration. Potential confounding was addressed by adjustment for baseline characteristics via stabilized inverse probability of treatment weighting (SIPTW) based on propensity scores. Cox proportional hazards regression with SIPTWs were used to estimate adjusted hazard ratio (aHR) and 95% CI comparing risk for outcomes between AA and BB groups.

RESULTS: We identified 80 598 patients with RH (mean age: 61 years, 51% males), of which 6626 initiated AA and 73 972 initiated BB as the fourth antihypertensive agent. Among patients with RH, initiation of AA as a fourth-line antihypertensive agent did not significantly reduce major adverse cardiovascular event risk relative to BB initiation (aHR, 0.77 [95% CI, 0.50–1.19]) but did substantially increase the risk of hyperkalemia (aHR, 3.86 [95% CI, 2.78–5.34]), gynecomastia (aHR, 9.51 [95% CI, 5.69–15.89]), and kidney function deterioration (aHR, 1.63 [95% CI, 1.34–1.99]).

CONCLUSIONS: Long-term clinical trials powered to assess major adverse cardiovascular events are necessary to understand the risk-benefit trade-off of AA as fourth-line therapy for RH. **(*Hypertension*. 2022;79:2305–2315. DOI: 10.1161/HYPERTENSIONAHA.122.19280.)** • **Supplemental Material**

Key Words: adrenergic beta-antagonists ■ aldosterone antagonists ■ comparative effectiveness research ■ hypertension ■ safety

Although most patients with hypertension achieve blood pressure (BP) control with 1 to 2 antihypertensive drug regimens, a significant proportion present with a more difficult-to-treat phenotype known as resistant hypertension (RH).[1] Current guidance for patients presenting with RH includes optimization of the background 3 antihypertensive drug regimen, which commonly includes an ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blockers, a long-acting calcium channel blocker, and a thiazide-like diuretic (also known as the "A+C+D" regimen).[2] Following this background regimen optimization, aldosterone antagonists (ie, spironolactone or eplerenone) are recommended as the preferred fourth agent, in part, because aldosterone excess is common in RH,[2–5] prompting excess volume retention and organ damage (eg, fibrosis).

PATHWAY-2, a large multicenter, double-blind, placebo-controlled, crossover trial investigated the optimal

Correspondence to: Steven M. Smith, Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida,1225 Center Dr, Suite 3334, Gainesville, FL 32610. Email ssmith@cop.ufl.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.122.19280.
For Sources of Funding and Disclosures, see page 2314.

Hypertension is available at www.ahajournals.org/journal/hyp

ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

This study is the first to evaluates safety and effectiveness outcomes of aldosterone antagonists as initial treatment for patients with resistant hypertension (RH) under real world treatment conditions in a US Commercially insured population.

What Is Relevant?

Aldosterone antagonists are effective in reducing short-term blood pressure in RH, but long-term efficacy and safety are unknown.

The optimal treatment for RH, in terms of long-term net benefit, also remains unclear.

Clinical/Pathophysiological implications

No significant difference was observed in major adverse cardiovascular event risk between aldosterone antagonists and beta blockers, though events were infrequent. Aldosterone antagonists were associated with increased risk for hyperkalemia, gynecomastia, and kidney function deterioration.

A definitive long-term RCT to evaluate comparative effectiveness and safety of aldosterone antagonists and other fourth line antihypertensive agents is warranted to understand whether more intensive blood pressure lowering in RH incurs a net benefit.

Nonstandard Abbreviations and Acronyms

AA	aldosterone antagonist
ACE	angiotensin-converting enzyme
aHR	adjusted hazard ratio
AMI	acute myocardial infarction
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BB	beta blocker
BP	blood pressure
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
MACE	major adverse cardiovascular event
RH	resistant hypertension
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

fourth-line agent among patients with RH who were already receiving an A+C+D regimen.[6] Based on greater BP response over 12 weeks, investigators concluded spironolactone was more effective than bisoprolol or doxazosin, all of which were more effective than placebo, for most patients.[6] However, the trial only evaluated short-term (12-week) BP changes, and it remains unknown whether this superiority of spironolactone, in terms of BP lowering, translates to superiority in reduction of cardiovascular outcomes. This knowledge gap is particularly important in light of data from observational studies suggesting that BP control in RH may not be associated with improved cardiovascular outcomes.[7,8]

Studies evaluating the long-term safety and effectiveness of spironolactone or eplerenone as fourth agents specifically in patients with RH are scarce. To the best of our knowledge, only one observational study has specifically investigated long-term safety and effectiveness of aldosterone antagonists as fourth line agents in RH.[9] In this UK-based study, investigators observed a significantly higher risk of major adverse cardiovascular events (MACEs) comparing aldosterone antagonists to beta-blockers (reference) in unadjusted analyses (HR, 1.45 [95% CI, 1.01–2.13]). After adjustment, no difference in the risk of MACE (HR, 1.23 [95% CI, 0.84–1.82]) was observed. However, this study included a relatively small sample (n=8639) and, as noted by the authors, there were significant concerns regarding residual confounding. Therefore, it remains unclear whether aldosterone antagonists are the preferred fourth agent for reducing cardiovascular outcomes in patients meeting RH criteria in a real-world setting. We aimed to compared safety and effectiveness of aldosterone antagonists versus beta blockers as fourth line agents in patients with RH under real world treatment conditions in the United States.

METHODS

Data Availability

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to https://www.ibm.com.

Data Sources

We conducted a retrospective cohort study using IBM MarketScan commercial claims and Medicare Supplemental claims databases (January 2007 through December 2019). The IBM MarketScan commercial claims database contains administrative claims data including de-identified information on enrollment, health care encounters and utilization, expenditures, and outpatient pharmacy records of >180 million employees and their dependents in United States covered by several health benefit plans. The MarketScan Medicare Supplemental claims database contains claims de-identified patient level data

for Medicare-eligible retirees with supplemental insurance plans offered by their former employers. The Marketscan database is considered representative of the United States population receiving health insurance under employer-sponsored programs,[10] which covered ≈48% to 54% of the US population across all study years.[11]

Study Population

We identified patients meeting RH criteria between January 1, 2008 and December 31, 2019 (2007 data were used to allow a 12-month baseline period). To mirror the definition of RH used in the PATHWAY-2 trial and based on the recommendations by current RH guidance,[6,12,13] to be classified as having RH, patients were required to have a diagnosis of hypertension (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]*: 401.x; *International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]*: I10.x) and concomitantly use 3 anti-hypertensive medications (A+C+D classes) and then initiate either an aldosterone antagonist or oral beta blocker (study drugs; Table S1). To determine an episode of concomitant use of A+C+D regimen with the study medications, we used the dispensing dates and the reported days' supply for each prescription and strung together consecutive fills for antihypertensive drugs prescribed.[14,15] We allowed a grace period of an extra 30% of submitted days' supply to allow for modest delays in refills of the A+C+D regimen.[15]

