Session #20

Real World Evidence Studies to Evaluate the Safety and Effectiveness of Therapeutic Interventions – Are the Data Fit for Purpose and How Will You Know?

24 June 2018

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Norman Stockbridge, MD, PhD
CSRC Mission & Milestones

To advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA’s Critical Path Initiative as well as other public health priorities.

- 2006 — Launch FDA Critical Path Initiative with Duke University
- Key Initiatives
  - Research Programs
  - Think Tanks
  - White Papers

Collaborative, non-competitive environment to focus on cardiac safety issues during drug development

A neutral ground that creates opportunities to share existing knowledge and data to facilitate

- Improvements in CV safety monitoring and risk management in drugs/devices development
- Allow for more efficient/effective drug/device development to ensure that these products get to the patients that need them
- Ensure that efforts are practical and can be implemented in a reasonable timeframe

Learn ↔ Influence

http://www.cardiac-safety.org/
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Learning Objectives

- Understand key epidemiological design principles central to interpreting the quality and validity of real-world (non-interventional) studies
- Apply these learnings by evaluating and discussing case presentations focused on CV outcomes assessments
- Recognize when RWE based approaches are of sufficient quality to enable decision-making
Agenda

- Introduction
- Use of Non-Interventional Studies to Assess Safety & Effectiveness
- Real World Studies to Assess Cardiovascular Outcomes
- Pragmatic Trials & Uses of RWE Beyond Safety
- Learning Exercise & Discussion
- Framework for Evaluating Whether Real World Data are Fit for Purpose
Introduction

Nancy Dreyer, PhD, MPH, FISPE, Fellow DIA
Chief Scientific Officer
IQVIA

Nancy.Dreyer@IQVIA.com
The end of the primary care blockbuster age requires new approaches to research

...implications for study design and execution TODAY

- More oriented to local stakeholders
- Smaller, smarter
- Market demands value, speed & cost efficiency

Proportion of Global Launches by Primary Care / Specialty*

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>82%</td>
<td>87%</td>
</tr>
<tr>
<td>Specialty</td>
<td>18%</td>
<td>13%</td>
</tr>
</tbody>
</table>

* Source: IQVIA global launch excellence
## Where does Real-World Evidence Come From?

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claims data</td>
<td>From <strong>payers’ reimbursement for care</strong> (pharmacy, outpatient, and inpatient); used to show <strong>resource utilization and patient journey</strong></td>
</tr>
<tr>
<td>Electronic Medical / Health Records (EMR / EHR)</td>
<td>Include medical history, risk factors, and some outcomes from laboratory and imaging results; used to gain a <strong>more granular view of patients’ journeys</strong></td>
</tr>
<tr>
<td>Social media, wearables, consumer data, etc.</td>
<td>Increasingly being used to gain insight into <strong>patient behavior, their treatment experience, and risk factors</strong></td>
</tr>
<tr>
<td>Lab &amp; genomics data</td>
<td>Gathered in routine clinical practice capture <strong>key diagnostic data</strong>, used to identify appropriate patients for specific lines of therapy</td>
</tr>
<tr>
<td>Registries</td>
<td>Structured approaches to track <strong>clinically rich data, treatment use and experience</strong> along with other factors; used for product safety, comparative effectiveness &amp; randomized registry trials</td>
</tr>
<tr>
<td>eCRF, ePRO</td>
<td>May be collected for study purposes</td>
</tr>
</tbody>
</table>
Regulators and Payers See Value of Real-World Evidence

**FDA**

“*The more widespread use of RWE can make our medical product development process more efficient…. This will ultimately help us achieve better outcomes, and safer and more efficient use of expensive technology.*”

- Scott Gottlieb, MD, FDA Commissioner

[https://www.fda.gov/NewsEvents/Speeches/ucm576519.htm](https://www.fda.gov/NewsEvents/Speeches/ucm576519.htm)

**EMA**

- EMA needs RWE to support adaptive approval pathways

<table>
<thead>
<tr>
<th>Time</th>
<th>Intensive monitoring of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Additional indication(s)</td>
</tr>
<tr>
<td></td>
<td>Intensive monitoring of patients</td>
</tr>
<tr>
<td></td>
<td>Initial Approval of niche indication</td>
</tr>
</tbody>
</table>

**FULL APPROVAL**
Regulators Show Growing Reliance on Real-World Evidence

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomized</th>
<th>Non randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Traditional RCT</td>
<td>Primary data</td>
</tr>
<tr>
<td></td>
<td>Pragmatic trials</td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>Now</td>
<td>Now</td>
</tr>
<tr>
<td>Label Extension</td>
<td>Now</td>
<td>New</td>
</tr>
<tr>
<td>Post Authorisation Safety</td>
<td>Now</td>
<td>New</td>
</tr>
</tbody>
</table>

No clear guidance or regulatory framework yet for use of RWE outside of safety
Stakeholder Needs Should Drive Design

Can it work?  Does it work?

<table>
<thead>
<tr>
<th>Randomized</th>
<th>Non-Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical Controlled trials</strong></td>
<td><strong>Pragmatic randomized trials</strong></td>
</tr>
<tr>
<td>Assesses the difference between a health intervention and placebo in a highly controlled setting</td>
<td>• Assesses difference between &gt;2 health interventions, including extraneous factors</td>
</tr>
<tr>
<td>• Aims to maximize generalizability to a broader patient population</td>
<td>• No placebo</td>
</tr>
</tbody>
</table>

- What is the intended study purpose?
- Is there openness to new models in the regions of interest?
- Could existing data be sufficient for follow-up or entire study?
Examples of Recent Regulatory Use of RW Evidence
Real-world comparator data facilitates rapid drug approval

**Real-world comparators provided context for regulatory filing of single arm Phase 2 trials**

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**Original Article**

**Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia**


We compared outcomes from a single-arm study of blinatumomab in adult patients with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia (R/R ALL) with a historical data set from Europe and the United States. Estimates of complete remission (CR) and overall survival (OS) were weighted by the frequency distribution of prognostic factors in the blinatumomab trial. Outcomes were also compared between the trial and historical data using propensity score methods. The historical cohort included 694 patients with CR data and 1112 patients with OS data compared with 189 patients with CR and survival data in the blinatumomab trial. The weighted analysis revealed a CR rate of 24% (95% CI: 20–27%) and a median OS of 3.3 months (95% CI: 2.8–3.6) in the historical cohort compared with a CR/CRh rate of 43% (95% CI: 36–50%) and a median OS of 6.1 months (95% CI: 4.2–7.5) in the blinatumomab trial. Propensity score analysis estimated increased odds of CR/CRh (OR = 2.68, 95% CI: 1.67–4.31) and improved OS (HR = 0.536, 95% CI: 0.394–0.730) with blinatumomab. The analysis demonstrates the application of different study designs and statistical methods to compare novel therapies for R/R ALL with historical data.

_Blood Cancer Journal_ (2016) 6, e473; doi:10.1038/bcj.2016.84; published online 23 September 2016

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**Figure 2.** Comparison of complete response and overall survival between blinatumomab clinical trial patients and historical patients. Outcomes were analyzed using both the IPTW and sIPTW approaches: Odds ratio (OR) for achieving a CR/CRh (blinatumomab patients) or CR (historical patients) and hazard ratio (HR) for overall survival.

