ADAPTABLE Aspirin Dosing:

A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness

Adaptable

The Aspirin Study

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

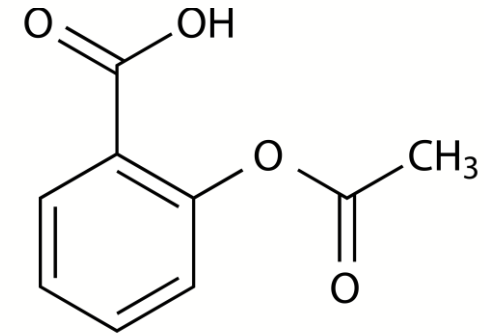
May 15, 2021

ACC Late-Breaking Clinical Trial presentation

AMERICAN COLLEGE of CARDIOLOGY

pcornet

Background



Acetylsalicylic acid

2014 AHA/ACC NSTE-ACS Guidelines

I	IIa	IIb	III
X			

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

Adaptable

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

American Heart Association. Learn and Live

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 Objectives 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

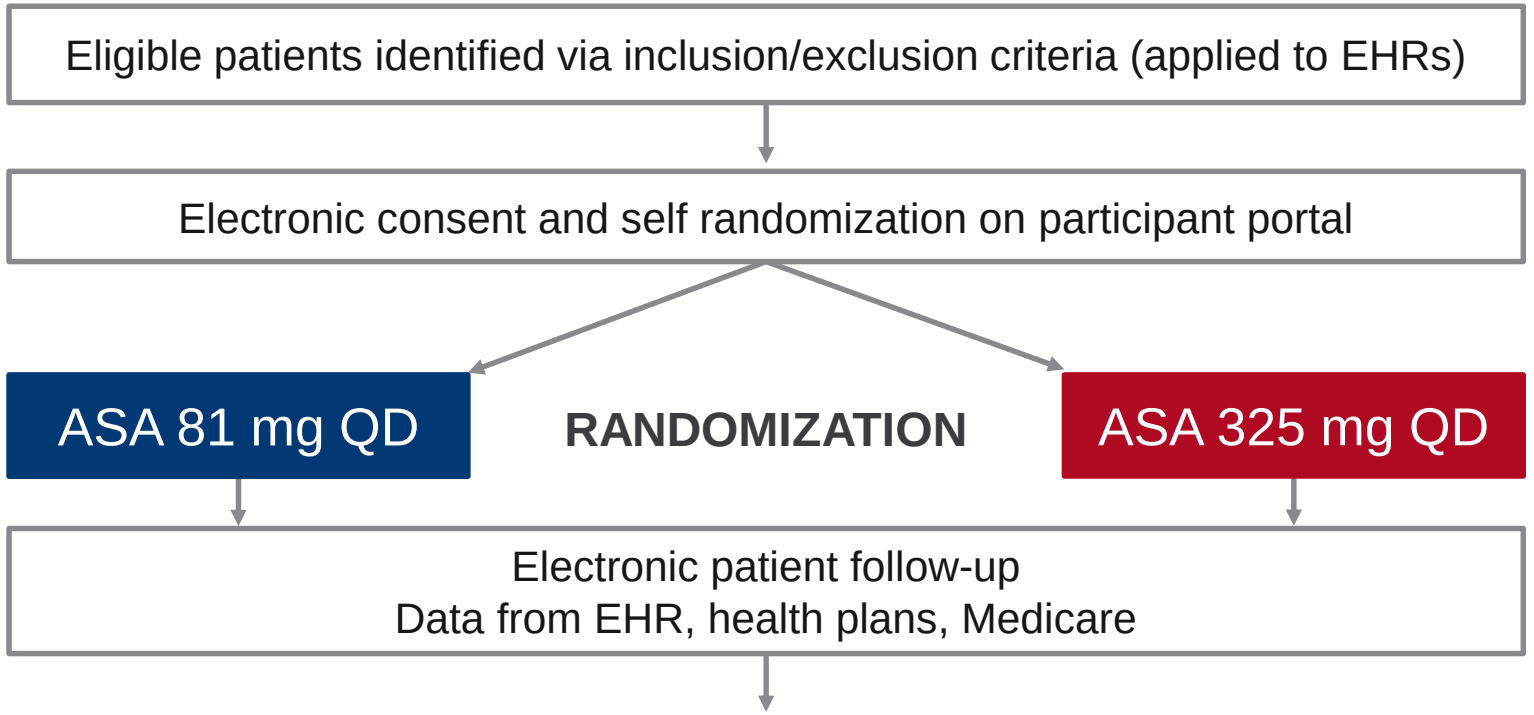
- **Primary Safety Endpoint:** Hospitalization for major bleeding that was associated with a blood product transfusion

