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Comparative effectiveness of antihypertensive drugs in nondiabetic patients with hypertension: A population-based study

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The authors compared the effectiveness of thiazide diuretic (TD), angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and calcium channel blocker (CCB) monotherapies for the treatment of nondiabetic hypertension using MarketScan Databases 2010–2014. Multivariable Cox regression models assessed whether the addition of a new antihypertensive drug, treatment discontinuation, or switch and major cardiovascular or cerebrovascular events varied across groups. A total of 565 009 patients started monotherapy with ACEIs (43.6%), CCBs (23.6%), TDs (18.8%), or ARBs (14.0%). Patients who took TDs had a higher risk for either drug addition or discontinuation than patients who took ACEIs (hazard ratio [HR], 0.69 [95% CI, 0.68–0.70] vs HR, 0.81 [95% CI, 0.80–0.81]), ARBs (HR, 0.67 [95% CI, 0.66–0.68] vs HR, 0.66 [95% CI, 0.65–0.67]), and CCBs (HR, 0.85 [95% CI, 0.84–0.87] vs HR, 0.94 [95% CI, 0.93–0.95]). Conversely, patients who took TDs experienced a lower risk of clinical events compared with patients who took ACEIs (HR, 1.24 [95% CI, 1.15–1.33]), ARBs (HR, 1.28 [95% CI, 1.18–1.39]), and CCBs (HR, 1.35 [95% CI, 1.25–1.46]). Our results provide a strong rationale for choosing TDs as first-line monotherapy for the control of hypertension.

1 | INTRODUCTION

The overall prevalence of hypertension in the United States is 38% in men and 40% in women.[1] Hypertension leads to major clinical, public health, and economic impacts attributable to its high prevalence and high risk for cardiovascular disease, such as coronary disease, stroke, peripheral artery disease, and heart failure.[2] Hypertension awareness and treatment have increased over the past 2 decades, leading to improvements in the proportion of patients with blood pressure (BP) control from 28% in 1999–2000 to 47% in 2009–2010 in the United States.[3]

As a result, direct costs for treating hypertension in the United States was $45 billion annually in 2011–2012 and 40% of this expense included prescription medication,[4] yet the appropriate treatment for hypertension is related to decreased mortality and morbidity associated with cardiovascular disease and, therefore, might be cost-effective.[5] According to the Eighth Joint National Committee (JNC 8), first-line therapy for hypertension in the general population should include thiazide diuretic (TD), calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) monotherapy.[6] TDs are cheaper than other antihypertensive classes and have great potential for cost-savings when used as first-line therapy in the treatment of hypertension.[7,8] Moreover, evidence from clinical trials, including a Cochrane review, has endorsed this class of drug as the preferred first-line treatment for hypertension.[9,10]

On the other hand, prescribing practices are not consistent with this evidence[11] and the debate as to which class of drugs should be the initial therapy needs to be further addressed. Comparative effectiveness research can inform about different interventions and strategies and enhance medical decision-making and improve health outcomes.[12] In this study, we compared the utilization patterns and effectiveness of the four drug classes recommended by JNC 8 with either TDs, ACEIs, ARBs, or CCBs given as monotherapy to adults with hypertension without diabetes mellitus in a large population-based cohort.

2 | METHODS

2.1 | Data source

We built a retrospective cohort using the Truven Health MarketScan Research Databases (2010–2014) that contain patient-level healthcare claims from employers, health plans, and hospitals in the United States. Americans with employer-provided health insurance have been included in a 230 million unique patient cohort since 1995. We used three databases: (1) the Commercial Plans and Encounters Database comprises comprehensive inpatient, outpatient, emergency department, pharmacy claims, enrollment, and eligibility information; (2) the Medicare Supplemental and Coordination of Benefits Database containing the same data elements as those appearing in the Commercial Database; and (3) the Health Risk Assessment Database with self-reported data on clinical variables.[13,14]

2.2 | Cohort

For cohort entry in this study, individuals were required to have at least one pharmacy claim for the medications under study (TDs, ACEIs, ARBs, or CCBs) between January 1, 2011, and September 30, 2014, and the cohort entry was defined as the date of the first claim for one of these drugs. Only patients on monotherapy with one of these drugs at cohort entry were included. Patients were eligible for the study if they were 18 years or older; had at least 12 continuous months of medical and pharmacy coverage prior to cohort entry; and had two physician outpatient billing claims or one hospital discharge with a primary or secondary diagnosis of hypertension (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 401.xx), 1 year before or 1 month after cohort entry.

We used a new-user design in which patients using any medication of interest 1 year before cohort entry were excluded. Patients were also excluded if they had a diagnosis of diabetes (*ICD-9* codes 250.xx). In addition, to eliminate patients with other indications for antihypertensive drugs, individuals were excluded if they had unstable angina (*ICD-9* codes 411.1x), congestive heart failure (*ICD-9* codes 428.X), atrial fibrillation (*ICD-9* codes 427.3x), or myocardial infarction (*ICD-9* codes 410.0-410.9) 1 year prior to the cohort entry. Finally, pregnant women (*ICD-9* code 650) with a diagnosis of hypertension or gestational hypertension (*ICD-9* code 642.xx) within 9 months before or 6 months after the pregnancy date were excluded.

2.3 | Outcomes

We evaluated drug use patterns and assessed, as a primary outcome, the addition of a new antihypertensive drug. Other outcomes were assessed separately, such as discontinuation of therapy and switching to a new antihypertensive drug. These events were considered to be evidence of suboptimal treatment (ineffectiveness or intolerance) with the initial drug. Adding a new drug was defined as a prescription for an antihypertensive drug from a different class without discontinuation of the index drug. The new drug must have been added on or before the end of the days supplied by the latest index drug prescription. An antihypertensive drug class was considered to be discontinued when no prescription from the same class was issued 90 days after the patient exhausted the supply provided in the most recent prescription. Switching was defined as a prescription of a drug in a different antihypertensive class after but within 90 days of the discontinuation date. Time to addition and time to switch were defined as the time from the cohort entry to the date of prescription of the new drug. Time to discontinuation was defined as the time from the cohort entry until the discontinuation date (the last prescription expired). Of note, not all such outcomes were mutually exclusive since switching could occur only after discontinuation (Figure 1).