**Strong benefit evident in the trial (treated) population compared to the ‘control’ population**
Accelerated approval for metastatic Merkel Cell Carcinoma: Single-arm trial with real-world data provided as context

- **BAVENCIO® (avelumab)**, the first immunotherapy for metastatic Merkel Cell Carcinoma (MCC)
- Approved in 2017 under **FDA accelerated approval** based on tumor response and duration of response. Also approved by EMA and PMDA.
- **JAVELIN Merkel 200 trial**: open-label, single-arm, multi-center study (n=88)
- External benchmark group provided context

<table>
<thead>
<tr>
<th>AVELUMAB</th>
<th>N = 88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Median duration of response among 29 responding patients</strong></td>
<td></td>
</tr>
<tr>
<td>• 86% &gt; 6 months</td>
<td></td>
</tr>
<tr>
<td>• 45% &gt; 12 months</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Natural history control group with chemotherapy</th>
<th>N = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Median duration of response among 4 responding patients</strong></td>
<td>1.7 months</td>
</tr>
</tbody>
</table>

Source: [www.accessdata.fda.gov](http://www.accessdata.fda.gov)

Broader Indication: Oncology

FDA Approval for Bevacizumab

Brand name(s): Avastin®

Metastatic Colorectal Cancer in Combination with Fluoropyrimidine-based Chemotherapy

On January 23, 2013, the Food and Drug Administration (FDA) approved bevacizumab (Avastin®, made by Genentech U.S., Inc.) for use in combination with fluoropyrimidine–irinotecan- or fluoropyrimidine–oxaliplatin-based chemotherapy for the treatment of patients with metastatic colorectal cancer (mCRC) whose disease has progressed (i.e., the cancer continues to grow or spread) while on first-line treatment with a bevacizumab-containing regimen. Bevacizumab is a recombinant humanized monoclonal antibody that binds to human vascular endothelial growth factor (VEGF), thereby preventing the interaction of VEGF with its receptors on the surface of endothelial cells.

Extension of an existing indication approved on the basis of:

- One randomized controlled trial
- 2 registry-based studies
Label Expansion for a Medical Device

Study protocol approved by FDA in 2017 after several meetings
Registry Data used to Expand Label

FDA NEWS RELEASE

For Immediate Release: Sept. 23, 2013  
Media Inquiries: Susan Laine, 301-796-5349, susan.laine@fda.hhs.gov  
Consumer Inquiries: 888-INFO-FDA

FDA approval expands access to artificial heart valve for inoperable patients

The FDA previously approved the valve for insertion through the femoral artery (transfemoral approach), through the leg or through the lower tip of the heart (transapical approach). The new labeling removes references to specific access points now making it available for inoperable patients who need an alternate access point.

“Just two years after the THV entered the market for a specific patient population, data from the TVTR was used to support FDA approval that expands patient access to a life-saving therapy,” said Jeffrey Shuren, M.D., director of the FDA’s Center for Devices and Radiological Health. “Medical device registries like the TVTR, not only play an important role in the FDA’s post market surveillance system, they also collect robust and timely data that can be used to identify additional patient populations that benefit from the therapy.

“Leveraging clinical research inside the framework of a device registry to expand access to therapy for more patients is a new paradigm for the FDA, researchers, registry sponsors and the medical device industry,” said Shuren. “We believe this approach can be used with future well-designed device registries to speed patient access to important, well-evaluated therapies.”
Pragmatic Trial Won Label Expansion

INVEGA SUSTENNA is the first and only antipsychotic for which the inclusion of real-world data led to a label expansion by FDA (Jan 3 2018)

Landmark Study Shows Once-Monthly Long-Acting Therapy INVEGA® SUSTENNA® (paliperidone palmitate) Significantly Delayed Time to Relapse in Patients with Schizophrenia Compared to Daily Oral Antipsychotic

First prospective, randomized clinical trial to reflect context of “real world” issues in treating schizophrenia, including recent incarceration and substance abuse

- 15 month, 50 site randomized, open-label, active controlled study of 444 adults with schizophrenia
- Broad enrollment criteria
  - Mean age 38 years
  - 60% of patients had comorbid substance abuse
  - Mean time since release from last incarceration=42 days
- Primary endpoint: time to first treatment failure including psych hospitalization, arrest/incarceration, treatment discontinuation, increased psych services to prevent psych hospitalization, suicide, etc.

Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS)

Review of 3 years of oversight by the Pharmacovigilance Risk Assessment Committee (PRAC)

- In general, more PASS used a primary data collection approach
- Those using secondary data sources (among available protocols, N=58):
  - 42% Chart abstraction
  - 37% Claims, database, Electronic Health Records
  - 21% Existing registries

Use of non-interventional studies to assess safety and effectiveness

M. Alan Brookhart, PhD
Professor, Dept. of Epidemiology
Gillings School of Public Health
UNC-Chapel Hill
Overview

- Why do we need to do observational studies?
- How do we do these well?
- Example study
Example: Antipsychotic Medication (APM) use in the elderly

- Approved to treat schizophrenia
- Widely used off-label to treat elderly patients with dementia
- No data supporting this use
- Two broad classes: conventional versus atypical
  Manufacturers of some of the atypicals conducted trials to assess effectiveness of the medications for controlling behavioral disturbances in elderly
- FDA meta-analysis: increased risk of mortality associated with atypical APMs (relative to placebo)
FDA Orders New Warning On Atypical Antipsychotics

JIM ROSACK

Published Online: 6 May 2005 | https://doi.org/10.1176/pn.40.9.0040001

The U.S. Food and Drug Administration (FDA) has ordered manufacturers of atypical, or second-generation, antipsychotic medications to add a new warning to already existing black-box warnings noting that the drugs are associated with an increased risk of death related to psychosis and behavioral problems in elderly patients with dementia.
**Clinical Dilemma**

- Should physicians switch patients to the first generation APMs?
- Older APMs have many known side effects, poor safety profile
- Head-to-head trial will never be done
- Question must be answered by analyzing existing data
Many other limitations of RCTs

- Expensive
- May take many years to get answers
- May not generalize to routine care, exclude many subgroups of interest
- May be unethical or impractical
  - > we need observational studies of medications
  - 85% of CER is non-experimental

Academy Health Report June 2009
Good non-experimental research should resemble the trial that we would like to do

- We can assess the effects of treatment decision when we can determine (from data) when treatment decisions are made
- Treatment decision design (Brookhart, AJE 2018)
- Example: comparative new user design (Ray, AJE 2003)
- Compare new users of a medication of interest to new users of a comparator drug/no treatment
Comparative New User Design mimics a parallel group RCT

Baseline period/
No past use of medication

Washout Period

Treatment
Prescribed

Drug A
Comparator

Treatment
Randomized

Drug A
Comparator
New user design example: Safety of opioids in hemodialysis patients

- Opioids widely used in dialysis patients
- No evidence of safety (or effectiveness)
- No trial will ever be done
- Goal of study: compare risk of mortality between new users of
  - Non-selective NSAIDs
  - Prescription opioids
- Study done in using clinical and administrative data from a large population of hemodialysis patients
Data Source

DaVita Data (2004-2008)

- Large dialysis provider in the U.S.
- 1,500 clinics
- Data on approximately 130,000 prevalent patients/year
- Rich source of clinical data, data from each dialysis session
  - Administered meds, vaccines
  - Laboratory values recorded regularly (every 2/weeks, 1/month)
  - BP, vascular access in use, dose of dialysis, etc
- Microbiology data
- KDQOL
Data, cont.

• **Linked to Medicare Data**
  – Claims data on hospitalizations, outpatient care
  – Data from physicians & dialysis encounters outside of DaVita
  – Date and cause of death
  – Transplant information
  – Demographic information
  – Part D prescription drug claims

• **Clinical data from a small dialysis provider**
  – Quality of life (KDQOL instrument)
Table 1: Characteristics of treatment groups

