TAILOR PCI

Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention

Naveen Pereira MD, FACC, FAHA, FRCPE, Professor of Medicine, Mayo Clinic
On Behalf of the TAILOR PCI RESEARCH GROUP
Funded by National Heart, Lung, and Blood Institute and Mayo Clinic

Background

CLOPIDOGREL

CYP2C19

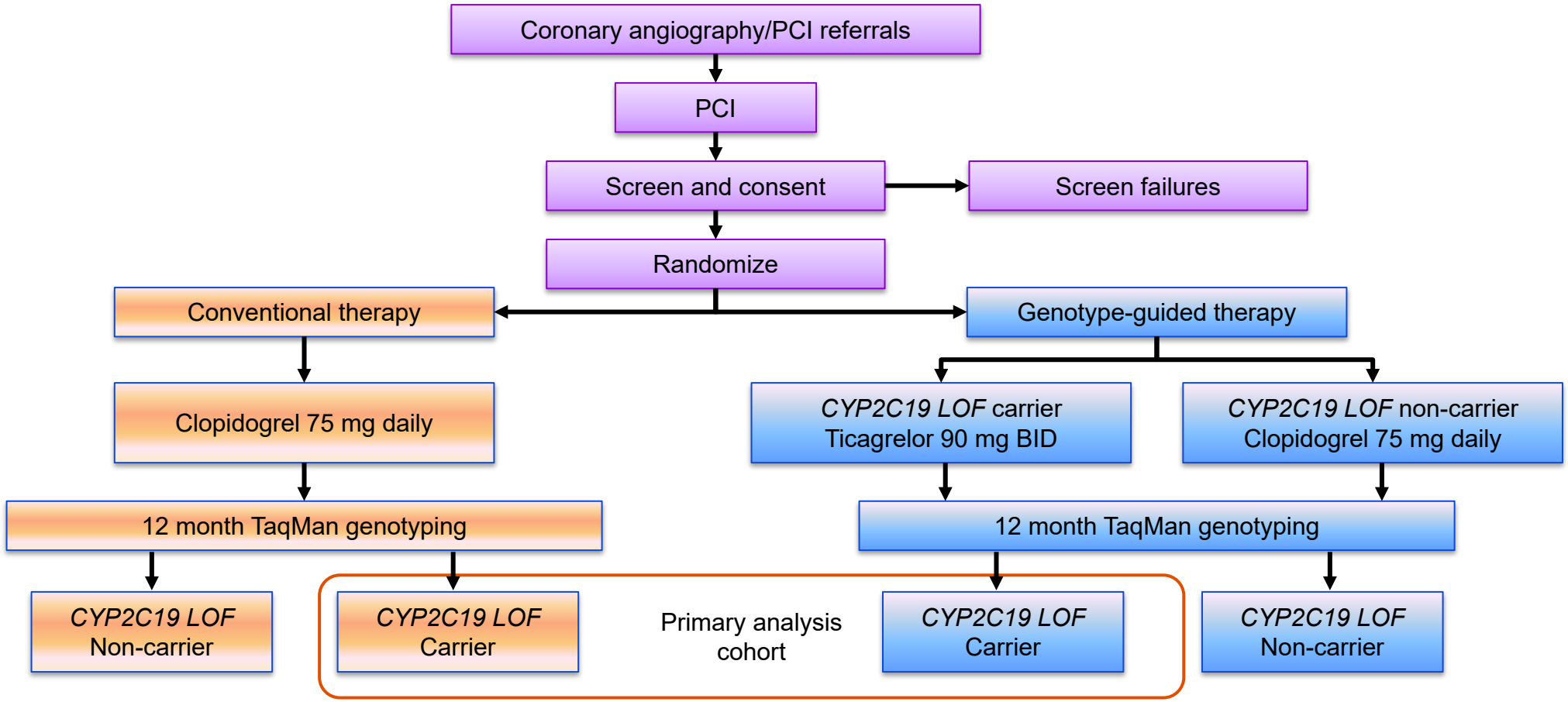
Prodrug → Active metabolite → ↑ Ischemic Events

CYP2C19 LOF carriers

BLACK BOX WARNING:

