Analysis of Dual Combination Therapies Used in Treatment of Hypertension in a Multinational Cohort

Yuan Lu, ScD
Assistant Professor
Yale School of Medicine
#OHDSIAPAC
OHDSI Asia Pacific Study Group
Analysis of Dual Combination Therapies Used in Treatment of Hypertension in a Multinational Cohort

Yuan Lu, ScD; Mui Van Zandt, BS; Yun Liu, PhD; Jing Li, MS; Xiaolin Wang, MS; Yong Chen, PhD; Zhengfeng Chen, MBBS, MMEd; Jaehyeong Cho, PhD; Sreemanee Raj Dorajoo, PhD; Mengling Feng, PhD; Min-Huei Hsu, MD, PhD; Jason C. Hsu, PhD; Usman Iqbal, PharmD, MBA; Pradeep Jitendra Jomnagaddala, PhD; Yu-Chuan Li, MD, PhD; Siaw-Teng Liaw, MBBS, PhD; Hong-Seok Lim, MD, PhD; Kee Yuan Ngiam, MBBS, MMed; Phung-Anh Nguyen, PhD; Rae Woong Park, MD, PhD; Nicole Pratt, PhD; Christian Reich, MD, PhD; Sang Yool Rhee, MD; Selva Muthu Kumaran Sathappan, MSC; Seo Jeong Shin, PhD; Hui Xing Tan, M Tech; Seng Chan You, MD, PhD; Xin Zhang, MS; Harlan M. Krumholz, MD, SM; Marc A. Suchard, MD, PhD; Hua Xu, PhD

Abstract

**IMPORATANCE** More than 1 billion adults have hypertension globally, of whom 70% cannot achieve their hypertension control goal with monotherapy alone. Data are lacking on clinical use patterns of dual combination therapies prescribed to patients who escalate from monotherapy.

**OBJECTIVE** To investigate the most common dual combinations prescribed for treatment escalation in different countries and how treatment use varies by age, sex, and history of cardiovascular disease.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study used data from 11 electronic health record databases that cover 118 million patients across 8 countries and regions between January 2000 and December 2019. Included participants were adult patients (ages ≥ 18 years) who newly initiated antihypertensive dual combination therapy after escalating from monotherapy. There were 2 databases included for 3 countries: the IQVIA Longitudinal Patient Database (LPD) Australia and Electronic Practice-based Research Network 2019 linked data set from South Western Sydney Local

Key Points

**Question** What are the most common antihypertensive dual combinations prescribed to patients who escalate from monotherapy in clinical practice, and how do the combinations differ by country and patient demographic subgroup?

**Findings** In this cohort study of 970,335 individuals from 11 large databases, 12 dual combinations of antihypertensive drug classes were commonly used, with large variation across countries and
50% of the global hypertension population live in Asia

• Region with the largest population of hypertension
• Marked increase from 1975 to 2015
• Mostly due to change in population size and age structure

NCD Risk Factor Collaboration, Lancet, 2017
OHDSI study on hypertension monotherapies (LEGEND-HTN)

However....

- For many patients, BP control goal not achieved by monotherapies
- Uncertainty about the optimal 2\textsuperscript{nd} drug added to monotherapies
- Lack of high-quality evidence from RCT
- Inability for guideline to recommend preferred drug for treatment escalation
Study objective

As an extension of the LEGEND-HTN initiative, we aim to conduct a large-scale observational study within the OHDSI collaborative community to characterize real-world utilization of dual antihypertensive combination therapies for treatment escalation among people with hypertension.
Cohort definition

Timeline:
- Observation period start (Jan. 2000)
- Initiation of the 1st drug
- >=365d prior continuous observation period
- A diagnosis of hypertension
- A history of antihypertensive monotherapy
- >= 30 days between the initiation of 1st drug class and the initiation of 2nd drug class
- Observation period end (Dec. 2019)

Cohort entry event:
- Start a new drug for treatment escalation
- Index date: initiation of the 2nd drug

Cohort exit:
- End of observation or treatment discontinuation

Four major drug classes:
- Angiotensin-converting enzyme inhibitor (ACEI) or Angiotensin receptor blocker (ARB)
- Calcium channel blocker (CCB)
- Beta-blocker
- Thiazide or thiazide-like diuretic
Twelve exposure cohorts

<table>
<thead>
<tr>
<th>Cohort #</th>
<th>1st Drug</th>
<th>2nd Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACEi/ARB</td>
<td>CCB</td>
</tr>
<tr>
<td>2</td>
<td>CCB</td>
<td>ACEi/ARB</td>
</tr>
<tr>
<td>3</td>
<td>ACEi/ARB</td>
<td>Diuretic</td>
</tr>
<tr>
<td>4</td>
<td>Diuretic</td>
<td>ACEi/ARB</td>
</tr>
<tr>
<td>5</td>
<td>ACEi/ARB</td>
<td>B-blocker</td>
</tr>
<tr>
<td>6</td>
<td>B-blocker</td>
<td>ACEi/ARB</td>
</tr>
<tr>
<td>7</td>
<td>CCB</td>
<td>Diuretic</td>
</tr>
<tr>
<td>8</td>
<td>Diuretic</td>
<td>CCB</td>
</tr>
<tr>
<td>9</td>
<td>CCB</td>
<td>B-blocker</td>
</tr>
<tr>
<td>10</td>
<td>B-blocker</td>
<td>CCB</td>
</tr>
<tr>
<td>11</td>
<td>Diuretic</td>
<td>B-blocker</td>
</tr>
<tr>
<td>12</td>
<td>B-blocker</td>
<td>Diuretic</td>
</tr>
</tbody>
</table>
Together, the committed data sources cover: 118 millions patients in 8 countries and districts
Use of 12 dual antihypertensive combinations

