Journal of the American Heart Association

ORIGINAL RESEARCH

Initial Antihypertensive Regimens in Newly Treated Patients: Real World Evidence From the OneFlorida+ Clinical Research Network

Steven M. Smith, PharmD, MPH; Almut G. Winterstein, PhD; Matthew J. Gurka, PhD; Marta G. Walsh, MS; Shailina Keshwani, MS; Anne M. Libby, PhD; William R. Hogan, MD, MS; Carl J. Pepine, MD; Rhonda M. Cooper-DeHoff, PharmD, MS

BACKGROUND: Knowledge of real-world antihypertensive use is limited to prevalent hypertension, limiting our understanding of how treatment evolves and its contribution to persistently poor blood pressure control. We sought to characterize antihypertensive initiation among new users.

METHODS AND RESULTS: Using Medicaid and Medicare data from the OneFlorida+ Clinical Research Consortium, we identified new users of ≥1 first-line antihypertensives (angiotensin-converting enzyme inhibitor, calcium channel blocker, angiotensin receptor blocker, thiazide diuretic, or β-blocker) between 2013 and 2021 among adults with diagnosed hypertension, and no antihypertensive fill during the prior 12 months. We evaluated initial antihypertensive regimens by class and drug overall and across study years and examined variation in antihypertensive initiation across demographics (sex, race, and ethnicity) and comorbidity (chronic kidney disease, diabetes, and atherosclerotic cardiovascular disease). We identified 143 054 patients initiating 188 995 antihypertensives (75% monotherapy; 25% combination therapy), with mean age 59 years and 57% of whom were women. The most commonly initiated antihypertensive class overall was angiotensin-converting enzyme inhibitors (39%) followed by β-blockers (31%), calcium channel blockers (24%), thiazides (19%), and angiotensin receptor blockers (11%). With the exception of β-blockers, a single drug accounted for ≥75% of use of each class. β-blocker use decreased (35%–26%), and calcium channel blocker use increased (24%–28%) over the study period, while initiation of most other classes remained relatively stable. We also observed significant differences in antihypertensive selection across demographic and comorbidity strata.

CONCLUSIONS: These findings indicate that substantial variation exists in initial antihypertensive prescribing, and there remain significant gaps between current guideline recommendations and real-world implementation in early hypertension care.

Key Words: angiotensin receptor antagonists ■ angiotensin-converting enzyme inhibitors ■ antihypertensive agents ■ calcium channel blockers ■ ethnicity ■ Medicaid ■ Medicare ■ sodium chloride symporter inhibitors

Hypertension affects an estimated 120 million individuals in the United States and is the leading modifiable risk factor for cardiovascular disease and death.[1] Nearly all of these individuals ultimately require antihypertensive therapy to achieve blood pressure control, and as a consequence, several antihypertensive drugs are among the most commonly used medications worldwide. Consensus US and international guidelines have long recommended certain antihypertensive classes as "first-line" therapies—namely, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), thiazide diuretics, calcium channel blockers (CCBs), and, until relatively recently, β-blockers.[2,3] However, for most patients with uncomplicated hypertension, guidelines generally do not prioritize any of these classes except

Correspondence to: Steven M. Smith, PharmD, MPH, PO Box 100496, Gainesville, FL 32610-0496. Email: ssmith@cop.ufl.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026652

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Prior studies of real-world antihypertensive treatment patterns have focused primarily on prevalent hypertension cohorts.
- We characterized initial antihypertensive regimens in newly treated patients with hypertension to better understand how antihypertensive regimens begin and whether such early treatment patterns may help explain gaps in care quality that contribute to poor blood pressure control or disparities in care.

What Are the Clinical Implications?

- Substantial variation exists among first-line classes prescribed, with <40% of patients initiating any single antihypertensive class and, with 1 exception, no class predominated in >50% of any of the prespecified demographic and comorbidity subgroups studied.
- Conversely, a single drug predominated within each first-line antihypertensive class, accounting for ≥75% of all initiations within that class.
- Findings suggest uptake of clinical guideline recommendations (eg, increased calcium channel blockers and less β-blocker initiation) but also infrequent multidrug regimens that often included potentially suboptimal combinations and suboptimal use of some classes in patients for whom they are explicitly recommended (eg, calcium channel blockers or thiazide in Black patients).

Nonstandard Abbreviations and Acronyms

SMD	standardized mean difference

in select circumstances, leaving prescribers to choose from some 30 to 40 antihypertensive drugs when initiating antihypertensive therapy.

Real-world antihypertensive utilization patterns have been studied extensively, but in almost all cases, the focus of these studies has been on treatment patterns in prevalent hypertension cohorts.[4–13] These studies provide useful insight into overall antihypertensive use in populations. However, they rarely have distinguished between patients who are early in their treatment course from those with long-standing hypertension and who may have extensive treatment histories and multidrug regimens that have evolved over time. Thus, very little is known about contemporary patterns of early antihypertensive care, including initial antihypertensive regimens and to what extent these accord with care typically recommended in consensus guidelines. These gaps are noteworthy in light of the fact that only ≈1 in 5 US patients with hypertension have blood pressure controlled to <130/80 mm Hg.[1] Thus, delays in achieving blood pressure control are exceedingly common in routine practice and extend high-risk periods, leading to worse outcomes.[14,15] A greater understanding of how antihypertensive regimens emerge and evolve early in therapy may aid in identifying quality care gaps for which interventions can be achieved.

To address this gap, we used the OneFlorida+ Clinical Research Consortium (hereafter, OneFlorida+) to characterize initial treatment regimens among a diverse cohort of new users of antihypertensive therapy. We were principally interested in the distribution of classes, specific antihypertensive drugs within classes, how these distributions differed in prespecified demographic and clinical groups, and their trends over time.

METHODS

We conducted a cross-sectional study of initial antihypertensive medication use among individuals with newly treated hypertension using patient-level data from OneFlorida+ from 2012 through September 2021. The study was approved by the University of Florida Institutional Review Board, with a full waiver of informed consent for research involving data previously collected for nonresearch purposes. The OneFlorida+ steering committee also approved the study. Data underlying this study may be obtained through the OneFlorida+ Front Door (https://onefloridaconsortium.org/) by qualified researchers trained in human subject confidentiality protocols.

Data Source

OneFlorida+ is 1 of 8 clinical research networks comprising the Patient-Centered Outcomes Research network. OneFlorida+ serves as a data repository for patient-level data from both health system partners and insurers. Administrative claims data for this project included all available Florida Medicaid (January 1, 2012 through September 30, 2021) and Medicare (January 1, 2012 through December 31, 2017) data. All data sources are mapped to the Patient-Centered Outcomes Research network common data model (version 6.0) to ensure standardization of data elements across sources. Major data elements in the common data model include demographics, enrollment, encounters, diagnoses, procedures, dispensed

medications, and deaths. In the present study, we included only Florida Medicaid or Medicare recipients with claims data available. This approach was chosen to minimize misclassification of new antihypertensive users, by ensuring a sustained period of continuous eligibility (≥1 year) without any dispensing history of antihypertensive therapy before the index antihypertensive fill.

Participants and Cohort Development

The study design and data collection are summarized in Figure S1. Patients were included if they were aged ≥18 years, dispensed a new antihypertensive medication from ≥1 of 5 "first-line" classes (ACEIs, ARBs, CCBs, thiazide diuretics, or β-blockers) between December 31, 2012 and December 31, 2017 (for Medicare recipients) or September 30, 2021 (Medicaid recipients), and were continuously enrolled in the respective coverage for 365 days before and including the date of first dispensing of the above antihypertensive medication(s). The date of first antihypertensive medication fill was considered the index date, and data for all antihypertensives filled on the index date were collected, even if ≥1 of these newly filled antihypertensives were not "first-line" classes. Patients filling antihypertensives from second-line classes before the first fill date of the above first-line classes were not considered new users and were excluded from the cohort. Eligible antihypertensive drugs are summarized in Table S1, and a complete list of national drug codes can be downloaded at https://github.com/ssmithm/rxnorm-drug-lists/tree/master/antihypertensive_drugs. Patients were also required to have a hypertension diagnosis (*International Classification of Diseases, Ninth Revision* [*ICD-9*], 401.X; *International Classification of Diseases, Tenth Revision* [*ICD-10*], I10) within the baseline period defined as 365 days before and including the index date.

Data Collection

Baseline characteristics were measured during the baseline period (generally 1 year before and including index date), as per the definitions summarized in Table S2. Demographic information (sex, race, ethnicity, and birth date) was drawn from the original claims data demographic files (mapped to the Patient-Centered Outcomes Research network common data model); when possible, we supplemented missing values with linked electronic health record (EHR)–based data for sex, race, and ethnicity (each patient-reported). Discrepancies between claims and EHR-based demographic data were resolved by giving self-report EHR data primacy. Antihypertensive regimen information was collected for all antihypertensives dispensed on the index date, with antihypertensives grouped into classes as summarized in Table S1.

Statistical Analysis

We summarized baseline characteristics using mean and SD for continuous variables and n (%) for categorical variables in the overall study population and stratified by insurer (Medicaid, Medicare). Within insurance strata, we calculated the proportion of individuals initiating each class and, within class, each drug. In addition to stratifying analyses by insurer, we performed stratified analyses by prespecified demographic (sex, race, and ethnicity) and comorbidity (chronic kidney disease [CKD], diabetes, and clinical atherosclerotic cardiovascular disease [ASCVD]) strata and assessed differences by calculating standardized mean differences (SMD) between groups.[16] We further assessed use of recommended therapy among Black patients with and without CKD or heart failure (HF), based on explicit recommendations in the current US guidelines (ie, dihydropyridine CCBs or thiazides as preferred initial agents among those without CKD or HF).[3,17] For patients initiating dual antihypertensive regimens, we calculated the proportion of regimens that were guideline concordant (2 first-line antihypertensives from different classes), partially concordant (1 first-line and 1 second-line) or discordant (2 second-line agents or 2 first-line agents from the same class) according to current US guidelines.[3] Finally, we analyzed changes over time in initial antihypertensive regimens by stratifying medication use according to the year of the index date and graphically displaying these data to identify trends in proportion of each class prescribed. The Cochrane–Armitage test was used for trend tests of antihypertensive classes. All data were analyzed with R 4.2.0 (R Foundation, Vienna, Austria).

RESULTS

We identified a total of 143 054 patients with newly treated hypertension, with approximately similar numbers of Medicaid (n=71 774; 50.1% of total cohort) and Medicare (n=71 280; 49.8% of total cohort) recipients (Figure S2). Baseline characteristics of the cohort are summarized in the Table. Briefly, patients were aged 59 years on average (Medicaid, 47 years versus Medicare, 72 years), and 57% were women. A plurality of patients self-reported as White (49% overall; Medicaid, 35% versus Medicare, 63%), 24% (Medicaid, 31%; Medicare, 17%) as Black, and 12% had missing race information; 16% (Medicaid, 18%; Medicare, 14%) were Hispanic. The most common comorbidities were diabetes (21%) and depression (18%), and nearly one-quarter were current smokers. CKD and ASCVD were

Table. Baseline Characteristics of New Antihypertensive Users

Baseline characteristic	New antihypertensive users			
	Overall cohort (N=143 054)	Medicaid cohort (N=71 774)	Medicare cohort (N=71 280)	SMD[†]
Age, y	59.1±21.6	46.5±14.3	71.8±20.1	1.45
<45	38 213 (26.7%)	33 176 (46.2%)	5037 (7.1%)	
45–64	51 007 (35.7%)	34 274 (47.8%)	16 733 (23.5%)	
>65	53 834 (37.6%)	4324 (6.0%)	49 510 (69.5%)	
Sex				0.12
Female	81 555 (57.0%)	43 011 (59.9%)	38 544 (54.1%)	
Male	61 493 (43.0%)	28 760 (40.1%)	32 733 (45.9%)	
Missing	6 (0.0%)	3 (0.0%)	3 (0.0%)	
Race				0.62
American Indian or Alaska Native	334 (0.2%)	165 (0.2%)	169 (0.2%)	
Asian	1447 (1.0%)	659 (0.9%)	788 (1.1%)	
Black	33 814 (23.6%)	22 041 (30.7%)	11 773 (16.5%)	
Native Hawaiian or Other Pacific Islander	33 (0.0%)	11 (0.0%)	22 (0.0%)	
White	70 156 (49.0%)	25 304 (35.3%)	44 852 (62.9%)	
Multiple race	503 (0.4%)	167 (0.2%)	336 (0.5%)	
Other	20 555 (14.4%)	11 610 (16.2%)	8945 (12.5%)	
Unknown	16 212 (11.3%)	11 817 (16.5%)	4395 (6.2%)	
Ethnicity				0.35
Hispanic	22 680 (15.9%)	13 016 (18.1%)	9664 (13.6%)	
Non-Hispanic	99 483 (69.5%)	44 696 (62.3%)	54 787 (76.9%)	
Unknown	16 203 (11.3%)	11 865 (16.5%)	4338 (6.1%)	
Missing	4688 (3.3%)	2197 (3.1%)	2491 (3.5%)	
Comorbidities				
Current smoker	32 080 (22.4%)	17 035 (23.7%)	15 045 (21.1%)	0.06
Diabetes	29 633 (20.7%)	13 802 (19.2%)	15 831 (22.2%)	0.07
Chronic kidney disease	17 626 (12.3%)	5111 (7.1%)	12 515 (17.6%)	0.32
End-stage renal disease	1072 (0.7%)	233 (0.3%)	839 (1.2%)	0.10
HF with reduced EF	2858 (2.0%)	1264 (1.8%)	1594 (2.2%)	0.03
Coronary heart disease	7940 (5.6%)	2742 (3.8%)	5198 (7.3%)	0.15
Prior coronary revascularization	728 (0.5%)	142 (0.2%)	586 (0.8%)	0.09
Prior stroke or TIA	2292 (1.6%)	309 (0.4%)	1983 (2.8%)	0.19
Peripheral arterial disease	9388 (6.6%)	1483 (2.1%)	7905 (11.1%)	0.37
History of clinical ASCVD	17 416 (12.2%)	4229 (5.9%)	13 187 (18.5%)	0.39
Atrial fibrillation	10 024 (7.0%)	1375 (1.9%)	8649 (12.1%)	0.41
COPD	7769 (5.4%)	4588 (6.4%)	3181 (4.5%)	0.09
Asthma	6066 (4.2%)	4855 (6.8%)	1211 (1.7%)	0.25
Depression	25 690 (18.0%)	10 670 (14.9%)	15 020 (21.1%)	0.16
Charlson comorbidity score	2.54±3.53	1.57±2.82	3.51±3.89	0.57
Other medication use				
Statin	31 421 (22.0%)	13 201 (18.4%)	18 220 (25.6%)	0.17
Aspirin	11 663 (8.2%)	6115 (8.5%)	5548 (7.8%)	0.03
Index year				
2012[*]	32 (0.0%)	1 (0.0%)	31 (0.0%)	
2013	17 728 (12.4%)	485 (0.7%)	17 243 (24.2%)	
2014	31 711 (22.2%)	11 457 (16.0%)	20 254 (28.4%)	

(*Continued*)

Table. Continued

Baseline characteristic	New antihypertensive users			
	Overall cohort (N=143 054)	Medicaid cohort (N=71 774)	Medicare cohort (N=71 280)	SMD†
2015	27 205 (19.0%)	11 039 (15.4%)	16 166 (22.7%)	
2016	19 283 (13.5%)	10 664 (14.9%)	8619 (12.1%)	
2017	18 661 (13.0%)	9694 (13.5%)	8967 (12.6%)	
2018	8963 (6.3%)	8963 (12.5%)	0 (0%)	
2019	8164 (5.7%)	8164 (11.4%)	0 (0%)	
2020	7520 (5.3%)	7520 (10.5%)	0 (0%)	
2021	3787 (2.6%)	3787 (5.3%)	0 (0%)	

ASCVD indicates atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; SMD, standardized mean difference; and TIA, transient ischemic attack.