<table>
<thead>
<tr>
<th></th>
<th>NSAI D</th>
<th></th>
<th>Opioid</th>
<th></th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/N</td>
<td>SD/%</td>
<td>Mean/N</td>
<td>SD/%</td>
<td></td>
</tr>
<tr>
<td>Age, Mean (SD)</td>
<td>61.43</td>
<td>-13.5</td>
<td>60.94</td>
<td>-14.21</td>
<td>0.04</td>
</tr>
<tr>
<td>Black, Mean (SD)</td>
<td>0.4</td>
<td>-0.49</td>
<td>0.45</td>
<td>-0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Albumin, Mean (SD)</td>
<td>3.94</td>
<td>-0.35</td>
<td>3.86</td>
<td>-0.41</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI, Mean (SD)</td>
<td>27.82</td>
<td>-7.22</td>
<td>28.01</td>
<td>-7.22</td>
<td>0.03</td>
</tr>
<tr>
<td>Days in hospital in previous 1 month, Mean (SD)</td>
<td>0.33</td>
<td>-1.31</td>
<td>0.89</td>
<td>-2.2</td>
<td>0.31</td>
</tr>
<tr>
<td>History of Substance Abuse, N(%)</td>
<td>831</td>
<td>3.03</td>
<td>1316</td>
<td>4.81</td>
<td>0.09</td>
</tr>
<tr>
<td>Current use of HD catheter, N(%)</td>
<td>2728</td>
<td>9.96</td>
<td>4608</td>
<td>16.82</td>
<td>0.2</td>
</tr>
<tr>
<td>History of Fracture, N(%)</td>
<td>73</td>
<td>0.27</td>
<td>176</td>
<td>0.64</td>
<td>0.06</td>
</tr>
<tr>
<td>History of GI Bleed, N(%)</td>
<td>171</td>
<td>0.63</td>
<td>319</td>
<td>1.17</td>
<td>0.06</td>
</tr>
<tr>
<td>History of Diabetes, N(%)</td>
<td>18299</td>
<td>66.81</td>
<td>17948</td>
<td>65.52</td>
<td>0.03</td>
</tr>
<tr>
<td>History of MI, N(%)</td>
<td>530</td>
<td>1.93</td>
<td>747</td>
<td>2.73</td>
<td>0.05</td>
</tr>
<tr>
<td>History of Serious Infection, N(%)</td>
<td>307</td>
<td>1.12</td>
<td>461</td>
<td>1.68</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Confounding by Indication / Disease Severity

Disease Severity
(clinical need)

Initiation of Therapy

→

Outcome of Interest
Other sources of confounding

- Treatment specific contraindications
- Serious comorbidity, cognitive impairment
- Healthy user/adherer effect
Controlling Confounding with Statistical Models

Propensity Score and IPTW Methods

Confounders

X
Treatment

C

Y
Outcome (Mortality)

Multivariable Outcome Models
Estimating the Propensity Score

Propensity scores are not known -- must be estimated

\[ \text{Prob}[X=1 \mid C] = \text{expit}(b_0 + b_1 \text{age} + b_2 \text{sex} + b_3 \text{CHD} + \ldots) \]

For each patient a predicted probability of receiving treatment is computed -- the estimated propensity score (PS)
Distribution of propensity scores
Inverse-probability of treatment weighting (IPTW)

- Each subject weighted by the inverse of the probability that they received their observed treatment
- Inverse probability of treatment (IPTW) estimator
  - Fit a standard regression, but weight by
    \[
    \frac{1}{PS(X)}, \text{ in treated patients}
    \]
    \[
    \frac{1}{1 - PS(X)}, \text{ in untreated patients}
    \]
IPTW creates a pseudopopulation where treatment is effectively randomized with respect to observed factors.

No association between analgesic choice (X) and baseline risk in pseudopopulation.
Table 1: Characteristics of sample in IP weighted population

<table>
<thead>
<tr>
<th></th>
<th>NSAID</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean/N</td>
<td>SD/%</td>
</tr>
<tr>
<td>Age, Mean (SD)</td>
<td>60.83</td>
<td>-13.85</td>
</tr>
<tr>
<td>Black, Mean (SD)</td>
<td>0.45</td>
<td>-0.5</td>
</tr>
<tr>
<td>Albumin, Mean (SD)</td>
<td>3.9</td>
<td>-0.37</td>
</tr>
<tr>
<td>BMI, Mean (SD)</td>
<td>28.13</td>
<td>-7.99</td>
</tr>
<tr>
<td>Days in hospital in previous 1 month, Mean (SD)</td>
<td>0.8</td>
<td>-2.05</td>
</tr>
<tr>
<td>History of Substance Abuse, N(%)</td>
<td>1162</td>
<td>4.21</td>
</tr>
<tr>
<td>Current use of HD catheter, N(%)</td>
<td>4377</td>
<td>15.85</td>
</tr>
<tr>
<td>History of Fracture, N(%)</td>
<td>196</td>
<td>0.71</td>
</tr>
<tr>
<td>History of GI Bleed, N(%)</td>
<td>294</td>
<td>1.06</td>
</tr>
<tr>
<td>History of Diabetes, N(%)</td>
<td>18377</td>
<td>66.57</td>
</tr>
<tr>
<td>History of MI, N(%)</td>
<td>756</td>
<td>2.74</td>
</tr>
<tr>
<td>History of Serious Infection, N(%)</td>
<td>496</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Cumulative risk of mortality: NSAID vs Opioid, Adjusted and unadjusted analyses
Cumulative risk difference of mortality: NSAID vs Opioid, Adjusted and unadjusted analyses
Can also estimate per-protocol effect using inverse-probability of censoring weighting

- Subjects who discontinue treatment (deviate from “protocol”) are artificially censored
- Inverse probability of censoring weights are used to re-weight population to address informative censoring
- Allows one to estimate the effect of starting and remaining adherent to treatment
Cumulative risk difference of mortality: NSAID vs Opioid, Adjusted and per-protocol analysis
Subgroup effects: NSAID vs Opioid

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>NSAID Cohort (N)</th>
<th>Opioid Cohort (N)</th>
<th>% Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1674</td>
<td>3439</td>
<td>2.0 (0.0, 3.8)</td>
</tr>
<tr>
<td>Female</td>
<td>837</td>
<td>1857</td>
<td>2.0 (-0.5, 4.3)</td>
</tr>
<tr>
<td>Age in 60–74</td>
<td>682</td>
<td>1342</td>
<td>1.9 (-0.6, 4.4)</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>318</td>
<td>664</td>
<td>1.6 (-3.7, 6.6)</td>
</tr>
<tr>
<td>Central Venous Catheter</td>
<td>174</td>
<td>432</td>
<td>0.8 (-7.1, 7.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>204</td>
<td>585</td>
<td>6.9 (0.2, 12.3)</td>
</tr>
<tr>
<td>Recent MI, Stroke</td>
<td>172</td>
<td>423</td>
<td>8.0 (1.9, 13.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1087</td>
<td>2322</td>
<td>2.2 (-0.1, 4.5)</td>
</tr>
<tr>
<td>History of Serious Infection</td>
<td>141</td>
<td>464</td>
<td>2.3 (-4.4, 9.9)</td>
</tr>
<tr>
<td>History of Osteoarthritis</td>
<td>172</td>
<td>361</td>
<td>6.6 (-1.5, 12.5)</td>
</tr>
<tr>
<td>History of Neuropathy</td>
<td>240</td>
<td>590</td>
<td>4.7 (0.8, 8.2)</td>
</tr>
<tr>
<td>History of PVD</td>
<td>1674</td>
<td>3439</td>
<td>2.0 (0.0, 3.8)</td>
</tr>
<tr>
<td>History of Psychiatric Disorders</td>
<td>104</td>
<td>228</td>
<td>1.8 (-9.0, 10.8)</td>
</tr>
<tr>
<td>Obesity</td>
<td>265</td>
<td>554</td>
<td>1.9 (-0.8, 4.4)</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10g/dL</td>
<td>77</td>
<td>209</td>
<td>-0.3 (-11.0, 9.2)</td>
</tr>
<tr>
<td>Albumin &lt; 3.5g/dL</td>
<td>213</td>
<td>626</td>
<td>3.0 (-3.6, 10.3)</td>
</tr>
<tr>
<td>Vintage 1–4 years</td>
<td>678</td>
<td>1437</td>
<td>2.9 (0.3, 5.3)</td>
</tr>
<tr>
<td>Vintage &gt;4 years</td>
<td>663</td>
<td>1278</td>
<td>1.5 (-1.5, 4.2)</td>
</tr>
</tbody>
</table>
Discussion

• Analysis suggests opioids may increase short-term risk of mortality relative to NSAIDs
• Patients with a history of pulmonary and cardiovascular disease may be particularly vulnerable
• Main limitation: unobserved and uncontrolled differences between groups
• Can explore the plausibility of this assumptions in various ways: negative control outcomes
• Can consider other analytic methods that do not make this assumption (e.g., natural experiments)
Note on problems with prevalent user designs

