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Comparison of First-Line Dual Combination Treatments in Hypertension: Real-World Evidence from Multinational Heterogeneous Cohorts

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ABSTRACT

Background and Objectives: 2018 ESC/ESH Hypertension guideline recommends 2-drug combination as initial anti-hypertensive therapy. However, real-world evidence for effectiveness of recommended regimens remains limited. We aimed to compare the effectiveness of first-line anti-hypertensive treatment combining 2 out of the following classes: angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blocker (A), calcium channel blocker (C), and thiazide-type diuretics (D).
Methods: Treatment-naïve hypertensive adults without cardiovascular disease (CVD) who initiated dual anti-hypertensive medications were identified in 5 databases from US and Korea. The patients were matched for each comparison set by large-scale propensity score matching. Primary endpoint was all-cause mortality. Myocardial infarction, heart failure, stroke, and major adverse cardiac and cerebrovascular events as a composite outcome comprised the secondary measure.
Results: A total of 987,983 patients met the eligibility criteria. After matching, 222,686, 32,344, and 38,513 patients were allocated to A+C vs. A+D, C+D vs. A+C, and C+D vs. A+D comparison, respectively. There was no significant difference in the mortality during total of 1,806,077 person-years: A+C vs. A+D (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.97–1.20; p=0.127), C+D vs. A+C (HR, 0.93; 95% CI, 0.87–1.01; p=0.067), and C+D vs. A+D (HR, 1.18; 95% CI, 0.95–1.47; p=0.104). A+C was associated with a slightly higher risk of heart failure (HR, 1.09; 95% CI, 1.01–1.18; p=0.040) and stroke (HR, 1.08; 95% CI, 1.01–1.17; p=0.040) than A+D.

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Conclusions: There was no significant difference in mortality among A+C, A+D, and C+D combination treatment in patients without previous CVD. This finding was consistent across multi-national heterogeneous cohorts in real-world practice.

Keywords: Hypertension; Antihypertensive agents; Angiotensin receptor antagonists; Calcium channel blockers; Diuretics

INTRODUCTION

High blood pressure (BP) is the leading global cause of death and disability.[1] While extensive evidence supports the beneficial effects of rapid BP control below the target in preventing mortality and cardiovascular disease (CVD),[2] initial treatment with monotherapy is often insufficient or slow to achieve the BP target.[3] Observational studies and meta-analyses have suggested that initial combination of hypertensive treatments confers a decreased risk for CVD compared to monotherapy.[4-6] Therefore 2018 European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guideline recommends dual combination treatment as initial therapy in most hypertensive patients rather than monotherapy.[7] Despite the evidences from previous randomized controlled trials (RCTs) that directly compared the effects of different combination regimens,[8-11] the optimal first-line antihypertensive combination regimen is a matter of controversy because 1) the results were heterogeneous, 2) the baseline characteristics of the study population were mostly at a high risk for CVD, and 3) most participants had taken anti-hypertension medications at baseline in these RCTs.

Therefore, we aimed to compare the therapeutic effectiveness of dual combination regimens in large cohorts of treatment-naïve hypertensive patients without CVD at baseline who initiated treatment with 2 out of the following 3 classes of drugs: angiotensin system blockage (angiotensin converting enzyme inhibitors [ACEIs]/angiotensin-receptor blockers [ARBs]), calcium channel blockers (CCBs), and thiazide diuretics (TZDs).

METHODS

Data source

The study consisted of a retrospective analysis of five data sources encoded in the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM) version 5 from participating research partners across the Observational Health Data Sciences and Informatics (OHDSI) community.[12] All 5 data sources are administrative claims databases: OptumInsight's Clinformatics™ Data Mart (CEDM, 79,600,000 subjects), Truven MarketScan Commercial Claims and Encounters (CCAE, 135,000,000 subjects), Truven MarketScan Medicare Supplemental Beneficiaries (Medicare, 9,800,000 subjects), Truven MarketScan Multi-State Medicaid (Medicaid, 25,500,000 subjects) from US, and the National Health Insurance Service-National Sample Cohort (NHIS-NSC, 1,100,000 subjects)[13] from Korea.

This study was performed through a network model of OHDSI, where access to data and statistical testing was executed inside each data partner's institution. The entire analytical process was pre-specified before execution. Only pre-specified aggregated results lacking patient-level information were collected for interpretation and meta-analysis. Each data

partner obtained the necessary Institutional Review Board (IRB) approval or exemption (IRB number: AJIRB-MED-EXP-17-054).

Study population

The cohort included adults (≥20 years) with hypertension whose first anti-hypertensive treatment was initiated with recommended first-line dual combination regimens from 2001 to 2017. The entry date in the cohort (index date) was defined as the date of first prescription of one of the combination drugs. The second class of antihypertensive medications should have been started within 30 days after index date. Only patients, enrolled in the database for at least 1 year before the index date, were included to avoid left censoring. Patients who had a prescription containing an ACEI/ARB, β-blocker, CCB, or TZD during the 12 months preceding the index date were excluded to limit the study to treatment-naïve subjects. The list of anti-hypertensive drugs is presented in the **Supplementary Table 1**. Patients who had a previous history of ischemic heart disease, stroke, or heart failure before the index date were also excluded.

Exposure

Three matched cohorts using the recommended combination treatments were created: ACEI/ARB+CCB (A+C) vs. ACEI/ARB+TZD (A+D), CCB+TZD (C+D) vs. A+C, and C+D vs. A+D. The exposure was started when one drug of interest was prescribed without history of any anti-hypertensive medication within previous 365 days. Continuous drug exposures were constructed by allowing fewer than 30-day gaps between prescriptions. Only patients who continued both classes of drugs for more than 180 days were included in the primary analysis. Patients starting a third class of drug within 180 days of the index date were excluded.

Outcomes

The primary outcome was all-cause mortality occurring at least 180 days after the index date. The secondary outcomes were incident myocardial infarction (MI) requiring hospitalization, stroke requiring hospitalization, heart failure requiring hospitalization, and major adverse cardiac and cerebrovascular events (MACCE) as a composite outcome including MI, stroke, heart failure, and mortality occurring at least 180 days after the index date. Diagnosis codes for outcomes are listed in **Supplementary Table 2**.

Statistical analysis

Large-scale propensity score (PS)[14] matching was used to balance the differences in baseline characteristics between treatment groups (R, "CohortMethod" package). PS was estimated using L1-regularized large-scale logistic regression models based on all available demographic characteristics, medical, medication, and procedure history with the L_1 penalty hyper-parameter selected through 10-fold cross-validation using high-performance computing.[15] The details of covariates for propensity score matching and prespecified statistical analysis plan are presented in supplemental statistical analytic plan.

The PS was transformed to preference scores that account for differences in drug prevalence and availability. Confounding control was assessed by preference score distributions and covariate balance metrics. One-to-one greedy-search matching was used to match patients using a caliper of 0.15 times the standard deviation of the propensity score distribution. Cox proportional hazards models were used to compare the matched cohorts. After combining the results from five data sources, random effects model meta-analysis was performed to calculate summary hazard ratios and rate differences.

The same analytical process was adopted for subgroup and sensitivity analyses. Subgroup analyses included stratification by age (<60 years and ≥60 years) and gender. Medicare data were not included in the subgroup analysis for younger patients.

A pre-specified p<0.05 was considered statistically significant for all two-sided tests. The entire analytical protocol and code is available on github (https://github.com/OHDSI/StudyProtocolSandbox/tree/master/HypertensionCombination) for reproducibility, which enables other researchers to perform and replicate this study with any database in the format of OMOP-CDM.

Sensitivity analyses

To assess the robustness of results with respect to the definition of combination treatment, we re-ran the same analyses using 30-day, 1-year, and 2-year periods of initial regimen continuation. This could also estimate proportion of continuation over 180 days and the trend of survival difference along the duration of the initial regimen continuation.[16]

A total of 39 negative control outcomes were employed to quantify systematic error.[17] These negative control outcomes were unlikely to have a relationship with anti-hypertensive medications, identified through a data-rich algorithm.[18] For further calibration of p values for the outcomes, we fit an empirical null distribution to these negative control point estimates to allow further calibration of p values.[19] While also pre-specified, sensitivity and subgroup analyses were nonetheless regarded exploratory. After collection of the results, the meta-analysis aggregating only the results from US data sources was conducted as a sensitivity analysis.

RESULTS

Baseline characteristics of study population

A total of 1,062,605 patients were identified across five data sources. Three one-to-one propensity-score-matched cohorts were created by comparing A+C vs. A+D (n=445,372), C+D vs. A+C (n=64,688), and C+D vs. A+D (n=77,026). Among these patients, the covariates were well-balanced between treatment regimens after PS matching in each data source. The aggregated baseline characteristics of the study population across data sources before and after PS matching of three comparisons are summarized in **Table 1**. The PS distribution and the baseline characteristics of each data source before and after matching are presented in **Supplementary Figure 1** and **Supplementary Tables 3**-**7**.

The total follow-up duration was 1,806,077 person-years (mean, 3.1 years). The median age ranged from 55 to 59 years in A+C vs. A+D, 60 to 64 years in C+D vs. A+C, and 60 to 64 years in C+D vs. A+D comparison. Approximately one-third of study patients (29.6–35.6%) had been treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors previously. The frequency of patients with a history of diabetes ranged from 13.6% to 21.4% and was the highest in the A+C and A+D comparison. About one-fifth of the cohort from NHIS-NSC also had results from a national health examination during the previous year of enrollment. Most examination measurements including BP were balanced after matching other patient characteristics, even though data from examinations were not included in the model to calculate the propensity score (**Supplementary Table 7**).