*Individuals who met study eligibility criteria on December 31, 2012.

†Standardized mean difference comparing Medicaid- vs Medicare-insured populations.

considerably more common in the Medicare versus Medicaid population.

Initial Antihypertensive Use

In the overall population, most patients (75.4%) were initiated on a single agent, whereas 18.8% were initiated on 2 agents simultaneously and 5.8% on ≥3 agents simultaneously. Crude rates of combination therapy were higher among Medicare- (28%) versus Medicaid-insured (21%) individuals, though these differences were minimized substantially after age adjustment (Table S3).

Figure 1 summarizes the proportion of Medicaid-insured patients initiating each class of antihypertensives, as well as the proportion initiating each drug within each class. Briefly, the most common classes initiated were ACEIs (39% of patients) and β-blockers (31%), followed by dihydropyridine CCBs (22%), thiazide diuretics (19%) and ARBs (11%). Use of most classes was predominated by a single agent, namely, lisinopril (94% of ACEI initiators), amlodipine (87% of dihydropyridine CCB initiators), hydrochlorothiazide (94% of thiazide initiators), and losartan (88% of ARB initiators). β-blockers were more evenly distributed across metoprolol (47%), propranolol (17%), carvedilol (14%), and atenolol and labetalol (each 11%). Figure 2 presents corresponding information for Medicare-insured patients, in which ACEIs (37%) and β-blockers (36%) were the most often initiated, followed by dihydropyridine CCBs (21%), thiazide diuretics (17%), and ARBs (13%). The rank-order of drugs within class was generally similar among the Medicare-, compared with Medicaid-insured, cohorts.

Antihypertensive use patterns among patients initiating monotherapy within the Medicaid cohort were generally similar to the overall Medicaid cohort in terms of rank ordering of classes and drugs within class (Figure S3). Likewise, compared with the overall Medicare cohort, patients initiating monotherapy had similar antihypertensive initiation patterns except that ARBs were initiated more often than thiazide diuretics (10% versus 7% among monotherapy initiators; 13% versus 17% among all Medicare patients) (Figure S4). Among patients initiating 2 antihypertensives simultaneously, the most common combination was an ACEI + thiazide diuretic (24% of all 2-drug combinations overall), which was the preferred 2-drug combination in both cohorts (31% of all 2-drug combinations in the Medicaid cohort and 18% in the Medicare cohort; Table S4). The next 3 most common combinations were ACEI + β-blocker (14% overall), ARB + thiazide diuretic (11% overall), and ACEI + CCB (10% overall). Among Medicaid recipients, only 59% of all 2-drug combinations were considered guideline-concordant (ie, using drugs from 2 first-line antihypertensives) per current US guidelines, whereas 36% were partially concordant (combining 1 first-line and 1 second-line antihypertensive) and 5% were fully discordant (Figure S5). Among Medicare recipients, 47% of patients initiated guideline-concordant 2-drug combinations, whereas 45% were partially concordant and 8% were fully discordant (Figure S6). Finally, among all patients initiating ≥2 antihypertensives concomitantly, nearly one-third (33.8%) used at least 1 fixed-dose combination product, with a slightly higher proportion among Medicaid versus Medicare recipients (35.2% versus 32.7%).

Time Trends

Figure 3 and Figure S7 summarize the proportion of patients starting each class over time. Notable changes from 2013 through 2021 were increased use of dihydropyridine CCBs (20% to 27% overall; $P<0.0001$) and decreased use of β-blockers (32% to 26%; $P<0.0001$) among Medicaid recipients. Dihydropyridine CCB initiation also increased over time in Medicare recipients (20% in 2013 to 24% in 2017), whereas no change was

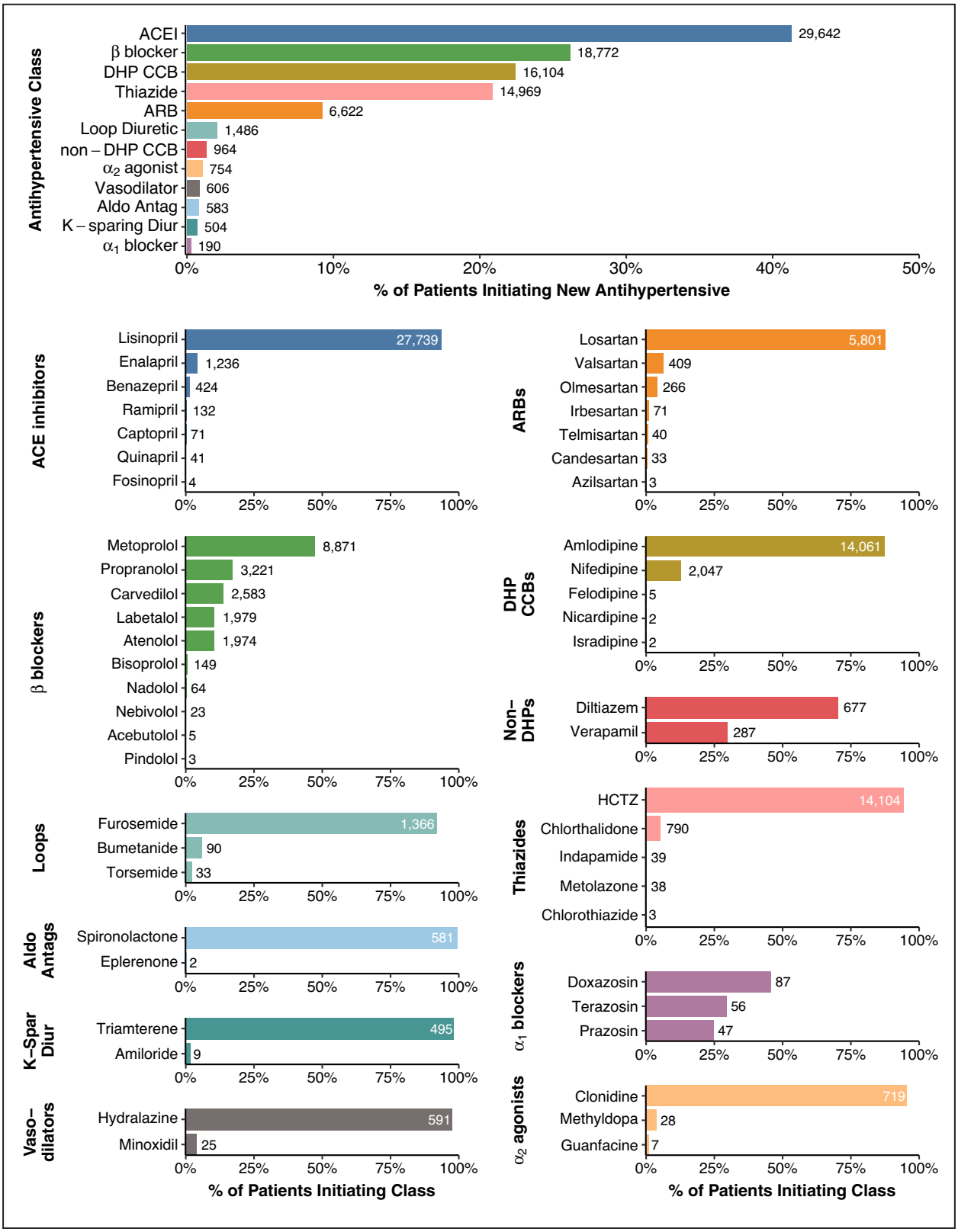


Figure 1. Proportion of patients prescribed each antihypertensive class, among Medicaid-insured patients with newly treated hypertension.

Numbers to the right of bars represent distinct patients. Patients initiating multiple therapies are included in each category. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and DHP CCB, dihydropyridine calcium channel blocker.

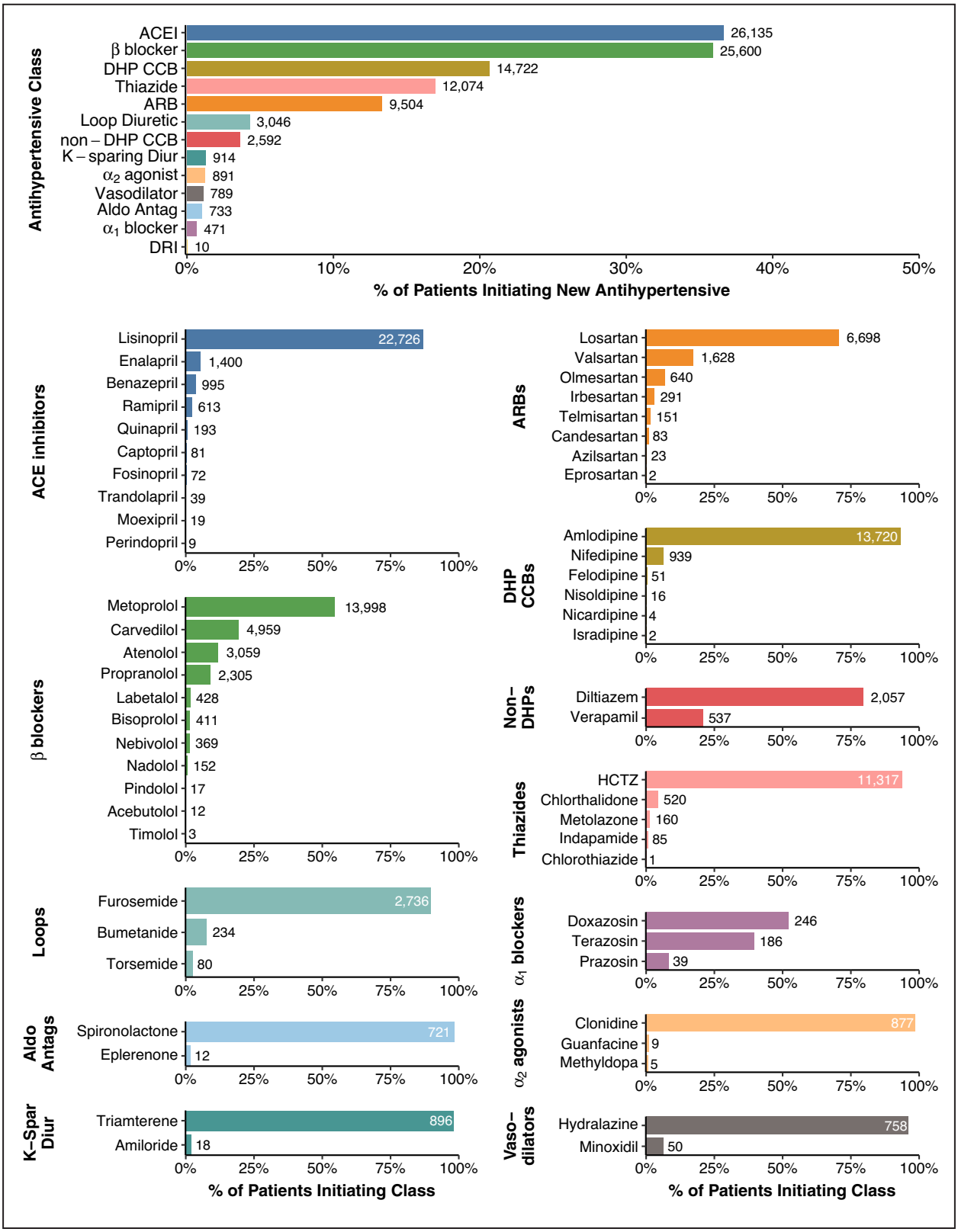


Figure 2. Proportion of patients prescribed each antihypertensive class, among Medicare-insured patients with newly treated hypertension.

Numbers to the right of bars represent distinct patients. Patients initiating multiple therapies are included in each category. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP CCB, dihydropyridine calcium channel blocker; and DRI, direct renin inhibitor (aliskiren).

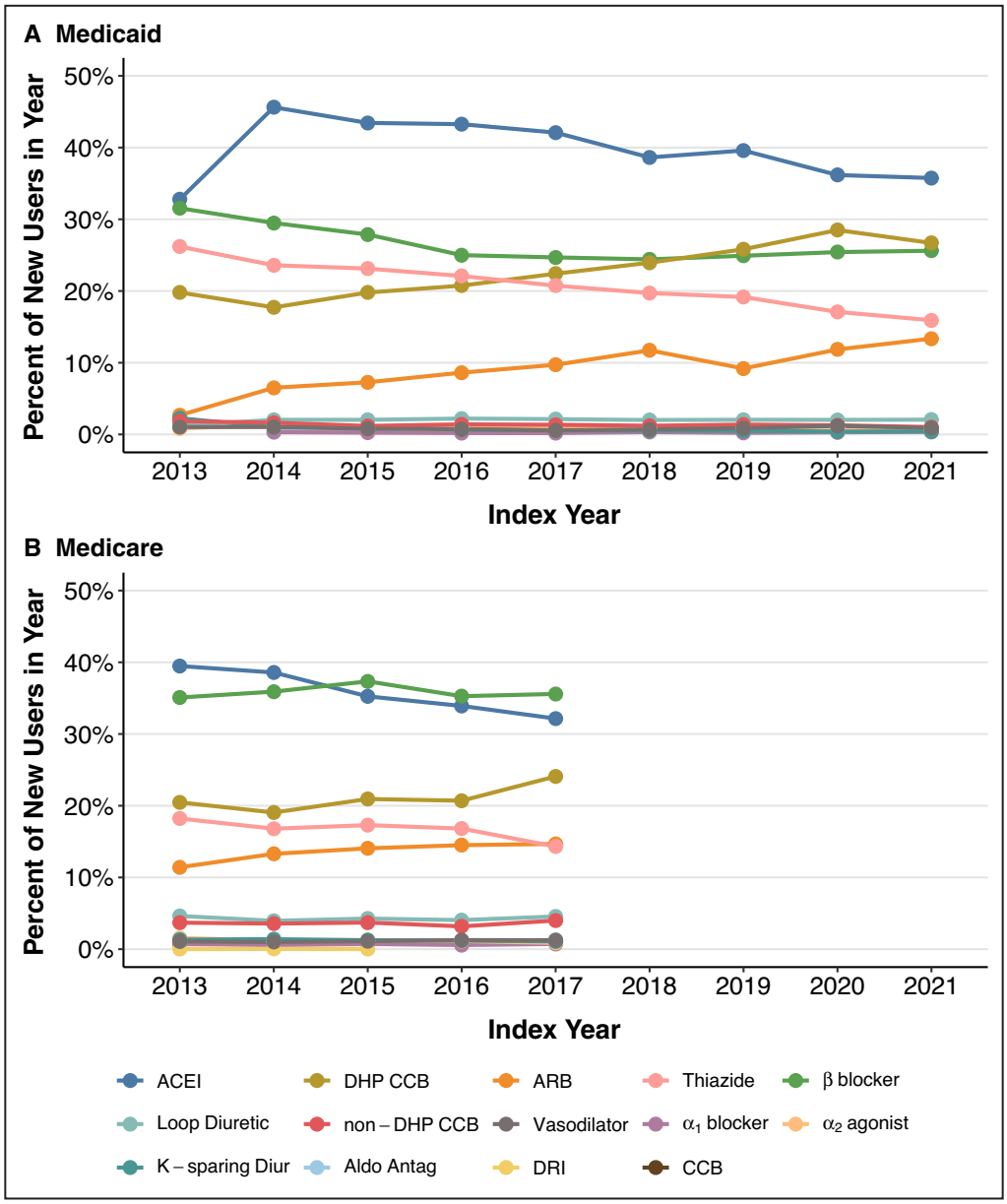


Figure 3. Time trends in initial use of antihypertensive classes, 2013 to 2021.
A, Medicaid-insured individuals; **(B)** Medicare-insured individuals. All trends for major classes of antihypertensives in each cohort were significant at $P<0.0001$, except β-blockers in the Medicare cohort, $P=0.48$, using the Cochrane–Armitage test. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP CCB, dihydropyridine calcium channel blocker; and DRI, direct renin inhibitor (aliskiren).

observed for β-blockers. ACEI initiation decreased modestly overall (39% to 36%; $P<0.0001$) and in each cohort separately, as did thiazide use (Medicaid, 26% to 16%, $P<0.0001$; Medicare, 18% to 14%, $P<0.0001$). ARB initiation increased by a similar magnitude (Medicaid, 3% to 13%, $P<0.0001$; Medicare, 11% to 15%, $P<0.0001$). Time trends of drug within class are presented in Figures S8 and S9. Analyses limited to patients initiating monotherapy showed remarkably similar trends (data not shown).

