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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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#### **Conflict of Interest**

The authors declare the following disclosures: Mr. Swerdel, Dr. Ryan, and Dr. Schuemie are employees of Janssen Research & Development. The rest of the authors declare no conflict of interest.

#### **Author Contributions**

Conceptualization: You SC, Suchard MA, Cho J, Hripcsak G, Park S; Data curation: You SC, Jung S, Swerdel JN, Suchard MA, Lee S, Hripcsak G; Formal analysis: You SC, Suchard MA, Lee S; Funding acquisition: Lee S, Park RW; Investigation: You SC, Jung S, Cho J, Park RW; Methodology: You SC, Jung S, Swerdel JN, Schuemie MJ, Cho J, Hripcsak G; Project administration: You SC, Cho J, Park RW, Park S; Resources: Swerdel JN; Software: You SC. Swerdel JN. Schuemie MJ. Suchard MA: Supervision: Ryan PB, Schuemie MJ, Lee S, Park RW, Park S; Validation: Ryan PB, Lee S, Cho J; Visualization: You SC; Writing - original draft: You SC, Ryan PB, Schuemie MJ, Suchard MA, Hripcsak G, Park S

**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.<sup>1)</sup> While extensive evidence supports the beneficial effects of rapid BP control below the target in preventing mortality and cardiovascular disease (CVD),<sup>2)</sup> initial treatment with monotherapy is often insufficient or slow to achieve the BP target.<sup>3)</sup> Observational studies and meta-analyses have suggested that initial combination of hypertensive treatments confers a decreased risk for CVD compared to monotherapy.<sup>4-6)</sup> 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.<sup>7)</sup> Despite the evidences from previous randomized controlled trials (RCTs) that directly compared the effects of different combination regimens,<sup>8-11)</sup> 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.<sup>12)</sup> 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)<sup>13)</sup> 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 ( $\geq$ 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,  $\beta$ -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)<sup>14)</sup> 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.<sup>15)</sup> 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  $\geq$ 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.<sup>16</sup>

A total of 39 negative control outcomes were employed to quantify systematic error.<sup>17)</sup> These negative control outcomes were unlikely to have a relationship with anti-hypertensive medications, identified through a data-rich algorithm.<sup>18)</sup> 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.<sup>19)</sup> 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**).

#### **Combination Therapy in Hypertension**

Table	<ol> <li>Baselin</li> </ol>	ie characteristi	cs of all n	propensity	/-score-mat	ched patients

	A	+C vs. A+D		C	C+D vs. A+C		C	C+D vs. A+D	
Characteristics	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**.

## **Combination Therapy in Hypertension**



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.

Α			A+C				A+D			Eavor A+		
Data Source	Total No.	Event No.	Person -Years	Event rate*	Total No.	Event No.	Person -Years	Event rate	HR (95% CI)			Weigh
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	Ó		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	ń —	•	4.6%
NHIS-NSC	4,747	198	16,407	12.1	4,747	170	17,072	10.0	1.27 (0.96-1.69	ý		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	)	$\Leftrightarrow$	100.0
Heterogeneity:12 =	4.6%								p=0.127	0.5	1	2
										Hazard	Ratio (95% CI)	
В			C+D				A+C			Favor C+D	Favor A+C	
Data Source	Total No.	Event No.	Person -Years	Event rate*	Total No.	Event No.	Person -Years	Event rate*	HR (95% CI)			Weigh
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)		x	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)	<b>←</b> →		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:12	= 0.0%								p=0.067	0.5	1	2
-										Hazard	Ratio (95% CI)	
С			C+D				A+D			<b>F</b>		
Data Source	Total No.	Event No.	Person -Years	Event rate*	Total No.	Event No.	Person -Years	Event rate*	HR (95% CI)	Favor C+D	Favor A+D	Weight
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:12	= 14.2%								p=0.104	0.5	1	2
										Hazard F	atio (95% CI)	

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 twothirds 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