Table 1. Baseline characteristics of all propensity-score-matched patients

Characteristics	A+C vs. A+D			C+D vs. A+C			C+D vs. A+D		
	A+C (n=222,686)	A+D (n=222,686)	SD (%)	C+D (n=32,344)	A+C (n=32,344)	SD (%)	C+D (n=38,513)	A+D (n=38,513)	SD (%)
Age group									
≤40	11,797 (5.3)	11,980 (5.4)	0.4	1,639 (5.1)	1,623 (5.0)	0.2	1,903 (4.9)	1,939 (5.0)	0.4
40–49	37,084 (16.7)	36,837 (16.5)	0.3	4,794 (14.8)	4,812 (14.9)	0.2	5,567 (14.5)	5,427 (14.1)	0.1
50–59	73,936 (33.2)	73,964 (33.2)	<0.1	9,525 (29.4)	9,580 (29.6)	0.4	11,217 (29.1)	11,164 (29.0)	0.3
60–69	58,696 (26.4)	58,327 (26.2)	0.4	8,429 (26.1)	8,266 (25.6)	1.2	10,074 (26.2)	10,089 (26.2)	0.1
70–79	28,323 (12.7)	28,538 (12.8)	0.3	5,222 (16.1)	5,349 (16.5)	1.1	6,486 (16.8)	6,640 (17.2)	1.1
≥80	12,763 (5.7)	12,966 (5.7)	0.4	2,695 (8.3)	2,685 (8.3)	0.1	3,236 (8.4)	3,231 (8.4)	<0.1
Gender									
Women	93,676 (42.1)	90,820 (40.8)	2.6	18,762 (58.0)	19,574 (60.5)	5.1	23,537 (61.1)	23,938 (62.2)	2.1
Comorbidities									
Diabetes mellitus, type II	47,256 (21.2)	47,730 (21.4)	0.5	4,815 (14.9)	4,719 (14.6)	0.8	5,305 (13.8)	5,225 (13.6)	0.6
Chronic kidney disease	5,963 (2.7)	6,081 (2.7)	0.3	889 (2.7)	954 (2.9)	1.2	997 (2.6)	1,048 (2.7)	0.8
Atrial fibrillation	3,343 (1.5)	3,280 (1.5)	0.2	611 (1.9)	601 (1.9)	0.2	685 (1.8)	706 (1.8)	0.4
Valvular heart disease	6,671 (3.0)	6,818 (3.1)	0.4	959 (3.0)	953 (2.9)	0.1	1,098 (2.9)	1,100 (2.9)	0.0
Dyslipidemia	106,065 (47.6)	106,372 (47.8)	0.3	13,413 (41.5)	13,107 (40.5)	1.9	15,598 (40.5)	15,375 (39.9)	1.2
Malignant neoplastic disease	17,722 (8.0)	17,985 (8.1)	0.4	2,826 (8.7)	2,842 (8.8)	0.2	3,357 (8.7)	3,369 (8.7)	0.1
Medication									
HMG-CoA reductase inhibitors	79,028 (35.5)	79,291 (35.6)	0.2	9,949 (30.8)	9,718 (30.0)	1.6	11,393 (29.6)	11,467 (29.8)	0.4
Hypoglycemic drugs except insulin	34,989 (15.7)	35,354 (15.9)	0.4	3,301 (10.2)	3,285 (10.2)	0.2	3,549 (9.2)	3,486 (9.1)	0.6
Insulin	4,726 (2.1)	4,747 (2.1)	0.1	462 (1.4)	421 (1.3)	1.1	463 (1.2)	452 (1.2)	0.3
Antithrombotic agent	10,789 (4.8)	10,902 (4.9)	0.2	2,221 (6.9)	2,210 (6.8)	0.1	2,808 (7.3)	2,846 (7.4)	0.4

Values are presented as number of patients (%) not otherwise specified.
A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; D = thiazide diuretics; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; SD = standardized difference.

Primary and secondary outcome assessment

For the primary outcome of overall mortality, there were no significant differences between any of the combination treatment in each data source (**Figure 1**). Moreover, the summary hazard ratio (HR) from 5 data sources did not demonstrate a statistically significant difference in mortality between recommended dual combination regimens (summary rate difference [RD], 0.53 [95% confidence interval {CI}, −0.06 to 1.13] per 1,000 person-years; summary HR, 1.08 [95% CI, 0.97 to 1.20]; p=0.127 for A+C vs. A+D; summary RD, −0.45 [95% CI, −0.95 to 0.04]; summary HR, 0.93 [95% CI, 0.87 to 1.01]; p=0.067 for C+D vs. A+C; summary RD, 0.72 [95% CI, −0.74 to 2.18]; summary HR, 1.18 [95% CI, 0.95 to 1.47]; p=0.104 for C+D vs. A+D) (**Figure 2**).

The result for secondary outcomes is summarized in **Figure 3**. The combination treatment regimens had similar effectiveness for prevention of MI (all p>0.05). A+C combination was associated with slightly higher risk of heart failure compared to A+D combination (summary HR, 1.09 [95% CI, 1.01 to 1.18]; p=0.040). A+C combination also was related with worse outcome for stroke admission compared to A+D combination (summary HR, 1.08 [95% CI, 1.01 to 1.17]; p=0.040). MACCE risk was not different across the matched cohorts (summary HR, 1.05 [95% CI, 1.00 to 1.11]; p=0.051 for A+C vs. A+D; summary HR, 1.01 [95% CI, 0.85 to 1.21]; p=0.857 for C+D vs. A+C; summary HR, 1.12 [95% CI, 0.85 to 1.43]; p=0.263 for C+D vs. A+D). The relationship between combination treatment and secondary outcome in each data source is described in **Supplementary Figure 2**.
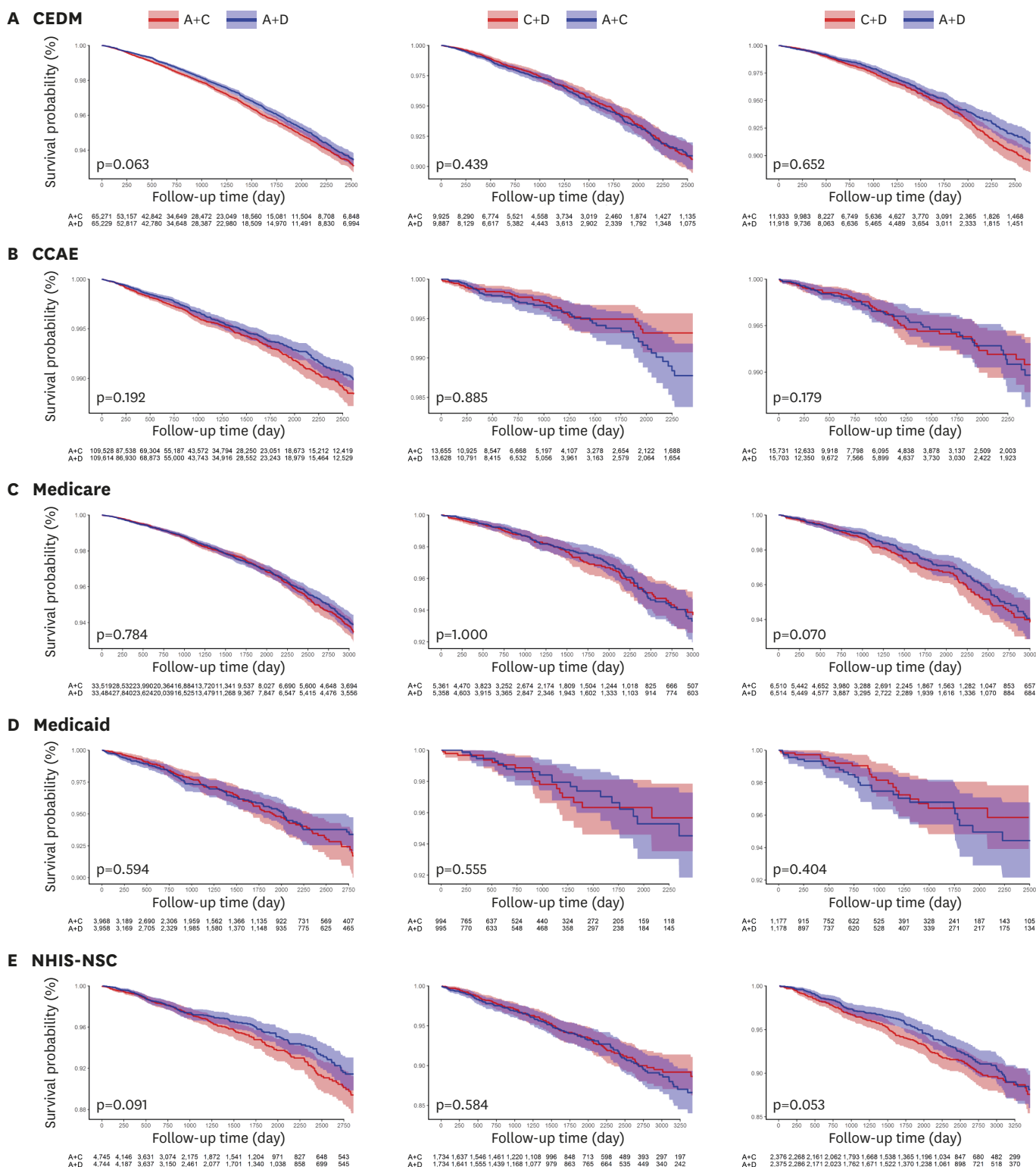
Figure 1. Kaplan-Meier plots for overall survival comparing different dual combination treatments in propensity score-matched cohorts from each data source. (A) CEDM, (B) CCAE, (C) Medicare, (D) Medicaid, and (E) NHIS-NSC.
A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; CCAE = Truven MarketScan Commercial Claims and Encounters; CEDM = OptumInsight's Clinformatics™ Data Mart; D = thiazide diuretics; Medicaid = Truven MarketScan Multi-State Medicaid; Medicare = Truven MarketScan Medicare Supplemental Beneficiaries; NHIS-NSC = National Health Insurance Service-National Sample Cohort.