Stratified Analyses: Demographics and Comorbidities

The proportions of patients initiating each of the 5 major classes across prespecified strata are summarized in Figure 4 (Medicaid) and Figure 5 (Medicare), with additional detailed data in Table S5. Among both cohorts, men were more likely than women to initiate ACEIs, whereas the reverse was true for thiazides, especially among Medicaid recipients (Panel A). Black patients were more likely to initiate CCBs

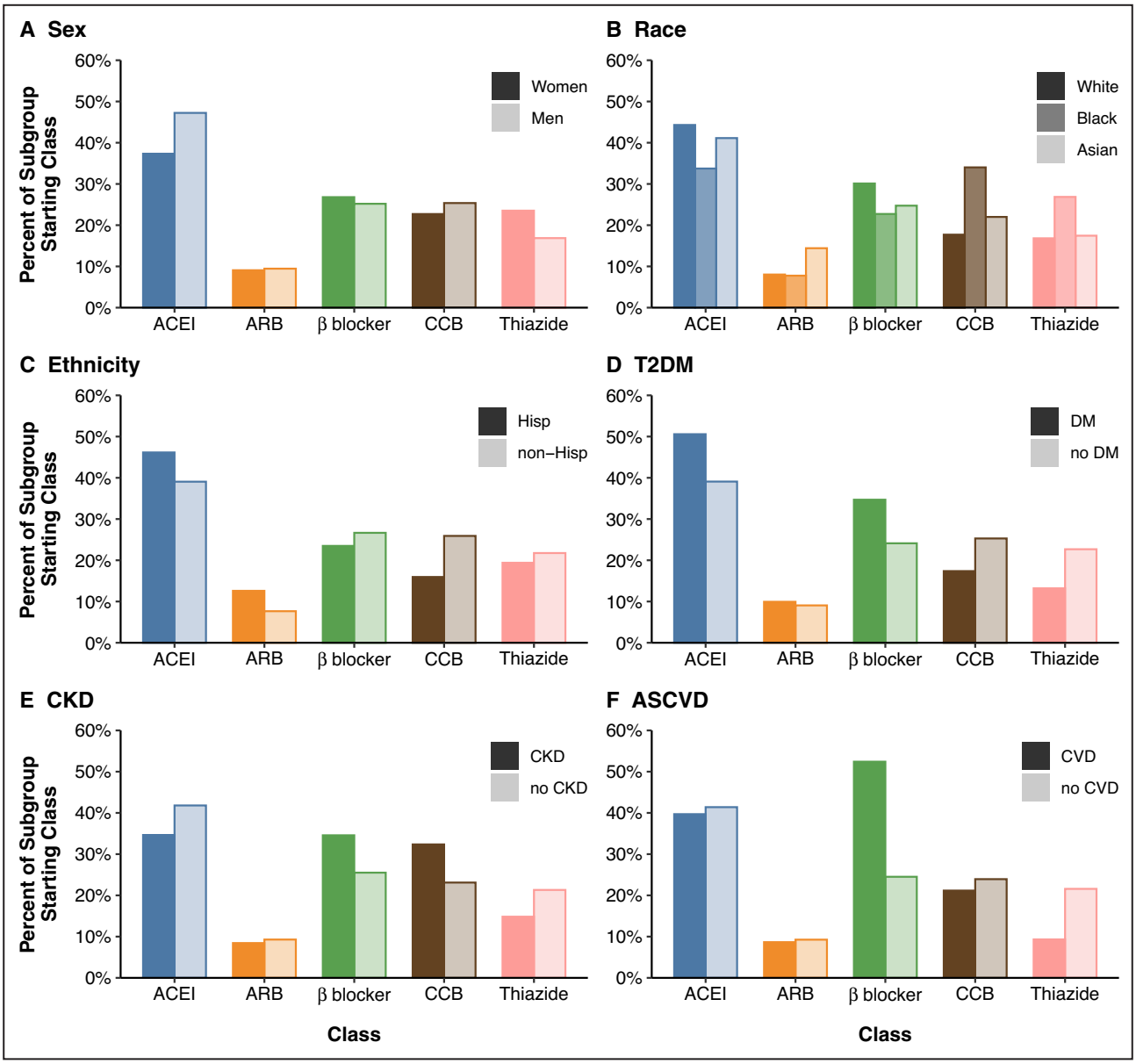


Figure 4. Proportion of Medicaid-insured patients prescribed first-line antihypertensive classes, stratified by selected demographics and comorbidities.

Data are presented by sex (**A**), race including only racial groups with sufficient representation (**B**), ethnicity (**C**), and presence/absence of type 2 diabetes (**D**), CKD (**E**), or clinical ASCVD (**F**). Legends for each panel correspond to darker or lighter shaded bars within each antihypertensive class. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CCB, calcium channel blocker; CKD, chronic kidney disease; and T2DM, type 2 diabetes mellitus.

(primarily dihydropyridine CCBs) or thiazides, compared with White and Asian patients in both cohorts (Panel B). Black patients, compared with White and Asian patients, were also less likely to initiate ACEIs in the Medicaid cohort, whereas no meaningful difference was observed in Medicare-insured individuals. Additional analyses among monotherapy-treated Black participants with and without CKD or HF are summarized in Figure S10. Briefly, comparing those with either CKD or HF versus without CKD nor HF, we observed fewer patients initiating ACEIs (24% versus 27% [SMD, 0.08] in the Medicaid cohort; 20% versus 31% [SMD, 0.26] in the Medicare cohort) and thiazides (12% versus 18% [SMD, 0.16] in Medicaid; 6% versus 12% [SMD, 0.23] in Medicare), and similar proportions initiating ARBs. In the Medicare cohort, β-blocker use was much higher in the CKD/HF population (36%) compared with those with neither CKD nor HF (22%;

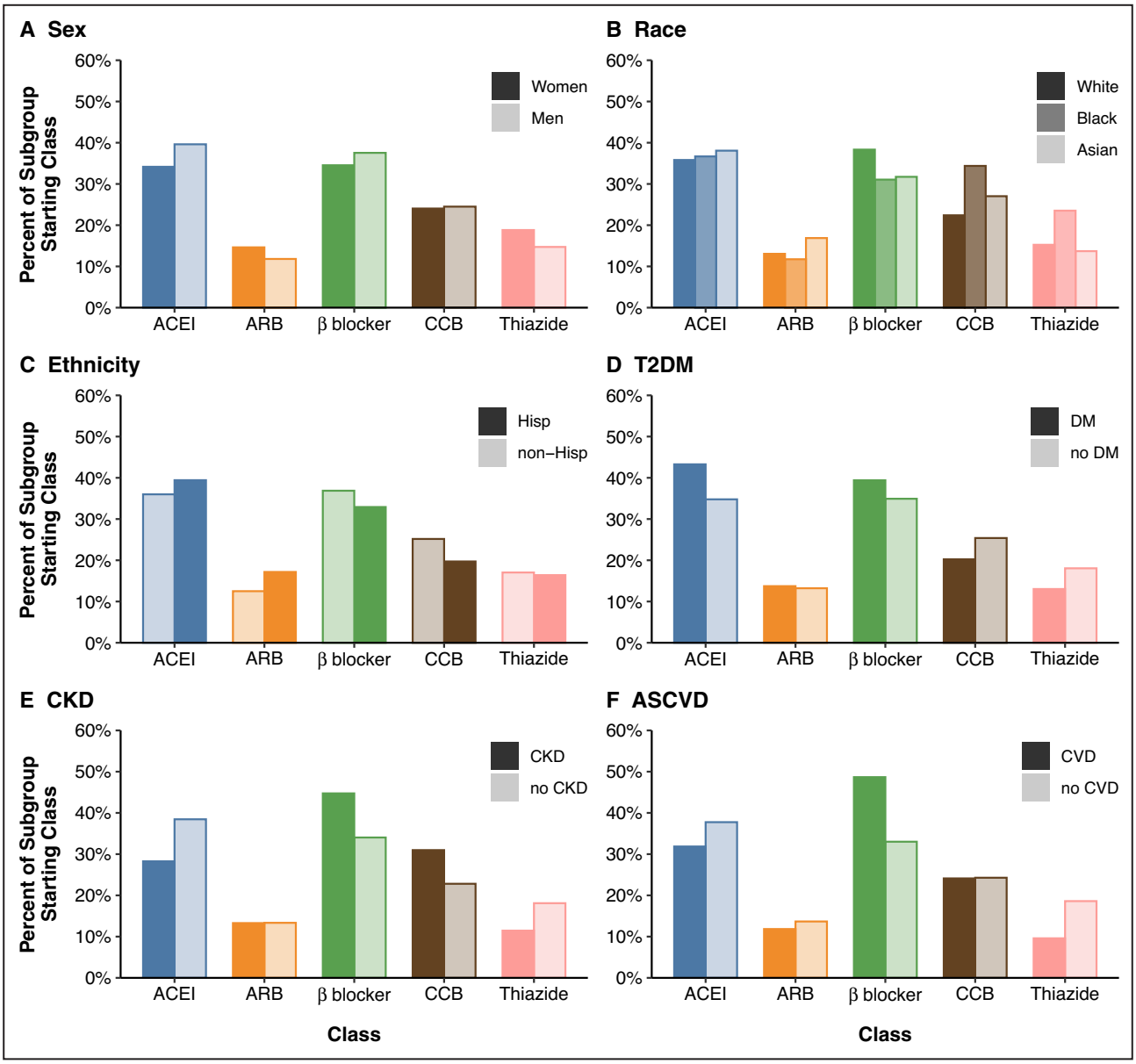


Figure 5. Proportion of Medicare-insured patients prescribed first-line antihypertensive classes, stratified by selected demographics and comorbidities.

Data are presented by sex (**A**), race including only racial groups with sufficient representation (**B**), ethnicity (**C**), and presence/absence of type 2 diabetes (**D**), CKD (**E**), or clinical ASCVD (**F**). Legends for each panel correspond to darker or lighter shaded bars within each antihypertensive class. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CCB, calcium channel blocker; CKD, chronic kidney disease; and T2DM, type 2 diabetes mellitus.

SMD, 0.31), whereas we observed little difference in β-blocker use in these populations among Medicaid-insured (22% versus 18%; SMD, 0.08).

Hispanic patients had moderately higher initiation of ACEI or ARB therapy and lower initiation of CCBs or β-blockers in each cohort (Figures 4 and 5, Panel C). Diabetes, versus no diabetes, was associated with greater ACEI but not ARB use in both cohorts, as well as higher β-blocker use, but lower CCB and thiazide use (Figures 4 and 5, Panel D). ACEIs were initiated in only 30% of patients meeting CKD criteria overall (Medicaid, 35%; Medicare, 28%), versus 40% of those not meeting CKD criteria (Medicaid, 42%; Medicare, 39%); CCBs and β-blockers were each initiated considerably more commonly in those with CKD, whereas thiazides were initiated more commonly in those without CKD (Figures 4 and 5, Panel E). Finally, among patients with ASCVD in both cohorts, approximately

half initiated a β-blocker, whereas only 10% initiated a thiazide, and use of other classes differed only modestly (≤6%) between those with and without ASCVD (Figures 4 and 5, Panel F).

DISCUSSION

In this large, population-based study, we characterized antihypertensive regimens among patients with newly treated hypertension. We focused our cohort among Medicare and Medicaid recipients who initiated ≥1 first-line antihypertensive classes (including β-blockers, considered first-line therapy during a portion of our study years), to better understand treatment initiation patterns and to complement existing literature that provide data on prevalent hypertension cohorts. Our principal findings are that initiation of monotherapy remains remarkably common, and significant variation exists in initial antihypertensive regimens, with ≤41% of patients prescribed any single class in either study population. Within classes, there exists very little variation in choice of initial antihypertensive drug, especially among current first-line therapies (ACEI, ARB, CCBs, and thiazides), in which a single drug predominates in ≥70% of cases. Time trends in antihypertensive initiation have remained fairly stable, although ACEI and β-blocker use (among Medicaid recipients) has decreased significantly, replaced by increased dihydropyridine CCB and ARB use between 2013 and 2021. Finally, we observed notable differences in antihypertensive initiation in stratified analyses across demographic and clinical characteristics. To our knowledge, this is one of the largest and most detailed characterizations of real-world utilization of antihypertensives in newly treated patients.