Cohort Development

Patients entered the cohort (ie, index date) when they newly initiated either the aldosterone antagonist or beta blocker while continuing the A+C+D regimen in the claims database. New initiation was defined as an initial fill of a study drug without a dispensing of any study drug in the previous 365 days. For aldosterone antagonists and beta blockers, we allowed gaps of up to 14 days between the end of the days of supply for one dispensing and the date of the next dispensing (a 14-day grace period). The 14-day grace period was selected to account for the carryover effects of the discontinued medications and to allow a biologically plausible time for the outcome to occur. We selected beta blockers as the active comparator because they represent a comparable therapeutic alternative to aldosterone antagonists and remain the most frequently used antihypertensive class outside of diuretics, ACE inhibitors, angiotensin receptor blockers and calcium channel blockers, thus minimizing concerns related to confounding by indication.[16] Patients were required to have continuous medical and pharmacy enrollment for at least 12 months before the index date (ie, 12-month baseline period); see Table S2 for additional details on continuous enrollment of the study population. Patients with both an aldosterone antagonist and beta blocker on the index date of cohort entry were excluded. Additionally, patients using any other antihypertensives (besides A+C+D) on the index date were excluded. Patients were excluded also if, during the 12-month baseline period, they had any diagnosis of hyperaldosteronism (*ICD-9-CM*: 255.10 or *ICD-10-CM*: E26.9), or heart failure (*ICD-9-CM*: 398.91, 402.x1, 404.x1, 404.x3, 428.xx or *ICD-10-CM*: I09.81, I11.0, I13.0, I13.2, I50.xx). Finally, we excluded patients with prior occurrence of effectiveness or safety outcomes in the 12-month baseline period. We allowed patients to enter the cohort only once, on the first occurrence of meeting study criteria, ie, patients could not rejoin the cohort after discontinuation and re-initiation of study medications.

Effectiveness and Safety Outcomes

The effectiveness outcome of interest was a composite outcome of MACEs defined as the first occurrence of stroke (ischemic or hemorrhagic) or acute myocardial infarction (AMI). Stroke was identified via *ICD-9-CM* codes 430.xx, 431.xx, 433.x1, 434.xx (excluding 434.x0), or 436.xx, or *ICD-10-CM* codes I60.xx, I61.x, or I63.xxx in the primary position of an inpatient hospital discharge. Acute myocardial infarction was identified by *ICD-9-CM* codes 410.x or *ICD-10-CM* codes I21.0-I21.4, or I22.x, in the primary or secondary position of the inpatient hospital discharge. The claims-based algorithms to individually identify AMI and stroke have been validated and have a positive predictive value >90%.[17,18] The date of first occurrence of MACE was defined as the date of the effectiveness outcome. Secondary effectiveness outcomes included individual components of the primary outcome.

The safety outcomes of interest were hyperkalemia, gynecomastia, and kidney function deterioration. We identified hyperkalemia by requiring at least one inpatient hospital discharge or one outpatient visit with a qualifying diagnosis of hyperkalemia (*ICD-9-CM*: 276.7 or *ICD-10-CM*: E87.5) in the primary position. We identified gynecomastia by requiring at least one inpatient hospital discharge or one outpatient visits with a qualifying diagnosis of gynecomastia (*ICD-9-CM*: 611.1 or *ICD-10-CM*: N62) in the primary position. Kidney function deterioration was a composite outcome defined as the first occurrence of chronic kidney disease (*ICD-9-CM*: 585.3, 585.4, 585.5 or *ICD-10-CM*: N18.3, N18.4, N18.5), or end-stage renal disease, (identified by occurrence of 2 end-stage renal disease/dialysis codes at least 30 days apart), or kidney transplant (occurrence of ≥1 code for kidney transplant). A detailed description of codes used to identify patients with end-stage renal disease and kidney transplant has been previously published.[19] The earliest date of diagnosis for each safety outcome was defined as the date of safety outcome.

In each effectiveness and safety analysis, patients were followed up from the index date until the first of the following: (1) the occurrence of an outcome, (2) end of enrollment (ie, the day their insurance was terminated), (3) switching to comparator drug (ie, aldosterone antagonists to beta blockers and vice versa), (4) discontinuation of study medications (following the 14-day grace period), that is, a gap between dispensing of a study drug exceeding 14 days, (5) diagnosis of hyperaldosteronism, or (6) study end date (31st December 2019). We did not censor patients based on any changes to the A+C+D regimen under the assumption that once patients met stringent RH criteria (adherent to recommended A+C+D regimen and requiring additional antihypertensive therapy, that is, aldosterone antagonists or beta blockers), they were considered to have RH thereafter, except in the situation of a subsequent hyperaldosteronism diagnosis, where an aldosterone antagonists would be clearly indicated.

Covariates

We measured >40 baseline covariates potentially associated with both choice of fourth line antihypertensive agents and outcomes, using relevant medical or pharmacy data during

12-month baseline period. Briefly, we included demographic characteristics, comorbidities (Table S3),[9,19] prior medication use,[9,19] and health care utilization patterns.[9] Additionally, to better account for potential confounding by other comorbidities, we used the Quan-Charlson comorbidity index (calculated based on the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*) and *ICD-10-CM* diagnosis codes) incorporating 17 comorbidities.[20] Comorbidities were identified by requiring at least one diagnosis (*ICD-9-CM* or *ICD-10-CM*), in any position, in any setting. We used prior publications to identify an initial list of *ICD-9-CM* and *ICD-10-CM* diagnosis codes (see Table S3). To confirm that the *ICD-9-CM* diagnosis codes were correctly mapped to *ICD-10-CM* diagnosis codes, we performed forward mapping (*ICD-9-CM* to *ICD-10-CM*) using the publicly available database created by the Center for Medicare and Medicaid Services and the Centers for Disease Control and Prevention.[21] More information on *ICD-9-CM* and *ICD-10-CM* mapping is available at the National Bureau of Economic Research website (www.nber.org). Prior medication use was identified using the national drug coded from outpatient dispensing claims.