A

Data Source	A+C				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	66,894	1,893	200,097	9.5	66,894	1,731	200,514	8.6	1.10 (1.00-1.21)	50.6%
CCAE	112,710	502	326,432	1.5	112,710	452	326,919	1.4	1.13 (0.94-1.37)	15.1%
Medicare	34,329	806	121,680	6.6	34,329	739	119,344	6.2	0.98 (0.84-1.14)	22.6%
Medicaid	4,006	127	13,105	9.7	4,006	125	13,304	9.4	0.91 (0.64-1.29)	4.6%
NHIS-NSC	4,747	198	16,407	12.1	4,747	170	17,072	10.0	1.27 (0.96-1.69)	7.2%
Overall	222,686	3,526	677,721	5.2	222,686	3,217	677,153	4.8	1.08 (0.97-1.20)	100.0

Heterogeneity: I^2 = 4.6%   p=0.127

Favor A+C | Favor A+D — Hazard Ratio (95% CI), 0.5–1–2

B

Data Source	C+D				A+C				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	10,139	395	32,033	12.3	10,139	391	31,072	12.6	0.92 (0.74-1.14)	48.3%
CCAE	14,000	45	39,047	1.2	14,000	62	38,406	1.6	1.04 (0.59-1.86)	6.9%
Medicare	5,465	136	19,008	7.2	5,465	146	20,138	7.3	1.00 (0.69-1.44)	17.2%
Medicaid	1,005	21	2,821	7.4	1,005	22	2,977	7.4	0.79 (0.35-1.73)	3.6%
NHIS-NSC	1,735	112	8,594	13.0	1,735	124	8,755	14.2	0.92 (0.67-1.25)	24.1%
Overall	32,344	709	101,503	7.0	32,344	745	101,348	7.4	0.93 (0.87-1.01)	100.0

Heterogeneity: I^2 = 0.0%   p=0.067

Favor C+D | Favor A+C — Hazard Ratio (95% CI), 0.5–1–2

C

Data Source	C+D				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	12,186	505	39,600	12.8	12,186	428	38,751	11.0	1.05 (0.86-1.27)	42.7%
CCAE	16,120	61	45,711	1.3	16,120	61	44,477	1.4	1.45 (0.85-2.53)	7.7%
Medicare	6,639	166	23,447	7.1	6,639	147	23,632	6.2	1.38 (0.98-1.95)	17.7%
Medicaid	1,191	23	3,345	6.9	1,191	31	3,462	9.0	0.69 (0.29-1.60)	3.2%
NHIS-NSC	2,377	174	12,886	13.5	2,377	149	13,042	11.4	1.29 (1.00-1.67)	28.8%
Overall	38,513	929	124,989	7.4	38,513	816	123,364	6.6	1.18 (0.95-1.47)	100.0

Heterogeneity: I^2 = 14.2%   p=0.104

Favor C+D | Favor A+D — Hazard Ratio (95% CI), 0.5–1–2

Figure 2. Forest plots depicting HR and 95% CI for primary outcome in each data source. The overall HRs were calculated using a random-effects model. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs. (A) A+C vs. A+D, (B) C+D vs. A+C, and (C) C+D vs. A+D.
A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; CCAE = Truven MarketScan Commercial Claims and Encounters; CEDM = OptumInsight's Clinformatics™ Data Mart; CI = confidential interval; D = thiazide diuretics; HR = hazard ratio; Medicaid = Truven MarketScan Multi-State Medicaid; Medicare = Truven MarketScan Medicare Supplemental Beneficiaries; NHIS-NSC = National Health Insurance Service-National Sample Cohort.
*Event rate per 1,000 person-year.

Subgroup analysis

The summary HRs of overall mortality in subgroups stratified by gender and age are depicted in **Figure 4**. In women, A+C therapy was related with worse survival than A+D therapy (summary HR, 1.20 [95% CI, 1.09 to 1.31]; p=0.006). In men, C+D therapy was associated with worse survival outcome compared to A+D therapy (summary HR, 1.31 [95% CI, 1.12 to 1.53]; p=0.009). There was no difference in overall mortality between recommended combination therapies in young (<60 years) and old patient (≥60 years) groups.

Sensitivity analyses

The proportion of patients with adherence to initial combination therapy was about two-thirds for 365 days and about one-thirds for 730 days compared to 180 days: 63.7% in A+C, 61.7% in A+D, 62.2% in C+D group for 365 days; 31.6% in A+C, 29.5% in A+D, 28.6% in C+D group for 730 days. A+C cohorts with minimum 365 days on continuation of combination therapy showed worse survival than A+D cohorts (summary HR, 1.15 [95% CI, 1.03 to 1.29]; p=0.026). Other results from the sensitivity analyses using various minimum periods of dual drug continuation did not indicate any significant difference in all-cause mortality (**Supplementary Figure 3**).

In the absence of bias, estimates among 95% of negative control outcomes are theoretically expected to include a HR of 1. Among 39 negative control outcomes, less than 5% analyses had a significant relationship with the specific combination treatment. All results from

A Myocardial infarction

Data Source	A+C				A+D				HR (95% CI)		Weight
	Total No.	Events	Person-Years	Event rate*	Total No.	Events	Person-Years	Event rate*			
CEDM	66,868	700	198,211	3.5	66,868	737	198,524	3.7	0.92 (0.80-1.07)		32.8%
CCAE	112,687	703	324,310	2.2	112,687	700	324,866	2.2	0.94 (0.81-1.10)		30.8%
Medicare	34,302	714	119,581	6.0	34,302	714	117,170	6.1	0.95 (0.82-1.10)		30.8%
Medicaid	4,004	86	12,872	6.7	4,004	74	13,089	5.7	1.35 (0.90-2.04)		4.1%
NHIS-NSC	4,745	32	16,281	2.0	4,745	30	16,978	1.8	1.33 (0.69-2.65)		1.5%
Overall	222,606	2,235	671,255	3.3	222,606	2,255	670,627	3.4	0.96 (0.85-1.07) p=0.351		100.0%

Heterogeneity:I^2 = 0.0%

Data Source	C+D				A+C				HR (95% CI)		Weight
	Total No.	Events	Person-Years	Event rate*	Total No.	Events	Person-Years	Event rate*			
CEDM	10,138	137	31,678	4.3	10,138	116	30,801	3.8	1.51 (1.06-2.18)		28.2%
CCAE	13,995	89	38,773	2.3	13,995	62	38,223	1.6	2.12 (1.33-3.47)		21.7%
Medicare	5,463	123	18,637	6.6	5,463	118	19,740	6.0	0.96 (0.66-1.41)		27.0%
Medicaid	1,005	18	2,778	6.5	1,005	20	2,921	6.8	1.09 (0.48-2.51)		10.4%
NHIS-NSC	1,735	22	8,519	2.6	1,735	14	8,690	1.6	1.58 (0.78-3.35)		12.6%
Overall	32,336	389	100,385	3.9	32,336	330	100,375	3.3	1.40 (0.93-2.10) p=0.082		100.0%

Heterogeneity:I^2 = 44.4%

Data Source	C+D				A+D				HR (95% CI)		Weight
	Total No.	Events	Person-Years	Event rate*	Total No.	Events	Person-Years	Event rate*			
CEDM	12,183	171	39,141	4.4	12,183	151	38,326	3.9	1.39 (1.03-1.89)		36.1%
CCAE	16,116	104	45,382	2.3	16,116	71	44,238	1.6	1.37 (0.86-2.21)		17.7%
Medicare	6,637	149	23,013	6.5	6,637	125	23,247	5.4	0.96 (0.68-1.34)		30.4%
Medicaid	1,192	20	3,296	6.1	1,192	12	3,436	3.5	1.67 (0.62-4.90)		4.1%
NHIS-NSC	2,377	27	12,796	2.1	2,377	31	12,954	2.4	0.83 (0.46-1.51)		11.7%
Overall	38,505	471	123,628	3.8	38,505	390	122,201	3.2	1.17 (0.87-1.58) p=0.209		100.0%