- IDENTIFY
- ALTERNATIVE THERAPY

Study Design

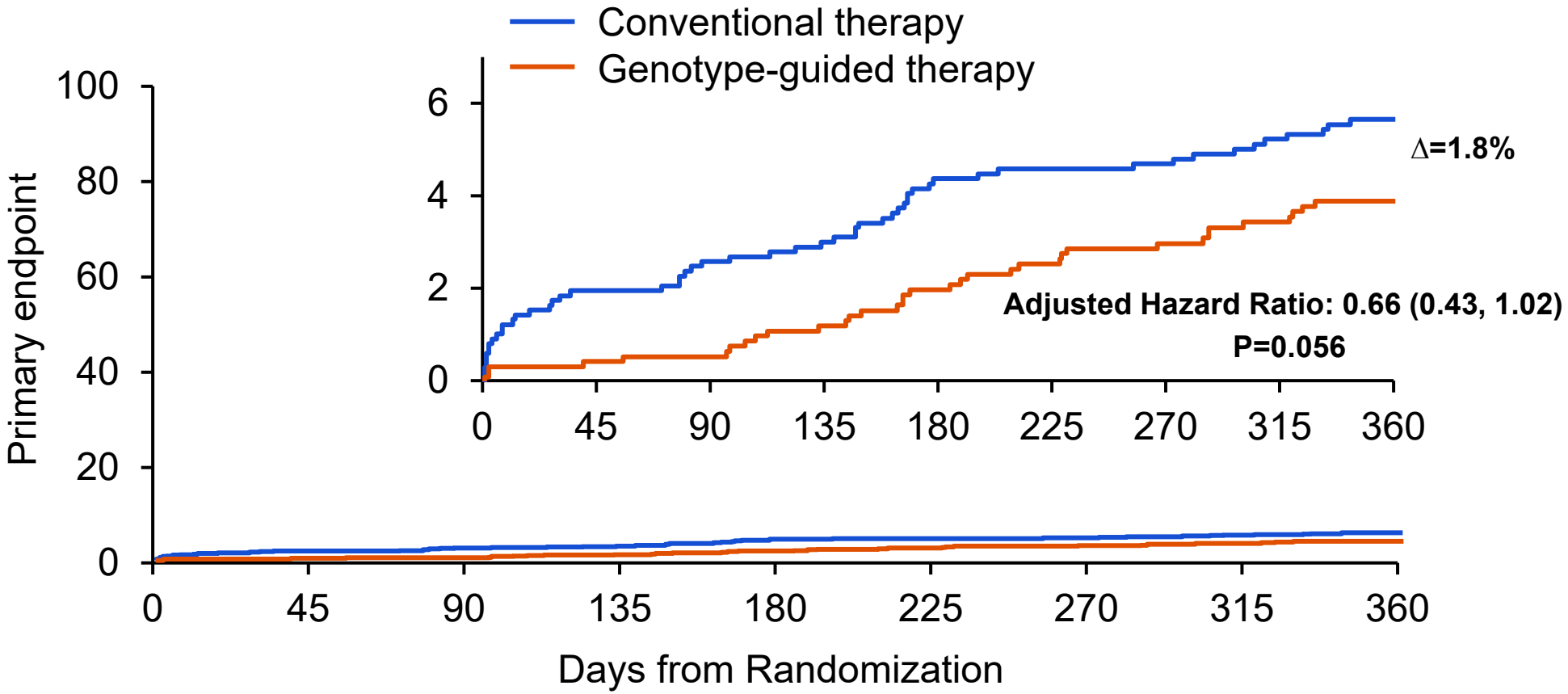


Study Endpoints

- Primary endpoint was the composite of cardiovascular death, myocardial infarction, stroke, definite or probable stent thrombosis, and severe recurrent ischemia
  - within 1 year for TAILOR PCI trial
  - beyond 1 year after index PCI for the extended follow-up
- Safety endpoint was major or minor bleeding as defined by the TIMI criteria
- Study endpoints were adjudicated by a blinded, central committee and assessed at
  - hospital discharge,1-month, 6-months and 12-months post-PCI by telephone or medical record review
  - extended follow-up was conducted at 18 and 24 months, or at a single post 24-month assessment

Primary Endpoint (TAILOR PCI trial)

Composite of CV death, MI, stroke, stent thrombosis, severe recurrent ischemia



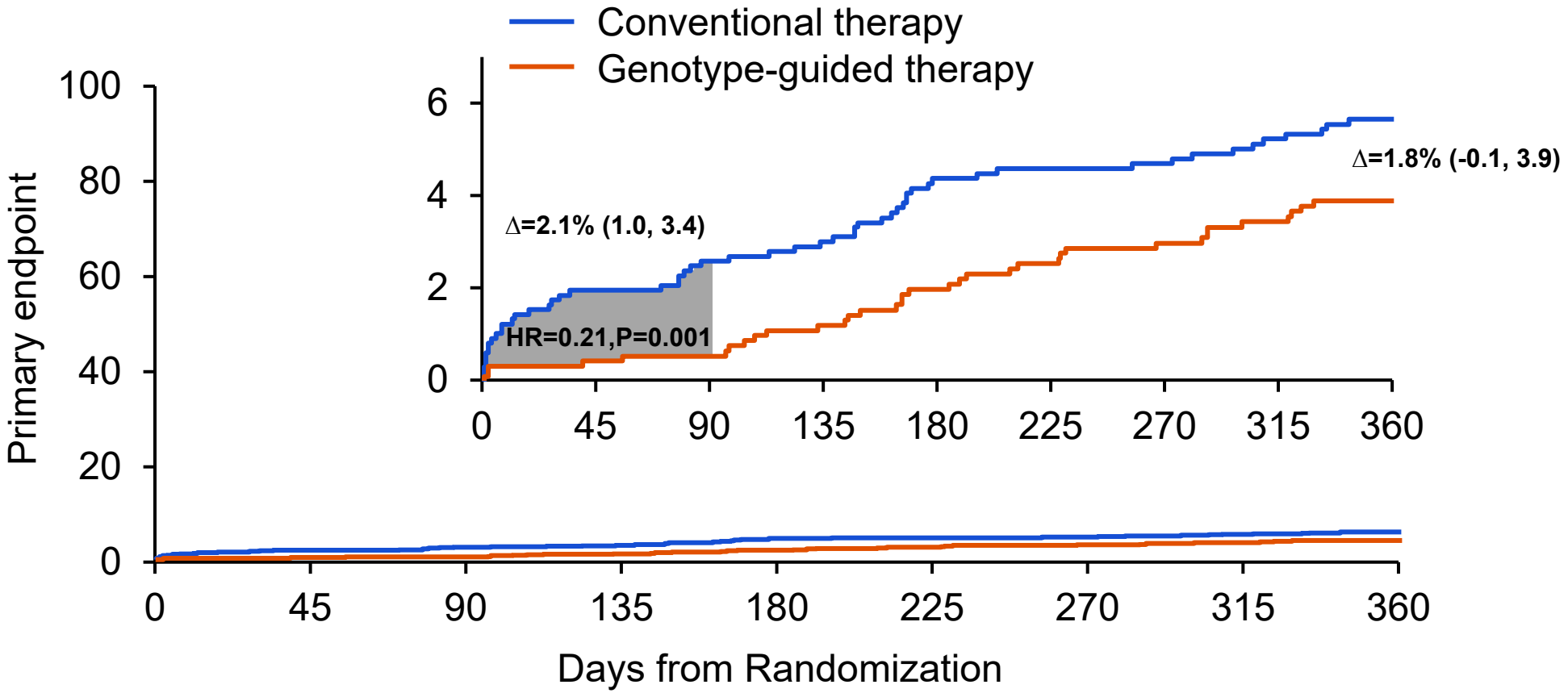
Conventional therapy	946	906	898	894	876	867	864	859	604
Genotype-guided therapy	903	875	870	863	854	838	833	824	556

TAILOR PCI

Data From: Pereira et al, JAMA 2020

Primary Endpoint (TAILOR PCI trial)

Post-Hoc Analysis



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TAILOR PCI Extended Follow-Up Primary Question

- Does identifying loss of function *CYP2C19* allele carriers and altering P2Y12 inhibitor therapy based on *CYP2C19* genotype reduce ischemic outcomes over the long-term (>12 months)?

