Comparison of combination treatment in hypertension

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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)

ESC guideline, 2013

Green: recommended
Red: contraindicated

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


• 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

<table>
<thead>
<tr>
<th>Target vs. Comparator</th>
<th>Total negative outcomes</th>
<th>False Positive count</th>
<th>False positive proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC vs AD</td>
<td>38</td>
<td>1</td>
<td>0.026</td>
</tr>
<tr>
<td>CD vs AD</td>
<td>38</td>
<td>2</td>
<td>0.053</td>
</tr>
<tr>
<td>CD vs AC</td>
<td>37</td>
<td>1</td>
<td>0.027</td>
</tr>
</tbody>
</table>
Result: Age distribution before and after matching
Result: Inclusion year distribution
**Result:** baseline characteristics after matching

<table>
<thead>
<tr>
<th></th>
<th>A+C vs A+D</th>
<th>C+D vs A+C</th>
<th>C+D vs A+D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A+C (n=4751)</td>
<td>A+D (n=4751)</td>
<td>C+D (n=1739)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2065 (43.5)</td>
<td>1932 (40.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>1593 (33.5)</td>
<td>1581 (33.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>111 (2.3)</td>
<td>79 (1.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>2249 (47.3)</td>
<td>2252 (47.4)</td>
<td>0.00</td>
</tr>
<tr>
<td>CCI, mean</td>
<td>2.6</td>
<td>2.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; CKD, chronic kidney disease; AF, atrial fibrillation; CCI, Charlson comorbidity index
Result: Primary endpoint (All-cause mortality)

\[ P = 0.465 \] for A+C versus A+D

\[ P = 0.465 \] for C+D versus A+C

\[ P = 0.478 \] for C+D versus A+D
**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)

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

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