Heterogeneity:I^2 = 14.4%

B Heart failure

Data Source	A+C				A+D				HR (95% CI)		Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	66,811	1,621	195,639	8.3	66,811	1,577	196,237	8.0	1.10 (0.99-1.22)		35.4%
CCAE	112,664	856	324,216	2.6	112,664	746	324,993	2.3	1.18 (1.02-1.37)		17.7%
Medicare	34,258	1,816	116,711	15.6	34,258	1,717	114,289	15.0	1.03 (0.93-1.13)		39.5%
Medicaid	3,991	253	12,386	20.4	3,991	220	12,622	17.4	1.18 (0.92-1.51)		6.0%
NHIS-NSC	4,740	58	16,221	3.6	4,740	45	16,920	2.7	1.22 (0.74-2.05)		1.4%
Overall	222,464	4,604	665,173	6.9	222,464	4,305	665,061	6.5	1.09 (1.01-1.18) p=0.040		100.0%

Heterogeneity:I^2 = 0.0%

Data Source	C+D				A+C				HR (95% CI)		Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	10,118	346	31,064	11.1	10,118	301	30,240	1.0	1.19 (0.94-1.50)		28.1%
CCAE	13,995	121	38,741	3.1	13,995	99	38,112	2.6	1.30 (0.89-1.91)		21.5%
Medicare	5,455	318	18,174	17.5	5,455	315	19,345	16.3	1.02 (0.80-1.30)		27.7%
Medicaid	1,004	25	2,744	9.1	1,004	53	2,836	18.7	0.43 (0.22-0.81)		12.4%
NHIS-NSC	1,733	19	8,535	2.2	1,733	29	8,645	3.4	0.58 (0.27-1.20)		10.3%
Overall	32,305	829	99,258	8.4	32,305	797	99,178	8.0	0.93 (0.87-1.01) p=0.943		100.0%

Heterogeneity:I^2 = 65.9%

Data Source	C+D				A+D				HR (95% CI)		Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	12,167	420	38,422	10.9	12,167	356	37,800	9.4	1.19 (0.96-1.47)		26.5%
CCAE	16,112	134	45,363	3.0	16,112	83	44,244	1.9	1.60 (1.09-2.36)		20.2%
Medicare	6,632	383	22,452	17.1	6,632	358	22,618	15.8	1.33 (1.06-1.66)		26.1%
Medicaid	1,192	32	3,254	9.8	1,192	47	3,293	14.3	0.34 (0.16-0.68)		10.9%
NHIS-NSC	2,374	40	12,770	3.1	2,374	44	12,883	3.4	0.97 (0.58-1.60)		16.3%
Overall	38,477	1,009	122,261	8.3	38,477	888	120,838	7.3	1.18 (0.95-1.47) p=0.486		100.0%

Heterogeneity:I^2 = 73.0%

Figure 3. Forest plots depicting HR and 95% CI for secondary outcomes in each data source. The overall HRs were calculated using a random-effects model. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs. (A) Myocardial infarction, (B) Heart failure, (C) Stroke, and (D) MACCE. A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; CCAE = Truven MarketScan Commercial Claims and Encounters; CEDM = OptumInsight's Clinformatics™ Data Mart; CI = confidential interval; D = thiazide diuretics; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; Medicaid = Truven MarketScan Multi-State Medicaid; Medicare = Truven MarketScan Medicare Supplemental Beneficiaries; NHIS-NSC = National Health Insurance Service-National Sample Cohort.
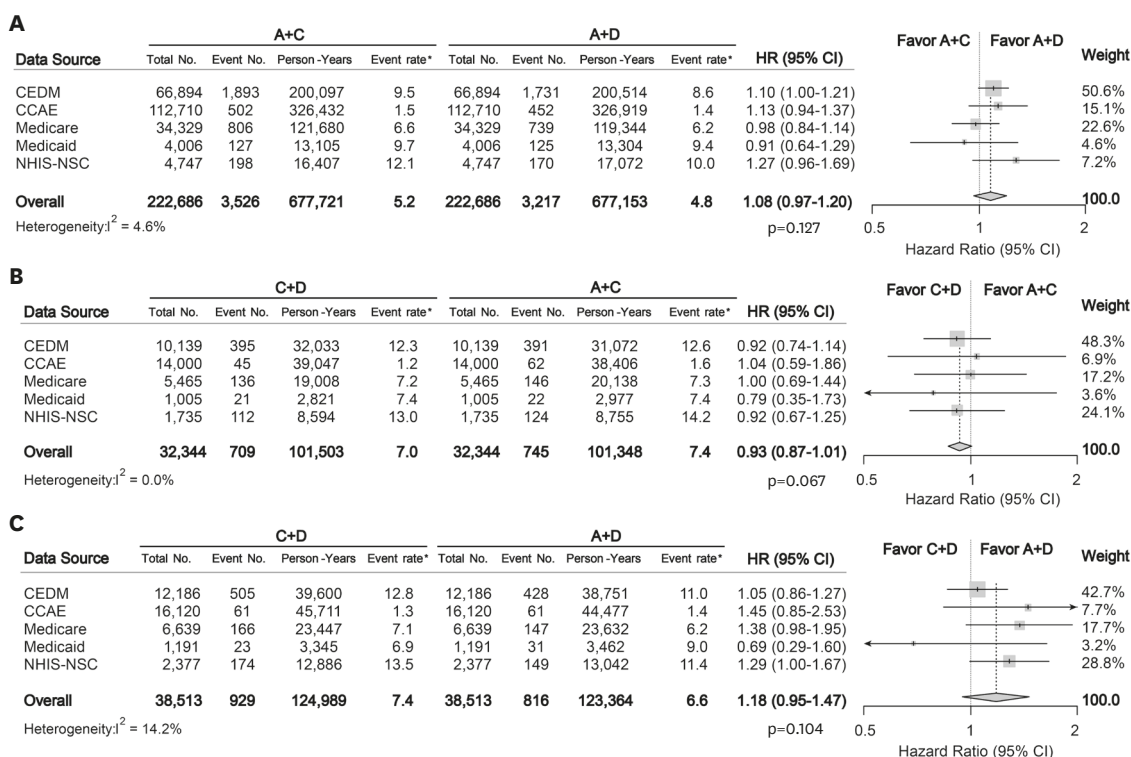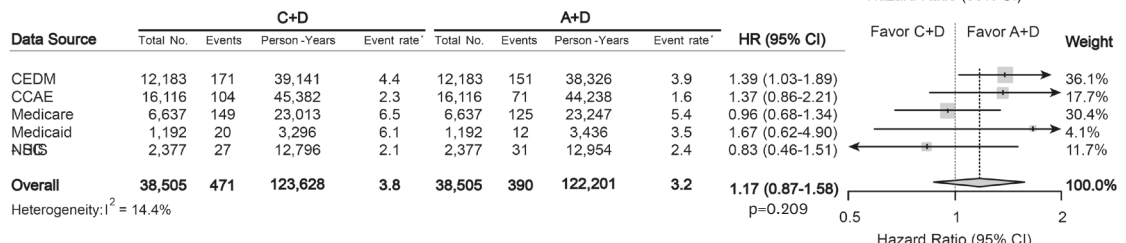*Event rate per 1,000 person-year.

C Stroke

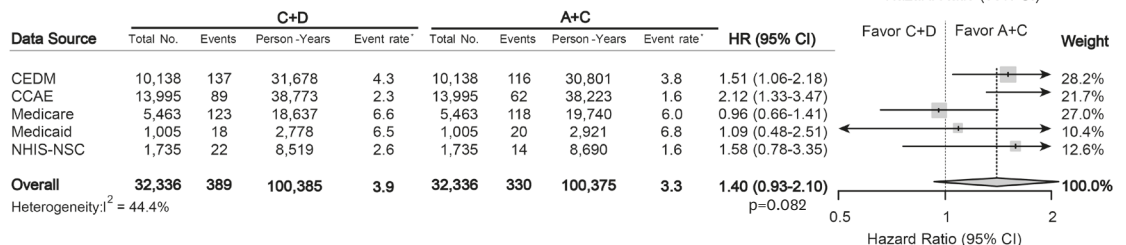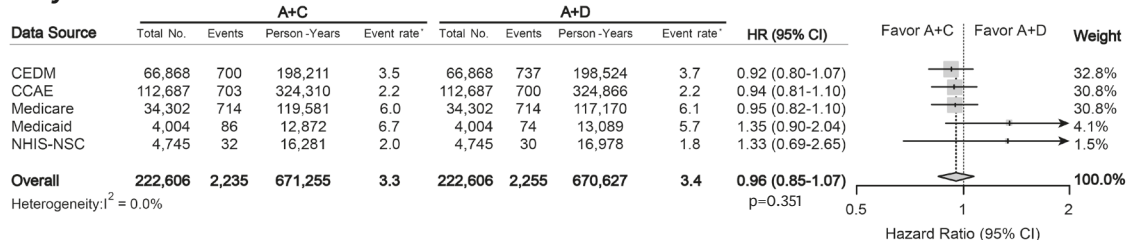| Data Source	A+C				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	66,755	1,028	197,093	5.2	66,755	939	197,699	4.7	1.16 (1.02-1.32)	33.9%
CCAE	112,570	650	324,374	2.0	112,570	587	325,049	1.8	1.07 (0.90-1.26)	20.1%
Medicare	34,196	1,123	118,117	9.5	34,196	1,048	115,900	9.0	1.04 (0.92-1.17)	37.7%
Medicaid	3,990	104	12,729	8.2	3,990	110	12,967	8.5	1.02 (0.71-1.46)	4.3%
NHIS-NSC	4,740	97	16,077	6.0	4,740	88	16,742	5.3	1.04 (0.71-1.50)	4.0%
Overall	222,251	3,002	668,390	4.5	222,251	2,772	668,357	4.1	1.08 (1.01-1.17) p=0.040	100.0%