Statistical Considerations

- **Final Trial Sample Size = 15,000**
  - At least 88% power to detect 15% RRR, assuming primary effectiveness outcome rate of 4.6% per year in higher-risk arm
  - Minimum follow-up = 18 mo; maximum follow-up = 50 mo
- **Statistical Analysis Plan**
  - Intention-to-treat
  - Cumulative event rates accounting for competing risks of death
  - Cox proportional hazards models for event-free survival

ADAPTABLE Study Design

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



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

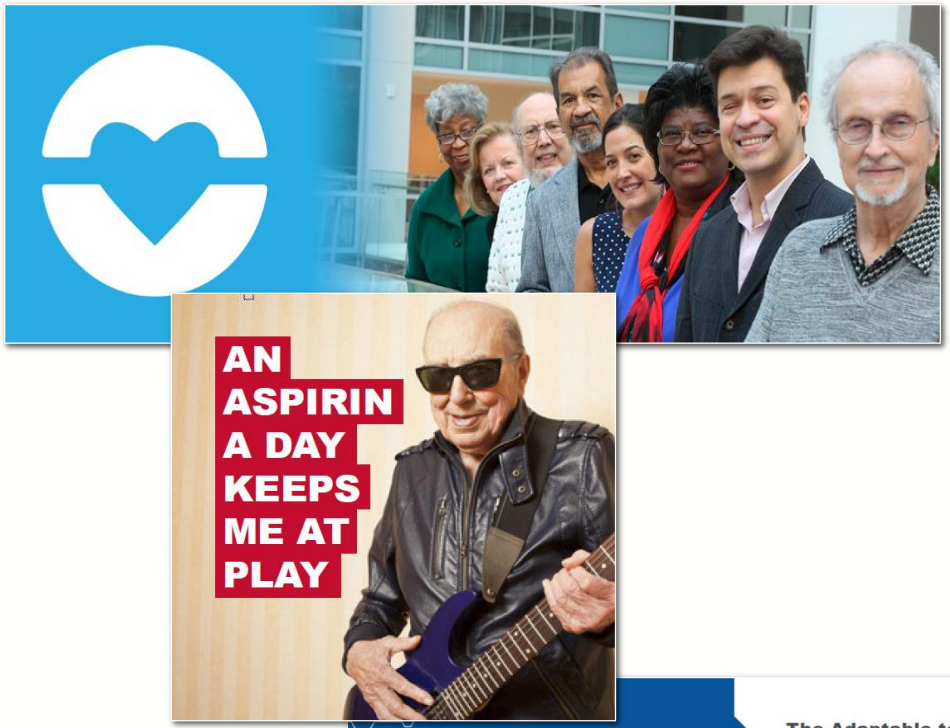
- ✓ Age ≥ 65 years
- ✓ Creatinine ≥ 1.5 mg/dL
- ✓ Diabetes mellitus
- ✓ Known 3-vessel CAD
- ✓ Cerebrovascular disease
- ✓ Peripheral artery disease
- ✓ Current smoker
- ✓ Known LVEF < 50%
- ✓ Chronic systolic or diastolic heart failure
- ✓ SBP ≥ 140 (within past 12 mos)
- ✓ LDL ≥ 130 (within past 12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

