



Stanford
M E D I C I N E

Pragmatism in Randomized Clinical Trials: Lessons from Cardiovascular Medicine

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- **Research grants/contracts (active)**
 - RCT: NHLBI (ISCHEMIA), Duke/PCORI (ADAPTABLE), Janssen
 - DSMB: Harvard (Baim Institute), NHLBI (REPRIEVE)
- **Consulting/Advisory**
 - NHLBI (CONNECTS), Element Science, WebMD
- **Board of Directors**
 - AHA

Pragmatism in RCTs

- Types of RCTs frequently employed in understanding drugs, devices, technologies and strategies in CV medicine
- Essential elements of an RCT to reliably establish causal inference
- Some observations on the large, simple trial in CV medicine
- Challenges and limitations of conventional RCTs
- The concept of pragmatism in RCT designs
- Pragmatic Explanatory Continuum Indicator Summary (PRECIS) tool
- A recent examples of pragmatism in CV RCTs
 - ADAPTABLE (ASA dose comparison)
- Summary

Types of Clinical Trial

- **Explanatory or mechanistic trials**
 - aimed at impact of a treatment on biological measures
- **Evaluative or clinical outcome trials**
 - aimed at impact of a treatment on what matters to patients and their care providers (living longer, feeling better, avoiding unpleasant experiences, spending less money)

Answers to complex questions cannot be derived from “simple” trials

Eric J Topol, Robert M Califf

“Both types of trials are needed to advance the clinical treatment of acute myocardial infarction. Mega-trials can provide definitive evidence about the mortality reduction afforded by a class of therapy so that broad changes in clinical practice can be justified. Mini-trials can explain why a treatment is effective to allow development of more effective approaches attacking the identified mechanisms.”

What is A Quality Clinical Trial?

1. Relevant question being addressed
2. A protocol that is clear, practical, focused
3. Adequate number of events to answer question with confidence
4. In a general practice setting to make results generalizable
5. With proper randomization
6. With reasonable assurance that patients receive (and stay on) assigned treatment
7. With reasonably complete follow-up and ascertainment of primary outcome (and other key outcomes like death)
8. With a plan for ongoing measurement, feedback, improvement of quality measures during trial conduct
9. With safeguards against bias in determining clinically relevant outcomes
10. With protection of rights of research patients

Looking Back at a Disruptive Technology

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOKINASI
NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction ($p=0\cdot0002$, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

The Lancet · Saturday 22 February 1986



“It started with no funding and skepticism in some quarters but today GISSI is recognized as an Italian achievement that has changed cardiology treatment worldwide.”

Current State of Clinical Trials

 VIEWPOINT

Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

Elliott M. Antman, MD

Robert A. Harrington, MD

Perhaps the most exciting opportunity for CVD researchers is to capitalize on the advances in systems and computational biology that can inform first-in-human, proof-of-

“As large trials became popular...the original simplicity was lost...leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuring costs. An ideal opportunity would be to embed randomization in the EMR... introducing randomization into registries sponsored by societies.”

-Antman E, Harrington RA. JAMA 2012;338:1743-4.



“This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we’ve forgotten why.”



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D.,
Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D.,
Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D.,
Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D.,
Lars Hellsten, M.D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D.,
Amra Kåregren, M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertsson, M.D.,
Lennart Sandhall, M.D., Iwar Sjögren, M.D., Ollie Östlund, Ph.D.,
Jan Harnek, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL



Unmet Aspirations — Where To Now for Catheter Thrombectomy?

Robert A. Byrne, M.B., B.Ch., Ph.D., and Adnan Kastrati, M.D.

Perspective

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for

United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as

CENTRAL ILLUSTRATION: U.S. Landscape of Randomized Clinical Trials in Cardiovascular Disease

Randomized Clinical Trials (RCTs) in Cardiovascular Disease

 Current challenges	 Goals for future RCTs	A pragmatic solution: Registry-based trials
Scientific and operational complexity	Simplify operational approach	 Identify sites and candidates using health registry data
Waning site and patient participation	Large sample sizes with representative populations	
Regulatory issues	Fewer restrictions	 Informed consent, randomization and patient comprehension via internet portal
Inefficient and costly	Embed trials within routine clinical care processes Leverage electronic records and data	
		 Follow up: Outcomes ascertained via patient report, electronic health records, and administrative claims

Jones, W.S. et al. J Am Coll Cardiol. 2016;68(17):1898-907.



