Comparison of initial combination treatments in hypertension: global collaborative research using OHDSI network

Seng Chan You MD[1]; Sungjae Jung MS[1]; Joel N. Swerdel MS MPH[2]; Martijn J. Schuemie PhD[2]; Patrick B. Ryan, PhD[2]; Sungha Park, MD[3]; Rae Woong Park, MD PhD[1,4]

[1]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea; [2]Janssen Research and Development, Titusville, NJ, USA; [3]Division of Cardiology, Yonsei University College of Medicine, Seoul, Korea; [4]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, Korea

Background

- Since monotherapy is often insufficient or slow to reach blood pressure target quickly, guidelines recommend combining two out of the following three classes of drug, ACE inhibitors/angiotensin-receptor blocker (ACEi/ARB), calcium antagonist (CCB) and thiazide diuretics, for initial combination treatment in high risk hypertension patients.
- Only a few randomized clinical trials (RCT), however, have directly compared the effects of different regimens of combination.
- To the best of our knowledge, real-world comparative effectiveness research comparing the various regimens of combination treatment in patients with essential hypertension has not been conducted until now.

Purpose

- We aim to compare the therapeutic effectiveness of combination regimens between patients initiating dual antihypertensive treatment.

Methods

Data sources and study population

- The study consisted of a retrospective analysis of three data sources encoded in the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM) version 5 from participating research partners across the OHDSI community. All three data sources are claim records: National Health Insurance Service-National Sample Cohort (NHIS-NSC, 1.1M) from Korea, Truven MarketScan-Medicare (9.8M) from US, and Truven MarketScan-Medicaid (25.5M) from US.
- The patients who initiate and continue dual combination treatment against hypertension more than 180 days were categorized into three regimen arms: ACEi/ARB + CCB (AC), ACEi/ARB + thiazide diuretics (AD), and CCB + thiazide diuretics (CD).
- The primary outcome was overall mortality. Secondary outcomes were incident myocardial infarction, heart failure, stroke diagnosed in in-patient or emergency-room setting, and major adverse cardiocerebral event (MACCE) as a composite endpoint of all above.
- The patients with previous history of secondary outcomes were excluded.

Statistical analysis

- Large-scale propensity score (PS) matching through OHDSI "CohortMethod" R package was adopted before Cox regression between groups. All available patient demographic and drug exposure, medical condition and procedure codes were matched as covariates in the PS model as potential confounders instead of a pre-specified set of investigator-selected confounders.
- To validate the proper propensity score matching in the claim databases, the baseline characteristics from general health examination were compared in NHIS-NSC between before and after matching.
- For sensitivity analysis, the same analyses were conducted with various minimum drug period: 30, 365 and 730 days
- Total of 38 negative controls were employed to address systematic error in each data source.
- The summary hazard ratios of primary and secondary outcomes were calculated by combining estimates from data sources through a random effects model meta-analysis.
- The protocol and analytic code are available at github: https://github.com/OHDSI/StudyProtocolSandbox/tree/master/HypertensionCombination

Results

Baseline characteristics of study population

- Across all data sources, 46,747, 115,253 and 11,066 patients were identified to meet eligible criteria for AC, AD and CD combination regimen respectively
- The baseline characteristics from the result of NHIS-NSC before and after PS matching were shown in **Table 1**.
- None of mean standardized differences of the variables including demographic, medical history and laboratory values exceeded 0.25.

Table 1. Baseline characteristics of patients in NHIS-NSC after propensity score matching