We also assessed the occurrence of a clinical outcome that included cardiovascular and cerebrovascular fatal and nonfatal events that occurred between 90 days after cohort entry until the end of follow-up. We defined a composite measure of the first event among stroke (*ICD-9* codes 430, 431, 432.0x, 432.1x, 432.9x, 433.1x 434.90, 434.91, 435, and 436), acute myocardial infarction (*ICD-9* codes 410.0–410.9), congestive heart failure (*ICD-9* codes 428.X), and unstable angina (*ICD-9* codes 411.1x), and the events were also assessed separately. The time to event was defined as the time from cohort entry to the first of either physician outpatient billing claims or hospital discharges with a primary or secondary diagnosis related to one of the four events described above.[15] For all analyses, we looked for the first occurrence of the outcome.

2.4 | Exposure

We considered four groups of exposure based on the initial monotherapy (TDs, ACEIs, ARBs, or CCBs). Patients were followed from cohort entry until the earliest date of the outcome of interest (considered separately in the two sets of analyses), loss of medical and pharmacy coverage, death, or end of study data (December 31, 2014). Date of death was obtained from hospital discharge data. For clinical outcomes, patients were additionally censored when one of the four clinical events of interest occurred.

2.5 | Statistical analyses

Descriptive analyses compared baseline characteristics of patients using means, standard deviations, medians, and interquartile intervals for continuous variables and frequency distributions for categorical variables.

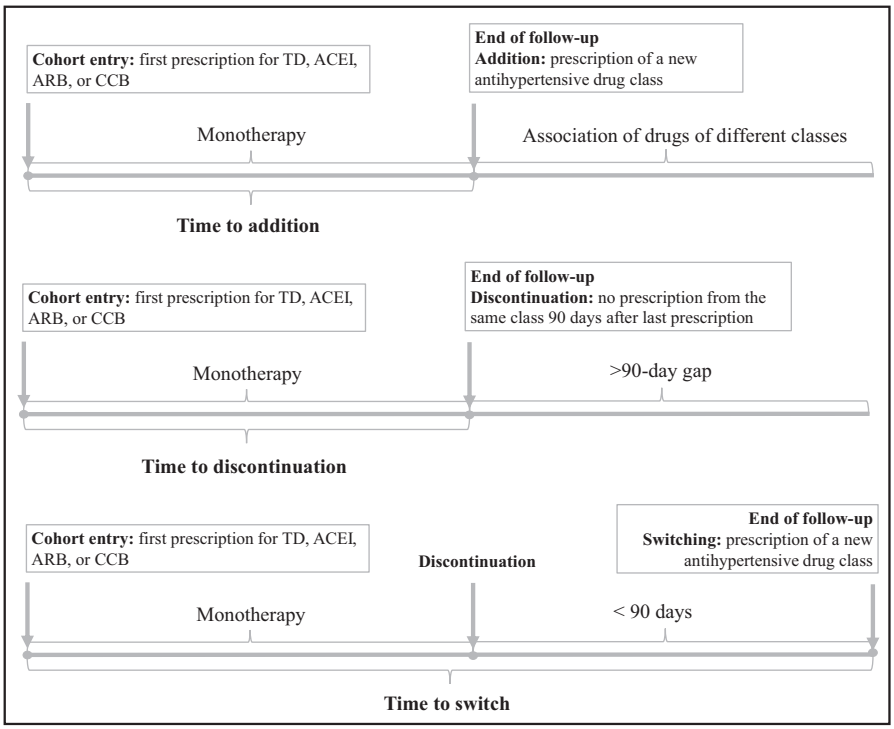

FIGURE 1 Outcomes definition: addition of a new antihypertensive drug, discontinuation of therapy, and switch to a new antihypertensive drug. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; TD, thiazide diuretic

We plotted drug-specific Kaplan-Meier curves for addition, discontinuation, switch, and composite clinical outcomes and compared them using the log-rank test. We also estimated the adjusted hazard ratios (HRs) and 95% confidence intervals (CI) using multivariable Cox proportional hazards models to assess, in separate analyses, the risks of: (1) addition, (2) discontinuation, (3) switching, and clinical outcomes, (4) separately for each event, and (5) using the composite clinical outcome. In all between-drugs comparisons, TD was used as the reference category. In the multivariable models, we adjusted the differences between the drug groups for baseline (cohort entry) potential confounders: age, sex, year of cohort entry, employment status (full-time vs other), and region of residence (rural vs urban). We also adjusted for potential confounders that were measured during the 1 year prior to cohort entry: diagnosis of cerebrovascular disease, dyslipidemia, Charlson comorbity index, and three indicators of health service use, assessed by the number of: (1) emergency department visits, (2) physician visits, and (3) hospitalizations. To test the proportional hazards assumption and, for continuous covariates, to test for their possibly nonlinear associations with the logarithm of the hazard, we used flexible spline-based extension of the Cox model of the composite clinical outcome.[16] To explore whether the comparisons of the effects of different drugs differed between women and men, we tested two-way sex-by-drug interactions. In the case of a significant interaction ($P<.05$ for the multivariable model–based Wald test), the corresponding analyses were repeated separately for men and women.