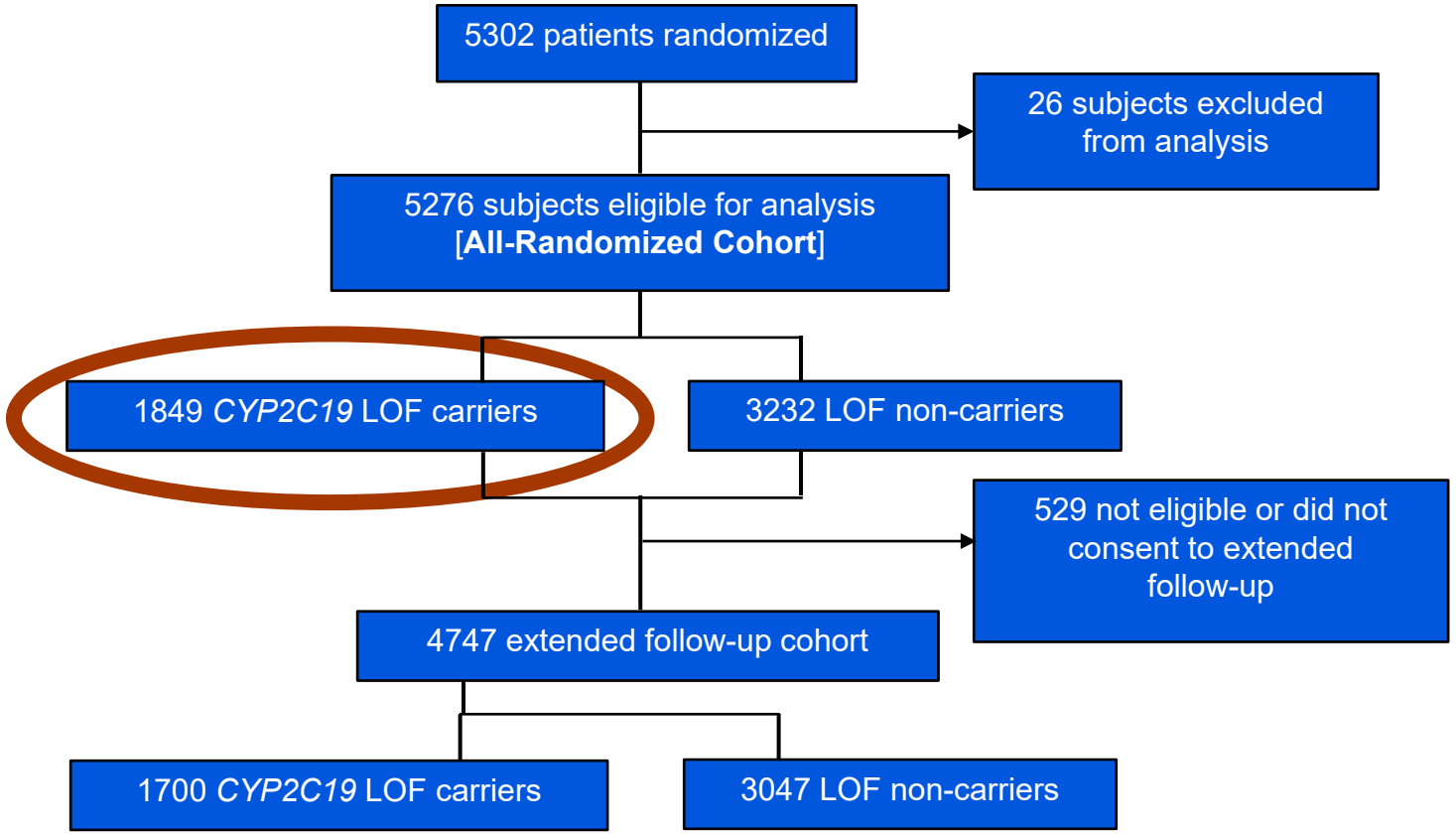
Statistical Analysis (Extended Follow-up)

- Primary analysis
  - Primary cohort: randomized subjects with *CYP2C19 LOF* alleles
  - Cox proportional hazards models adjusted for age, sex, CAD presentation (stable/ACS/NSTEMI) and site of enrollment
- Sensitivity analyses
  - Analysis of multiple events per subject, rather than first event only
  - Time dependent analysis of the genotype guided P2Y12 inhibitor treatment effect over yearly intervals of follow-up

CONSORT diagram

The primary analysis is conducted on the same 1849 patients as in the main trial.

Median (IQR) follow-up in the primary cohort was 39 (24, 53) months - 40 (24, 54) months in the conventional therapy and 38 (24, 52) months in the genotype-guided groups.



