The Megatrial of Aspirin Dosing: PCORnet’s first pragmatic clinical trial
PCORnet’s goal

PCORnet seeks to improve the nation’s capacity to conduct *clinical research* by creating a large, highly representative, national patient-centered network that supports more efficient clinical trials and observational studies.
Early Opportunity

- Large, highly representative electronic data infrastructure to facilitate efficient research
  - Observational
  - Pragmatic randomized trials

- PCORI has identified a unique early opportunity to support an interventional individual-level randomized clinical trial that will inform future research studies in PCORnet
About the trial

- The trial should be characterized by **operational simplicity** and **clinical relevance**.
- The trial will make extensive use of **EHR** to identify patients and report outcomes.
- The study will complete in no more than **18 months** with a total cost of **$10 million**.
- PCORI has identified **6 viable topics** from the network for prioritization.
Process

Step 1
- Topic generation—over 40 trials nominated by PPRNs and CDRNs!

Step 2
- Topic prioritization

Step 3
- PCORI Program Development Committee (PDC) & PCORI Board of Governors Approve Final Topic for the Clinical Trial

Step 4
- PCORI issues request Q3-Q4 2014 (TBC)
What will constitute a good fit for PCORI’s first clinical trial?
Prioritization Criteria

- Patient-Centeredness
- Impact of the Condition on the Health of Individuals and Populations
- Assessment of Current Options
- Likelihood of Implementation in Practice
- Durability of Information
- Feasibility of the clinical trial within health systems
In addition, the following criteria were used by PCORI to assess the suitability of the topic for the first interventional trial for PCORnet:

- **Question and outcome** should be meaningful to patients and providers.
- The trial should be one that is better conducted as a **multi-network** rather than single-network study.
- The intervention should be **relatively simple to implement and monitor**:
  - should not require significant administrative or operational training
  - should involve minimal clinical burden and workflow disruptions
- **Patient recruitment** and **follow-up** should be facilitated using **routinely collected electronic health data**:
  - relatively **stable** patient populations preferable
  - outcomes can be identified using routinely collected electronic health data
  - outcomes from **questionnaires or similar instruments** may require substantial effort to develop, administer and interpret uniformly.
From over 40 Concepts 6 were chosen for further consideration (almost all were considered worthwhile and important trials)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topic 1: Stroke prevention in nonvalvular atrial fibrillation</td>
<td>Dr. Chrischilles (Great Plains) Dr. Chuang (PaTH)</td>
</tr>
<tr>
<td>Topic 2: Role of spacers in asthma</td>
<td>Dr. Rothman (MidSouth)</td>
</tr>
<tr>
<td>Topic 3: Optimal maintenance aspirin dose for patients with coronary artery disease</td>
<td>Dr. Chen (Kaiser)</td>
</tr>
<tr>
<td>Topic 4: Mindfulness-based weight reduction using a simple web-based training</td>
<td>Dr. Nierenberg (Mood)</td>
</tr>
<tr>
<td>Topic 5: Interventions to maximize and maintain weight loss after bariatric surgery</td>
<td>Dr. Chuang (PaTH)</td>
</tr>
<tr>
<td>Topic 6: Optimal second line treatment for glycemic control in type 2 diabetes</td>
<td>Dr. Rothman (MidSouth) Dr. Chuang (PaTH)</td>
</tr>
</tbody>
</table>
PCORI Advisory Panel Prioritization
About the panel

- The panel is an experienced group of scientists, patients, and other stakeholders charged with prioritizing CER topics for PCORI.
- We asked the 19 member panel to review the 6 nominated topic briefs as submitted by PCORnet PIs.
- Each topic received a presentation from 3 panel members and a 15-20 minute discussion.
- Topics were prioritized immediately following discussion of the 6 using pre-determined PCORI prioritization criteria, including feasibility criteria unique to this PCORnet opportunity.
Topic 3: Optimal maintenance aspirin dose for patients with coronary artery disease
### Presentation, Discussion of Topics: Topic 3

<table>
<thead>
<tr>
<th>Topic 3</th>
<th>Optimal maintenance aspirin dose for patients with coronary artery disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors (Network)</td>
<td>Dr. Chen (PORTAL)</td>
</tr>
<tr>
<td>Population</td>
<td>Patients with CAD taking aspirin</td>
</tr>
</tbody>
</table>
| Intervention | Aspirin high dose (325mg)  
Aspirin low dose (81mg) |
| Primary outcome | hospitalization for GI bleeding, hospitalization for recurrent MI or ACS, repeat PCI or bypass surgery, and all-cause death |
Establishing the optimal maintenance aspirin dose for secondary prevention of coronary artery disease