We performed five sensitivity analyses. First, available data for deaths were only registered in hospital data; thus, to ensure that patients were still alive during the follow-up, we performed a sensitivity analysis using the date of the last encounter with health service (pharmacy claim, medical visit, or hospitalization) as an additional criterion for censoring patients. Second, we considered only patients who had at least two pharmacy claims. In a third analysis, the clinical outcomes were defined when a cardiovascular and cerebrovascular event occurred at any time after cohort entry. The last two sensitivity analyses were performed with a cohort of patients who had at least one measurement of BP within 6 months prior or up to 7 days after cohort entry, and we additionally adjusted the models for systolic BP and body mass index (both variables were not available for the entire cohort). One analysis was performed using the same approach applied in the main analysis and the other in which we assessed drug exposure in a time-dependent manner, so that each patient's follow-up time was divided into consecutive time intervals, with a new interval starting whenever the antihypertensive therapy changed. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

3 | RESULTS

A total of 565 099 patients with hypertension who filled at least one prescription for any of the medications of interest and met our cohort entry criteria were included in the study (Figure 2). The most frequent initial monotherapy involved ACEIs (43.6%) followed by CCBs (23.6%), TDs (18.8%), and ARBs (14.0%). The list of the most frequent drugs included within each of the classes is presented in Table S1. The overall median age was 55 years (interquartile interval, 46–63 years) and half of the patients were women (51.7%). Baseline clinical characteristics were similar across groups, with the exception that TD initiators had a lower frequency of dyslipidemia and CCB initiators

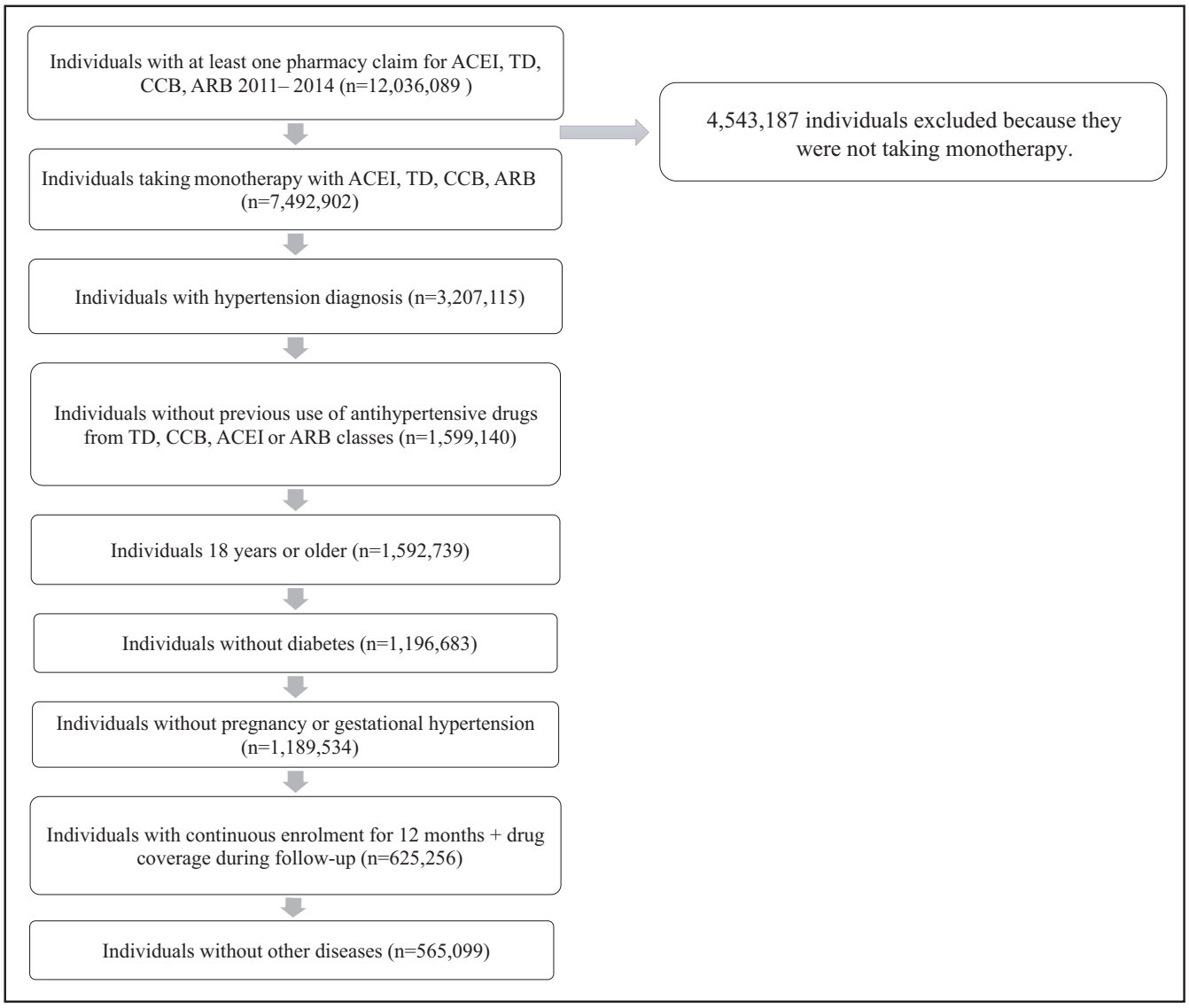

FIGURE 2 Flow diagram of included patients in the cohort. From individuals excluded because they were not taking monotherapy, 3 816 044 (84%) were using combination of two drugs and the most frequent combinations were thiazide diuretics (TDs)/angiotensin-converting enzyme inhibitors (ACEIs) (26%), TDs/angiotensin receptor blockers (ARBs) (20%), ACEIs/calcium channel blockers (CCBs) (10%), ACEIs/β-blockers (BBs) (8%), and TDs/BBs (6%)

had a higher frequency of acute renal disease, cerebrovascular diseases, and kidney disease (Table 1).