- Prevalent users are enriched with long-term users (short-term users under-represented)

- Long-term users:
  - Tolerate medication
  - Have not already experienced adverse event
  - Are more likely to be healthy and free of serious comorbidities
  - Are less likely to be frail and cognitively impaired

- Design largely discredited in epidemiology
Missing and mis-measured data often a threat to validity

- Missing lab values
- Missing prescriptions
- Poorly measured outcomes and covariates
- Loss of follow-up due to disenrollment from insurance, changing health systems, lack of medical care
Using Medicare claims data, we did a comparative new user design. Used variations in physician prescribing across physicians as an IV + conventional approaches. Compared elderly new users of atypical to new users of conventional antipsychotics (n=22,890). Primary finding: 37% increased risk of death among new users of conventional antipsychotics after 180 days.
Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients

Sebastian Schneeweiss, Soko Setoguchi, Alan Brookhart, Colin Dormuth, Philip S. Wang

- Same design, same analysis, done using claims data from the British Columbia Ministry of Health
- 37,241 elderly patients
- Same finding: 32% increased risk among new users of the conventional APM

- Similar finding reported in Ontario, CA (Gill, et al Ann of Int Med, 2007)
FDA Extends Black-Box Warning to All Antipsychotics

JUN YAN

Published Online: 18 Jul 2008 | https://doi.org/10.1176/pn.43.14.0001

Three years after the Food and Drug Administration (FDA) instituted a black-box warning for all second-generation antipsychotic (SGA) medications about increased risk of death in elderly dementia patients, a similar warning is being added to the labels of first-generation antipsychotics (FGAs) such as haloperidol and perphenazine.
Questions?

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RW Studies Assessing Cardiovascular Outcomes

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VP & TA Lead, Drug Development Services
ICON plc
Co-Chair, Scientific Oversight Committee
Cardiac Safety Research Consortium

Maryjane.geiger@iconplc.com
CV Outcomes in Randomized Clinical Trials

- In RCTS assessing CV outcomes, a composite endpoint called MACE is commonly used
  - MACE = major adverse cardiovascular event
- MACE typically includes CV death, nonfatal myocardial infarction (MI) or non-fatal stroke ± hospitalization for unstable angina or heart failure, or revascularization (or other events)
- Events are adjudicated by an Independent Clinical Events Committee
  - Event definitions are prespecified
  - Source documents are collected such as hospital discharge summary, electrocardiograms (ECG), laboratory data (e.g., troponin)
  - Plan implemented to minimize “missed events”
    - Review of AE/SAE
## Quality & Reliability of CV Outcomes in RW Data
### Ascertainment and Missingness

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Points to Consider</th>
<th>Data Sources in US</th>
</tr>
</thead>
</table>
| **Death** | • Hard endpoint / Reliable  
• Cause of death usually not attainable - Most deaths occur out of hospital  
• Lag in capture of deaths in data sources  
• Typically not captured in EHR | • National Death Index  
• Social Security Death Master File |
| **Procedure Based Endpoints** (PCI, CABG, TAVR) | • Highly reliable due to need for reimbursement and clinical consultation  
• Procedure-related details (such as angiographic findings) may be available in registries but typically not in claims databases or EHRs | • Claims data bases |
| **Hospitalization-based Non-Fatal Events** (MI, stroke, heart failure, major bleeding) | • Coding based on diagnostic (ICD) codes – coding algorithms have high positive predictive value (PPV)  
• Ascertainment reliability is highly variable (many vs fewer ICD codes)  
• Unlikely to have access to details such as labs, ECGs  
• Consider code in 1\textsuperscript{st} or 2\textsuperscript{nd} position (diagnoses) | • Claims data bases |

### Outcome ICD-9 Codes Position PPV

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ICD-9 Codes</th>
<th>Position</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>410 (all)</td>
<td>1\textsuperscript{st} or 2\textsuperscript{nd}</td>
<td>89% to 97%</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>433.x1, 434.x (except subcode: x0), 436</td>
<td>1st</td>
<td>88% to 99%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>30, 431, 432, 852.0, 852.2, 852.4, 853.0</td>
<td>1st</td>
<td>88% to 97%</td>
</tr>
</tbody>
</table>

Adapted from Graham D et al Circ 2015
Is Adjudication of RW CV Outcomes Necessary?

- To compare major CHD outcomes ascertained from Medicare with physician adjudicated outcomes in WHI
- Population: women ≥65 in Medicare
- WHI participants linked to CMS data
- Primary Outcome: incident acute MI
  - defined by ICD-9 code 410.x0 or 410.x1
- Secondary Outcome: coronary revascularization
  - defined by ICD-9 codes 36.1, 36.2 (CABG) or 00.66, 36.0, 36.00, 36.01, 36.02, 36.05, 36.06, 36.07 (PCI)
- There was good agreement between adjudicated data and RWD, suggesting administrative data may be reliable in assessing coronary outcomes in persons aged >65 and older

Hlatky Circ CV Qual Outcomes 2014
CV Safety Signals Have Been Investigated in a Variety of Therapeutics

- NSAIDS
- Weight loss drugs
- Chantix (smoking cessation aid)
- PAMORAs
- Zelnorm (tegaserod) – 5-HT\textsubscript{4} agonist for IBS

- Diabetes Drugs
- Azithromycin
- Loperamide (anti-diarrheal)
- Stalevo (for Parkinson’s)
- Benicar (olmesartan) – antihypertensive (ARB)
CV Risk Assessment is Required for the Development of Type 2 Diabetes Therapies

- 2008 FDA Guidance: show new drug for type 2 diabetes (T2D) will not result in an unacceptable increase in CV risk (pre- & post-marketing thresholds)

<table>
<thead>
<tr>
<th>Estimated # CV Events Needed to Meet Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Inferiority Margin</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>1.8</td>
</tr>
<tr>
<td>1.3</td>
</tr>
</tbody>
</table>

- Consequently a large number of CV outcomes trials have/are being conducted to accrue sufficient events to satisfy the 1.3 margin

SGLT2 Inhibitors (new class)

- 3 drugs (canagliflozin, empagliflozin & dapagliflozin) approved between 2013 and 2014
- CV Outcomes trial conducted for each drug to satisfy regulatory requirements
  - Both empagliflozin (EMPA-Reg NEJM 2015) and canagliflozin (CANVAS NEJM 2017) were shown to reduce the incidence of MACE (CV death, MI and stroke) in patients with T2D at high risk for CV events in RCTs (dapa CVOT ongoing)
  - Both drugs were also shown to reduce hospitalizations from heart failure (secondary endpoint)
CVD-REAL Study – 1st Real World Study to Assess SGLT2i in Clinical Practice and CV Outcomes

Following EMPA-Reg RCT, many questions remained
  – Applicability of findings to real world clinical practice?
  – Benefits specific to empagliflozin or class effect?
  – Do CV benefits extend to T2D patients with broader CV risk?