Aim: Randomize patients with prior CAD (MI, ACS, PCI, bypass surgery) who currently take high-dose aspirin (325mg) daily to either low-dose (81 mg) or remaining on high-dose daily aspirin

Hypotheses:

- Low-dose aspirin is non-inferior to high-dose aspirin with respect to hospitalization for coronary events and/or all-cause death
- Low-dose aspirin is superior to high-dose aspirin with respect to hospitalization for gastrointestinal (GI) bleeding

High scientific and clinical impact:

- ACC-AHA clinical guidelines-- “aspirin 81mg is preferred maintenance dose, but Class of Evidence (IIa), Level of Evidence (B)
- half of the 15 million CAD patients in US prescribed high dose aspirin

Operational simplicity:

- simple intervention, established therapy, inexpensive, large pool of patients for recruitment
Establishing the optimal maintenance aspirin dose for secondary prevention of coronary artery disease

- Minimum requirements for multi-network design
  - Can sites provide data on a single drug? claims data for outcomes?

- Electronic health records
  - EHR used for recruitment (diagnosis/procedure codes), intervention (aspirin dose), and outcomes (cardiac and GI bleeding events)

- General Feasibility
  - 7500 subjects total to detect 1.1% absolute reduction in GI bleeding hospitalizations (high-dose 3.5% vs 2.4% low-dose)
  - 7500 subjects allows for non-inferiority limit of 1.5% assuming baseline 7.5% for recurrent CAD events
  - Demonstrates unique strengths of PCORnet to recruit a large cohort simply and inexpensively
Topic 3: Optimal maintenance aspirin dose for patients with coronary artery disease

Comments from the Advisory Panel:

Perhaps highest impact of proposed studies - an important question that maybe only PCORnet could answer

Significant sample size needed, though otherwise noticeably simple to implement

Consideration may be given to combination therapies in the pragmatic setting

Questions of time frame. Is 18 months sufficient?
Leading Causes of Death Worldwide

1990

1. Ischemic heart diseases
2. Cerebrovascular diseases
3. Lower respiratory infections
4. Diarrheal diseases
5. Perinatal conditions

2020

1. Ischemic heart diseases
2. Cerebrovascular diseases
3. COPD
4. Lower respiratory infections
5. Trachea, bronchus, lung cancers

The Disparity Will Only Get Worse

1990: 25% of all deaths were from CVD.

2020: 40% of all deaths will be from CVD.

In developing countries, MI and CVD deaths occur 10–20 years earlier.

- CVD deaths < 70 y.o. in developing countries: 50%
- CVD deaths < 70 y.o. in Western countries: 20%

—Reddy KS. NEJM 2004
MAD: Megatrial in Aspirin Dosing

Aspirin: A “Wonder” Drug
Aspirin Therapy in ACS
Limitations and Unresolved Issues

- Mechanism of antiplatelet effect
  - thromboxane $A_2$
- Established efficacy
- Dosing
- Resistance
  - Biochemical
  - Clinical
- Dose modifiers
  - Genetics
  - Clopidogrel
- Intolerance
- Non-platelet effects
  - inflammation
PHILADELPHIA—In a medical breakthrough that should come as welcome news for millions of at-risk Americans, University of Pennsylvania cardiologists announced Tuesday that taking one aspirin tablet and a fifth of bourbon daily can "significantly reduce" an individual's awareness of heart attacks.
Acute Coronary Disease: Contributing Factors

**Quiescent plaque**
- Lipid core

**Vulnerable plaque**
- Inflammation
  - TF → Clotting Cascade
- Collagen → platelet activation
- Macrophages
- Metalloproteinases

**Plaque rupture**
- Platelet-thrombin micro-emboli

**Process**
- Plaque formation

**Marker**
- Cholesterol
- LDL
- Inflammation
  - Multiple factors
  - ? Infection
- Plaque Rupture
  - ? Macrophages
  - Metalloproteinases
- Thrombosis
  - Platelet Activation
  - Thrombin
- C-Reactive Protein
- Adhesion Molecules
- Interleukin 6, TNFα,
  - sCD-40 ligand
- MDA Modified LDL
- D-dimer
- Fibrinogen
- Troponin
MAD: Megatrial in Aspirin Dosing

