Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study

Tracy Y. Wang, MD, MHS, MSc, FACC, FAHA

presenting on behalf of ARTEMIS Investigators
Guidelines – DAPT after ACS

**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.

---

**STEMI or NSTE-ACS PCI (BMS or DES)**

**Medical Therapy**

**CABG**

Class I:
- At least 1 year of DAPT

Class I:
- At least 1 year of DAPT

- clopidogrel
- ticagrelor
- prasugrel

---

Duke Clinical Research Institute

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
P2Y\(_{12}\) Inhibitor Use and Persistence in the US

**Post-MI Patients Discharged on a P2Y\(_{12}\) inhibitor**

- Clopidogrel: 65%
- Prasugrel: 18%
- Ticagrelor: 17%

**Among post-MI patients in the US:**

- Clopidogrel is the most commonly prescribed P2Y\(_{12}\) inhibitor
- 30-60% of patients stop P2Y\(_{12}\) inhibitor treatment within 1 year
- Affordability thought to be a key factor for both

Duke Clinical Research Institute

Hypotheses

By reducing and equalizing the out-of-pocket cost for generic and brand antiplatelet agents

- 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 $\text{P2Y}_{12}$ inhibitor therapy will lead to better clinical outcomes
Top 10 Enrolling Sites
Reid Hospital (Z. Mirza)
University of Massachusetts (N. Kakouros)
Regions Hospital (W. Nelson)
Spectrum Health (R. McNamara)
Winchester Medical Center (J. Call)
Indiana University (A. Ferguson)
Norton Cardiovascular (V. Panchal)
Hudson Valley Heart Center (L. Kantaros)
Iowa Heart Center (M. Tannenbaum)
Rockford Cardiovascular (A. Sheikh)
STEMI or NSTEMI patients on P2Y$_{12}$ inhibitor therapy enrolled before discharge
US-based health insurance (commercial or government)

Cluster Randomization *

Copayment Intervention
Usual Care

*Randomization stratified by annual MI volume and baseline % ticagrelor use
Copayment Intervention

- $\text{P2Y}_{12}$ inhibitor choice and duration of therapy determined by the treating physicians
  - Enrolled patients could be treated with any $\text{P2Y}_{12}$ inhibitor

- Intervention site patients provided a copayment voucher card for either a generic (clopidogrel) or brand (ticagrelor) $\text{P2Y}_{12}$ inhibitor

- No other interventions to improve adherence were given
Endpoints

Co-Primary Endpoints

• Non-persistence of P2Y_{12} inhibitor therapy, defined as:
  • % patients who reported ≥30 days gap in P2Y_{12} inhibitor use within 1 year

• MACE (death, recurrent myocardial infarction, and stroke within 1 year)

Key Secondary Endpoints

• P2Y_{12} inhibitor therapy selection at discharge:
  • % of patients prescribed ticagrelor vs. clopidogrel vs. prasugrel

• Non-persistence by pharmacy fill:
  • % patients with pharmacy fill supply gap ≥30 days

• Non-persistence by blood levels:
  • % patients without drug metabolite in blood on random draw
Analysis

• Because of the un-blinded cluster design, analyses were adjusted for baseline covariates using a propensity model

• Among patients discharged on clopidogrel or ticagrelor
  • Non-persistence of P2Y\textsubscript{12} inhibitor - logistic regression model with generalized estimating equations to account for within hospital clustering
  • MACE - Cox proportional hazards model with robust standard errors to account for within hospital clustering

• Intention to treat and as-treated (voucher use)
Enrollment Trend

1:2 randomization (Intervention: Usual Care)

199/300 planned sites randomized

Number of patients enrolled

- Intervention
- Usual Care
11,001 MI patients at 301 US hospitals

**Intervention**
135 sites randomized, 6,436 patients
- (n=16) Died before discharge
- (n=1) Withdrew before discharge
- (n=1) Discharged without P2Y<sub>12</sub> inhibitor
- (n=283, 4.4%) Discharged on prasugrel

**Usual Care**
166 sites randomized, 4,565 patients
- (n=8) Died before discharge
- (n=0) Withdrew before discharge
- (n=3) Discharged without P2Y<sub>12</sub> inhibitor
- (n=587, 12.9%) Discharged on prasugrel

**Enrollment and Randomization**

- Intervention: 131 sites enrolled 6,135 patients
- Usual Care: 156 sites enrolled 3,967 patients
## Hospital Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention N=135</th>
<th>Usual Care N=166</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bed size</strong></td>
<td>369 (268, 516)</td>
<td>397 (262, 620)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Teaching hospital</strong></td>
<td>22.2%</td>
<td>26.5%</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Annual MI volume</strong></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Low (&lt;400)</td>
<td>43.0%</td>
<td>45.2%</td>
<td></td>
</tr>
<tr>
<td>High (≥400)</td>
<td>57.0%</td>
<td>54.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Ticagrelor use before ARTEMIS</strong></td>
<td></td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Low (&lt;15%)</td>
<td>43.7%</td>
<td>41.0%</td>
<td></td>
</tr>
<tr>
<td>High (≥15%)</td>
<td>56.3%</td>
<td>59.0%</td>
<td></td>
</tr>
<tr>
<td><strong># of patients enrolled per site</strong></td>
<td>37 (18, 66)</td>
<td>18 (7, 37)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
# Patient Demographic 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       |
| Private Insurance        | 63.0%               | 64.0%             | 0.02       |
| Employed                 | 46.7%               | 44.4%             | 0.08       |