Limited data have been published regarding initial use of antihypertensive classes. A recent study examined time trends in first-line antihypertensives between 2008 and 2017 in Medicare recipients, primarily focused on patients initiating monotherapy.[18] In that population, thiazide initiation decreased and CCB initiation increased, similar to our findings. In contrast, they found reduced initiation of β-blockers over time, whereas we observed stable β-blocker initiation, though β-blockers remain one of the most commonly initiated antihypertensives through 2017 in both studies. Finally, they observed increased use of ACEIs and ARBs, particularly among individuals without any comorbidities. It remains unclear to what extent this finding was driven by increased ACEI initiation, ARB initiation, or both. Among both our Medicare and Medicaid populations, we found consistent decreases in ACEI initiation over time, whereas ARB initiation increased in both cohorts.[18] Thus, it is possible that these findings are consistent. On the other hand, our data suggest that comparatively few patients initiate ARBs compared with ACEIs, even in the most recent years. Few other studies have explicitly characterized antihypertensive new user regimens; however, some additional insights may be gleaned from "real-world" comparative effectiveness studies enrolling only new antihypertensive users. For example, the LEGEND-HTN (Large scale Evidence Generation and Evaluation across a Network of Databases for hypertension) study included only new antihypertensive users of first-line antihypertensives from multiple claims and EHR-based cohorts and found, similar to our study, that ACEIs were the most common antihypertensive initiated across multiple claims and EHR-based cohorts, followed by dihydropyridine CCBs, thiazides, ARBs, and nondihydropyridine CCBs (β-blockers were not studied).[19]

Compared with recent data from US prevalent hypertension cohorts, our findings regarding initial antihypertensive classes share some similarities but also noteworthy differences. For example, a recent analysis of National Health and Nutrition Examination Survey data found that from 2013 to 2016, nearly three-quarters (74%) of antihypertensive regimens contained an ACEI or ARB, whereas 43% contained a diuretic, 35% contained a β-blocker, and 29% contained a CCB.[13] Our data, as well, showed ACEIs as the predominant class initiated overall and in the Medicaid cohort for every year over the study period and only used marginally less in the Medicare cohort. However, we observed considerably lower proportions of initial regimens containing CCBs (<25%) and thiazides (<20%), despite having a considerably higher proportion of Black patients and, as might be expected with a newly diagnosed hypertensive population, fewer patients with diagnosed CKD or HF, than in the National Health and Nutrition Examination Survey samples. Similar trends were observed among those initiating only monotherapy in our study. Our results also revealed remarkably low ARB initiation, though there was evidence of a moderate shift over time from ACEI to ARB as preferred renin angiotensin system inhibitor. This finding may reflect increasingly robust evidence for their equivalent outcomes in hypertension and greater tolerability with ARBs,[20,21] as well as a narrowing of practice differences between US and international cohorts, the latter of which generally show considerably higher ARB initiation among new antihypertensive users.[4,22,23] Finally, among Medicaid recipients, we observed reduced initiation of β-blockers and greater initiation of dihydropyridine CCBs, such that by 2021, dihydropyridine CCBs (and CCBs, overall) were initiated more frequently than β-blockers. Among Medicare patients, we saw a similar rise in dihydropyridine CCB use but no change in β-blocker use. These findings are consistent

with the evolving recognition of dihydropyridine CCB effectiveness as antihypertensives and concerns that β-blockers still have a role in patients with ASCVD but may be less effective at reducing risk of major adverse outcomes in uncomplicated hypertension.[24–26]

Within antihypertensive classes, we saw remarkably little variation in prescribing. For all first-line classes except β-blockers, a single drug accounted for ≥70% of all initiations within class. Indeed, the 4 predominant drugs (lisinopril, amlodipine, hydrochlorothiazide, and losartan) accounted for >60% of all antihypertensives initiated, and at least 1 of these drugs was present in 70% of regimens. Analysis of trends over time revealed generally stable market for most first-line agents share during the study period, with 1 notable exception: losartan made up 64% of all ARB initiations in 2013, increasing to 91% in 2021. Increasing trends were observed in both the Medicare- and Medicaid-insured cohorts over time, though the latter tended to initiate losartan at a ≈10% higher rate each year than the Medicare-insured cohort. This increasing use of losartan is somewhat surprising in light of the fact that losartan often requires twice- or thrice-daily dosing and has lower persistence compared with other ARBs.[27]

Our overall findings must also be considered in the context of the populations in which they were observed. Specifically, our data also revealed several noteworthy differences in antihypertensive prescribing across demographic variables. Our overall cohort comprised ≈57% women, and we observed significantly greater initiation of ACEIs and less initiation of thiazides in this group compared with men. This finding is qualitatively consistent with prior research in prevalent hypertensive cohorts,[13] though the magnitudes of difference observed in our population were markedly greater. Interestingly, in comparisons across races, we found that ACEIs were most commonly initiated across all races, followed by β-blockers (White and Asian patients) and CCBs (Black patients), particularly in the absence of ASCVD. The greater frequency of ACEI initiation observed in Black patients is only partially explained by their greater likelihood of receiving dual therapy compared with White patients (29% versus 25%). Even among Black patients receiving monotherapy, renin angiotensin system inhibitors (including β-blockers) accounted for >50% of initial regimens in both Medicaid- and Medicare-insured patients. Current guidelines recommend a CCB or thiazide diuretic in Black patients without compelling indications for specific antihypertensive classes,[3] yet fewer than half of Black patients received such therapy (≈45% of all Black patients and ≈46% of those without CKD/HF who initiated monotherapy). Also, we observed comparatively less initiation of ACEI/ARB therapy in Black individuals with diagnosed CKD or HF. Combined with recent findings regarding racial disparities in treatment intensification,[28] our findings may help explain some of the well-known disparities in hypertension control comparing White and Black Americans.[28,29]

Our study has several noteworthy limitations. First, our cohorts were derived from insurance claims in OneFlorida (Medicaid, Medicare), rather than EHR data. We chose this approach because insurance claims ensure more complete information capture (during continuous eligibility periods), whereas an EHR-based approach would have likely resulted in significant misclassification of prevalent treated hypertension as newly treated hypertension because we could not ensure a sustained period of no antihypertensive use before first observed prescription. This design choice has several important implications. First, our study describes only antihypertensives ultimately filled by patients. We presume that the conversion rate of prescriptions to medication fills was nondifferential across first-line classes and thus prescribing patterns would reflect similar antihypertensive initiation patterns, but we cannot be certain. Second, although we followed well-established and robust methods for identifying a new-user cohort from claims data, we cannot be certain that all patients initiated therapy specifically for hypertension. Indeed, it is plausible that some patients, particularly those initiating combination regimens, may have had other indications in addition to hypertension that guided antihypertensive selection. Accordingly, the prevalences of partially concordant and fully discordant combination therapy observed may reflect, at least in part, patients with multiple comorbid conditions (hypertension and, eg, HF, coronary disease, or CKD) in which the comorbidities prompted use of "second-line" therapy. Relatedly, we required all patients to initiate ≥1 first-line antihypertensive, and this approach excluded a relatively small number of patients initiating second-line agents only (Figure S1). Such patients were presumed to be likelier to initiate "antihypertensives" for indications other than hypertension, which we could not rule out. However, it is probable that we excluded some patients who initiated second-line therapy for hypertension. We suspect these cases are relatively infrequent, as guideline recommendations regarding which classes constitute first-line therapy (other than for β-blockers) have been generally stable for decades. Nevertheless, our analyses of second-line agents overall, and their combinations, should be considered in this context. Fourth, we had limited data on socioeconomic information for patients included in the study; consequently, we were not able to ascertain the extent to which differences in socioeconomic status may have influenced (eg, racial differences) medication initiation. Finally, our findings come from publicly insured individuals and may have

limited generalizability to commercially insured or uninsured individuals.

In summary, we conducted a detailed characterization of antihypertensive initiation patterns in newly treated patients with hypertension. Although ACEIs were most commonly initiated across almost all analyses, we observed substantial variation across first-line classes overall and within prespecified demographic and comorbidity strata. We also observed some trends suggesting uptake of current clinical guideline recommendations, namely, greater initiation of CCBs and less initiation of β-blockers. Nevertheless, we noted several findings largely inconsistent with current recommendations in the United States, including infrequent initiation of multidrug regimens, moderately frequent use of combination regimens that do not prioritize first-line classes, and suboptimal use of some classes in patients for whom they are explicitly prioritized. Additional research is needed to better understand why such initial treatment choices are made and whether intervening on these factors may improve outcomes in these patients.

ARTICLE INFORMATION

Received May 2, 2022; accepted November 29, 2022.

Affiliations

Department of Pharmaceutical Outcomes and Policy, College of Pharmacy (S.M.S., A.G.W., M.G.W., S.K., W.R.H.); Division of Cardiovascular Medicine, Department of Medicine, College of Medicine (S.M.S., C.J.P., R.M.C.); Center for Integrative Cardiovascular and Metabolic Disease (S.M.S., R.M.C.); and Department of Health Outcomes and Biomedical Informatics, College of Medicine (M.J.G.), University of Florida, Gainesville, FL; Department of Emergency Medicine, School of Medicine, University of Colorado Denver, Aurora, CO (A.M.L.); and Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL (R.M.C.).

Sources of Funding

This work was funded by the National Heart, Lung, and Blood Institute, K01 HL138172 (Dr Smith). Research reported in this publication was also supported in part by the UF Center for Drug Evaluation and Safety; in part by the OneFlorida Clinical Data Network, funded by the Patient-Centered Outcomes Research Institute numbers CDRN-1501-26692 and RI-CRN-2020-005; in part by the OneFlorida Cancer Control Alliance, funded by the Florida Department of Health's James and Esther King Biomedical Research Program number 4KB16; and in part by the University of Florida Clinical and Translational Science Institute and its Clinical and Translational Science Award (CTSA) hub partner, Florida State University, which are supported in part by 3 CTSA Program grants awarded on August 15, 2015, and renewed for 5 years on July 2, 2019, by the National Center for Advancing Translational Sciences of the National Institutes of Health. The UF-FSU CTSA grant numbers are UL1TR001427, KL2TR001429, and TL1TR001428. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, Patient-Centered Outcomes Research Institute (PCORI) or *its Board of Governors or Methodology*, the OneFlorida Clinical Research Consortium, the UF-FSU Clinical and Translational Science Institute, or the Florida Department of Health.

Disclosures

The authors have no conflicts of interest to disclose.

Supplemental Material

Table S1–S5
Figure S1–S10

REFERENCES

1. Muntner P, Miles MA, Jaeger BC, Hannon L III, Hardy ST, Ostchega Y, Wozniak G, Schwartz JE. Blood pressure control among US adults, 2009 to 2012 through 2017 to 2020. *Hypertension*. 2022;79:1971–1980. doi: 10.1161/HYPERTENSIONAHA.122.19222
2. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
3. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, 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
4. Hou W, Li D, Shen S, Lin J, Lou A, Wen A. Frequency and patterns of prescribing antihypertensive agents in outpatient kidney transplant recipients among six cities in China from 2011 to 2018. *Clin Ther*. 2021;43:602–612. doi: 10.1016/j.clinthera.2021.01.013
5. Gu A, Yue Y, Argulian E. Age differences in treatment and control of hypertension in US physician offices, 2003-2010: a serial cross-sectional study. *Am J Med*. 2016;129:50–58. doi: 10.1016/j.amjmed.2015.07.031
6. Gu A, Farzadeh SN, Chang YJ, Kwong A, Lam S. Patterns of antihypertensive drug utilization among US adults with diabetes and comorbid hypertension: the National Health and nutrition examination survey 1999-2014. *Clin Med Insights Cardiol*. 2019;13:117954681983941. doi: 10.1177/1179546819839418
7. Shah SJ, Stafford RS. Current trends of hypertension treatment in the United States. *Am J Hypertens*. 2017;30:1008–1014. doi: 10.1093/ajh/hpx085
8. Gu A, Yue Y, Desai RP, Argulian E. Racial and ethnic differences in antihypertensive medication use and blood pressure control among US adults with hypertension. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003166. doi: 10.1161/CIRCOUTCOMES.116.003166
9. Zhou M, Daubresse M, Stafford RS, Alexander GC. National trends in the ambulatory treatment of hypertension in the United States, 1997-2012. *PLoS One*. 2015;10:e0119292. doi: 10.1371/journal.pone.0119292
10. Koifman E, Tanne D, Molshatzki N, Leibowitz A, Grossman E. Trends in antihypertensive treatment—lessons from the National Acute Stroke Israeli (NASIS) registry. *Blood Press*. 2014;23:262–269. doi: 10.3109/08037051.2013.876771
11. Wang Z, Wang X, Chen Z, Wang W, Zhu H, Chen W, Zhu M, Hu S, Staessen JA, Liu L, et al. Hypertension control in community health centers across China: analysis of antihypertensive drug treatment patterns. *Am J Hypertens*. 2014;27:252–259. doi: 10.1093/ajh/hpt186
12. Zheutlin AR, Derington CG, King JB, Berchie RO, Herrick JS, Dixon DL, Cohen JB, Shimbo D, Kronish IM, Saseen JJ, et al. Factors associated with antihypertensive monotherapy among US adults with treated hypertension and uncontrolled blood pressure overall and by race/ethnicity, National Health and nutrition examination survey 2013-2018. *Am Heart J*. 2022;248:150–159. doi: 10.1016/j.ahj.2021.10.184
13. Derington CG, King JB, Herrick JS, Shimbo D, Kronish IM, Saseen JJ, Muntner P, Moran AE, Bress AP. Trends in antihypertensive medication monotherapy and combination use among US adults, National Health and nutrition examination survey 2005-2016. *Hypertension*. 2020;75:973–981. doi: 10.1161/HYPERTENSIONAHA.119.14360
14. O'Connor PJ, Vazquez-Benitez G, Schmittdiel JA, Parker ED, Trower NK, Desai JR, Margolis KL, Magid DJ. Benefits of early hypertension control on cardiovascular outcomes in patients with diabetes. *Diabetes Care*. 2013;36:322–327. doi: 10.2337/dc12-0284
15. Weir MR, Zappe D, Orloski LA, Sowers JR. How early should blood pressure control be achieved for optimal cardiovascular outcomes? *J Hum Hypertens*. 2011;25:211–217. doi: 10.1038/jhh.2010.64
16. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput*. 2009;38:1228–1234.
17. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint National Committee (JNC 8). *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427

18. Anderson TS, Ayanian JZ, Zaslavsky AM, Souza J, Landon BE. National trends in antihypertensive treatment among older adults by race and presence of comorbidity, 2008 to 2017. *J Gen Intern Med*. 2022;37:4223–4232. doi: 10.1007/s11606-022-07612-3
19. Suchard MA, Schuemie MJ, Krumholz HM, You SC, Chen R, Pratt N, Reich CG, Duke J, Madigan D, Hripcsak G, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet*. 2019;394:1816–1826. doi: 10.1016/S0140-6736(19)32317-7
20. Chen R, Suchard MA, Krumholz HM, Schuemie MJ, Shea S, Duke J, Pratt N, Reich CG, Madigan D, You SC, et al. Comparative first-line effectiveness and safety of ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers: a multinational cohort study. *Hypertension*. 2021;78:591–603. doi: 10.1161/HYPERTENSIONAHA.120.16667
21. Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? Insights from 254,301 patients from randomized trials. *Mayo Clin Proc*. 2016;91:51–60. doi: 10.1016/j.mayocp.2015.10.019
22. Rea F, Savaré L, Franchi M, Corrao G, Mancia G. Adherence to treatment by initial antihypertensive mono and combination therapies. *Am J Hypertens*. 2021;34:1083–1091. doi: 10.1093/ajh/hpab083
23. Selmer R, Blix HS, Landmark K, Reikvam Å. Choice of initial antihypertensive drugs and persistence of drug use-a 4-year follow-up of 78,453 incident users. *Eur J Clin Pharmacol*. 2012;68:1435–1442. doi: 10.1007/s00228-012-1261-2
24. You SC, Krumholz HM, Suchard MA, Schuemie MJ, Hripcsak G, Chen RJ, Shea S, Duke J, Pratt N, Reich CG, et al. Comprehensive comparative effectiveness and safety of first-line β-blocker monotherapy in hypertensive patients: a large-scale multicenter observational study. *Hypertension*. 2021;77:1528–1538. doi: 10.1161/HYPERTENSIONAHA.120.16402
25. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428. doi: 10.1056/NEJMoa0806182
26. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2017;1:CD002003. doi: 10.1002/14651858.CD002003.pub5
27. Hasford J, Mimran A, Simons WR. A population-based European cohort study of persistence in newly diagnosed hypertensive patients. *J Hum Hypertens*. 2002;16:569–575. doi: 10.1038/sj.jhh.1001451
28. Fontil V, Pacca L, Bellows BK, Khoong E, McCulloch CE, Pletcher M, Bibbins-Domingo K. Association of differences in treatment intensification, missed visits, and scheduled follow-up interval with racial or ethnic disparities in blood pressure control. *JAMA Cardiol*. 2022;7:204–212. doi: 10.1001/jamacardio.2021.4996
29. Aggarwal R, Chiu N, Wadhera RK, Moran AE, Raber I, Shen C, Yeh RW, Kazi DS. Racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control in the United States, 2013 to 2018. *Hypertension*. 2021;78:1719–1726. doi: 10.1161/HYPERTENSIONAHA.121.17570

SUPPLEMENTAL MATERIAL

Table S1. Antihypertensive medications considered acceptable for cohort inclusion.