Aspirin: A “Wonder” Drug

- Proven clinical benefit in reducing ischemic vascular events
- Cost effective
- Most effective dose uncertain
- Benefit with combination antiplatelet therapies
- Emerging evidence for dose modifiers (ASA resistance, inherited polymorphisms)
MAD: Megatrial in Aspirin Dosing

**COX 1 and 2**

**COX 1** (Constitutive)
- Platelets
- Vascular SMC, Foam Cells
- Thromboxane A2

**COX 2** (Inducible)
- Vascular SMC, Foam Cells
- Prostacyclins
- COXIBs

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NIH Collaboratory
Rethinking Clinical Trials
# MAD: Megatrial in Aspirin Dosing

## Benefit of Aspirin as Preventive Therapy

### Secondary Prevention

<table>
<thead>
<tr>
<th>Condition</th>
<th>Participants</th>
<th>Odds Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>19791</td>
<td>25%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>18773</td>
<td>29%</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>11707</td>
<td>22%</td>
</tr>
<tr>
<td>All High Risk</td>
<td>73247</td>
<td>27%</td>
</tr>
</tbody>
</table>

*Antiplatelet Therapy Better*

*Antiplatelet Therapy Worse*

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*Antiplatelet Trialists’ Collaboration BMJ 1994*
MAD: Megatrial in Aspirin Dosing
Risks of Aspirin Therapy

- Intracranial Hemorrhage
  - 0.04% per year
MAD: Megatrial in Aspirin Dosing
Risks of Aspirin Therapy

- Intracranial Hemorrhage
- Gastrointestinal Bleeding

- Clear dose-dependent relationship
  - 75mg  2.3 OR
  - 150mg  3.2 OR
  - 300mg  3.9 OR

- Risk of death from GI bleed 0.5-10%
## MAD: Megatrial in Aspirin Dosing
### Aspirin Intolerance

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patients Ever Reporting</th>
<th>Requiring Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Rash</td>
<td>578 (6.02%)</td>
<td>442 (4.61%)*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>428 (4.46%)</td>
<td>322 (3.36%)*</td>
</tr>
<tr>
<td>Indigestion/nausea/vomiting</td>
<td>1441</td>
<td>1686</td>
</tr>
<tr>
<td></td>
<td>(15.01%)</td>
<td>(17.59%)*</td>
</tr>
<tr>
<td>Any bleeding disorder</td>
<td>890 (9.27%)</td>
<td>890 (9.28%)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>34 (0.35%)</td>
<td>47 (0.49%)</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>191 (1.99%)</td>
<td>255 (2.66%)*</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>285 (2.97%)</td>
<td>302 (3.15%)*</td>
</tr>
</tbody>
</table>

* p<0.05

CAPRIE Lancet 1997
25,087 ACS Patients (UA/NSTEMI 70.8%, STEMI 29.2%)

- Planned Early (<24 h) Invasive Management with intended PCI
- Ischemic ECG Δ (80.8%) or ↑ cardiac biomarker (42%)

PCI = percutaneous coronary intervention; UA/NSTEMI = unstable angina/non-ST-segment elevation myocardial infarction

ASA low-dose group
At least 300 mg Day 1; 75-100 mg from Day 2 to 30

ASA high-dose group
At least 300 mg Day 1; 300-325 mg from Day 2 to 30
ASA Dose Comparison: Primary Outcome and All-Cause Death

<table>
<thead>
<tr>
<th>ASA</th>
<th>81-100 mg %</th>
<th>300-325 mg %</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death/MI/Stroke</td>
<td>4.4</td>
<td>4.2</td>
<td>0.97</td>
<td>0.86-1.09</td>
<td>0.61</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death</td>
<td>2.3</td>
<td>2.1</td>
<td>0.90</td>
<td>0.76-1.06</td>
<td>0.22</td>
</tr>
<tr>
<td>MI</td>
<td>2.1</td>
<td>2.0</td>
<td>0.97</td>
<td>0.82-1.15</td>
<td>0.76</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5</td>
<td>0.6</td>
<td>1.19</td>
<td>0.84-1.68</td>
<td>0.32</td>
</tr>
<tr>
<td>All-Cause Death</td>
<td>2.5</td>
<td>2.2</td>
<td>0.87</td>
<td>0.74-1.03</td>
<td>0.10</td>
</tr>
</tbody>
</table>
## ASA Dose Comparison: Bleeding