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

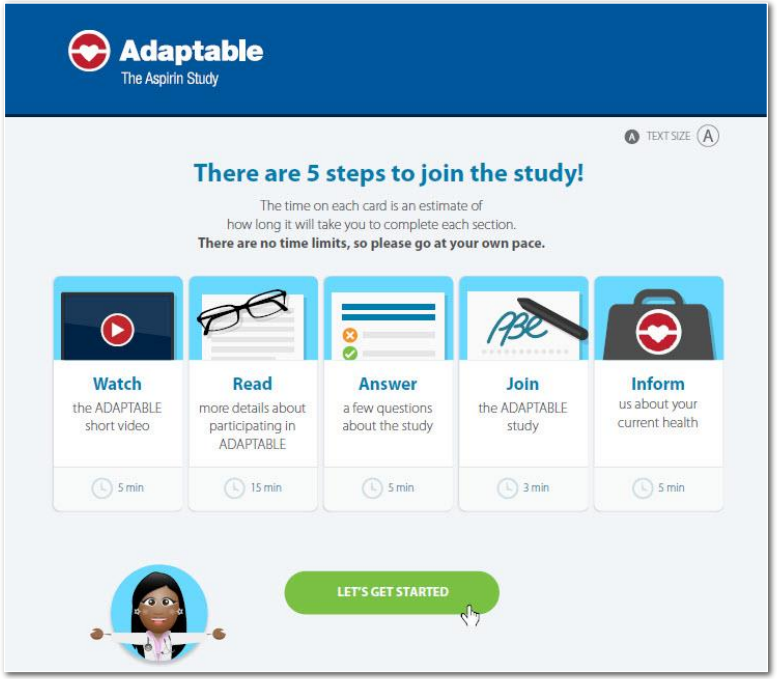
Patient Engagement

PATIENT BLOGS



FACEBOOK LIVE

PATIENT ENGAGEMENT PAVILION



Adaptable

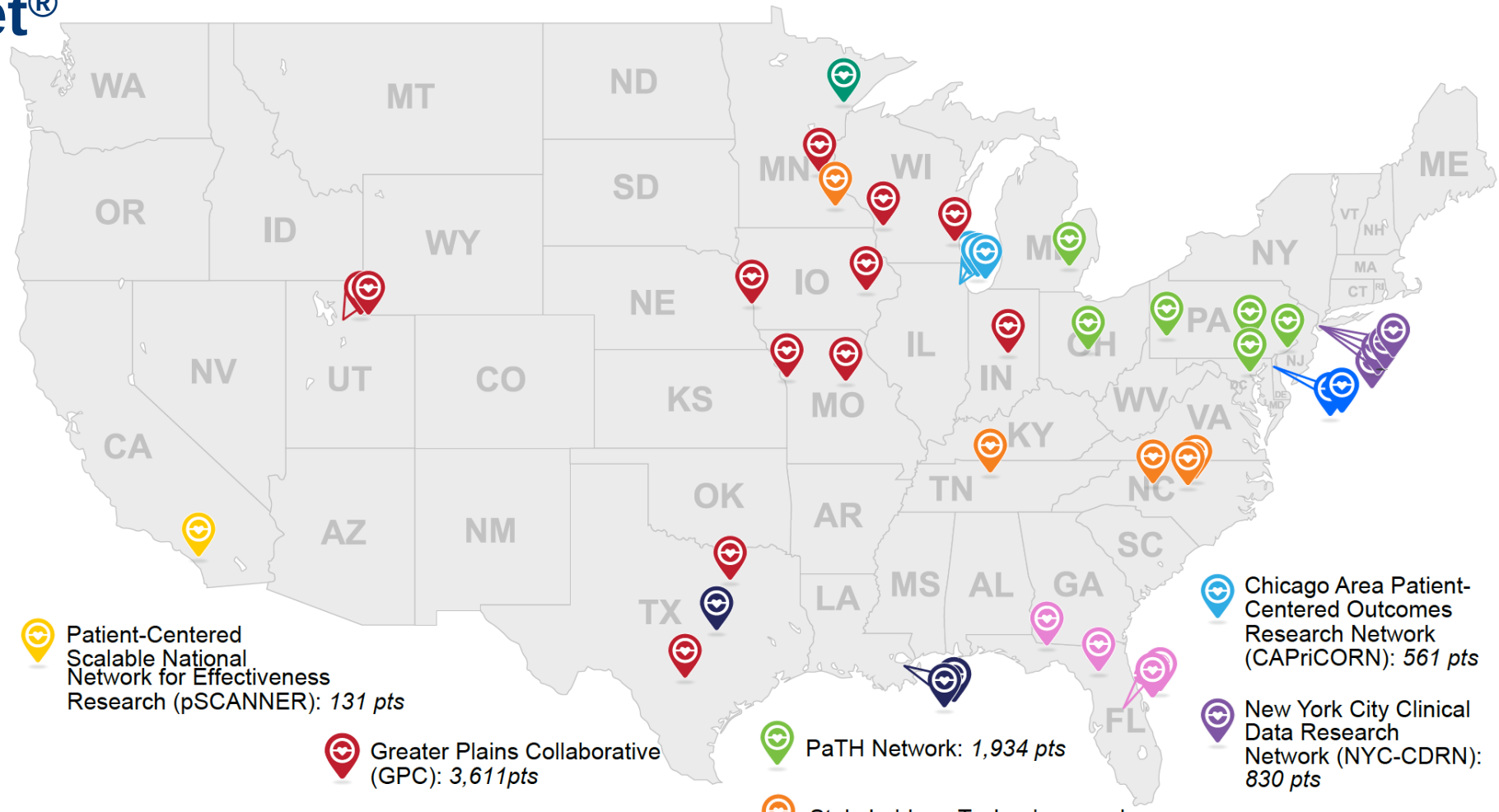
Endpoint Confirmation

- 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®



