Clopidogrel vs. Ticagrelor: How to Use Common Data Model in Clinical Research

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College of Medicine

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Disclosure

• Dr. You is a CTO of PHI Digital Healthcare but does not hold any shares in the company.
• Dr. You is the incoming associate editor of Journal of American Journal of Cardiology (JACC); however, this presentation does not necessarily represent the views of JACC.
Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Seng Chan You, MD, MS; Yeunsook Rho, PhD; Behnoood Bikdeli, MD, MS; Jiwoo Kim, MS; Anastasios Siapos, MSc; James Weaver, MSc; Ajit Londhe, MPH; Jaehyeong Cho, BS; Jimyung Park, BS; Martijn Schuemie, PhD; Marc A. Suchard, MD, PhD; David Madigan, PhD; George Hripcsak, MD, MS; Aakriti Gupta, MD, MS; Christian G. Reich, MD; Patrick B. Ryan, PhD; Rae Woong Park, MD, PhD; Harlan M. Krumholz, MD, SM

IMPORTANCE Current guidelines recommend ticagrelor as the preferred P2Y12 platelet inhibitor for patients with acute coronary syndrome (ACS), primarily based on a single large randomized clinical trial. The benefits and risks associated with ticagrelor vs clopidogrel in routine practice merits attention.

OBJECTIVE To determine the association of ticagrelor vs clopidogrel with ischemic and hemorrhagic events in patients undergoing percutaneous coronary intervention (PCI) for ACS in clinical practice.

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
History of Dual AntiPlatelet Therapy (DAPT) in patients with coronary artery disease
Primary End Point: Vascular death, myocardial infarction and stroke
Current clinical guideline for DAPT in ACS solely based on PLATO trial

### Recommendations

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.\(^\text{20}\)

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

2017 ESC/EACTS DAPT guideline

### Recommendations for Specific P2Y\(_{12}\) Inhibitors

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>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 P2Y(_{12}) inhibitor therapy (53,71,72).</td>
</tr>
</tbody>
</table>

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).
Aspirin dosing might matter

- More patients in the United States (53.6%) than in the rest of the world (1.7%) took a median aspirin dose $\geq 300$ mg/d.

The lowest risk of cardiovascular death, myocardial infarction, or stroke with ticagrelor compared with clopidogrel is associated with a low maintenance dose of concomitant aspirin.
Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs.

<table>
<thead>
<tr>
<th>Group by Comparison</th>
<th>Trial, Year</th>
<th>Statistics for each study</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel v Clopidogrel</td>
<td>The Elderly ACS II, 2018</td>
<td></td>
<td>0.85</td>
<td>0.51</td>
<td>1.41</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>The PRASFIT-ACS, 2013</td>
<td></td>
<td>1.21</td>
<td>0.48</td>
<td>3.06</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>TRILOGY ACS, 2012</td>
<td></td>
<td>0.93</td>
<td>0.80</td>
<td>1.09</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>TRITON-TIMI 38, 2009</td>
<td></td>
<td>0.89</td>
<td>0.70</td>
<td>1.13</td>
<td>0.33</td>
</tr>
<tr>
<td>Prasugrel v Ticagrelor</td>
<td>ISAR-REACT 5, 2019</td>
<td></td>
<td>0.94</td>
<td>0.66</td>
<td>1.34</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>PRAGUE-18, 2017</td>
<td></td>
<td>1.10</td>
<td>0.59</td>
<td>2.06</td>
<td>0.77</td>
</tr>
<tr>
<td>Ticagrelor v Clopidogrel</td>
<td>POPular AGE, 2019</td>
<td></td>
<td>0.85</td>
<td>0.44</td>
<td>1.61</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>PHILO, 2015</td>
<td></td>
<td>1.28</td>
<td>0.48</td>
<td>3.43</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>PLATO, 2009</td>
<td></td>
<td>0.79</td>
<td>0.69</td>
<td>0.91</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Tang et al., 2016</td>
<td></td>
<td>0.60</td>
<td>0.14</td>
<td>2.51</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Wang et al., 2016</td>
<td></td>
<td>0.38</td>
<td>0.15</td>
<td>0.97</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>TICAKOREA, 2019</td>
<td></td>
<td>2.61</td>
<td>1.01</td>
<td>6.73</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.80</td>
<td>0.71</td>
<td>0.92</td>
<td>0.00</td>
</tr>
</tbody>
</table>

CV mortality

Serebruany, CARDIOLOGY, 2010
Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

**POPular-AGE**

- Multi-center, open-label RCT (Netherland)
- Investigator-initiated
- Old(≥70yr) NSTE-ACS (N = 1002)
Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs

**PHILO**

- Multi-national (Japan, Korea, Taiwan), Multi-center, double-blind RCT
- Sponsor-initiated
- ACS intended to PCI (N = 801)

### Table 3. Adverse Events for All Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticagrelor (90 mg b.i.d.)</th>
<th>Clopidogrel (75 mg o.d.)</th>
<th>HR for ticagrelor (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding (PLATO-defined)</td>
<td>40 (10.3)</td>
<td>26 (6.8)</td>
<td>1.54 (0.94–2.53)</td>
</tr>
</tbody>
</table>

### Table 4. Primary and Secondary Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ticagrelor (90 mg b.i.d. (n=401))</th>
<th>Clopidogrel (75 mg o.d. (n=400))</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of CV death/MI (excluding silent MI)/stroke</td>
<td>36 (9.0)</td>
<td>25 (6.3)</td>
<td>1.47 (0.88–2.44)</td>
</tr>
</tbody>
</table>

Goto et al., Cir J, 2015
Superiority of ticagrelor over clopidogrel or prasugrel has never been replicated in RCTs.