			A+C				A+D					
Data Source	Total No.	Events	Person -Years	Event rate	Total No.	Events	Person -Years	Event rate	HR (95% CI)	Favor A+C	Favor A+D	Weight
CEDM	66 868	700	198 211	35	66 868	737	198 524	37	0.92 (0.80-1.07)		<u> </u>	32.8%
CCAF	112 687	703	324 310	2.2	112 687	700	324 866	22	0.94 (0.81-1.10)		<b>—</b>	30.8%
Medicare	34,302	714	119.581	6.0	34,302	714	117,170	6.1	0.95 (0.82-1.10)		<u> </u>	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%
<b>.</b>										_	L	400.00
Overall 2	222,606	2,235	671,255	3.3	222,606	2,255	670,627	3.4	0.96 (0.85-1.07)		F	100.0%
Heterogeneity:1	= 0.0%								p=0.351	0.5	1	2
										Hazard Rat	io (95% CI)	
			C+D				A+C		_			
Data Source	Total No.	Events	Person -Years	Event rate*	Total No.	Events F	Person -Years	Event rate	HR (95% CI)	Favor C+D	avor A+C	Weight
CEDM	10 138	137	31 678	43	10 138	116	30 801	3.8	1 51 (1 06-2 18)	_	; • _ <b>&gt;</b>	28.2%
CCAE	13,995	89	38.773	2.3	13,995	62	38.223	1.6	2.12 (1.33-3.47)		$\rightarrow$	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)	( IIII IIII IIII IIII IIII IIII IIII I	$\rightarrow$	10.4%
NHIS-NSC	1,735	22	8,519	2.6	1,735	14	8,690	1.6	1.58 (0.78-3.35)		$\rightarrow$	12.6%
Overall	20.000	200	100.005		20.226	220	400.075					- 400.00/
	32,330	209	100,385	3.9	32,330	330	100,375	3.3	1.40 (0.93-2.10)			100.0%
Heterogeneity:	= 44.4%								p=0.082	5 1		2
										Hazard Ratio	(95% CI)	
			C+D				A+D		_			
Data Source	Total No.	Events	Person -Years	Event rate	Total No.	Events	Person -Years	Event rate'	HR (95% CI)	Favor C+D	Favor A+D	Weight
CEDM	12 183	171	39 141	44	12 183	151	38 326	39	1.39 (1.03-1.89)	-	$\rightarrow$	36.1%
CCAF	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)		<u> </u>	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%
NBICS	2,377	27	12,796	2.1	2,377	31	12,954	2.4	0.83 (0.46-1.51)	< <u> </u>		11.7%
Overall	38,505	471	123,628	3.8	38,505	390	122,201	3.2	1.17 (0.87-1.58)			100.0%
Heterogeneity: I2	= 14.4%								p=0.209	5 1		2
			A+C				A+D					
Data Source	Total No.	Event No.	Person -Years	Event rate*	Total No.	Event No.	Person -Years	Event rate	HR (95% CI)	Favor A+C	Favor A+D	Weight
CEDM	66 811	1 621	195 639	83	66 811	1 577	196 237	8.0	1 10 (0 99-1 22)		-	35 4%
CCAF	112 664	856	324 216	2.6	112 664	746	324 993	0.0	1 18 (1 02-1 37)			47 70/
Medicare	34.258	1.816	116.711	2.0		140	021.000	2.3				1/////0
Medicaid	3,991	050	,	15.6	34,258	1.717	114 289	2.3 15.0	1.03 (0.93-1.13)	-	-	39.5%
NHIS-NSC	1 740	253	12,386	15.6 20.4	34,258 3,991	1,717 220	114,289 12,622	2.3 15.0 17.4	1.03 (0.93-1.13) 1.18 (0.92-1.51)	-	-	39.5% 6.0%
Overall	4,740	253 58	12,386 16,221	15.6 20.4 3.6	34,258 3,991 4,740	1,717 220 45	114,289 12,622 16,920	2.3 15.0 17.4 2.7	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05)	_	•	39.5% 6.0% 1.4%
	222.464	58 <b>4.604</b>	12,386 16,221 <b>665.173</b>	15.6 20.4 3.6 <b>6.9</b>	34,258 3,991 4,740 222.464	1,717 220 45 <b>4.305</b>	114,289 12,622 16,920	2.3 15.0 17.4 2.7	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05)			17.7% 39.5% 6.0% 1.4% <b>100.0%</b>
Heterogeneity:12 =	<b>222,464</b> = 0.0%	253 58 <b>4,604</b>	12,386 16,221 <b>665,173</b>	15.6 20.4 3.6 <b>6.9</b>	34,258 3,991 4,740 <b>222,464</b>	1,717 220 45 <b>4,305</b>	114,289 12,622 16,920 665,061	2.3 15.0 17.4 2.7 <b>6.5</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) <b>1.09 (1.01-1.18)</b>			17.7% 39.5% 6.0% 1.4% <b>100.0%</b>
Heterogeneity:I <sup>2</sup> =	<b>222,464</b> = 0.0%	253 58 <b>4,604</b>	12,386 16,221 665,173	15.6 20.4 3.6 <b>6.9</b>	34,258 3,991 4,740 <b>222,464</b>	1,717 220 45 <b>4,305</b>	114,289 12,622 16,920 665,061	2.3 15.0 17.4 2.7 <b>6.5</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) <b>1.09 (1.01-1.18)</b> p=0.040 0	.25 0.5 1	2	17.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4
Heterogeneity:1 <sup>2</sup> =	<b>222,464</b> = 0.0%	253 58 <b>4,604</b>	12,386 16,221 665,173 C+D	15.6 20.4 3.6 <b>6.9</b>	34,258 3,991 4,740 222,464	1,717 220 45 <b>4,305</b>	114,289 12,622 16,920 665,061 A+C Person-Years	2.3 15.0 17.4 2.7 <b>6.5</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HB (95% Cl)	.25 0.5 1 Hazard Rati	2 0 (95% CI)	17.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4
Heterogeneity:l <sup>2</sup> = Data Source	<b>222,464</b> = 0.0%	253 58 <b>4,604</b>	12,386 16,221 665,173 C+D . Person -Years	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup>	34,258 3,991 4,740 222,464	1,717 220 45 <b>4,305</b> Event No.	114,289 12,622 16,920 665,061 A+C Person -Years	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 - HR (95% CI)	.25 0.5 1 Hazard Rati Favor C+D	2 o (95% Cl) Favor A+C	17.7% 39.5% 6.0% 1.4% 100.0% 4
Heterogeneity:I <sup>2</sup> = Data Source CEDM	222,464 = 0.0% Total No. 10,118	253 58 <b>4,604</b> . Event No. 346	12,386 16,221 665,173 C+D . Person -Years 31,064	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup>	34,258 3,991 4,740 222,464 Total No. E	1,717 220 45 <b>4,305</b> Event No.	114,289 12,622 16,920 665,061 A+C Person -Years 30,240	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>*</sup>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) <b>1.09 (1.01-1.18)</b> p=0.040 0 <b>HR (95% CI)</b> 1.19 (0.94-1.50)	.25 0.5 1 Hazard Rati Favor C+D	2 o (95% Cl) Favor A+C	17.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4 <b>Weight</b> 28.1%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE	<b>222,464</b> = 0.0% Total No. 10,118 13,995	253 58 <b>4,604</b> . Event No. 346 121	12,386 16,221 665,173 C+D Person -Years 31,064 38,741	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup> 11.1 3.1	10,118 13,991 14,740 222,464	1,717 220 45 <b>4,305</b> Event No.	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) <b>1.09 (1.01-1.18)</b> p=0.040 0 <b>HR (95% CI)</b> 1.19 (0.94-1.50) 1.30 (0.89-1.91)	.25 0.5 1 Hazard Rati Favor C+D	2 o (95% Cl) Favor A+C	17.7% 39.5% 6.0% 1.4% 4 Weight 28.1% 21.5%
Heterogeneity:1 <sup>2</sup> = <b>Data Source</b> CEDM CCAE Medicare	4,740 222,464 = 0.0% Total No. 10,118 13,995 5,455	253 58 <b>4,604</b> . Event No. 346 121 318	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup> 11.1 3.1 17.5	10,118 13,258 3,991 4,740 222,464 Total No. E 10,118 13,995 5,455	1,717 220 45 <b>4,305</b> Event No. 301 99 315	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) <b>1.09 (1.01-1.18)</b> p=0.040 0 <b>HR (95% CI)</b> 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30)	.25 0.5 1 Hazard Rati Favor C+D	2 o (95% CI) Favor A+C	17.7% 39.5% 6.0% 1.4% 4 Weight 28.1% 21.5% 27.7%
Heterogeneity:1 <sup>2</sup> = <b>Data Source</b> CEDM CCAE Medicare Medicaid	4,740 222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004	253 58 4,604 . Event No. 346 121 318 25	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174 2,744	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup> 11.1 3.1 17.5 9.1	10,118 13,995 5,455 1,004	1,717 220 45 <b>4,305</b> Event No. 301 99 315 53	114,289 12,622 16,920 665,061 A+C Person-Years 30,240 38,112 19,345 2,836	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81)	.25 0.5 1 Hazard Rati Favor C+D	2 o (95% Cl) Favor A+C	17.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4 <b>Weight</b> 28.1% 21.5% 27.7% 12.4%
Heterogeneity:/ <sup>2</sup> = Data Source CEDM CCAE Medicare Medicaid NHIS-NSC	4,740 222,464 = 0.0% 10,118 13,995 5,455 1,004 1,733	253 58 4,604 . Event No. 346 121 318 25 19	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174 2,744 8,535	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup> 11.1 3.1 17.5 9.1 2.2	34,258 3,991 4,740 <b>222,464</b> Total No. E 10,118 13,995 5,455 1,004 1,733	1,717 220 45 <b>4,305</b> Event No. 301 99 315 53 29	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20)	.25 0.5 1 Hazard Rati	2 o (95% Cl) Favor A+C	4 Weight 28.1% 27.7% 10.3%
Heterogeneity:/ <sup>2</sup> = Data Source CEDM CCAE Medicare Medicaid NHIS-NSC Overall	4,740 222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 32,305	253 58 4,604 . Event No. 346 121 318 25 19 829	12,386 16,221 665,173 C+D Person-Years 31,064 38,741 18,174 2,744 8,535 99,258	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b>	34,258 3,991 4,740 222,464 Total No. E 10,118 13,995 5,455 1,004 1,733 32,305	1,717 220 45 <b>4,305</b> Event No. 301 99 315 53 29 <b>797</b>	114,289 12,622 16,920 665,061 A+C Person-Years 30,240 38,112 19,345 2,836 8,645 99,178	2.3 15.0 17.4 2.7 <b>6.5</b> <u>Event rate'</u> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% CI) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01)	.25 0.5 1 Hazard Rati	2 o (95% Cl) Favor A+C	1.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4 <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicaid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup>	222,464 = 0.0% Total No. 10,118 13,995 5,455 5,455 5,004 1,733 2,305 = 65,9%	253 58 4,604 . Event No. 346 121 318 25 19 829	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174 2,744 8,535 99,258	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>**</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b>	34,258 3,991 4,740 222,464 10,118 13,995 5,455 1,004 1,733 32,305	1,717 220 45 <b>4,305</b> Event No. 301 99 315 53 29 <b>797</b>	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.01) p=0.943	25 0.5 1 Hazard Rati Favor C+D	2 o (95% Cl) Favor A+C	1.7% 39.5% 6.0% 1.4% 100.0% 4 Weight 28.1% 21.5% 27.7% 12.4% 10.3%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicaid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup>	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 22,305 2 = 65.9%	253 58 4,604 . Event No. 346 121 318 25 19 829	12,386 16,221 665,173 C+D . Person-Years 31,064 38,741 18,174 2,744 8,535 99,258	15.6 20.4 3.6 <b>6.9</b> 11.1 17.5 9.1 2.2 <b>8.4</b>	34,258 3,991 4,740 222,464 Total No. E 10,118 13,995 5,455 1,004 1,733 32,305	1,717 220 45 <b>4,305</b> Event No. 301 99 315 53 29 <b>797</b>	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>*</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% CI) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.22	25 0.5 1 Hazard Rati Favor C+D	2 o (95% Cl) Favor A+C	1.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4 <b>Weight</b> 28.1% 27.7% 12.4% 10.3% <b>100.0%</b> 4
Heterogeneity:1 <sup>2</sup> - Data Source CEDM CCAE Medicare Medicaid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup>	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 32,305 <sup>2</sup> = 65.9%	253 58 4,604 . Event No. 346 121 318 25 19 829	12,386 16,221 665,173 C+D Person-Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D	15.6 20.4 3.6 <b>6.9</b> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b>	34,258 3,991 4,740 222,464 Total No. E 10,118 13,995 5,455 1,004 1,733 32,305	1,717 220 45 4,305 2vent No. 301 99 315 53 29 797	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178	2.3 15.0 17.4 2.7 <b>6.5</b> <b>Event rate</b> <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% CI) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.30 (0.89-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.21	25 0.5 1 Hazard Ratio	2 o (95% Cl) Favor A+C - - 2 (95% Cl)	4 Weight 28.1% 27.7% 12.4% 100.0% 4 4 Weight 28.1% 27.7% 12.4% 10.3% 4
Heterogeneity:1 <sup>2</sup> - Data Source CEDM CCAE Medicare Medicare NHIS-NSC Overall Heterogeneity:1 <sup>2</sup>	222,464 222,464 Total No. 10,118 13,995 5,455 1,004 1,733 2= 65.9% Total No.	253 58 4,604 . Event No. 346 121 318 25 19 829 829	12,386 16,221 665,173 C+D Person-Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person-Years	15.6 20.4 3.6 6.9 Event rate <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 8.4	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305	1,717 220 45 4,305 Event No. 301 99 315 53 29 <b>797</b>	114,289 12,622 16,920 665,061 A+C 9erson -Years 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person -Years	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> Event rate <sup>-</sup>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% CI) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HB (95% CI)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - 2 (95% Cl) Favor A+D	1.7% 39.5% 6.0% 1.4% <b>100.0%</b> 4 <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3% <b>100.0%</b> 4