	A+C vs A+D			C+D vs A+C			C+D vs A+D		
	A+C (n=4751)	A+D (n=4751)	SMD	C+D (n=1739)	A+C (n=1739)	SMD	C+D (n=2382)	A+D (n=2382)	SMD
Female, n	2065 (43.5)	1932 (40.7)	0.06	859 (49.5)	882 (50.8)	-0.03	1340 (56.4)	1354 (57.0)	0.01
Diabetes mellitus, n	1593 (33.5)	1581 (33.3)	0.01	264 (15.2)	243 (14.0)	0.03	591 (24.9)	532 (22.4)	0.06
Chronic kidney disease, n	111 (2.3)	79 (1.7)	0.05	30 (1.7)	21 (1.2)	0.04	33 (1.4)	20 (1.0)	0.05
Dyslipidemia, n	2249 (47.3)	2252 (47.4)	0.00	577 (33.3)	510 (29.4)	0.08	706 (29.7)	655 (27.6)	0.05
CCI, mean	2.6	2.5	0.03	2.1	1.9	0.08	1.9	1.7	0.11
Height, cm	164.0 (9.0)	164.0(8.7)	0.00	161.4 (8.7)	161.5 (9.0)	0.02	160.4 (8.9)	161.8 (9.2)	0.15
Weight, kg	68.6 (12.2)	68.1 (11.2)	0.04	65.7 (10.5)	65.7 (11.4)	0.01	64.9 (10.5)	65.6 (10.5)	0.07
Waist circumference, cm	85.3 (8.8)	85.4 (7.9)	0.00	85.1 (8.2)	84.0 (8.3)	0.13	85.2 (8.2)	84.7 (7.3)	0.07
Systolic blood pressure, mmHg	138.8 (16.5)	139.1(16.7)	0.01	138.7 (16.2)	138.6 (17.0)	0.01	139.5 (16.8)	140.3 (16.8)	0.05
Diastolic blood pressure, mmHg	86.6 (11.9)	86.1 (11.3)	0.04	85.5 (11.8)	86.0 (11.5)	0.05	85.7 (11.6)	86.5 (11.3)	0.07
Fasting plasma glucose, mg/dL	104.6 (27.8)	106.7 (31.7)	0.07	102.0 (24.9)	99.17 (21.8)	0.12	101.0 (25.5)	101.3 (24.7)	0.01
Serum creatinine, mg/dL	1.03 (0.99)	0.99 (0.71)	0.05	0.97 (0.65)	1.05 (1.04)	0.08	0.96 (0.641)	1.13 (1.27)	0.16
Hemoglobin	14.3 (1.6)	14.4 (1.5)	0.03	14.1 (1.6)	14.1 (1.6)	0.02	14.0 (1.5)	14.0 (1.5)	0.02
Total cholesterol, mg/dL	163.3 (109.8)	158.1 (98.0)	0.05	166.8 (126.2)	155.4 (109.8)	0.10	168.0 (127.2)	145.0 (83.8)	0.21
Triglyceride, mg/dL	202.7 (37.4)	204.3 (37.0)	0.04	206.0 (38.4)	202.1 (38.8)	0.10	206.1 (36.8)	202.5 (34.4)	0.10
LDL-cholesterol, mg/dL	118.9 (35.6)	121.3 (46.1)	0.06	118.3 (37.5)	118.9 (39.3)	0.01	118.2 (37.2)	124.4 (75.4)	0.10
HDL-cholesterol, mg/dL	53.3 (13.4)	52.8 (12.9)	0.04	52.8 (13.9)	54.5 (15.0)	0.12	53.0 (14.3)	57.4 (36.7)	0.16
GGT, U/L	49.5 (55.6)	50.5 (62.4)	0.02	46.2 (53.3)	46.2 (54.4)	0.00	42.5 (49.2)	40.0 (46.6)	0.05
AST, IU/L	28.0 (15.4)	28.0 (16.1)	0.00	28.5 (21.1)	27.8 (15.8)	0.04	28.2 (19.5)	26.6 (14.0)	0.09
ALT, IU/L	29.2 (20.4)	29.8 (22.1)	0.03	28.4 (19.1)	26.7 (14.7)	0.10	27.6 (18.9)	26.1 (19.0)	0.08

Values are expressed as the mean ± SD (range) or n (%). HDL, high-density lipoprotein; LDL, low-density lipoprotein; GGT, Gamma-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CCI, Charlson comorbidity index; SMD, Standardized mean difference

Primary outcome assessment

- The risk of overall mortality did not differ in any comparison between combination regimens.
- This result was consistent across the databases and meta-analysis (**Figure 1** and **Figure 2**).
- In the sensitivity analysis with various minimum drug period, there is no consistent evidence preferring one combination regimen to others (data are not shown).
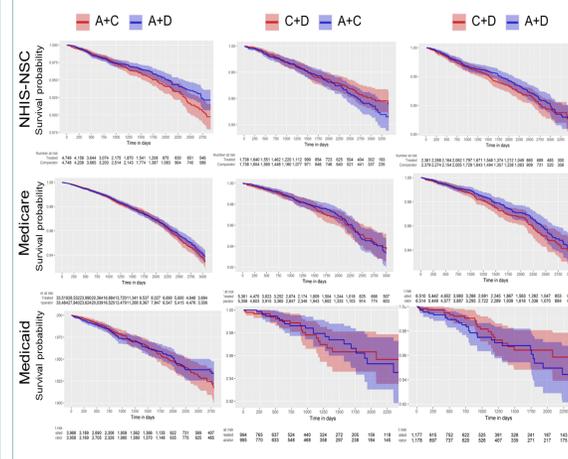

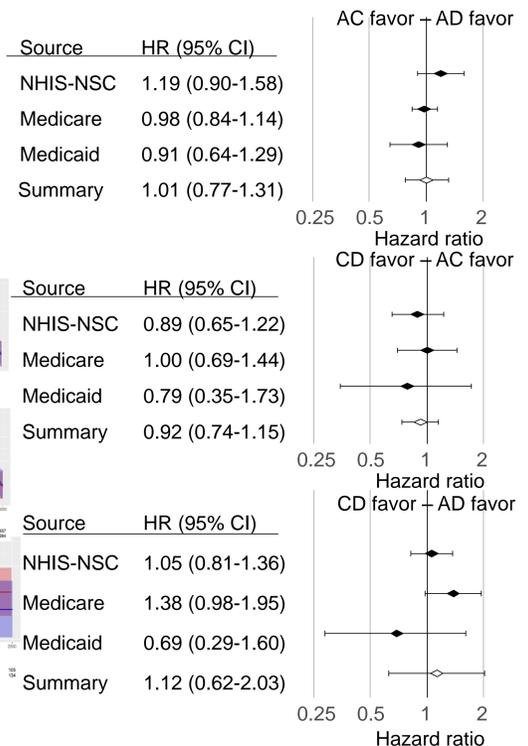**Figure 1.** Survival curve for the primary analysis across the data sources