Pragmatism From Beginning to End

Study Design



- EHR-informed estimates of eligible patients/events
- Simple inclusion/exclusion criteria
- Quality-by-design directed by regulatory guiding principles

Sites



- Site networks linked by electronic document exchange
- Standardized contracting across network
- Central IRB or collaborative IRB agreements

Enrollment Process

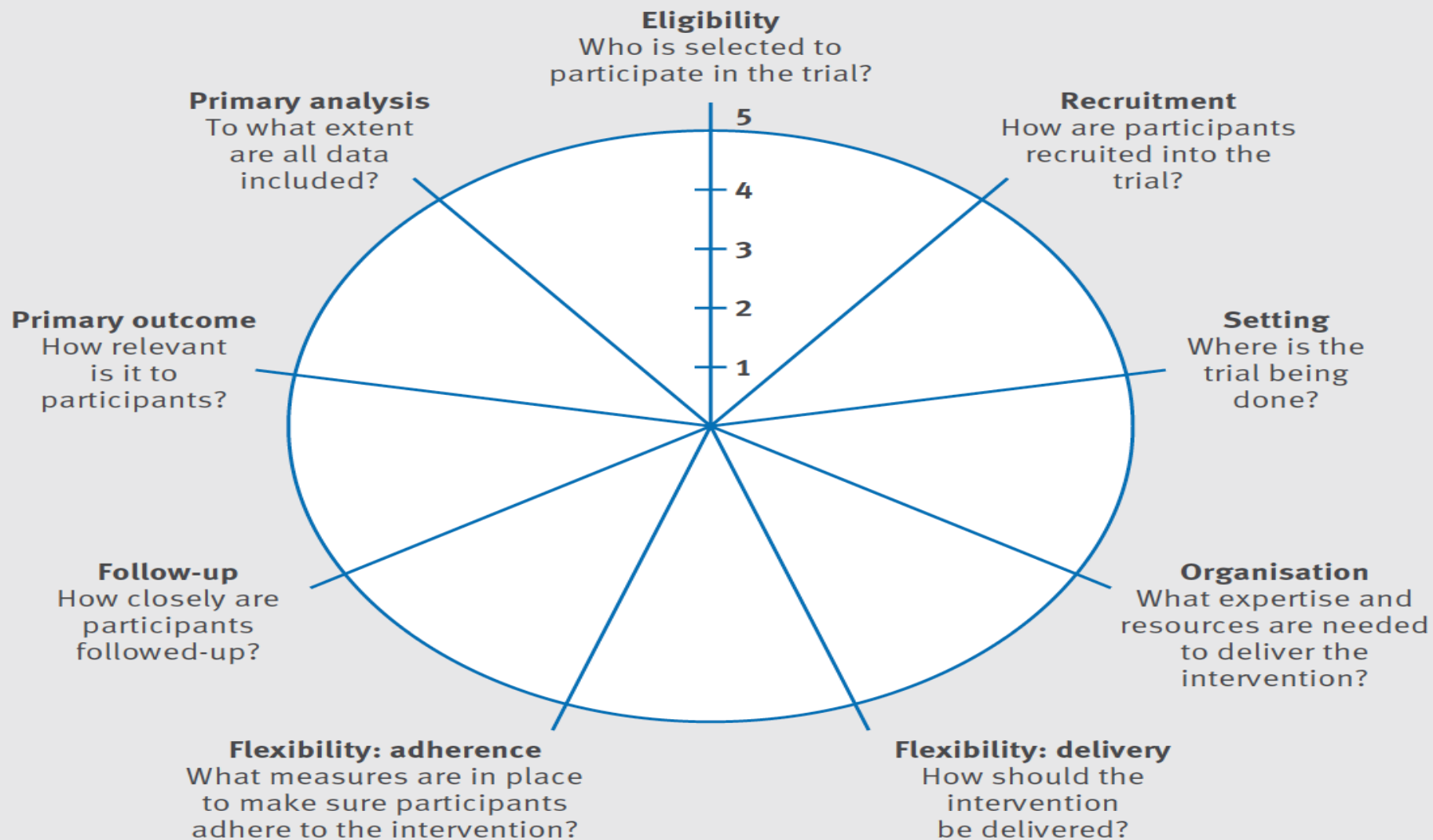


- Eligible patient identification via EHR
- Real-time 'trial alerts' embedded in EHR
- Group recruitment models vs patients 'owned' by primary MD
- Special screening and enrollment clinics
- Online e-consent with comprehension questions