Heterogeneity:1 <sup>2</sup> - Data Source CEDM CCAE Medicare Medicarid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 32,305 = 65.9% Total No.	253 58 4,604 . Event No. 346 121 318 25 19 829 Event No.	12,386 16,221 665,173 C+D Person -Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person -Years	15.6 20.4 3.6 <b>6.9</b> Event rate <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> Event rate <sup>*</sup>	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.	1,717 220 45 4,305 20 301 99 315 53 29 797 Event No.	114,289 12,622 16,920 665,061 A+C 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person-Years	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>*</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> Event rate <sup>*</sup>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% Cl)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - 2 (95% Cl) Favor A+D	1.7% 39.5% 6.0% 1.4% <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3% <b>120.0%</b> 4 <b>Weight</b>
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicarid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 32,305 2 = 65.9% Total No. 12,167	253 58 4,604 . Event No. 346 121 318 25 19 829 Event No. 420	12,386 16,221 665,173 C+D . Person-Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person-Years 38,422	15.6 20.4 3.6 <b>6.9</b> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> Event rate <sup>*</sup>	34,258         3,991           3,740         222,464           Total No. E         10,118           13,995         5,455           1,004         1,733           32,305         Total No.           Total No.         12,167	1,717 220 45 4,305 20 301 99 315 53 29 <b>797</b> Event No. 356	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178 Person -Years 37,800	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> Event rate <sup>-</sup> 9.4	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% Cl) 1.19 (0.96-1.47)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - 2 (95% Cl) Favor A+D Favor A+D	1.7% 39.5% 6.0% 1.4% 4 Weight 28.1% 27.7% 12.4% 10.3% 4 100.0% 4 Weight 26.5%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicaid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE	4,140           222,464           = 0.0%           Total No.           10,118           13,995           5,455           1,004           1,733           32,305           2           Total No.           12,167           16,112	253 58 4,604 . Event No. 346 121 318 25 19 829 Event No. 420 134	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person -Years 38,422 45,363	15.6 20.4 3.6 <b>6.9</b> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> Event rate <sup>7</sup> 10.9 3.0	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.           Total No.           12,167           16,112	1,717 220 45 4,305 2vent No. 301 99 315 53 29 <b>797</b> Event No. 356 83	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person -Years 37,800 44,244	2.3 15.0 17.4 2.7 <b>6.5</b> <b>Event rate</b> <sup>*</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> <b>Event rate</b> <sup>*</sup> 9.4 1.9	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.22 HR (95% Cl) 1.19 (0.96-1.47) 1.60 (1.09-2.36)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - 2 (95% Cl) Favor A+D Favor A+D	1.7% 39.5% 6.0% 1.4% 4 Weight 28.1% 21.5% 27.7% 12.4% 10.3% 4 <b>Weight</b> 4 <b>Weight</b> 26.5% 20.2%
Heterogeneity:1 <sup>2</sup> - Data Source CEDM CCAE Medicare Medicare NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE Medicare	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 2 = 65.9% Total No. 12,167 16,112 6,632	253 58 4,604 . Event No. 346 121 318 25 19 829 829 Event No. 420 134 383	12,386 16,221 665,173 C+D Person-Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person-Years 38,422 45,363 22,452	15.6 20.4 3.6 <b>6.9</b> <u>Event rate</u> <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> <u>Event rate</u> <sup>*</sup> 10.9 3.0 17.1	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.           12,167           16,632	1,717 220 45 4,305 20 301 99 315 53 29 <b>797</b> Event No. 258 253 29 <b>797</b>	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person -Years 37,800 44,224 22,618	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> Event rate <sup>-</sup> 9.4 15.8	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% CI) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% CI) 1.19 (0.96-1.47) 1.60 (1.09-2.36) 1.33 (1.06-1.66)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - 2 (95% Cl) Favor A+D -	1.7% 39.5% 6.0% 1.4% <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3% <b>100.0%</b> 4 <b>Weight</b> 26.5% 20.2% 26.1%
Heterogeneity:1 <sup>2</sup> - Data Source CEDM CCAE Medicare Medicarid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE Medicare Medicare	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 2= 65.9% Total No. 12,167 16,112 6,632 1,192	253 58 4,604 . Event No. 346 121 318 25 19 829 829 Event No. 420 134 383 32	12,386 16,221 665,173 C+D Person -Years 31,064 38,741 18,174 2,744 8,535 99,258 Person -Years 38,422 45,363 22,452 3,254	15.6 20.4 3.6 <b>6.9</b> <b>Event rate</b> <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> <b>Event rate</b> <sup>*</sup> 10.9 3.0 17.1 9.8	34,258         3,991           3,921         4,740           222,464         10,118           13,995         5,455           1,004         1,733           32,305         1,004           Total No.         12,167           16,312         6,632           1,192         1,192	1,717 220 45 4,305 Event No. 301 99 315 53 29 <b>797</b> Event No. 356 83 358 83 47	114,289 12,622 16,920 665,061 A+C Person-Years 30,240 38,112 19,345 2,836 8,645 99,178 Person-Years 37,800 44,244 22,618 3,293	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> Event rate <sup>-</sup> 9.4 1.5.8 14.3	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.43 (0.22-0.81) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% Cl) 1.19 (0.96-1.47) 1.60 (1.09-2.36) 1.33 (1.06-1.66) 0.34 (0.16-0.68)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - 2 (95% Cl) Favor A+D	1.7% 39.5% 6.0% 1.4% <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3% <b>Weight</b> 26.5% 20.2% 26.1% 26.1%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicare MHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE Medicare Medicare Medicare Medicare	4,140           222,464           = 0.0%           Total No.           10,118           13,955           5,455           1,004           1,733           32,305           2 = 65.9%           Total No.           12,167           16,112           6,632           1,192           2,374	253 58 4,604 . Event No. 346 121 318 25 19 829 829 Event No. 420 134 382 32 40	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person -Years 38,422 45,363 22,452 3,254 12,770	15.6 20.4 3.6 <b>6.9</b> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> Event rate <sup>*</sup> 10.9 3.0 17.1 9.8 3.1	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.           12,167           16,512           6,632           1,192           2,374	1,717 220 45 4,305 Event No. 301 99 315 53 29 <b>797</b> Event No. 356 83 358 83 47 44	114,289 12,622 16,920 665,061 A+C Person-Years 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person-Years 37,800 44,244 22,618 3,293 12,883	2.3 15.0 17.4 2.7 <b>6.5</b> <b>Event rate</b> <sup>*</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> <b>Event rate</b> <sup>*</sup> 9.4 1.9 15.8 14.3 3.4	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% Cl) 1.19 (0.96-1.47) 1.60 (1.09-2.36) 1.33 (1.06-1.66) 0.34 (0.16-0.68) 0.97 (0.58-1.60)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - - - - - - - - - - - - - - - - - -	1.7% 39.5% 6.0% 1.4% <b>4</b> <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3% <b>100.0%</b> 4 <b>Weight</b> 26.5% 20.2% 26.1% 10.9% 10.9%
Heterogeneity:1 <sup>2</sup> : Data Source CEDM CCAE Medicare Medicaid NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE Medicare Medicare Medicare Medicare CEDM CCAE	4,140           222,464           = 0.0%           Total No.           10,118           13,995           5,455           1,004           1,733           32,305           2 = 65.9%           Total No.           12,167           16,112           6,632           1,192           2,374           38,477	253 58 4,604 . Event No. 346 121 318 25 19 829 Event No. 420 134 383 32 40	12,386 16,221 665,173 C+D . Person -Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person -Years 38,422 45,363 22,452 3,254 12,770	15.6 20.4 3.6 6.9 11.1 3.1 17.5 9.1 2.2 8.4 Event rate <sup>*</sup> 10.9 3.0 17.1 9.8 3.1	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.           12,167           16,112           6,632           1,192           2,374           38,477	1,717 220 45 4,305 20 301 99 315 53 29 <b>797</b> Event No. 356 83 358 47 44	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person -Years 37,800 44,244 22,618 3,293 12,883 120,838	2.3 15.0 17.4 2.7 <b>6.5</b> <b>Event rate'</b> 1.0 2.6 <b>5</b> 18.7 3.4 <b>8.0</b> <b>Event rate'</b> 9.4 1.9 15.8 14.3 3.4 <b>7</b> 3.4	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.22 HR (95% Cl) 1.19 (0.96-1.47) 1.60 (1.09-2.36) 1.33 (1.06-1.66) 0.34 (0.16-0.68) 0.97 (0.58-1.60) 1.48 (0.56-1.47)	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - 2 (95% Cl) Favor A+D -	1.7% 39.5% 6.0% 1.4% <b>Weight</b> 28.1% 21.5% 27.7% 12.4% 10.3% <b>100.0%</b> 4 <b>Weight</b> 26.5% 20.2% 26.1% 10.9% 16.3%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicare NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE Medicare Medic	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 2 = 65.9% Total No. 12,167 16,112 6,632 1,192 2,38,77 2 = 3,000	253 58 4,604 . Event No. 346 121 318 25 19 829 Event No. 420 134 383 32 40 1,009	12,386 16,221 665,173 C+D Person-Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person-Years 38,422 45,363 22,452 3,254 12,770 122,261	15.6 20.4 3.6 <b>6.9</b> <b>Event rate</b> <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> <b>Event rate</b> <sup>*</sup> 10.9 3.0 17.1 9.8 3.1 <b>8.3</b>	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.           12,167           16,632           1,192           2,374           38,477	1,717 220 45 4,305 29 315 53 29 797 Event No. 356 83 358 47 44 888	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178 A+D Person -Years 37,800 44,244 22,618 3,293 12,883 120,838	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>-</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> 9.4 15.8 14.3 3.4 <b>7.3</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% CI) 1.19 (0.84-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% CI) 1.19 (0.96-1.47) 1.60 (1.09-2.36) 1.33 (1.06-1.66) 0.34 (0.16-0.68) 0.97 (0.58-1.64) 1.18 (0.95-1.47) p=0.486	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - 2 (95% Cl) Favor A+D - -	1.7% 39.5% 6.0% 1.4% <b>Weight</b> 28.1% 21.5% 10.3% 100.0% 4 <b>Weight</b> 26.5% 20.2% 20.2% 20.2% 26.1% 10.9% 16.3%
Heterogeneity:1 <sup>2</sup> = Data Source CEDM CCAE Medicare Medicare NHIS-NSC Overall Heterogeneity:1 <sup>2</sup> Data Source CEDM CCAE Medicare Medicare Medicare Medicare Medicare Medicare Medicare Medicare Medicare Overall Heterogeneity:1 <sup>2</sup>	222,464 = 0.0% Total No. 10,118 13,995 5,455 1,004 1,733 2 = 65.9% Total No. 12,167 16,112 6,632 1,192 2,374 38,477 2 = 73.0%	253 58 4,604 . Event No. 346 121 318 25 19 829 829 Event No. 420 134 382 32 40 1,009	12,386 16,221 665,173 C+D . Person-Years 31,064 38,741 18,174 2,744 8,535 99,258 C+D Person-Years 38,422 45,363 22,452 3,254 12,770 122,261	15.6 20.4 3.6 <b>6.9</b> <b>Event rate</b> <sup>*</sup> 11.1 3.1 17.5 9.1 2.2 <b>8.4</b> <b>Event rate</b> <sup>*</sup> 10.9 3.0 17.1 9.8 3.1 <b>8.3</b>	34,258           3,991           4,740           222,464           Total No. E           10,118           13,995           5,455           1,004           1,733           32,305           Total No.           12,167           16,632           1,192           2,374           38,477	1,717 220 45 4,305 5 301 99 315 53 29 <b>797</b> Event No. 356 83 358 47 44 <b>888</b>	114,289 12,622 16,920 665,061 A+C Person -Years 30,240 38,112 19,345 2,836 8,645 99,178 Person -Years 37,800 44,244 22,618 3,293 12,883 120,838	2.3 15.0 17.4 2.7 <b>6.5</b> Event rate <sup>*</sup> 1.0 2.6 16.3 18.7 3.4 <b>8.0</b> Event rate <sup>*</sup> 9.4 1.9 15.8 14.3 3.4 <b>7.3</b>	1.03 (0.93-1.13) 1.18 (0.92-1.51) 1.22 (0.74-2.05) 1.09 (1.01-1.18) p=0.040 0 HR (95% Cl) 1.19 (0.94-1.50) 1.30 (0.89-1.91) 1.02 (0.80-1.30) 0.43 (0.22-0.81) 0.58 (0.27-1.20) 0.93 (0.87-1.01) p=0.943 0.2 HR (95% Cl) 1.19 (0.96-1.47) 1.60 (1.09-2.36) 1.33 (1.06-1.66) 0.34 (0.16-0.68) 0.97 (0.58-1.60) 1.18 (0.95-1.47) p=0.486 0.2	25 0.5 1 Hazard Rati Favor C+D 25 0.5 1 Hazard Ratio Favor C+D	2 o (95% Cl) Favor A+C - - 2 (95% Cl) Favor A+D - - 2 (95% Cl)	1.7% 39.5% 6.0% 1.4% 4 Weight 28.1% 21.5% 27.7% 12.4% 10.3% 4 <b>Weight</b> 26.5% 20.2% 26.5% 20.2% 26.5% 20.2% 10.9% 16.3% 109.0% 4