Statistical Analysis

We conducted descriptive analyses by reporting means for continuous variables and frequencies and percentages for categorical variables and compare baseline characteristics among the 2 exposure groups (ie, aldosterone antagonists versus beta blockers). To control for potential confounding, we used stabilized inverse probability of treatment weighting (SIPTW) based on propensity scores. We assessed performance of the SIPTW by cross tabulating baseline covariates before and after SIPTW by exposure groups and calculated standardized mean differences. Variables with a standardized mean difference <0.1 were considered balanced.[22] Cox proportional hazard models (Cox PH) weighted by SIPTWs were used to estimate adjusted hazard ratios (aHRs) and 95% CI for each outcome among users of aldosterone antagonists versus beta blockers (reference). The proportional hazard assumption was tested using Schoenfeld residuals. Kaplan-Meier plots were generated to visualize the risk of outcome in the exposure groups and its significance was tested using Log-rank test. We used SAS 9.4 (SAS Institute, Inc, Cary, NC) for data analyses and data management. $P<0.05$ were considered statistically significant.

Sensitivity, Subgroup, and Secondary Analysis

To evaluate robustness of our study results, we conducted several sensitivity and subgroup analyses. First, we used an alternate definition of RH that was more restrictive: concomitant use of A+C+D and study medications for at least 60 days. The 60-day period was chosen to ensure concomitant, persistent use of 4 antihypertensive drug classes (ie, ensuring aldosterone antagonist or beta blocker was added to the regimen, rather than representing a switch from A, C, or D). Second, we used alternate definitions of RH that were less restrictive: (1) concomitant use of a thiazide or thiazide-like diuretic and any 2 other antihypertensive medications (at the time at which a study medication was started) and (2) concomitant use of any 3 antihypertensive medications (at the time at which a study medication was started). For these latter 2 definitions, qualifying antihypertensives had to be from classes other than the study medications. Third, to avoid informative censoring, we used an intention-to-treat approach, wherein follow-up and censoring occurred as in the main analysis, with the exception that treatment changes (ie, switching or discontinuation) were not considered censoring criteria. In other words, we only censored patients at the first occurrence of outcome, end of enrollment, diagnosis of hyperaldosteronism, or study end date (December 31, 2019). Fourth, we varied the grace period between consecutive refills of study medications from 14 days to 7 days and 30 days.

We also conducted several prespecified subgroup analyses to determine the heterogeneity of treatment effect. First, because depression causes abnormalities in the autonomic nervous system and activates sympathetic nervous system,[23] presence of depression could possibly affect the way RH patients respond to aldosterone antagonists and other fourth line agents. Therefore, we examined the presence of potential effect modification by depression status (yes versus no). Additionally, to assess the potential for effect modification, we also stratified the analyses by age (18–64 years versus ≥65 years), sex (male versus female), and history of hyperlipidemia (yes versus no). Within each subgroup, we re-calculated SIPTWs to maintain balance. An interaction $P<0.05$ was used to denote a significant difference in the association between exposure and outcome between the 2 groups. Finally, in the secondary analysis, we examined risk for the effectiveness and safety outcomes in a subgroup of patients newly initiating (1) spironolactone versus metoprolol (reference) and (2) spironolactone versus atenolol (reference). For this comparison, we re-estimated the SIPTWs to maintain balance between exposure groups.

RESULTS

We identified 106 037 new users of aldosterone antagonists or beta blockers as add-on therapy to an A+C+D regimen. After inclusion and exclusion criteria were applied, the study sample consisted of 80 598 patients with RH: 6626 in the aldosterone antagonist group and 73 972 in the beta blockers group (Figure S1). Table 1 summarizes baseline characteristics of patients initiating study medications before and after applying SIPTW. After applying SIPTW, baseline characteristics were well balanced between the 2 groups (no standardized mean differences exceeded 0.1). Overall, study patients were aged 61 years, on average, 51% were men, and a majority (44%) lived in the Southern region of the United States. Hyperlipidemia was the most prevalent comorbidity (54%), and statins were the most frequently used nonantihypertensive medications (48%). In the aldosterone antagonist group, patients overwhelmingly initiated spironolactone (97.8%), whereas, in the beta blocker group, most patients initiated metoprolol (57.3%), followed by atenolol (16.9%). The median follow-up time on treatment was ≈8 months and 10 months for aldosterone antagonist and beta blocker groups, respectively. The primary censoring criteria were study treatment