3.1 | Addition of a new drug

More TD initiators added a new antihypertensive drug compared with ACEI, ARB, and CCB initiators. The median time to adding a new drug was 90 days (interquartile interval, 30–269) for TD initiators, which was shorter than the other groups (Table 2). This trend was confirmed in Kaplan-Meier curves (*P*<.0001 for log-rank test, Figure 3) and in adjusted Cox models (ACEI initiators: HR, 0.69 [95% CI, 0.68–0.70]; ARB initiators: HR, 0.67 [95% CI, 0.66–0.68]; CCB initiators: HR, 0.85 [95% CI, 0.84–0.87] compared with TD initiators) (Figure 4). There were significant interactions by sex for this outcome. TD initiators of both sexes had higher risk of a new drug addition compared with the other drug groups; however, the risks among women and men differed as the HRs for women were closer to the null value 1.0 (*P* for interaction <.0001, Figure 4).

3.2 | Discontinuation

Risk of treatment discontinuation was higher among patients starting with TDs compared with CCBs, ACEIs, and ARBs (*P*<.0001 for log-rank test; Table 2, Figure 3). After adjustment for covariates, patients who started therapy with ACEIs (HR, 0.81; 95% CI, 0.80–0.81), ARBs (HR, 0.66; 95% CI, 0.65–0.67), CCBs (HR, 0.94; 95% CI, 0.93–0.95) were significantly less likely to discontinue their initial therapy than those who started with TD initiators (Figure 4). Among women, the risk of discontinuation was similar for CCB and TD initiators (HR, 0.99; 95% CI, 0.97–1.01) but men were significantly less likely to discontinue the CCB treatment than to

TABLE 1 Baseline characteristics of patients with hypertension included in the study

	All patients (N=565 099)	TD (n=106 409)	ACEI (n=246 282)	ARB (n=79 081)	CCB (n=133 327)
Women, No.	51.7	64.2	45.1	50.1	55.0
Age, median (IQI), y	55 (46–63)	53 (44–61)	54 (46–62)	56 (47–63)	57 (47–65)
Year of cohort entry					
2011	35.2	37.2	34.9	34.1	34.9
2012	30.8	30.4	30.9	31.5	30.4
2013	20.9	20.4	20.8	21.7	21.2
2014	13.1	12.0	13.4	12.7	13.5
Urban residency	81.9	81.7	79.9	85.0	83.9
Full-time employment	39.8	42.8	40.2	40.6	36.4
Charlson comorbidity index, mean (SD)[a]	0.31 (0.72)	0.25 (0.63)	0.28 (0.68)	0.30 (0.67)	0.44 (0.85)
Comorbidities[a]					
Acute renal disease	1.1	0.5	0.7	0.7	2.7
Cerebrovascular diseases	6.4	4.2	6.2	5.8	8.9
Chronic obstructive pulmonary disease	11.8	11.0	10.3	12.0	15.2
Dyslipidemia	41.3	36.1	42.4	46.2	40.6
Moderate or severe kidney disease	2.3	1.2	1.8	2.4	4.1
No. of emergency department visits, mean (SD)[a]	0.49 (1.18)	0.48 (1.15)	0.44 (1.02)	0.38 (0.89)	0.65 (1.56)
No. of physician visits, mean (SD)[a]	10.09 (11.38)	9.39 (10.42)	9.09 (10.30)	10.42 (10.87)	12.28 (13.74)
No. of hospitalizations, mean (SD)[a]	0.16 (0.49)	0.11 (0.41)	0.13 (0.45)	0.11 (0.39)	0.27 (0.66)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQI, interquartile interval; TD, thiazide diuretic. SD, standard deviation.

[a]Based on outpatient and/or inpatient claims within 1 year prior to index date.

discontinue TD treatment (HR, 0.87; 95% CI, 0.85–0.88 [*P* for interaction <.0001]) (Figure 4). In contrast, among the users of the two other drugs, for both women and men, the time to discontinuation was significantly longer than among the TD users (*P* for interaction <.0001, Figure 4).

3.3 | Switching to a new drug

Among patients who discontinued therapy, TD initiators were more likely to switch to another drug compared with those initiated on ACEIs (HR, 0.80; 95% CI, 0.78–0.83) and ARBs (HR, 0.75, 95% CI, 0.72–0.78) (Figure 4).

3.4 | Cardiovascular outcomes

During a mean follow-up of 273 days while on monotherapy with any of the four drug groups, 9024 cardiovascular or cerebrovascular events were observed. The incidence rates for the composite outcome of cardiovascular and cerebrovascular events were 1.7, 2.5, 2.7, and 3.7 per 100 person-years for users of TDs, ACEIs, ARBs, and CCBs, respectively (Table 2). Results from the Kaplan-Meier curves confirm this trend (*P*<.0001 for log-rank test, Figure 3). The composite outcome was driven mostly by stroke, with incidence rates of 1.1, 1.6, 1.9, and 2.3 per 100 person-years for TDs, ACEIs, ARBs, and CCBs, respectively (Table 2). After adjusting for potential confounders, monotherapy with ACEIs (HR, 1.24; 95% CI, 1.15–1.33), ARBs (HR, 1.28; 95% CI, 1.18–1.39), or CCBs (HR, 1.35; 95% CI, 1.25–1.46) was associated with significantly higher risks of cardiovascular or cerebrovascular events compared with TD monotherapy. The adjusted HR for stroke followed a similar trend in all comparisons as well as when comparing ACEIs or CCBs with TDs for the outcome of congestive heart failure; however, for other outcomes, there was no difference between agents (Figure 5). There were no significant interactions by sex for the composite clinical outcome and stroke. For the other less frequent clinical outcomes, the interactions with sex were also not statistically significant, possibly because of a low number of events and, thus, inadequate statistical power (data not shown).