CVD-REAL Study
  – First prospective RW study in subjects with T2D with or without cardiovascular (CV) disease
  – Purpose: to assess outcomes of hospitalization for heart failure (HHF) and all-cause mortality in new users of SGLT2i vs other glucose lowering agents
## CVD-REAL Methods: Data Sources & Patient Cohort

### Data Sources
Deidentified health records in 6 countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Truven Health &amp; Medicare (&gt;300 employers; &gt;25 plans)</td>
</tr>
<tr>
<td></td>
<td>Inpatient/outpatient medical claims and outpatient pharmacy claims</td>
</tr>
<tr>
<td>Germany</td>
<td>Diabetes Prospective Follow-Up Initiative</td>
</tr>
<tr>
<td></td>
<td>Registry with &gt;425 centers</td>
</tr>
<tr>
<td>UK</td>
<td>Clinical Practice Research DataLink and Health Improvement Network</td>
</tr>
<tr>
<td></td>
<td>&gt;670 general practitioners linked with hospitalization and mortality records</td>
</tr>
<tr>
<td>Denmark/Norway/Sweden</td>
<td>Mandatory full population registry in each country</td>
</tr>
</tbody>
</table>

### Patient Cohort
- **Age ≥18 years**
- **T2D**
  - Based on diagnostic codes
- **>1 year data history in database before index date**
  - Index date = prescription date for new SGLT2 or oGLD
- Newly started on SGLT2i or other glucose lowering drugs (oGLD)
  - Beginning on date of 1st prescription or pharmacy dispensation
  - Start date Nov 2012 in UK to July 2013 in Sweden
  - New user = individual filled a prescription for empa, cana or dapa or oLGD with no issued prescription of that medication in the preceding 1 year
- **Excluded**
  - Type 1 or gestational diabetes

*Circulation. 2017;136:249–259*
CVD-REAL Methods: Outcomes

**Primary outcome: hospitalization for HF (HHF)**
- Defined as hospital admission for HF
  - US – primary discharge code
  - UK – primary discharge code and documentation from EHR
  - Germany – documentation in EHR
  - Sweden/Norway/Denmark: any hospital visit, in- or outpatient (ie, prognostically equivalent outpatient heart failure [HF] event) with a registered primary diagnosis of HF

**Secondary outcomes**
- All cause death
- HHF or all cause death, whichever occurs first
  - all countries except Germany
  - In US used MarketScan Mortality File – info from SSA integrated with insurance enrollment and claims data supplemented by claims for in hospital deaths, covering about 61% of overall US based propensity-matched patient cohort
    - Characteristics of US pts with and without vital status were similar indicating data were missing completely at random because of administrative reasons

_Circulation. 2017;136:249–259_
Means to Control for Confounding
- Propensity Score developed within each country for being initiated on a SGLT2i
  - Variables that may have affected treatment or outcomes were included
    - Nearly 50 variables were used but what was used depended on what information was collected in each database
    - Examples: age, gender, duration of DM, complications of DM, commonly used medications

Power Calculation
- For the primary outcome (HHF) a risk reduction of 20% for SGLT-2i versus oGLD was considered clinically meaningful
- For 85% power to detect a risk reduction of 20% with a 2-sided α-level of 0.05 and a 1:1 treatment allocation (SGLT-2i vs. oGLD), a total of 730 events across the matched treatment groups in all the datasets was required.
  - 961 HHF events occurred within the matched cohorts, yielding sufficient power to perform the HHF analysis

Circulation. 2017;136:249–259
CVD-REAL: Baseline Characteristics of >300,000 Patients were Well Matched Overall and by Country

<table>
<thead>
<tr>
<th>Condition</th>
<th>SGLT-2 Inhibitor (N=154,528)</th>
<th>Other GLD (N=154,528)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yr</td>
<td>56.9 (10.0)</td>
<td>57.0 (10.6)</td>
</tr>
<tr>
<td>Women</td>
<td>68,420 (44.3)</td>
<td>68,772 (44.5)</td>
</tr>
<tr>
<td>Established cardiovascular disease*</td>
<td>20,044 (13.0)</td>
<td>20,302 (13.1)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>3,793 (2.5)</td>
<td>3,882 (2.5)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>2,529 (1.6)</td>
<td>2,568 (1.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4,714 (3.1)</td>
<td>4,759 (3.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5,632 (3.6)</td>
<td>5,698 (3.7)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6,337 (4.1)</td>
<td>6,394 (4.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>5,729 (3.4)</td>
<td>5,229 (3.4)</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>42,217 (27.3)</td>
<td>42,215 (27.3)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3,920 (2.5)</td>
<td>4,171 (2.7)</td>
</tr>
<tr>
<td>Frailty (yes)†</td>
<td>11,982 (7.8)</td>
<td>12,731 (8.2)</td>
</tr>
<tr>
<td>Baseline glucose-lowering therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>121,500 (78.6)</td>
<td>123,432 (79.9)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>59,406 (38.4)</td>
<td>59,788 (38.7)</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitor</td>
<td>51,400 (33.3)</td>
<td>50,088 (32.4)</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>13,650 (8.8)</td>
<td>12,970 (8.4)</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 receptor agonist</td>
<td>31,355 (20.3)</td>
<td>27,088 (17.5)</td>
</tr>
<tr>
<td>Insulin</td>
<td>45,573 (29.5)</td>
<td>45,097 (29.2)</td>
</tr>
<tr>
<td>Cardiovascular therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy‡</td>
<td>123,696 (80.0)</td>
<td>123,563 (80.0)</td>
</tr>
</tbody>
</table>

Patients were excluded due to the protocol mandated 1:1 match

*Circulation. 2017;136:249–259*
SGLT2i Use Was Associated with a 39% Lower Risk for HHF and 51% Lower Rate of Death

**HHF (961 events)**

<table>
<thead>
<tr>
<th>Study</th>
<th>P-value for SGLT-2i vs. oGLD comparison:</th>
<th>P-value for Heterogeneity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Truven MarketScan</td>
<td>≥0.001</td>
<td>0.055 [0.44, 0.66]</td>
</tr>
<tr>
<td>Norway National Registers</td>
<td>≥0.001</td>
<td>0.62 [0.49, 0.79]</td>
</tr>
<tr>
<td>Denmark National Registers</td>
<td>≥0.001</td>
<td>0.77 [0.59, 1.01]</td>
</tr>
<tr>
<td>Sweden National Registers</td>
<td>≥0.001</td>
<td>0.61 [0.45, 0.82]</td>
</tr>
<tr>
<td>UK CPRD/THIN</td>
<td>≥0.001</td>
<td>0.38 [0.12, 1.13]</td>
</tr>
<tr>
<td>Germany DPV</td>
<td>≥0.001</td>
<td>0.14 [0.03, 0.68]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>≥0.001</td>
<td>0.61 [0.51, 0.73]</td>
</tr>
</tbody>
</table>

**Mortality (1334 deaths)**

<table>
<thead>
<tr>
<th>Study</th>
<th>P-value for SGLT-2i vs. oGLD comparison:</th>
<th>P-value for Heterogeneity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Truven MarketScan</td>
<td>≥0.001</td>
<td>0.33 [0.28, 0.50]</td>
</tr>
<tr>
<td>Norway National Registers</td>
<td>≥0.001</td>
<td>0.55 [0.44, 0.69]</td>
</tr>
<tr>
<td>Denmark National Registers</td>
<td>≥0.001</td>
<td>0.46 [0.37, 0.57]</td>
</tr>
<tr>
<td>Sweden National Registers</td>
<td>≥0.001</td>
<td>0.47 [0.37, 0.60]</td>
</tr>
<tr>
<td>UK CPRD/THIN</td>
<td>≥0.001</td>
<td>0.73 [0.47, 1.15]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>≥0.001</td>
<td>0.49 [0.41, 0.57]</td>
</tr>
</tbody>
</table>

---

*SGLT2i exposure*

- 53% canagliflozin
- 42% dapagliflozin
- 5% empagliflozin

*Circulation. 2017;136:249–259*
Did CVD-REAL Answer the Scientific Questions Posed?

- **Effect of SGLT2i on HHF outcomes and all-cause death?**
  - Treatment with SGLT-2i versus oGLD was associated with a 39% RRR in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite, consistent with the effects previously reported in a randomized clinical trial of empagliflozin.

- **Benefits specific to empagliflozin or class effect?**
  - The lower rates of HHF and death associated with SGLT-2i are likely class related, as there was no significant heterogeneity across countries, despite geographic variations in the use of specific SGLT-2i (≈76% canagliflozin in the US and ≈92% dapagliflozin in Europe).

- **Do CV benefits extend to T2D patients with broader CV risk?**
  - Approximately 87% of patients did not have known CV disease, suggesting possible CV benefits for a broad population of patients with T2D.

- **What Next?**
  - 2 RCTs are currently recruiting to evaluate the effects of empagliflozin on HHF and CV death (EMPEROR-Preserved & EMPEROR-Reduced).