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. (continued to the next page)

\*Event rate per 1,000 person-year.



#### C Stroke

			A+C				A+D					
Data Source	Total No.	Event No.	Person -Years	Event rate	Total No.	Event No.	Person -Years	Event rate	HR (95% CI)	Favor A+C	Favor A+D	Weight
CEDM	66 755	1.028	107 003	5.2	66 755	030	107 600	47	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 1 2 3	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)		<u>+</u>	4.3%
NHIS-NSC	4,740	97	16,077	6.0	4,740	88	16,742	5.3	1.04 (0.71-1.50)		<u> </u>	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)		÷	100.0%
+eterogeneity:1 <sup>2</sup> =	= 0.0%								p=0.040	0.25 0.5	1 2	4
										Hazard Rati	io (95% CI)	
			C+D				A+C			E	E	
Data Source	Total No.	Event No.	Person -Years	Event rate	Total No.	Event No.	Person -Years	Event rate	HR (95% CI)	Favor C+D	Favor A+C	Weight
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)	i. i.		32.5%
Medicald	1,002	17 52	2,763	6.2	1,002	20 54	2,904	6.9	1.09 (0.48-2.51) 1.09 (0.68-1.76)			4.2% 12.7%
•	1,704		0,440	0.2	1,704	500	00 740	5.0	1.00 (0.00 1.70)			12.7 /0
Overall	32,289	541	99,887	10.0	32,289	532	99,742	5.3	1.00 (0.87-1.15)			100.0%
Heterogeneity:1 <sup>-</sup>	= 0.0%								p=0.945 0	.25 0.5 1	2	4
			C+D				A+D			Hazard Ratio	95% CI)	
Data Source	Total No.	Event No.	Person -Years	Event rate	Total No.	Event No.	Person -Years	Event rate	- HR (95% CI)	Favor C+D	Favor A+D	Weight
CEDM	40.474	201	20 750	<u> </u>	40.474	044	28.004	<u> </u>	4.00 (0.85.4.40)		<u> </u>	20.0%
CEDM	12,171	264	38,759	6.8	12,171	241	38,091	6.3	1.09 (0.85-1.40)			36.9%
Medicare	6 6 2 9	92	40,447	2.0	6 6 2 9	211	44,150	2.0	1.07 (0.70-1.64)		-	13.0%
Medicaid	1 188	18	3 273	5.5	1 188	211	3 405	5.2 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	29.450	670	100.000		29.450	CEC.	404 079	<b>E</b> 4	4 04 (0 00 4 00)			100.0%
Heterogeneity:12	<b>36,459</b>	670	122,900	5.5	30,439	000	121,273	5.4	n=0.486	ΓΓΓŤ	1	_100.0%
MACCE			A+C				A+D					
Data Source	Total No.	Event No.	Person -Years	Event rate	Total No.	Event No.	Person -Years	Event rate	- HR (95% CI)	Favor A+C	Favor A+D	Weight
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)	Ť	-	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)		L .	31.9%
	3,972	460 326	11,965 15,855	38.4	3,972	420	12,239	34.3	1.07 (0.89-1.28)	_	<u> </u>	4.7%
1110-1100	4,755	520	10,000	20.0	4,755	200	10,540	17.2	1.10 (0.30-1.40)			5.570
Overall	221,937	10,950	652,493	16.8	221,937	10,299	652,819	15.8	1.05 (1.00-1.11)	×	>	100.0%
-leterogeneity:l <sup>-</sup>	= 0.0%								p=0.051	0.5 1		2
										Hazard Rati	o (95% CI)	
Data Source	Tatal Na E	unat No. D	C+D	Event rate"	Total No. 5	unat No. 7	A+C	Event esta'		Eavor C+D	avor A+C	Weight
Data Source	TOTAL NO. E	Vent No. P	erson - rears	Event rate	TOTAL NO. E	Vent NO. P	reison - rears	Event rate	HK (95% CI)			Weight
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%
NHIS-NSC	1,732	182	2,650 8,341	25.3 21.8	1,732	98 191	8,435	22.6	0.93 (0.73-1.19)		_	7.2% 16.3%
0	00.000	4 007	07.407		20.020	4 002	07.024	00 F	1 01 (0 85 1 01)		_	400.00/
Heterogeneity:	<sup>2</sup> = 32.4%	1,967	97,127	20.5	32,230	1,995	97,034	20.5	n=0.857	Ť		100.0%
									p=0.037 0.	5 1	(050( 01)	2
			C+D				A+D			Hazard Ratio	(95% CI)	
Data Source	Total No. E	Event No. I	Person -Years	Event rate*	Total No. E	Event No.	Person -Years	Event rate	HR (95% CI)	Favor C+D	Favor A+D	Weight
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 2,370	75 277	3,157 12,441	23.8 22.3	1,185 2,370	89 259	3,239 12,492	27.5 20.7	0.65 (0.41-1.01) 1.06 (0.87-1.28)		<u> </u>	7.7% 21.3%
	2,070		·, · · Ŧ ·		2,070	200	,	20.1			1	21.070
										1	1	
Overall	38,411	2,475	119,533	20.7	38,411	2,214	118,298	18.7	1.12 (0.85-1.43)	$ \longrightarrow $		100.0%
Overall Heterogeneity:l <sup>2</sup>	<b>38,411</b> <sup>2</sup> = 58.9%	2,475	119,533	20.7	38,411	2,214	118,298	18.7	<b>1.12 (0.85-1.43)</b> p=0.263 0	.5 1		<b>100.0%</b> 2

Figure 3. (Continued) Forest plots depicting HR and 95% CI for secondary outcomes in each data source. The overall HRs were calculated using a randomeffects 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				A+D					
Data Source	Total No.	Event No.	Person -Years	Event rate*	Total No.	Event No.	Person -Years	Event rate*	HR (95% CI)		Favor A+C Favor A+D	Weight
CEDM	28.240	1.002	88.620	10.0	28 240	020	80.000	10.4	1 22 (1 08 1 40)		-	50.00/
	20,249	1,005	00,029	12.0	20,249	929	09,220	10.4	1.22 (1.00-1.40)		1.	59.270
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)	)	11	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:1	= 0.0%								p=0.006	0.25	0.5 1 2	4
										0.20		, <del>,</del>
											Hazard Ratio (95% CI	)
			C+D				A+C				Frank Ov D & Frank 10	
Data Source	Total No. E	Event No.	Person -Years	Event rate*	Total No.	Event No.	Person -Years	Event rate*	HR (95% CI)		Favor C+D Favor A+C	Weight
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	11 720	6.8	3 477	100	12 517	8.0	1 03 (0 63-1 70)	(		16 2%
Medicaid	672	14	1 012	7.3	672	13	2 0 2 8	6.4	0.80 (0.20 3.02)	-		- 2.2%
	072	F2	1,912	12.0	072	62	2,020	15.9	0.80 (0.20-3.02)			2.270
NHIS-NSC	603	52	4,072	12.8	663	63	3,999	15.6	0.69 (0.56-1.42)	)	T	18.5%
Overall	18 821	131	59 545	73	18 821	456	59 992	76	0 91 (0 82-1 01	`	$\diamond$	100.0%
Hotorogonoit//1 <sup>2</sup>	- 0.0%	404	53,545	7.5	10,021	400	33,332	7.0	0.01 (0.02-1.01	′	<u> </u>	100.078
Heterogeneity.	- 0.0%								p=0.060	0.25	0.5 1 2	4
											Hazard Ratio (95% CI)	
Data Gaussi			C+D				A+D					
Data Source	Total No. E	vent No.	Person -Years	Event rate	Total No. E	vent No.	Person - Years	Event rate	HR (95% CI)			Weight
CEDM	7 569	347	25 492	13.6	7 569	261	25 166	10.4	1 08 (0 85-1 38	)		52.2%
CCAE	0.351	3/	26,402	13	9 351	201	25,100	0.4	1.60 (0.00-1.00	<u>,</u>		- 1 9%
Medicare	4,306	06	15 252	1.5	4,306	23	15 140	0.3 E 1	1.00 (0.74-3.03	<u>,</u>	<u> </u>	4.570
Medicare	4,396	90	15,255	0.3	4,396	10	15,149	5.1	1.46 (0.93-2.40	2		- 0.7%
Medicald	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%
0	00 500	507	77 040	7.0	00 500	404	75 505	6.4	4 4 4 (0 00 4 00)			100.0%
Overall	23,503	567	77,340	7.6	23,503	464	75,535	0.1	1.14(0.93-1.38)	' -		100.0 %
Heterogeneity:	= 0.0%								p=0.145	0.25	0.5 1 2	4
										0.20		-
											Hazard Ratio (95% CI	,
B Men												
			A+C				A+D					
Data Source	Total No.	Event No	. Person -Years	Event rate	Total No.	Event No	Person -Years	Event rate.	HR (95% CI)		Favor A+C Favor A+D	Weight
									. ,			
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 <sup>-</sup>	= 50.1%								p=0.611	0.5		
										0.5	Hererd Datia (05% CI)	2
			C+D				A+C					Woight
Data Source	Total No.	Event No.	Person -Years	Event rate.	Total No.	Event No.	Person -Years	Event rate.	HR (95% CI)		Favor ATC Favor ATD	weight
CEDM	4,108	136	12.324	11.0	4,108	115	12.063	9.5	1.13 (0.78-1.64)			41.4%
CCAF	6 215	25	17 187	1.5	6 215	21	17,009	12	1 08 (0 49-2 41)		<u>\</u>	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	9/3	7.4	334	7	1 048	67	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%
	000	04	4,004	14.7	000	02	4,070	11.0	1.00 (0.00-1.02)		I	00.170
Overall	13,464	296	41,999	7.0	13,464	261	42,027	6.2	1.07 (0.90-1.26)		$\diamond$	100.0%
Heterogeneity:12	= 0.0%								n=0.354		1 1 1	
									P	0.25	0.5 1 2	4
											Hazard Ratio (95% CI)	
			C+D				A+D					Weight
Data Source	Total No.	Event No.	Person -Years	Event rate.	Total No.	Event No.	Person -Years	Event rate.	HR (95% CI)		Favor C+D Favor A+D	maight
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:l <sup>*</sup>	= 0.0%								p=0.009			
										0.25	0.5 1 2	4
											Userand Datia (050( OI)	