The analyses based on the flexible model revealed that the proportional hazards assumption was rejected for ACEIs: the associated hazard increase was highest in the first few months of follow-up and then gradually decreased toward the null effect after about 1 year. No violations of the proportional hazards hypothesis were found for other drug classes, indicating that the corresponding HRs were stable across the follow-up interval.

3.5 | Sensitivity analyses

The results for Cox regression analysis did not change materially in all sensitivity analyses, with few exceptions. The analyses that included only patients with BP measures at baseline showed that the

TABLE 2 Number of events, incidence, and time to event for drug use outcomes and clinical outcomes

Outcomes	TD (n=106 409)	ACEI (n=246 282)	ARB (n=79 081)	CCB (n=133 327)
Addition				
No. of events	41 766	78 007	26 251	48 661
Incidence per 100 person-y	90.7	54.4	50.0	76.8
Time to event, median (IQI), d	90 (30–269)	110 (30–306)	152 (47–382)	115 (30–332)
Discontinuation				
No. of events	45 527	102 729	29 001	55 781
Incidence per 100 person-y	98.8	71.7	55.2	88.0
Time to event, median (IQI), d	66 (30–162)	90 (30–206)	90 (30–247)	54 (30–145)
Switch				
No. of events	6784	14 252	4532	8802
Incidence per 100 person-y	12.2	8.7	7.8	11.8
Time to event, median (IQI), d	120 (100–171)	120 (91–182)	142 (120–240)	120 (97–148)
Composite of clinical outcomes				
No. of events	940	3918	1539	2627
Incidence per 100 person-y	1.7	2.5	2.7	3.7
Time to event, median (IQI), d	215 (131–391)	233 (144–405)	251 (154–434)	222 (137–385)
Stroke				
No. of events	590	2599	1080	1613
Incidence per 100 person-y	1.1	1.6	1.9	2.3
Time to event, median (IQI), d	205 (133–365)	229 (142–404)	245 (152–420)	222 (137–389)
Acute myocardial infarction				
No. of events	120	388	120	261
Incidence per 100 person-y	0.2	0.3	0.2	0.4
Time to event, median (IQI), d	264 (144–489)	242 (152–406)	283 (170–509)	259 (153–436)
Congestive heart failure				
No. of events	196	734	267	698
Incidence per 100 person-y	0.4	0.5	0.5	1.0
Time to event, median (IQI), d	212 (117–396)	240 (143–391)	251 (152–457)	224 (136–379)
Unstable angina				
No. of events	99	375	127	193
Incidence per 100 person-y	0.2	0.2	0.2	0.3
Time to event, median (IQI), d	257 (162–417)	234 (148–429)	261 (153–507)	221 (134–431)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; IQI, interquartile interval; TD, thiazide diuretic.

comparisons of CCBs vs TDs for addition, discontinuation, and switch did not reach significance, and all comparisons for the clinical outcomes were inconclusive. However, when this cohort of patients was analyzed using drug exposure as a time-dependent variable, those who took TDs were less likely to experience clinical outcomes compared with those who took ACEIs and CCBs (Tables S2–S6).

4 | DISCUSSION

This retrospective cohort study shows that patients with hypertension who add a new drug or discontinue their first therapy do so a few months after initiation, and drug classes are associated with different risk of addition, discontinuation, and switch. TDs as first monotherapy were associated with higher risk of addition and discontinuation compared with initiators of ACEIs, ARBs, or CCBs. On the other hand, TDs as monotherapy was associated with a lower risk of cardiovascular and cerebrovascular events compared with monotherapy with ACEIs, ARBs, or CCBs. Stroke, a leading outcome related to hypertension, drove the results of the composite outcome in our study.

TD initiation was associated with a higher rate of addition in our study. However, an Asian cohort showed a different result: women who initiated first antihypertensive therapy with ACEIs had a higher rate of addition (31.1%) compared with diuretics (9.9%) and CCBs

