OHDSI Study pipeline and Research experience using Common Data Model

Seng Chan You
Odyssey (noun): \oh-d-si\ 

1. A long journal full of adventures
OHDSI (Observational Health Data Sciences and Informatics)

The odyssey to evidence generation

Patient-level data in source system/schema
History of OHDSI

• **OMOP (2008-2013)** [www.omop.org](http://www.omop.org)
  – OMOP = Observational Medical Outcomes Partnership
  – Research on methods for drug safety evaluation
    • Methods library developed; positive/negative drug outcome pairs
  – **Common Data Model** (then, was a byproduct)
  – Foundation for the NHI
    • Transition to Reagan Udall Foundation for the FDA

• **OHDSI (after 2013)** [www.ohdsi.org](http://www.ohdsi.org)
  – OHDSI = Observational Health Data Science and Informatics
  – Continues to use the name ‘OMOP CDM’
  – Community of researchers; public; non-pharma funded
New, script based input data mapping for every study

"What's the adherence to my drug in the data assets I can analyze?"

Analytical method: Adherence to Drug

Application to data

One SAS or R script for each study

- Not scalable
- Expensive
- Slow
- Prohibitive to non-expert routine use
Data standardization enables systematic research: Scalability across the World

OHDSI Tools

OMOP CDM
Why Common Data Model (CDM)?

기존의 다기관 연구방법
연구 수행 때마다 데이터 모델을 맞추는 변환 작업을 수행해야 함
CDM in Distributed Research Network

- Source 1
- Source 2
- Source 3

Common Data Model

- Analytic Method
- Results

- Aggregated Results

- 다기관 데이터 통합분석
- EMR 자료 연계
- 공통 분석코드 이용가능

민감 개인정보 유출 없음
How OHDSI works

Source data warehouse, with identifiable patient-level data → ETL → Standardized, de-identified patient-level database (OMOP CDM v5) → Standardized large-scale analytics → Analysis results

OHDSI Coordinating Center:
- Data network support
- Analytics development and testing
- Research and education

OHDSI Data Partners

OHDSI.org
OHDSI projects was initiated to improve health, by empowering a community to collaboratively generate the evidence with adopting OMOP CDM to aggregate health data across world.
Mission, Vision, and Values of OHDSI

• Our Mission
To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care.

• Our Vision
A world in which observational research produces a comprehensive understanding of health and disease.
Objectives of OHDSI

• **Innovation** 혁신성: Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.

• **Reproducibility** 재현성: Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.

• **Openness** 개방성: We strive to make all our community’s proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.

• **Community** 공동체 정신: Everyone is welcome to actively participate in OHDSI, whether you are a patient, a health professional, a researcher, or someone who simply believes in our cause.

• **Collaboration** 협력 정신: We work collectively to prioritize and address the real world needs of our community’s participants.

• **Beneficence** 선행의 정신: We seek to protect the rights of individuals and organizations within our community at all times.
Objectives of OHDSI

- Innovation 혁신성
- Reproducibility 재현성
- Openness 개방성
- Community 공동체 정신
- Collaboration 협력 정신
- Beneficence 선행의 정신

Collaborative International Community for Open Science and federated Reproducible Research
What evidence does OHDSI seek to generate from observational data?

• Clinical characterization
  – Natural history: Who are the patients who have diabetes? Among those patients, who takes metformin?
  – Quality improvement: What proportion of patients with diabetes experience disease-related complications?

• Population-level estimation
  – Safety surveillance: Does metformin cause lactic acidosis?
  – Comparative effectiveness: Does metformin cause lactic acidosis more than glyburide?

• Patient-level prediction
  – Precision medicine: Given everything you know about me and my medical history, if I start taking metformin, what is the chance that I am going to have lactic acidosis in the next year?
  – Disease interception: Given everything you know about me, what is the chance I will develop diabetes?
### Cohort Method
- New-user cohort studies using large-scale regression for propensity and outcome models.

### Self-Controlled Case Series
- Self-Controlled Case Series analysis using few or many predictors, includes splines for age and seasonality.

### Self-Controlled Cohort
- A self-controlled cohort design, where time preceding exposure is used as control.

### IC Temporal Pattern Disc.
- A self-controlled design, but using temporal patterns around other exposures and outcomes to correct for time-varying confounding.

### Case-control
- Case-control studies, matching controls on age, gender, provider, and visit date. Allows nesting of the study in another cohort.

### Case-crossover
- Case-crossover design including the option to adjust for time-trends in exposures (so-called case-time-control).

### Patient Level Prediction
- Build and evaluate predictive models for user-specified outcomes, using a wide array of machine learning algorithms.

### Feature Extraction
- Automatically extract large sets of features for user-specified cohorts using data in the CDM.

### Empirical Calibration
- Use negative control exposure-outcome pairs to profile and calibrate a particular analysis design.