**TICA-KOREA**

- Multi-center, open-label RCT
- Investigator-initiated
- ACS patients (N=800)

![Graph showing cumulative incidence of clinically significant bleeding](image)

- Log-rank p=0.004
- Ticagrelor: 11.7%
- Clopidogrel: 5.3%

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Ticagrelor (N=400)</th>
<th>Clopidogrel (N=400)</th>
<th>Hazard Ratio for Ticagrelor Group (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiovascular event</td>
<td>36 (9.2)</td>
<td>23 (5.8)</td>
<td>1.62 (0.96–2.74)</td>
<td>0.07</td>
</tr>
<tr>
<td>Composite of cardiovascular death, myocardial infarction, or stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Superiority of ticagrelor over clopidogrel has been challenged in an observational study by Turgeon et al., *JAMA Internal Medicine*, 2020.

### Association of Ticagrelor vs Clopidogrel With Major Adverse Coronary Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel Group (n = 3711)</th>
<th>Ticagrelor Group (n = 3711)</th>
<th>P Value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACE</strong></td>
<td>368 (9.9)</td>
<td>380 (10.2)</td>
<td>.64</td>
<td>1.00 (0.86-1.17)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>54 (1.5)</td>
<td>61 (1.6)</td>
<td>.51</td>
<td>1.10 (0.75-1.61)</td>
</tr>
<tr>
<td>ACS</td>
<td>228 (6.1)</td>
<td>235 (6.3)</td>
<td>.74</td>
<td>1.02 (0.84-1.24)</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>168 (4.5)</td>
<td>157 (4.2)</td>
<td>.53</td>
<td>0.86 (0.67-1.09)</td>
</tr>
<tr>
<td>PCI</td>
<td>121 (3.3)</td>
<td>114 (3.1)</td>
<td>.64</td>
<td>0.90 (0.68-1.19)</td>
</tr>
<tr>
<td>CABG</td>
<td>50 (1.3)</td>
<td>44 (1.2)</td>
<td>.53</td>
<td>0.74 (0.47-1.15)</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>7 (0.2)</td>
<td>18 (0.5)</td>
<td>.03</td>
<td>2.57 (1.07-6.16)</td>
</tr>
<tr>
<td>Composite of all-cause death, ACS, or stroke</td>
<td>290 (7.8)</td>
<td>299 (8.1)</td>
<td>.70</td>
<td>1.02 (0.86-1.21)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>18 (0.5)</td>
<td>17 (0.5)</td>
<td>.87</td>
<td>0.94 (0.48-1.86)</td>
</tr>
<tr>
<td><strong>Major bleed</strong></td>
<td>182 (4.9)</td>
<td>261 (7.0)</td>
<td>&lt;.001</td>
<td>1.52 (1.24-1.87)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>&gt;.99</td>
<td>1.00 (0.14-7.10)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>53 (1.4)</td>
<td>95 (2.6)</td>
<td>&lt;.001</td>
<td>2.10 (1.44-3.06)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>81 (2.2)</td>
<td>105 (2.8)</td>
<td>.08</td>
<td>1.32 (0.97-1.80)</td>
</tr>
<tr>
<td>Urologic</td>
<td>29 (0.8)</td>
<td>37 (1.0)</td>
<td>.32</td>
<td>1.32 (0.79-2.22)</td>
</tr>
<tr>
<td>Other</td>
<td>32 (0.9)</td>
<td>38 (1.0)</td>
<td>.47</td>
<td>1.29 (0.78-2.11)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>46 (1.2)</td>
<td>116 (3.1)</td>
<td>&lt;.001</td>
<td>2.42 (1.70-3.45)</td>
</tr>
</tbody>
</table>

*Data: Canadian Coronary Heart Disease Registry*
“East Asian Paradox”: Challenge for the Current Antiplatelet Strategy of “One-Guideline-Fits-All Races” in Acute Coronary Syndrome

Young-Hoon Jeong

• Although there have been no conclusive large-scale clinical trials including East Asians only, recent pharmacodynamic and clinical studies have suggested more insight and confidence for the ‘East Asian Paradox’
Is newer, more expensive treatment always better?

Trends in Platelet Adenosine Diphosphate P2Y$_{12}$ Receptor Inhibitor Use and Adherence Among Antiplatelet-Naive Patients After Percutaneous Coronary Intervention, 2008-2016

Elias J. Dayoub, MD, MPP; Matthew Seigerman, MD; Sony Tuteja, PharmD, MS; Taisei Kobayashi, MD; Daniel M. Kolansky, MD; Jay Giri, MD, MPH; Peter W. Groeneveld, MD, MS

**IMPORTANCE** Current guidelines recommend prasugrel hydrochloride and ticagrelor hydrochloride as preferred therapies for patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI). However, it is not well known how frequently these newer agents are being used in clinical practice or how adherence varies among the platelet adenosine diphosphate P2Y$_{12}$ receptor (P2Y$_{12}$) inhibitors.
Newer, more expensive treatment may aggravate inequity in health.