<table>
<thead>
<tr>
<th></th>
<th>ASA 75-100 mg</th>
<th>ASA 300-325 mg</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURRENT Major Bleed</td>
<td>2.3</td>
<td>2.3</td>
<td>0.99</td>
<td>0.84-1.17</td>
<td>0.90</td>
</tr>
<tr>
<td>CURRENT Severe Bleed</td>
<td>1.7</td>
<td>1.7</td>
<td>1.01</td>
<td>0.83-1.21</td>
<td>0.93</td>
</tr>
<tr>
<td>Fatal Bleed</td>
<td>0.1 (15)</td>
<td>0.1 (16)</td>
<td>1.07</td>
<td>0.53-2.17</td>
<td>0.85</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>0.24 (29)</td>
<td>0.38 (47)</td>
<td>1.6</td>
<td></td>
<td>0.039</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>4.4</td>
<td>5.0</td>
<td>1.13</td>
<td>1.00-1.26</td>
<td>0.042</td>
</tr>
</tbody>
</table>
ASA Dose Comparison
Death at 30 days

Cumulative Hazard

HR 0.86 (0.73-1.02)
P = 0.077

ASA 81-100 mg
ASA 300-325 mg
MAD: Megatrial In Aspirin Dosing  
Potential Impact of Proper ASA Dosing

*In United States,*

12 million CHD…

CHD deaths 460,000

MI 1,100,000

Strokes 500,000

Hosp 2,200,000

Revasc 1,500,000
### In United States,

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD deaths</td>
<td>460,000</td>
</tr>
<tr>
<td>MI</td>
<td>1,100,000</td>
</tr>
<tr>
<td>Strokes</td>
<td>500,000</td>
</tr>
<tr>
<td>Hosp</td>
<td>2,200,000</td>
</tr>
<tr>
<td>Revasc</td>
<td>1,500,000</td>
</tr>
</tbody>
</table>

- 325mg ASA
- 20% ↓ Ischemic
- 3% GI bleed

MAD: Megatrial In Aspirin Dosing
Potential Impact of Proper ASA Dosing
MAD: Megatrial In Aspirin Dosing
Potential Impact of Proper ASA Dosing

In United States,
12 million CHD...
CHD deaths 460,000
MI 1,100,000
Strokes 500,000
Hosp 2,200,000
Revasc 1,500,000

325mg ASA
20%↓ Ischemic
3% GI bleed

MI  220,000
CHD Death  92,000
GI Bleed  360,000
Deaths from GI bleeding  36,000
Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

<table>
<thead>
<tr>
<th>Antiplatelet therapy</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 162- to 325-mg load before procedure</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• 81- to 325-mg daily maintenance dose (indefinite)*</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>• 81 mg daily is the preferred maintenance dose*</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>P2Y₁₂ inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clopidogrel: 600 mg as early as possible or at time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• Prasugrel: 60 mg as early as possible or at time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• Ticagrelor: 180 mg as early as possible or at time of PCI</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.
Contemporary Patterns of Discharge Aspirin Dosing after Acute Myocardial Infarction in the United States

Hurst HM et al; Circ Cardiovasc Qual Outcomes
July 2014 online

221,199 post-MI patients
National Cardiovascular Registry—American College of Cardiology
Quarterly proportion of high-dose (325 mg) aspirin prescription at discharge from 2007-2011 among patients with acute myocardial infarction, overall and in clinically interesting subgroups by management strategy or concomitant medication use.
Distribution of Aspirin Dosing at Discharge

- 81 mg: 61%
- 162 mg: 3%
- 325 mg: 36%
- other: 0.01%
Percent High-Dose ASA at Discharge

- ASA + Warfarin: 26%
- ASA alone: 44%
- ASA + ...: 51%
- ASA + ...: 69%
Percent High-Dose ASA at Discharge

- ASA + Warfarin: 26%
- ASA alone: 51%
- ASA + …: 69%
- Medical: 45%
- CABG: 48%
- PTCA alone: 66%
- PCI - BMS: 73%
- PCI - DES: 74%
Percent High-Dose ASA at Discharge