### Method Evaluation
- Use real data and established reference sets as well as simulations injected in real data to evaluate the performance of methods.

### Database Connector
- Connect directly to a wide range of database platforms, including SQL Server, Oracle, and PostgreSQL.

### Sql Render
- Generate SQL on the fly for the various SQL dialects.

### Cyclops
- Highly efficient implementation of regularized logistic, Poisson and Cox regression.

### Ohdsi R Tools
- Support tools that didn’t fit other categories, including tools for maintaining R libraries.

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*Under construction*
What do epi studies currently look like?
Most epidemiologists view a study as a journey from data set to paper.
- The protocol might be your map
- You will come across obstacles that you will have to overcome
- Several steps will require manual intervention
- In the end, it will be impossible to retrace your exact steps
A study should be like a pipeline
- A fully automated process from database to paper
- ‘Performing a study’ = building the pipeline
OHDSI best practices

1. OHDSI Development
   Software
   The OHDSI developer community is committed to the development of open-source, high-quality, and easy to use tools for making the most out of observational health data.
   - Developer Guidelines
   - Architecture Overview
   - Release Schedule
   - GitHub Issue Tracker
   - WebAPI services

2. Methodology
   OHDSI Methodology developers comprise experts in the fields of epidemiology, biostatistics, computer science, and clinical research who are committed to creating and validating high-quality methods for observational data research.

development/overview.txt | Last modified: 2016/03/30 07:43 by schuemie
General principles

• **Prespecify** what you're going to estimate and how: this will avoid hidden multiple testing (publication bias, p-value hacking). Run your analysis only once.

• **Validation of your analysis**: you should have evidence that your analysis does what you say it does (showing that statistics that are produced have nominal operating characteristics (e.g. p-value calibration), showing that specific important assumptions are met (e.g. covariate balance), using unit tests to validate pieces of code, etc.)

• **Transparency**: others should be able to reproduce your study in every detail using the information you provide.
Best practices (generic)

• **Write a full protocol**, and make it public prior to running the study
  – Research question + hypotheses to be tested
  – Which method(s), data, cohort definitions. What is the primary analyses and what are sensitivity analyses?
  – Quality control
  – Amendments and Updates

• **Validate all code** used to produce estimates. The purpose of validation is to ensure the code is doing what we require it to do. Possible options are:
  – Unit testing
  – Simulation
  – Double coding
  – Code review

• Include **negative controls** (exposure-outcome pairs where we believe there is no effect)

• Produce **calibrated p-values**

• Make all analysis code available as **open source** so others can easily replicate your study
Study Pipeline 1. Define cohort: A database is full of cohorts, some of which may represent valid comparisons.
Study Pipeline 1. Define cohort

- CIRCE [ATLAS]
Study Pipeline 1. Define cohort

- CIRCE [ATLAS]

**Cohort definition:** A cohort is defined as the set of persons satisfying one or more inclusion criteria for a duration of time. One person may qualify for one cohort multiple times during non-overlapping time intervals. Cohorts are constructed in ATLAS by specifying cohort entry criteria and cohort exit criteria.

Cohort entry criteria involve selecting one or more initial events, which determine the start date for cohort entry, and optionally specifying additional inclusion criteria which filter to the qualifying events. Cohort exit criteria are applied to each cohort entry record to determine the end date when the person's episode no longer qualifies for the cohort.

Patients who measures LDL level at 2009 and without prior statin for a year, previous IHD or stroke history.

**Initial event cohort:** Events are recorded time-stamped observations for the persons, such as drug exposures, conditions, procedures, measurements and visits. All events have a start date and end date, though some events may have a start date and end date with the same value (such as procedures or measurements). The event index date is set to be equal to the event start date.

People having any of the following: Add Initial Event...

- Observation periods with the following criteria:
  - Observation period start on or before: 2002-01-01
  - Observation period end on or after: 2008-12-31
  - With age at period start: Greater than: 30

With continuous observation of at least 0 days before and 0 days after event index date

Limit initial events to: all events per person.

Add initial event inclusion criteria

**Additional qualifying inclusion criteria:** The qualifying cohort will be defined as all persons who have an initial event, satisfy the initial event inclusion criteria, and fulfill all additional qualifying inclusion criteria. Each qualifying inclusion criteria will be evaluated to determine the impact of the criteria on the attrition of persons from the initial cohort.

New qualifying inclusion criteria

1. No prior IHD
   - No prior ischemic heart disease
2. No prior stroke
   - No prior stroke
3. No prior brain imaging
   - No prior brain CT or MRI before:
4. No prior CAG or coronary revascularization

No prior IHD

No prior ischemic heart disease

Having all of the following criteria: Add New Criteria...