Heterogeneity:I² = 0.0%

Data Source	C+D				A+C				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	10,120	210	31,379	6.7	10,120	185	30,523	6.1	1.09 (0.82-1.44)	35.6%
CCAE	13,979	80	38,823	2.1	13,979	87	38,121	2.3	0.82 (0.53-1.27)	15.0%
Medicare	5,454	182	18,477	9.9	5,454	186	19,617	9.5	0.97 (0.72-1.30)	32.5%
Medicaid	1,002	17	2,763	6.2	1,002	20	2,904	6.9	1.09 (0.48-2.51)	4.2%
NHIS-NSC	1,734	52	8,445	6.2	1,734	54	8,577	6.3	1.09 (0.68-1.76)	12.7%
Overall	32,289	541	99,887	10.0	32,289	532	99,742	5.3	1.00 (0.87-1.15) p=0.943	100.0%

Heterogeneity:I² = 0.0%

Data Source	C+D				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	12,171	264	38,759	6.8	12,171	241	38,091	6.3	1.09 (0.85-1.40)	36.9%
CCAE	16,099	92	45,447	2.0	16,099	89	44,156	2.0	1.07 (0.70-1.64)	13.0%
Medicare	6,628	214	22,821	9.4	6,628	211	22,933	9.2	1.12 (0.83-1.50)	26.5%
Medicaid	1,188	18	3,273	5.5	1,188	24	3,405	7.0	0.77 (0.33-1.75)	3.3%
NHIS-NSC	2,373	82	12,608	6.5	2,373	91	12,688	7.2	0.89 (0.63-1.24)	20.3%
Overall	38,459	670	122,908	5.5	38,459	656	121,273	5.4	1.04 (0.90-1.20) p=0.486	100.0%

Heterogeneity:I² = 0.0%

D MACCE

Data Source	A+C				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	66,646	4,221	191,661	22.0	66,646	4,023	192,283	20.9	1.07 (1.00-1.14)	38.8%
CCAE	112,496	2,362	320,599	7.4	112,496	2,199	321,483	6.8	1.07 (0.98-1.16)	21.2%
Medicare	34,090	3,581	112,413	31.9	34,090	3,372	110,268	30.6	1.00 (0.94-1.08)	31.9%
Medicaid	3,972	460	11,965	38.4	3,972	420	12,239	34.3	1.07 (0.89-1.28)	4.7%
NHIS-NSC	4,733	326	15,855	20.6	4,733	285	16,546	17.2	1.18 (0.96-1.46)	3.5%
Overall	221,937	10,950	652,493	16.8	221,937	10,299	652,819	15.8	1.05 (1.00-1.11) p=0.051	100.0%

Heterogeneity:I² = 0.0%

Data Source	C+D				A+C				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	10,099	839	30,332	27.7	10,099	804	29,569	27.2	1.01 (0.87-1.16)	32.2%
CCAE	13,969	297	38,281	7.8	13,969	273	37,671	7.2	1.25 (0.99-1.58)	17.4%
Medicare	5,440	602	17,523	34.4	5,440	627	18,622	33.7	1.01 (0.86-1.20)	26.8%
Medicaid	998	67	2,650	25.3	998	98	2,737	35.8	0.73 (0.49-1.09)	7.2%
NHIS-NSC	1,732	182	8,341	21.8	1,732	191	8,435	22.6	0.93 (0.73-1.19)	16.3%
Overall	32,238	1,987	97,127	20.5	32,238	1,993	97,034	20.5	1.01 (0.85-1.21) p=0.857	100.0%

Heterogeneity:I² = 32.4%

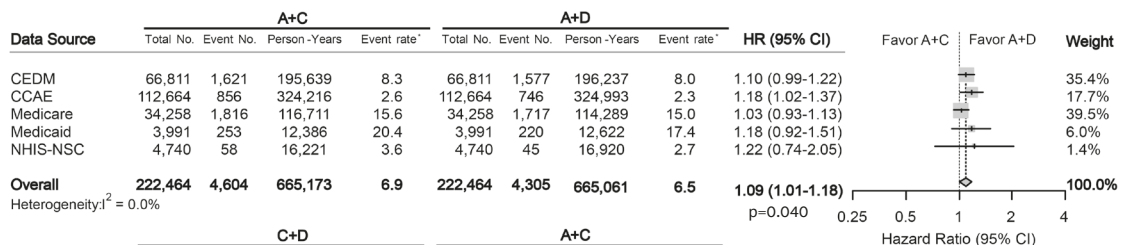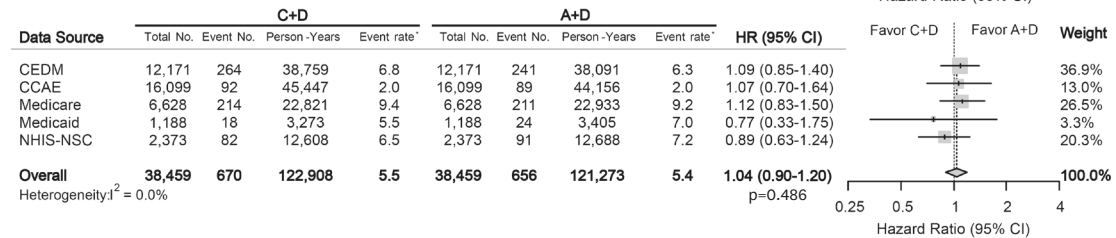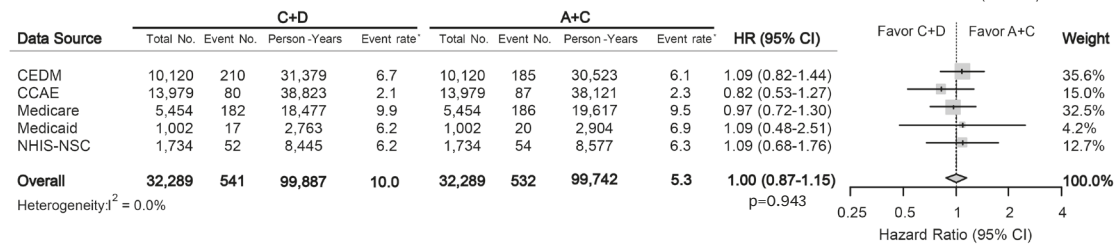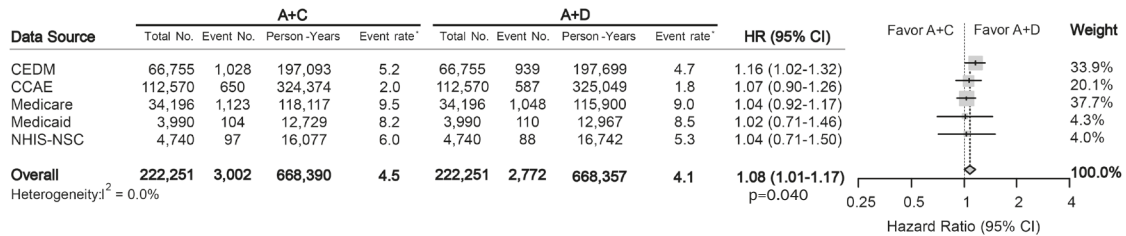| Data Source	C+D				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	12,150	1,047	37,461	27.9	12,150	930	36,915	25.2	1.11 (0.97-1.26)	28.0%
CCAE	16,087	343	44,810	7.7	16,087	275	43,721	6.3	1.30 (1.03-1.64)	18.2%
Medicare	6,619	733	21,664	33.8	6,619	661	21,931	30.1	1.27 (1.08-1.49)	24.9%
Medicaid	1,185	75	3,157	23.8	1,185	89	3,239	27.5	0.65 (0.41-1.01)	7.7%
NHIS-NSC	2,370	277	12,441	22.3	2,370	259	12,492	20.7	1.06 (0.87-1.28)	21.3%
Overall	38,411	2,475	119,533	20.7	38,411	2,214	118,298	18.7	1.12 (0.85-1.43) p=0.263	100.0%

Heterogeneity:I² = 58.9%

Figure 3. (Continued) Forest plots depicting HR and 95% CI for secondary outcomes in each data source. The overall HRs were calculated using a random-effects model. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs. (A) Myocardial infarction, (B) Heart failure, (C) Stroke, and (D) MACCE.
A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; CCAE = Truven MarketScan Commercial Claims and Encounters; CEDM = OptumInsight's Clinformatics™ Data Mart; CI = confidential interval; D = thiazide diuretics; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; Medicaid = Truven MarketScan Multi-State Medicaid; Medicare = Truven MarketScan Medicare Supplemental Beneficiaries; NHIS-NSC = National Health Insurance Service-National Sample Cohort.
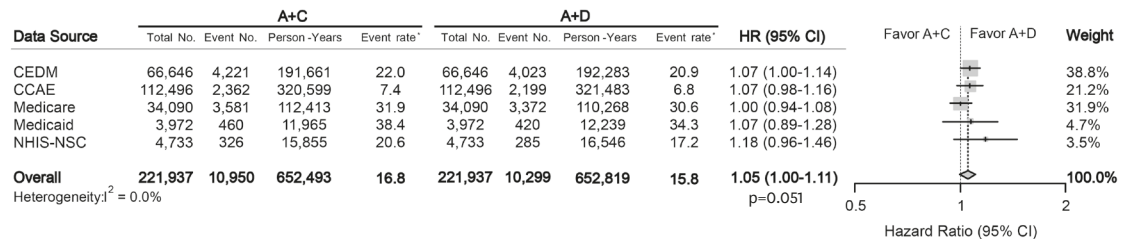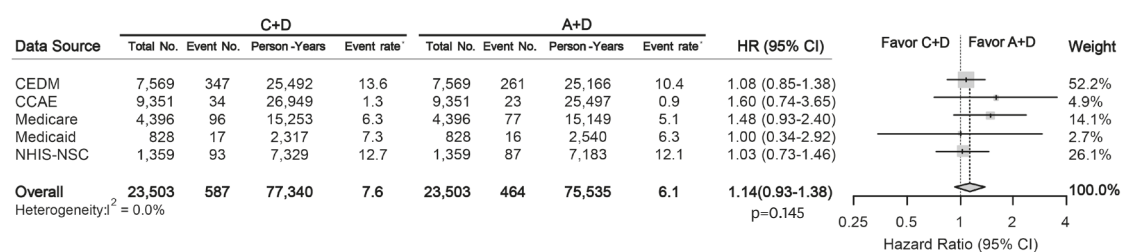*Event rate per 1,000 person-year.