Efficient Trial Conduct



- Risk-based site monitoring
- Streamlined serious adverse event reporting
- Technology to facilitate trial tracking



The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.

-Loudon K, et al. *BMJ* 2015;350: 2147

Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial

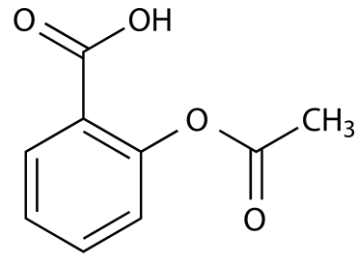
PCORnet's First Pragmatic Clinical Trial



pcornet

The National Patient-Centered Clinical Research Network

Background



Acetylsalicylic acid



2014 AHA/ACC NSTEMI-ACS Guidelines



I IIa IIb III



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

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

ASA 81 mg QD

RANDOMIZATION

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

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

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 use of an oral anticoagulant or ticagrelor
- ✗ Female patients who were pregnant or nursing

Endpoint Confirmation

Data sources:

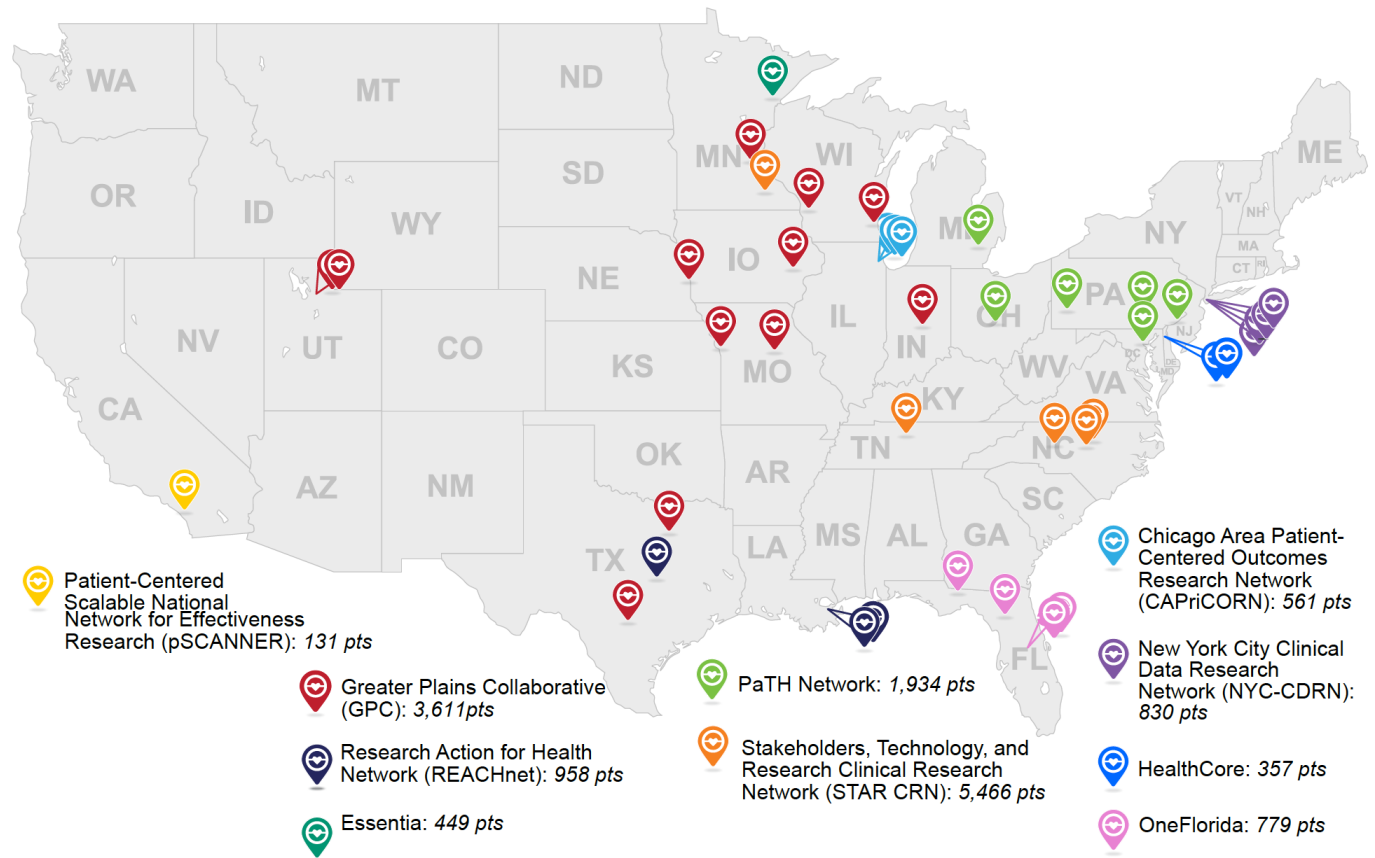
- Participant report
- EHR data
- Claims data →