Baseline and Procedural Characteristics

	Loss of Function (*CYP2C19* *2/*3) Carriers				All Randomized Subjects			
	Conventional Therapy (n=946)		Genotype-Guided Therapy (n=903)		Conventional Therapy (n=2,635)		Genotype-Guided Therapy (n=2,641)	
	No.	%	No.	%	No.	%	No.	%
Age – median (range)	62 (21,93)		62 (26, 95)		62 (21, 93)		62 (26, 95)	
Sex								
Male	728	77	676	75	1,990	76	1,993	75
Female	218	23	227	25	645	24	648	25
Ethnicity								
Caucasian	447	47	428	47	1,684	64	1,672	64
East Asian	363	38	345	38	592	22	595	23
South Asian	66	7	62	7	120	5	116	4
African-American	20	2	17	2	67	3	57	2
Hispanic or Latino	15	2	14	2	70	3	78	3
Other/Unknown	35	4	36	4	99	4	107	4
Region of enrollment								
United States	380	40	345	38	1,358	52	1,359	51
South Korea	397	42	381	42	650	25	654	25
Canada	161	17	168	19	580	22	577	22
Mexico	8	1	9	1	47	2	51	2

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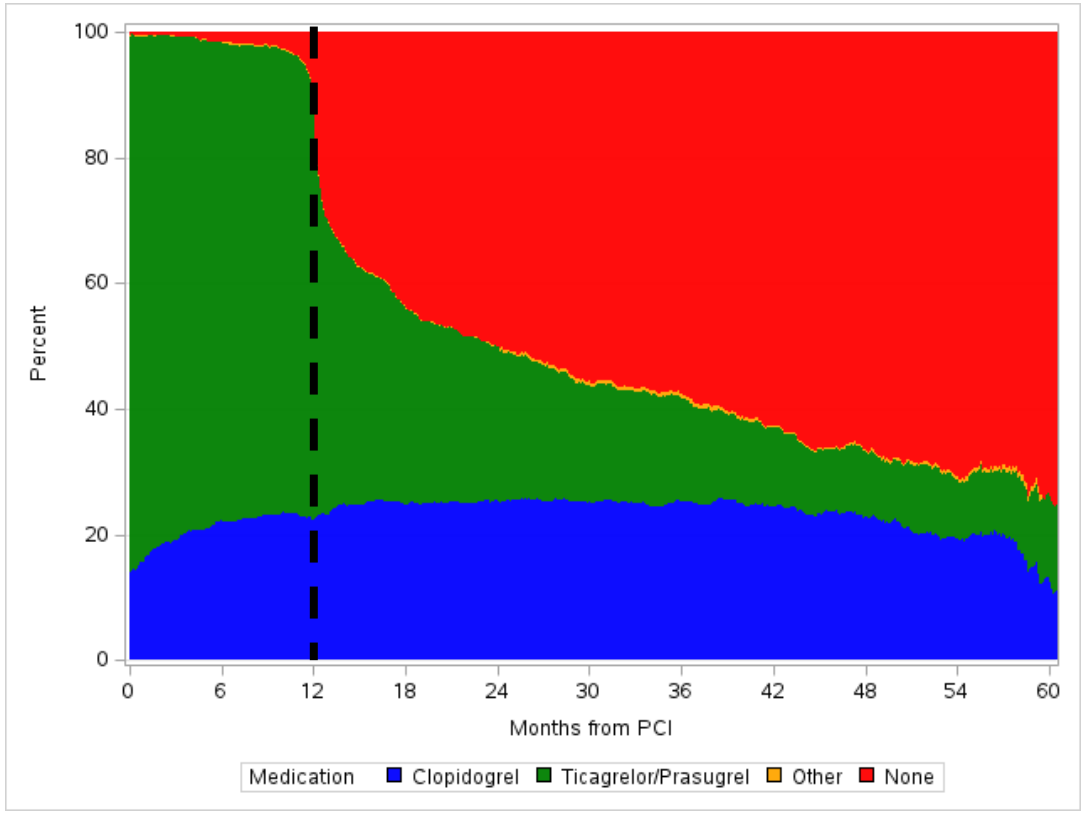
	No.	%	No.	%	No.	%	No.	%
Comorbidities								
Diabetes mellitus	257	27	253	28	695	26	733	28
Hypertension	575	61	531	59	1,667	63	1,636	62
Dyslipidemia	416	44	414	46	1,384	53	1,363	52
Hx of heart failure	105	11	107	12	219	8	225	9
Current smoker	239	25	228	25	637	24	648	25
Prior MI	111	12	112	12	371	14	387	15
Peripheral arterial disease	18	2	20	2	61	2	75	3
Prior PCI	188	20	174	19	612	23	612	23
Prior CABG	53	6	53	6	188	7	196	7
CVA/TIA	27	3	28	3	76	3	72	3
Presentation								
Stable CAD	148	16	127	14	484	18	488	18
ACS	798	84	776	86	2,151	82	2,153	82
Renal Function [MDRD‡] <60	94	11	100	12	296	12	243	10
Multi-vessel disease	343	36	379	42	1,099	42	1,120	43

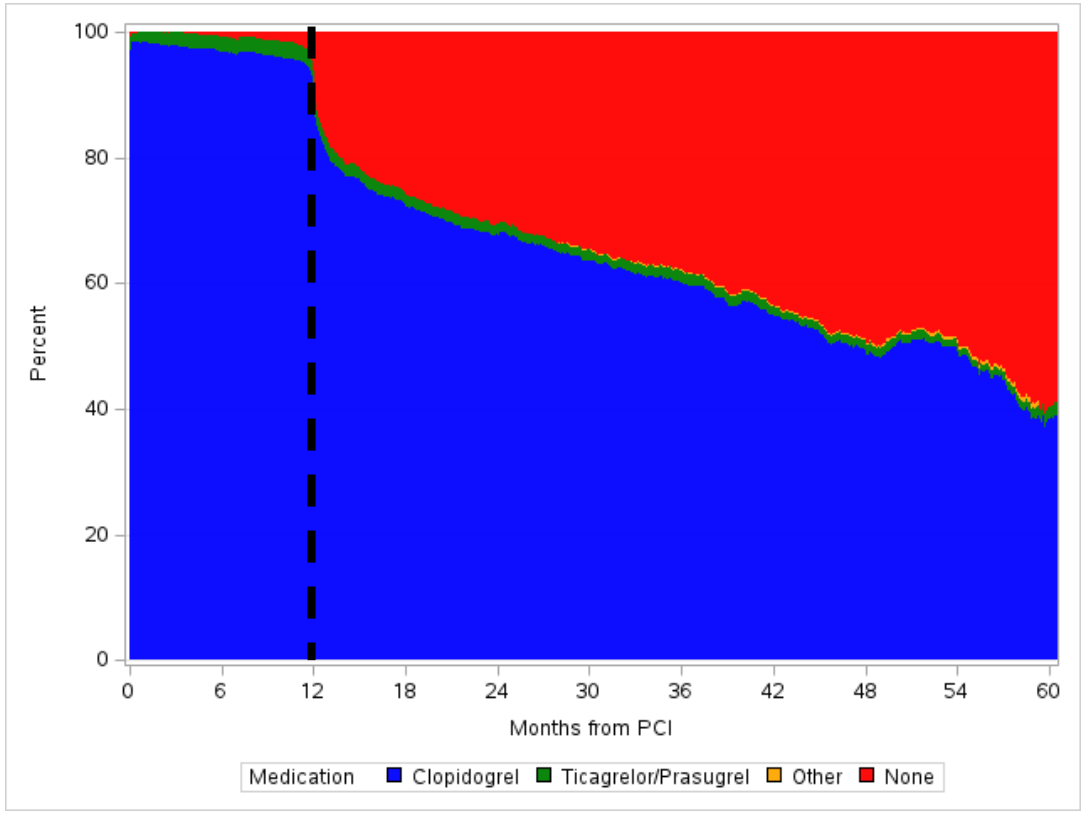
‡MDRD eGFR=186* ([serum creatinine]^(-1.154))*([age, y]^(-0.203))*(0.742^[female])*(1.21^[black])

