



Comparison of combination treatment in hypertension

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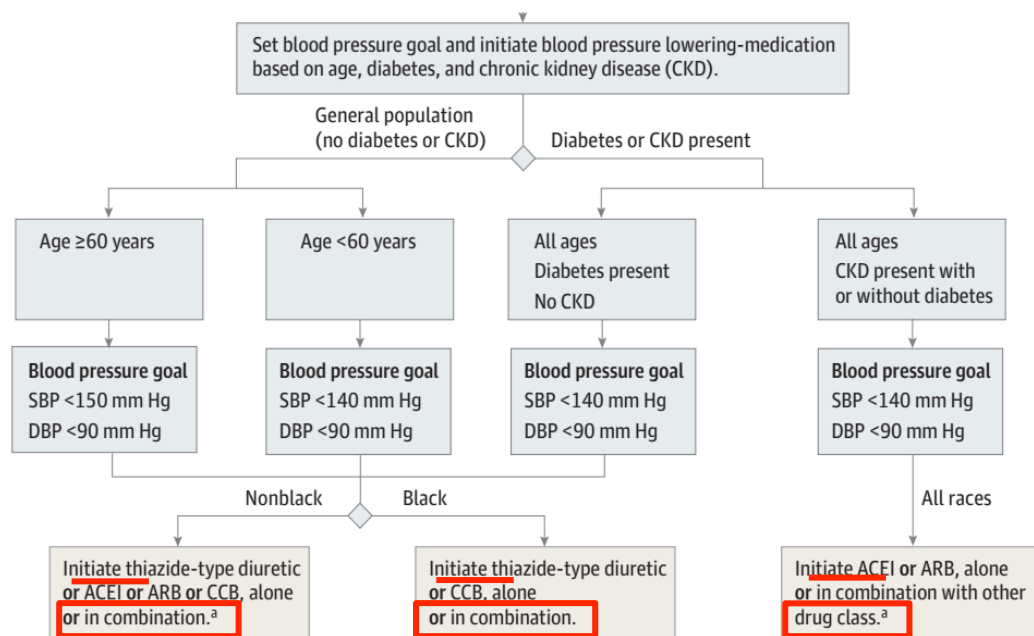
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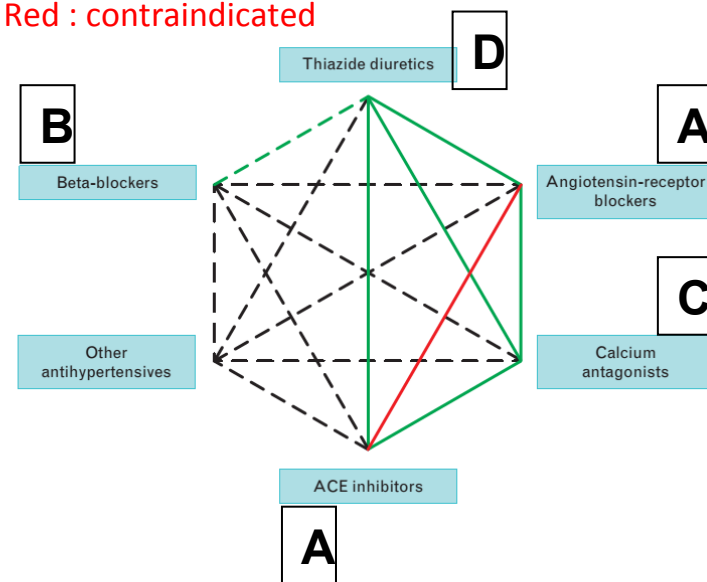
Background: Current guidelines for treatment of hypertension



JNC 8 guideline, 2014

- Recommended combination
 - ACEi/ARB + CCB (AC)
 - ACEi/ARB + Thiazide-diuretics (AD)
 - CCB + Thiazide-diuretics (CD)