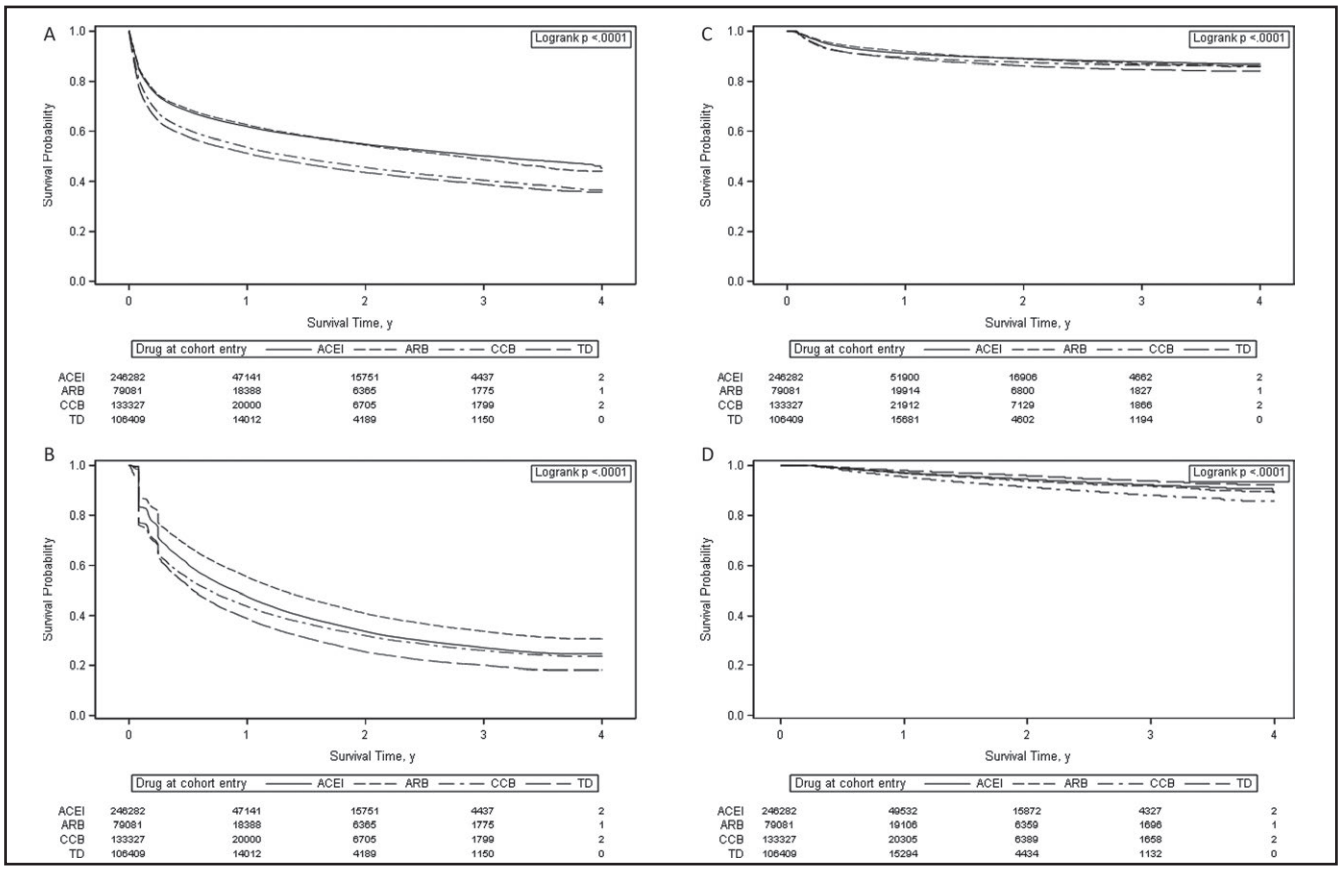

FIGURE 3 Kaplan-Meier curves for outcomes of (A) addition of a new antihypertensive drug, (B) therapy discontinuation, (C) switch to a new antihypertensive drug, and (D) composite of clinical outcomes. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; TD, thiazide diuretic

(9.6%).[17] The literature otherwise shows similar results for the outcome of discontinuation presented in our study. A previous study using MarketScan Research Data from 2001 and 2003 reported that patients using hydrochlorothiazide were more likely to discontinue therapy than those starting amlodipine, lisinopril, and valsartan.[18] Our investigation adds to this study the analysis of the outcomes of addition and switch as well as clinical events. In a cohort of Medicaid beneficiaries, after 6 months of therapy, those using diuretics had a 2-fold higher likelihood of discontinuing therapy compared with patients using CCBs or ACEIs.[19] Elderly patients from the province of Ontario, Canada, initially prescribed diuretics were less likely to persist on therapy compared with those taking ACEIs, ARBs, or CCBs.[20] Finally, a study in the United Kingdom using a database of general practitioner visits showed that 20% of patients with newly diagnosed and treated hypertension discontinued drug therapy within 6 months and the median time until discontinuation was shorter for those taking TDs (1.50 years) than those taking ACEIs (2.24 years) and CCBs (1.86 years).[21] Thus, TDs appear to be associated with higher rates of discontinuation in several cohorts, possibly because of lesser ability to control BP.

Our study showed that TD users were less likely to experience cardiovascular and cerebrovascular events. However, previous studies have indicated that some antihypertensive drug classes lead to similar clinical outcomes. A cohort study from the province of Saskatchewan, Canada, found similar frequency of death from any cause, stroke or transient ischemic attack, myocardial infarction, and unstable angina among users of atenolol (2.3%), ACEIs (3.6%), hydrochlorothiazide (2.9%), and calcium antagonists (3.9%), while atenolol was not associated with difference in risk compared to other drugs after adjustment by covariates.[22] A study including women aged 50 years or older reported that there was a slight increase of risk for patients taking CCBs compared with TDs; however, this became nonsignificant after adjustment for risk factors and exclusion of women with diabetes mellitus. There were no significant differences in coronary disease events and strokes between patients taking ACEIs or diuretics.[23] On the other hand, a Cochrane review and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported different results. The review indicated that using thiazides as a first-line choice reduces coronary heart disease events compared with other classes.[9] ALLHAT showed that chlorthalidone was similarly effective in preventing coronary heart disease compared with doxazosin, lisinopril, and amlodipine, but chlorthalidone was more effective in preventing heart failure and stroke (than doxazosin or lisinopril only).[10] Other observational studies assessed intermediate outcomes, such as the CARTaGENE study, which reported that peripheral and central BP measurements were

