Pragmatic Trial Design to Study Health Policy Interventions: Lessons Learned from ARTEMIS

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June 22, 2018
Disclosures

- Research grants to the Duke Clinical Research Institute from
  - NIH, PCORI, AHRQ, FDA
  - Amgen, AstraZeneca, Bristol Myers Squibb, Cryolife, Novartis, Pfizer, Portola and Regeneron

- Consulting honoraria from
  - Grifols and Gilead.
Guideline Recommendations

 PCI (BMS or DES)

 STEMI or NSTE-ACS

 Medical Therapy

 CABG

0 months

Class I: At least 1 year of DAPT
- clopidogrel
- prasugrel
- ticagrelor

6 months

Class I: At least 1 year of DAPT
- clopidogrel
- ticagrelor

12 months

Class I: 1 year of DAPT

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy
2015/2017 ESC Guidelines for the Management of Acute Coronary Syndrome and STEMI
Guideline Recommendations

ACC/AHA Class IIa Recommendation
It is reasonable to choose ticagrelor or prasugrel over clopidogrel for patients not at high risk for bleeding

ESC Class I Recommendation
Clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy
2015/2017 ESC Guidelines for the Management of Acute Coronary Syndrome and STEMI
Medication Use and Persistence

In the US:

- Higher potency (non-generic) P2Y\textsubscript{12} inhibitors under-utilized
- 30-60% of patients stop treatment within 1 year
- Patients’ inability to afford medications is frequently cited as a barrier to both

New medication users 3x more likely to fill late/abandon

>$50 prescription cost 5x more likely to abandon

Hypotheses

By reducing and equalizing the out-of-pocket cost for generic and brand P2Y$_{12}$ inhibitors

- Antiplatelet medication choice will be driven more by evidence than patient affordability
- Patients will be more likely to complete 1 year of therapy as recommended by practice guidelines
- Improved persistence to P2Y$_{12}$ inhibitor therapy will lead to better clinical outcomes
Why This Study?

- Stimulate health system and payer consideration of novel cost-sharing models to
  - promote patient and provider adherence to evidence based therapies
  - Allow choice of therapies to be driven by differences in risk-benefit rather than the cost of the intervention
  - Improve patient outcomes
- Can we innovate the design of pragmatic health policy trials?
**Study Design**

- **MI patients**
  - US-based health insurance (commercial or government) enrolled before discharge

- **Cluster Randomization** *

  - **Copayment Intervention**
  - **Usual Care**

- Treatment choice and duration of therapy determined by the treating physicians

- Intervention site patients provided a copayment voucher card for either generic clopidogrel or brand ticagrelor
Cluster Randomization

- Hospital- vs. patient-level randomization
  - Not dangling benefit in front of the patient
  - Preserves provider treatment decision-making
  - Patient-level randomization was considered impossible
    - unacceptably higher lost-to-follow-up rate for patients who were consented and randomized to no co-payment reduction
Cluster Randomization

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- Vulnerable to imbalances in enrollment rate and type of enrolled
Trial Design Considerations

- Need to ensure both arms enroll as consecutively as possible with similar follow-up rates between groups
  - Make enrollment criteria as inclusive as possible
  - Make enrollment burden as light as possible for sites
  - Reduce patient barriers to enrollment and follow-up
  - Reduce loss to follow-up even in the group of patients not benefiting from an intervention
**Broad Inclusion Criteria**

- MI patients ≥18 years of age treated with a P2Y$_{12}$ receptor inhibitor at the time of enrollment
- Have United States-based health insurance coverage with prescription drug benefit
- Able to provide consent for longitudinal follow-up
  - Do we need this requirement for future pragmatic trials when linkage to clinical data sources may be sufficient?
Reducing Site Burden

- Site responsibilities:
  - Identifying patients
  - Obtain consent
  - Baseline case report form
  - Medical record query 1 year later
Reducing Site Burden

• Site responsibilities:
  • Identifying patients
  • Obtain consent
  • Baseline case report form
  • Medical record query 1 year later