With at most 0 using all occurrences of:

- A condition occurrence of ischemic heart disease

Starting between all days before and 0 days after event index date and ending any time.
Study Pipeline 2. Database connection / Cohort extraction

SCYou:HTN_combI_A_D180_per protocol(17.7.3)

Available CDM Sources

<table>
<thead>
<tr>
<th>Source Name</th>
<th>Generation Status</th>
<th>Distinct People</th>
<th>Generated</th>
<th>Generation Duration</th>
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</thead>
<tbody>
<tr>
<td>Camel_D8</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>NHID</td>
<td>COMPLETE</td>
<td>9942</td>
<td>5/10/2017 9:36:44 PM</td>
<td>37.8125</td>
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</table>

Inclusion Report for NHID

<table>
<thead>
<tr>
<th>Inclusion Rule</th>
<th>Match Rate</th>
<th>N</th>
<th>% Remain</th>
<th>% Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No RAS blocker during previous one year</td>
<td>32.99%</td>
<td>20,932</td>
<td>69.46%</td>
<td>30.54%</td>
</tr>
<tr>
<td>2. No diuretics during previous one year</td>
<td>32.99%</td>
<td>19,745</td>
<td>65.52%</td>
<td>3.94%</td>
</tr>
<tr>
<td>3. No beta-blocker during previous one year and within 180 days after index date</td>
<td>32.99%</td>
<td>15,952</td>
<td>52.93%</td>
<td>12.59%</td>
</tr>
<tr>
<td>4. No diuretics during previous one year and within 180 days after index date</td>
<td>32.99%</td>
<td>13,767</td>
<td>45.68%</td>
<td>7.25%</td>
</tr>
<tr>
<td>5. No previous or early death</td>
<td>32.99%</td>
<td>13,767</td>
<td>45.68%</td>
<td>0.00%</td>
</tr>
<tr>
<td>6. No previous IHD</td>
<td>32.99%</td>
<td>11,226</td>
<td>37.23%</td>
<td>8.43%</td>
</tr>
<tr>
<td>7. No previous HF</td>
<td>32.99%</td>
<td>10,683</td>
<td>35.45%</td>
<td>1.80%</td>
</tr>
<tr>
<td>8. No previous stroke</td>
<td>32.99%</td>
<td>9,942</td>
<td>32.99%</td>
<td>2.46%</td>
</tr>
</tbody>
</table>
Study Pipeline 3. Define the statistical model and Compare

Choose your target cohort:
- SCYou:HTN_combi_AC180_wo_hx_per protocol

Choose your comparator cohort:
- SCYou:HTN_combi_AD180_wo_hx_per protocol

Choose your outcome cohort:
- SCYou:(outcome)any death

Specify the statistical model used to estimate the risk of outcome between target and comparator cohorts:
- Cox proportional hazards

Define the time-at-risk window start, relative to target/comparator cohort entry:
- 0 days from cohort start date

Define the time-at-risk window end:
- 0 days from cohort start date

Minimum washout period applied to target and comparator cohorts:
- 0

Minimum required days at risk, applied to target and comparator cohorts:
- 0

Remove patients who enter both cohorts?
- Yes

Remove patients who have observed the outcome prior to cohort entry?
- Yes

Use propensity score adjustment as a confounding adjustment strategy for baseline covariates?
- Yes
Study Pipeline 3. Define the statistical model and Compare

Specify the statistical model used to estimate the risk of outcome between target and comparator cohorts:

- Cox proportional hazards

Define the time-at-risk window start, relative to target/comparator cohort entry:

- 0 days from cohort start date

Define the time-at-risk window end:

- 0 days from cohort start date

Minimum washout period applied to target and comparator cohorts:

- 0

Minimum required days at risk, applied to target and comparator cohorts:

- 0

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Remove patients who have observed the outcome prior to cohort entry?

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- Yes
Study Pipeline 3. Define the statistical model and Compare

<table>
<thead>
<tr>
<th>Specification</th>
<th>Utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choose your target cohort:</td>
<td></td>
</tr>
<tr>
<td>SCYou:HTN_combi_AC180_wo_hx_per protocol</td>
<td></td>
</tr>
<tr>
<td>Choose your comparator cohort:</td>
<td></td>
</tr>
<tr>
<td>SCYou:HTN_combi_AD180_wo_hx_per protocol</td>
<td></td>
</tr>
<tr>
<td>Choose your outcome cohort:</td>
<td></td>
</tr>
<tr>
<td>SCYou:(outcome)any death</td>
<td></td>
</tr>
</tbody>
</table>

Specify the statistical model used to estimate the risk of outcome between target and comparator cohorts:

- **Cox proportional hazards**

Define the time-at-risk window start, relative to target/comparator cohort entry:

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- **0** days from cohort start date

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- **0**

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- **Yes**

Use propensity score adjustment as a confounding adjustment strategy for baseline covariates?