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

#### Hazaro Ratio (95% UI)

											E		14/-:-
Data Source	Total No.	Event No	<ul> <li>Person -Years</li> </ul>	Event rate	Total No	. Event No	<ol> <li>Person -Years</li> </ol>	s Event rate	HR (95% CI)		Favor A+C	Favor A+D	vveig
	33 503	1 686	102 039	16.5	33 503	1 5 3 0	104 014	14.7	1 13 (1 02-1 25)			-	50.2
	33,393	1,000	102,039	10.5	33,393	1,000	104,014	14.7	1.13 (1.02-1.23)				J9.Z
JUAE	29,304	121	47,898	2.5	29,304	104	46,145	2.2	1.11 (0.77-1.61)		_		4.7%
Nedicare	34,126	807	120,595	6.7	34,126	5 772	118,005	6.5	1.00 (0.85-1.16)		-	1	26.7
/ledicaid	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	3 146	7,435	19.6	1.18 (0.86-1.62)		-		6.4%
Overall	100.475	2.849	282.550	10.1	100.475	5 2.626	282.922	9.3	1.09 (1.00-1.89)			\$	100.
leterogeneity:12 =	0.0%	,							p=0.052		I	1 1	
									0	).25	0.5 · Hazard Ra	l 2 tio (95% CI)	4
			C+D				A+C					. ,	
Data Source	Total No. E	vent No.	Person -Years	Event rate*	Total No. I	Event No.	Person -Years	Event rate*	HR (95% CI)		Favor C+D	Favor A+C	Weig
	5 004	277	10.452	10.4	5 904	207	10 965	17.2	1 10 (0 97 1 30)		_	-	50.0
	3,304	47	0,400	0.7	3,304	40	0,000	0.0	1.10 (0.07-1.33)				→ 0.0.0
JUAE	3,070	105	0,322	2.7	3,670	13	6,350	2.0	1.50 (0.54-4.47)			_	2.47
vledicare	5,442	135	18,786	7.2	5,442	155	19,904	7.8	0.93 (0.66-1.30)				23.3
/ledicaid	328	12	1,060	11.3	328	17	1,187	14.3	0.87 (0.31-2.44)	_			2.5%
IHIS-NSC	915	104	4,101	25.4	915	101	4,009	25.2	0.95 (0.66-1.36)				20.8
Verall	16 459	645	49 722	13.0	16 459	613	50.315	12.2	1.03 (0.89-1.18)		4	>	100
$eterogeneity: ^2 =$	0.0%	040	,	10.0	10,400	010	,		p=0.615		- Í	1	
									0.2	25	0.5 1	2	4
										1	Hazard Ratio	o (95% CI)	
			C+D				A+D						
Data Source	Total No. E	vent No.	Person -Years	Event rate.	Total No. I	Event No.	Person -Years	Event rate*	HR (95% CI)		Favor C+D	Favor A+D	Weig
EDM	7.095	476	24,122	19.7	7.095	397	24,100	16.5	1.17 (0.96-1.42)		H	•	35.9
	1 181	16	7 303	2.2	1 181	21	7 4 4 1	2.8	0.55(0.19-1.42)	←	-		5 30
	4,401	100	7,000	2.2	4,401	445	7,441	2.0	1 02 (0 72 1 49)				0.07
viedicare	6,593	163	23,160	7.0	6,593	145	23,229	0.2	1.03 (0.72-1.46)	-			23.0
ledicaid	4.040	15	1,243	12.1	374	23	1,344	17.1	0.47 (0.18-1.11)				6.4
HIS-NSC	1,316	146	6,682	21.8	1,316	145	6,204	23.4	0.83 (0.62-1.11)				28.6
woroll	19 859	816	62,600	13.0	19,859	731	62,318	11.7	0.93 (0.65-1.35)		_ 🚢	>	100
leterogeneity:1 <sup>2</sup> =	49.8%								D=0.027				
Heterogeneity: $l^2 =$	49.8%								p=0.627	25	0.5 1	2	4
Heterogeneity:1 <sup>2</sup> =	49.8%								ρ=0.627 0.2	25	0.5 1 Hazard Rati	2 o (95% CI)	4
                	49.8%								p=0.627 0.2	25	0.5 1 Hazard Rati	2 o (95% CI)	4
 deterogeneity:1 <sup>2</sup> = <60 years	49.8%		A+C				A+D		p=0.627 0.2	25	0.5 1 Hazard Rati	2 o (95% CI)	4 Wei
Heterogeneity:1 <sup>2</sup> =	49.8%	Event No.	A+C Person -Years	Event rate*	Total No.	Event No.	A+D Person -Years	Event rate*	p=0.627 0.2 HR (95% CI)	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei
<pre>deterogeneity:1<sup>2</sup> =   &lt;60 years   data Source     EEDM</pre>	49.8% Total No. 33,297	Event No. 209	A+C Person -Years 98,010	Event rate* 2.1	Total No. 33,297	Event No. 214	A+D Person-Years 97,417	Event rate*	p=0.627 0.2 HR (95% CI) 0.99 (0.73-1.33)	25	0.5 1 Hazard Rati Favor A+C	2 o (95% CI) Favor A+D	4 Wei 29.3
<pre>deterogeneity:1<sup>2</sup> =   &lt;60 years   data Source     CEDM     CAE</pre>	49.8% Total No. 33,297 84,035	Event No. 209 388	A+C Person-Years 98,010 280,517	Event rate• 2.1 1.4	Total No. 33,297 84,035	Event No. 214 339	A+D Person -Years 97,417 280,883	Event rate* 2.2 1.2	P=0.627 0.2 HR (95% Cl) 0.99 (0.73-1.33) 1.03 (0.83-1.28)	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9
<pre>deterogeneity:1<sup>2</sup> =   &lt;60 years   <a href="https://www.searce.com">deta Source</a></pre>	49.8% Total No. 33,297 84,035 2,498	Event No. 209 388 48	A+C Person-Years 98,010 280,517 7,920	Event rate* 2.1 1.4 6.1	Total No. 33,297 84,035 2,498	Event No. 214 339 50	A+D Person -Years 97,417 280,883 7,946	Event rate* 2.2 1.2 6.3	P=0.627 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22)	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.79
Aeterogeneity:1 <sup>2</sup> = <60 years Data Source DEDM CCAE Medicaid IHIS-NSC	49.8% Total No. 33,297 84,035 2,498 2,885	Event No. 209 388 48 35	A+C Person-Years 98,010 280,517 7,920 9,911	Event rate• 2.1 1.4 6.1 3.5	Total No. 33,297 84,035 2,498 2,885	Event No. 214 339 50 28	A+D Person -Years 97,417 280,883 7,946 10,945	Event rate* 2.2 1.2 6.3 2.6	HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27)	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.79 6.19
<pre>deterogeneity1<sup>2</sup> =</pre>	Total No. 33,297 84,035 2,498 2,885	Event No. 209 388 48 35 680	A+C Person-Years 98,010 280,517 7,920 9,911 306 358	Event rate• 2.1 1.4 6.1 3.5	Total No. 33,297 84,035 2,498 2,885	Event No. 214 339 50 28 631	A+D Person-Years 97,417 280,883 7,946 10,945 307 191	Event rate* 2.2 1.2 6.3 2.6	HR (95% CI) 0.2 0.2 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22)	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.79 6.19
<pre>set all teterogeneityd<sup>2</sup> =</pre>	49.8% Total No. 33,297 84,035 2,498 2,885 122,715 0.0%	Event No. 209 388 48 35 <b>680</b>	A+C Person-Years 98,010 280,517 7,920 9,911 <b>396,358</b>	Event rate* 2.1 1.4 6.1 3.5 <b>1.7</b>	Total No. 33,297 84,035 2,498 2,885 122,715	Event No. 214 339 50 28 631	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b>	Event rate* 2.2 1.2 6.3 2.6 <b>1.6</b>	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22)	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.79 6.19 
<pre>idercogeneityd<sup>2</sup> =</pre>	49.8% Total No. 33,297 84,035 2,498 2,885 122,715 0.0%	Event No. 209 388 48 35 680	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b>	Event rate* 2.1 1.4 6.1 3.5 <b>1.7</b>	Total No. 33,297 84,035 2,498 2,885 122,715	Event No. 214 339 50 28 631	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b>	Event rate • 2.2 1.2 6.3 2.6 1.6	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930	25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.77 6.10 
verall       4eterogeneityd <sup>2</sup> =       <60 years	49.8% Total No. 33,297 84,035 2,498 2,885 122,715 0,0%	Event No. 209 388 48 35 680	A+C Person-Years 98,010 280,517 7,920 9,911 <b>396,358</b>	Event rate* 2.1 1.4 6.1 3.5 1.7	Total No. 33,297 84,035 2,498 2,885 122,715	Event No. 214 339 50 28 631	A+D Person -Years 97,417 280,883 7,946 10,945 <b>397,191</b>	Event rate • 2.2 1.2 6.3 2.6 1.6	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0.	25 .25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.79 6.19 100 4
leterogeneityd <sup>2</sup> = <b>60 years</b> <b>ata Source</b> EDM CCAE Medicaid IHIS-NSC <b>Overall</b> leterogeneityd <sup>2</sup> = (	Total No. 33,297 84,035 2,498 2,885 122,715 0.0%	Event No. 209 388 48 35 680	A+C Person-Years 98,010 280,517 7,920 9,911 <b>396,358</b>	Event rate 2.1 1.4 6.1 3.5 1.7	Total No. 33,297 84,035 2,498 2,885 122,715	Event No. 214 339 50 28 631	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b>	Event rate 2.2 6.3 2.6 <b>1.6</b>	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.74 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0.	25 .25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D	4 Wei 29.3 55.9 8.77 6.19 4
voterali       leterogeneityd <sup>2</sup> =       <60 years	Total No. 1 33,297 84,035 2,498 2,885 122,715 0,0%	Event No. 209 388 48 35 680	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate	Total No. 33,297 84,035 2,498 2,885 122,715	Event No. 214 339 50 28 631 Event No.	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years	Event rate* 2.2 1.2 6.3 2.6 1.6 Event rate*	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI)	25 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 io (95% CI) Favor A+C	4 Wei 29.3 55.9 8.7° 6.1° 100 4
eleterogeneily:1 <sup>2</sup> = <b>60 years</b> eata Source EDM CAE HIS-NSC hverall eterogeneily:1 <sup>2</sup> = 1 hata Source FDM	Total No. 1 33,297 84,035 2,498 2,885 122,715 0,0%	Event No. 209 388 48 35 680 Event No.	A+C Person-Years 98,010 280,517 7,920 9,911 396,358 C+D Person-Years 10,000	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate	Total No. 33,297 84,035 2,498 2,885 122,715 Total No.	Event No. 214 339 50 28 631 Event No.	A+D Person -Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person -Years	Event rate* 2.2 6.3 2.6 1.6 Event rate*	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.74 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.07 (0.52.2.27)	25 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 itio (95% CI) Favor A+C	4 Wei 29.3 55.9 8.7° 6.1° 100 4 Wei
voterali       <60 years	Total No. 33,297 84,035 2,498 2,885 122,715 0,0%	Event No. 209 388 48 35 680 Event No. 34	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 20,552	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7	Total No. 33,297 84,035 2,498 2,885 122,715 Total No. 4,270	Event No. 214 339 50 28 631 Event No. 28	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 20,552	Event rate* 2.2 1.2 6.3 2.6 1.6 Event rate* 2.2	HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.27 (0.58-2.87) 1.5 (0.58-2.87)	25 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 tio (95% CI) Favor A+C	4 Wei 29.3 55.5 8.77 6.10 4 Wei 29.3
verail       <60 years	Total No. 1 Total No. 1 2,285 122,715 0.0% Total No. 1 4,270 10,168	Event No. 209 388 48 35 <b>680</b> Event No. 34 34	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0	Total No.           33,297           84,035           2,498           2,885           122,715           Total No.           4,270           10,168	Event No. 214 339 50 28 631 Event No. 28 40	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> <b>A+C</b> Person-Years 12,551 32,010	Event rate* 2.2 6.3 2.6 1.6 1.6 Event rate* 2.2 1.2	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46)	25 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 lio (95% CI) Favor A+C	4 We 29.: 55: 8.7' 6.1' 100 4 We 29.: 33.:
verail       eterogeneity:1 <sup>2</sup> =       <60 years	Total No. 33,297 84,035 2,498 2,885 122,715 0,0% Total No. I 4,270 10,168 676	Event No. 209 388 48 35 <b>680</b> Event No. 34 34 7	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 4.0	Total No. 33,297 84,035 2,498 2,885 122,715 Total No. 4,270 10,168 676	Event No. 214 339 50 28 631 Event No. 28 40 9	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822	Event rate* 2.2 1.2 6.3 2.6 <b>1.6</b> Event rate* 2.2 1.2 4.9	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-4.23)	225 .25 ₽	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 tio (95% CI) Favor A+C	4 We 29. 55. 8.7 6.1 100 4 We 29. 33 ∍,0
verail       <60 years	Total No. 33,297 84,035 2,498 2,885 122,715 0.0% Total No. I 4,270 10,168 676 775	Event No. 209 388 48 35 <b>680</b> Event No. 34 34 7 17	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 3.9	Total No. 33,297 84,035 2,498 2,885 122,715 Total No. 4,270 10,168 676 775	Event No. 214 339 50 28 631 Event No. 28 40 9 15	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392	Event rate* 2.2 1.2 6.3 2.6 <b>1.6</b> Event rate* 2.2 1.2 4.9 3.4	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.55 (0.55-2.46) 1.00 (0.24-4.23) 1.50 (0.68-3.45)	.25 ₽ ₽	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 1 1 1 1 1 1 1 1 1 1 1 1	4 We 29. 55: 8.7 6.1 100 4 We 29. 33. 9.0 28.
verail       <60 years	Total No. 1 33,297 84,035 2,498 2,885 122,715 0.0% Total No. 1 4,270 10,168 676 775	Event No. 209 388 48 35 <b>680</b> Event No. 34 34 7 17 92	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 51,856	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0 4.0 3.9 1.8	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 Total No. 4,270 10,168 676 7755	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b>	Event rate 2.2 1.2 6.3 2.6 1.6 Event rate 2.2 1.2 4.9 3.4 1 P	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-4.23) 1.50 (0.68-3.45) 1.26 (10.4.67)	.25 ₽	0.5 1 Hazard Rati	2 0 (95% CI) Favor A+D 2 1 2 2 1 5 Favor A+C Favor A+C	4 We 29.55.8.7' 6.1' 100 4 We 29.3.3.3 3.3. 3.2. 28.3 100
<pre>verail leterogeneityd<sup>2</sup> = &lt;60 years ata Source EDM CAE ledicaid HIS-NSC verail eterogeneityd<sup>2</sup> = ( verail eterogeneityd<sup>2</sup> = ( cAE ledicaid HIS-NSC verail eterogeneityd<sup>2</sup> = ( verail eterogeneityd<sup>2</sup> = ( verail eterogen</pre>	Total No. 33,297 84,035 2,498 2,885 122,715 0,0% Total No. I 4,270 10,168 676 775 15,889 0,0%	Event No. 209 388 48 35 <b>680</b> Event No. 34 7 17 92	A+C Person-Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person-Years 12,820 32,959 1,760 4,317 <b>51,856</b>	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 4.0 3.9 1.8	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 122,715 15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92	A+D Person -Years 97,417 280,883 7,946 10,945 <b>397,191</b> <b>A+C</b> Person -Years 12,551 32,010 1,822 4,392 <b>50,775</b>	Event rate* 2.2 6.3 2.6 1.6 2.2 1.2 4.9 3.4 1.8	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.58-2.87) 1.50 (0.68-3.45) 1.50 (0.68-3.45) 1.26 (1.00-1.60)	25 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 tio (95% CI) Favor A+C	4 Wei 29.55.5. 8.7' 6.1' 4 Wei 29.0 33.7 9.0' 28.3 100
verail       eterogeneityd <sup>2</sup> =       <60 years	Total No. 33,297 84,035 2,498 2,885 122,715 0.0% Total No. I 4,270 10,168 676 775 15,889 0.0%	Event No. 209 388 48 35 680 Event No. 34 34 34 7 17 92	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b>	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 4.0 3.9 1.8	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 Total No. 4,270 10,168 676 775 15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b>	Event rate* 2.2 1.2 6.3 2.6 1.6 Event rate* 2.2 1.2 4.9 3.4 1.8	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.55 (0.55-2.46) 1.00 (0.24-4.23) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050	.25 F	0.5 1 Hazard Rati	2 0 (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	4 Wei 29.955.5.8.7 6.1 100 4 Wei 33.3.3 9.0 28.9 100
<pre>verail eterogeneity:1<sup>2</sup> =</pre>	Total No. 33,297 84,035 2,885 122,715 0.0% Total No. 1 4,270 10,168 676 775 15,889 0.0%	Event No. 209 388 48 35 680 680 34 34 7 17 92	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b>	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0 4.0 3.9 1.8	Total No.           33,297           84,035           2,498           2,885           122,715           Total No.           4,270           10,168           676           775           15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b>	Event rate* 2.2 1.2 6.3 2.6 1.6 2.6 1.6 2.2 1.2 4.9 3.4 3.4 1.8	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-4.23) 1.50 (0.68-3.45) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2	225 .25 • •	0.5 1 Hazard Rati	2 0 (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 Favor A+C 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2	4 We 29.55.8.7' 6.1' 4 We 29.33.3 33.3 20.2 2.1 100 2.8.1 100 4
verail       <60 years	Total No. 33,297 84,035 2,498 2,885 122,715 0.0% Total No. 1 4,270 10,168 676 775 15,889 0.0%	Event No. 209 388 48 35 680 Event No. 34 34 7 17 92	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b>	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0 4.0 3.9 1.8	Total No.           33,297           84,035           2,498           2,885           122,715           Total No.           4,270           10,168           676           775           15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92	A+D Person -Years 97,417 280,883 7,946 10,945 <b>397,191</b> <b>A+C</b> Person -Years 12,551 32,010 1,822 4,392 <b>50,775</b>	Event rate* 2.2 6.3 2.6 1.6 2.6 1.8 2.2 1.2 4.9 3.4 1.8	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-4.23) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2	225 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 tio (95% CI) Favor A+C 2 tio (95% CI)	4 We 29.9.55 8.7' 6.1' 100 4 We 29.3 3.3.3 9.0' 28.3 100 4
<pre>verail eterogeneity1<sup>2</sup> =</pre>	Total No. 33,297 84,035 2,498 2,885 122,715 0.0% Total No. 1 4,270 10,168 676 775 15,889 0.0%	Event No. 209 388 48 35 680 680 34 34 7 17 92	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b>	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0 4.0 3.9 1.8	Total No.           33,297           84,035           2,498           2,885           122,715           Total No.           4,270           10,168           676           775           15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b>	Event rate* 2.2 1.2 6.3 2.6 1.6  Event rate* 2.2 1.2 4.9 3.4 1.8	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-4.23) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2	225 .25 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 lio (95% CI) Favor A+C	4 We 29.5.5 8.7' 6.1' 100 4 We 29.9 33.3 9.0' 28.3 100 4
verail       <60 years	Total No. 10,1068 Total No. 10,	Event No. 209 388 48 35 680 Event No. 34 34 7 17 92 Event No.	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 4.0 3.9 1.8 Event rate*	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 122,715 122,715 122,715 122,715 15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Solution 92 92 Solution 92 Solu	A+D Person -Years 97,417 280,883 7,946 10,945 <b>397,191</b> <b>A+C</b> Person -Years 12,551 32,010 1,822 4,392 <b>50,775</b> <b>A+D</b> Person -Years	Event rate* 2.2 1.2 6.3 2.6 1.6 1.6 Event rate* 2.2 1.2 4.9 3.4 1.8 Event rate*	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.68-3.45) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI)	225 .225 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 lio (95% CI) Favor A+C 2 c (95% CI) Favor A+D	4 We 29, 55. 8.7 6.1. 100 4 We 23. 3, 9.0 28. 100 4 We 24 We 24 20 24 20 25. 24 20 25. 24 20 25. 25. 24 25. 25. 25. 25. 25. 25. 25. 25. 25. 25.
Verail       leterogeneity12 =       <60 years	Total No. E 5,105	Event No. 209 388 48 35 680 Event No. 34 7 17 92	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 3.9 1.8 Event rate* 2.5	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 10,168 676 775 15,889	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25	A+D           Person-Years           97,417           280,883           7,946           10,945           397,191           A+C           Person-Years           12,551           32,010           1,822           4,392           50,775           A+D           Person-Years           14,907	Event rate* 2.2 6.3 2.6 1.6 2.2 1.2 6.3 2.6 1.6 2.2 1.2 4.9 3.4 1.8 Event rate* 1.7	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-2.33) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 2.33 (1.10-5.37)	225 .25 ₹  225 F	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 tio (95% CI) Favor A+C 2 tio (95% CI) Favor A+D	4 Wei 29.55.5.8.7° 6.1° 4 Wei 29.9.28.3 9.0° 28.3 100 4 Wei 4 Wei 29.3 28.3 100 4 4 Wei 28.5 5 5.5 5.5 5.5 5.5 5.5 5.5 5.5 5.5 5.