Antihypertensive Class	Medication Name
Angiotensin converting enzyme inhibitors	benazepril
	captopril
	enalapril
	fosinopril
	lisinopril
	moexipril
	perindopril
	quinapril
	ramipril
	trandolapril
Angiotensin receptor blockers	azilsartan
	candesartan
	eprosartan
	irbesartan
	losartan
	olmesartan
	telmisartan
	valsartan*
Alpha-blockers	doxazosin
	prazosin
	terazosin
Beta-blockers†	acebutolol
	atenolol
	nadolol
	oxprenolol
	betaxolol
	bisoprolol
	carteolol
	timolol
	bucindolol
	esmolol
	labetalol
	carvedilol
	metoprolol
	propranolol
	nebivolol
	penbutolol
	pindolol
	metipranolol
Calcium channel blockers	amlodipine
	felodipine
	isradipine
	nicardipine
	nifedipine‡
	nisoldipine
	diltiazem

	verapamil
Centrally acting agents	clonidine
	guanabenz
	guanfacine
	guanadrel
	guanethidine
	methyldopa
	reserpine
Direct vasodilators	hydralazine
	minoxidil
Direct renin inhibitors	aliskiren
Aldosterone receptor antagonists	spironolactone
	eplerenone
Loop diuretics	bumetanide
	ethacrynic acid
	furosemide
	torsemide
Potassium-sparing diuretics	amiloride
	triamterene
Thiazide and thiazide-like diuretics	bendroflumethiazide
	chlorothiazide
	chlorthalidone
	hydrochlorothiazide
	indapamide
	metolazone

*Excludes sacubitril/valsartan products.
†Excludes ophthalmologic products.
‡Excludes nifedipine rectal ointment products.

Table S2. Measurement criteria for baseline characteristics. Variable names are characterized as "TABLE.VARIABLE_NAME" according to the PCORnet Common Data Model (version 6.0 at the time of this study).

Variable	Definition
Age	Age calculated on the index date based on date of birth in DEMOGRAPHIC.BIRTH_DATE.
Sex	As per DEMOGRAPHIC.SEX
Race-ethnicity	As per DEMOGRAPHIC.RACE and DEMOGRAPHIC.HISPANIC
Current Smoking	Any of the following within one year prior to the index date (including the index date): (a) Most recent VITAL.SMOKING in 01, 02, 07, or 08 (b) ICD-9 codes: a. ≥1 hospitalization with a discharge diagnosis code (any position) of tobacco use of 305.1, 649.0x, 989.84, or V15.82 in any discharge position b. ≥1 physician evaluation and management visit with a discharge diagnosis code (any position) of tobacco use of 305.1, 649.0x, 989.84, or V15.82 in any discharge position (c) ICD-10 codes: a. ≥1 hospitalization with a discharge diagnosis code (any position) of tobacco use of F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, or Z87.891 in any discharge position b. ≥1 outpatient visit with a discharge diagnosis code (any position) of tobacco of F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, or Z87.891 in any discharge position (d) ≥1 visit with an evaluation and management code and evidence of tobacco use, identified via CPT code (any position) of 99406, 99407, G0436, G0437, G9016, S9453, S4995, G9276, G9458, 1034F, 4004F, or 4001F (e) ≥1 pharmacy prescription or fill for nicotine or varenicline in the 365 days before the index date (including the index date).
Insurance type	As per ENCOUNTER.PAYER_TYPE_PRIMARY on index encounter (if specified). Categorized as Medicare, Medicaid, Other Government, Commercial Insurance and Managed Care, Self-pay or charity care, Other, or Unknown.
Diabetes	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 250.xx, 357.2, 362.0x, or 366.41. b. At least 2 outpatient claims with diagnosis code (any position) of 250.xx, 357.2, 362.0x, or 366.41, with the 2 claims occurring ≥7 days apart. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of E0836, E08.42, E09.36, E09.42, E10.10, E10.11, E10.29, E10.311, E10.319, E10.36, E10.39, E10.40, E10.42, E10.51, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.29, E11.311, E11.319, E11.329, E11.339, E11.349, E11.359, E11.36, E11.39, E11.40, E11.42, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.10, E13.36, or E13.42. b. ≥2 outpatient claims with diagnosis code (any position) of E0836, E08.42, E09.36, E09.42, E10.10, E10.11, E10.29, E10.311, E10.319, E10.36, E10.39, E10.40, E10.42, E10.51, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.29, E11.311, E11.319, E11.329, E11.339, E11.349, E11.359, E11.36, E11.39, E11.40, E11.42, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.10, E13.36, or E13.42, with the 2 claims occurring ≥7 days apart. (c) ≥1 prescription or fill for an oral or injectable antidiabetic drug in the one-year pre-index period. (d) Positive indication of T2DM via the PCORnet-validated T2DM phenotype
Chronic kidney disease	Any of the following using all available diagnoses prior to the index date (including the index date): (a) ICD-9 codes:

	a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 585.5, 585.1, 582.9, 582.81, 582.2, 585.9, 581, 404.9, 403.9, 403.1, 249.41, 637.32, 637.31, 580, 442.1, 404.1, 250.43, 249.4, 581.3, 404.12, 404, 403, 250.42, 582.89, 582.4, 582, 581.1, 404.02, 403.11, 250.4, 639.3, 585.2, 585, 580.81, 586, 581.9, 581.81, 403.91, 585.6, 585.3, 582.1, 580.8, 403.01, 582.8, 580.89, 404.93, 250.41, 637.3, 404.92, 585.4, 581.89, 581.8, 580.9, 404.13, 581.2, 404.91, 404.11, 404.03, or 404.01. b. At least 2 outpatient claims with diagnosis code (any position) of 585.5, 585.1, 582.9, 582.81, 582.2, 585.9, 581, 404.9, 403.9, 403.1, 249.41, 637.32, 637.31, 580, 442.1, 404.1, 250.43, 249.4, 581.3, 404.12, 404, 403, 250.42, 582.89, 582.4, 582, 581.1, 404.02, 403.11, 250.4, 639.3, 585.2, 585, 580.81, 586, 581.9, 581.81, 403.91, 585.6, 585.3, 582.1, 580.8, 403.01, 582.8, 580.89, 404.93, 250.41, 637.3, 404.92, 585.4, 581.89, 581.8, 580.9, 404.13, 581.2, 404.91, 404.11, 404.03, or 404.01, with the 2 claims occurring ≥7 days apart. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of E11.29, N26.2, E10.29, I13.11, E11.22, E11.21, O10.311, O10.213, O10.33, O10.312, E09.29, O10.211, M32.14, E13.22, E09.22, O10.32, O10.313, E13.29, E10.21, E09.21, E08.22, Q87.81, O10.212, N18.6, E10.22, I13.10, E13.21, O10.319, O10.23, O10.22, O10.219, E08.21, P96.0, N99.0, N19, N18.9, N18.5, N18.4, N18.3, N18.2, N18.1, N07.7, N07.5, N07.4, N07.3, N07.2, N05.9, N05.8, N05.7, N05.6, N05.5, N05.4, N05.3, N05.2, N05.1, N05.0, N04.9, N04.8, N04.7, N04.6, N04.5, N04.4, N04.3, N04.2, N04.1, N04.0, N03.9, N03.8, N03.7, N03.6, N03.5, N03.4, N03.3, N03.2, N03.1, N03.0, N02.7, N02.6, N02.4, N00.7, I72.2, I13.2, I13.0, I12.9, I12.0, O10.31, O10.3, O10.21, O10.2, N18, N05, N04, N03, I13.1, I13, I12, E13.2, E11.2, E10.2, or E09.2. b. ≥1 outpatient claim with a diagnosis code (any position) of E11.29, N26.2, E10.29, I13.11, E11.22, E11.21, O10.311, O10.213, O10.33, O10.312, E09.29, O10.211, M32.14, E13.22, E09.22, O10.32, O10.313, E13.29, E10.21, E09.21, E08.22, Q87.81, O10.212, N18.6, E10.22, I13.10, E13.21, O10.319, O10.23, O10.22, O10.219, E08.21, P96.0, N99.0, N19, N18.9, N18.5, N18.4, N18.3, N18.2, N18.1, N07.7, N07.5, N07.4, N07.3, N07.2, N05.9, N05.8, N05.7, N05.6, N05.5, N05.4, N05.3, N05.2, N05.1, N05.0, N04.9, N04.8, N04.7, N04.6, N04.5, N04.4, N04.3, N04.2, N04.1, N04.0, N03.9, N03.8, N03.7, N03.6, N03.5, N03.4, N03.3, N03.2, N03.1, N03.0, N02.7, N02.6, N02.4, N00.7, I72.2, I13.2, I13.0, I12.9, I12.0, O10.31, O10.3, O10.21, O10.2, N18, N05, N04, N03, I13.1, I13, I12, E13.2, E11.2, E10.2, or E09.2, with the 2 claims occurring ≥7 days apart. (c) Estimated glomerular filtration rate of <60 mL/min/1.73 m^2.The eGFR value used is as defined above for eGFR. (d) Positive indication of CKD via the eMERGE-validated phenotype
Heart failure with reduced ejection fraction	Any one of the following using all available claims before the index date: (a) ICD-9 codes: a. ≥1 inpatient claim with discharge diagnosis code (any position) of 428.0x, 428.1x, 428.2x, or 428.4x. b. ≥2 outpatient claims on separate calendar days with diagnosis code (any position) of 428.0x, 428.1x, 428.2x, or 428.4x. (b) ICD-10 codes: a. ≥1 inpatient claim with discharge diagnosis code (any position) of I50.1, I50.2x, I50.4x, or I50.9. b. ≥2 outpatient claims on separate calendar days with diagnosis code (any position) of I50.1, I50.2x, I50.4x, or I50.9. (c) At least one prescription for sacubitril/valsartan in the 104 days prior to the index date.
History of CHD	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 encounter with a discharge diagnosis code (any position) of 410.xx-414.xx, V45.81, or V45.82. b. ≥2 outpatient encounter with diagnosis code (any position) of 410.xx-414.xx, V45.81, or V45.82. (b) ICD-10 codes: a. ≥1 inpatient encounter with a discharge diagnosis code (any position) of I20.0, I21.xx, I22.xx, I24.0, I24.8, I24.9, I25.10, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1, or Z98.61. b. ≥2 outpatient encounters with diagnosis codes of codes I20.0, I21.xx, I22.xx, I24.0, I24.8, I24.9, I25.10, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1, or Z98.61. Patients who met the definition of a prior coronary revascularization, as defined below, are also considered to have a history of CHD.

Prior coronary revascularization	Defined by ≥1 inpatient or outpatient procedure with a CPT code for coronary revascularization (33510-33519, 33521-33523, 33530, 33533-33536, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, or 92996), an ICD-9 procedure code (any position) of 00.66, 36.0, 36.01-36.19, or 36.2, or an ICD-10 procedure code starting with any of the following: 0210, 0211, 0212, 0213, 0270, 0271, 0272, 0273, 02C0, 02C1, 02C2, 02C3, or 3E07 using all available claims prior to the index date (including the index date). In addition to having 1 inpatient or outpatient procedure, patients are required to meet ≥1 of the following criteria: (a) Have no inpatient claims with a discharge diagnosis code for acute myocardial infarction (ICD-9 codes 410.x0 or 410.x1 or ICD-10 codes I21.xx or I22.xx) within 60 days prior to the procedure. (b) Have primary discharge diagnosis code for non-elective CHD-related hospitalization prior to the index date (including the index date): a. Arrhythmia: ICD-9 diagnosis code of 427.xx [except 427.5] or ICD-10 diagnosis code of I47.1, I47.2, I47.9, I48.91, I48.92, I49.01, I49.02, I49.1, I49.3, I49.40, I49.49, I49.5, I49.8, I49.9, R00.1. b. Cardiac arrest: ICD-9 diagnosis code of 427.5, or ICD-10 diagnosis code of I46.9. c. Heart failure: ICD-9 diagnosis code of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, or 428.x, or ICD-10 diagnosis code of I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, or I50.9. d. Unstable angina: ICD-9 diagnosis code of 411.xx or ICD-10 diagnosis code of I20.0, I24.0, I24.1, I24.8.
History of Stroke	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code in the primary or secondary position of 433.x1 or 434.x1. b. ≥1 outpatient claim with a diagnosis code (any position) of 433.x1 or 434.x1. (b) ICD-10 codes: a. ≥1 inpatient discharge diagnosis code in the primary or secondary position of I63.xx. b. ≥1 outpatient claim with diagnosis code (any position) of I63.xx. c. ≥1 inpatient ICD-10 procedure code of 03CH0ZZ, 03CH4ZZ, 03CJ0ZZ, 03CJ4ZZ, 03CK0ZZ, 03CK4ZZ, 03CL0ZZ, 03CL4ZZ, 03CM0ZZ, 03CM4ZZ, 03CN0ZZ, 03CN4ZZ, 03RH07Z, 03RH0JZ, 03RH0KZ, 03RH47Z, 03RH4JZ, 03RH4KZ, 03RJ07Z, 03RJ0JZ, 03RJ0KZ, 03RJ47Z, 03RJ4JZ, 03RJ4KZ,03RK07Z, 03RK0JZ, 03RK0KZ, 03RK47Z, 03RK4JZ, 03RK4KZ, 03RL07Z, 03RL0JZ, 03RL0KZ, 03RL47Z, 03RL4JZ, 03RL4KZ, 03RM07Z, 03RM0JZ, 03RM0KZ, 03RM47Z, 03RM4JZ, 03RM4KZ, 03RN07Z, 03RN0JZ, 03RN0KZ, 03RN47Z, 03RN4JZ, or 03RN4KZ. (c) CPT codes: ≥1 inpatient or outpatient claim with a CPT code for carotid revascularization of 35301, 35390, 37215, 37216, 0005T, 0075T, or 0076.
History of PAD	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 440.20-440.24, 440.31, 444.2, 443.9, or 444.81. b. ≥2 physician evaluation and management or outpatient claims with diagnosis code (any position) of 440.20-440.24, 440.31, 444.2, 443.9, or 444.81 on separate days. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of I70.209, I70.219, I70.229, I70.25, I70.269, I70.499, I73.9. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of I70.209, I70.219, I70.229, I70.25, I70.269, I70.499, I73.9 on separate days. (c) CPT codes: ≥1 inpatient or outpatient claim with a CPT code of 37205 or 75962.
History of ASCVD	Defined by a history of CHD, cerebrovascular disease, or peripheral artery disease, as defined above.
End-stage renal disease	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 585.5. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of 585.5.

