How Employers can Support People with Heart Disease

A close look at Aspirin Dosing Effectiveness and beyond.

July 20, 11am ET
Webinar Agenda

- Welcome/Introduction – Karen van Caulil
- PCORI Update – Rachel Mosbacher
- Schuyler Jones, MD – PCORI-funded Study
- Reactor Panelist Introductions | Project Translation
- Questions/Discussion from Reactor Panelists
- Questions from the Audience Wrap up and thank you.
- Survey
Welcome | Introduction

Karen L. van Caulil, PhD
President and CEO
Florida Alliance for Healthcare Value

Rachel Mosbacher, MPA
Senior Program Officer, Engagement Awards
PCORI
PCORI Update

https://www.pcori.org/webform/pcoris-national-priorities-health-proposed-priorities-public-comment
PCORI/ CER Principal Investigator

William Schuyler
Jones, MD
Duke University
PCORI-funded Principal Investigator
ADAPTABLE
Aspirin Dosing:
A Patient-Centric Trial
Assessing Benefits and
Long-Term Effectiveness

Schuyler Jones, MD
On behalf of the entire ADAPTABLE study team

July 2021
Background

For patients who experience NSTE-ACS, a maintenance dose of aspirin (81 mg/d to 325 mg/d) should be continued indefinitely.

2014 AHA/ACC NSTE-ACS Guidelines

I IIa IIb III

For patients who experience NSTE-ACS, a maintenance dose of aspirin (81 mg/d to 325 mg/d) should be continued indefinitely.
Research Question

In patients with established or pre-existing cardiovascular disease, is a strategy of 81 mg or 325 mg of aspirin better?

Everyday decision for patients (OTC medication)

The correct dose of aspirin may **PREVENT**:

- Thousands of deaths / heart attacks
- or
- Thousands of bleeds

*Annually in the United States*
Main Objective of the ADAPTABLE Trial

To compare the effectiveness and safety of two doses of aspirin (81 mg and 325 mg) in high-risk patients with coronary artery disease.

⚠️ **Primary Effectiveness Endpoint:** Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

⚠️ **Primary Safety Endpoint:** Hospitalization for major bleeding that was associated with a blood product transfusion
ADAPTABLE Study Design

15,000 patients with known ASCVD + ≥ 1 “enrichment factor”

Eligible patients identified via inclusion/exclusion criteria (applied to EHRs)

Electronic consent and self randomization on participant portal

Randomization:
- ASA 81 mg QD
- ASA 325 mg QD

Electronic patient follow-up
Data from EHR, health plans, Medicare

Primary Endpoint:
Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary Safety Endpoint:
Hospitalization for major bleeding

ClinicalTrials.gov: NCT02697916
**ADAPTABLE Inclusion Criteria**

- Prior myocardial infarction
- Prior revascularization (PCI or CABG)
- Prior angiogram showing significant CAD
- History of chronic ischemic heart disease, CAD, or ASCVD

**ADAPTABLE Exclusion Criteria**

- History of significant allergy to aspirin
- History of GI bleeding within 12 months
- Bleeding disorder that precludes the use of aspirin
- Current or planned used of an oral anticoagulant or ticagrelor
- Female patients who were pregnant or nursing

**Known Cardiovascular Disease**

- Age ≥ 65 years
- Creatinine ≥ 1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Cerebrovascular disease
- Peripheral artery disease
- Prior myocardial infarction
- Prior revascularization (PCI or CABG)
- Prior angiogram showing significant CAD
- History of chronic ischemic heart disease, CAD, or ASCVD

**≥ 1 Enrichment Risk Factor**

- Age ≥ 65 years
- Creatinine ≥ 1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Cerebrovascular disease
- Peripheral artery disease
- Current smoker
- Known LVEF < 50%
- Chronic systolic or diastolic heart failure
- SBP ≥ 140 (within past 12 mos)
- LDL ≥ 130 (within past 12 mos)
Endpoint Confirmation

Data sources:
- Participant report
- EHR data
- Claims data

Nonfatal endpoints defined by *ICD-10* algorithms

All-cause death captured by EHR, health insurance claims, or proxy
40 Study Centers within PCORnet®