A Women

A+C vs A+D

Data Source	A+C				A+D				HR (95% CI)	Favor A+C / Favor A+D	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	28,249	1,063	88,629	12.0	28,249	929	89,226	10.4	1.22 (1.08-1.40)		59.2%
CCAE	41,441	179	121,334	1.5	41,441	134	122,583	1.1	1.32 (0.95-1.85)		9.3%
Medicare	18,844	428	66,189	6.5	18,844	366	64,609	5.7	1.16 (0.93-1.44)		21.6%
Medicaid	2,530	72	8,450	8.5	2,530	83	8,507	9.8	1.06 (0.67-1.67)		4.8%
NHIS-NSC	2,000	93	6,769	13.7	2,000	72	7,226	10.0	0.97 (0.63-1.52)		5.2%
Overall	93,064	1,835	291,371	6.3	93,064	1,584	292,151	5.4	1.20 (1.09-1.31)		100.0%

Heterogeneity: I^2 = 0.0%   p=0.006

C+D vs A+C

Data Source	C+D				A+C				HR (95% CI)	Favor C+D / Favor A+C	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	6,023	263	19,826	13.3	6,023	244	19,599	12.4	0.90 (0.69-1.18)		56.1%
CCAE	7,786	25	22,006	1.1	7,786	36	21,849	1.6	0.75 (0.35-1.58)		7.0%
Medicare	3,477	80	11,729	6.8	3,477	100	12,517	8.0	1.03 (0.63-1.70)		16.2%
Medicaid	672	14	1,912	7.3	672	13	2,028	6.4	0.80 (0.20-3.02)		2.2%
NHIS-NSC	863	52	4,072	12.8	863	63	3,999	15.8	0.89 (0.56-1.42)		18.5%
Overall	18,821	434	59,545	7.3	18,821	456	59,992	7.6	0.91 (0.82-1.01)		100.0%

Heterogeneity: I^2 = 0.0%   p=0.060

C+D vs A+D

Data Source	C+D				A+D				HR (95% CI)	Favor C+D / Favor A+D	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	7,569	347	25,492	13.6	7,569	261	25,166	10.4	1.08 (0.85-1.38)		52.2%
CCAE	9,351	34	26,949	1.3	9,351	23	25,497	0.9	1.60 (0.74-3.65)		4.9%
Medicare	4,396	96	15,253	6.3	4,396	77	15,149	5.1	1.48 (0.93-2.40)		14.1%
Medicaid	828	17	2,317	7.3	828	16	2,540	6.3	1.00 (0.34-2.92)		2.7%
NHIS-NSC	1,359	93	7,329	12.7	1,359	87	7,183	12.1	1.03 (0.73-1.46)		26.1%
Overall	23,503	587	77,340	7.6	23,503	464	75,535	6.1	1.14 (0.93-1.38)		100.0%

Heterogeneity: I^2 = 0.0%   p=0.145

B Men

A+C vs A+D

Data Source	A+C				A+D				HR (95% CI)	Favor A+C / Favor A+D	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	38,518	827	111,086	7.4	38,518	809	111,560	7.3	0.95 (0.82-1.10)		32.7%
CCAE	71,163	316	204,299	1.5	71,163	257	204,380	1.3	1.40 (1.09-1.80)		22.4%
Medicare	15,259	365	54,686	6.7	15,259	382	53,135	7.2	0.91 (0.73-1.13)		24.8%
Medicaid	1,477	46	4,670	9.8	1,477	35	4,597	7.6	1.00 (0.54-1.87)		6.3%
NHIS-NSC	2,580	99	9,168	10.8	2,580	103	9,454	10.9	1.08 (0.74-1.57)		13.7%
Overall	128,997	1,653	383,909	4.3	128,997	1,586	383,126	4.1	1.05 (0.83-1.31)		100.0%

Heterogeneity: I^2 = 50.1%   p=0.611

C+D vs A+C

Data Source	C+D				A+C				HR (95% CI)	Favor A+C / Favor A+D	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	4,108	136	12,324	11.0	4,108	115	12,063	9.5	1.13 (0.78-1.64)		41.4%
CCAE	6,215	25	17,187	1.5	6,215	21	17,009	1.2	1.08 (0.49-2.41)		9.0%
Medicare	1,977	64	7,191	8.9	1,977	66	7,529	8.8	0.88 (0.50-1.55)		17.8%
Medicaid	334	7	943	7.4	334	7	1,048	6.7	2.00 (0.39-14.42)		1.7%
NHIS-NSC	830	64	4,354	14.7	830	52	4,378	11.9	1.05 (0.68-1.62)		30.1%
Overall	13,464	296	41,999	7.0	13,464	261	42,027	6.2	1.07 (0.90-1.26)		100.0%

Heterogeneity: I^2 = 0.0%   p=0.354

C+D vs A+D

Data Source	C+D				A+D				HR (95% CI)	Favor C+D / Favor A+D	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*			
CEDM	6,723	26	18,623	1.4	6,723	29	18,108	1.6	1.62 (0.68-4.10)		6.6%
CCAE	4,616	161	14,085	11.4	4,616	141	13,892	10.1	1.24 (0.86-1.82)		37.2%
Medicare	2,222	71	8,101	8.8	2,222	63	8,210	7.7	1.25 (0.73-2.16)		18.1%
Medicaid	356	7	993	7.0	356	4	997	4.0	0.75 (0.15-3.40)		2.2%
NHIS-NSC	1,004	78	5,509	14.2	1,004	69	5,408	12.8	1.40 (0.96-2.06)		35.9%
Overall	14,921	343	47,311	7.2	14,921	306	46,615	6.6	1.31 (1.12-1.53)		100.0%