*Circulation.* 2017;136:249–259
Peripherally Acting Mu Opioid Receptor Antagonists (PANMORAs) & CV Safety Signal

- Opioid induced Constipation (OIC); post operative ileus
  - Entereg (alvimopan)
  - Relistor (methylnaltrexone)
  - Movantik (naloxegol)

- Abuse Deterrent Opioids [targiniq (naloxone+oxycodone)]

- CV safety signal observed with alvimopan
  - Imbalance in MIs in 12-month RCT for opioid induced constipation

- No CV signal in naloxegol development program (~2100 subjects in Phase 2 and 3 trials) or targiniq

- 2014 Advisory Committee recommendations
  - Weak signal therefore no CVOT needed
  - 12-month controlled modestly sized trial pre-approval
  - Collect post marketing data on cardiac safety via observational studies

- FDA has required post market observational studies for Movantik, Relistor, and Targiniq
Movantik (naloxegol) Observational CV Safety Study

New User Cohort NonInferiority Design

- **Objective**: to assess the risk of MACE among naloxegol treated patients compared to patients on non-peripherally acting mu-opioid antagonist treatment for OIC

- **Primary endpoint**: MACE (acute MI, stroke and CV death)
  - events will be adjudicated by an independent committee

- **Study size and duration**: 4400 person-years of naloxegol and 4400 person-years of comparison treatment to satisfy power requirements & estimated incidence of MACE
  - Goal to reject a doubling of risk for MACE in current naloxegol users vs users of comparison products

- **Data sources**:
  - 2 large commercially available insured populations
  - Pharmacy dispensing records
  - US National Death Index and other mortality registries

- **Exposure**: date of dispensing through 3x the number of days supply available for dispensing (# of days dispensed + any unused days dispensed before the previous dispensing days supplied is exhausted).
  - Exposure will be censored when a new treatment (other than study drug) is dispensed
  - Earliest Index date will be once naloxegol is accepted on formularies (late 2015 or early 2016)

http://www.encepp.eu/encepp/openAttachment/fullProtocol/18612;jsessionid=PamaP8bVNpibGr2udKVQXPPi/VUertQTXj-DNia-O5PQ6fl2f027f1888174422
**Movantik (naloxegol) New User Comparative Cohort Design**

**Cohorts:**
- New users of naloxegol (while chronically exposed to opioids) vs. those initiating lubiprostone or linaclotide
- Matched based on propensity scores
  - Covariates = CV risk factors, duration/intensity of opioid use, dx of constipation, treatments, & demographics in medical records

http://www.encepp.eu/encepp/openAttachment/fullProtocol/18612;jsessionid=PamaP8bVNpibtGr2udKVQXPPiVUertQTXj-DNia-O5PQ6fl2f027f1888174422
Dabigatran, Direct Thrombin Inhibitor (anticoagulant), and Risk of Major Bleeding

- FDA approved in 2010 for prevention of stroke in patients with non-valvular atrial fibrillation (warfarin approved in 1954)
- RE-LY, Phase 3 RCT comparing dabigatran vs. warfarin showed dabigatran significantly reduced rate of stroke (vs warfarin) and rates of bleeding between treatments were similar
- Post marketing reports of bleeding in FDA AE Reporting system, literature, regulatory authority alerts were greater than expected raising concern postmarketing use of dabigatran might differ from use in RE-LY trial
- FDA compared bleeding rates using insurance claim data and administrative data programs from the FDA Mini-Sentinel database and found bleeding rates did not appear to be higher than with warfarin

“The Mini-Sentinel assessment suggests that bleeding rates associated with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY.” NEJM 2013
Dabigatran Observational Study in Medicare Showed Increased Risk of Major Gastrointestinal (GI) Bleeding

- New user retrospective cohort design
- 134,000 patients initiated on dabigatran vs warfarin for NVAF
- Medicare, age ≥ 65
- Propensity score matched
- Outcomes: ischemic stroke, MI, intracranial hemorrhage, major GI bleed and death
  - Events identified by ICD-9 codes
  - Deaths – Social Security Master Beneficiary Death Record
CMS Study Led to FDA Safety Communication in 2014 but Additional RW Studies Conducted Support Safety of Dabigatran

Drug Safety Communications

FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin.

This information is in follow-up to the FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran) that was issued on November 2, 2012.

Safety Announcement
(05-13-2014) In its ongoing review of the blood thinner Pradaxa (dabigatran), the U.S. Food and Drug Administration (FDA) recently completed a new study in Medicare patients comparing Pradaxa to the blood thinner warfarin (Coumadin, Jantoven, and generics), for risk of ischemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. Pradaxa and warfarin are used to reduce the risk of stroke and blood clots in patients with a common type of abnormal heart rhythm called non-valvular atrial fibrillation (AF).

https://www.fda.gov/Drugs/DrugSafety/ucm396470.htm

SAFETY SUPPORTED IN MULTIPLE REAL-WORLD STUDIES6-9,12

Results from real-world studies are not intended for comparisons with clinical trials. Real-world studies were observational trials. Differences in study designs, patient populations, outcome definitions, and methods of collecting data make it difficult to make comparisons with clinical trials or with each other. Real-world data should be viewed as complementary information.

Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation.5

Note
There are no randomized head-to-head comparisons of PRADAXA and rivaroxaban for safety and efficacy.

Objective
Assess primary outcomes of:
• Thromboembolic stroke
• Intracranial hemorrhage
• Major extracranial bleeding, including gastrointestinal bleeding

Method
• Retrospective, observational FDA- & CMS-funded analysis under SafeRx program
• 118,891 patients ≥65 years old with NVAF enrolled in Medicare
• PRADAXA 150 mg BID or rivaroxaban 20 mg QD
• From November 2011- June 2014

SAFETY INFORMATION

https://www.pradaxapro.com/safety/real-world-studies

INDICATIONS AND USAGE
RWE Supports Safety of Rivaroxaban
Factor Xa inhibitor, Approved to Reduce Risk of Stroke in Patients with NVAF

**CONSISTENT® CLINICAL AND REAL-WORLD SAFETY OUTCOMES—TIME AND TIME AGAIN**

Results are not intended for direct comparison with clinical trials because the real-world studies were observational trials with no comparator arm. Differences in study designs, patient populations, definitions of safety or efficacy outcomes, as well as data collection methods, make it difficult to make direct comparisons either with clinical trials or with each other.

**XANTUS study design:** International, noninterventional, observational study investigated safety and efficacy in a real-world clinical setting through 311 clinical centers in Europe, Israel, and Canada. Consecutive consenting patients with NVAF newly started on XARELTO® (n = 6784) were eligible and were followed up at 3-month intervals for 1 year or for at least 30 days after permanent discontinuation.

**XANTUS: Primary outcomes** Included major bleeding events (defined using ISTH criteria), all-cause death, and any other AEs and SAEs. Secondary outcomes included symptomatic thromboembolic events (stroke, non-CNS SE, TIA, and MI) and nonmajor bleeding events.

**Limitations:** This was a single-arm, open-label study, and there was no comparator arm in the trial. Selection biases may have occurred because of patient self-selection participation or investigator selection around intact cognitive function. Outcomes per rivaroxaban dose were not adjusted for baseline risk factors.

**REVISIT-US®**

**REVISIT-US study design:** Retrospective study using US Truven MarketScan claims from January 2012 to October 2014 of newly initiated patients taking rivaroxaban (n = 11,411), apixaban (n = 4083), or warfarin (n = 15,494) and 180 days of continuous medical and prescription benefits. Patients with a prior stroke, SE, or ICH were excluded.

**REVISIT-US: Primary endpoint** was the combination of ischemic stroke or ICH. Each component of this endpoint was also evaluated separately.