- Patient-Centered Scalable National Network for Effectiveness Research (pSCANNER): 131 pts
- Greater Plains Collaborative (GPC): 3,611 pts
- Research Action for Health Network (REACHnet): 958 pts
- Essentia: 449 pts
- PaTH Network: 1,934 pts
- Stakeholders, Technology, and Research Clinical Research Network (STAR CRN): 5,466 pts
- Chicago Area Patient-Centered Outcomes Research Network (CAPriCORN): 581 pts
- New York City Clinical Data Research Network (NYC-CDRN): 830 pts
- HealthCore: 357 pts
- OneFlorida: 779 pts
40 Sites Currently Active & Have Enrolled

- 450,577 of 657,215* of total eligible approached
- 32,087 Golden Tickets Entered
- 15,076 Participants Randomized
- 2,966 Non-Internet Enrolled

ClinicalTrials.gov: NCT02697916
Approximately **450,000** people were approached for the study

**32,164** individuals visited the patient portal

**15,076** participants enrolled and underwent randomization

- **7540** randomized to **81 mg group**
- **7536** randomized to **325 mg group**

Withdrawal of consent (overall 4.1%)
- **81 mg (2.9%)**
- **325 mg (5.2%)**

Limited participation (overall 2.3%)
- **81 mg (1.8%)**
- **325 mg (3.4%)**
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>81 mg group</th>
<th>325 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>, median, (25th, 75th), years</td>
<td>67.7 (60.7, 73.6)</td>
<td>67.5 (60.7, 73.5)</td>
</tr>
<tr>
<td><strong>Female sex</strong>, no. (%)</td>
<td>2307 (30.6%)</td>
<td>2417 (32.1%)</td>
</tr>
<tr>
<td><strong>Race, Black or African American, no. (%)</strong></td>
<td>664 (8.8%)</td>
<td>647 (8.6%)</td>
</tr>
<tr>
<td><strong>Race, White, no. (%)</strong></td>
<td>6014 (79.8%)</td>
<td>5976 (79.3%)</td>
</tr>
<tr>
<td><strong>Hispanic ethnicity, no. (%)</strong></td>
<td>249 (3.3%)</td>
<td>232 (3.1%)</td>
</tr>
<tr>
<td><strong>Weight</strong>, median (25th, 75th), kg</td>
<td>90.0 (78.6, 103.6)</td>
<td>90.0 (78.2, 104.1)</td>
</tr>
<tr>
<td><strong>Current Tobacco use, no. (%)</strong></td>
<td>696 (9.2%)</td>
<td>686 (9.1%)</td>
</tr>
<tr>
<td><strong>Aspirin use before study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81 mg</td>
<td>5823/6850 (85.0%)</td>
<td>5724/6687 (85.6%)</td>
</tr>
<tr>
<td>162 mg</td>
<td>168/6850 (2.5%)</td>
<td>142/6687 (2.1%)</td>
</tr>
<tr>
<td>325 mg</td>
<td>845/6850 (12.3%)</td>
<td>812/6687 (12.1%)</td>
</tr>
<tr>
<td><strong>Dual antiplatelet use at baseline</strong></td>
<td>1570 (22.5%)</td>
<td>1511 (22.1%)</td>
</tr>
</tbody>
</table>
# Medical History

<table>
<thead>
<tr>
<th>Condition</th>
<th>81 mg group</th>
<th>325 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior PCI</td>
<td>3005 (40.0%)</td>
<td>2941 (39.1%)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1786 (23.8%)</td>
<td>1741 (23.2%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>2674 (35.6%)</td>
<td>2631 (35.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6264 (83.3%)</td>
<td>6248 (83.1%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6472 (86.1%)</td>
<td>6474 (86.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2820 (37.5%)</td>
<td>2856 (38.0%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>605 (8.0%)</td>
<td>628 (8.4%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1718 (22.8%)</td>
<td>1786 (23.8%)</td>
</tr>
<tr>
<td>Prior GI hemorrhage</td>
<td>455 (6.1%)</td>
<td>495 (6.6%)</td>
</tr>
<tr>
<td>Prior intracranial hemorrhage</td>
<td>98 (1.3%)</td>
<td>110 (1.5%)</td>
</tr>
</tbody>
</table>

*Medical history was obtained from EHR queries, with look back of 5 years*
Primary Effectiveness Endpoint
(All-cause death, hospitalization for MI, or hospitalization for stroke)