P2Y12 inhibitor use in the Primary Analysis Cohort
(% of patients on medication)

Genotype-guided Therapy



Conventional Therapy

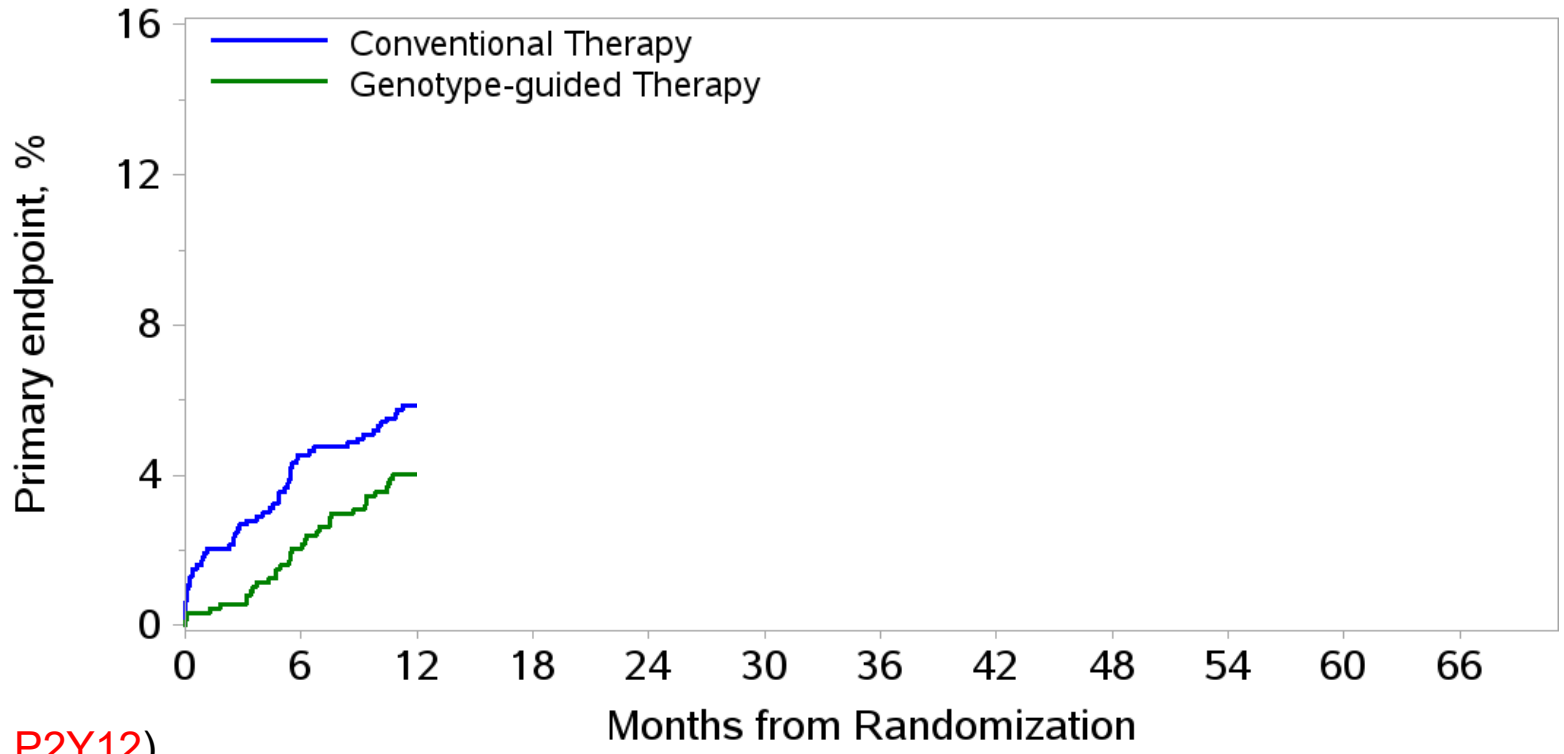


P2Y12 inhibitor use in the Primary Analysis Cohort
(% of person days on medication)

	Genotype-guided arm		Conventional therapy	
	1st year post-PCI	Extended Follow-up	1st year post-PCI	Extended Follow-up
Person Years	852	1911	896	2093
% DAPT	98%	43%	98%	57%
% Ticagrelor	75%	23%	2%	1%
% Clopidogrel	21%	24%	97%	63%
% ASA use	99%	92%	99%	89%

Primary Endpoint (Extended F/U)