Table 1. Baseline Characteristics of Study Cohort Before and After Weighting

	Before SIPTW			After SIPTW		
Variables	Beta blockers	Aldosterone antagonist	SMD	Beta blockers	Aldosterone antagonist	SMD
n	73 972	6626		73 972	6626	
Demographics						
Age	61.5±13.0	59.0±12.3	−0.20	61.3±13.0	61.0±12.6	−0.03
Female	35 747 (48.3)	3732 (56.3)	−0.05	36 236 (49.0)	3189 (48.6)	−0.00
Region						
Northeast	12 125 (16.4)	941 (14.2)	0.24	11 993 (16.2)	1045 (15.9)	0.02
North Central	20 293 (27.4)	1573 (23.7)		20 068 (27.1)	1720 (26.2)	
South	31 852 (43.1)	3149 (47.5)		32 128 (43.4)	2893 (44.1)	
West	9220 (12.5)	919 (13.9)		9309 (12.6)	867 (13.2)	
Unknown	482 (0.7)	44 (0.7)		483 (0.7)	41 (0.6)	
Comorbidities						
Obesity	12 827 (17.3)	1551 (23.4)	0.15	13 200 (17.8)	1174 (17.9)	0.00
Hyperlipidemia	39 904 (53.9)	3535 (53.4)	−0.01	39 877 (53.9)	3582 (54.5)	0.01
AF	5409 (7.3)	256 (3.9)	−0.15	5200 (7.0)	492 (7.5)	0.02
Asthma	4412 (6.0)	663 (10.0)	0.15	4665 (6.3)	461 (7.0)	0.03
Pneumonia	1838 (2.5)	169 (2.6)	0.00	1844 (2.5)	184 (2.8)	0.02
Angina	3664 (5.0)	154 (2.3)	−0.14	3504 (4.7)	297 (4.5)	−0.01
CAD	11 816 (16.0)	626 (9.4)	−0.20	11 419 (15.4)	977 (14.9)	−0.02
Diabetes	23 208 (31.4)	1953 (29.5)	−0.04	23 098 (31.2)	2087 (31.8)	0.01
Depression	6069 (8.2)	640 (9.7)	0.05	6165 (8.3)	589 (9.0)	0.02
OSA	8357 (11.3)	1042 (15.7)	0.13	8638 (11.7)	833 (12.7)	0.03
Osteoarthritis	8865 (12.0)	907 (13.7)	0.05	8977 (12.1)	846 (12.9)	0.02
Coronary revascularization	1734 (2.3)	43 (0.6)	−0.14	1631 (2.2)	127 (1.9)	−0.02
Charlson Comorbidity Index	1.1±1.5	1.1±1.7	0.02	1.1±1.6	1.1±1.6	0.01
Medications						
Statins	35 896 (48.5)	2970 (44.8)	−0.07	35 679 (48.2)	3137 (47.8)	−0.01
Bisphosphates	2859 (3.9)	176 (2.7)	−0.07	2785 (3.8)	232 (3.5)	−0.01
Benzodiazepines	9919 (13.4)	931 (14.1)	0.02	9966 (13.5)	962 (14.6)	0.03
Anticonvulsants	5761 (7.8)	609 (9.2)	0.05	5855 (7.9)	561 (8.5)	0.02
Opioids	27 787 (37.6)	2595 (39.2)	0.03	27 897 (37.7)	2576 (39.2)	0.03
Antiplatelets	3472 (4.7)	172 (2.6)	−0.11	3344 (4.5)	281 (4.3)	−0.01
PPIs	16 246 (22.0)	1495 (22.6)	0.01	16 290 (22.0)	1454 (22.1)	0.00
Antidiabetics	19 092 (25.8)	1715 (25.9)	0.00	19 100 (25.8)	1737 (26.4)	0.01
Nitrates	2886 (3.9)	131 (2.0)	−0.11	2769 (3.7)	213 (3.2)	−0.03
Anticoagulants	3396 (4.6)	276 (4.2)	−0.02	3377 (4.6)	353 (5.4)	0.04
Antibiotics	35 259 (47.7)	3548 (53.5)	0.12	35 629 (48.2)	3247 (49.4)	0.03
Antihistamines	5451 (7.4)	543 (8.2)	0.03	5506 (7.4)	519 (7.9)	0.02
Antivirals	3938 (5.3)	445 (6.7)	0.06	4025 (5.4)	364 (5.5)	0.00
Antidepressants	16 108 (21.8)	1629 (24.6)	0.07	16 294 (22.0)	1555 (23.7)	0.04
NSAIDs	26 629 (36.0)	2491 (37.6)	0.03	26 736 (36.1)	2450 (37.3)	0.02
ESA	17 (0.0)	1 (0.0)	−0.01	16 (0.0)	1 (0.0)	−0.01
HCAs	721 (1.0)	111 (1.7)	0.06	765 (1.0)	77 (1.2)	0.01
Oral corticosteroids	16 438 (22.2)	1827 (27.6)	0.12	16 778 (22.7)	1580 (24.1)	0.03
Health care utilization						
No. prescription claims	19.7±14.1	22.0±15.0	0.16	19.9±14.3	20.5±13.7	0.04
No. outpatient visits	15.5±14.0	17.2±15.5	−0.09	15.7±14.2	16.4±14.6	0.03
No. inpatient visits	0.8±3.0	0.5±2.4	0.11	0.8±2.9	0.9±3.8	0.05

Data are presented as mean±SD or n (%). AF indicates atrial fibrillation; CAD, coronary artery disease; ESA, erythropoietin-stimulating agents; HCAs, hormonal contraceptive agents; NSAIDs, non-steroidal anti-inflammatory drugs; OSA, obstructive sleep apnea; PPI, proton pump inhibitor; SIPTW, stabilized inverse probability of treatment weighting; and SMD, standardized mean difference.

discontinuation (≈76%) or end of medical and pharmacy enrollment (≈21%).

Effectiveness Outcomes

Among 6626 aldosterone antagonist users, there were 26 MACE events, for an incidence of 7.0 per 1000 person-years. Among 73 972 beta blocker users, there were 479 MACE events and an incidence of 9.2 per 1000 person-years. In the Cox PH model applying SIPTW, we observed no significant difference in risk of MACE comparing initiation of an aldosterone antagonist versus beta-blocker (adjusted HR [aHR], 0.77 [95% CI, 0.50–1.19]; Table 2). Similar findings were observed for the individual components of MACE, with no significant difference in risk of stroke (aHR, 0.90 [95% CI, 0.53–1.55]) or AMI (aHR, 0.63 [95% CI, 0.31–1.27]). Kaplan-Meier curves comparing the cumulative incidence of MACE, stroke, and AMI are shown in Figure [A] through [C].

Risk of Safety Outcomes

In the aldosterone antagonist group, we identified 56 hyperkalemia events (incidence, 15.1 per 1000 person-years), compared with 164 events (incidence, 3.1 per 1000 person-years) in the beta blocker group (Table 2). Aldosterone antagonist initiation was associated with > 3-fold increase in the risk of hyperkalemia (aHR, 3.86 [95% CI, 2.78–5.34]; Table 2). In the aldosterone antagonist group, we identified 28 events of gynecomastia (incidence, 7.5 per 1000 person-years), compared with 51 events of gynecomastia (incidence, 1.0 per 1000 person-years) in the beta blocker group. Aldosterone antagonist initiation was associated with more than 9-fold increase in the risk of gynecomastia (aHR, 9.51 [95% CI, 5.69–15.89]). In the aldosterone antagonist group, we identified 165 events of kidney function deterioration (incidence, 45.1 per 1000 person-years) compared with 1360 events (incidence, 26.4 per 1000 person-years) in the beta blocker group. Aldosterone antagonist initiation was associated with a significant increase in the risk of kidney function deterioration (aHR, 1.63 [95% CI, 1.34–1.99]). Kaplan-Meier curves comparing the cumulative incidence of hyperkalemia, gynecomastia, and kidney function deterioration are presented in Figure [D] through [F].

Sensitivity, Subgroup, and Secondary Analysis

Findings from sensitivity and subgroup analysis were consistent with the main analysis. Using alternate definitions of RH did not change the overall findings (Table S4). Similarly, in the intention-to-treat approach, the risk of MACE did not differ among the 2 groups (aHR, 1.01 [95% CI, 0.84–1.21]). However, aldosterone antagonist initiation remained associated with higher risk of hyperkalemia (aHR, 1.99 [95% CI, 1.61–2.45]), gynecomastia (aHR, 3.94 [95% CI, 2.89–5.38]), and kidney function deterioration (aHR, 1.18 [95% CI, 1.06–1.32]). Modifying permissible grace period from 14 days to 7 days and 30 days did not appreciably change the point estimates of the main analysis (Table S5). Additionally, we found no evidence of effect modification by age, sex, hyperlipidemia, or depression (Table S5). The results for the effectiveness and safety outcomes remained consistent for the secondary analysis comparing spironolactone versus metoprolol (Table S6) and for spironolactone versus atenolol (Table S7).