	(b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of N18.6. a. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of N18.6.
History of kidney transplant	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of V42.0. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of V42.0. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of Z94.0. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of Z94.0.
Atrial fibrillation	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 427.31. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of 427.31. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of I48.0, I48.2, I48.91. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of I48.0, I48.2, I48.91.
Chronic obstructive pulmonary disease	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 491.x or 492.x or 496.x. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of 491.x or 492.x or 496.x. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of J41.x, J42.x, J43.x, or J44.x. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of J41.x, J42.x, J43.x, or J44.x.
Asthma	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 493.x. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of 493.x. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of J45.x. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of J45.x.
History of depression	Any of the following using all available claims prior to the index date (including the index date): (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of 296.2, 296.3, 296.5, 300.4, 309.x, or 311. b. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of 296.2, 296.3, 296.5, 300.4, 309.x, or 311. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code (any position) of F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, or F43.2. c. ≥2 physician evaluation and management or outpatient claims with a diagnosis code (any position) of F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, or F43.2.
Charlson Comorbidity Score	Continuous variable to represent chronic disease burden. Calculated according to Elixhauser method using publicly available MINI-SENTINEL software.

Aspirin Use	At least 1 dispensing record with a DISPENSING.NDC value representing a product containing aspirin (including combination products). The list of NDC values reflecting aspirin-containing products is derived from the National Library of Medicine's RxNorm medical terminology (https://www.nlm.nih.gov/research/umls/rxnorm/index.html) and can be viewed here: https://github.com/ssmithm/rxnorm-drug-lists
Statin Use	At least 1 dispensing record with a DISPENSING.NDC value representing a product containing any statin (including combination products). The list of NDC values reflecting statin-containing products is derived from the National Library of Medicine's RxNorm medical terminology (https://www.nlm.nih.gov/research/umls/rxnorm/index.html) and can be viewed here: https://github.com/ssmithm/rxnorm-drug-lists

Table S3. Number of antihypertensives initially started, stratified by insurance.

No. of Antihypertensives	**Pooled Medicaid and Medicare** (N=143,054)	**Medicaid-Insured** (n=71,774)	**Medicare-Insured** (N=71,280)
Crude Prevalence			
1	75.4%	78.6%	72.2%
2	18.8%	16.9%	20.6%
3+	5.8%	4.5%	7.2%
Age-Adjusted Prevalence			
1	81.4%	82.1%	83.4%
2	15.0%	14.6%	13.0%
3+	3.6%	3.3%	3.6%

Age-adjusted (direct method) to 2000 U.S. Census population (single ages to 84 and 85+ years).

Table S4. Class combinations and frequencies for patients initiating dual antihypertensive therapy.

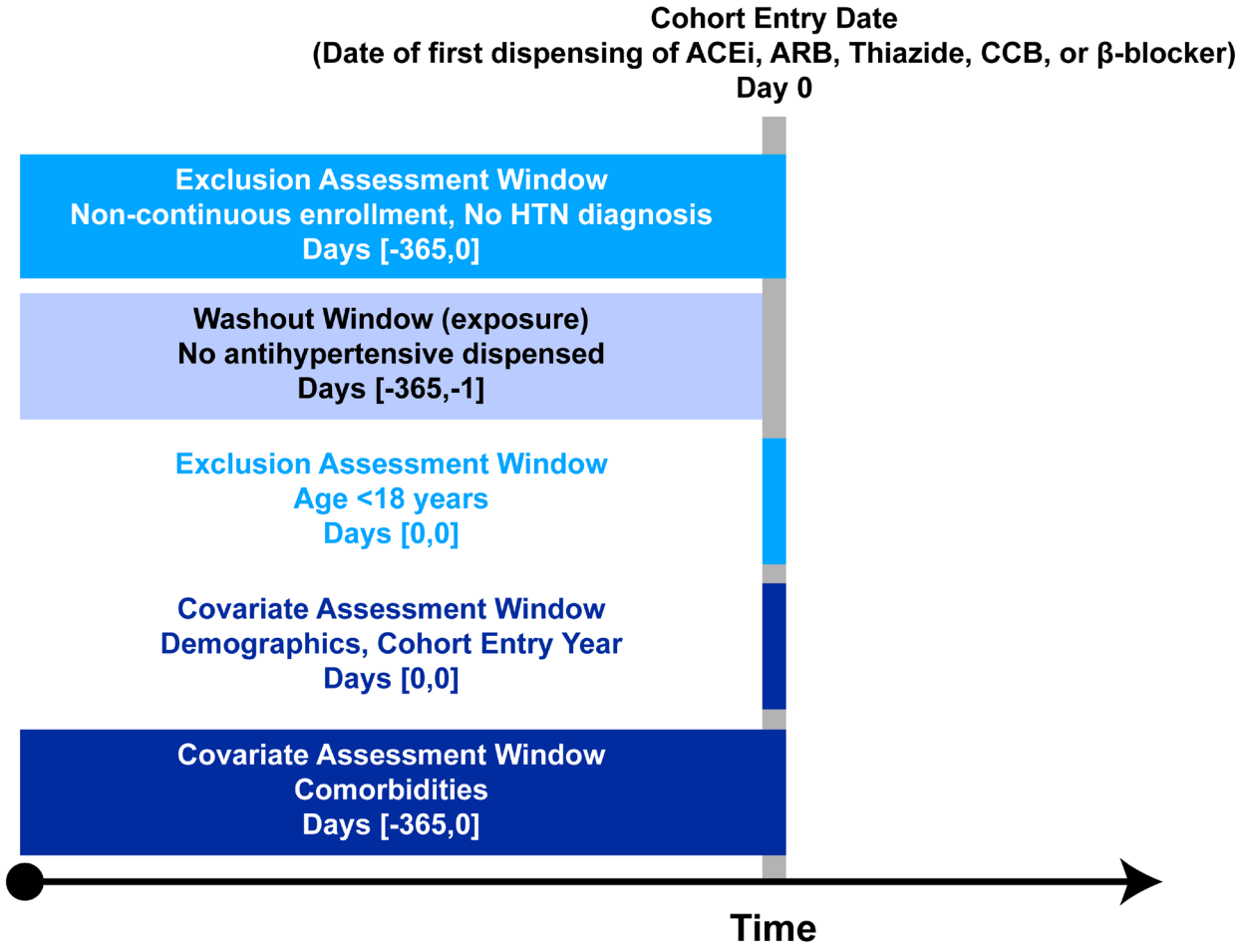
Class Combination	Combined Cohort (n = 26,840)	Medicaid (n = 12,152)	Medicare (n = 14,688)
ACEI + Thiazide	6,419 (23.9%)	3,720 (30.6%)	2,699 (18.4%)
ACEI + β-blocker	3,820 (14.2%)	1,534 (12.6%)	2,286 (15.6%)
ARB + Thiazide	2,893 (10.8%)	1,230 (10.1%)	1,663 (11.3%)
ACEI + CCB	2,792 (10.4%)	1,271 (10.5%)	1,521 (10.4%)
β-blocker + CCB	2,052 (7.6%)	869 (7.2%)	1,183 (8.1%)
β-blocker + Thiazide	1,100 (4.1%)	526 (4.3%)	574 (3.9%)
Thiazide + K-sparing diuretic	1,031 (3.8%)	390 (3.2%)	641 (4.4%)
CCB + Thiazide	1,001 (3.7%)	626 (5.2%)	375 (2.6%)
β-blocker + Loop diuretic	975 (3.6%)	278 (2.3%)	697 (4.7%)
ARB + CCB	878 (3.3%)	300 (2.5%)	578 (3.9%)
ARB + β-blocker	866 (3.2%)	277 (2.3%)	589 (4.0%)
ACEI + Loop diuretic	524 (2.0%)	157 (1.3%)	367 (2.5%)
CCB + α_2 agonist	204 (0.8%)	109 (0.9%)	95 (0.6%)
β-blocker + α_2 agonist	202 (0.8%)	96 (0.8%)	106 (0.7%)
β-blocker + Vasodilator	206 (0.8%)	76 (0.6%)	130 (0.9%)
ACEI + α_2 agonist	193 (0.7%)	102 (0.8%)	91 (0.6%)
CCB + Vasodilator	153 (0.6%)	76 (0.6%)	77 (0.5%)
Other combinations	1,531 (5.7%)	515 (4.2%)	1,016 (6.9%)

Table S5. Stratified analyses with standardized mean differences, by demographic and comorbidity categories.

	Sex			Race				Ethnicity			T2DM			CKD			ASCVD		
Class	Women	Men	SMD	Asian	Black	White	SMD	Hispanic	Non-Hispanic	SMD	T2DM	no T2DM	SMD	CKD	no CKD	SMD	ASCVD	no ASCVD	SMD
Medicaid, n	43,011	28,760		659	22,041	25,304		13,016	44,696		13,802	57,972		5,111	66,663		4,229	67,545	
ACEI	37.3%	47.2%	0.20	41.1%	33.7%	44.3%	0.15	46.2%	39.1%	0.14	50.6%	39.1%	0.23	34.7%	41.8%	0.15	39.7%	41.4%	0.03
ARB	9.1%	9.5%	0.01	14.4%	7.8%	8%	0.14	12.6%	7.6%	0.16	9.9%	9.1%	0.03	8.4%	9.3%	0.03	8.7%	9.3%	0.02
CCB	22.7%	25.4%	0.06	22.0%	34.0%	17.7%	0.25	15.9%	25.9%	0.25	17.4%	25.3%	0.19	32.4%	23.1%	0.21	21.2%	23.9%	0.07
BB	26.8%	25.2%	0.04	24.7%	22.7%	30.1%	0.11	23.5%	26.7%	0.07	34.7%	24.1%	0.23	34.6%	25.5%	0.2	52.4%	24.5%	0.6
Thiazide	23.5%	16.9%	0.17	17.5%	26.9%	16.8%	0.16	19.4%	21.8%	0.06	13.2%	22.7%	0.25	14.8%	21.3%	0.17	9.3%	21.6%	0.34
Medicare, n	38,544	32,733		788	11,773	44,852		9,664	54,787		15,831	55,449		12,515	58,765		13,187	58,093	
ACEI	34.2%	39.6%	0.11	38.1%	36.7%	35.8%	0.03	39.4%	36%	0.07	43.3%	34.8%	0.17	28.3%	38.5%	0.22	31.9%	37.8%	0.12
ARB	14.6%	11.8%	0.08	16.9%	11.7%	13.1%	0.10	17.2%	12.5%	0.13	13.7%	13.2%	0.01	13.3%	13.3%	<0.01	11.8%	13.7%	0.06
CCB	24%	24.5%	0.01	27%	34.4%	22.4%	0.18	19.7%	25.2%	0.13	20.2%	25.4%	0.12	31%	22.8%	0.18	24.1%	24.3%	<0.01
BB	34.5%	37.5%	0.06	31.7%	31.1%	38.3%	0.10	32.9%	36.9%	0.08	39.4%	34.9%	0.09	44.7%	34%	0.22	48.7%	33%	0.32
Thiazide	18.8%	14.7%	0.11	13.7%	23.5%	15.2%	0.17	16.4%	17%	0.02	13%	18.1%	0.14	11.5%	18.1%	0.19	9.6%	18.6%	0.26

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BB, β-blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; SMD, standardized mean difference; T2DM, type 2 diabetes mellitus.

Figure S1. Study design schematic for building the new antihypertensive user cohort.



A 1-year look-back period was required for all patients, thus the earliest possible enrollment date was December 31, 2012 (for patients with continuous enrollment for all of 2012), using all of 2012 as the look-back period, and the latest possible enrollment date was December 31, 2017 (for Medicare) or September 30, 2021 (for Medicaid).

Figure S2. Flow diagram for cohort development.

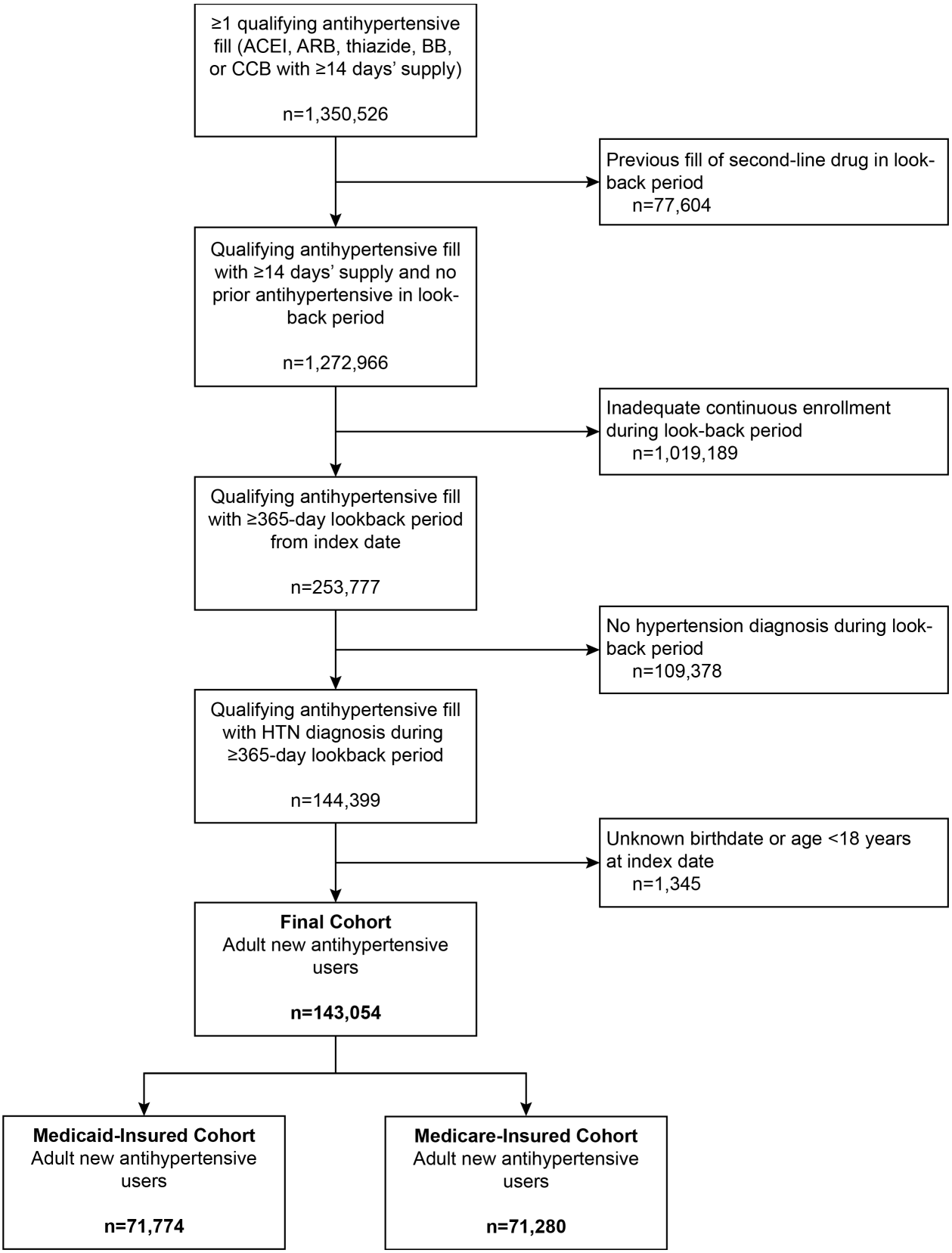


Figure S3. Antihypertensive use among Medicaid-insured patients initiating monotherapy only.