Patient-Centered Scalable National Network for Effectiveness Research (pSCANNER): *131 pts*

Greater Plains Collaborative (GPC): *3,611pts*

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): *561 pts*

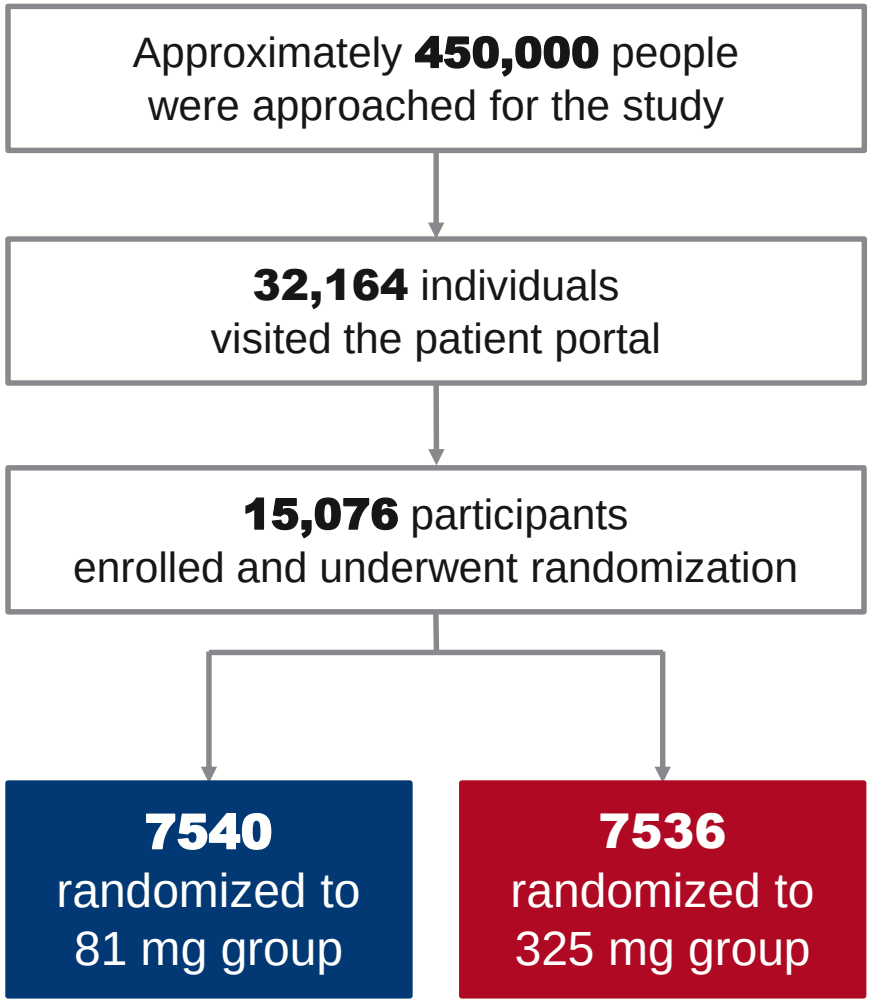
New York City Clinical Data Research Network (NYC-CDRN): *830 pts*