**CONCLUSIONS AND RELEVANCE** Between 2008 and 2016, increased use of prasugrel and ticagrelor was accompanied by increased nonfilling of prescriptions for P2Y₁₂ inhibitors within 30 days of discharge. Prasugrel and ticagrelor had higher patient costs and lower adherence in the year following PCI compared with clopidogrel. The introduction of newer, more expensive P2Y₁₂ inhibitors was associated with lower adherence to these therapies.

An important policy ramification of our findings is that the introduction of new pharmacotherapies may have exacerbated socioeconomic health disparities. This phenomenon has...

You et al., *JAMA*, 2020

You et al., *JAMA Internal Medicine*, 2018
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.
International collaborative consortium applying open-source data analytic solutions based on OMOP-Common Data Model (CDM) to a large network of health databases across the world.

OHDSI Collaborators:
- >100 researchers in academia, industry and government
- >10 countries

OHDSI Data Network:
- >40 databases standardized to OMOP common data model
- >500 million patients
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**: Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.

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

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

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

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

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

革新：観察研究は破壊的思考から大いに恩恵を受ける分野です。私たちは研究において新しい方法論的アプローチを積極的に求め、奨励しています

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

再現性：正確で再現可能で、よく校正された証拠は健康改善に必要です。

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

開放性：私たちは、生成する方法、ツール、および証拠を含む、コミュニティの成果をすべて公開し、公にアクセス可能にすることを目指しています。

• **Community**: 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.

コミュニティ：患者、医療専門家、研究者、または単に私たちの理念を信じる人であれ、誰でもOHDSIに積極的に参加することを歓迎します。

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

協働：私たちは集団として、コミュニティの参加者の現実のニーズを優先し、対処するために協力します。

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

恩恵：私たちは常にコミュニティ内の個人および組織の権利を保護することを目指しています。
1. This remains a hopelessly flawed observational design using claims database data, to compare efficacy and safety. Despite all the care taken by the authors, some critical information is missing such as the duration of actual therapy with each agent, or the frequency of drug interruption or switching after initiation, adherence to therapy (in an observational type of study, this is a huge issue). Patients were entered in the study at the time of PCI as opposed to the time of ACS which is how ticagrelor was tested in the PLATO trial and is recommended for use. Censoring events after initiation of therapy and starting at the time of PCI creates a well-documented bias. Patients were eligible up to 7 days after ACS, a period during which patients are at the highest risk of ischemic events which were not accounted for. This is particularly important given that by 3 months, 37% of ticagrelor treated patients were no longer on the drug, and 25% of clopidogrel treated patients. The huge issue of lack of adherence and the magnitude of the difference between groups illustrates the critical importance of a double-blind design in the comparison of these agents. The use of claims data or EHR data is also an important concern as some important information is missing: I was not able to locate information regarding smoking or creatinine in the data, but is best illustrated by the simple fact that while the authors discuss "Acute Coronary Syndromes", they are unable to provide a simple basic information: what was the proportion of STEMI, NSTEMI and UA in each group? This shows that while the databases used here are large, the quality of the information available can be woefully inadequate.
We appreciate these comments and that the Editors have expressed interest in giving us the opportunity to reply to these points. 

The Reviewer is correct that we are missing some information that would be helpful in characterizing the patients. We did have access to an immense amount of data on each patient and used this information to the greatest extent possible. Per this comment, we added the information for types of ACS in the baseline characteristics tables.

We emphasize that our approach represents a significant advance in observational research, with a series of publications in leading peer-reviewed methodological journals describing the components of our approach along with their validation. Our balance of thousands of variables coupled with concrete demonstration of balance on every single one of them we believe not only addresses measured confounding but also can begin to address unmeasured confounding. Our use of 96 falsification endpoints goes far beyond current recommendations to include one or a few controls; a large number are needed to make claims of robustness. We published our entire protocol and all our source code before running our trial, to prohibit opportunity for p-hacking. We ran across databases inside and outside the US and looked for consistency. And we ran large sets of sensitivity analyses to assess the robustness of the findings.
Strength in methodology

- Reproducibility
- Pre-specification of statistical analytic plan
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- Large-scale propensity score model
- 96 Negative controls (Falsification endpoint)
- Large set of sensitivity analyses
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions
Strength in methodology

- Reproducible and Open science
- Pre-specification of statistical analytic plan
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- Large-scale propensity score model
- 96 Negative controls (Falsification endpoint)
- Large set of sensitivity analyses
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  - Narrow outcome definitions
Crisis of reproducibility: Lancet, NEJM retract controversial COVID-19 studies based on Surgisphere data

Prof. Chambers (Chair of Center for Open Science and Member of the UK Reproducibility Network Steering Group) said: “The failure to resolve such basic concerns about the data during the course of normal peer review raises serious questions about the standard of editing at the Lancet and NEJM. If these journals take issues of reproducibility and scientific integrity as seriously as they claim, then they should forthwith submit themselves and their internal review processes to an independent inquiry.”
End-to-end executable statistical program is available at GitHub