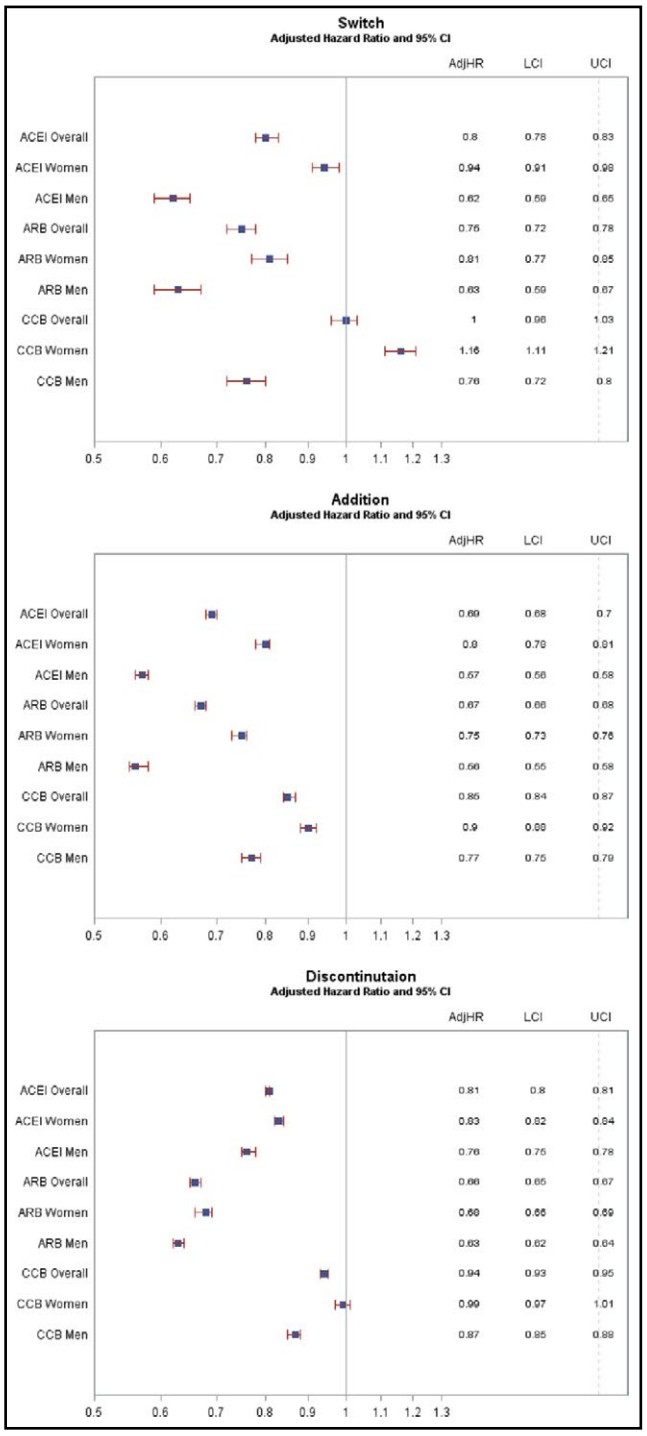

FIGURE 4 Adjusted hazard ratios for comparisons of monotherapy of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) vs thiazide diuretic (TDs) for outcomes of utilization patterns: addition of a new antihypertensive drug, therapy discontinuation, switch to a new antihypertensive drug. Cox regression models were adjusted by sex (except the models with drug-sex interaction), age, age squared, year of cohort entry, urban area, number of emergency department visits 1 year prior, number of physician visits 1 year prior, number of hospitalizations 1 year prior, Charlson comorbidity index, and cerebrovascular diseases and dyslipidemia 1 year prior. AdjHR indicates adjusted hazard ratio; LCI, lower confidence interval; UCI, upper confidence interval

similar across groups receiving monotherapy of TDs, ACEIs, ARBs, or CCBs in patients with hypertension aged 40 to 69 years from the province of Quebec, Canada.[24] A study of patients on monotherapy indicated that TDs, ACEIs, ARBs, and CCBs had nonclinical relevant differences in the decrease of BP during follow-up (median duration of 6.5 months); however, patients initiated on ACEIs had significantly higher rates of goal attainment (defined by Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7] guidelines) than patients initiated on TDs.[25] In summary, previous cohorts showed that TDs are at least as effective as other drug groups in patients with hypertension.

Our study investigated effect modifications by sex. A review of population-based studies indicated that women at all ages have a 30% higher likelihood than men to be treated pharmacologically for hypertension.[26] In our study, women were more often prescribed TDs, and differences were observed regarding addition, discontinuation, and switch of antihypertensive drugs among women and men; however, no interaction by sex was found for clinical outcomes. Sex differences in stroke risk have been reported and women are at higher risk likely because of longer life expectancy and older age at the time of stroke onset.[27] However, an analysis from ALLHAT showed that systolic BP decreased slightly less in women than men following antihypertensive therapy and fewer women reached outcomes of all-cause mortality, coronary heart disease, cardiovascular disease, stroke, heart failure, and cancer.[28]

Our study indicates that TDs are an effective antihypertensive therapy and, according to the literature, are likely cost-effective.[29] A cost-effectiveness analysis from ALLHAT indicates that the lifetime cost for patients initially treated with chlorthalidone was lower than for amlodipine or lisinopril therapies, whereas lifetime quality-adjusted days were not significantly different with amlodipine or lisinopril compared with chlorthalidone. This economic analysis concludes that using chlorthalidone as the first drug for the treatment of hypertension can be cost-saving.[29] Despite this evidence, other drug classes have been prescribed more frequently than TDs for patients with hypertension as shown by our study and other investigations. Less than 17% of patients on monotherapy from the Primary Care Audit of Global Risk Management (PARADIGM) study were using diuretics and elderly patients from Ontario starting therapy had a decrease in prescriptions of diuretics from 23.1% in 1999/2000 to 16.5% in 2009/2010 and an increase in prescriptions of ARBs from 1.3% to 14.2%.[30,31] Thus, TDs should be favored as first-line therapy in patients with hypertension.

5 | STUDY LIMITATIONS

Our study has some limitations that should be taken into account. First, the study design precludes the assessment of reasons for addition, discontinuation, or switch, as well as of BP measurements during follow-up, race or ethnicity, and other clinical and lifestyle information that could be associated with the study outcomes. Of note, discontinuation may have occurred after BP levels achieved control. Second, there is a potential for confounding by indication