HR = 1.02 (0.91 - 1.14), p = 0.75

Death / MI / Stroke (%)

Months from Randomization

At risk
81 mg dose 7540 7357 7177 5627 4190 2712 1558 636
325 mg dose 7536 7297 7095 5544 4090 2613 1489 592
Primary Safety Endpoint
(Hospitalization for major bleeding with associated blood product transfusion)

HR (95% CI) = 1.18 (0.79 - 1.77)

At risk
81 mg dose 325 mg dose
7540 7536
7434 7348
7309 7185
5777 5667
4329 4205
2810 2709
1610 1559
674 624

81 mg = 0.63%
325 mg = 0.60%
## Effectiveness and Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>81 mg group</th>
<th>325 mg group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7434</td>
<td>7330</td>
<td></td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>590 (7.28%)</td>
<td>569 (7.51%)</td>
<td>1.02 (0.91 - 1.14)</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td>53 (0.63%)</td>
<td>44 (0.60%)</td>
<td>1.18 (0.79 - 1.77)</td>
</tr>
<tr>
<td><strong>All-cause death</strong></td>
<td>315 (3.80%)</td>
<td>357 (4.43%)</td>
<td>0.87 (0.75 - 1.01)</td>
</tr>
<tr>
<td><strong>Non-fatal MI</strong></td>
<td>228 (2.99%)</td>
<td>213 (2.87%)</td>
<td>1.06 (0.88 - 1.27)</td>
</tr>
<tr>
<td><strong>Non-fatal stroke</strong></td>
<td>102 (1.23%)</td>
<td>92 (1.27%)</td>
<td>1.09 (0.82 - 1.45)</td>
</tr>
<tr>
<td><strong>PCI or CABG</strong></td>
<td>471 (6.05%)</td>
<td>446 (5.96%)</td>
<td>1.04 (0.92 - 1.19)</td>
</tr>
</tbody>
</table>
# Subgroup Analyses

(Primary effectiveness endpoint)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>81 mg dose N (Rate)</th>
<th>325 mg dose N (Rate)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>590 (7.28%)</td>
<td>569 (7.51%)</td>
<td>1.02 (0.91 - 1.14)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;= 65 yrs</td>
<td>364 (7.12%)</td>
<td>378 (7.96%)</td>
<td>0.94 (0.79 - 1.12)</td>
</tr>
<tr>
<td>&lt; 65 yrs</td>
<td>226 (7.54%)</td>
<td>191 (6.80%)</td>
<td>1.24 (1.00 - 1.53)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>186 (7.79%)</td>
<td>193 (8.43%)</td>
<td>0.99 (0.81 - 1.21)</td>
</tr>
<tr>
<td>Male</td>
<td>404 (7.06%)</td>
<td>376 (7.08%)</td>
<td>1.03 (0.90 - 1.19)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>432 (6.70%)</td>
<td>433 (7.12%)</td>
<td>0.97 (0.85 - 1.11)</td>
</tr>
<tr>
<td>Black</td>
<td>91 (12.27%)</td>
<td>68 (10.69%)</td>
<td>1.36 (0.99 - 1.86)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (6.88%)</td>
<td>33 (7.69%)</td>
<td>0.86 (0.53 - 1.39)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 (7.67%)</td>
<td>14 (5.94%)</td>
<td>1.61 (0.83 - 3.11)</td>
</tr>
<tr>
<td>Not Hispanic</td>
<td>530 (7.26%)</td>
<td>513 (7.44%)</td>
<td>1.01 (0.89 - 1.14)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>283 (5.97%)</td>
<td>258 (5.82%)</td>
<td>1.06 (0.89 - 1.25)</td>
</tr>
<tr>
<td>Yes</td>
<td>288 (9.28%)</td>
<td>295 (9.99%)</td>
<td>0.99 (0.84 - 1.17)</td>
</tr>
<tr>
<td><strong>Chronic kidney disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>370 (5.82%)</td>
<td>347 (5.65%)</td>
<td>1.05 (0.90 - 1.21)</td>
</tr>
<tr>
<td>Yes</td>
<td>201 (13.73%)</td>
<td>206 (15.68%)</td>
<td>0.97 (0.80 - 1.18)</td>
</tr>
<tr>
<td><strong>P2Y12 inhibitor use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>359 (5.87%)</td>
<td>361 (6.64%)</td>
<td>0.96 (0.83 - 1.11)</td>
</tr>
<tr>
<td>Yes</td>
<td>188 (11.49%)</td>
<td>161 (10.08%)</td>
<td>1.16 (0.94 - 1.44)</td>
</tr>
<tr>
<td><strong>Study visit method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internet</td>
<td>439 (6.28%)</td>
<td>449 (6.70%)</td>
<td>0.97 (0.85 - 1.10)</td>
</tr>
<tr>
<td>Non-Internet</td>
<td>151 (13.73%)</td>
<td>120 (12.96%)</td>
<td>1.18 (0.93 - 1.50)</td>
</tr>
</tbody>
</table>