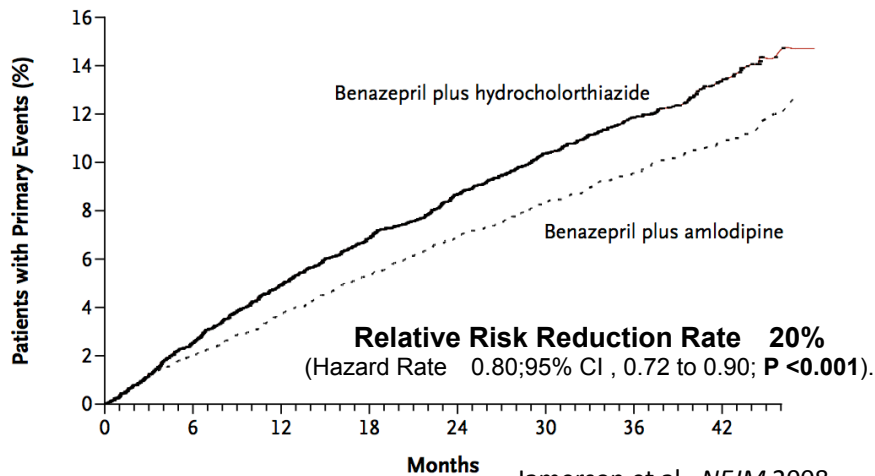
Green: recommended
Red : contraindicated



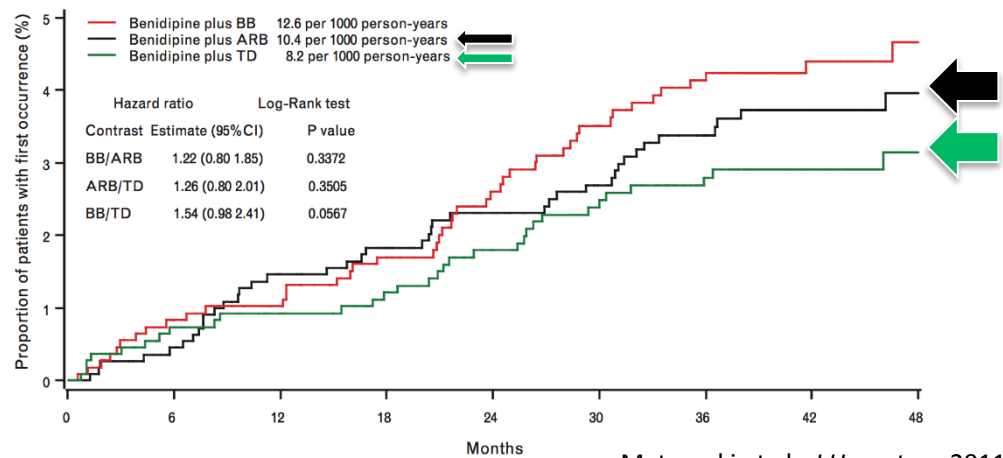
ESC guideline, 2013



Background: Previous studies



- Western patients with high risk for cardiovascular events included
- $A+C > A+D$ for MACE



- Japanese patients without high risk for cardiovascular events
- $A+C = C+D$ for MACE