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
The response of European Medicines Agency (EMA) on OHDSI study

Renin-angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis

Daniel R Morales, Mitchell M Conover, Seng Chan You, Nicole Pratt, Kristin Kostka, Talita Duarte-Salles, Sergio Fernández-Bertolín, Maria Aragón, Scott L DuVall, Kristine Lynch, Thomas Falconer, Kees van Bochove, Cynthia Sung, Michael E Matheny, Christophe G Lambert, Fredrik Nyberg, Thamir M Alshammari, Andrew E Williams, RaeWoong Park, James Weaver, Anthony G Sena, Martijn J Schuemie, Peter R Rijnbeek, Ross D Williams, Jennifer C E Lane, Albert Prats-Uribe, Lin Zhang, Carlos Arela, Harian M Krumholz, Daniel Prieto-Alhambra, Patrick B Ryan, George Hripcsak, Marc A Suchard
My research experience using personal GitHub repository

https://github.com/chandryou/TicagrelorVsClopidogrel
Strength in methodology

• Reproducibility
• **Pre-specification of statistical analytic plan**
• Active Comparator, New-User cohort design
• Using three large databases from US and Korea
• Large-scale propensity score model
• 96 Negative controls (Falsification endpoint)
• Large set of sensitivity analyses
  – 1:1 PS matching / variable-ratio PS matching / PS stratification
  – Diverse time windows
  – Narrow outcome definitions
Method: Statistical Analytic Plan

## 4 Amendments and Updates

<table>
<thead>
<tr>
<th>Amendment</th>
<th>Date</th>
<th>SC You</th>
<th>Change Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>11 December 2018</td>
<td>SC You</td>
<td>Initial draft</td>
</tr>
<tr>
<td>0.2</td>
<td>16 February 2019</td>
<td>SC You</td>
<td>Revision of definition in outcome definition. More covariates were added for estimation of propensity score.</td>
</tr>
<tr>
<td>0.3</td>
<td>3 March 2019</td>
<td>SC You</td>
<td>Revision of the manuscript of statistical analytic plan. Statistical method of primary analysis was changed from 1-to-1 matching to variable ratio matching to avoid inferior covariate balance and bias reduction. Sensitivity analyses, which includes only those who start the clopidogrel or ticagrelor from 2013 to 2017, and outcome with narrow definition were added.</td>
</tr>
<tr>
<td>1.0</td>
<td>9 May 2019</td>
<td>SC You</td>
<td>Revision of index event for the study population from drug initiation to PCI due to ACS. Positive control section was removed. Some negative controls, which have potential relationship with cardiovascular diseases or antiplatelet drug were removed. Adding sensitivity analysis with 28-day blanking period of 28 days to exclude duplicated coding for the outcomes.</td>
</tr>
<tr>
<td>1.1</td>
<td>24 May 2019</td>
<td>SCYou</td>
<td>Revision of target and comparator cohort: Because there are databases do not have visit ID link between drug exposure and procedure, the primary inclusion criteria was revised to use time based rule rather than same visit based rule. Because many US patients take aspirin over-the-count, the constraint for the concomitant use of aspirin in target and comparator cohort was removed.</td>
</tr>
<tr>
<td>1.2</td>
<td>3 September 2019</td>
<td>SCYou</td>
<td>Changing primary analysis from variable ratio PS matching to unconditioned one-to-one PS matching</td>
</tr>
<tr>
<td>1.3</td>
<td>28 October 2019</td>
<td>SCYou</td>
<td>Revising the query to extract individual secondary outcome cohorts. The documented definitions were also changed to add ‘first time’ criteria to stroke and GI bleeding outcomes. Adding NACE or mortality outcome as a secondary outcome. Adding variable-ratio matching and PS stratification with blanking period analysis</td>
</tr>
</tbody>
</table>

## 11 Appendix: Concept Set Definitions

### 1. Percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Concept Id</th>
<th>Concept Name</th>
<th>Domain</th>
<th>Vocabulary</th>
<th>Excluded</th>
<th>Descendants</th>
<th>Mapped</th>
</tr>
</thead>
<tbody>
<tr>
<td>400788</td>
<td>Percutaneous transluminal coronary angioplasty</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>420653</td>
<td>Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4159198</td>
<td>Percutaneous transluminal atherectomy of artery</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4173997</td>
<td>Percutaneous transluminal thrombectomy and reconstruction of artery</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4175148</td>
<td>Placement of stent in anterior descending branch of left coronary artery</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4185025</td>
<td>Percutaneous transluminal balloon angioplasty with insertion of stent into coronary artery</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2008064</td>
<td>Percutaneous transluminal coronary angioplasty [PTCA]</td>
<td>Procedure</td>
<td>ICD9Proc</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2001505</td>
<td>Insertion of drug-eluting coronary artery stent(s)</td>
<td>Procedure</td>
<td>ICD9Proc</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>2001506</td>
<td>Insertion of drug-eluting coronary artery stent(s)</td>
<td>Procedure</td>
<td>ICD9Proc</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>4171077</td>
<td>Fluoroscopic angiography of coronary artery and insertion of stent</td>
<td>Procedure</td>
<td>SNOMED</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