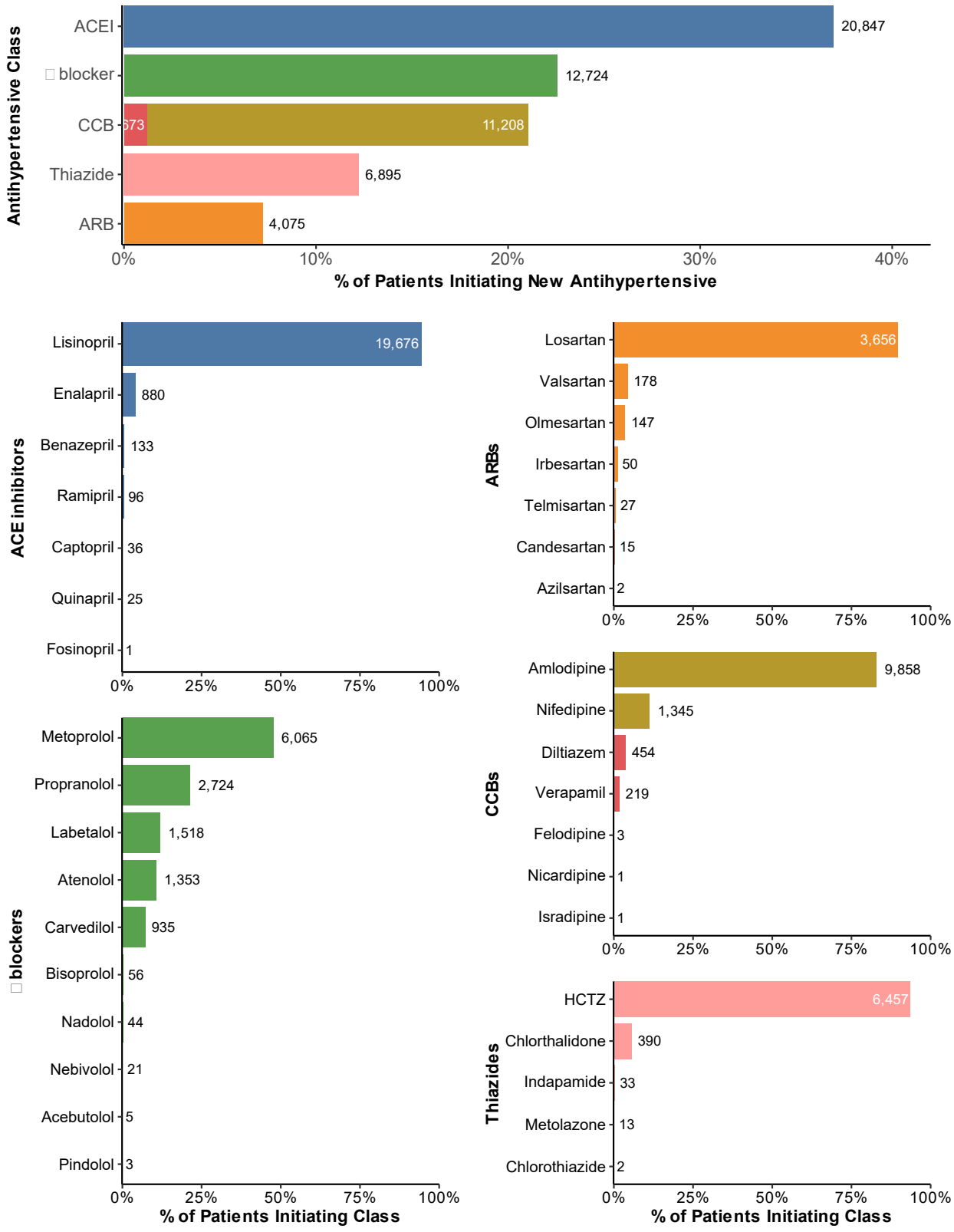


Figure S4. Antihypertensive use among Medicare-insured patients initiating monotherapy only.

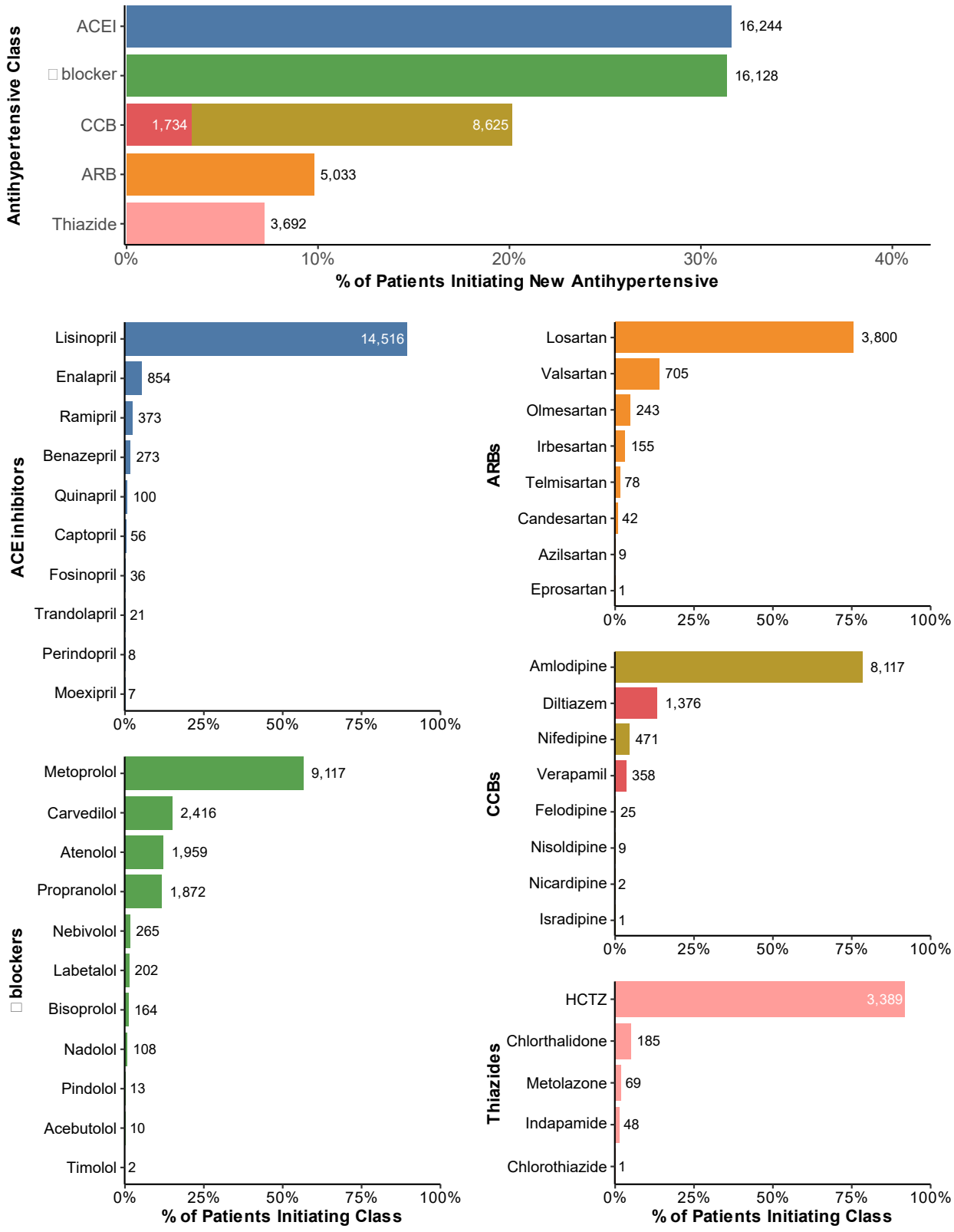
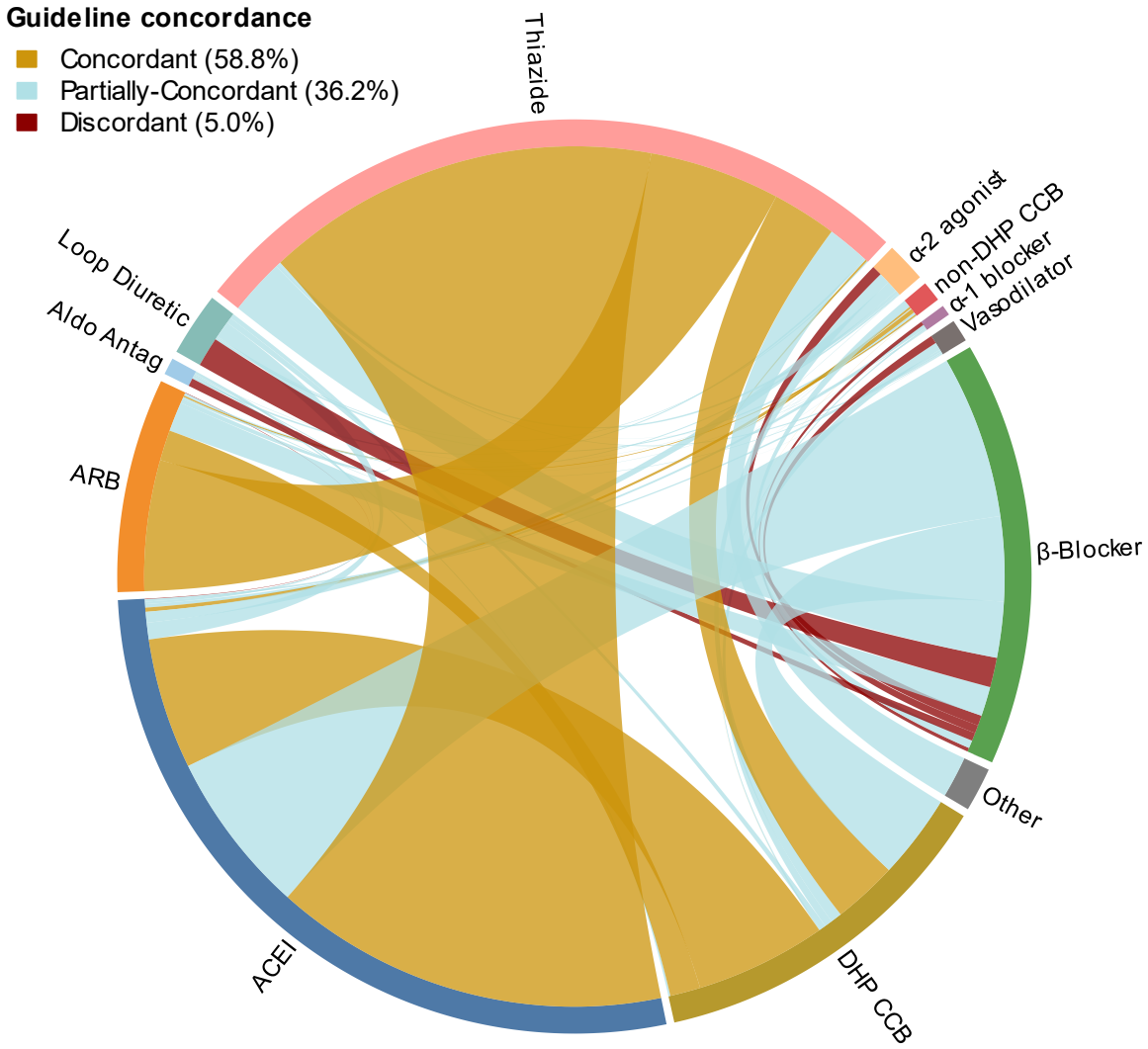
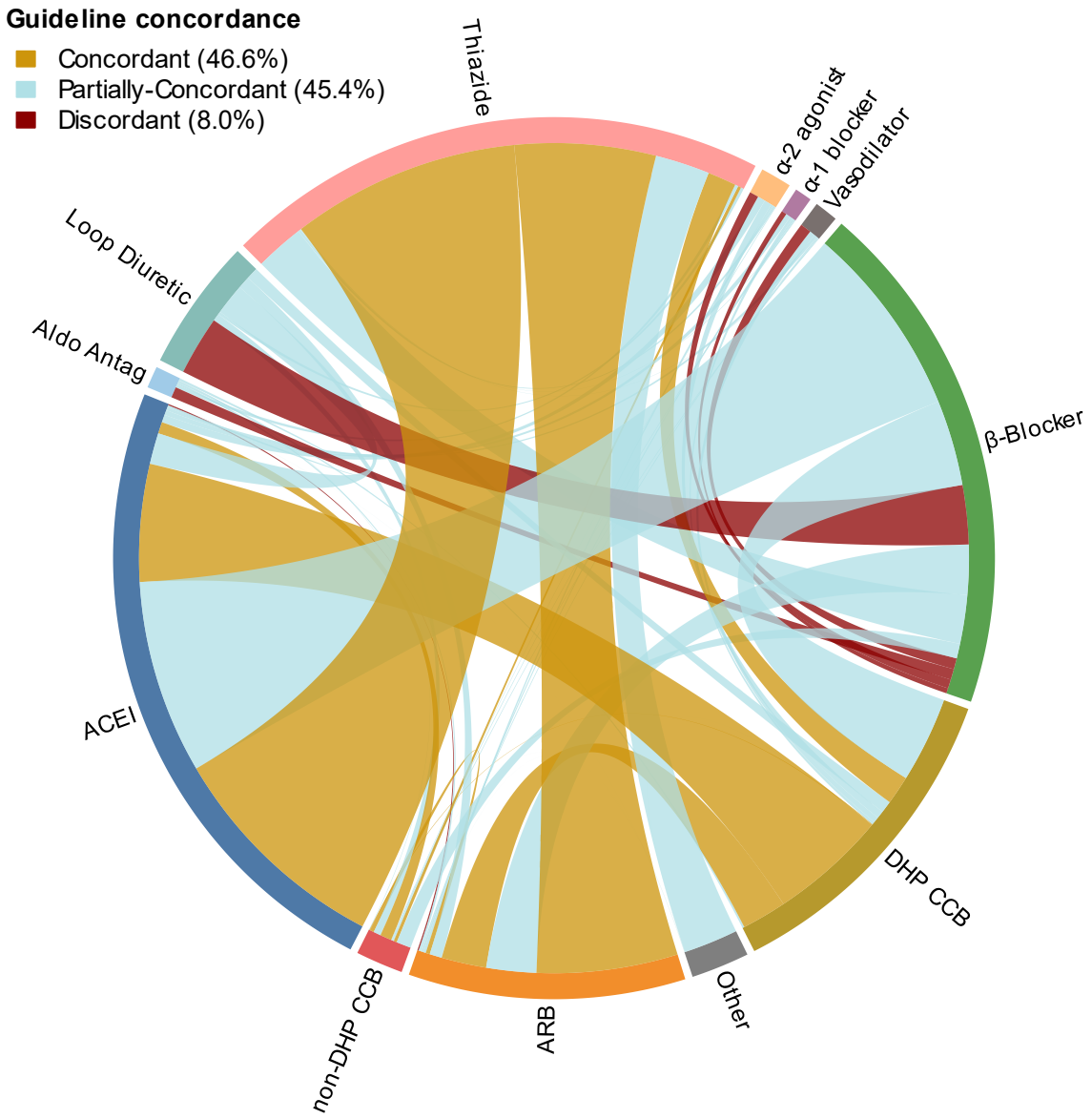


Figure S5. Dual combination therapy initiation and concordance with current U.S. hypertension guidelines, among Medicaid-insured patients.