Composite of CV death, MI, stroke, stent thrombosis, severe recurrent ischemia

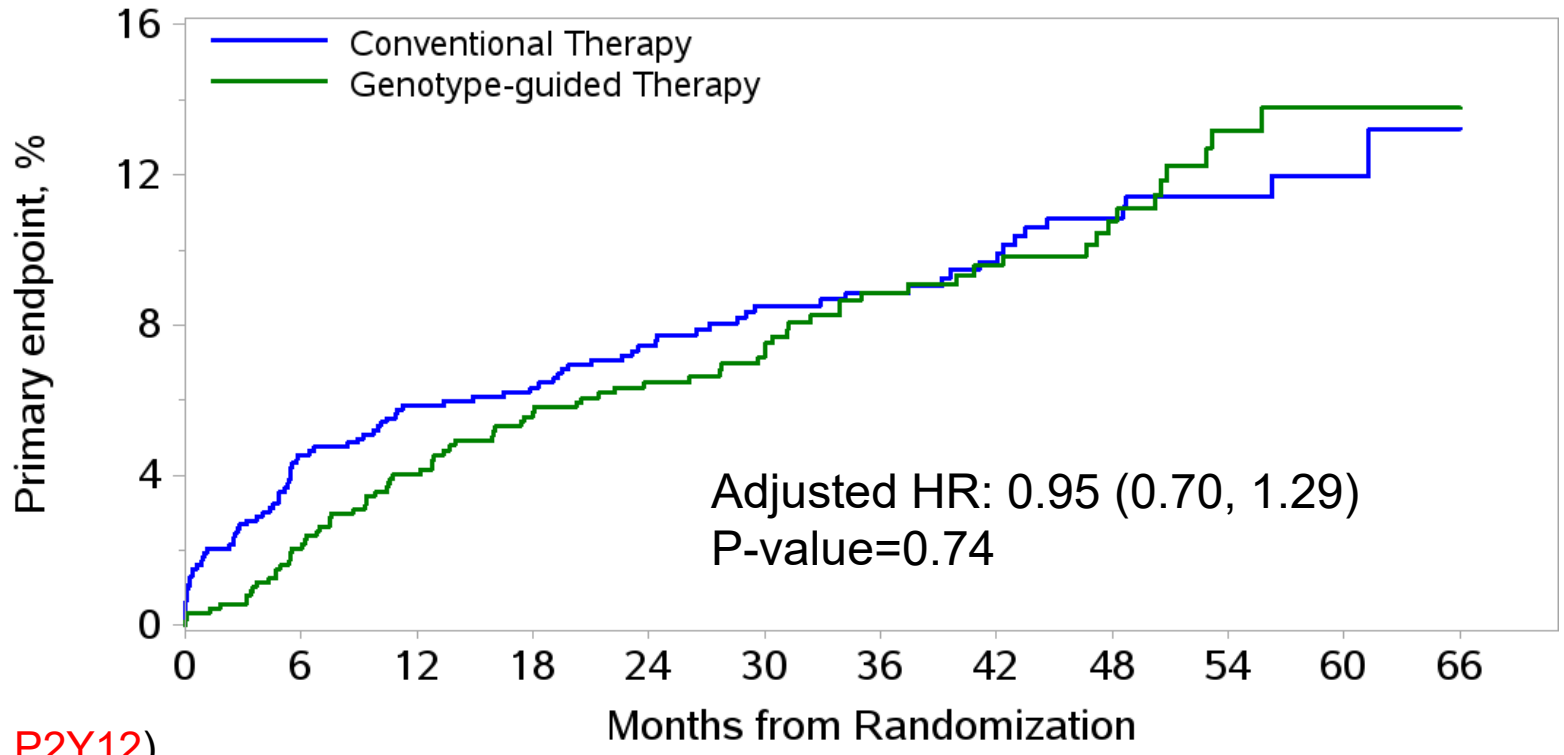


No. at risk (% on P2Y12)

Conventional Therapy	946 (100%)	824 (95%)	698 (69%)	477 (62%)	317 (51%)	91 (40%)
Genotype-guided Therapy	903 (100%)	797 (90%)	653 (50%)	430 (42%)	274 (34%)	71 (27%)

Primary Endpoint (Extended F/U)