Heterogeneity: I^2 = 0.0%   p=0.009

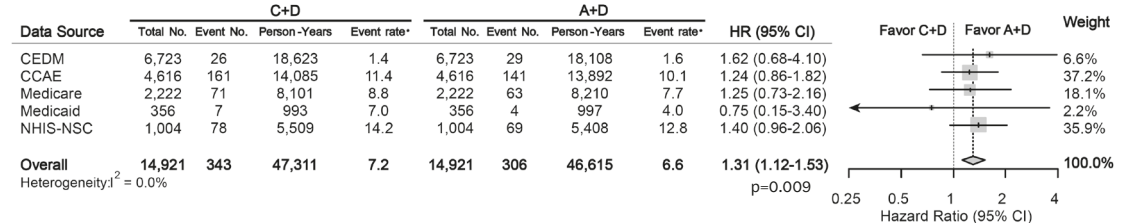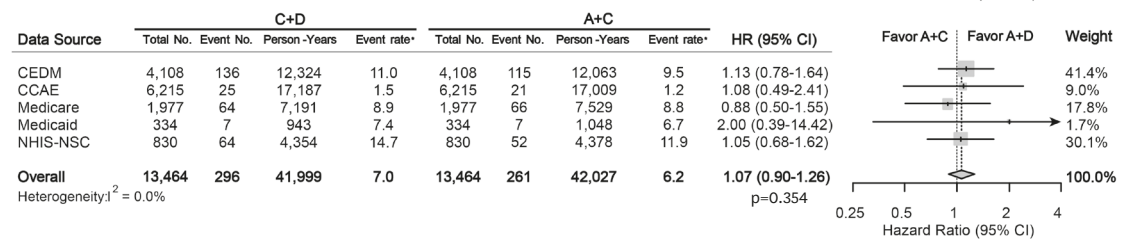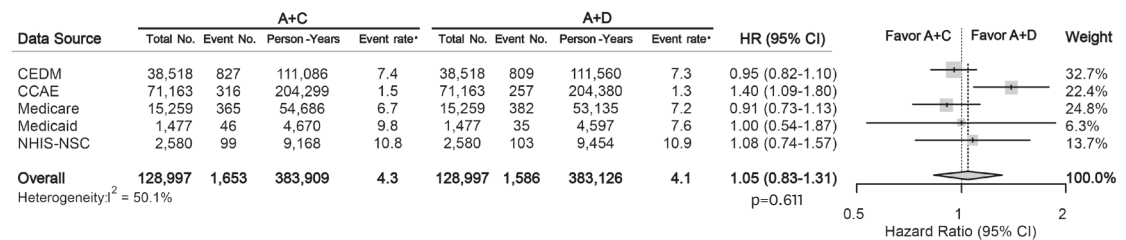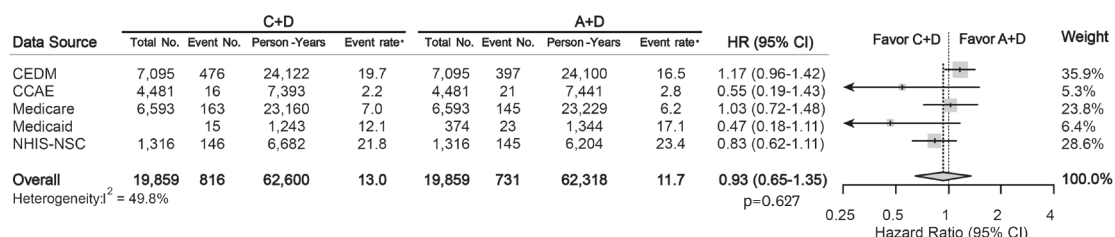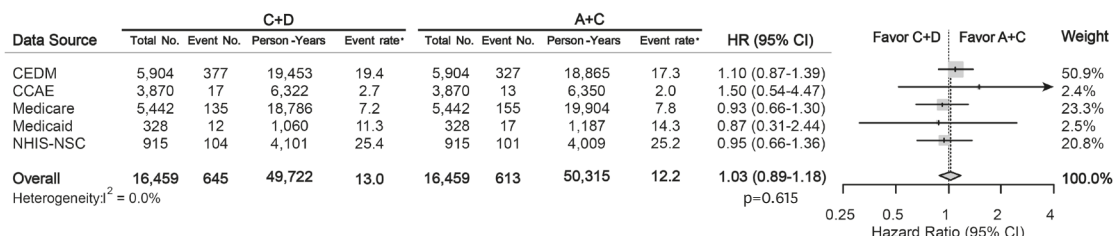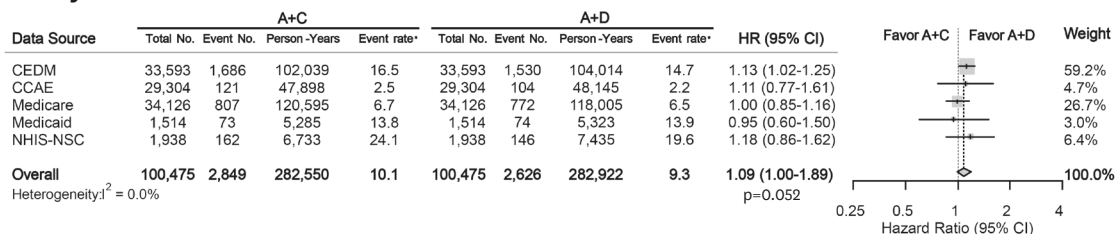**Figure 4.** Forest plots depicting HR and 95% CI for primary outcome in subgroups. The overall HRs were calculated using a random-effects model. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs. (A) Women, (B) Men, (C) ≥60 years, (D) <60 years.
A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; CCAE = Truven MarketScan Commercial Claims and Encounters; CEDM = OptumInsight's Clinformatics™ Data Mart; CI = confidential interval; D = thiazide diuretics; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; Medicaid = Truven MarketScan Multi-State Medicaid; Medicare = Truven MarketScan Medicare Supplemental Beneficiaries; NHIS-NSC = National Health Insurance Service-National Sample Cohort.
*Event rate per 1,000 person-year.
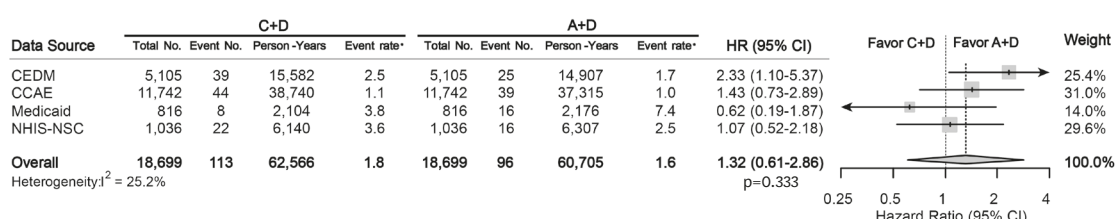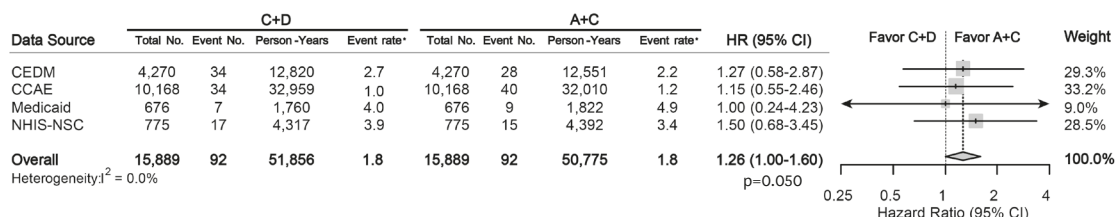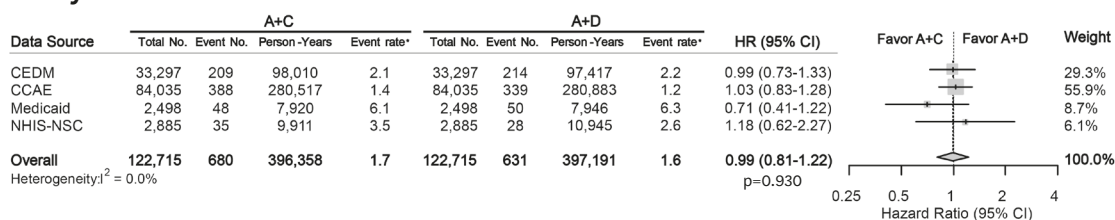
(continued to the next page)

C ≥60 years

Data Source	A+C				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	33,593	1,686	102,039	16.5	33,593	1,530	104,014	14.7	1.13 (1.02-1.25)	59.2%
CCAE	29,304	121	47,898	2.5	29,304	104	48,145	2.2	1.11 (0.77-1.61)	4.7%
Medicare	34,126	807	120,595	6.7	34,126	772	118,005	6.5	1.00 (0.85-1.16)	26.7%
Medicaid	1,514	73	5,285	13.8	1,514	74	5,323	13.9	0.95 (0.60-1.50)	3.0%
NHIS-NSC	1,938	162	6,733	24.1	1,938	146	7,435	19.6	1.18 (0.86-1.62)	6.4%
Overall	100,475	2,849	282,550	10.1	100,475	2,626	282,922	9.3	1.09 (1.00-1.89) p=0.052	100.0%
Heterogeneity:I² = 0.0%										

Data Source	C+D				A+C				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	5,904	377	19,453	19.4	5,904	327	18,865	17.3	1.10 (0.87-1.39)	50.9%
CCAE	3,870	17	6,322	2.7	3,870	13	6,350	2.0	1.50 (0.54-4.47)	2.4%
Medicare	5,442	135	18,786	7.2	5,442	155	19,904	7.8	0.93 (0.66-1.30)	23.3%
Medicaid	328	12	1,060	11.3	328	17	1,187	14.3	0.87 (0.31-2.44)	2.5%
NHIS-NSC	915	104	4,101	25.4	915	101	4,009	25.2	0.95 (0.66-1.36)	20.8%
Overall	16,459	645	49,722	13.0	16,459	613	50,315	12.2	1.03 (0.89-1.18) p=0.615	100.0%
Heterogeneity:I² = 0.0%										

Data Source	C+D				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	7,095	476	24,122	19.7	7,095	397	24,100	16.5	1.17 (0.96-1.42)	35.9%
CCAE	4,481	16	7,393	2.2	4,481	21	7,441	2.8	0.55 (0.19-1.43)	5.3%
Medicare	6,593	163	23,160	7.0	6,593	145	23,229	6.2	1.03 (0.72-1.48)	23.8%
Medicaid		15	1,243	12.1	374	23	1,344	17.1	0.47 (0.18-1.11)	6.4%
NHIS-NSC	1,316	146	6,682	21.8	1,316	145	6,204	23.4	0.83 (0.62-1.11)	28.6%
Overall	19,859	816	62,600	13.0	19,859	731	62,318	11.7	0.93 (0.65-1.35) p=0.627	100.0%
Heterogeneity:I² = 49.8%										

D <60 years

Data Source	A+C				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	33,297	209	98,010	2.1	33,297	214	97,417	2.2	0.99 (0.73-1.33)	29.3%
CCAE	84,035	388	280,517	1.4	84,035	339	280,883	1.2	1.03 (0.83-1.28)	55.9%
Medicaid	2,498	48	7,920	6.1	2,498	50	7,946	6.3	0.71 (0.41-1.22)	8.7%
NHIS-NSC	2,885	35	9,911	3.5	2,885	28	10,945	2.6	1.18 (0.62-2.27)	6.1%
Overall	122,715	680	396,358	1.7	122,715	631	397,191	1.6	0.99 (0.81-1.22) p=0.930	100.0%
Heterogeneity:I² = 0.0%										