### 2. Ticagrelor

<table>
<thead>
<tr>
<th>Concept Id</th>
<th>Concept Name</th>
<th>Domain</th>
<th>Vocabulary</th>
<th>Excluded</th>
<th>Descendants</th>
<th>Mapped</th>
</tr>
</thead>
<tbody>
<tr>
<td>40241186</td>
<td>Ticagrelor</td>
<td>Drug</td>
<td>RxNorm</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

### 3. Clopidogrel

<table>
<thead>
<tr>
<th>Concept Id</th>
<th>Concept Name</th>
<th>Domain</th>
<th>Vocabulary</th>
<th>Excluded</th>
<th>Descendants</th>
<th>Mapped</th>
</tr>
</thead>
<tbody>
<tr>
<td>1322148</td>
<td>clopidogrel</td>
<td>Drug</td>
<td>RxNorm</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

[https://github.com/ohdsi-studies/TicagrelorVsClopidogrel/tree/master/documents](https://github.com/ohdsi-studies/TicagrelorVsClopidogrel/tree/master/documents)
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
**eMethod 3. Individual outcome definitions**

For each outcome, we developed an operational phenotype definition to determine if observational data could in fact support evaluation of the outcome. Where possible, concept sets originated with published code lists (eg ICD-9-CM and ICD-10). We developed definition of outcome cohorts and query to extract them using ATLAS, the OHDSI open-source platform ([https://github.com/OHDSI/atlas](https://github.com/OHDSI/atlas)). We executed these definitions on EHR data of Korean tertiary hospital to validate the definitions. Positive predictive values were estimated by a physician’s manual chart review of discharge notes.

**Supplementary Table. Outcome definition**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Logical description</th>
<th>ICD-9-CM</th>
<th>ICD-10</th>
<th>CPT4</th>
<th>PPV, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>Record of acute myocardial infarction during an inpatient or ER visit</td>
<td>410;410.01;410.02;410.1;410.11;410.12;410.2;410.21;410.22;410.3;410.31;410.32;410.4;410.41;410.42;410.5;410.51;410.52;410.7;410.71;410.72;410.8;410.81;410.82;410.9;410.91;410.92</td>
<td>I21.0;I21.1;I21.2;I21.3;I21.4;I21.9</td>
<td></td>
<td>83.8 (83/99)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>Record of PCI or CABG during an inpatient or ER visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Earliest record of ischemic stroke during an inpatient or ER visit</td>
<td>346.6;346.6;346.61;346.62;346.63;433.01;433.11;433.21;433.31;433.81;433.91;433.01;434.11;434.14;34.91;997.02</td>
<td>I63.9;I63.8;I63.6;I63.5;I63.4;I63.3;I63.2;I63.1;I63.0;I63;G46.7;G46.6;G46.5;F01.3;F01.1;F01.0</td>
<td></td>
<td>72.9 (70/96)</td>
</tr>
</tbody>
</table>
Strength in methodology

• Reproducibility
• Pre-specification of statistical analytic plan
• **Active Comparator, New-User cohort design**
• Using three large databases from US and Korea
• Large-scale propensity score model
• 96 Negative controls (Falsification endpoint)
• Large set of sensitivity analyses
  – 1:1 PS matching / variable-ratio PS matching / PS stratification
  – Diverse time windows
  – Narrow outcome definitions
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
The Active Comparator, New User Study Design in Pharmacoepidemiology: Historical Foundations and Contemporary Application

Jennifer L. Lund, David B. Richardson, Til Stürmer
Strength in methodology

• Reproducibility
• Pre-specification of statistical analytic plan
• Active Comparator, New-User cohort design
• Using three large databases from US and Korea
• Large-scale propensity score model
• 96 Negative controls (Falsification endpoint)
• Large set of sensitivity analyses
  – 1:1 PS matching / variable-ratio PS matching / PS stratification
  – Diverse time windows
  – Narrow outcome definitions
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)

---

**Optum® de-identified Electronic Health Record dataset**

Optum electronic health record (EHR) is an aggregated and de-identified electronic health record repository from US health systems. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical notes using natural language processing (NLP). The data from November 20, 2011 to March 3, 2019 were used for this study. New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

**IQVIA-Hospital Charge Data Master**

Anonymized patient level data are sourced from hospital charge data masters and collected from resource management software within short-term, acute-care and non-federal hospitals in the United States. Data covers over 86 million patients, 122,000 providers, 230 specialties and more than 530 million unique visits from 2007 to 2018. The data from November 14, 2011 to June 29, 2018 were used for this study. A retrospective database study on this de-identified data is deemed not human subject research. Approval is provided for OHDSI community studies.

**HIRA**

HIRA claims data include healthcare utilization information of the entire population of South Korea, consisting of diagnosis, procedure, drug, medical material, healthcare resource, etc. The current study is conducted based on the converted CDM data of the patients who received PCI’s between 2007 and 2016. The CDM data include 462,486 patients with more than 155 million claims information. The data from February 28, 2013 to December 31, 2016 were used for this study. The present study was approved by the Scientific and Ethical Advisory Board of the HIRA (Project number: 2017-034-002)

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
Strength in methodology

- Reproducibility
- Pre-specification of statistical analytic plan
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- **96 Negative controls (Falsification endpoint)**
- Large-scale propensity score model
- Large set of sensitivity analyses
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions
Prespecified Falsification End Points
Can They Validate True Observational Associations?