% High-dose ASA

ASA + Warfarin: 26
ASA + ...: 44
ASA alone: 51
ASA + ...: 69

Medical...: 45
CABG: 48
PTCA alone: 66
PCI - BMS: 73
PCI - DES: 74

Major bleeding: 57
No major bleeding: 64
MAD: Megatrial in Aspirin Dosing

The Stage is Set…A Randomized Trial of Optimal Aspirin Dosing
MAD: Megatrial in Aspirin Dosing

The Stage is Set… A Randomized Trial of Optimal Aspirin Dosing

“In this corner, weighing in at 81 mg”
MAD: Megatrial in Aspirin Dosing

The Stage is Set... A Randomized Trial of Optimal Aspirin Dosing

“In this corner, weighing in at 81 mg”

“And in this corner, the challenger, weighing in at 325mg”
Prioritization

1. Choose Topic
2. Prioritize Key Questions

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Design

2

- Contact and Involve Patients
- Assess Population
- Refine Protocol Design
- Select Protocol Design Committee
- Contract / Budget
- Simulate Trial Procedures
- Design Data Collection Instruments
- Simulate with Providers and Patients
- Assess EHR / Registries / Other
- Design Data Collection Instruments
- Patients / Providers
- Select sites and Steering Committee and Data Monitoring Committee
- Refine Protocol
- Finalize Protocol
Start up

1. Start with Final Protocol, Contract and Budget
2. Send to Sites
3. Site Training
4. Develop and Distribute Study Materials
5. Assess Regulatory Status
6. Site Initiated

- Contract and Budget
- IRB
- Provider and Administration
- Patients and Facilities
- Devise Quality by Design Plan
Implementation

Enroll Patients

Conduct Trial

Data Monitoring Committee

Evaluate HRPP Plan as trial goes on

QBD Reassess Early for Issues

QBD Reassess

Trial Communication, Protocol Amendments

Data Monitoring Committee / HRPP

Trial Closeout

Study Closeout

Data Cleanup

Database Lock

Study Closeout

Data Cleanup

Database Lock

QBD Reassess Early for Issues

Evaluate HRPP Plan as trial goes on

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Evaluate HRPP Plan as trial goes on

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Study Closeout

Data Cleanup

Database Lock
Analysis
Dissemination Board

Membership

- Patients, caregivers, clinicians, other decision-makers at all participating PCORnet sites (CDRNs, PPRNs) invited
- Some may have also participated in selecting the research question, defining other study design elements, or monitoring study conduct
- Individuals with “marketing” experience encouraged

Role

- Complement traditional researcher dissemination activities targeting non-researcher stakeholders at PCORnet sites, as well as other local venues (e.g., churches, schools, businesses / purchasers, payers)

Funding

- Separate PCORI budget for Dissemination Board activities
Dissemination

**Researcher (national, international venues)**
- Journals
- PCORnet Website
- Meeting presentations, continuing education
- ClinicalTrials.gov
- Distribution of data for others to analyze
- Results made public within 90 days of analysis

**Dissemination Board (local venues)**
- Talking points for non-researchers using multiple media (print, online, radio, TV, social media)
- Results to study participants, patients, caregivers, clinicians, health plan administrators
- Churches, book clubs, schools, businesses, healthcare centers, ....
Major Questions—Technical

Should only 2 doses be compared?

What about enteric coated vs not enteric coated?

Should it be a noninferiority trial or a superiority trial?

Should prevention of ischemic events and bleeding events be treated separately or in a composite endpoint?

Should the trial be masked or open label?

Should it only enroll chronic aspirin users or both initial and chronic users?

Should it enroll only patients currently taking 325 mg?

What are the expected:

- Event rates?
- Effect size?
- Sample size?
Major Questions: Operational

- Will patients be interested?
- Will doctors and administrators be interested?
- Will the baseline data be available from EHR plus claims?
- Will the outcomes be available form the EHR plus claims?
- Can we construct a simple web based system to:
  - Collect PRO’s
  - Follow people who are lost to the enrolling health system
Summary

Coronary heart disease is a major cause of death and disability

Getting the dose of aspirin right could save up to 100,000 lives in the US alone (or prevent several hundred thousand major bleeding episodes)
  - And multiple times that number globally

The logistical problems are daunting, but if anyone can do it, PCORnet should

We hope that all relevant CDRN’s and PPRN’s will participate

Committees are forming to plan the trial
We Want YOU...

To practice evidence-based medicine