**Limitations:** The analysis excluded patients with prior stroke, SE, or ICH, which may have contributed to the low number of events. Propensity-score matching generated cohorts that were comparable in key characteristics; only those variables measured in US Truven MarketScan could be matched upon, and residual confounding cannot be excluded. Also, it was not possible to determine the duration of time warfarin users spent in the therapeutic INR range of 2.0 to 3.0. The US Truven MarketScan database does not allow reporting of lab (serum creatinine) and clinical data (body weight), which are required to determine whether rivaroxaban was consistent with labeling.
# Pragmatic, Observational & Registry Trial Studies Assessing CV Outcomes

<table>
<thead>
<tr>
<th>Example</th>
<th>Design</th>
<th>Data Sources</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADAPTABLE</strong> (NCT02697916)</td>
<td>Randomized trial of 20,000 subjects with CHD to either low dose (81 mg) or high dose (325 mg) aspirin to answer which dosage is best for patients with CHD</td>
<td>• PCORnet – network that combines 130 health care systems across the US</td>
<td>• MACE = all cause death, hospitalization for nonfatal MI or stroke&lt;br&gt;• PCORnet routinely queried to capture and classify CV events&lt;br&gt;• Standardized, validated coding algorithms used</td>
</tr>
<tr>
<td><strong>TRANSLATE ACS</strong> (NCT01088503)</td>
<td>Prospective observational study to evaluate the use of prasugrel in 12,200 patients with AMI treated with PCI</td>
<td>• 233 US hospitals</td>
<td>• MACE = all-cause death, MI, stroke, or unplanned coronary revascularization</td>
</tr>
<tr>
<td><strong>ARTEMIS</strong> (NCT02406677)</td>
<td>Multicenter cluster randomized trial to examine whether eliminating patient copayment for P2Y&lt;sub&gt;12&lt;/sub&gt; receptor inhibitor therapy affects medication persistence and clinical outcomes in 11,000 patients with AMI</td>
<td>• 300 US hospitals</td>
<td>• MACE = death, recurrent MI or stroke in 1 yr</td>
</tr>
<tr>
<td><strong>Diuretic Comparison Project</strong> (NCT02185417)</td>
<td>Randomized trial assessing effects of hydrochlorothiazide vs. chlorthalidone on CV outcomes in 13,500 veterans ≥65 yrs</td>
<td>• Veteran’s Affairs Medical Center EHR and other non VA data bases&lt;br&gt;• Uses centralized processes&lt;br&gt;• Relies on patient’s PCP to approve/disapprove contacting patient&lt;br&gt;• ICF via phone</td>
<td>• Time to MACE defined as stroke, MI, urgent coronary revascularization because of unstable angina, hospitalization for acute heart failure, &amp; non-cancer death</td>
</tr>
<tr>
<td><strong>SWEDHEART</strong> (European Heart Journal (2009) 30, 2165–2173)</td>
<td>National Registry in Sweden Includes all hospitals</td>
<td>• Single payor system in Denmark&lt;br&gt;• Includes all hospitals&lt;br&gt;• Outcomes of every patient hospitalized for ACS or undergoing coronary or valve surgery are captured&lt;br&gt;• Data across hospitals is merged on a routine schedule&lt;br&gt;• Allows for long-term longitudinal follow-up</td>
<td></td>
</tr>
</tbody>
</table>
Pragmatic Trials
What are Randomized Pragmatic Trials?

The key is randomization, generalizability, and effectiveness & safety

Clinical trials that measure effectiveness (or the degree of beneficial effect of a drug or intervention in real clinical practice) by testing a full range of patients who might be treated with the drug or intervention, including those with variable adherence, co-morbidities and polypharmacy


Pragmatic trials are trials that take place where routine care occurs, such as community clinics, hospitals, and health systems and they involve diverse, representative populations and multiple, heterogeneous settings


Pragmatic trials aim to generate real-world evidence on the (relative) effects of treatments, generalizable to routine practice.

IMI Get Real
JCE 2017
Designing pragmatic trials that are fit for purpose

1. Be clear about the research question & intended purpose
2. Consider the design choices around the wheel
3. Score your choices 1 (explanatory) to 5 very pragmatic
4. Compare your scores to your study purpose

- Need to be carefully designed, with considerations for different practices by region
- Be aware that the design may evolve over time, especially with operational considerations – may need to revisit

# Design and methodological considerations for pragmatic randomized trials (pRCTs)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization can yield higher level of evidence (GRADE) than observational studies if trial is well designed</td>
<td>Real-world setting introduces variability</td>
</tr>
<tr>
<td>SOC comparator arm provides answer to highly relevant clinical question(s)</td>
<td>Inclusion of multiple therapies in SOC comparator arm poses challenges to interpretation</td>
</tr>
<tr>
<td>More generalizable/representative than traditional RCT</td>
<td>More switching, cross-overs than RCT</td>
</tr>
<tr>
<td>May leverage existing data (registries such as CORRONA, EMR, claims) for efficiency and to best address specific questions e.g. adherence, cost and HRU</td>
<td>Compared to a RCT, the effect size may be diluted</td>
</tr>
</tbody>
</table>

pRCTs balance internal and external validity to provide a representative estimate of benefit/harm in typical patients.
Why pragmatic randomized trials are used

1) Assures that exposed patients of interest will be available to study and that product will be used the way you want to study it, regardless of current label.

2) Randomization is a familiar, reliable design that minimizes differences between treated and comparator group(s), and addresses channeling bias.

3) Pragmatic outcomes are of interest to patients, clinicians, and payers.

4) Payers and clinicians are particularly interested in comparators used in typical practice, not placebos.
Pragmatic trials blend RCTs and observational studies by offering randomization in a real-world setting

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Classic RCT</th>
<th>Pragmatic RCT</th>
<th>Non-interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>NME, label expansion</td>
<td>~Label expansion, RWE for clinicians, payers &amp; patients</td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Study Pop’n</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-points</td>
<td>May include intermediate endpoints</td>
<td>Endpoints typically encountered in clinical care</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>Mandated testing &amp; visit schedule</td>
<td>Testing and care provided in naturalistic settings</td>
<td></td>
</tr>
<tr>
<td>Data Monitoring</td>
<td>Heavy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Innovative designs need to be considered early in the study concept stage

The path to study design

**“COMMON WAY”**

- Purpose of study **unclear** and/or not aligned with research strategy
- No alternative designs considered
- Choice of endpoints **not driven by study purpose** or overall research strategy
- Alternate designs and **secondary data use not considered**

Design choices are limited, once end-points are defined

**“IDEAL WAY”**

- Purpose aligned with overall research strategy
- **Knowledge of alternative designs used in planning phase** → allows for a wide range of choices
- Defined endpoints feed study purpose
- Alternate designs are openly considered

Consider design choices that feed the endpoints and are fit for purpose & region

PATTERN: PURPOSE ENDPOINTS DESIGN
Endpoints for pragmatic trials

- Outcomes should be measurable by data elements routinely collected in usual care by research-naïve, usual care sites - without extensive training or new equipment – or by other record sources
- No undue interference with patient care
- May be feasible to collect supplemental data in usual care setting or use “hybrid” approaches which combine existing data with primary data collection
- May be feasible to collect all data through EHR, claims or registries after randomization.
EMR-based algorithm to identify Major Adverse Cardiac Events (MACE) for patients taking statins

- Development of strict definitions for identification criteria
  E.g., MACE = AMI or revascularization. AMI: ≥2 AMI relevant ICD9 codes within a 5-day window + abnormal lab test.

- Use of information commonly available within patient EMR data
  E.g., Use of ICD9-CM codes, CPT codes, and laboratory test results for development of algorithm to identify a MACE event.

- KnowledgeMap Concept Indexer (KMCI)
  Scans patient notes for key data points entered within non-standardized EMR fields.

- EMR-based algorithm had 90-97% positive predictive value for identification of MACE cases and 1st MACE event when compared to manual chart review
  False positives resulted from coding errors in patient chart (e.g., ‘stent’ coded for esophageal stent placement).

Establishing a framework to operationalize and validate real-world data – NSCLC test case

**Situation**

- The goal of this initiative by Friends of Cancer Research is to combine, organize, and analyze data from various information sources, including IQVIA.
- These sources include electronic health records, insurance claims, and patient reports for the purposes of exploring potential endpoints that may be fit for regulatory purposes as well as assessing long term benefits of a product.

**Solution**

- Each of the partners will create a retrospective observational analysis of data available to each respective entity to fit an established and agreed upon framework.
- Data will be curated and analyzed to address the key objectives set forth by FOCR.