Vinay Prasad, MD
Anupam B. Jena, MD, PhD

As observational studies have increased in number—fueled by a boom in electronic recordkeeping and the ease with which observational analyses of large databases can be performed—so too have failures to confirm initial research findings.¹ Several solutions to the problem of incorrect observational results have been suggested,¹,² emphasizing the importance of a record not only of significant findings but of all analyses conducted.²

An important and increasingly familiar type of observational analysis involves studies in which the outcome of interest is fracture.³ For example, in a study of patients treated with proton pump inhibitors (PPIs), fractures were reported in a subset of patients.³ This analysis demonstrated an increased risk of atypical fractures associated with bisphosphonate use and was validated by another large population-based study.

However, analyses in large data sets are not necessarily correct simply because they are larger. Control groups might not eliminate potential confounders, or many varying definitions of exposure to the agent may be tested (alternative thresholds for dose or duration of a drug)—a form of multiple-hypothesis testing.² Just as small, true signals can be identified by these analyses, so too can small, erroneous associations. For instance, several observational studies have found an association between use of PPIs and development of pneumonia, and it is biologically plausible that elevated...
Negative controls

Arnold & Ecrumen. “Negative Control Outcomes: A Tool to Detect Bias in Randomized Trials.” JAMA

The formal definition of a negative control outcome is one that shares the same potential sources of bias with the primary outcome but cannot plausibly be related to the treatment of interest.
Knowledge database for drug adverse events

Accuracy of an automated knowledge base for identifying drug adverse reactions

E.A. Voss \textsuperscript{a,b,c,*}, R.D. Boyce \textsuperscript{d,c}, P.B. Ryan \textsuperscript{a,e,c}, J. van der Lei \textsuperscript{b,c}, P.R. Rijnbeek \textsuperscript{b,c}, M.J. Schuemie \textsuperscript{a,c}

Table 1
Description of LAERTES sources.

<table>
<thead>
<tr>
<th>Data source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAERS Proportional Reporting Ratio (FAERS PRR)</td>
<td>Data files from the FDA Adverse Event Reporting System (FAERS) Latest Quarterly Data Files website \cite{44} were used to generate evidence. The FAERS drug/outcome pairs were standardized from free text drug names and outcomes in MedDRA Preferred Terms to RxNorm OMOP concepts and MedDRA condition OMOP concepts. In addition, the MedDRA condition concepts were mapped to SNOMED-CT concepts based on the OMOP mappings available in the OMOP Vocabulary. The ETL process also included logic to remove duplicate adverse drug event reports \cite{22}. The PRR metric generated by work by Van Puijenbroek et al. \cite{21}. The FAERS data currently available in LAERTES covers Q4 2004 through Q4 2014.</td>
</tr>
<tr>
<td>FAERS Report Count (FAERS Report Count)</td>
<td>Similar to FAERS PRR except a count of reports is provided for each drug-condition pair.</td>
</tr>
<tr>
<td>Medline MeSH Clinical Trials (MEDLINE MeSH ClinTrial)</td>
<td>Looking for ADRs in MeSH terms for clinical trials in Medline. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE MeSH_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>Medline MeSH Case Reports (MEDLINE MeSH CR)</td>
<td>Similar to MEDLINE MeSH_ClinTrial except for case reports for clinical trials in Medline. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE MeSH_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>Medline Mesh Other (MEDLINE MeSH Other)</td>
<td>Similar to MEDLINE MeSH_ClinTrial except for case reports for Medline MeSH Other. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE MeSH_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>Medline SemMedDB Clinical Trials (MEDLINE SemMedDB ClinTrial)</td>
<td>For clinical trials, provides MeSH tagged drug-HOI clinical trial abstracts from PubMed that look for associations such as: causes, affects, associated with, complicates, or disrupts \cite{24}. All of these associations also have a negative modality, meaning SemMedDB provides both positive and negative associations. The data was last mined June 30, 2015. Similar to MEDLINE SemMedDB_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>Medline SemMedDB Case Reports (MEDLINE SemMedDB CT)</td>
<td>Similar to MEDLINE SemMedDB_ClinTrial except for case reports for clinical trials in Medline. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE SemMedDB_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>Medline SemMedDB Other (MEDLINE SemMedDB Other)</td>
<td>Similar to MEDLINE SemMedDB_ClinTrial except for case reports for Medline SemMedDB Other. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE SemMedDB_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>Structured Product Label Adverse Drug Reactions from SPLICER (SPL SPLICER ADR)</td>
<td>Similar to MEDLINE SemMedDB_ClinTrial except for case reports for structured product label data from SPLICER. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE SemMedDB_ClinTrial except for case reports.</td>
</tr>
<tr>
<td>European Product Label Adverse Drug Reactions (SPL EU SPC)</td>
<td>Similar to MEDLINE SemMedDB_ClinTrial except for case reports for European product label data. The process to identify ADRs was leveraged from Avillach et al. \cite{23}. The Avillach method using MeSH tagged publications from Medline looked for adverse drug reactions based on the co-occurrence of a drug and an adverse event on the same citation. The source of the data used was directly from the National Library of Medicine and gathered from 1946 until September 2015. Similar to MEDLINE SemMedDB_ClinTrial except for case reports.</td>
</tr>
</tbody>
</table>
Method 5. Falsification endpoints

Falsification endpoints (negative control outcomes) are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Total of 96 falsification endpoints are selected using a similar process to that outlined by Voss et al.\textsuperscript{2} The concept IDs and SNOMED codes are described below.