voterali       leterogeneity:1 <sup>2</sup> =       <60 years	Total No. I 49.8% Total No. I 4,270 10,168 676 775 15,889 0.0% Total No. E 5,105 11,742	Event No. 209 388 48 35 680 Event No. 34 34 7 17 92 Event No. 39 44	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582 38,740	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0 4.0 3.9 1.8 Event rate 2.5 1.1	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 122,715 122,715 15,889 Total No. E 5,105 11,742	Event No. 214 339 50 28 <b>631</b> Event No. 28 40 9 15 <b>92</b> Event No. 25 39	A+D Person -Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person -Years 12,551 32,010 1,822 4,392 <b>50,775</b> A+D Person -Years 14,907 37,315	Event rate 2.2 1.2 6.3 2.6 <b>1.6</b> Event rate 2.2 1.2 4.9 3.4 <b>1.8</b> Event rate 1.7 1.0	HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 1.26 (3.00-1.60) p=0.050 0.2 HR (95% CI) 1.23 (1.10-5.37) 1.43 (0.73-2.89)	225 .25 F 225	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 1 2 1 5 5 5 5 5 5 5 5 5 5 5 5 5	4 Wei 55.5 8.7° 6.1° 4 Wei 29.3 55.5 8.7° 6.1° 4 29.3 3.3 28.8° 28.8° 28.8° 28.8° 100 4 4 Wei 4 29.31 100 29.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 4 29.3 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 55.5 8.7° 6.1° 55.5 55.5 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 6.1° 55.5 55.5 8.7° 55.5 55.5 8.7° 6.1° 55.5 8.7° 55.5 8.7° 8.7° 55.5 55.5 55.5 55.5 55.5 55.5 55.5 5
Verail       leterogeneityd <sup>2</sup> =       <60 years	Total No. E 5,105 11,742 2,685 122,715 0,0% Total No. E 5,105 11,742 8,16 8,105 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 8,16 11,742 11,745 11,745 11,745 11,745 11,745 11,745 11,745 11,745	Event No. 209 388 48 35 680 Event No. 34 7 17 92 Event No. 39 44 8	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582 38,740 2,104	Event rate 2.1 1.4 6.1 3.5 <b>1.7</b> Event rate 2.7 1.0 4.0 3.9 <b>1.8</b> Event rate 2.5 1.3 8	Total No. 33,297 84,035 2,498 2,885 122,715 10,168 676 775 15,889 Total No. E 5,105 11,742 816	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25 39 16	A+D           Person-Years           97,417           280,883           7,946           10,945           397,191           A+C           Person-Years           12,551           32,010           1,822           4,392           50,775           A+D           Person-Years           14,907           37,315           2,176	Event rate* 2.2 6.3 2.6 1.6 Event rate* 2.2 1.2 4.9 3.4 1.8 Event rate* 1.7 1.0 7.4	HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.59 (0.58-2.87) 1.50 (0.58-2.48) 1.50 (0.58-2.48) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 2.33 (1.10-5.37) 1.43 (0.73-2.89) 0.2	.25 F	0.5 1 Hazard Rati	2 0 (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 2 0 (95% CI) Favor A+D 1 5 7 7 8 8 8 7 8 7 8 7 8 7 8 7 8 8 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 8 8 8 8 8 8 8 8 8 8 8 8	4 Wei 29, 55, 5, 8, 7' 6, 1' 4 Wei 23, 3, 3' 28, 2' 28, 3' 28, 3' 28, 3' 28, 3' 28, 3' 28, 3' 28, 4' 24, 4' 4 Wei 24, 4' 24, 4'
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Verail       leterogeneityd <sup>2</sup> =       <60 years	Total No. 13,297 84,035 2,488 2,885 122,715 0.0% Total No. 14,270 10,168 676 775 15,889 0.0% Total No. 15 5,105 11,742 816 1,036	Event No. 209 388 48 35 680 Event No. 34 34 7 17 92 Svent No. 39 44 8 22	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> Person -Years 15,582 38,740 2,104 6,140	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 4.0 3.9 1.8 Event rate* 2.5 1.1 3.8 3.6	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 122,715 122,715 122,715 122,715 15,889 15,889 5,105 11,742 8,16 1,036	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25 39 16 16	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b> Person-Years 14,907 37,315 2,176 6,307	Event rate* 2.2 1.2 6.3 2.6 1.6 2.2 1.2 4.9 3.4 1.8 Event rate* 1.7 1.0 7.4 2.5	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.68-3.45) 1.50 (0.68-3.45) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 HR (95% CI) 2.33 (1.10-5.37) 1.43 (0.73-2.89) 0.62 (0.19-1.87) 1.07 (0.52-2.18)	225 .25 F 225	0.5 1 Hazard Rati	2 0 (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 2 0 (95% CI) Favor A+D 1 5 7 7 8 8 8 7 8 8 8 8 8 8 8 8 8 8 8 8 8	4 Wei 29.:55 55. 8.7' 6.1' 100 4 Wei 29.:28. 28. 100 4 Wei 4 Wei 25. 31.0 1100 4
	Total No. E 5,105 11,742 816 1,036 18,600 10,168 15,889 0,0%	Event No. 209 388 48 35 680 Event No. 34 34 7 17 92 39 44 8 22 113	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582 38,740 2,104 6,140 62 566	Event rate* 2.1 1.4 6.1 3.5 1.7 Event rate* 2.7 1.0 3.9 1.8 Event rate* 2.5 1.1 3.8 3.6 1.9	Total No. 33,297 84,035 2,498 2,885 122,715 122,715 10,168 676 775 15,889 Total No. E 5,105 11,742 816 1,036 1,036	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25 39 16 96	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b> A+D Person-Years 14,907 37,315 2,176 6,307 6,307	Event rate 2.2 1.2 6.3 2.6 1.6 Event rate 2.2 1.2 4.9 3.4 1.8 Event rate 1.7 1.0 7.4 2.5 1.6	HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.15 (0.55-2.46) 1.00 (0.24-2.33) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 2.33 (1.10-5.37) 1.43 (0.73-2.89) 0.62 (0.19-1.87) 1.07 (0.52-2.18) 1.32 (0.51-2.86)	.25 F € 25	0.5 1 Hazard Rati	2 o (95% CI) Favor A+D 2 itio (95% CI) Favor A+C 2 itio (95% CI) Favor A+D 1 2 itio (95% CI)	4 Wei 29.3 55.5 8.7 6.1 9.0 29.3 29.0 28.5 100 4 Wei 29.3 29.0 28.5 100 4 4 Wei 29.3 23.2 23.2 3.3 23.2 100 4 4
A constant in the second	Total No. I 49.8% Total No. I 4,270 10,168 676 775 15,889 0.0% Total No. E 5,105 11,742 816 1,036 18,699 26.2%	Event No. 209 388 48 35 680 Event No. 34 34 34 7 17 92 Event No. 39 44 8 22 113	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582 38,740 2,104 6,140 <b>62,566</b>	Event rate 2.1 1.4 6.1 3.5 1.7 Event rate 2.7 1.0 4.0 3.9 1.8 Event rate 2.5 1.1 3.8 3.6 1.8	Total No. 33,297 84,035 2,498 2,885 122,715 Total No. 4,270 10,168 676 775 15,889 Total No. 8 5,105 11,742 816 1,036 18,699	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25 39 16 16 36 96	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b> A+D Person-Years 14,907 37,315 2,176 6,307 <b>60,705</b>	Event rate 2.2 1.2 6.3 2.6 1.6 Event rate 2.2 1.2 3.4 1.8 Event rate 1.7 1.0 7.4 2.5 1.6	HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.58-2.87) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 1.23 (1.10-5.37) 1.43 (0.73-2.89) 0.62 (0.19-1.87) 1.77 (0.52-2.18) 1.32 (0.612-2.80) 0.62 (0.19-1.87) 1.77 (0.52-2.18) 1.32 (0.612-2.80) 0.62 (0.19-1.87) 1.62 (0.19-2.80) 0.62 (0.19-1.87) 1.77 (0.52-2.18) 1.32 (0.612-2.80) 0.62 (0.19-1.87) 1.57 (0.52-2.18) 1.32 (0.612-2.80) 0.62 (0.19-1.87) 1.57 (0.52-2.18) 1.57 (0.52-2.	225 .25 F 225	0.5 1 Hazard Rati	2 (95% CI) Favor A+D 2 1 2 1 5 4 5 5 6 (95% CI) Favor A+C 1 5 6 (95% CI) Favor A+D 1 5 7 7 7 7 7 7 7 7 7 7 7 7 7	4 Wei 29.3 55.5.8.77 6.19 4 29.3 3.0 28.5 100 4 4 Wei 28.5 31.0 14.0 29.6 31.0 14.0 29.6 31.0 14.0 29.6 31.0 14.0 29.6 14.0 29.6 29.6 20.5 55.5 20.5 55.5 20.5 55.5 20.5 20.5
<pre>verail eterogeneity:1<sup>2</sup> = </pre> <pre>    <pre>     <pre>     <pre>   <pre>    <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre>   <pre< td=""><td>Total No. 13,297 84,035 2,498 2,885 122,715 0,0% Total No. 14,270 10,168 676 775 15,889 0,0% Total No. 15 5,105 11,742 816 1,036 18,699 25.2%</td><td>Event No. 209 388 48 35 680 Event No. 34 7 17 92 Svent No. 39 44 8 22 113</td><td>A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582 38,740 2,104 6,140 62,566</td><td>Event rate* 2.1 1.4 6.1 3.5 1.7 2.7 1.0 4.0 3.9 1.8 Event rate* 2.5 1.1 3.8 3.6 1.8</td><td>Total No. 33,297 84,035 2,498 2,885 122,715 10,168 676 775 15,889 Total No. E 5,105 11,742 816 1,036 18,699</td><td>Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25 39 16 16 96</td><td>A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b> A+D Person-Years 14,907 37,315 2,176 6,307 <b>60,705</b></td><td>Event rate 2.2 1.2 6.3 2.6 1.6 Event rate 2.2 1.2 4.9 3.4 1.8 Event rate 1.7 1.0 7.4 2.5 1.6</td><td>HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.58-2.87) 1.50 (0.58-2.48) 1.50 (0.58-2.48) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 2.33 (1.10-5.37) 1.43 (0.73-2.89) 0.62 (0.19-1.87) 1.07 (0.52-2.18) 1.32 (0.61-2.86) p=0.333</td><td>225 .25 F 25 F</td><td>0.5 1 Hazard Rati</td><td>2 0 (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 2 0 (95% CI) Favor A+D</td><td>4 Wei 29.55.6 8.77 6.19 4 Wei 29.3 29.3 29.09 28.5 100 4 Wei 23.3 23.3 24.5 100 4 Wei 24.5 100 24.5 100 4 4 100 24.5 25.5 25.5 25.5 25.5 25.5 25.5 25.5</td></pre<></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre></pre>	Total No. 13,297 84,035 2,498 2,885 122,715 0,0% Total No. 14,270 10,168 676 775 15,889 0,0% Total No. 15 5,105 11,742 816 1,036 18,699 25.2%	Event No. 209 388 48 35 680 Event No. 34 7 17 92 Svent No. 39 44 8 22 113	A+C Person -Years 98,010 280,517 7,920 9,911 <b>396,358</b> C+D Person -Years 12,820 32,959 1,760 4,317 <b>51,856</b> C+D Person -Years 15,582 38,740 2,104 6,140 62,566	Event rate* 2.1 1.4 6.1 3.5 1.7 2.7 1.0 4.0 3.9 1.8 Event rate* 2.5 1.1 3.8 3.6 1.8	Total No. 33,297 84,035 2,498 2,885 122,715 10,168 676 775 15,889 Total No. E 5,105 11,742 816 1,036 18,699	Event No. 214 339 50 28 631 Event No. 28 40 9 15 92 Event No. 25 39 16 16 96	A+D Person-Years 97,417 280,883 7,946 10,945 <b>397,191</b> A+C Person-Years 12,551 32,010 1,822 4,392 <b>50,775</b> A+D Person-Years 14,907 37,315 2,176 6,307 <b>60,705</b>	Event rate 2.2 1.2 6.3 2.6 1.6 Event rate 2.2 1.2 4.9 3.4 1.8 Event rate 1.7 1.0 7.4 2.5 1.6	HR (95% CI) 0.2 HR (95% CI) 0.99 (0.73-1.33) 1.03 (0.83-1.28) 0.71 (0.41-1.22) 1.18 (0.62-2.27) 0.99 (0.81-1.22) p=0.930 0. HR (95% CI) 1.27 (0.58-2.87) 1.50 (0.58-2.87) 1.50 (0.58-2.48) 1.50 (0.58-2.48) 1.50 (0.68-3.45) 1.26 (1.00-1.60) p=0.050 0.2 HR (95% CI) 2.33 (1.10-5.37) 1.43 (0.73-2.89) 0.62 (0.19-1.87) 1.07 (0.52-2.18) 1.32 (0.61-2.86) p=0.333	225 .25 F 25 F	0.5 1 Hazard Rati	2 0 (95% CI) Favor A+D 2 10 (95% CI) Favor A+C 1 2 0 (95% CI) Favor A+D	4 Wei 29.55.6 8.77 6.19 4 Wei 29.3 29.3 29.09 28.5 100 4 Wei 23.3 23.3 24.5 100 4 Wei 24.5 100 24.5 100 4 4 100 24.5 25.5 25.5 25.5 25.5 25.5 25.5 25.5