The figure illustrates the hazard ratio (HR) and 95% confidence interval (CI) for each subgroup analysis comparing the 81 mg dose with the 325 mg dose. The analysis shows that the 81 mg dose may be favored in certain subgroups, as indicated by the HR values.
### Study Medication in ADAPTABLE

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>81 mg</th>
<th>325 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose switching, % *</td>
<td>24.2%</td>
<td>7.1%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Aspirin discontinuation, % **</td>
<td>9.1%</td>
<td>7.0%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Median days of exposure, assigned as</td>
<td>551 days (139 - 737)</td>
<td>650 days (415 – 922)</td>
<td>434 days (139 – 737)</td>
</tr>
<tr>
<td></td>
<td>aspirin dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days of exposure, any aspirin</td>
<td>658 days (426 - 932)</td>
<td>670 days (439 – 944)</td>
<td>646 days (412 – 922)</td>
</tr>
<tr>
<td></td>
<td>dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Defined as at least one dose change

** Reasons for aspirin discontinuation:
- 25% participant did not want to continue
- 75% doctor’s decision or medical condition (e.g., atrial fibrillation, dyspepsia)
### Sensitivity Analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>81 mg dose</th>
<th>325 mg dose</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (rate)</td>
<td>N (rate)</td>
<td>325 mg vs 81 mg</td>
</tr>
<tr>
<td><strong>Impact of actual dose taken</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death / MI / Stroke</td>
<td>673</td>
<td>321</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>(3.6 events per 100 patient-years)</td>
<td>(2.9 events per 100 patient-years)</td>
<td>(1.10 - 1.43)</td>
</tr>
</tbody>
</table>

Rates are calculated at median follow-up (26.2 months) using the Kalbfleisch & Prentice cumulative incidence function estimator.

Rates and HR reflect the effect of the time-varying reported dose on the primary effectiveness end point.

Rates are calculated as annualized event rates (events per 100 patient-years).
Strengths and Limitations

- We successfully completed this virtual, pragmatic study

- We performed this study in a real-world environment, utilized multiple, heterogeneous datasets, and engaged patient-partners to make our study better

- Open-label study
  - Inability to blind study drug may have affected adherence, dose switching, and drug discontinuation

- Improving diversity and inclusion remains an important goal and may not be fully addressed with virtual studies

Adaptable
Conclusions

- No observed difference in death / MI / stroke in patients assigned to 81 mg vs. 325 mg

- There was a difference in fidelity to the study dose/intervention (more dose switching in 325 mg group)
  - Multiple reasons that patients did not stay on the 325 mg dose
    - Tolerability
    - Medical reasons
    - Participant preferences
    - Clinician practices
Messages to Patients

- **If you are on 81 mg now**, staying (rather than switching) is probably right given the similar study results for the primary endpoint.

- **If you are resuming aspirin**, starting a lower dose (81 mg) is probably right due to better tolerability and we did not find conclusive evidence that higher dose is better.

- **If you are tolerating 325 mg now**, staying on this dose may be okay and associated with moderate benefit.
Unique Aspects of ADAPTABLE
Patient Engagement

PATIENT BLOGS

For more than 40 years, doctors have been telling patients with heart disease to take aspirin. Now there is a nationwide study to determine the best dose of aspirin to prevent heart attacks or strokes for these patients.

The Adaptable team of local UFHealth researchers invites you to be part of the answer.

If you are 18 years or older, can safely take aspirin and have been diagnosed with heart disease, you may qualify.

Study enrollment and followup will be done entirely online or over the phone. You will not have to visit a clinic for the study.

Participants will receive compensation for their time.