Follow-up Interviews conducted by the DCRI

3  6  9  12  15

Discharge

Duke Clinical Research Institute
US Representation

301 Sites

23% Teaching Hospitals
Balancing Enrollment

11,001 patients (42%) enrolled among screen eligible

1:2 randomization (Intervention: Usual Care)
199/301 sites already randomized

Patients declined more at usual care hospitals (29% vs. 26%, p<0.01)
| Patient Characteristics | **Intervention** N=6135 | **Usual Care** N=3967 | |StdDiff| |
|-------------------------|------------------------|----------------------|------|
| Age                     | 62 (54, 70)            | 62 (54, 70)          | 0.00 |
| Female                  | 31.7%                  | 32.4%                | 0.02 |
| **Non-white race**      | **10.4%**              | **13.9%**            | **0.11** |
| STEMI                   | 46.4%                  | 45.2%                | 0.02 |
| Prior MI                | 19.6%                  | 21.7%                | 0.05 |
| Prior stroke/TIA        | 6.2%                   | 7.5%                 | 0.05 |
| Diabetes                | 31.6%                  | 34.0%                | 0.05 |
| Creatinine clearance (ml/min) | 71 (53, 90) | 69 (52, 87) | 0.04 |
| Weight (kg)             | 89 (77, 103)           | 89 (76, 104)         | 0.01 |
| Multivessel disease     | 47.2%                  | 45.2%                | 0.02 |
| PCI during index MI     | 90.1%                  | 87.6%                | 0.08 |

StdDiff (standardized difference) >0.10 denotes significant difference
Reduce Patient Barriers

- No need to return to enrolling site for follow-up
- Follow-up interviews kept short
- Patients can choose phone- or web- follow-up
- Rescue mechanisms to complete follow-up
Reduce Patient Barriers

- No need to return to enrolling site for follow-up
- Follow-up interviews kept short
- Patients can choose phone- or web- follow-up
- Rescue mechanisms to complete follow-up

Patient Contact: 87% through 1 year

Lost-to-follow-up for MACE assessment: 1.8%
34% patients elected web-based follow-up

<table>
<thead>
<tr>
<th></th>
<th>Phone (n=7288)</th>
<th>Web (n=3688)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>63 (55,72)</td>
<td>59 (52,66)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>35%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Non-white</strong></td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>full time</td>
<td>32%</td>
<td>55%</td>
</tr>
<tr>
<td>part time</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>College of higher education</strong></td>
<td>40%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Low Health Literacy</strong></td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>EQ5D VAS</strong></td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

All p <0.001
Rescuses for Web-Based Follow-up

- 72% patients needed rescue
  - Most of these (75%) needed rescue more than once

<table>
<thead>
<tr>
<th></th>
<th>Rescued &gt;1x (n=2039)</th>
<th>Mostly Web (n=1649)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58 (50,66)</td>
<td>60 (53,67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>25%</td>
<td>22%</td>
<td>0.11</td>
</tr>
<tr>
<td>Non-white</td>
<td>9%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not working</td>
<td>35%</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>College of higher education</td>
<td>62%</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low Health Literacy</td>
<td>9%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>10%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EQ5D VAS</td>
<td>70</td>
<td>74</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Intervention Increased Guideline Adherence

% Prescribed at Discharge

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention Arm</td>
<td>36.0%</td>
<td>59.6%</td>
<td>4.4%</td>
<td>54.7%</td>
<td>32.4%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Usual Care Arm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.0001

*absolute difference between intervention and usual care arms
Measuring Medication Use

- **Patient report**
  - % of patients who reported ≥30 days gap in use

- **Pharmacy fill**
  - % patients with pharmacy fill supply gap ≥30 days

- **Blood levels**
  - % patients without drug metabolite in blood draw
Measuring Medication Use

- **Patient report**
  - % of patients who reported ≥30 days gap in use

- **Pharmacy fill**
  - % patients with pharmacy fill supply gap ≥30 days

- **Blood levels**
  - % patients without drug metabolite in blood draw

Overall population (n=10,973)

Phlebotomy substudy (10%)

Linked to pharmacy data (80%)
## Effect on Medication Persistence

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Intervention</th>
<th>Usual Care</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-Reported n=10,102</td>
<td>12.96%</td>
<td>16.21%</td>
<td>&lt;0.0001</td>
<td>Unadjusted 0.76 (0.65, 0.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted 0.84 (0.72, 0.98)</td>
</tr>
<tr>
<td><strong>Secondary Analyses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy Fills n=8,360</td>
<td>44.80%</td>
<td>53.71%</td>
<td>&lt;0.0001</td>
<td>Unadjusted 0.64 (0.57, 0.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted 0.68 (0.60, 0.77)</td>
</tr>
<tr>
<td>Randomly-Selected Blood Draws</td>
<td>8.23%</td>
<td>12.35%</td>
<td>0.04</td>
<td>Unadjusted 0.64 (0.42, 0.98)</td>
</tr>
<tr>
<td>n=944</td>
<td></td>
<td></td>
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</tbody>
</table>
Centralized Data Collection