**Supplementary Table.** Falsification endpoint list

<table>
<thead>
<tr>
<th>OMOP Concept ID</th>
<th>SNOMED code</th>
<th>Outcome Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>378256</td>
<td>46670006</td>
<td>Abnormal reflex</td>
</tr>
<tr>
<td>4218106</td>
<td>7200002</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>440424</td>
<td>87486003</td>
<td>Aphasia</td>
</tr>
<tr>
<td>439237</td>
<td>52684005</td>
<td>Assault</td>
</tr>
<tr>
<td>378424</td>
<td>82649003</td>
<td>Astigmatism</td>
</tr>
<tr>
<td>261880</td>
<td>46621007</td>
<td>Atelectasis</td>
</tr>
<tr>
<td>134118</td>
<td>400190005</td>
<td>Atrophic condition of skin</td>
</tr>
<tr>
<td>4224118</td>
<td>40492006</td>
<td>Bladder dysfunction</td>
</tr>
<tr>
<td>80509</td>
<td>203465002</td>
<td>Bone cyst</td>
</tr>
<tr>
<td>434626</td>
<td>20010003</td>
<td>Borderline personality disorder</td>
</tr>
<tr>
<td>438407</td>
<td>78004001</td>
<td>Bulimia nervosa</td>
</tr>
<tr>
<td>134765</td>
<td>238108007</td>
<td>Cachexia</td>
</tr>
<tr>
<td>4172458</td>
<td>49883006</td>
<td>Candidiasis of skin</td>
</tr>
<tr>
<td>436740</td>
<td>17382005</td>
<td>Cervical incompetence</td>
</tr>
<tr>
<td>381581</td>
<td>1482004</td>
<td>Chalazion</td>
</tr>
<tr>
<td>4307254</td>
<td>423125000</td>
<td>Closed fracture</td>
</tr>
<tr>
<td>4047787</td>
<td>123971006</td>
<td>Colles' fracture</td>
</tr>
<tr>
<td>198075</td>
<td>240542006</td>
<td>Condyloma acuminatum</td>
</tr>
<tr>
<td>73302</td>
<td>64217002</td>
<td>Curvature of spine</td>
</tr>
<tr>
<td>4242416</td>
<td>58588007</td>
<td>Cutis laxa</td>
</tr>
<tr>
<td>433163</td>
<td>238107002</td>
<td>Deficiency of macronutrients</td>
</tr>
<tr>
<td>4047269</td>
<td>229844004</td>
<td>Deformity of foot</td>
</tr>
<tr>
<td>133228</td>
<td>80967001</td>
<td>Dental caries</td>
</tr>
</tbody>
</table>
No use of falsification endpoint can be a limitation

ticagrelor, but after adjustment with IPTW the two groups were balanced on this covariate. The study database did not include any falsification endpoint, i.e. an endpoint that is known to be unrelated to treatment under study, which could have supported that the analyses were unbiased. In addition, all data were analyzed as intention-to-treat, and early termination of a drug was not accounted for. It is possible that some patients crossed over from one drug to another,

Szummer et al., “Comparison Between Ticagrelor and Clopidogrel in Elderly Patients with an Acute Coronary Syndrome: Insights from the SWEDEHEART Registry.” Circulation
Strength in methodology

- Reproducibility
- Pre-specification of statistical analytic plan
- Active Comparator, New-User cohort design
- Using three large databases from US and Korea
- 96 Negative controls (Falsification endpoint)
- Large-scale propensity score model
- Large set of sensitivity analyses
  - 1:1 PS matching / variable-ratio PS matching / PS stratification
  - Diverse time windows
  - Narrow outcome definitions
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
  – Blanking rule + Limited study date + Restricted outcome def + P value calibration

• Assessment of systemic errors
  – 96 Negative controls
    → 144 analyses (3x3x2x2x2)

https://github.com/ohdsi-studies/TicagrelorVsClopidogrel
Balance before and after PS matching and Systematic error control