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.<sup>5)20)</sup> 2018 ESC/ESH guideline recommends anti-hypertensive therapy should be initiated with combination regimen preferentially based on A+C or A+D.<sup>7)</sup> 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.<sup>8)</sup> Conversely, two Japanese studies did not demonstrate a significant difference between various combination regimens in preventing cardiovascular events. Matsuzaki et al.<sup>21)</sup> compared the CCB-based combinations with ARB,  $\beta$ -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.,<sup>9)</sup> 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.<sup>22)</sup>

It is well-known that TZD is better for the prevention of heart failure compared to CCB.<sup>23)24)</sup> 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.<sup>23)24)</sup> 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.<sup>25)</sup> However, in another meta-analysis, there was no significant gender difference in efficacy among various classes of anti-hypertensive agents between men and women.<sup>26)</sup> 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 subcohort 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.<sup>27)</sup>

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 nonfatal 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 antihypertensive 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.<sup>28)</sup> 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 metaanalysis showed no significant differences in cardiovascular outcomes between ACEIs and ARBs,<sup>29)</sup> 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.<sup>30</sup>

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.

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## SUPPLEMENTARY MATERIALS

Supplementary Table 1

Drug code list

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## **Supplementary Table 2**

Disease code list

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#### 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

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## **Supplementary Table 8**

Calibrated p-values in each data source

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## **Supplementary Table 9**

Meta-analysis using the result from the four US data sources

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#### **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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# REFERENCES

- GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388:1659-724.
   PUBMED | CROSSREF
- Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022-31.
   PUBMED | CROSSREF
- Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich) 2002;4:393-404.
   PUBMED | CROSSREF
- Basile JN, Bloch MJ. Analysis of recent papers in hypertension. Initial combination therapy provides more prompt blood pressure control and reduces cardiovascular events but remains underutilized. *J Clin Hypertens (Greenwich)* 2013;15:523-5.
   PUBMED | CROSSREF
- Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. *Hypertension* 2013;61:309-18.
   PUBMED | CROSSREF

 Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension* 2012;59:1124-31.
 PUBMED | CROSSREF

- Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021-104.
   PUBMED I CROSSREF
- Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417-28.
- Ogihara T, Saruta T, Rakugi H, et al. Combinations of olmesartan and a calcium channel blocker or a diuretic in elderly hypertensive patients: a randomized, controlled trial. *J Hypertens* 2014;32:2054-63.
   PUBMED | CROSSREF
- Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;290:2805-16.
   PUBMED | CROSSREF
- 11. Weber MA, Jamerson K, Bakris GL, et al. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. *Lancet* 2013;381:537-45.

PUBMED | CROSSREF

- Hripcsak G, Duke JD, Shah NH, et al. Observational Health Data Sciences and Informatics (OHDSI): opportunities for observational researchers. *Stud Health Technol Inform* 2015;216:574-8.
   PUBMED | CROSSREF
- Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017;46:e15.

  PUBMED | CROSSREF
- Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through realworld and synthetic data experiments. *Int J Epidemiol* 2018;47:2005-14.
   PUBMED | CROSSREF
- Suchard MA, Simpson SE, Zorych I, Ryan P, Madigan D. Massive parallelization of serial inference algorithms for a complex generalized linear model. *ACM Trans Model Comput Simul* 2013;23:10.1145/2414416.2414791.
   PUBMED | CROSSREF
- Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003;168:49-53.
   PUBMED | CROSSREF
- Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;21:383-8.
- Voss EA, Boyce RD, Ryan PB, van der Lei J, Rijnbeek PR, Schuemie MJ. Accuracy of an automated knowledge base for identifying drug adverse reactions. *J Biomed Inform* 2017;66:72-81.
- Schuemie MJ, Hripcsak G, Ryan PB, Madigan D, Suchard MA. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proc Natl Acad Sci U S A* 2018;115:2571-7.
   PUBMED | CROSSREF
- Lee H, Park S, Kim HC. Temporal and geospatial trends of hypertension management in Korea: a nationwide study 2002–2016. *Korean Circ J* 2019;49:514-27.
- Matsuzaki M, Ogihara T, Umemoto S, et al. Prevention of cardiovascular events with calcium channel blocker-based combination therapies in patients with hypertension: a randomized controlled trial. *J Hypertens* 2011;29:1649-59.
   PUBMED | CROSSREF
- 22. Chi C, Tai C, Bai B, et al. Angiotensin system blockade combined with calcium channel blockers is superior to other combinations in cardiovascular protection with similar blood pressure reduction: a meta-analysis in 20,451 hypertensive patients. *J Clin Hypertens (Greenwich)* 2016;18:801-8.
  PUBMED | CROSSREF
- 23. Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003;289:2534-44. PUBMED | CROSSREF
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs - overview and meta-analyses. *J Hypertens* 2015;33:1321-41.
   PUBMED | CROSSREF

- Wassertheil-Smoller S, Psaty B, Greenland P, et al. Association between cardiovascular outcomes and antihypertensive drug treatment in older women. *JAMA* 2004;292:2849-59.
   PUBMED | CROSSREF
- Turnbull F, Woodward M, Neal B, et al. Do men and women respond differently to blood pressurelowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J* 2008;29:2669-80.
   PUBMED | CROSSREF
- 27. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens* 2008;26:819-24.
   PUBMED | CROSSREF
- Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010;55:399-407.
   PUBMED | CROSSREF
- Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? *J Am Coll Cardiol* 2018;71:1474-82.
   PUBMED | CROSSREF
- Lin DY, Zeng D. On the relative efficiency of using summary statistics versus individual-level data in meta-analysis. *Biometrika* 2010;97:321-32.
   PUBMED CROSSREF