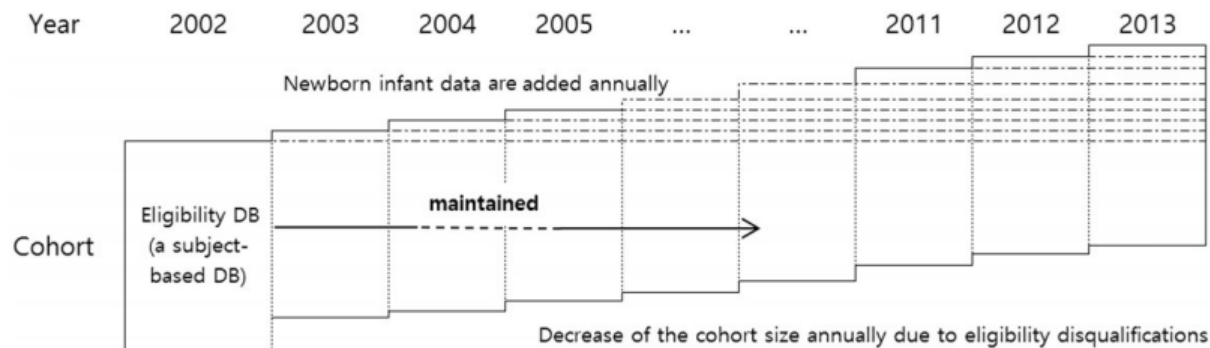
- Only limited evidence for optimal combination regimen in treating hypertension
- There is **no real-world evidence** comparing combination treatment

- Head-to-head comparison of the mortality risk of **combination anti-hypertensive regimens** among patients without high risk for cardiovascular event
 - Target regimens:
 - ACEi/ARB + CCB (AC)
 - ACEi/ARB + Thiazide-diuretics (AD)
 - CCB + Thiazide-diuretics (CD)



Method: study population

- NHIS-national sample cohort (NHIS-NSC) DB
 - Consecutive observation for 1M patients who were randomly sampled from whole Korean population between 2002-2013
 - converted into OMOP Common Data Model version 5.0



Lee et al.,
Int J
Epidemiol.
2016



Method: inclusion algorithm

- Inclusion criteria
 - Adults (≥ 20 years) who used dual anti-hypertensive drugs within 30 days for treating hypertension
 - **180 days** or more consecutive days of the two-drug prescription
 - At least 365 days of pre-observation period before initiating the drugs. (preventing left-censoring)
- Exclusion criteria
 - Prescription with anti-hypertensive medication during previous one year
 - Any diagnosis for ischemic heart disease, heart failure, stroke, and death before drug initiation
 - Use other anti-hypertensive drugs except the two before or within **180 days** after drug initiation



Method: outcomes

- Primary Outcome: All-cause mortality
- Secondary outcome:
 - Cardiovascular death
 - Newly developed myocardial infarction (MI)
 - Newly developed heart failure (HF)
 - Newly developed stroke
 - MACCE (MI+HF+Stroke+Any death)



Method: statistics

- Large scale propensity score matching

- Caliper: 0.15
- Max Ratio: 1:1
- Univariate Cox regression with stratification

Martijn J. Schuemie, Marc A. Suchard and Patrick B. Ryan (2017). CohortMethod: New-user cohort method with large scale propensity and outcome models. R package version 2.4.3.

- Sensitivity analysis

- Same analysis on patients **with various minimum periods (30, 365, 730 days)** of continuation of the drug regimen

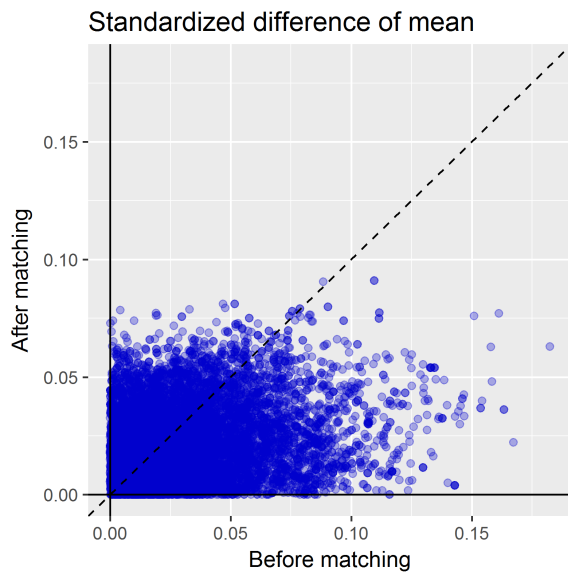
- Analytic code (R) is available for reproducible research:

<https://github.com/OHDSI/StudyProtocolSandbox/tree/master/HypertensionCombination>

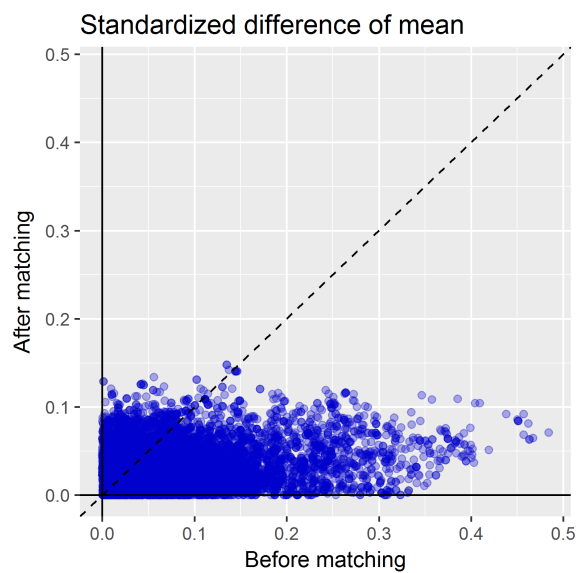


Result: Balance scatter plot

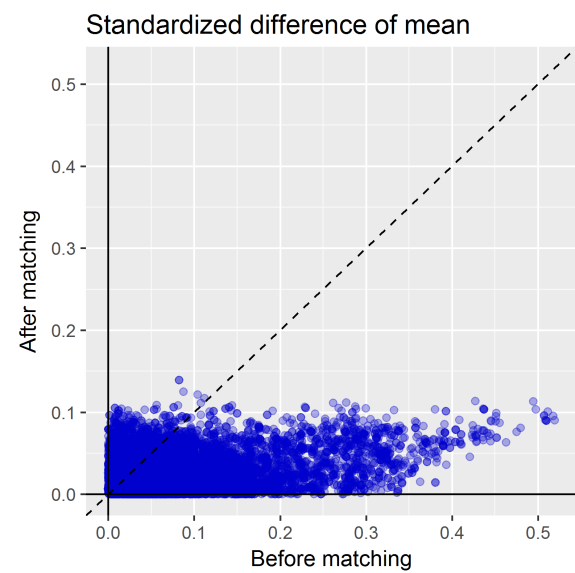
A+C vs A+D



C+D vs A+C

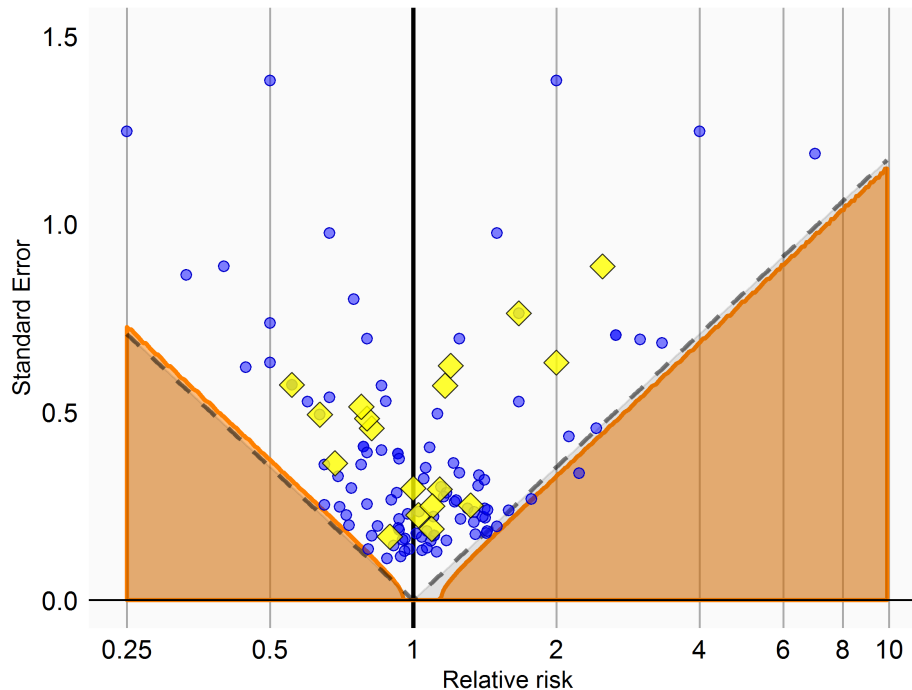