HealthCore: *357 pts*

OneFlorida: *779 pts*

Adaptable

Study Flow



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%)**

Adaptable

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%)

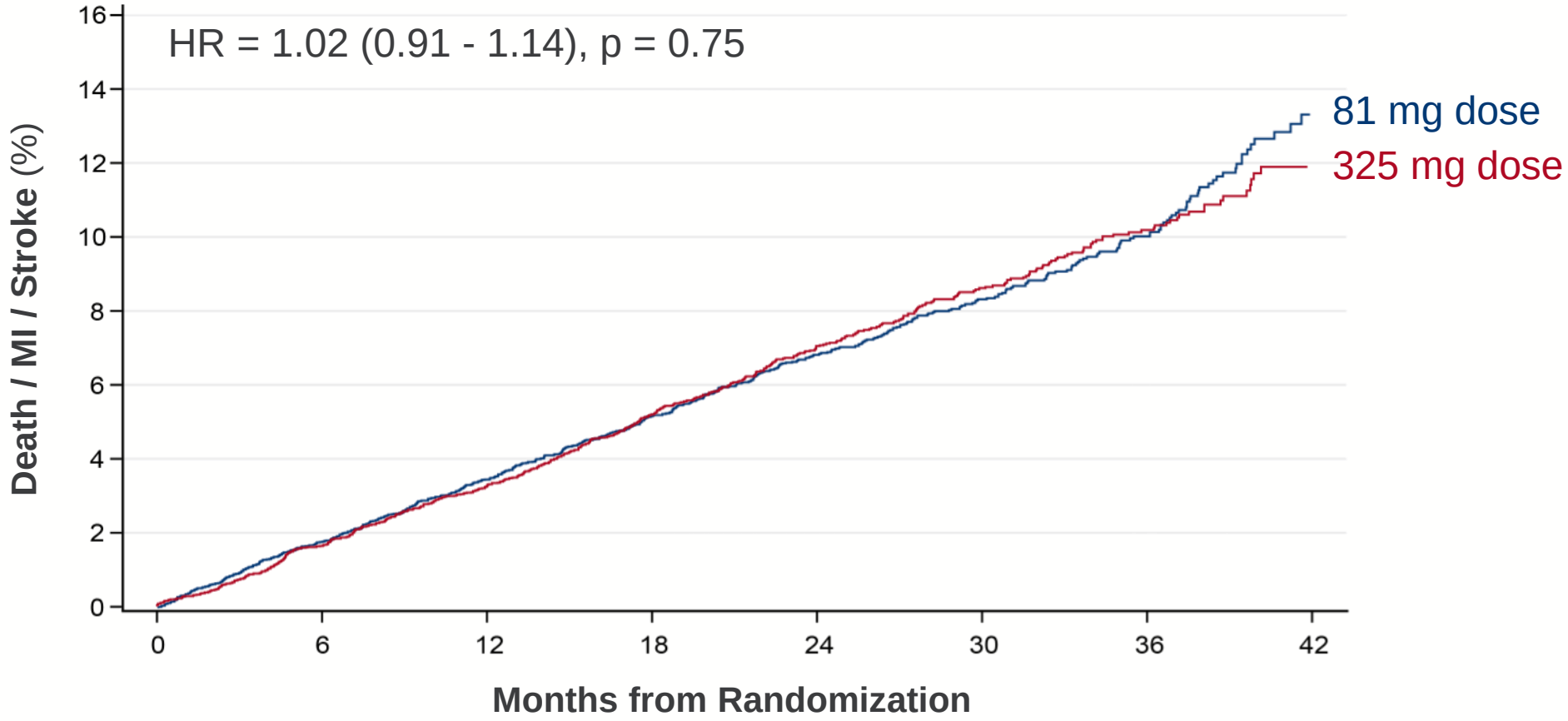
Medical History

	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)