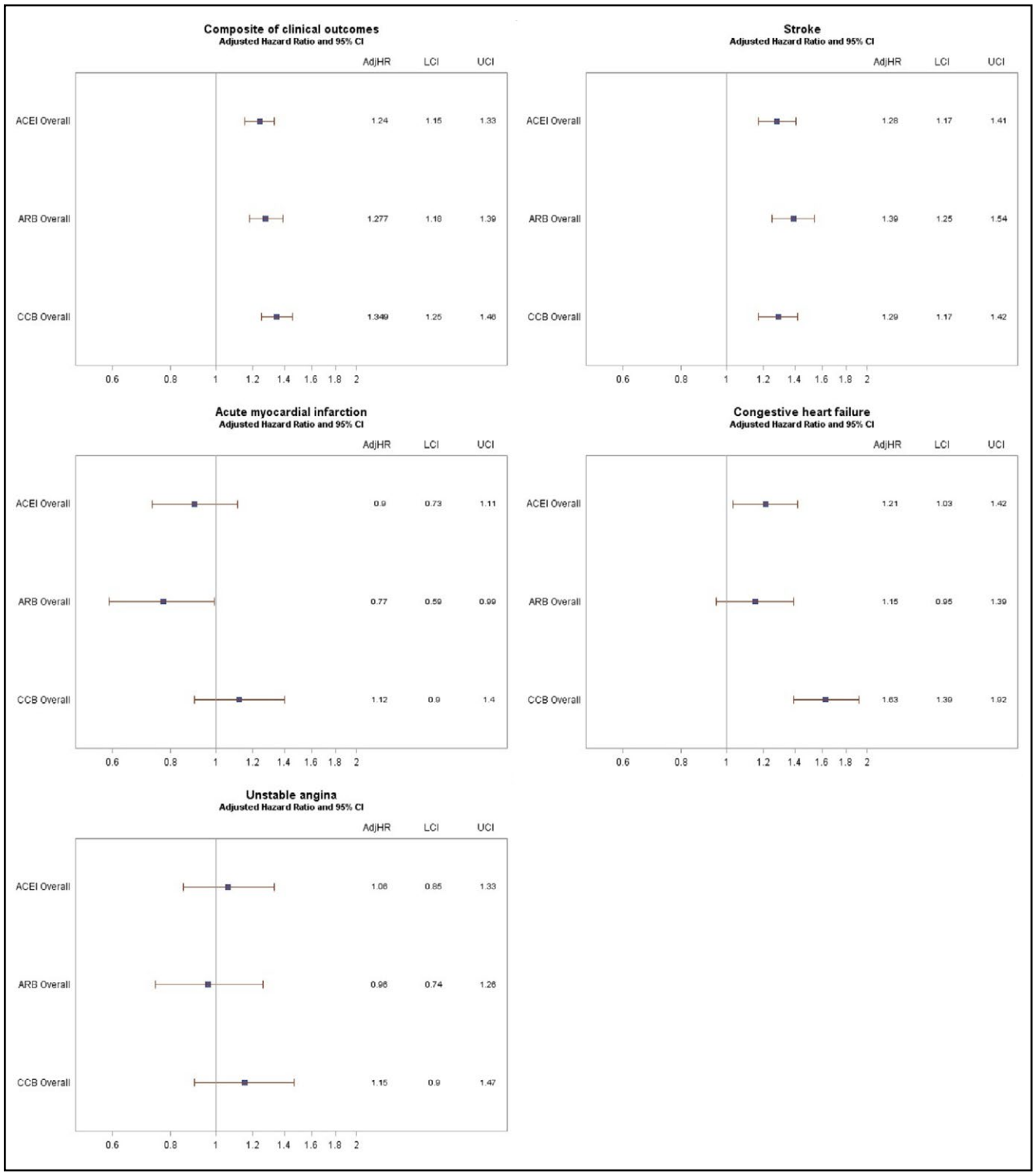

FIGURE 5 Adjusted hazard ratios for comparisons of monotherapy of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) vs thiazide diuretics (TDs) for outcomes of cardiovascular and cerebrovascular events: composite of clinical outcomes, stroke, acute myocardial infarction, congestive heart failure, and unstable angina. Cox regression models were adjusted by sex, age, age squared, year of cohort entry, urban area, number of emergency department visits 1 year prior, number of physician visits 1 year prior, number of hospitalizations 1 year prior, Charlson comorbidity index, and cerebrovascular diseases and dyslipidemia 1 year prior. AdjHR indicates adjusted hazard ratio; LCI, lower confidence interval; UCI, upper confidence interval

because it is possible that patients with higher susceptibility to cardiovascular events were less likely to be prescribed TD monotherapy, as CCBs are commonly used in patients with cardiovascular diseases. The short time period from cohort entry to cardiovascular and cerebrovascular events indicates that confounding by indication may partially explain the results. In addition, this study included only

patients covered by commercial medical and pharmacy plans in the United States, thus the results are not generalizable to others without these benefits. Also, in an analysis of pharmacy claims, the rate of discontinuation may be underestimated because patients could obtain their drug therapies outside the health plan. The use of *ICD* codes from administrative databases to define hypertension can be debatable; however, patients who were taking antihypertensive drug and those with other diagnoses for which these drugs are indicated were excluded. Thus, we can assure a low level of uncertainty in the definition of our sample. Nevertheless, the large sample size of our study allowed for comparison of antihypertensive drug classes in terms of drug utilization and effectiveness. Finally, differences in outcomes were still identified and this potential misclassification could bias the results towards the null.

6 | CONCLUSIONS

Our study offers evidence from a real-world population and supports prior findings that TDs are a preferred first-choice drug class in treating hypertension in adults without diabetes mellitus. Patients with hypertension on monotherapy with TDs exhibited a lower risk of cardiovascular and cerebrovascular events compared with patients taking ACEIs, ARBs, and CCBs. However, TD initiators were more likely to add a new antihypertensive drug or discontinue treatment compared with ACEI, ARB, or CCB initiators.

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DISCLOSURE

The authors report no conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

MAAM and CSM contributed to the design, data analyses, data interpretation, and manuscript preparation. YW and CD contributed to data analyses and data interpretation. MA contributed to acquisition of data, data analyses, data interpretation, and manuscript preparation. SB contributed to acquisition of data, data interpretation, and manuscript preparation. HB contributed to data analyses. LP contributed to acquisition of data, concept, design, data interpretation, and manuscript preparation.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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