C+D vs A+D





Result: Method evaluation by using negative controls



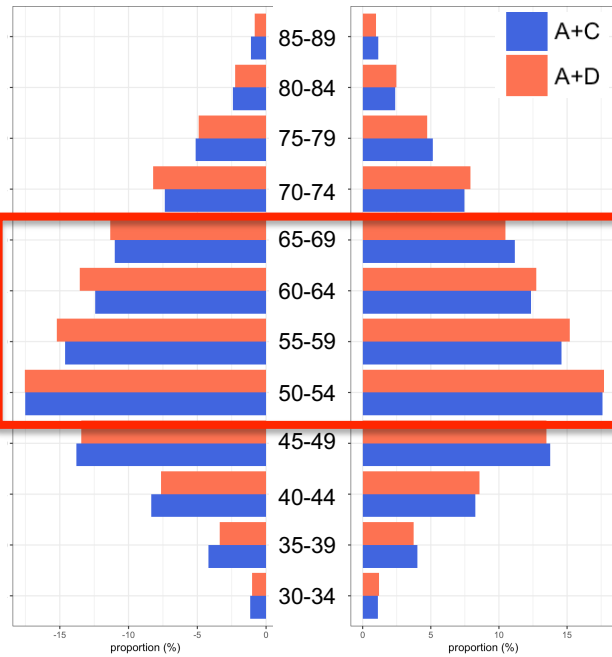
Target vs. Comparator	Total negative outcomes	False Positive count	False positive proportion
AC vs AD	38	1	0.026
CD vs AD	38	2	0.053
CD vs AC	37	1	0.027