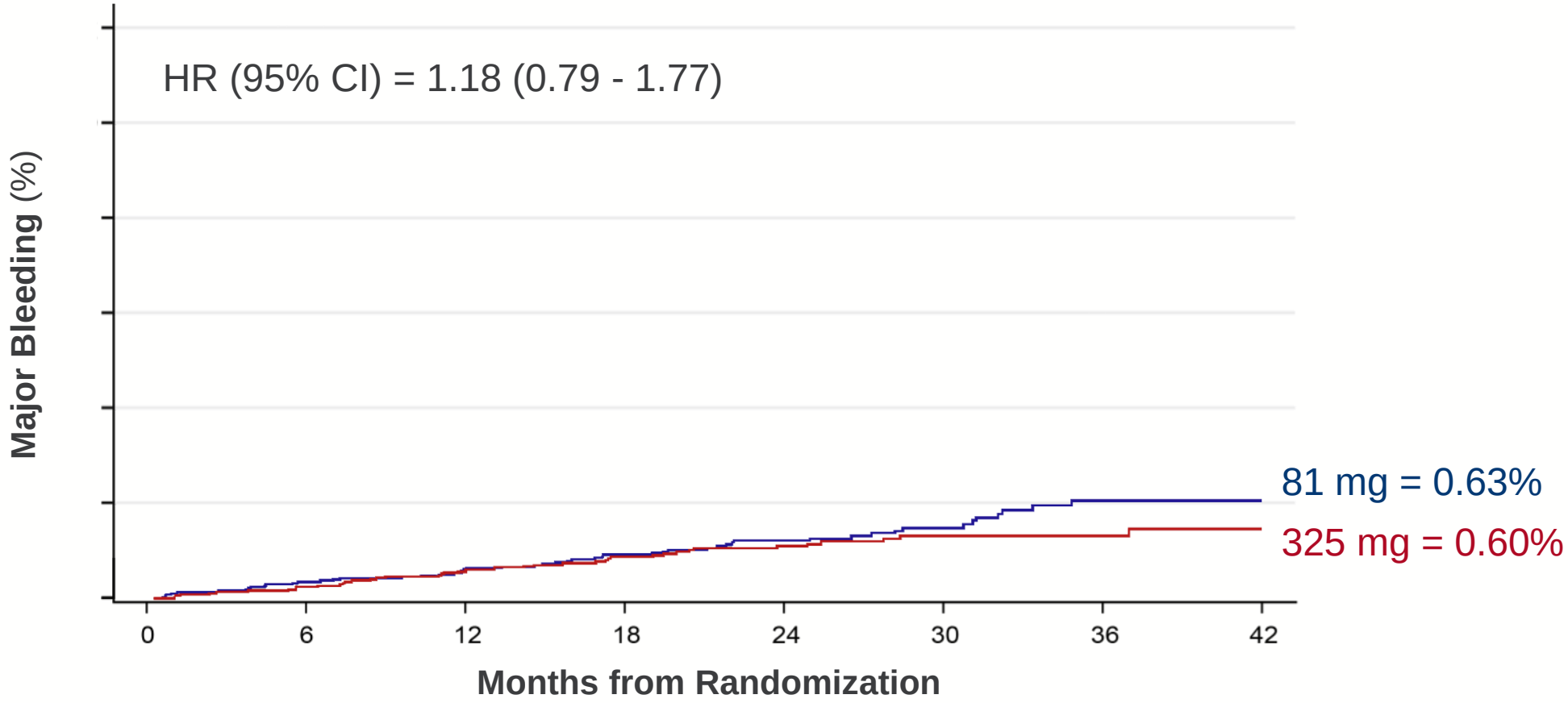


At risk								
81 mg dose	7540	7357	7177	5627	4190	2712	1558	636
325 mg dose	7536	7297	7095	5544	4090	2613	1489	592