Discussion

In this large, US claims-based pharmacoepidemiologic study, we compared risk of MACE and clinically important adverse events among patients initiating aldosterone antagonists versus beta blockers in patients with RH. We found no strong evidence that aldosterone antagonists reduce the risk of stroke or AMI relative to beta blockers, when added to the generally preferred A+C+D antihypertensive regimen. However, aldosterone antagonists were associated with a markedly greater risk of hyperkalemia, gynecomastia, and kidney function deterioration. These findings were robust across multiple sensitivity and subgroup analysis, and in a cohort of patients similar to RH cohorts observed in prior studies with respect to age, sex, geographic location, and presence of several comorbidities.[24–27]

We hypothesized that aldosterone antagonists would be associated with significantly lower risk of cardiovascular events, compared with beta blockers, based on several lines of evidence. First, aldosterone antagonists seem to provide superior BP control relative to other fourth line agents, including beta blockers. In PATHWAY-2,[6] compared with bisoprolol, spironolactone reduced home systolic BP by 4.5 mm Hg over 3 months in patients with RH on an A+C+D regimen. A more recent systematic review and meta-analysis achieved similar conclusions.[28] Moreover, in one of the secondary analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist),[29] the investigators concluded that the use of spironolactone was associated with significant decrease in systolic and diastolic BP and decreased cardiovascular risk compared with placebo in patients with heart failure with preserved ejection fraction meeting RH criteria. Similar results were obtained in another study of patients with heart failure with preserved ejection fraction meeting RH criteria.[30] Moreover, several clinical trials and epidemiological studies have indicated that even smaller reductions (eg, 5 mm Hg reduction in office BP) are expected to translate to important reductions in subsequent cardiovascular disease and death (ie, 14% reduction in mortality due to stroke, 9% reduction in mortality due to coronary

Table 2. Incidence and Risk of Effectiveness and Safety Outcomes Comparing Among Initiators of Aldosterone Antagonists Versus Beta Blockers (N=80 598)

Outcomes	Aldosterone antagonists (n=6626)	Beta blockers (n=73 972)
Effectiveness outcomes		
MACEs		
Days of follow-up, mean (median [IQR])	205 (105 [45–247])	258.1 (127 [49.5–318])
No. of events, n	26	479
Total person-years	3721	52,309
Incidence rate per 1000 person-years	7.0	9.2
Adjusted HR (95% CI)	0.77 (0.50–1.19)	Reference
Stroke		
Days of follow-up, mean (median [IQR])	205.1 (105 [45–248])	258.6 (128 [50–319])
No. of events, n	17	257
Total person-years	3723	52 417
Incidence rate per 1000 person-years	4.6	4.9
Adjusted HR (95% CI)	0.90 (0.53–1.55)	Reference
Acute myocardial infarction		
Days of follow-up, mean (median [IQR])	205.4 (105 [45–248])	258.7 (128 [50–319])
No. of events, n	10	234
Total person-years	3729	52 435
Incidence rate per 1000 person-years	2.7	4.5
Adjusted HR (95% CI)	0.63 (0.31–1.27)	Reference
Safety outcomes		
Hyperkalemia		
Days of follow-up, mean (median [IQR])	204.3 (105 [45–247])	258.6 (128 [50–319])
No. of events, n	56	164
Total person-years	3709	52 412
Incidence rate per 1000 person-years	15.1	3.1
NNH	0.08	Reference
Adjusted HR (95% CI)	3.86 (2.78–5.34)	Reference
Gynecomastia		
Days of follow-up, mean (median [IQR])	205.2 (105 [45–247])	259.1 (128 [50–320])
No. of events, n	28	51
Total person-years	3724	52 505
Incidence rate per 1000 person-years	7.5	1.0
NNH	0.15	Reference
Adjusted HR (95% CI)	9.51 (5.69–15.89)	Reference
Kidney function deterioration		
Days of follow-up, mean (median [IQR])	201.4 (105 [45–244])	254.3 (125 [47–314])
No. of events, n	165	1360
Total person-years	3656	51 544
Incidence rate per 1000 person-years	45.1	26.4
NNH	0.05	Reference
Adjusted HR (95% CI)	1.63 (1.34–1.99)	Reference

HR indicates hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular event; and NNH, number needed to harm.

heart disease, 7% decrease in all-cause mortality).[31–33] Second, some evidence suggests beta blockers are less effective than other first-line antihypertensives in primary prevention of cardiovascular events, even when brachial BP lowering is of a similar magnitude.[34] For instance, in the Conduit Artery Functional Evaluation substudy of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), atenolol±thiazide and amlodipine±perindopril regimens