Result: Age distribution before and after matching

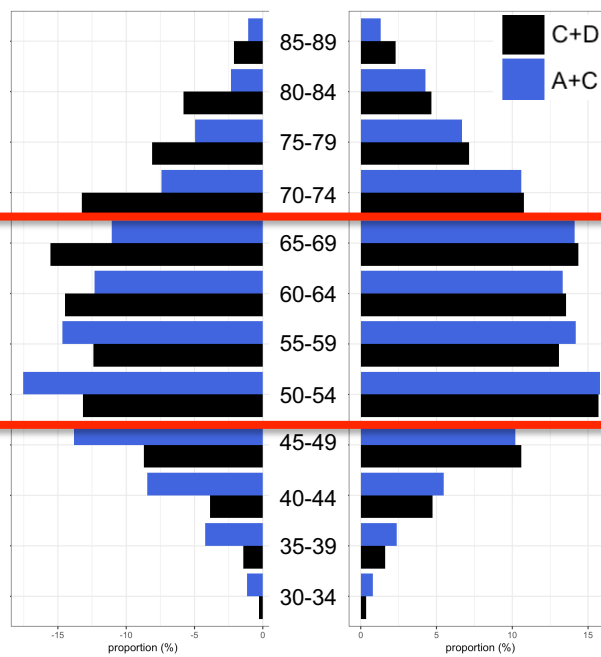
Before matching

After matching



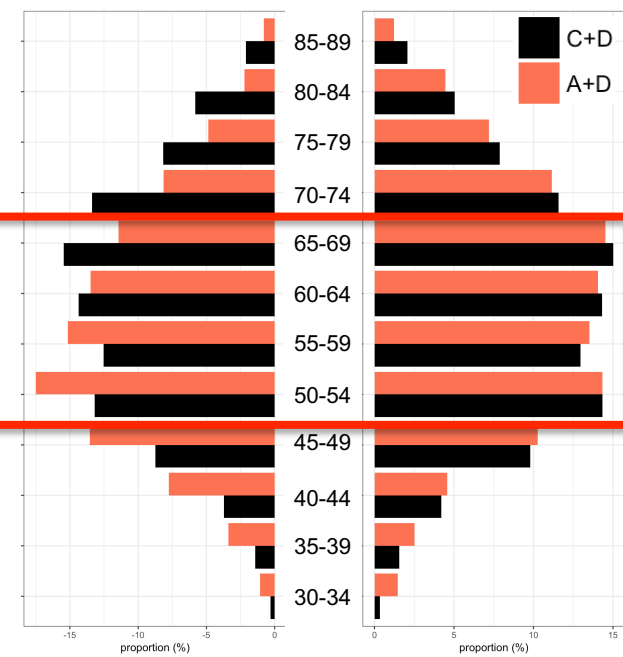
Before matching

After matching



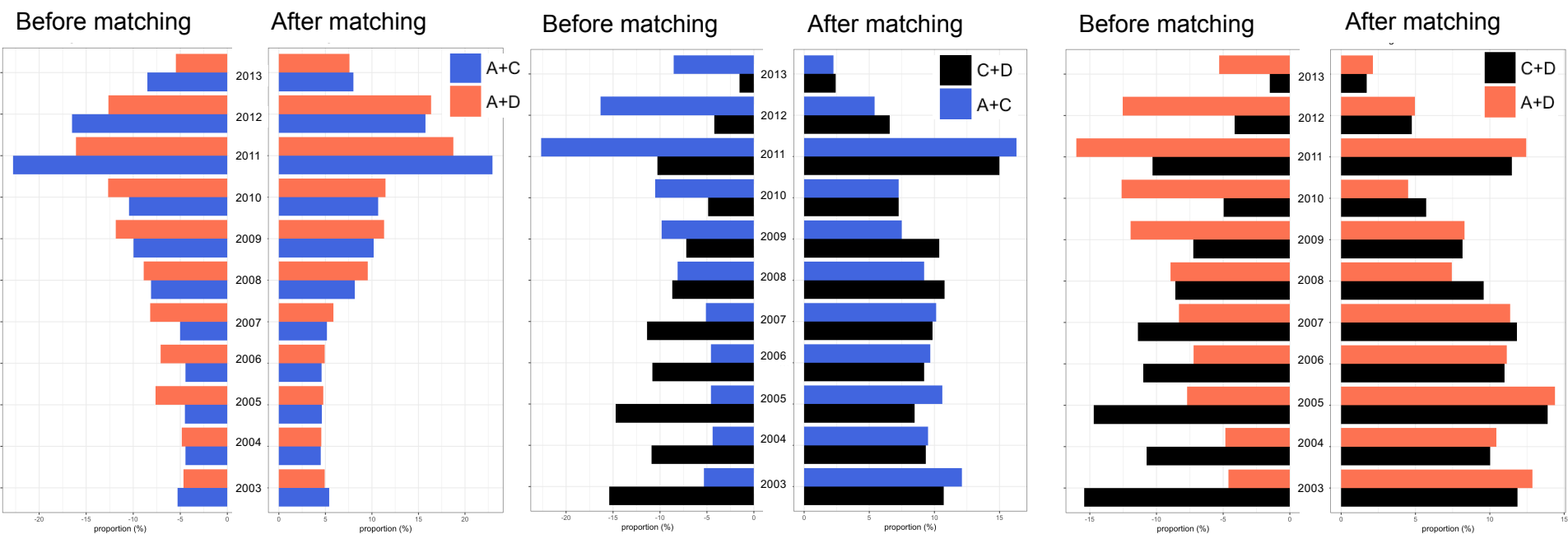
Before matching

After matching





Result: Inclusion year distribution





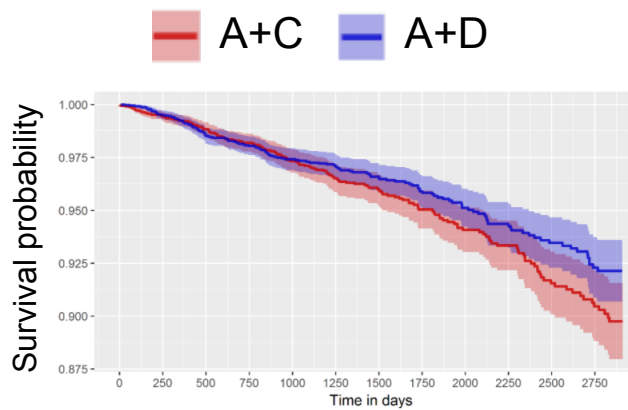
Result: baseline characteristics after matching

	A+C vs A+D			C+D vs A+C			C+D vs A+D		
	A+C (n=4751)	A+D (n=4751)	SD	C+D (n=1739)	A+C (n=1739)	SD	C+D (n=2382)	A+D (n=2382)	SD
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
DM, 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
CKD, 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