1. Private insurance (Aetna, Anthem, Humana) data
2. CMS (fee-for-service Medicare) data

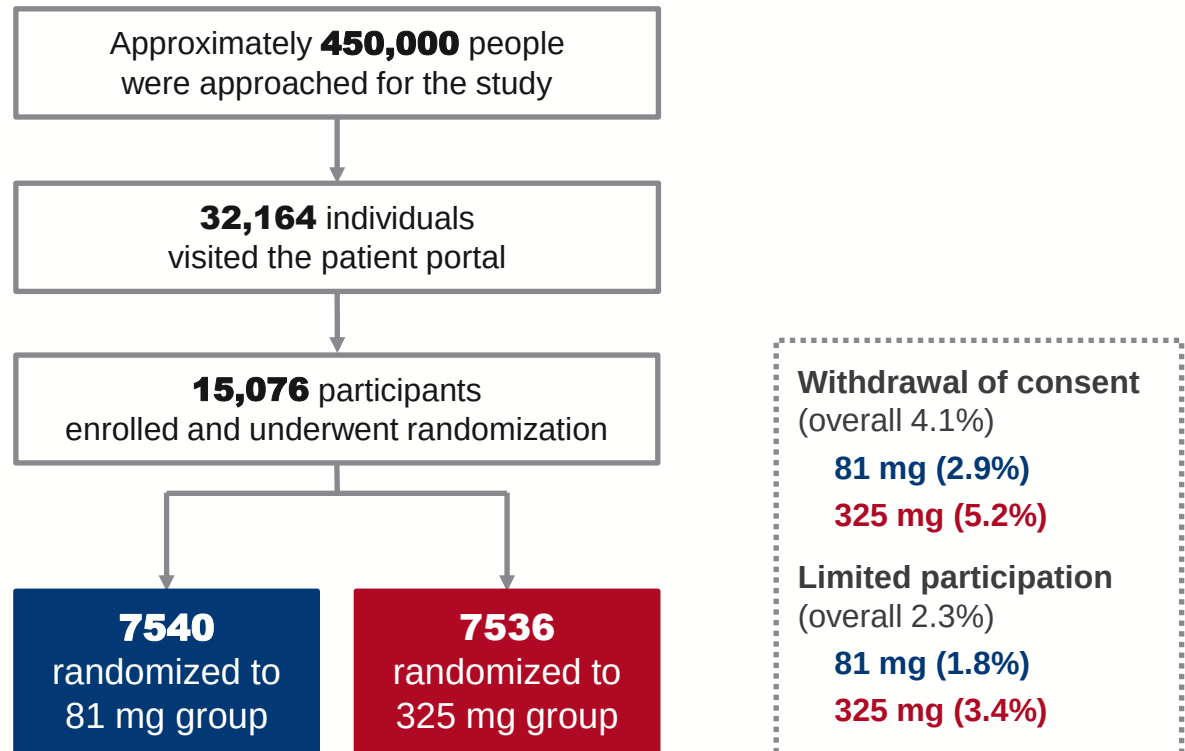
 Nonfatal endpoints defined by *ICD-10* algorithms