AC favor — AD favor

Source	HR (95% CI)
NHIS-NSC	1.19 (0.90-1.58)
Medicare	0.98 (0.84-1.14)
Medicaid	0.91 (0.64-1.29)
Summary	1.01 (0.77-1.31)

CD favor — AC favor

Source	HR (95% CI)
NHIS-NSC	0.89 (0.65-1.22)
Medicare	1.00 (0.69-1.44)
Medicaid	0.79 (0.35-1.73)
Summary	0.92 (0.74-1.15)

CD favor — AD favor

Source	HR (95% CI)
NHIS-NSC	1.05 (0.81-1.36)
Medicare	1.38 (0.98-1.95)
Medicaid	0.69 (0.29-1.60)
Summary	1.12 (0.62-2.03)

Figure 2. Meta-analysis for the primary analysis

Secondary outcome assessment

- There is no difference in the risk for incident myocardial infarction, heart failure, stroke and MACCE between dual combination of anti-hypertensive medication
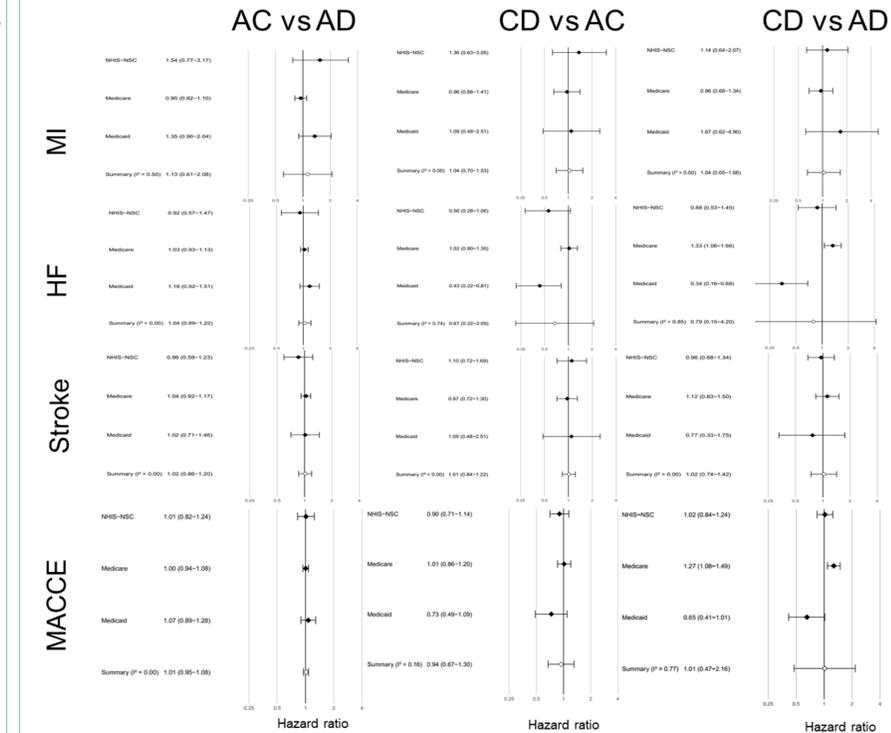

Figure 3. Meta-analysis result for secondary outcomes from each data source. There is no significant association between drug regimen and the outcomes. MI, myocardial infarction; HF, heart failure, MACCE, major adverse cardio-cerebral event

Negative control outcome

- Figure 3 shows the distribution of hazard ratios estimates and their associated standard errors from each of negative controls in each data source. The large majority of estimates do lie above the line, suggesting low residual bias.
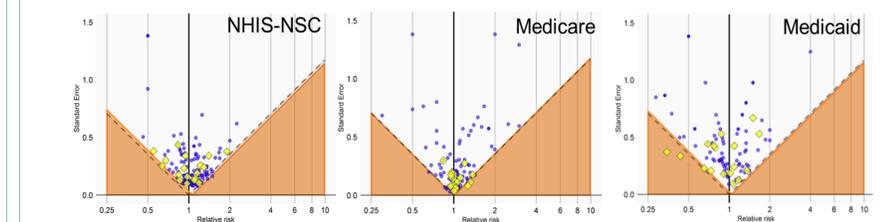

Figure 4. Negative control results from each data source. Blue dots indicate negative controls and yellow dot indicate primary and secondary outcomes. Estimates below the dashed line have p>0.05.

Conclusion

- To our knowledge, this is the first real-world comparative effectiveness research comparing the recommended regimens of dual combination treatment in patient initiating antihypertensive medication.
- The results suggest that there is no significant difference in all-cause mortality and adverse cardio-cerebral events among recommended dual combination treatment regimen among the population in Korea and US.