Adaptable

Primary Safety Endpoint

(Hospitalization for major bleeding with associated blood product transfusion)



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

Adaptable

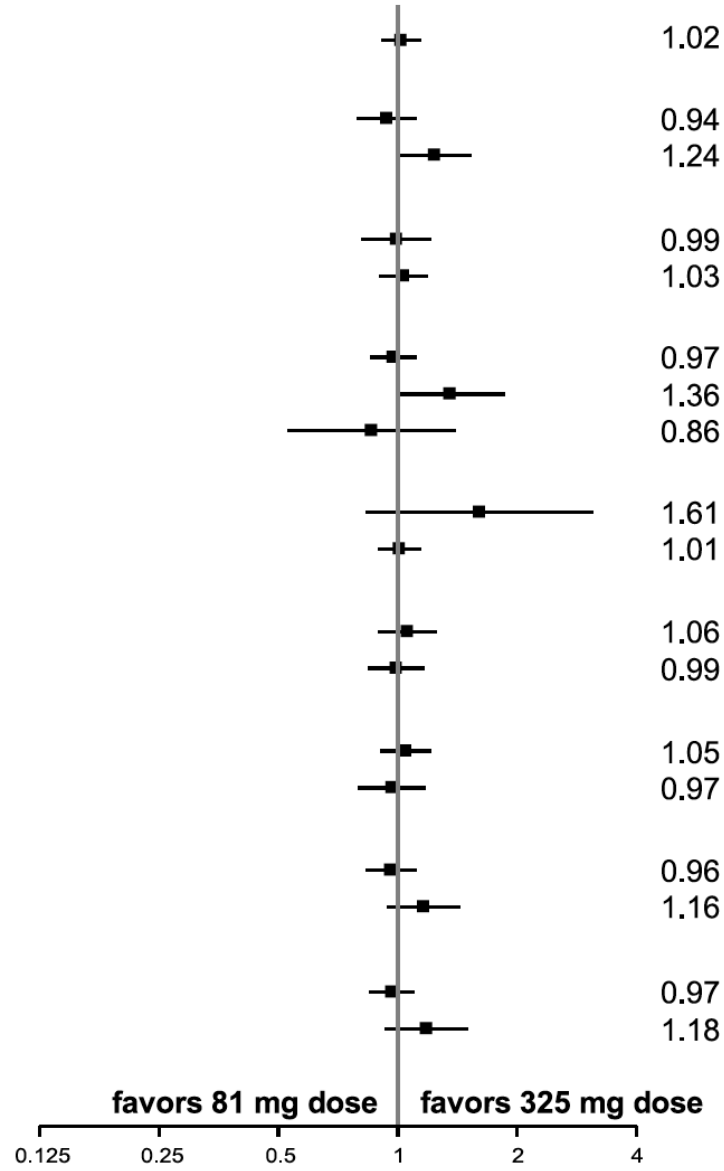
Effectiveness and Safety Outcomes

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

Subgroup Analyses

(Primary effectiveness endpoint)

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



Adaptable

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, assigned aspirin dose	551 days (139 - 737)	650 days (415 – 922)	434 days (139 – 737)
Median days of exposure, any 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)

Sensitivity Analyses

Outcome	**81 mg dose** N (rate)	**325 mg dose** N (rate)	**HR** (95% CI) **325 mg vs 81 mg**
Impact of actual dose taken			
Death / MI / Stroke	**673** (3.6 events per 100 patient-years)	**321** (2.9 events per 100 patient-years)	**1.25** (1.10 - 1.43)