To enroll or for more information, call 352-294-8770.

Visit us online at AdaptablePatient.com/ and enter your unique code: H2XXX

FACEBOOK LIVE

PATIENT ENGAGEMENT PAVILION
Lay Summary

THE ADAPTABLE STUDY
Summary of Results
Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness

On behalf of the ADAPTABLE team of patient partners, researchers, and clinicians we would like to thank you for participating in ADAPTABLE. As a research participant, you played a critical role in generating these study results. We truly appreciate your time and commitment to help advance the care of people with heart disease.

WHO WAS INVOLVED?

15,076 people with heart disease

WHY WAS ADAPTABLE VITAL?

40 large health systems and one health plan across the nation that are part of PCORnet®, The National Patient-Centered Clinical Research Network.

WHAT IS THE PURPOSE OF ADAPTABLE?
The purpose of ADAPTABLE is to find the best dose of aspirin, 81 mg or 325 mg, for people with known or existing heart disease to prevent death or another heart attack or stroke.

WHEN DID ADAPTABLE TAKE PLACE?
The full research study was conducted from May 2015 to May 2021. The first participant enrolled in April 2016, and the last participant enrolled in June 2019.

WHY IS THIS RESEARCH IMPORTANT TO PATIENTS, CLINICIANS, AND OTHER RESEARCHERS?
Aspirin can help keep blood flowing. It is recommended for people with heart disease to prevent another heart attack or stroke. However, the best dose for people with heart disease is not known. This is most likely due to the lack of data from clinical trials.
Congratulations @PCORI #ADAPTABLEstudy team for enrolling the 15,000th participant. Very excited to have reached our enrollment goal! One step closer to finding the best dose of aspirin for people with #heartdisease.

Adrian F. Hernandez @texhern · Jun 25
Congrats all of @ADAPTABLEstudy and @PCORnetwork

Robert M Califf @califf001 · Jun 26
Replying to @ADAPTABLEstudy @a_sharlow and 9 others
Great achievement by the ADAPTABLE team: people who volunteered for study; study staff; clinicians, researchers and information scientists. Enrollment completed relatively quickly at a fraction of the cost of traditional, regulated clinical trials. @dukeforge @DCRNews

Joe Selby MD, MPH @joevselby · Jun 26
Thanks and congrats to intrepid team @ADAPTABLEstudy - researchers, patients, clinicians, systems are all playing pivotal roles in a ground-breaking study. Millions waiting for the results of this most pragmatic study question. @PCORI @califf001
Direct-to-Participant Research

Screening of CDRN EHR data with computable phenotype

Electronic outreach to potential patients with trial introduction and link to ADAPTABLE web portal

Web-Based, Electronic Informed Consent
- Initial patient contact via web portal text and video consent options
- Developing a common consent form with selected local adaptations
- Focused questions to confirm patient comprehension for informed consent and eligibility for randomization after consent

Randomization and Aspirin dose assignment

Let’s get started!
Thank you for taking the time to find out more details about the ADAPTABLE aspirin study. With your help, we hope to find out what is the right dose of aspirin for people with heart disease.

Got a code?
Please enter in the special code that was included in your invitation:
AX3BN

No code? No problem!
You can still learn more about this study even if you have not been asked to participate.

Already have a profile? Login
Electronic Data Collection and Follow-Up

N=15,000

ADAPTABLE enrollee

Baseline data

Web portal follow-up
- Randomized to 3 vs 6 mos contact
- Patient-reported hospitalizations
- Medication use
- Health outcomes

PCORnet Coordinating Center follow-up
- Via Common Data Model
- Validated coding algorithms for endpoints

CMS and private health plans follow-up
- Longitudinal health outcomes
- Validated coding algorithms for endpoints

DCRI call center
- Patients who miss 2 contacts
- Patients without internet access
- Validated coding algorithms for endpoints

DeathAscertainment
- CDM and Social Security Databases
- Alternate contacts via DCRI Call Center

ClinicalTrials.gov: NCT02697916
Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease

Reactor Panel Introduction and Statements

J. Greg Merritt, PhD
Founder
Patient is Partner, LLC

K. Andrew Crighton, MD
CEO
Crighton Consulting Group

John M. Clymer
Executive Director
National Forum for Heart Disease & Stroke Prevention
Thank you and Survey.