 All-cause death captured by EHR, health insurance claims, or proxy

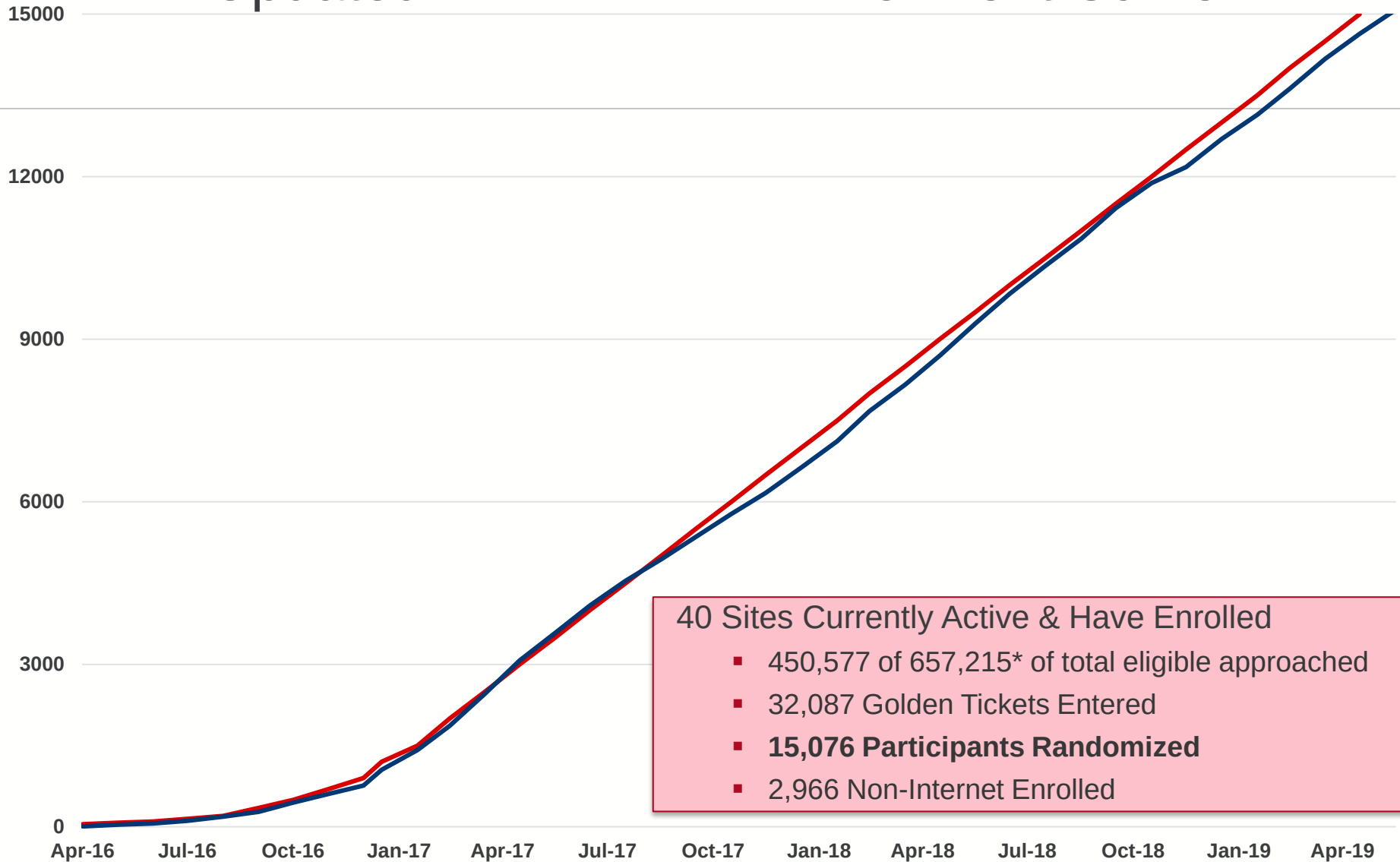
40 Study Centers within PCORnet®



Study Flow



Updated ADAPTABLE Enrollment Curve



Baseline Characteristics

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

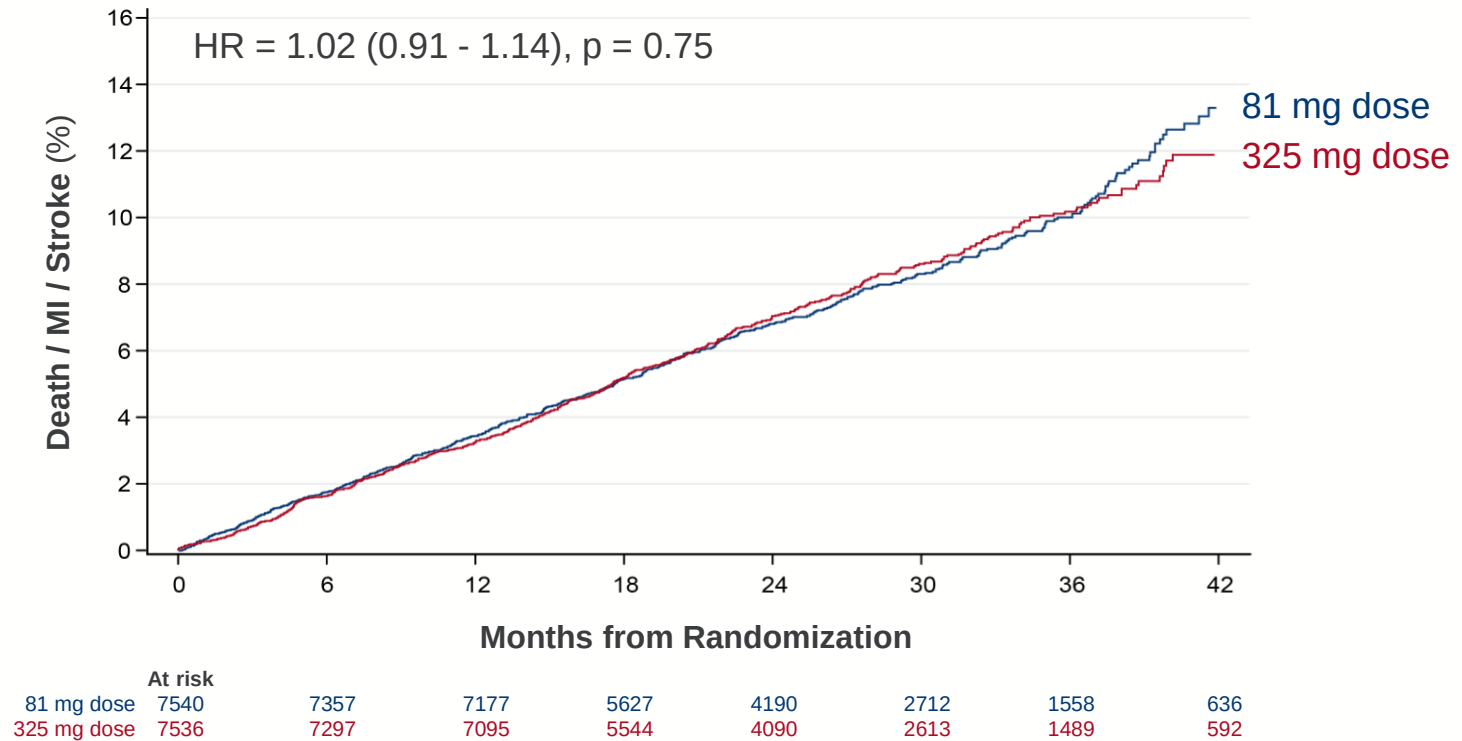
Medical History

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

Medical history was obtained from EHR queries, with look back of 5 years

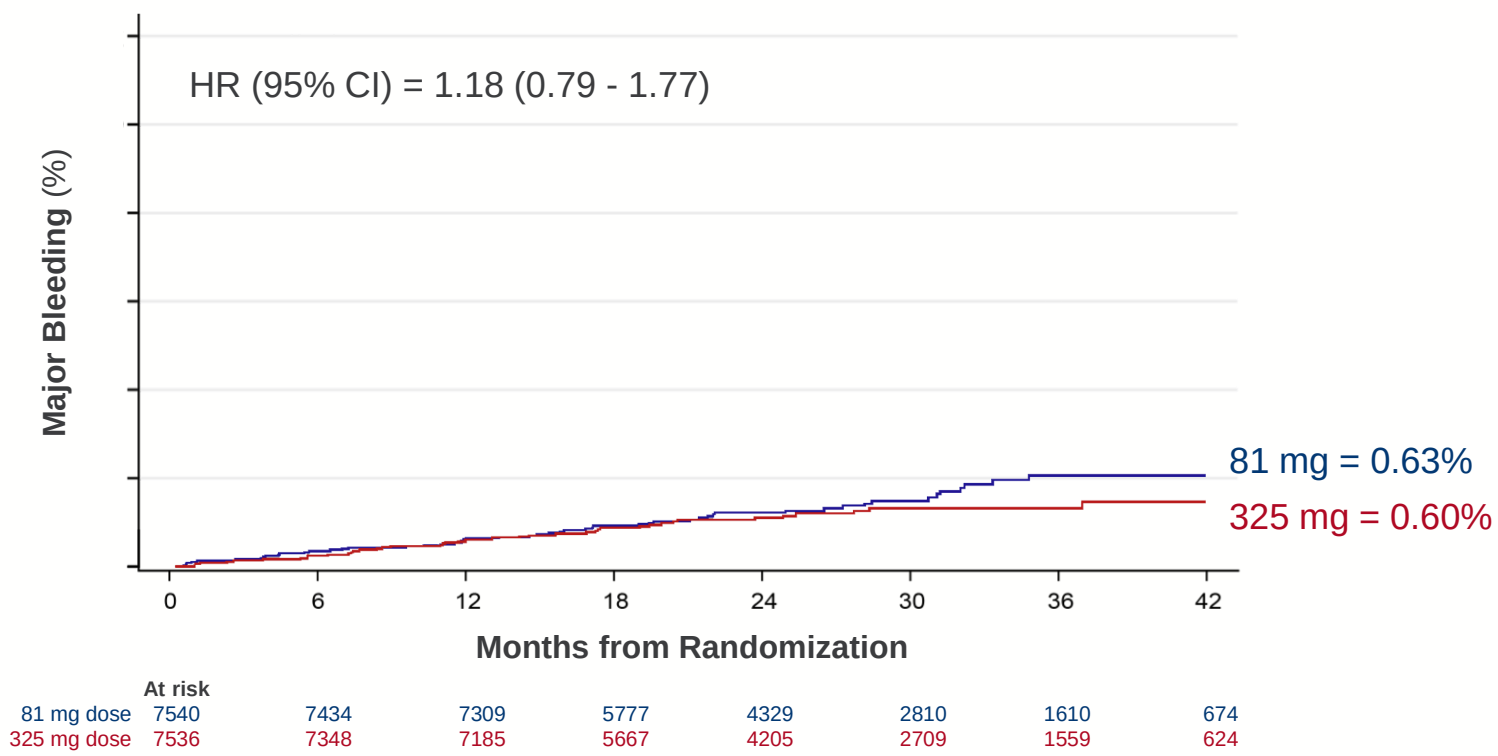
Primary Effectiveness Endpoint

(All-cause death, hospitalization for MI, or hospitalization for stroke)



Primary Safety Endpoint

(Hospitalization for major bleeding with associated blood product transfusion)



Study Medication in ADAPTABLE

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

* 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)

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



Disrupting the Norm

Traditional Trials vs. ADAPTABLE

	Traditional	ADAPTABLE
Inclusion/Exclusion criteria review	Sample via monitor visit	EHR and CDM (Common Data Model)
Representative cohort	Narrow	Broad
Consent	In Person Facilitated	Patient-directed
Comprehension tested	No	Yes
Format	Paper	Electronic (e-consent)
Data collection	Patient-reported Site-recorded	Patient-reported CDM
Source documents	Only seen by site	EHR data via CDM
Endpoint adjudication	Yes	No
Patient involvement	Participants only	Protocol design, DSMB, analyses, dissemination