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

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

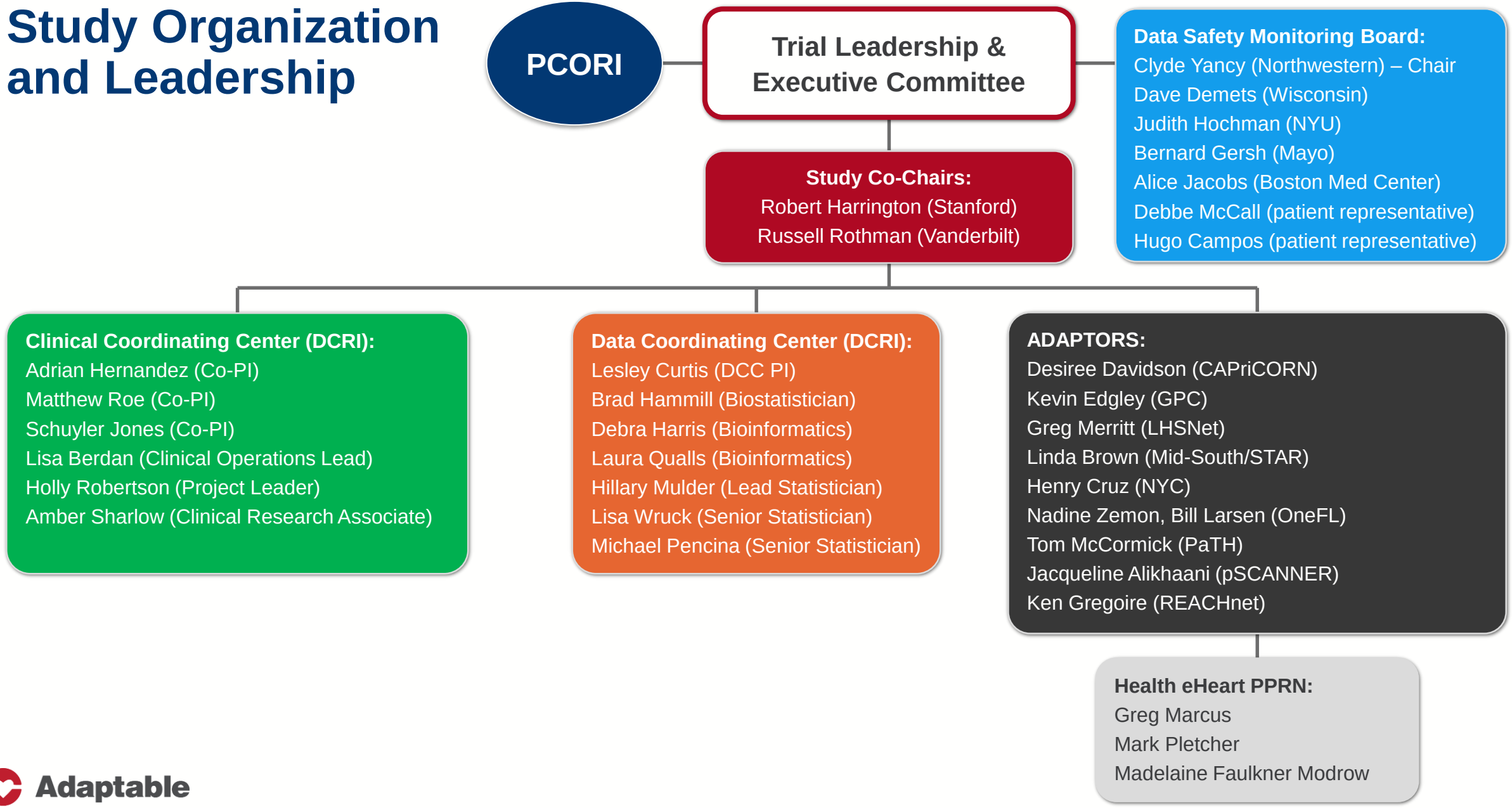
- **If you are resuming aspirin**, starting a lower dose (81 mg) is probably right due to better tolerability and we did not find conclusive evidence that higher dose is better

- **If you are tolerating 325 mg now**, staying on this dose may be okay and associated with moderate benefit

Thanks!

- The dedication of thousands of participants
- Our partners (ADAPTORs, investigators, researchers)
- PCORI

Study Organization and Leadership



Adaptable

Simultaneous Publication