Composite of CV death, MI, stroke, stent thrombosis, severe recurrent ischemia



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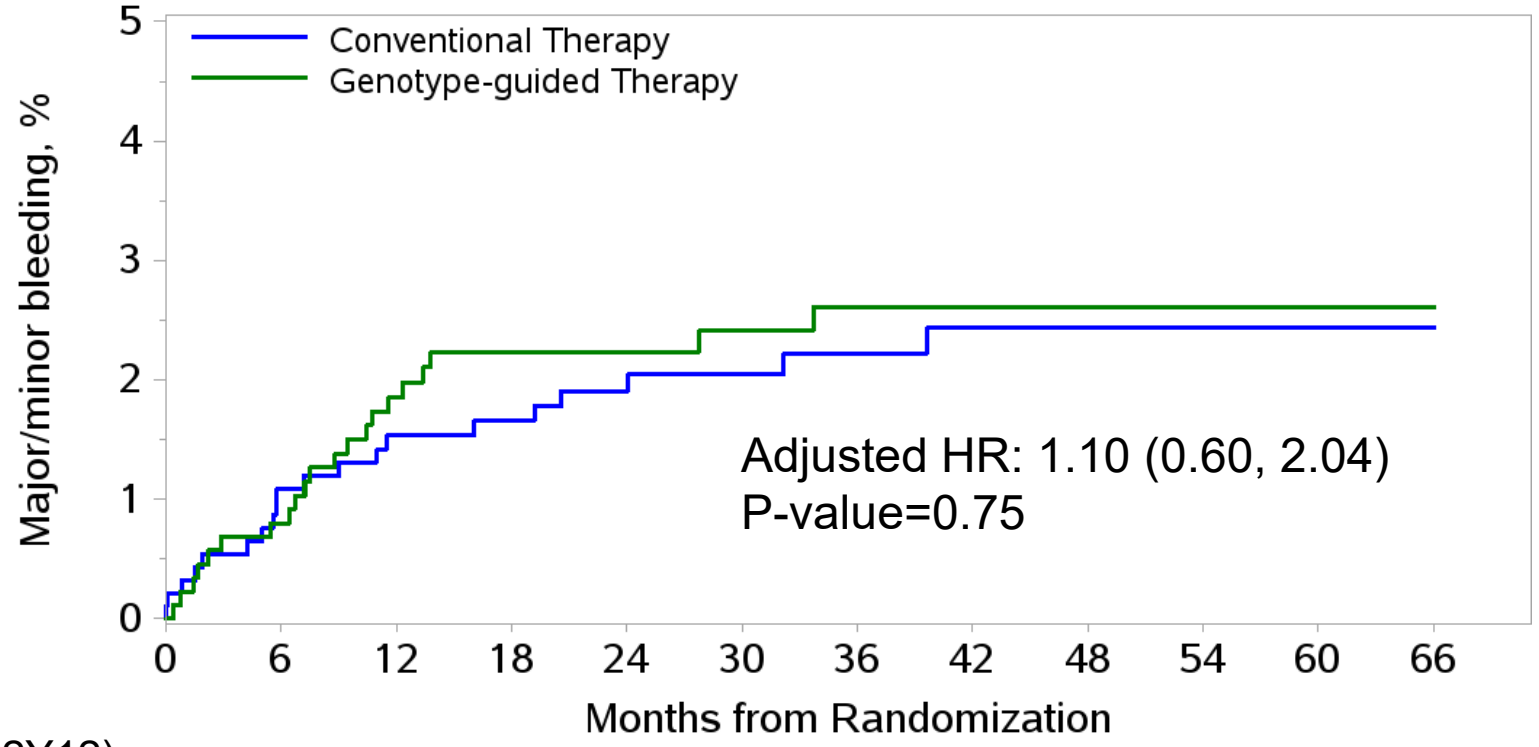
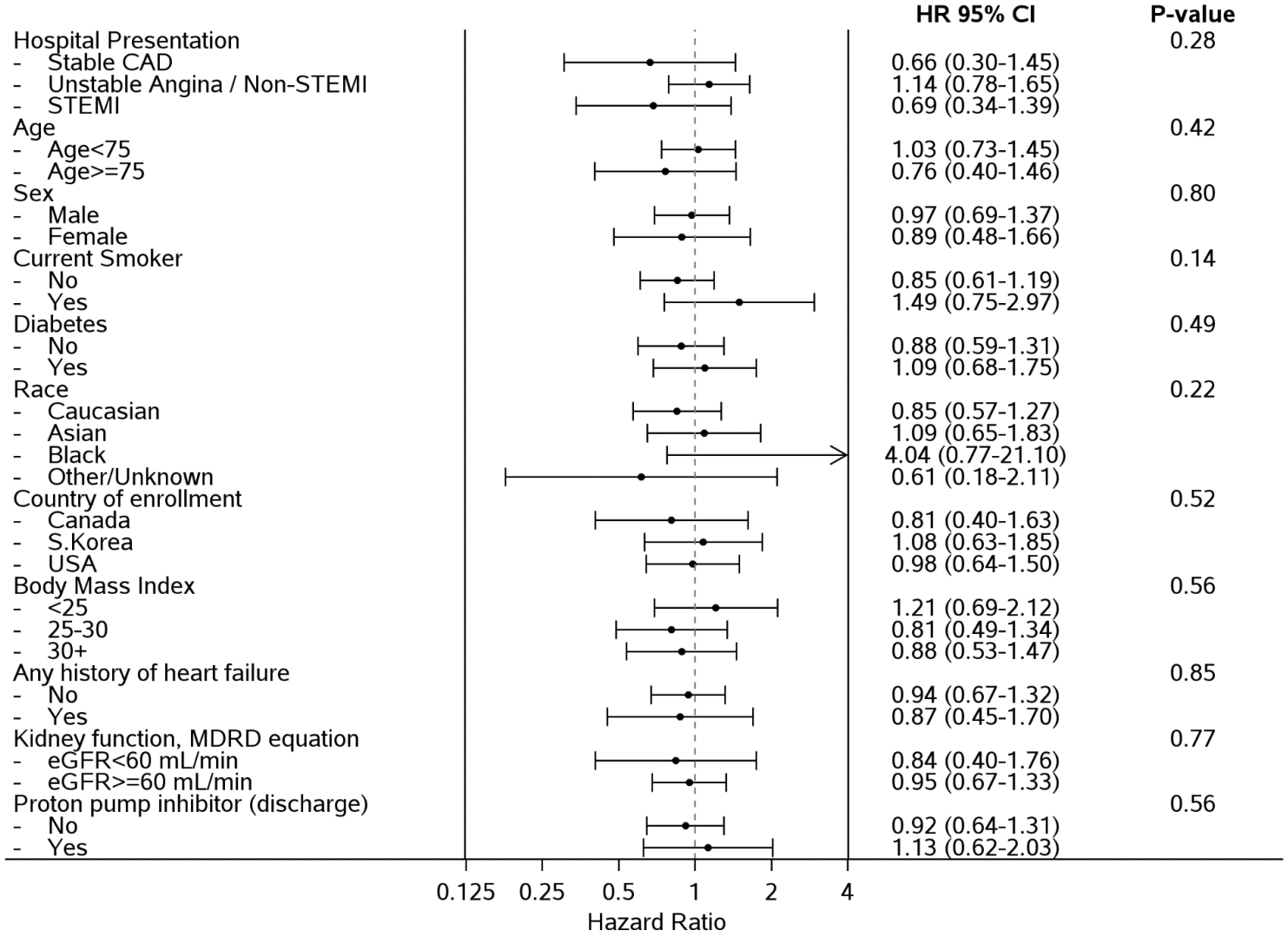
Safety Endpoint
TIMI Major or Minor Bleeding