- **Yes**
Study on comparison of combination treatment in hypertension

Objective: The objective of this study is to compare the effectiveness and adverse events between the combination treatments in hypertension

Rationale: The goal of antihypertensive therapy is to reduce cardiovascular endpoints including stroke, myocardial infarction, and heart failure by lowering blood pressure. Although it is evident that BP reduction per se is the primary determinant of CV risk reduction, the choice of initial drug therapy can exert some effect on long-term outcomes. Many large randomized trials have shown that two or more antihypertensive agents are required for reaching their treatment goals. Furthermore, recent data have suggested that the use of combination therapy in patients with hypertension may be beneficial for blood-pressure-lowering efficacy, obtaining blood pressure goals earlier, and reducing major adverse cardiovascular events. To date, however, the best combination treatment in hypertension have not been demonstrated. The evidence through OHDSI network can help clinicians to select the combination treatment for their patients.

Project Leads: Seng Chan You, Sungjae Jung, and Rae Woong Park from Ajou university

Please provide any comments or suggestions
4. Recruiting data partners and Aggregating their results

**Figure 1.**
Forest plots showing the HRs for angioedema with exposure to levetiracetam compared with phenytoin in patients with seizure disorder across multiple databases, as well as combined estimate, for the per-protocol and intent-to-treat analyses.

*Epilepsy* © ILAE
Our experience

• Head-to-head comparison of the mortality risk of combination anti-hypertensive regimens among patients without high risk for cardiovascular event

• AIM
  – To compare the **mortality risk** of combination regimens among patients initiating antihypertensive treatment
  – Analysis based on CDM for **reproducible research**
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 continuing the drug regimen

- Analytic R code is available for reproducible research: https://github.com/OHDSI/StudyProtocolSandbox/tree/master/HypertensionCombination
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)
### 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>859 (49.5)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>1593 (33.5)</td>
<td>1581 (33.3)</td>
<td>264 (15.2)</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>111 (2.3)</td>
<td>79 (1.7)</td>
<td>30 (1.7)</td>
</tr>
<tr>
<td>Dyslipidemia, n</td>
<td>2249 (47.3)</td>
<td>2252 (47.4)</td>
<td>577 (33.3)</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI, mean</td>
<td>2.6</td>
<td>2.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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

\[ P = 0.465 \]

\[ P = 0.465 \]

\[ P = 0.478 \]
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)

<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
OHDSI study: comparison of combination treatment in hypertension

Study on comparison of combination treatment in hypertension

Researchers

SCYou, Sang Chan You

The new study below is planned to post to the OHDSI Research Network.

Comparison of combination treatment in hypertension

Objective: The objective of this study is to compare the effectiveness and adverse events between the combination treatments in hypertension.

Rationale: The goal of antihypertensive therapy is to reduce cardiovascular end points including stroke, myocardial infarction, and heart failure by lowering blood pressure. Although it is evident that BP reduction per se is the primary determinant of CV risk reduction, the choice of initial drug therapy can exert some effect on long-term outcomes. Many large randomized trials have shown that two or more antihypertensive agents are required for reaching their treatment goals. Furthermore, recent data have suggested that the use of...
Hi Chan:

You did a great job presenting at the OHDSI Symposium.

I just got internal J&J permission to participate in your study, so we are set to go. On Monday, I have my next team meeting, where executing your study will be a new project that will get assigned within the team. Martin has already expressed interest in participating, and I suspect that at least one other in my team will want to join in as well. In terms of database contributions, I suspect we should have sufficient information in a few different US databases (Truven CCAE, Truven MDCR, Optum SES), in the IMS Germany and JMDC databases. We could consider applying for ISAC approval to use CPRD for UK EHR. It could be worth applying, but our experience is that can be quite time-consuming so we may not want to wait for the results before moving forward.

It was great seeing you and Rae at the Symposium. Thank you for all your valuable contributions to the community.

Cheers,

Patrick
OHDSI study: comparison of combination treatment in hypertension

Study on comparison of combination treatment in hypertension

Researchers

SCYou  Sang Chan You

The new study below is planned to post to the OHDSI Research Network.

Comparison of combination treatment in hypertension

Hi Choel,

Greetings and congrats on your award. I'd like to join. I'm at the Univ of Colorado. We have not completed our medication mappings to OMOP- and obviously this will need to be done. Do you have an expected date that the data pull?

I'm also with the University of California Medical Centers, and I'll solicit their involvement too.

When I have chance, I'll review the protocol, etc

Lisa

Lisa Schilling, MD, MSPH
Professor of Medicine
Department of Medicine, Division of General Internal Medicine
University of Colorado, School of Medicine
Result: Primary endpoint (All-cause mortality) in US (medicaid & medicare)
Result: Primary endpoint (All-cause mortality)

There is **no difference in mortality** between dual combination of anti-hypertensive medication.
Large-Scale Evidence Generation and Evaluation in a Network of Databases (LEGEND)

Patrick Ryan, Martijn Schuemie, Marc Suchard on behalf of the LEGEND team

OHDSI Symposium
12 October 2018
What’s in a guideline?