<table>
<thead>
<tr>
<th>Cohort #</th>
<th>Dual combination</th>
<th>Australia LPD</th>
<th>ePBRN SWLSD</th>
<th>Korea Ajou University</th>
<th>KHMC</th>
<th>KTPH</th>
<th>NUH</th>
<th>Singapore</th>
<th>China Jiangsu</th>
<th>Taiwan TMUCRD</th>
<th>France LPD</th>
<th>Italy LPD</th>
<th>United States US</th>
<th>AmbEMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACEI/ARB + Beta-blocker</td>
<td>1,184</td>
<td>268</td>
<td>392</td>
<td>49</td>
<td>105</td>
<td>144</td>
<td>46</td>
<td>1,464</td>
<td>11,236</td>
<td>11,844</td>
<td>110,579</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ACEI/ARB + CCB</td>
<td>4,254</td>
<td>698</td>
<td>1,216</td>
<td>147</td>
<td>216</td>
<td>439</td>
<td>3,127</td>
<td>2,812</td>
<td>22,523</td>
<td>14,628</td>
<td>95,284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>ACEI/ARB + Diuretic</td>
<td>2,066</td>
<td>508</td>
<td>474</td>
<td>12</td>
<td>16</td>
<td>31</td>
<td>111</td>
<td>8</td>
<td>22,399</td>
<td>16,988</td>
<td>123,940</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Beta-blocker + ACEI/ARB</td>
<td>717</td>
<td>210</td>
<td>386</td>
<td>98</td>
<td>68</td>
<td>128</td>
<td>26</td>
<td>2,357</td>
<td>11,116</td>
<td>8,264</td>
<td>106,380</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Beta-blocker + CCB</td>
<td>159</td>
<td>54</td>
<td>614</td>
<td>199</td>
<td>97</td>
<td>243</td>
<td>19</td>
<td>2,484</td>
<td>5,972</td>
<td>2,755</td>
<td>41,388</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Beta-blocker + Diuretic</td>
<td>27</td>
<td>17</td>
<td>51</td>
<td>10</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>4,316</td>
<td>2,967</td>
<td>36,303</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CCB + ACEI/ARB</td>
<td>1,339</td>
<td>246</td>
<td>1,487</td>
<td>193</td>
<td>191</td>
<td>133</td>
<td>3,312</td>
<td>5,015</td>
<td>15,749</td>
<td>5,841</td>
<td>54,297</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CCB + Beta-blocker</td>
<td>190</td>
<td>41</td>
<td>814</td>
<td>217</td>
<td>120</td>
<td>101</td>
<td>34</td>
<td>2,518</td>
<td>3,866</td>
<td>2,475</td>
<td>30,593</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CCB + Diuretic</td>
<td>74</td>
<td>28</td>
<td>259</td>
<td>15</td>
<td>11</td>
<td>6</td>
<td>78</td>
<td>4</td>
<td>1,660</td>
<td>1,103</td>
<td>21,108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Diuretic + ACEI/ARB</td>
<td>251</td>
<td>94</td>
<td>154</td>
<td>2</td>
<td>8</td>
<td>7</td>
<td>114</td>
<td>-</td>
<td>3,281</td>
<td>5,749</td>
<td>84,275</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Diuretic + Beta-blocker</td>
<td>27</td>
<td>14</td>
<td>43</td>
<td>5</td>
<td>1</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>779</td>
<td>1,929</td>
<td>27,422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Diuretic + CCB</td>
<td>50</td>
<td>25</td>
<td>139</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>140</td>
<td>-</td>
<td>1,097</td>
<td>1,539</td>
<td>22,568</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Significant variations in use across country
- ACEI/ARB + CCB most commonly prescribed in Australia and Singapore
- In South Korea, CCB + ACEI/ARB, CCB + β-blocker, and ACEI/ARB + CCB were the 3 most commonly prescribed combinations.
Younger patients were more likely to be prescribed ACEi/ARB then a CCB or a diuretic compared with older patients.
Women were more likely to be prescribed diuretics than an ACEi/ARB or a CCB compared with men.
Diverse array of treatment trajectories across countries

(A) IQVIA LPD Australia

(B) Australia ePBRN SWSLHD

(C) Korea Ajou University

(D) Korea KHMC
Diverse array of treatment trajectories across countries
Diverse array of treatment trajectories across countries

(I) IQVIA LPD France

(J) IQVIA Italy LPD

(K) IQVIA US AmbEMR
Main findings and lessons learned

• Large variation in the transition between monotherapy and dual combination therapy for hypertension across countries and by demographic groups.

• Future research is needed to identify what dual combinations work best for which patients.

• Using LEGEND principles can help mobilize collaboration with OHDSI data partners, but substantial effort was required to ensure data quality and alignment of methods across data sources.