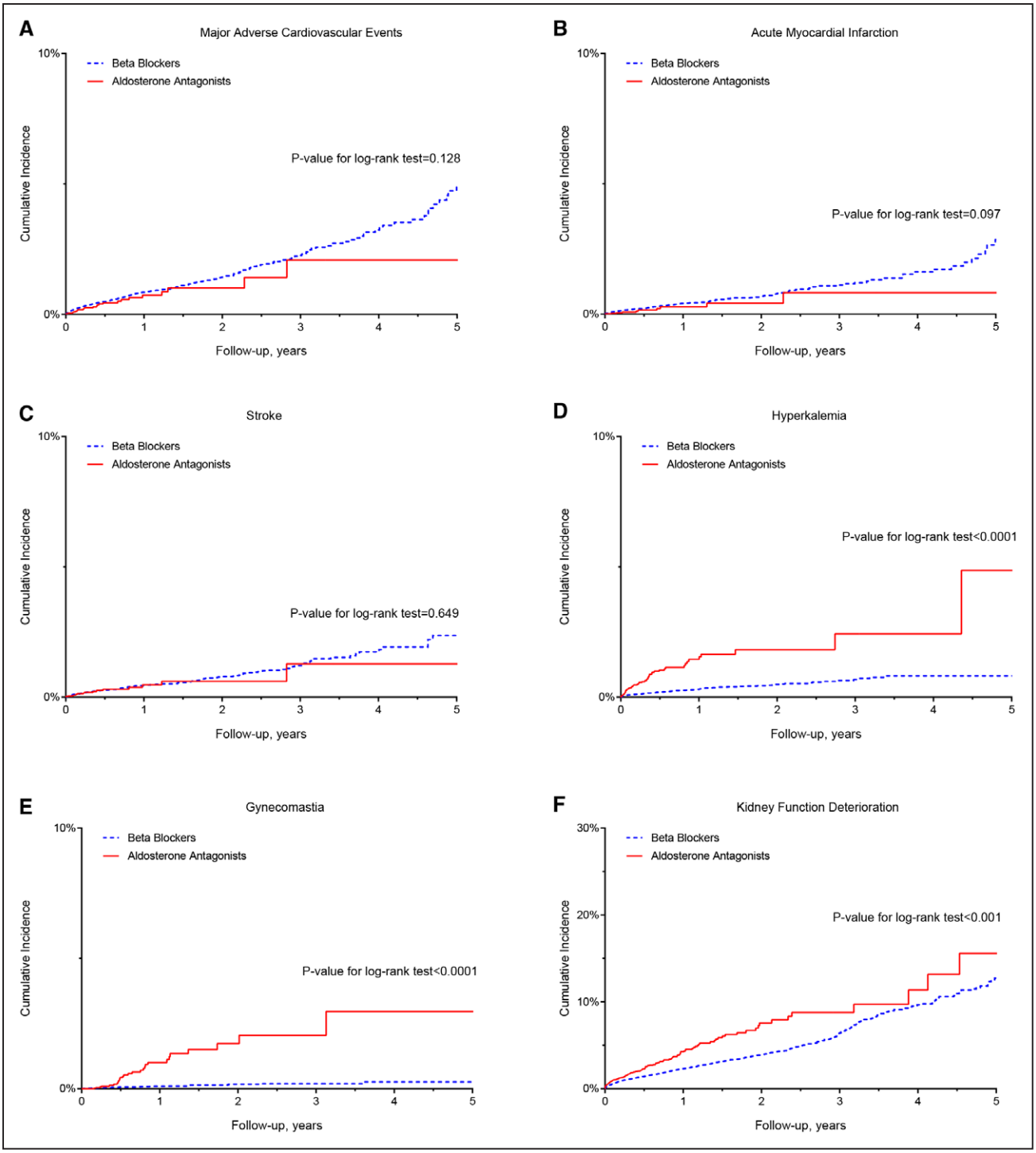

Figure. Unadjusted cumulative incidence rates among patients with resistant hypertension initiating aldosterone antagonists versus beta blockers as the fourth antihypertensive agent.

A, Incidence of major adverse cardiovascular events, (**B**) incidence of acute myocardial infarction (AMI), (**C**) incidence of stroke, (**D**) incidence of hyperkalemia, (**E**) incidence of gynecomastia, (**F**) incidence of kidney function deterioration. Note: *y*-axis is represented as 10% for all figures except kidney function deterioration.

achieved similar brachial systolic BP reductions but the amlodipine±perindopril regimen achieved significantly better central aortic BP reductions and more favorable central hemodynamic measures.[35] These differential central aortic BP effects were associated with the composite outcome of total cardiovascular events in this study, and given as one explanation for the worse outcomes with the beta-blocker±thiazide regimen in overall ASCOT, and in similar findings in more recent and larger meta-analyses.[34]

Our finding of no difference in the risk of MACE with the initiation of aldosterone antagonists versus beta blockers may have some support in studies suggesting that lower BP is not associated with significant reductions in risk of cardiovascular events in patients with RH. For example, we have previously observed no difference in all-cause and cardiovascular related mortality comparing patients with controlled versus uncontrolled RH, despite a mean difference of 28/10 mm Hg between the 2 groups.[8] Likewise, over a median follow-up of 6 years, another study conducted in the United States did not find any difference in the risk of mortality or stroke between patients with uncontrolled RH versus those with controlled RH.[36] Patients with RH typically have many comorbidities that increase cardiovascular risk, and it is at least plausible that fairly minor reductions in BP, such as that seen in PATHWAY-2 (ie, 4.5 mm Hg) have limited impact on reducing risk for cardiovascular events in the setting of so many competing risk factors.[37] Unfortunately, we were not able to examine differences in BP response during follow-up, and it is therefore possible that the lack of difference observed in cardiovascular events is merely reflective of minimal or no differences in BP response between comparators in our population. On the other hand, given the point estimate and confidence interval observed in our main analysis (aHR, 0.77 [95% CI, 0.50–1.19]), we cannot exclude the possibility that aldosterone antagonists do in fact reduce risk of cardiovascular events, but which our study was underpowered to detect.

Aldosterone antagonists have generally well-defined safety profiles. However, there exists very little data on safety outcomes during moderate- to long-term use of these agents in RH. For instance, Wang et al[38] found a 2-fold increased risk of hyperkalemia with the use of aldosterone antagonist in older patients (≥65 years) with myocardial infarction compared with nonusers. The risk is even greater (ie, 3-fold increased risk of hyperkalemia with spironolactone) in patients with chronic kidney disease.[39] Our findings regarding hyperkalemia in the present study (aldosterone antagonists versus beta blocker, aHR, 3.86 [95% CI, 2.78–5.34]) were remarkably similar to these prior findings, and most cases occurred within the first year of therapy. Aldosterone antagonists, particularly spironolactone, are also known to cause gynecomastia. In our study, gynecomastia was uncommon overall, but markedly increased in the aldosterone antagonist group (aHR: 9.51 [95% CI, 5.69–15.89]). These findings align closely with a recent secondary analysis of the TOPCAT trial, in which use of spironolactone was associated with > 9-fold increase in the risk of gynecomastia compared with placebo (HR, 9.15 [95% CI, 1.16–72.23]) in patients with heart failure with preserved ejection fraction who also met RH criteria.[29] Finally, our study also adds to limited comparisons of aldosterone antagonists and beta blockers with respect to the risk of kidney function deterioration in patients with RH. Our findings are similar to a previous study, which investigated the association between baseline estimated glomerular filtration rate and worsening renal function in patients with heart failure with preserved ejection fraction due to the use of spironolactone using data from patients enrolled in the TOPCAT trial (N=1767).[40] In that study, investigators concluded that compared with placebo, spironolactone was associated with >2-fold increase (HR, 2.50 [95% CI, 1.38–4.53]) in the risk for worsening renal function across all estimated glomerular filtration rate categories, even in patients with a normal renal function (ie, estimated glomerular filtration rate between >60 mL/min per 1.73 m^2), moderately higher than our finding of an aHR of 1.63 (95% CI, 1.34–1.99).