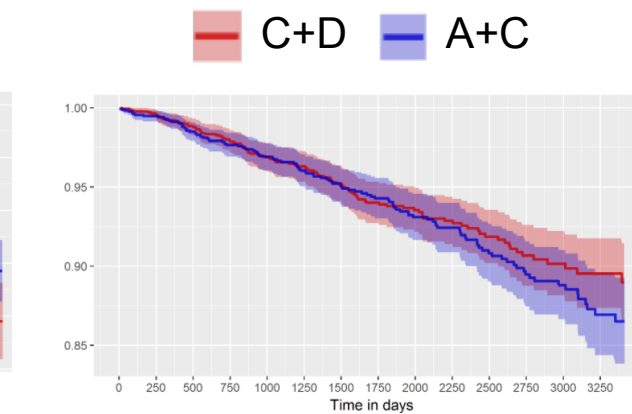
DM, diabetes mellitus; CKD, chronic kidney disease; AF, atrial fibrillation; CCI, Charlson comorbidity index



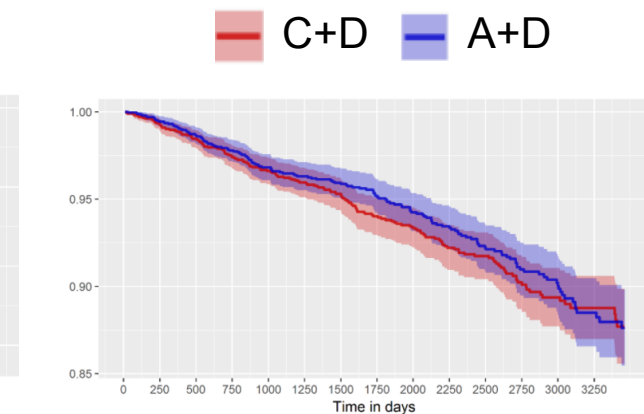
Result: Primary endpoint (All-cause mortality)



$P = 0.465$



$P = 0.465$



$P = 0.478$



Result: Primary endpoint (All-cause mortality)

Result: All-cause mortality between dual combination treatment group after large scale propensity score matching (Minimum drug period : 180 days)

Active drug group	Comparator group	Number of active group after matching	Number of comparator group after matching	Hazard ratio	95% CI	P value
A+C	A+D	4751	4751	1.11	0.84-1.49	0.465
C+D	A+C	1739	1739	1.03	0.71-1.33	0.465
C+D	A+D	2382	2382	1.09	0.85-1.41	0.478