Clinical Practice Guideline: Executive Summary


A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

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56 pages containing 106 recommendations
### 8.1.6. Choice of Initial Medication

#### Recommendation for Choice of Initial Medication

References that support the recommendation are summarized in **Online Data Supplement 27 and Systematic Review Report**.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A&lt;sup&gt;SR&lt;/sup&gt;</td>
<td>1. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. &lt;sup&gt;S8.1.6-1,S8.1.6-2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

SR indicates systematic review.
For initiation of antihypertensive drug therapy, how SHOULD patients be treated?

What evidence do we have about the comparative effects about alternative antihypertensive drugs?
40 RCTs comparing 2 or more of the 57 listed drugs.
RCT evidence about comparative effectiveness for myocardial infarction

Figure 3.3 Network of clinical trials of antihypertensive drug classes in which myocardial infarction was reported (N=29). *
Dissecting the comparative evidence of ACE vs THZ on AMI

- **ACE**
  - Comparator
  - ALLHAT, ANBP2, PHYLLIS
  - Target
  - THZ
  - Effect estimate: 1.2 (0.78-2.0)

### Study Details

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Target Drug</th>
<th>Exposed</th>
<th>Events</th>
<th>Comparator Drug</th>
<th>Exposed</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>Prior (treated) stage 1/2 hypertension with &gt;=1 CVD risk factor</td>
<td>Chlorthalidone</td>
<td>15,255</td>
<td>1,362</td>
<td>Lisinopril</td>
<td>9,054</td>
<td>796</td>
</tr>
<tr>
<td>ANBP2</td>
<td>Australians aged 65-84 with SBP &gt; 160mmHg (62% previously treated)</td>
<td>Hydrochlorothiazide</td>
<td>3,039</td>
<td>82</td>
<td>Enalapril</td>
<td>3,044</td>
<td>58</td>
</tr>
<tr>
<td>PHYLLIS</td>
<td>Italians age 45-70 with hypertension and hypercholesterolemia</td>
<td>Hydrochlorothiazide</td>
<td>127</td>
<td>3</td>
<td>Fosinopril</td>
<td>127</td>
<td></td>
</tr>
</tbody>
</table>

### Effect Estimate

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>LB95CI</th>
<th>UB95CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>1.01</td>
<td>0.93</td>
<td>1.10</td>
</tr>
<tr>
<td>ANBP2</td>
<td>1.47</td>
<td>1.02</td>
<td>2.13</td>
</tr>
<tr>
<td>PHYLLIS</td>
<td>not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Published observational study results

59,196 estimates
19.0% of CIs include 1

Suspicious cutoff at p=0.05
- Publication bias (leads to false positives)
- P-hacking (leads to false positives)
LEGEND

LARGE-SCALE EVIDENCE GENERATION AND EVALUATION IN A NETWORK OF DATABASES
Building the process to generate the evidence
LEGEND Guiding Principles

1. Evidence will be generated at **large-scale**.
2. **Dissemination** of the evidence will not depend on the estimated effects.
3. Evidence will be generated by consistently applying a **systematic approach** across all research questions.
4. The evidence will be generated using a **pre-specified** analysis design.
5. The evidence will be generated using **open source** software that is freely available to all.
6. The evidence generation process will be **empirically evaluated** by including control research questions where the true effect size is known.
7. The evidence will be generated using **best-practices**.
8. LEGEND will **not** be used to **evaluate methods**.
9. The evidence will be **updated** on a regular basis.
10. **No patient-level data** will be shared between sites in the network, only aggregated data.
What would the ‘target trial’ look like to compare efficacy of two initial therapies?

Treatment strategies:
- Monotherapy with chlorthalidone (CTD)
- Monotherapy with hydrochlorothiazide (HCTZ)

Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Medical history lookback time

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect

Follow-up time

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

Index:
- Time zero

Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure
- Safety:
  - Known or potential adverse events, e.g.
    - Acute renal failure
    - Angioedema
    - Cough
    - Diarrhea
    - Fall
    - Gout
    - Headache
    - Hyperkalemia
    - Hyponatremia
    - Hypotension
    - Impotence
    - Syncope
    - Vertigo

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards
Observational study to compare two initial therapies

Eligibility criteria:
- Diagnosed with hypertension in 1 year prior to index
- No prior antihypertensive drug use anytime prior to index