**Obtain Medical Bills**
- Patient report: Hospitalizations, ED visits, Procedures
- Site query: 12 months after enrollment

**Obtain Medical records:**
- Discharge summary
- Angiographic reports
- Procedure reports

**Screening by diagnosis and/or procedure codes**

**Clinical Outcomes**

**Cost Data**

**Independent Event Validation**
How Reliable are Patient-Reported Rehospitalizations? Implications for the Design of Future Practical Clinical Studies

Arun Krishnamoorthy, MD; Eric D. Peterson, MD, MPH; J. David Knight, MS; Kevin J. Anstrom, PhD; Mark B. Effron, MD; Marjorie E. Zettler, PhD, MPH; Linda Davidson-Ray, MS; Brian A. Baker, PharmD; Patrick L. McCollam, PharmD; Daniel B. Mark, MD, MPH; Tracy Y. Wang, MD, MHS, MSc

Background—Longitudinal clinical investigations often rely on patient reports to screen for postdischarge adverse outcomes events, yet few studies have examined the accuracy of such patient reports.

Methods and Results—Patients with acute myocardial infarction (MI) in the TRANSLATE-ACS study were asked during structured interviews at 6 weeks, 6 months, and 12 months postdischarge to report any rehospitalizations. The accuracy of patient-reported rehospitalizations within 1 year of postdischarge was determined using claims-based medical bill validation as the reference standard. The cumulative incidence of rehospitalizations was compared when identified by patient report versus medical bills. Patients were categorized by the accuracy in reporting events (accurate, under-, or over- reporters) and characteristics were compared between groups. Among 10,643 MI patients, 4,565 (43%) reported 7,734 rehospitalizations. The sensitivity and positive predictive value of patient-reported rehospitalizations were low at 67% and 59%, respectively. A higher cumulative incidence of rehospitalization was observed when identified by patient report versus medical bills (43% vs 37%; P<0.001). Overall, 18% of patients over-reported and 10% under-reported the number of hospitalizations. Compared with accurate reporters, under-reporters were more likely to be older, female, African American, unemployed, or a non-high-school graduate, and had greater prevalence of clinical comorbidities such as diabetes and past cardiovascular disease.

Conclusions—The accuracy of patient-reported rehospitalizations was low with patients both under- and over-reporting events. Longitudinal clinical research studies need additional mechanisms beyond patient report to accurately identify rehospitalization events.

Clinical Trial Registration—URL: https://clinicaltrials.gov. Unique identifier: NCT01088503. (J Am Heart Assoc. 2016;5:e002695 doi: 10.1161/JAHA.115.002695)

Key Words: myocardial infarction • patient outcome assessment • validation studies
Among 10,643 patients
- 4,565 patients (43%) reported 7,734 hospitalizations
- 5,015 patients had 6,786 bills collected

- 72% accurately reported # hospitalizations
  - 18% (n=1,911) over-reported
  - 10% (n=1,012) under-reported
## Can Patients Accurately Report MI/Stroke?

### Table 2. Comparison Between Patient-Reported Rehospitalization for MI and Stroke and Physician-Validated Recurrent MI and Stroke

<table>
<thead>
<tr>
<th>Patient-reported MI:</th>
<th>Physician Validated MI: Yes</th>
<th>Physician Validated MI: No</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>103</td>
<td>257</td>
</tr>
<tr>
<td>no</td>
<td>254</td>
<td>N/A</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient-reported stroke:</th>
<th>Physician Validated Stroke: Yes</th>
<th>Physician Validated Stroke: No</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>19</td>
<td>57</td>
</tr>
<tr>
<td>no</td>
<td>36</td>
<td>N/A</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>35%</td>
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</tbody>
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Are Claims Data Any Better?

Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Usual Care</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (%)</td>
<td>10.17%</td>
<td>10.63%</td>
<td>0.65</td>
</tr>
<tr>
<td>Unadjusted HR:</td>
<td>0.96 (0.80, 1.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted HR:</td>
<td>1.07 (0.93, 1.25)</td>
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</tbody>
</table>

![Graph showing comparison between Usual Care and Intervention](graph.png)
Take Home Messages

- Health policy and implementation studies require pragmatic trial design

- Cluster randomized design may be uniquely suited but more likely present operational challenges compared with patient-randomized designs

- Lessons learned on
  - how to enhance site and patient participation in research
  - Practically but accurately assess outcomes