No. at risk (% on P2Y12)

Conventional Therapy	946 (100%)	854 (95%)	717 (69%)	494 (62%)	330 (51%)	99 (40%)
Genotype-guided Therapy	903 (100%)	806 (90%)	672 (50%)	449 (42%)	287 (34%)	77 (27%)

Pre-Specified Subgroup Analyses (Extended F/U)



Conclusions

- An *initial* genotype-guided oral P2Y12 inhibitor strategy compared with conventional clopidogrel therapy without point-of-care genotyping in *CYP2C19 LOF* patients with ACS and stable CAD undergoing PCI resulted in no significant difference in reducing ischemic events over long-term median follow-up of 39 months
- There was likewise no significant difference in bleeding events between the two groups
- Patients in the genotype-guided group were *less likely* to continue P2Y12 inhibitors after 12 months compared to those in the conventional group
- Interpretation of these results should be made in the context of the observational nature of the follow-up and *variable P2Y12 inhibitor use beyond 12 months* after initial randomization
- The benefit of genotype-guided therapy and the effect of the drug-gene interaction appears to be most evident *within the first 3 months after PCI*

TAILOR PCI Leadership

National Heart, Lung & Blood Institute:
Yves Rosenberg, Nancy Geller,
Yi-Ping Fu, Ahmed Hasan, Erin Iturriaga

Principal Investigators:
Naveen Pereira, Michael Farkouh
Kent Bailey

Clinical Coordinating Center:
Naveen Pereira, Michael Farkouh, Julie Byrne, Shaun Goodman, Verghese Mathew, Vishu Murthy, Monica Olson, Charanjit Rihal, Derek So, Luanne Wussow

Executive Committee:
Charanjit Rihal (Chair), Kent Bailey, Linnea Baudhuin, Michael Farkouh, Yi-Ping Fu, Nancy Geller, Shaun Goodman, Ahmed Hasan, Erin Iturriaga, Ryan Lennon, Amir Lerman, Naveen Pereira, Yves Rosenberg, Liewei Wang, Richard Weinshilboum

Data Coordinating Center:
Kent Bailey,
Daniel Crusan, Ryan Lennon

Data Safety Monitoring Board:
Deepak Bhatt (Chair), George Sopko (Secretary), Jeffrey Anderson, Richard Conroy, Patricia Deverka, Mark Hlatky, Stephen Kimmel, Ruth Pfeiffer, Matthew Roe

Steering Committee:
Charanjit Rihal (Chair), J. Dawn Abbott, Jang-Ho Bae, Kent Bailey, Linnea Baudhuin, Michael Farkouh, Yi-Ping Fu, Nancy Geller, Bernard Gersh, Shaun Goodman, Paul Gordon, Ahmed Hasan, David Holmes, Erin Iturriaga, Myung Ho Jeong, Ryan Lennon, Amir Lerman, Verghese Mathew, Naveen Pereira, Yves Rosenberg, Jorge Saucedo, Derek So, Liewei Wang, Richard Weinshilboum

Clinical Event Adjudication Committee:
Robert Welsh (Co-Chair), Jean-Francois Tanguay (Co-Chair), Cheryl Jaigobin, Christine Lay, Mary Ann McLaughlin

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TAILOR PCI Network Enrolling Centers	Site PIs
University of Ottawa Heart Institute	Derek So, MD
Mayo Clinic - Rochester	Malcolm Bell, MD / Verghese Mathew, MD
Konyang University Hospital	Jang-Ho Bae, MD
The Heart Center of Chonnam National University Hospital	Myung Ho Jeong, MD
Minneapolis Heart Institute	Ivan Chavez, MD
The Miriam Hospital	Paul Gordon, MD
Rhode Island Hospital	J. Dawn Abbott, MD
Mayo Clinic Health System - La Crosse	Charles Cagin, DO
Ajou University Hospital	Hong-seok Lim, MD
Chung-Ang University Hospital	Sang Wook Kim, MD
Sunnybrook Research Institute	Minakshi Madan, MD
Mayo Clinic Health System - Eau Claire	D. Fearghas O'Cochlain, MD
Toronto General Hospital	Vlad Dzavik, MD / Chris Overgaard, MD
St. Michael's	John Graham, MB ChB
NorthShore University Health System	Justin Levisay, MD / Jorge Saucedo, MD, MBA
Albany Medical College	Mohammed El-Hajjar, MD
Winthrop University Hospital	Kevin Marzo, MD
Mayo Clinic - Jacksonville	Gary Lane, MD
Mayo Clinic - Scottsdale	John Sweeney, MD
La Raza	Jorge Escobedo, MD
Columbia University Medical Center	Tamim Nazif, MD
University of Mississippi Medical Center	William Campbell, MD / Cameron Guild, MD
Greenville Health System	Joshua Doll, MD
Esssentia Institute of Rural Health	Wilson Ginete, MD / Alok Bachuwar, MD
Loyola University Medical Center	Amir Darki, MD
Henry Ford Health System	Khaled Abdul-Nour, MD
Vancouver General Hospital	Jacqueline Saw, MD
NCH Healthcare System	Adam Frank, MD
New York University Langone Medical Center	Louai Razzouk, MD
Centromedico	Jorge Escobedo, MD
University of Minnesota	Ganesh Raveendran, MD
Cardiology Associates of Schenectady	Steven Weitz, MD
Sharp Healthcare, Center for Research	Ronald Goldberg, MD
Aurora Research Institute	Louie Kostopoulos, MD
Zuckerberg San Francisco General	Alan Wu, MD
Thunder Bay Regional Research Institute	Andrea MacDougall, MD
St. Elizabeth Healthcare	D. P. Suresh, MD
Regina General Hospital	Payam Dehghani, MD
Feinstein Institute for Medical Research - Lenox Hill	Carl Reimers, MD / Kirk Garratt, MD
Humber River Hospital	Irving Tiong, MD