Medical history lookback time

Follow-up time

Treatment strategies:
- Monotherapy with ACE
- Monotherapy with ARB

Causal contrasts of interest:
- Intent-to-treat effect
- On-treatment effect

Outcomes:
- Efficacy:
  - Myocardial infarction
  - Stroke
  - Heart Failure
- Safety:
  - Known or potential adverse events, e.g.
    - Acute renal failure
    - Angioedema
    - Cough
    - Diarrhea
    - Fall
    - Gout
    - Headache
    - Hyperkalemia
    - Hyponatremia
    - Hypotension
    - Impotence
    - Syncope
    - Vertigo

Analysis plan:
- Time-to-first-event analysis
- Cox proportional hazards

PS adjustment

Index:
Time zero
Hypertension mono-therapy

Truven Health MarketScan CCAE. Therapies > 2 ingredients not shown
Comparisons of hypertension treatments

<table>
<thead>
<tr>
<th></th>
<th>Theoretical</th>
<th>Observed (n &gt; 2,500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single ingredients</td>
<td>58</td>
<td>39</td>
</tr>
<tr>
<td>Single ingredient comparisons</td>
<td>58 * 57 = 3,306</td>
<td>1,296</td>
</tr>
<tr>
<td>Single drug classes</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Single class comparisons</td>
<td>15 * 14 = 210</td>
<td>156</td>
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</table>
## Comparisons of hypertension treatments

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</tr>
<tr>
<td>Single class comparisons</td>
<td>15 * 14 = 210</td>
<td>156</td>
</tr>
<tr>
<td>Dual ingredients</td>
<td>58 * 57 / 2 = 1,653</td>
<td>58</td>
</tr>
<tr>
<td>Single vs duo drug comparisons</td>
<td>58 * 1,653 = 95,874</td>
<td>3,810</td>
</tr>
<tr>
<td>Dual classes</td>
<td>15 * 14 / 2 = 105</td>
<td>32</td>
</tr>
<tr>
<td>Single vs duo class comparisons</td>
<td>15 * 105 = 1,575</td>
<td>832</td>
</tr>
<tr>
<td>Duo vs duo drug comparisons</td>
<td>1,653 * 1,652 = 2,730,756</td>
<td>2,784</td>
</tr>
<tr>
<td>Duo vs duo class comparisons</td>
<td>105 * 104 = 10,920</td>
<td>992</td>
</tr>
<tr>
<td>Total comparisons</td>
<td>2,843,250</td>
<td>10,278</td>
</tr>
</tbody>
</table>
LEGEND knowledge base for hypertension

Head-to-head HTN drug comparisons

- Trials: 40
- $N = 102 - [1148] - 33K$
- Comparisons: 10,278
- $N = 3502 - [212K] - 1.9M$
1,321,696 estimates
83.4% of CIs includes 1
Depression results publicly available

http://data.ohdsi.org/SystematicEvidence/
Acknowledgments

LEGEND Scientific Group:
- Martijn J. Schuemie
- Patrick B. Ryan
- Seng Chan You
- Nicole Pratt
- David Madigan
- George Hripcsak
- Marc A. Suchard

Clinical Advisory Team:
- RuiJun Chen
- Jon Duke
- Rae Woong Park
- Christian Reich
- Peter R. Rijnbeck
Global collaborative research through OHDSI network:

Net Clinical Benefit of Ticagrelor compared to Clopidogrel in patients with Acute Coronary Syndrome following Percutaneous Coronary Intervention

Seng Chan You¹; Yeunsook Rho²; Jiwoo Kim²; Anastasios Siapos³; Ajit Londhe⁴; Jaehyeong Cho⁵; Jimyung Park⁵; Martijn Schuemie⁴; Marc A Suchard, MD, PhD⁶,⁷; David Madigan PhD⁸; George Hripcsak MD⁹; Christian G. Reich³; Patrick B. Ryan⁴; Rae Woong Park, MD, PhD¹,⁵; Harlan M. Krumholz, MD¹⁰

¹Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Korea; ²Health Insurance Review and Assessment Service, Wonju, Korea; ³IQVIA, Durham, USA; ⁴Janssen Research and Development, Titusville, USA; ⁵Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, Korea; ⁶Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, CA, USA; ⁷Department of Biomathematics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA, USA; ⁸Department of Statistics, Columbia University, New York, NY, USA; ⁹Medical Informatics Services, New York-Presbyterian Hospital, New York, NY, USA; ¹⁰Yale University School of Medicine, USA

chandryou@ajou.ac.kr
Disclosures

• Potential Conflict of interests
  – Dr. Ryan, Dr. Schuemie, and Ajit Londhe are employees of Janssen Research & Development, a subsidiary of Johnson & Johnson. Dr. Reich and Mr. Siapos are employees of IQVIA. Neither Janssen nor IQVIA had input in the design, execution, interpretation of results or decision to publish.

