Comprehensive comparative effectiveness and safety of second-line antihypertensive agents: utilizing the LEGEND principles to mobilize collaboration across the OHDSI APAC network

Yuan Lu, ScD
Assistant Professor
Yale School of Medicine
#OHDSIAPAC
OHDSI Asia Pacific Study Group
Collaborators

Jing Li
Xialin Wang
Mui Van Zandt
Christian Reich

Sang Youl Rhee

Hua Xu

Yu-Chuan Li
Min-Huei Hsu
Usman Iqbal
Jason C.Hsu

Nicole Pratt

Seng Chan You
Jiyoung Hwang
Rae Woong Park

Mengling Feng

Jitendra Jonnagaddala
Collaborators

Lei Liu

Ian Chi Kei Wong

Tatsuo Hiramatsu

Yun Liu, Xin Zhang

Yong Huo
Hong Shi

Mengchun Gong

Patrick Ryan
Agenda

• Why this study?
• Objectives & Methods
• Data sources
• Findings to date
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• Findings to date
Global epidemic of hypertension

Age-adjusted prevalence of hypertension in adults, 2015

NCD Risk Factor Collaboration, Lancet, 2017
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 in response to hypertension epidemic

OHDSI study on hypertension monotherapies (LEGEND-HTN)

Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Summary
Background: Uncertainty remains about the optimal monotherapy for hypertension, with current guidelines recommending any primary agent among the first-line drug classes thiazide or thiazide-like diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and non-dihydropyridine calcium channel blockers, in the absence of comorbid indications. Randomised trials have not further refined this choice.

Methods: We developed a comprehensive framework for real-world evidence that enables comparative effectiveness and safety evaluation across many drugs and outcomes from observational data encompassing millions of patients, while minimising inherent bias. Using this framework, we did a systematic, large-scale study under a new-user cohort design to estimate the relative risks of these primary (acute myocardial infarction, hospitalisation for heart failure, and stroke) and six secondary effectiveness and safety outcomes comparing all first-line classes across a global network of six administrative claims and three electronic health record databases. The framework addressed residual confounding, publication bias, and p-hacking using large-scale propensity adjustment, a large set of control outcomes, and full disclosure of hypotheses tested.

Findings: Using 4-5 million patients, we generated 22,900 calibrated, propensity-score-adjusted hazard ratios (HRs) comparing all classes and outcomes across databases. Most estimates revealed no effectiveness differences between classes; however, thiazide or thiazide-like diuretics showed better primary effectiveness than angiotensin-converting enzyme inhibitors: acute myocardial infarction (HR 0.84, 95% CI 0.75–0.95), hospitalisation for heart failure (0.83, 0.74–0.95), and stroke (0.83, 0.74–0.95). Safety profiles also favoured thiazide or thiazide-like diuretics over angiotensin-converting enzyme inhibitors. The non-dihydropyridine calcium channel blockers were significantly inferior to the other four classes.

Interpretation: This comprehensive framework introduces a new way of doing observational health-care science at scale. The approach supports equivalence between drug classes for initiating monotherapy for hypertension—keeping with current guidelines, with the exception of thiazide or thiazide-like diuretics superiority to angiotensin-converting enzyme inhibitors and the inferiority of non-dihydropyridine calcium channel blockers.
OHDSI in response to hypertension epidemic

**OHDSI study on hypertension monotherapies (LEGEND-HTN)**

However...

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

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  - Data sources
- Findings to date
Study objective

As an extension of the LEGEND-HTN initiative, we aim to develop, implement and execute a systematic, large-scale observational study that provides comprehensive comparisons of dual combinations of four major antihypertensive agent classes for treatment escalation.
Study Aims

• Aim 1: To describe real-world utilization of dual antihypertensive combination therapies for treatment escalation among people with hypertension, overall and across subgroups by age, sex, history of CVD, and country.

• Aim 2: To determine real-world effectiveness of dual antihypertensive combination therapies for treatment escalation on nine effectiveness outcomes.

• Aim 3: To determine real-world risks of adverse events and benefits on 46 safety outcomes.

Full study protocol will be available on GitHub soon.
Study design

- Active comparator, new-user cohort design
- Model the study on LEGEND-HTN Lancet paper
- Apply LEGEND guiding principles

Schuemie et al, JAMIA, 2020
## 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>
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<td>ACEi/ARB</td>
<td>Diuretic</td>
</tr>
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</tr>
<tr>
<td>5</td>
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<td>B-blocker</td>
</tr>
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<td>B-blocker</td>
<td>ACEi/ARB</td>
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</tr>
<tr>
<td>12</td>
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Public Atlas Links to 12 Cohorts

<table>
<thead>
<tr>
<th>Cohort #</th>
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<th>2nd Drug</th>
<th>Atlas Cohort links</th>
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<td>Diuretic</td>
<td><a href="http://atlas-demo.ohdsi.org/#/cohortdefinition/1775051">http://atlas-demo.ohdsi.org/#/cohortdefinition/1775051</a></td>
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Eight comparisons