Data Source	C+D				A+C				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	4,270	34	12,820	2.7	4,270	28	12,551	2.2	1.27 (0.58-2.87)	29.3%
CCAE	10,168	34	32,959	1.0	10,168	40	32,010	1.2	1.15 (0.55-2.46)	33.2%
Medicaid	676	7	1,760	4.0	676	9	1,822	4.9	1.00 (0.24-4.23)	9.0%
NHIS-NSC	775	17	4,317	3.9	775	15	4,392	3.4	1.50 (0.68-3.45)	28.5%
Overall	15,889	92	51,856	1.8	15,889	92	50,775	1.8	1.26 (1.00-1.60) p=0.050	100.0%
Heterogeneity:I² = 0.0%										

Data Source	C+D				A+D				HR (95% CI)	Weight
	Total No.	Event No.	Person-Years	Event rate*	Total No.	Event No.	Person-Years	Event rate*		
CEDM	5,105	39	15,582	2.5	5,105	25	14,907	1.7	2.33 (1.10-5.37)	25.4%
CCAE	11,742	44	38,740	1.1	11,742	39	37,315	1.0	1.43 (0.73-2.89)	31.0%
Medicaid	816	8	2,104	3.8	816	16	2,176	7.4	0.62 (0.19-1.87)	14.0%
NHIS-NSC	1,036	22	6,140	3.6	1,036	16	6,307	2.5	1.07 (0.52-2.18)	29.6%
Overall	18,699	113	62,566	1.8	18,699	96	60,705	1.6	1.32 (0.61-2.86) p=0.333	100.0%
Heterogeneity:I² = 25.2%										

Figure 4. (Continued) Forest plots depicting HR and 95% CI for primary outcome in subgroups. The overall HRs were calculated using a random-effects model. The size of data markers indicates the weight of the study. Error bars indicate 95% CIs. (A) Women, (B) Men, (C) ≥60 years, (D) <60 years.
A = angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; C = calcium-channel blocker; CCAE = Truven MarketScan Commercial Claims and Encounters; CEDM = OptumInsight's Clinformatics™ Data Mart; CI = confidential interval; D = thiazide diuretics; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; Medicaid = Truven MarketScan Multi-State Medicaid; Medicare = Truven MarketScan Medicare Supplemental Beneficiaries; NHIS-NSC = National Health Insurance Service-National Sample Cohort.
*Event rate per 1,000 person-year.

analysis of negative control outcomes are presented in **Supplementary Figure 4**. Calibrated p values based on the results of negative control outcomes analysis are also shown in **Supplementary Table 8**. The finding from the meta-analysis combining only the results from the US data sources was concordant with the finding from meta-analysis combining all results including the results from NHIS-NSC. All confidential intervals of the HR were overlapped for primary and secondary outcomes (**Supplementary Table 9**).

DISCUSSION

Based on the results of this real-world retrospective cohort study, there appears to be no significant difference in all-cause mortality between A+C, A+D, and C+D combination as first-line treatments of hypertension. This finding is consistent across the heterogeneous cohorts in both US and Korea, regardless of variability in the healthcare system. There was a slight benefit with initial A+D combination treatment for heart failure and stroke prevention over A+C.

To the best of our knowledge, this is the first study comparing effectiveness of first-line dual anti-hypertensive combinations in patients without CVD at baseline. Dual combination treatment in hypertension increases effectiveness and reduces adverse effects compared to monotherapy.[5)20)] 2018 ESC/ESH guideline recommends anti-hypertensive therapy should be initiated with combination regimen preferentially based on A+C or A+D.[7)] Notwithstanding, the evidence for head-to-head comparison of the combination regimens has been scarce.

In 2008, Jamerson et al. reported benefits of A+C treatment over A+D in reducing cardiovascular events in Western patients with high risk for CVD.[8)] Conversely, two Japanese studies did not demonstrate a significant difference between various combination regimens in preventing cardiovascular events. Matsuzaki et al.[21)] compared the CCB-based combinations with ARB, β-blocker, or TZD and demonstrated that all three combinations had similar efficacy for prevention of CVD and the achievement of target BP in population without high risk for CVD. Moreover, in a study by Ogihara et al.,[9)] there was no significant difference in terms of reduction of cardiovascular events between a combination of ARB and CCB versus ARB and TZD. In a meta-analysis analyzing the aforementioned RCTs, the all-cause mortality was not different between A+C and other combinations.[22)]

It is well-known that TZD is better for the prevention of heart failure compared to CCB.[23)24)] Although a previous meta-analysis demonstrated that CCB is the most effective drug class for stroke prevention, the protective effects of CCB for stroke were not significant compared to TZD.[23)24)] In this study, A+D treatment was associated with lower incidence of heart failure and stroke compared to A+C treatment, which should be interpreted with caution. A+D also showed benefits over A+C in women. A previous study reported that CCB monotherapy was associated with a greater risk of cardiovascular death compared to diuretics monotherapy in women.[25)] However, in another meta-analysis, there was no significant gender difference in efficacy among various classes of anti-hypertensive agents between men and women.[26)] The long-term effectiveness of dual anti-hypertensive combinations between sexes should be investigated further.

For assessing study robustness and residual systemic error, extensive efforts were made, including analysis of negative control outcomes. We demonstrated that body mass index,

systolic BP, smoking history, and other laboratory measures were well-matched in the sub-cohort of NHIS-NSC after PS matching even though these variants were not included in the PS model. Furthermore, the results from analyses on various minimum drug continuation periods were consistent. The numbers of patients who took the initial combination therapy for at least 365 days and 730 days were about two-thirds and one-third of the number in the original 180-day cohort, respectively. Although this number is low, it is in line with a previous cohort study in Italy, which demonstrated a medication discontinuation rate of 41% at 1 year and 50% at 5 years after initiation of monotherapy.[27]

Consistent findings demonstrated across the US and Asian cohorts analyzed under the same pre-specified analysis suggest generalizability of the study. Since all protocols and analytic codes are available publicly, the detailed review and reproduction of this study is possible. Still, this study carries several limitations. First, because of the nature of retrospective study, the true balance of baseline characteristics between cohorts and accuracy of non-fatal cardiovascular outcomes cannot be guaranteed. Although this problem can only be solved by RCTs, a randomized outcomes study to compare three different regimens in treatment-naïve hypertensive patients without previous CVD is unlikely to be feasible. Second, we could not assess the racial proportions in data sources except in the Medicaid, although we demonstrated that there was no difference in the effectiveness of combination regimens between US and Korean populations. Third, the overall mortality rate might be underestimated in the four US administrative datasets, because only hospital-reported mortality was captured in these data sources. Fourth, we did not adjust for dosage of anti-hypertensive medications and single-pill combinations. Although adherence to the single-pill combination is reported to be higher than individual-pill combination, the meta-analysis concluded that beneficial effects of single-pill combination in changes to BP or adverse effects was not significant.[28] To assess potential bias caused by compliance, we replicated the same analysis in the cohorts with various initial regimen continuation periods, in which the results were consistent with those of the primary analysis. Fifth, although a recent meta-analysis showed no significant differences in cardiovascular outcomes between ACEIs and ARBs,[29] whether these two classes of drugs can be considered a single class may be a matter of controversy. Lastly, an aggregate meta-analysis approach without pooling the individual data can be another limitation of this study. Nonetheless, a previous study demonstrated that an aggregate meta-analysis approach generates estimates at least as accurate and precise as pooled dataset analysis, especially when the effects of interest are heterogeneous.[30]

In conclusion, this is the first observational study comparing effectiveness of first-line dual combination treatments in multi-national heterogeneous cohorts in real-world practice. In this study, there is no significant difference in mortality among recommended dual combination treatment regimens in treatment-naïve hypertensive patients without previous CVD. This finding provides evidence for comparable effectiveness between recommended initial anti-hypertensive combination treatments in real-world practice.

ACKNOWLEDGEMENTS

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Drug code list

Click here to view

Supplementary Table 2
Disease code list

Click here to view

Supplementary Table 3
Baseline characteristics in CEDM before and after propensity score matching

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Supplementary Table 4
Baseline characteristics in CCAE before and after propensity score matching

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Supplementary Table 5
Baseline characteristics in Medicare before and after propensity score matching

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Supplementary Table 6
Baseline characteristics in Medicaid before and after propensity score matching

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Supplementary Table 7
Baseline characteristics in NHIS-NSC before and after propensity score matching

Click here to view

Supplementary Table 8
Calibrated p-values in each data source

Click here to view

Supplementary Table 9
Meta-analysis using the result from the four US data sources

Click here to view

Supplementary Figure 1

PSs distribution before and after matching. (A), CEDM, (B) CCAE, (C) Medicare, (D) Medicaid, and (E) NHIS-NSC.

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Supplementary Figure 2

Kaplan-Meier plots for secondary outcomes comparing different dual combination treatment in propensity score-matched cohorts from each data source. (A) Myocardial infarction, (B) Stroke, (C) Heart failure, and (D) MACCE.

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Supplementary Figure 3

All-cause mortality in patients with various drug periods.

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Supplementary Figure 4

Funnel plot of negative control outcomes in each data source. (A) CEDM, (B) CCAE, (C) Medicare, (D) Medicaid, and (E) NHIS-NSC. A total of 39 negative control outcomes are shown as blue dots and the primary outcome (overall mortality) as yellow diamonds. The area below the dash line indicated estimates with p<0.05. The orange area indicates estimates with calibrated p<0.05. Overall, less than 5% of negative controls showed significant association with the treatment.

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