A. Optum PanTher

B. IQVIA-Hospital

C. HIRA

Number of covariates: 16,242

Number of covariates: 13,834

Number of covariates: 12,595

0.1
Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system

Jeremy A. Rassen* and Sebastian Schneeweiss

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA

ABSTRACT

Distributed medical product safety monitoring systems such as the Sentinel System, to be developed as a part of Food and Drug Administration’s Sentinel Initiative, will require automation of large parts of the safety evaluation process to achieve the necessary speed and scale at reasonable cost without sacrificing validity. Although certain functions will require investigator intervention, confounding control is one area that can largely be automated. The high-dimensional propensity score (hd-PS) algorithm is one option for automated confounding control in longitudinal healthcare databases. In this article, we discuss the use of hd-PS for automating confounding control in sequential database cohort studies, as applied to safety monitoring systems. In particular, we discuss the robustness of the covariate selection process, the potential for over- or under-selection of variables including the possibilities of M-bias and Z-bias, the computation requirements, the practical considerations in a federated database network, and the cases where automated confounding adjustment may not function optimally. We also outline recent improvements to the algorithm and show how the algorithm has performed in several published studies. We conclude that despite certain limitations, hd-PS offers substantial advantages over non-automated alternatives in active product safety monitoring systems.
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>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OptumPanTher</td>
<td>16,388</td>
<td>1,308</td>
<td>1.220</td>
<td>1.06 [0.98; 1.14]</td>
</tr>
<tr>
<td>IQVIA - Hospital</td>
<td>3,998</td>
<td>294</td>
<td>1.272</td>
<td>1.06 [0.90; 1.24]</td>
</tr>
<tr>
<td>HIRA</td>
<td>10,890</td>
<td>1,881</td>
<td>1.817</td>
<td>1.03 [0.96; 1.10]</td>
</tr>
</tbody>
</table>

Overall: 31,276 | 3,483 | 31,276 | 3,309 | 1.04 [0.99; 1.09]

Heterogeneity: $I^2 = 0.0\%$

$P = 0.100$
Consistency in the results of the primary endpoint in sensitivity analyses
Distribution of risk estimates for NACE
Summary

• 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.
1. This remains a hopelessly flawed observational design using claims database data, to compare efficacy and safety. Despite all the care taken by the authors, some critical information is missing such as the duration of actual therapy with each agent, or the frequency of drug interruption or switching after initiation, adherence to therapy (in an observational type of study, this is a huge issue). Patients were entered in the study at the time of PCI as opposed to the time of ACS which is how ticagrelor was tested in the PLATO trial and is recommended for use. Censoring events after initiation of therapy and starting at the time of PCI creates a well-documented bias. Patients were eligible up to 7 days after ACS, a period during which patients are at the highest risk of ischemic events which were not accounted for. This is particularly important given that by 3 months, 37% of ticagrelor treated patients were no longer on the drug, and 25% of clopidogrel treated patients. The huge issue of lack of adherence and the magnitude of the difference between groups illustrates the critical importance of a double-blind design in the comparison of these agents. The use of claims data or EHR data is also an important concern as some important information is missing: i was not able to locate information regarding smoking or creatinine in the data, but is best illustrated by the simple fact that while the authors discuss "Acute Coronary Syndromes", they are unable to provide a simple basic information: what was the proportion of STEMI, NSTEMI and UA in each group? This shows that while the databases used here are large, the quality of the information available can be woefully inadequate.
We appreciate these comments and that the Editors have expressed interest in giving us the opportunity to reply to these points.

The Reviewer is correct that we are missing some information that would be helpful in characterizing the patients. We did have access to an immense amount of data on each patient and used this information to the greatest extent possible. Per this comment, we added the information for types of ACS in the baseline characteristics tables.

We emphasize that our approach represents a significant advance in observational research, with a series of publications in leading peer-reviewed methodological journals describing the components of our approach along with their validation. Our balance of thousands of variables coupled with concrete demonstration of balance on every single one of them we believe not only addresses measured confounding but also can begin to address unmeasured confounding. Our use of 96 falsification endpoints goes far beyond current recommendations to include one or a few controls; a large number are needed to make claims of robustness. We published our entire protocol and all our source code before running our trial, to prohibit opportunity for p-hacking. We ran across databases inside and outside the US and looked for consistency. And we ran large sets of sensitivity analyses to assess the robustness of the findings.
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**: Observational research is a field which will benefit greatly from disruptive thinking. We actively seek and encourage fresh methodological approaches in our work.
  革新: 観察研究は破壊的思考から大いに恩恵を受ける分野です。私たちは研究において新しい方法論的アプローチを積極的に求め、奨励しています
• **Reproducibility**: Accurate, reproducible, and well-calibrated evidence is necessary for health improvement.
  再現性: 正確で再現可能で、よく校正された証拠は健康改善に必要です。
• **Openness**: We strive to make all our community’s proceeds open and publicly accessible, including the methods, tools and the evidence that we generate.
  開放性: 私たちは、生成する方法、ツール、および証拠を含む、コミュニティの成果をすべて公開し、公にアクセス可能にすることを目指しています。
• **Community**: 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.
  コミュニティ: 患者、医療専門家、研究者、または単に私たちの理念を信じる人であれ、誰でもOHDSIに積極的に参加することを歓迎します。
• **Collaboration**: We work collectively to prioritize and address the real world needs of our community’s participants.
  協働: 私たちは集団として、コミュニティの参加者の現実のニーズを優先し、対処するために協力します。
• **Beneficence**: We seek to protect the rights of individuals and organizations within our community at all times.
  恩恵: 私たちは常にコミュニティ内の個人および組織の権利を保護することを目指しています。
Remarks

• Interventional cardiology is an ever-evolving branch in cardiology
  – CCU, lipid-lowering medication, advance in stenting, …
• It may not be reasonable to stick to the evidence generated a decade ago in interventional cardiology.
• Observational study can generate high-level evidence
  – Pre-specification for avoiding p-hacking
  – Robust study design and control at least observed variables
• The objective of observational study is the investigation of possible cause–effect relationships
  (Cochrane)
Thank You for your time