<table>
<thead>
<tr>
<th>Target cohort</th>
<th>Comparator cohort</th>
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<tbody>
<tr>
<td>ACEi/ARB + CCB</td>
<td>ACEi/ARB + Diuretics</td>
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<tr>
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<td>ACEi/ARB + B-blocker</td>
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<tr>
<td>B-blocker + ACEi/ARB</td>
<td>B-blocker + CCB</td>
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<td>B-blocker + ACEi/ARB</td>
<td>B-blocker + Diuretics</td>
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<tr>
<td>CCB + ACEi/ARB</td>
<td>CCB + Diuretics</td>
</tr>
<tr>
<td>CCB + ACEi/ARB</td>
<td>CCB + B-blocker</td>
</tr>
<tr>
<td>Diuretics + ACEi/ARB</td>
<td>Diuretics + B-blocker</td>
</tr>
<tr>
<td>Diuretics + ACEi/ARB</td>
<td>Diuretics + CCB</td>
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</tbody>
</table>
Outcomes

- Three primary effectiveness outcomes based on 2017 AHA/ACC guidelines systematic review
- Six secondary effectiveness outcomes that major hypertension treatment RCTs have considered

<table>
<thead>
<tr>
<th>Primary effectiveness outcome</th>
<th>Secondary effectiveness outcome</th>
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</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>Cardiovascular event</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Stroke</td>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Sudden cardiac death</td>
</tr>
<tr>
<td></td>
<td>Unstable angina</td>
</tr>
</tbody>
</table>

- 46 safety outcomes

Phenotype definitions available at: [https://data.ohdsi.org/LegendBasicViewer/](https://data.ohdsi.org/LegendBasicViewer/)
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• Findings to date
Together, the committed data sources cover: 21 millions patients in 5 countries
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### Patient counts for 12 exposure cohorts

<table>
<thead>
<tr>
<th>Cohort #</th>
<th>1st Drug</th>
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<th>APAC Data Sources</th>
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<td></td>
<td></td>
<td></td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>IQVIA Australia</td>
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<tr>
<td>1</td>
<td>ACEi/ARB</td>
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<td>4,254</td>
</tr>
<tr>
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<td>CCB</td>
<td>ACEi/ARB</td>
<td>1,339</td>
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<tr>
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<td>ACEi/ARB</td>
<td>Diuretic</td>
<td>2,066</td>
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<tr>
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<td>Diuretic</td>
<td>ACEi/ARB</td>
<td>251</td>
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<td>CCB</td>
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<td>CCB</td>
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<td>Diuretic</td>
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<td>27</td>
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<tr>
<td>12</td>
<td>B-blocker</td>
<td>Diuretic</td>
<td>27</td>
</tr>
</tbody>
</table>
Cohort characterization by gender

- Gender ratio of hypertension patients is 1:1
- Women are more likely to be in Cohort #4 (Diuretic + ACEi/ARB), Cohort #8 (Diuretic + CCB), Cohort #12 (B-blocker + Diuretic)
Cohort characterization by age

- Majority of cohort #1 (ACEi/ARB + CCB), cohort #3 (ACEi/ARB + Diuretic) are in age 45-64.
- Majority of cohort #7 (CCB + Diuretic), cohort #9 (CCB + B-blocker), cohort #10 (B-blocker + Diuretic) are in age >=65.
- Drug utilization in Australia and Singapore is higher in age >=65, in Korea is higher in age 45-64.
Cohort characterization by history of CVD

- Most patients do not have history of CVD.
- Among people with history of CVD, cohort #5 (ACEi/ARB + B-blocker) and cohort #6 (B-blocker + ACEi/ARB) are prevalent, consistent with guidelines for secondary prevention of CVD.
Treatment pathway (Australia LPD)

Target Cohort
[APAC HTN] APAC overall population
- Target cohort count: 78,840
- Persons with pathways count: 69,213
- Persons with pathways portion: 87.8%

[APAC HTN] Beta-blocker use after hypertension diagnosis
[APAC HTN] CCB use after hypertension diagnosis
[APAC HTN] Diuretic use after hypertension diagnosis
[APAC HTN] ACEI/ARB use after hypertension diagnosis
Treatment pathway (Korea Ajou University)
Treatment pathway (Singapore NUH)

Legend

Target Cohort

[AAPC HTN] AAPC overall population
- Target cohort count: 16,774
- Persons with pathways count: 14,707
- Persons with pathways portion: 87.7%

Event Cohorts

- [AAPC HTN] ACE/ARB use after hypertension diagnosis
- [AAPC HTN] Beta-blocker use after hypertension diagnosis
- [AAPC HTN] CCB use after hypertension diagnosis
- [AAPC HTN] Diuretic use after hypertension diagnosis
Significant variations in drug utilization across countries

- Most common first-line therapy of patients in Australia and Singapore is ACEi/ARB.
- Most common first-line therapy of Korean patients is CCB.
- More patients in Australia had second-line treatment than Korean patients.
JOIN the OHDSI APAC team

Yuan Lu, ScD
Yale University
y.lu@yale.edu

Jing Li, MS
IQVIA (Asia)
jing.li2@iqvia.com