*StdDiff (standardized difference) >0.10 denotes significant difference*
# Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention N=6135</th>
<th>Usual Care N=3967</th>
<th>StdDiff</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>46.4%</td>
<td>45.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior MI</td>
<td>19.6%</td>
<td>21.7%</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>10.7%</td>
<td>12.0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>6.2%</td>
<td>7.5%</td>
<td>0.05</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>5.8%</td>
<td>7.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.6%</td>
<td>34.0%</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>71 (53, 90)</td>
<td>69 (52, 87)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89 (77, 103)</td>
<td>89 (76, 104)</td>
<td>0.01</td>
</tr>
<tr>
<td>Home aspirin</td>
<td>42.4%</td>
<td>44.6%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Home P2Y12 inhibitor</strong></td>
<td><strong>12.9%</strong></td>
<td><strong>16.5%</strong></td>
<td><strong>0.10</strong></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>47.2%</td>
<td>45.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>PCI during index MI</td>
<td>90.1%</td>
<td>87.6%</td>
<td>0.08</td>
</tr>
</tbody>
</table>

StdDiff (standardized difference) >0.10 denotes significant difference
Discharge $P2Y_{12}$ Inhibitor Selection

- **Intervention Arm**
  - Clopidogrel: 36.0%
  - Ticagrelor: 59.6%
  - Prasugrel: 4.4%

- **Usual Care Arm**
  - Clopidogrel: 54.7%
  - Ticagrelor: 32.4%
  - Prasugrel: 12.9%

- The difference between the intervention and usual care arms is significant at $p<0.0001$.

*absolute difference between intervention and usual care arms*
# Non-Persistence of P2Y\textsubscript{12} Inhibitor

<table>
<thead>
<tr>
<th>Analysis</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</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>n=10,102</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</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>n=8,360</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>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Duke Clinical Research Institute
Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th>Component</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</td>
<td>(0.80, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.07</td>
<td>(0.93, 1.25)</td>
<td></td>
</tr>
</tbody>
</table>

- Death: 3.86% vs. 3.88% (p = 0.98)
- Recurrent MI: 6.91% vs. 7.28% (p = 0.64)
- Stroke: 0.82% vs. 0.95% (p = 0.53)

Adjusted comparisons non-significant for each component.

Duke Clinical Research Institute
Non-Persistence of P2Y$_{12}$ Inhibitor
As Treated Analysis

- 1,742 (28%) intervention arm patients did not use study voucher

As Treated* vs. Usual Care

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Usual Care</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.95%</td>
<td>16.21%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Unadjusted OR: 0.56 (0.47, 0.66)
Adjusted OR: 0.65 (0.55, 0.78)

*as treated = voucher use
Major Adverse Cardiovascular Events
As Treated Analysis

As Treated* vs. Usual Care

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Usual Care</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (%)</td>
<td>7.49%</td>
<td>10.63%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Unadjusted HR:</td>
<td>0.70</td>
<td>(0.58, 0.84)</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR:</td>
<td>0.90</td>
<td>(0.76, 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

*as treated = voucher use
Limitations

• Patient-reported P2Y$_{12}$ persistence rates were high, reflecting the current emphasis on patient adherence education

• Imbalance in enrollment
  • Cluster randomized design intended to study clinician prescribing behavior but gave less incentive to enroll at control sites
  • Possible residual unmeasured confounding between clusters

• No perfect measure of drug persistence
  • Limitations to all measurement methods
Conclusions

• Copayment reduction significantly
  • Affected clinician choice of treatment
  • Improved persistence to treatment

• Despite increased evidence-based treatment, clinical outcomes were not significantly improved
Implications

• Why was copayment reduction alone not enough to change clinical outcomes?
  • Targeted single drug only
  • Modest co-pay differences and high baseline persistence
  • Incomplete use of co-pay vouchers
  • Significant albeit modest impact on persistence

• Broad-scale interventions likely needed to further improve medication persistence and patient outcomes
  • Consider copayment reduction as part of a multi-pronged strategy to enhance medication persistence and outcomes
Acknowledgments

**Coordinating Center**
Duke Clinical Research Institute

**Tracy Y. Wang**
Principal Investigator

**Eric D. Peterson**
Study Chair

**Kevin J. Anstrom**
Faculty Statistician

**Study Sponsor**
AstraZeneca

**Naeem D. Khan**

**Durgesh Bhandary**

**Steering Committee**

**Christopher Cannon**
Brigham and Women’s Hospital

**Niteesh K. Choudhry**
Harvard School of Public Health

**David J. Cohen**
Beth Israel Deaconess Medical Center

**Gregg C. Fonarow**
Ahmanson-UCLA

**Timothy D. Henry**
Cedars Sinai Medical Center

**Study Contributors**
301 US Hospitals and PIs

**Operational Leadership**

**Linda Davidson-Ray**
Project Leader

**Laura Webb**
Project Leader

**Lisa A. Kaltenbach**
Statistician

**Shannon Carr**
Site Management

**Alexander C. Fanaroff**
Study Fellow

**Jacob A. Doll**
Study Fellow