• Source of Funding
  – This work was supported by the Bio Industrial Strategic Technology Development Program (20001234) funded by the Ministry of Trade, Industry & Energy (MOTIE, Korea) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea [grant number: HI16C0992]
History of **Dual AntiPlatelet Therapy (DAPT)** in patients with coronary artery disease

Size of the circles denotes sample size

Perimeter of the circles denotes type of investigated population:
- Mixed clinical presentation at the time of stent implantation
- Acute coronary syndrome at presentation
- **DAPT** initiated in patients with prior myocardial infarction
- **DAPT** for primary prevention

**LEGEND**
- 2K pts
- 5K pts
- 10K pts
- 20K pts

©ESC 2017

2017 ESC DAPT guideline
PLATelet inhibition and patient Outcomes (PLATO) Trial

Primary End Point: Vascular death, myocardial infarction and stroke

Wallentin et al., NEJM, 2009
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications.20

2017 ESC/EACTS DAPT guideline

In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy (53,71,72).

2016 ACC/AHA DAPT guideline
PLATO trial did not demonstrate superiority of Ticagrelor in North America and Asia

Figure 1 Estimated treatment effects by geographic region for the primary endpoint (CV death, MI, or stroke) of the PLATO trial (hazard ratios with 95% CIs, interaction P-value 0.05).

Pocock et al., EHJ, 2013
Objectives

• Compare risk of net adverse clinical event (NACE) between ticagrelor and clopidogrel in patients with Acute Coronary Syndrome (ACS) following percutaneous coronary intervention (PCI) through OHDSI network.
Method: Study Population

• Inclusion Criteria
  – Adults (>=20 yrs) who initiated ticagrelor or clopidogrel due to acute coronary syndrome (ACS) and undertook percutaneous coronary intervention (PCI)

• Exclusion Criteria
  – Prior history of stroke or gastrointestinal bleeding
  – Use of prasugrel or opposing drug within previous 30 days from index date

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
Method: Outcome

Primary endpoint: Net Adverse Clinical Event (NACE)
- Composite of recurrent myocardial infarction, any revascularization, ischemic stroke, intracranial hemorrhage, or gastrointestinal bleeding

Secondary endpoint
- Ischemic Event
  - Recurrent myocardial infarction
  - Any revascularization (PCI + CABG)
  - Ischemic stroke
- Hemorrhagic Event (major bleeding)
  - Intracranial hemorrhage
  - Gastrointestinal bleeding
- Overall death
- Dyspnea (Positive control)

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
Method: Statistical Analysis

• Primary analysis
  – Time windows: From 1 day to 365 days after the index date
  – Unconditioned Cox regression after 1-to-1 PS matching

• Sensitivity analyses
  – Time windows
    • On-treatment
    • 5-year
  – Statistical analysis
    • 1-to-1 PS matching with blanking period of outcome (28 days)
    • Variable-ratio PS matching
    • PS stratification

• Assessment of systemic errors
  – 96 Negative controls

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
Method

• Data source
  – Optum Pan-Therapeutics (PanTher) : USA, EHR (86M)
  – IQVIA’s Hospital data : USA, EHR (85M)
  – HIRA: South Korea, Nationwide Claim for patients undertaking PCI (0.4M)

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
Proportion of ticagrelor across years and drug adherence in Korea

Proportion of Ticagrelor user among whole study population

Days of continuation of ticagrelor and clopidogrel

<table>
<thead>
<tr>
<th>Days of Drug Continuation</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>38</td>
<td>132</td>
<td>363</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>78</td>
<td>232</td>
<td>566</td>
</tr>
</tbody>
</table>
Balance before and after PS matching and Systematic error control

A. Optum PanTher

B. IQVIA Hospital

C. HIRA

Number of covariates: 17,644

Number of covariates: 13,674

Number of covariates: 12,059

160 estimates
97.5% of CIs include 1

52 estimates
92.3% of CIs include 1

64 estimates
90.6% of CIs include 1

True hazard ratio = 1

Standard Error

0.1 0.25 0.5 1 2 4 6 8 10

0.0 0.25 0.5 0.75 1

Hazard ratio

0.1 0.25 0.5 0.75 1 2 4 6 8 10

Uncalibrated
Primary endpoint: 1-year NACE

A. Optum PanTher

B. IQVIA-Hospital

C. HIRA

D. Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Event</td>
</tr>
<tr>
<td>Optum Panther</td>
<td>13,569</td>
<td>1,057</td>
</tr>
<tr>
<td>IQVIA - Hospital</td>
<td>4,002</td>
<td>299</td>
</tr>
<tr>
<td>HIRA</td>
<td>10,890</td>
<td>1,881</td>
</tr>
<tr>
<td>Overall</td>
<td>28,461</td>
<td>3,237</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.0\%$

**Hazard Ratio**

- Favors Ticagrelor
- Favors Clopidogrel

$P = 0.074$
Consistency in the results of the primary endpoint in sensitivity analyses