**Final Objectives and Results**

- Objective 1: Description of demographic and clinical characteristics of NSCLC patients treated with immune checkpoint inhibitors overall and by treatment setting / line of therapy.
- Objective 2: Assess ability to generate endpoints (OS, PFS, TTP, TTNT, TTF) for NSCLC patients treated with immune checkpoint inhibitors within the advanced treatment setting overall and by key characteristics.
- Objective 3: Assess correlation of endpoints (PFS, TTP, TTNT, TTF) to OS.
Principles of inclusion/exclusion criteria*

Should be defined:

✓ As broadly as possible

✓ Reflect the population to be treated with or benefit from the intervention of interest (i.e., the indication for treatment, expected use in usual care setting)

✓ Align with clinical guidelines that determine prescribing or treatment choice of the drug/treatments assessed

✓ Applied to all study participants

— Represent “clinical equipoise” in identifying patients who may equally be considered for treatment with any of the treatment options under study in keeping with current state of evidence and clinical practice

* Similar to considerations for observational CER study
Considerations for selecting a comparator

Single specific regimen (or multiple specific regimens)

- Provides clearer result as to whether “Treatment X” is more or less effective than each comparator
- May be more useful for HCPs in deciding between treatment options for their patients

Usual care combining multiple options per physician choice

- Cheaper than multiple arms for each UC regimen
- Variability of UC across countries and over time in mix of UC creates a challenge
- Difficult to address treatment effect heterogeneity within the UC comparator group—what if new “Treatment X” is more effective than one UC treatment but less effective than another?

Key Points

- There must be clinical equipoise in the selection of treatments
- Comparators may differ by region and country depending on usual care
- Access to treatment must be economically equivalent (e.g., equal co-pays)
Drug Supply in Pragmatic Randomized Trials

<table>
<thead>
<tr>
<th>EUROPE</th>
<th>US</th>
<th>Everywhere</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Study drug is generally supplied to sites and specially labeled for tracking, but not blinded</td>
<td>• Need balanced co-payments to achieve real-world equipoise</td>
<td>• Skeptics are concerned about studies that have little if any scientific value</td>
</tr>
<tr>
<td>• Some countries are asking for comparators products to be provided free of charge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Some countries are asking investigator sites to distribute comparator products as well</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No consistency between countries</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New EU Clinical Trial regulation is changing the way trials are conducted in Europe, particularly with regard to drug supply.
Do you need blinding?

What aspects of a pragmatic trial can be blinded?

- Treatment (patients & physicians)
- Outcome raters (e.g., adjudication)
- Data analyst?
- Others? Governance/Scientific committee?

Placebos are not used since the purpose of pragmatic trials is to make comparisons using real-world decision-making.

Careful assessment should be made of whether reporting of key outcomes may be biased and the likely impact of any such bias.
**Example: CVOT for label expansion**

<table>
<thead>
<tr>
<th>Study Design Elements</th>
<th>Classical CVOT</th>
<th>Classical CVOT streamlined</th>
<th>Pragmatic CVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Placebo (Double-blinded)</td>
<td>Placebo (Double-blinded)</td>
<td>Open Label; SoC</td>
</tr>
<tr>
<td>CRF</td>
<td>Extensive</td>
<td>Focused</td>
<td>Focused &amp; Subgroup with EHR and/or claims</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>All</td>
<td>Serious and expected + SAESI</td>
<td>Serious + SAESI</td>
</tr>
<tr>
<td>Monitoring</td>
<td>100% SDV</td>
<td>10 -15% SDV</td>
<td>1 Visit per Study; Remaining are Remote with 20% Risk-Based Selection</td>
</tr>
<tr>
<td>Follow-Up</td>
<td>Visits</td>
<td>Visits, Phone</td>
<td>Visits, Phone, Electronic</td>
</tr>
</tbody>
</table>

Marked product being tested in new therapeutic area to determine if drug reduces risk of CVO
Example for label expansion: differences, risks and cost

**Key Differences with using RWI CVOT**
- Standard of Care makes for greater generalizability
- Non-blinded drug but blinded Data Safety Monitoring Board (DSMB)
- Risk-based monitoring
- Can model utilization and cost from patient checklist and real world data
- Reduced cost

**Key Risks with using RWI CVOT**
- No guarantee at the outset that regulators will accept this level of evidence for label expansion, despite recent FDA push for NextGen Evidence
- Different regulators may have different requirements
- Some pharma clients will decide savings is worth risk

<table>
<thead>
<tr>
<th></th>
<th>Classical CVOT Streamlined</th>
<th>Pragmatic randomized CVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labor</td>
<td>$78.3M</td>
<td>$36.7M</td>
</tr>
<tr>
<td>Expenses</td>
<td>$15.3M</td>
<td>$3.4M</td>
</tr>
<tr>
<td>Total</td>
<td>$93.6M</td>
<td>$40.1M</td>
</tr>
</tbody>
</table>
Using RWE for More Perspective
Increase your return on investment for clinical research

Augment study data with existing real-world data for more insights

Study Patients

Primary data collection using Case Report Forms

• Clinicians and/or
• Patients

When patients consent for study enrollment, get permission for record linkage

Anticipate that these linked data may be used as a sub-study since not all patients may be matched to existing RWD depending on geography
Increase your return on investment for clinical research

Broden your study focus with matched or more diverse patient RW data

Study Patients

Primary data collection using Case Report Forms from
- Clinicians and/or
- Patients

Match accessible
- Health insurance claims
- Electronic medical records
- Patient registries, etc.

AUGMENT VALUE STORY by using existing RWD data to quantify burden of illness, cost of care, patient journey, etc.
Linking primary data with existing data supports many messages

- Calibrate Risk-Factor Measurement between clinical trial participants and target patient population
- Use overlap between two groups for calibration

Source: Mehdi Najafzadeh and Sebastian Schneeweiss. NEJM 2017; 376 (13):1203-1205
How Do You Know When RWE is Reliable?
Limited use of real-world evidence for label expansions

**Key Messages:**

- FDA is interested in assessing totality of evidence as mandated by 21st Century Cures Act
- FDA wants to see > 2 studies that replicate findings from different data sources
- Most use cases are in rare diseases, rare outcomes, special populations, long-term follow-up, or not feasible/ethical to randomize
Instead of trying to standardize data, develop standardized approach to evaluating data and analytic methods.

When is real-world evidence reliable?

Start by evaluating data and data sources

1. Are sufficient numbers of patients of interest likely to be available?

2. How well do the data characterize “must-have” exposures and outcomes of interest?

3. What is the likelihood that patients have been followed in the data for the desired length of time?

4. What is the potential for, and likely magnitude, of bias in the data?

Some handy reference materials (1 of 2)

AHRQ User's Guide
Standards and best practice guidelines for designing and implementing patient registries


AHRQ User's Guide
Standards and best practice guidelines for designing observational comparative effectiveness research

GRACE Checklist
GRACE Principles Initiative
Good practice principles for observational comparative effectiveness research & validated checklist. www.graceprinciples.org

GRACE is also recognized by NICE, among others.

AHRQ user guides are distributed by the US gov’t and are available in Chinese from IQVIA; Korean adaptation also available. All 3 guidance documents and GRACE are cited in ENCePP Methods Standards.
Some handy references (2 of 2)

- Guidance describing best practices pertaining to conducting & reporting on pharmacoepidemiologic safety studies that use EHR, which include administrative claims data and EMR data. [FDA Guidance Pharmacoepi Safety Reporting](#)

- Guidance on use of electronic consent [FDA Guidance on Electronic Informed Consent](#)

- ISPE-ISPOR Task Force on good practice guidance recommendations for RWE “[Joint ISPOR/ISPE Special Task Force on Real-World Evidence in Health Care Decision Making.](#)” The special task force has produced several companion papers that make specific recommendations for improving the transparency and reproducibility of RWE for use in health care decision making, especially those decisions at the regulatory and payer levels. Summit on October 20, 2017 in Washington, DC.

- National Health Council White paper on Patient Perspective:
  - [2015 NHC Guidance on patient guidance](#)
  - [2017 Guidance Patient Engagement for Regulatory Studies](#)
Thank You!

Join the conversation #DIA2018

http://www.cardiac-safety.org/