The findings of this study should be viewed in light of several limitations. First, although, we controlled for over 30 pertinent variables potentially associated with the choice of fourth line antihypertensive and risk of MACE and safety outcomes, claims data used for the study did not include information on important confounders such as BP measurements, body mass index, lifestyle factors (alcohol use, smoking) or laboratory values (eg, serum potassium, cholesterol, glomerular filtration rate etc). Therefore, this study is susceptible to residual confounding. Second, our database did not contain information on any BP measurements, particularly out of office BP. Therefore, we cannot be certain that all patients with pseudoresistance, particularly from causes such as nonadherence and white coat effect were excluded. Accordingly, it would be appropriate to consider that the patients included in our study had apparent RH. Nevertheless, we carried out multiple sensitivity analysis by using alternate definitions to identify patients with RH. For instance, in one of the sensitivity analyses, to be eligible to be classified as RH, patients were required to be adherent on A+C+D antihypertensive regimen for at least 60 days before initiating study medications, thereby, excluding patients with pseudoresistance caused due to nonadherence. Yet, the results were similar to the main analysis. Third, since we relied on *ICD-9-CM* and *ICD-10-CM* diagnosis codes to measure outcomes, we cannot rule out the possibility of outcome misclassification. Previous studies evaluating the validity of ICD codes for MACE (stroke and AMI) focused on *ICD-9-CM* but not *ICD-10-CM*. Since we use the same outcome definition for the 2 exposure groups, any misclassification is likely to be nondifferential between groups and likely to bias results to the null. Thus, it is possible outcome misclassification contributed to our negative findings on the MACE outcome. Fourth, it is possible that incomplete (for services out of network), missing or miscoded claims may impact the measurement of covariates and lead to covariate misclassification; however, coding errors are likely distributed evenly between the 2 exposure groups. Fifth, our findings are generalizable only to the US commercially insured population and may not be generalizable to patients with other insurance types of those lacking insurance. Sixth, we did not censor patients

when they died because the MarketScan database only provides inpatient death information until 2015 and information on deaths occurring outside of hospitals were not available. Despite these limitations, the main strengths of the study include longitudinal data, use of a large commercially insured population from the United States and use of rigorous pharmacoepidemiologic approaches such as new-user design and active comparator study design, and SIPTW for confounder adjustment.

In conclusion, we hypothesized that aldosterone antagonists (particularly spironolactone) would be associated with reduced risk of MACE based on prior high-quality evidence from the PATHWAY-2 trial showing their superiority over the beta blocker bisoprolol in terms of BP reduction. Yet, in this large, population-based cohort study of patients with RH, we found no difference in MACE risk between aldosterone antagonists and beta blockers. However, aldosterone antagonists, particularly spironolactone, were associated with increased risk for hyperkalemia, gynecomastia, and kidney function deterioration. Our findings suggest a need for a more definitive long-term RCT to evaluate comparative effectiveness and safety of aldosterone antagonists and other fourth line antihypertensive agents.

Perspectives

Our findings indicate that initiation of an aldosterone antagonist, as compared with a beta blocker, as a fourth line antihypertensive agents in patients with RH did not significantly reduce MACE risk, but did substantially increase the risk of hyperkalemia, gynecomastia, and kidney function deterioration. To gain perspective on these findings, a long-term randomized clinical trial powered to assess the risk of MACE is needed to understand the true risk-benefit trade-off of aldosterone antagonists as preferred therapy for RH.

ARTICLE INFORMATION

Received March 1, 2022; accepted July 7, 2022.

Affiliations

Department of Pharmaceutical Outcomes and Policy, College of Pharmacy (R.D., H.P., J.D.B., S.M.S.). Division of Nephrology, Hypertension and Renal Transplantation (R.M.) and Division of Cardiovascular Medicine (C.J.P., S.M.S.), Department of Medicine, College of Medicine, Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, Gainesville (S.M.S.).

Sources of Funding

None.

Disclosures

None.

REFERENCES

1. Whelton Paul K, Carey Robert M, Aronow Wilbert S, Casey Donald E, Jr, Collins Karen J, Himmelfarb Cheryl D, DePalma Sondra M, Gidding S, Jamerson Kenneth A, Jones Daniel W, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension*. 2018;71:e13–e115. doi:10.1161/HYP.0000000000000065
2. Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: mechanisms and treatment. *Curr Hypertens Rep*. 2017;19:56. doi: 10.1007/s11906-017-0754-x
3. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension*. 2002;40:892–896. doi: 10.1161/01.hyp.0000040261.30455.b6
4. Gallay BJ, Ahmad S, Xu L, Toivola B, Davidson RC. Screening for primary aldosteronism without discontinuing hypertensive medications: plasma aldosterone-renin ratio. *Am J Kidney Dis*. 2001;37:699–705. doi: 10.1016/s0272-6386(01)80117-7
5. Strauch B, Zelinka T, Hampf M, Bernhardt R, Widimsky J Jr. Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. *J Hum Hypertens*. 2003;17:349–352. doi: 10.1038/sj.jhh.1001554
6. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, et al; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386:2059–2068. doi: 10.1016/S0140-6736(15)00257-3
7. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Crowley K, Goto S, Ohman EM, Bakris GL, Perlstein TS, et al; REACH Registry Investigators. Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. *Eur Heart J*. 2013;34:1204–1214. doi: 10.1093/eurheartj/ehs368
8. Smith SM, Gong Y, Handberg E, Messerli FH, Bakris GL, Ahmed A, Bavry AA, Pepine CJ, Cooper-Dehoff RM. Predictors and outcomes of resistant hypertension among patients with coronary artery disease and hypertension. *J Hypertens*. 2014;32:635–643. doi: 10.1097/HJH.0000000000000051
9. Sinnott SJ, Smeeth L, Williamson E, Perel P, Nitsch D, Tomlinson LA, Douglas IJ. The comparative effectiveness of fourth-line drugs in resistant hypertension: An application in electronic health record data. *Pharmacoepidemiol Drug Saf*. 2019;28:1267–1277. doi: 10.1002/pds.4808
10. IBM MarketScan Research Databases for Health Services Researchers.:15.
11. Health Insurance Coverage of the Total Population. KFF; 2020. Accessed June 12, 2022. https://www.kff.org/other/state-indicator/total-population/
12. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, et al; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72:e53–e90. doi: 10.1161/HYP.0000000000000084
13. Recommendations | Hypertension in adults: diagnosis and management | Guidance | NICE. Accessed October 29, 2021. https://www.nice.org.uk/guidance/ng136/chapter/recommendations
14. Hwang Andrew Y, Dave Chintan, Smith Steven M. Trends in antihypertensive medication use among US patients with resistant hypertension, 2008 to 2014. *Hypertension*. 2016;68:1349–1354. doi:10.1161/HYPERTENSIONAHA.116.08128
15. Desai R, Park H, Dietrich EA, Smith SM. Trends in ambulatory blood pressure monitoring use for confirmation or monitoring of hypertension and resistant hypertension among the commercially insured in the U.S., 2008–2017. *Int J Cardiol Hypertens*. 2020:100033. doi:10.1016/j.ijchy.2020.100033
16. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*. 2015;11:437–441. doi: 10.1038/nrrheum.2015.30
17. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke*. 2002;33:2465–2470. doi: 10.1161/01.str.0000032240.28636.bd
18. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction:

estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004;148:99–104. doi: 10.1016/j.ahj.2004.02.013
19. Patorno E, Pawar A, Bessette LG, Kim DH, Dave C, Glynn RJ, Munshi MN, Schneeweiss S, Wexler DJ, Kim SC. Comparative effectiveness and safety of sodium-glucose cotransporter 2 inhibitors versus glucagon-like peptide 1 receptor agonists in older adults. *Diabetes Care*. 2021;44:826–835. doi: 10.2337/dc20-1464
20. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139. doi: 10.1097/01.mlr.0000182534.19832.83
21. ICD-9-CM to and from ICD-10-CM and ICD-10-PCS Crosswalk or General Equivalence Mappings. NBER. Accessed June 12, 2022. https://www.nber.org/research/data/icd-9-cm-and-icd-10-cm-and-icd-10-pcs-crosswalk-or-general-equivalence-mappings
22. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat - Simu. Comput*. 2009;38:1228–1234. doi:10.1080/03610910902859574
23. Biffi A, Scotti L, Corrao G. Use of antidepressants and the risk of cardiovascular and cerebrovascular disease: a meta-analysis of observational studies. *Eur J Clin Pharmacol*. 2017;73:487–497. doi: 10.1007/s00228-016-2187-x
24. Diaz KM, Booth JN 3rd, Calhoun DA, Irvin MR, Howard G, Safford MM, Muntner P, Shimbo D. Healthy lifestyle factors and risk of cardiovascular events and mortality in treatment-resistant hypertension: the Reasons for Geographic and Racial Differences in Stroke study. *Hypertension*. 2014;64:465–471. doi: 10.1161/HYPERTENSIONAHA.114.03565
25. Tanner RM, Calhoun DA, Bell EK, Bowling CB, Gutiérrez OM, Irvin MR, Lackland DT, Oparil S, McClellan W, Warnock DG, et al. Incident ESRD and treatment-resistant hypertension: the reasons for geographic and racial differences in stroke (REGARDS) study. *Am J Kidney Dis*. 2014;63:781–788. doi: 10.1053/j.ajkd.2013.11.016
26. Kaczmarski KR, Sozio SM, Chen J, Sang Y, Shafi T. Resistant hypertension and cardiovascular disease mortality in the US: results from the National Health and Nutrition Examination Survey (NHANES). *BMC Nephrol*. 2019;20:138. doi: 10.1186/s12882-019-1315-0
27. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of apparent treatment-resistant hypertension in the United States. *Hypertension*. 2019;73:424–431. doi: 10.1161/HYPERTENSIONAHA.118.12191
28. Sinnott SJ, Tomlinson LA, Root AA, Mathur R, Mansfield KE, Smeeth L, Douglas IJ. Comparative effectiveness of fourth-line anti-hypertensive agents in resistant hypertension: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24:228–238. doi: 10.1177/2047487316675194
29. Tsujimoto T, Kajio H. Spironolactone use and improved outcomes in patients with heart failure with preserved ejection fraction with resistant hypertension. *J Am Heart Assoc*. 2020;9:e018827. doi: 10.1161/JAHA.120.018827
30. Rossignol P, Claggett BL, Liu J, Vardeny O, Pitt B, Zannad F, Solomon S. Spironolactone and resistant hypertension in heart failure with preserved ejection fraction. *Am J Hypertens*. 2018;31:407–414. doi: 10.1093/ajh/hpx210
31. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252. doi: 10.1161/01.HYP.0000107251.49515.c2
32. Lee JH, Kim SH, Kang SH, Cho JH, Cho Y, Oh IY, Yoon CH, Lee HY, Youn TJ, Chae IH, et al. Blood pressure control and cardiovascular outcomes: real-world implications of the 2017 ACC/AHA hypertension guideline. *Sci Rep*. 2018;8:13155. doi: 10.1038/s41598-018-31549-5
33. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, et al; National High Blood Pressure Education Program Coordinating Committee. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA*. 2002;288:1882–1888. doi: 10.1001/jama.288.15.1882
34. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2017;2017:CD002003. doi:10.1002/14651858.CD002003.pub5
35. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure–lowering drugs on central aortic pressure and clinical outcomes. *Circulation*. 2006;113:1213–1225. doi:10.1161/CIRCULATIONAHA.105.595496
36. Irvin MR, Booth JN 3rd, Shimbo D, Lackland DT, Oparil S, Howard G, Safford MM, Muntner P, Calhoun DA. Apparent treatment-resistant hypertension and risk for stroke, coronary heart disease, and all-cause mortality. *J Am Soc Hypertens*. 2014;8:405–413. doi: 10.1016/j.jash.2014.03.003
37. Smith SM. Resistant hypertension and susceptible outcomes: exploring the benefits of aggressive blood pressure control. *J Clin Hypertens (Greenwich)*. 2016;18:40–2. doi:10.1111/jch.12677
38. Wang TY, Vora AN, Peng SA, Fonarow GC, Das S, de Lemos JA, Peterson ED. Effectiveness and safety of aldosterone antagonist therapy use among older patients with reduced ejection fraction after acute myocardial infarction. *J Am Heart Assoc*. 2016;5:e002612. doi: 10.1161/JAHA.115.002612
39. Yang CT, Kor CT, Hsieh YP. Long-term effects of spironolactone on kidney function and hyperkalemia-associated hospitalization in patients with chronic kidney disease. *J Clin Med*. 2018;7:E459. doi: 10.3390/jcm7110459
40. Beldhuis IE, Myhre PL, Claggett B, Damman K, Fang JC, Lewis EF, O'Meara E, Pitt B, Shah SJ, Voors AA, et al. Efficacy and safety of spironolactone in patients with HFpEF and chronic kidney disease. *JACC: Heart Failure*. 2019;7:25–32. doi:10.1016/j.jchf.2018.10.017