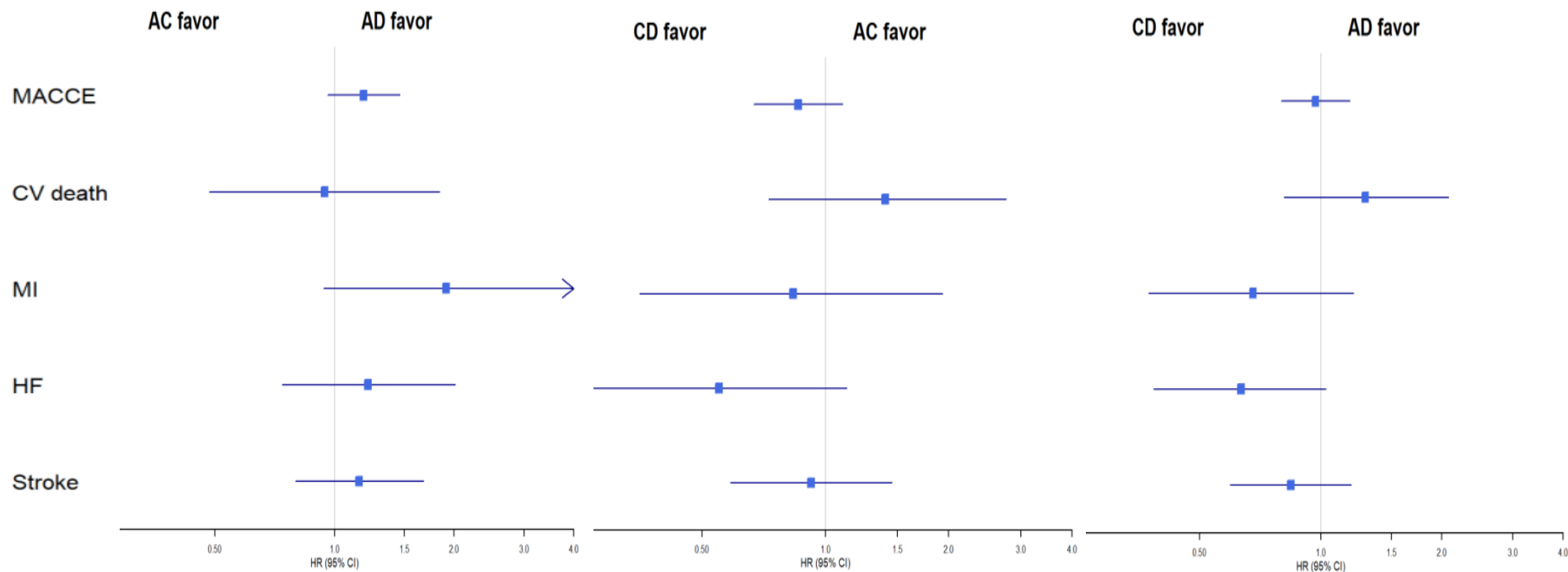
Abbreviations: CI, confidential interval; A, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; B, β -blocker; C, calcium channel blocker; D, thiazide-diuretics; CV, cardiovascular



There is **no difference in mortality between dual combination** of anti-hypertensive medication



Result: Secondary endpoint



Abbreviations: MACCE, major advanced cardio-cerebrovascular event; CV, cardiovascular; MI, myocardial infarction; HF, heart failure



Summary

- There is **no differences in reduction of mortality between anti-hypertensive dual-combination regimens** in a population without previous cardiovascular outcomes
- There is no difference in reduction of stroke, myocardial infarction, heart failure, or cardiovascular death among dual-combination regimens
- We're recruiting international data partners who will run our analytic code on their DB and share the results
- **Please, join the study**

THANK YOU
FOR YOUR
TIME