PanTher | IQVIA-Hospital | HIRA | Meta-analysis
--- | --- | --- | ---

Time At Risk Window

One-Year | Five-Year | On-Treatment

Hazard Ratio (95% Confidence Interval)

- 1-to-1 PS matching
- 1-to-1 PS matching with blanking period
- Variable-ratio PS matching
- PS stratification
• There appears to be no significant difference in 1-year NACE risk between ticagrelor and clopidogrel users with ACS following PCI
• The findings for primary endpoint were consistent across sensitivity analyses
• Ticagrelor is associated with higher risk of hemorrhagic events and dyspnea.
Please, Join the Journey

- Main homepage
  - www.ohdsi.org
- 2019 OHDSI Symposium
  - Sep. 15-17th
  - Bethesda
- Github
  - https://github.com/OHDSI
- OHDSI Community meeting: 1AM (Korean time), Wed
- Workgroup meeting
  - Eastern hemisphere meeting: 4PM (Korean time), Wed,
Please, Join the Journey

- **Forum**

- **OHDSI in Korea Forum**
공통 데이터모델 (CDM) 기반 헬스케어 융합 빅데이터 생태계 구축

산업통상자원부 CDM 사업을 통한 FEEDER-NET 확장

1. 분산형 바이오헬스 통합 플랫폼

2. 바이오헬스 데이터망

FEEDER-NET 3차병원 중심 데이터망
(27개 병원, 54M 환자정보)

기 FEEDER-NET 플랫폼
주관기관: 아주대, 책임자: 박래웅

플랫폼 고도화

총괄 협의체 운영/교육/홍보

협의체 운영

CDM 확산교육

CDM 세미나 활동

Cloud

OMOP CDM

OMOP CDM

OMOP CDM

CDM 활용 서비스

데이터 분석 도구

데이터 보안 지침 및 검증 기술

데이터 질 평가 지표 및 알고리즘

CDM 활용 수행 연구

 Gathering

CDM 표준/규약 과제(공동)

연구자 지원 및 정보보호기술 과제(보건복지부)

환경 지원 과제(산업통상자원부)
서문

이 책은 관찰 보건 데이터 과학 및 정보학 (Observational Health Data Scine and Informatics : OHDSI) 공동작업에 대한 내용을 담고있다. OHDSI 커뮤니티에 의해 작성된 이 책은 OHDSI 관련 모든 지식의 중앙저장소 역할을 담당하고자 쓰여졌으며 오픈소스 개발 도구들을 통해 커뮤니티에 의해 관리되는 생명력을 가진 문서로 계속 진화하고 있다. 또한 ohdsi-korea.github.io/TheBookOfOhdsiKorea에서 온라인으로 항상 최신 버전의 책을 무료로 받아 볼 수 있으며 실질로 구입을 원할 경우 Amazon 등에서 구입이 가능하다.

이 책의 목표

이 책은 OHDSI 관련 모든 지식의 중앙저장소 역할을 담당하고자 쓰여졌으며 OHDSI 커뮤니티, OHDSI 데이터 기준과 OHDSI 도구들에 중점을 두었다. OHDSI의 초보자와 속련자 모두를 위해 현실적으로 필요 이론과 사용법에 대한 교육을 제공하는 실용적인 부분에 목표를 두고 있다. 이책을 읽은 뒤 당신은 OHDSI란 무엇인지, 또한 그 영역에 어떻게 동참할 것인가에 관하여 이해하게 될 것이다. 또한 공통 데이터 모델(CDM)과 표준화된 용어들이 무엇인지, 이러한 것들이 관찰 보건 데이터베이스의 표준화에 어떻게 사용되는지 알게 될 것이다. 이 데이터에 대해 Clinical characterization, Population-level estimation,
2019 OHDSI KOREA
INTERNATIONAL SYMPOSIUM
December 12 (Thur) - 14 (Sat), 2019
Konjiam resort

Dec 12 (Thur)
Basic Tutorial: CDM and Vocabulary / Phenotyping by ATLAS

Dec 13 (Fri)
Opening ceremony (Long Min Baek)
Welcome to the Korean OHDSI journey (Rae Woong Park)
OHDSI Initiative (George Hripcauk)
EHDEN Project (Peter Rijnbeek)
OHDSI Network in Action
Parallel Session
National Perspectives on Bio-health IT in Korea
(Seongi Kim, Yunjeong Heo)
Adopting the OMOP CDM to Enable Standardized Analytics
(Christian Reich, Erica Voess, Mui van Zandt, Martja Schuemie)
Sharing the International Experience from Asian-Pacific Region
(Nicole Pratt, Hua Xu, Normin Feng, Akira Suzuki, Mui van Zandt, Seng Chan You)
Closing Remarks

Dec 14 (Sat)
Advanced Tutorial: Population Level Estimation / Patient-Like Prediction

WWW.OHDSI-KOREA.ORG
Thank You for your time