The plot summarizes combination therapy for all Medicaid patients initiating exactly 2 antihypertensives (n = 13,352). Patients initiating triamterene as part of a fixed dose combination (n=414 [3.1%]) as well as those initiating two distinct drugs within the same class (n=47 [0.4%]) are not shown. Guideline concordance was defined as “concordant” (initiated two first-line classes [ACEI, ARB, CCB, or thiazide]), “partially concordant” (one first-line class combined with a non-first-line class), and “discordant” (no first-line class). Patients initiating an ACEI + ARB were considered “discordant.”

Figure S6. Dual combination therapy initiation and concordance with current U.S. hypertension guidelines, among Medicare-insured patients.



The plot summarizes combination therapy for all patients initiating exactly 2 antihypertensives (n = 16,471). Patients initiating triamterene as part of a fixed dose combination (n=683 [4.1%]) as well as those initiating two distinct drugs within the same class (n=60 [0.4%]) are not shown. Guideline concordance was defined as “concordant” (initiated two first-line classes [ACEI, ARB, DHP CCB, or thiazide]), “partially concordant” (one first-line class combined with a non-first-line class), and “discordant” (no first-line class). Patients initiating an ACEI + ARB were considered “discordant.”

Figure S7. Detailed view of time trends in initial use of second-line antihypertensive classes, stratified by cohort.

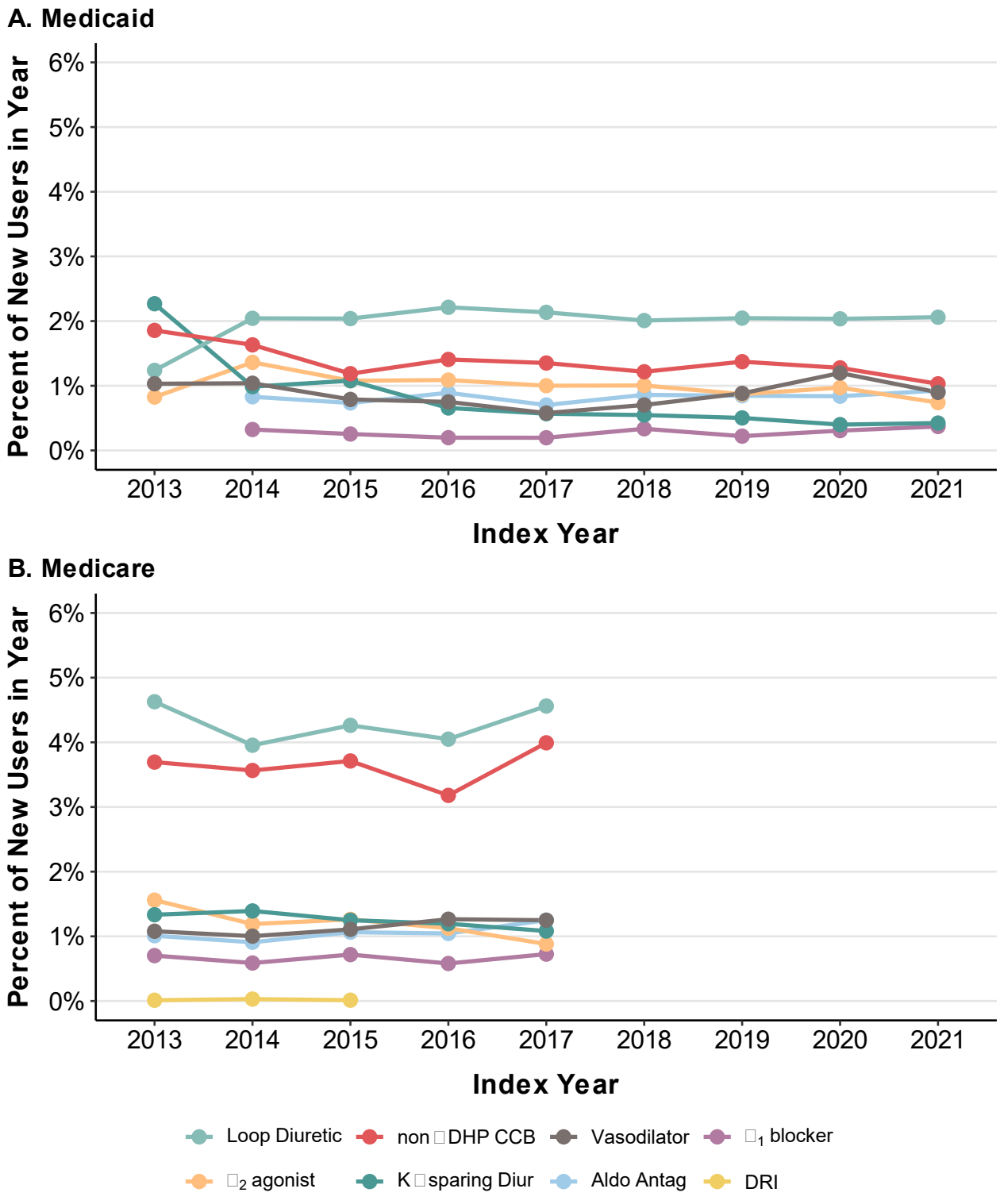
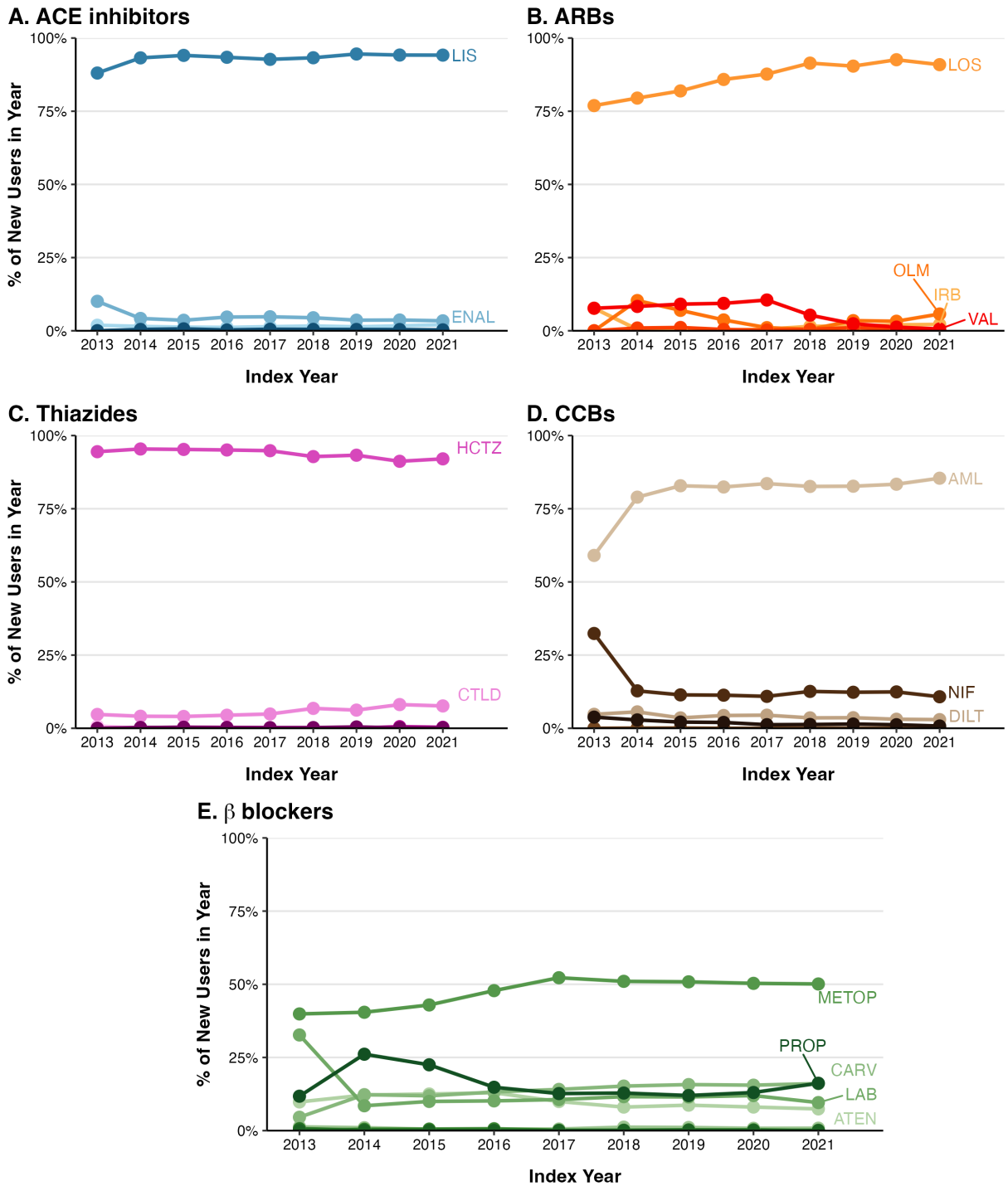
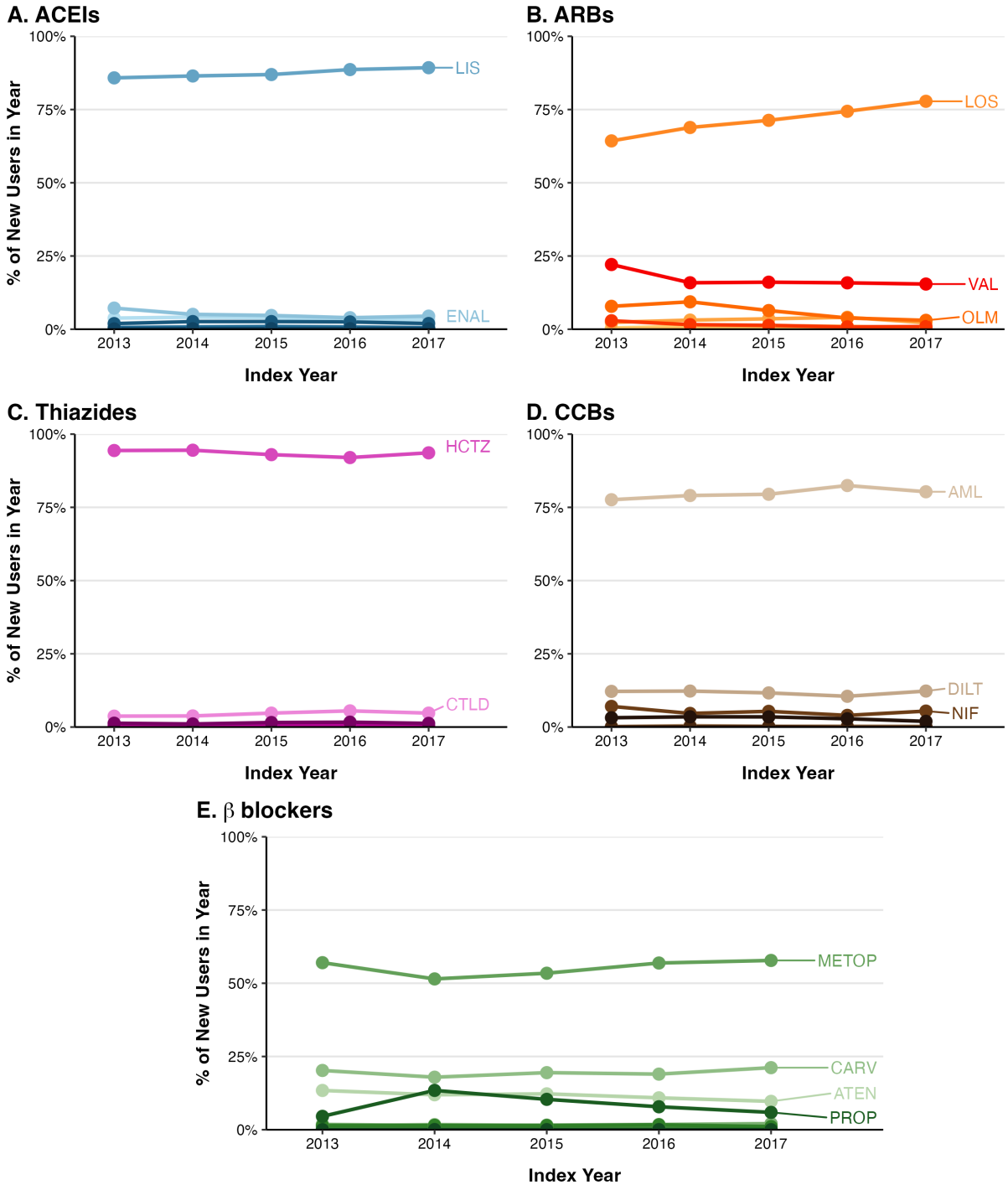


Figure S8. Time trends in initial use of individual antihypertensives within first-line classes, among Florida Medicaid-insured patients, 2013-2021.



Antihypertensives that never achieved ≥5% class share during the study period are unlabeled. AML, amlodipine; ATEN, atenolol; CARV, carvedilol; DILT, diltiazem; ENAL, enalapril; CTLD, chlorthalidone; HCTZ, hydrochlorothiazide; LAB, labetalol; LIS, lisinopril; LOS, losartan; MET, metoprolol; NIF, nifedipine; OLM, olmesartan; PROP, propranolol; VAL, valsartan.

Figure S9. Time trends in initial use of individual antihypertensives within first-line classes, among Medicare-insured patients, 2013-2017.



Antihypertensives that never achieved ≥5% class share during the study period are unlabeled. AML, amlodipine; ATEN, atenolol; CARV, carvedilol; DILT, diltiazem; ENAL, enalapril; CTLD, chlorthalidone; HCTZ, hydrochlorothiazide; LAB, labetalol; LIS, lisinopril; LOS, losartan; MET, metoprolol; NIF, nifedipine; OLM, olmesartan; PROP, propranolol; VAL, valsartan.

Figure S10. Initial antihypertensive utilization among Black patients starting monotherapy, overall and stratified by chronic kidney disease and heart failure status.