Cluster-Randomized Trial Examining the Impact of Platelet Function Testing on Practice:

The Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome Prospective Open-Label Antiplatelet (TRANSLATE-POPS) Study

TCT 2013 First Report Investigation

presented on behalf of the TRANSLATE-POPS Investigators

Disclosures

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Study Organization

Study Leadership

Duke Clinical Research Institute

Eric D. Peterson (PI)
Tracy Y. Wang (Co-PI)
Kevin J. Anstrom
Linda Davidson-Ray
Emily Honeycutt
Daniel B. Mark
Connie N. Hess
Kelley Ryan

Study Sponsor

Daiichi Sankyo and Eli Lilly

Mark B. Effron
Marjorie E. Zettler
Douglas E. Faries
Brian A. Baker
Jen-Fue Maa

Background

- Many patients treated with an ADP receptor inhibitor have high on-treatment platelet reactivity (HPR) suggesting inadequate platelet inhibition response
- HPR has been consistently associated with increased risk of CV adverse events
- To date, however, RCTs have failed to demonstrate that altering ADP therapy in response to platelet function testing improves patient outcomes.
  - Uncertain platelet function test threshold and therapeutic response
  - Low risk RCT populations studied
  - Inadequate study power

Current Recommendations for Platelet Function Testing

- 2010 ACC/AHA Expert Consensus Document[1]:
  - *The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.*
- 2011 ACC/AHA/SCAI PCI Guidelines[2]:
  - *Platelet function testing may be considered in patients at high risk for poor clinical outcome* **(Class IIb; LOE: C)**
- 2012 ACC/AHA UA/NSTEMI Focused Update[3]:
  - *Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or after ACS and PCI) on thienopyridine treatment may be considered if results of testing may alter management* **(Class IIb; LOE: B)**

[1]Holmes DR, et al. *J Am Coll Cardiol*. 2010
[2]Levine GN, et al. *Circulation*. 2011
[3]Jneid H, et al. *J Am Coll Cardiol.* 2012

Hypotheses

Among hospitals treating STEMI and NSTEMI patients with PCI, access to no-cost platelet function testing would:

- Increase therapeutic adjustments of ADP receptor inhibitor treatment prior to discharge
- Improve patients' early (30-day) and long-term (12-month) clinical outcomes

Study Design

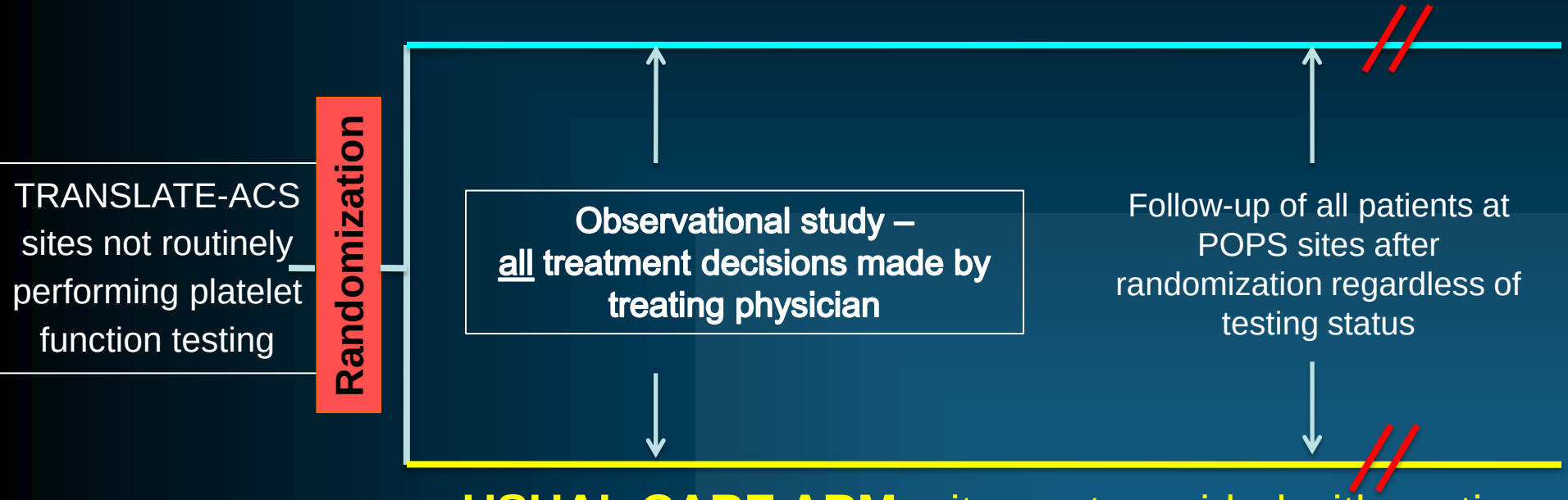
- Multicenter, prospective, cluster-randomized trial embedded within the TRANSLATE-ACS observational study
- **Patient Inclusion/Exclusion Criteria**: STEMI and NSTEMI patients treated with PCI and an ADP receptor inhibitor, excluding those:
  - unable to provide written consent for follow-up
  - participating in a RCT that specified ADP receptor inhibitor use in the first year after acute MI

  POPS included patients initially treated with clopidogrel/prasugrel
- **Site Eligibility**: All TRANSLATE-ACS hospitals who did not routinely (<30%) perform platelet function testing

TRANSLATE-ACS

DEVICE ARM: sites provided no-cost VerifyNow® P2Y12 test, encouraged to consent patients for testing

- Test prior to discharge and at least 12 hours after PCI
- Test result available to care team, response up to team



USUAL CARE ARM: sites *not* provided with routine platelet function testing.

- Care team could elect to perform testing if deemed clinically necessary

Duke Clinical Research Institute

Study End Points

Primary End Point: Incidence of ADP receptor inhibitor therapy adjustment before hospital discharge, including

- Change in dose of ADP receptor inhibitor
- Switching of ADP receptor inhibitor

Secondary End Points:

- 30-day major adverse cardiovascular events (MACE)
  - composite of all-cause death, recurrent MI, stroke, or unplanned coronary revascularization
- 30-day bleeding: using GUSTO criteria

Statistical Plan

- Intention-to-treat analyses
- Logistic regression with random effects model adjusting for correlated responses within each site
- Sample size: randomization of 150 sites would provide >90% power with α of 0.05 based on 10% LTFU and:
  - 75% patients initially treated with clopidogrel
  - 30% prevalence of HPR (PRU ≥235)
  - In the device arm, 66% of clopidogrel-treated patients with HPR and 10% without HPR will have therapeutic adjustments
  - In the usual care arm, 10% of all clopidogrel-treated and 20% of prasugrel-treated patients will have therapeutic adjustment

TRANSLATE-POPS Sites

100 US sites randomized with 50 sites in each arm

Baseline Clinical Characteristics

	Usual Care N=1,853	Device N=2,013	P*
Age, median (IQR), years	60 (52, 67)	59 (52-67)	0.23
Female	**25.6%**	**29.0%**	**0.01**
Non-white race	12.7%	11.8%	0.98
Prior MI	21.5%	19.4%	0.30
Prior PCI	22.1%	22.6%	0.80
Prior CABG	8.5%	9.9%	0.13
Prior stroke/TIA	5.2%	5.0%	0.78
Diabetes	25.4%	27.3%	0.23
Smoker	37.4%	37.1%	0.26
GRACE Risk Score	83 (65, 102)	82 (65, 101)	0.27
STEMI presentation	52.6%	49.9%	0.54

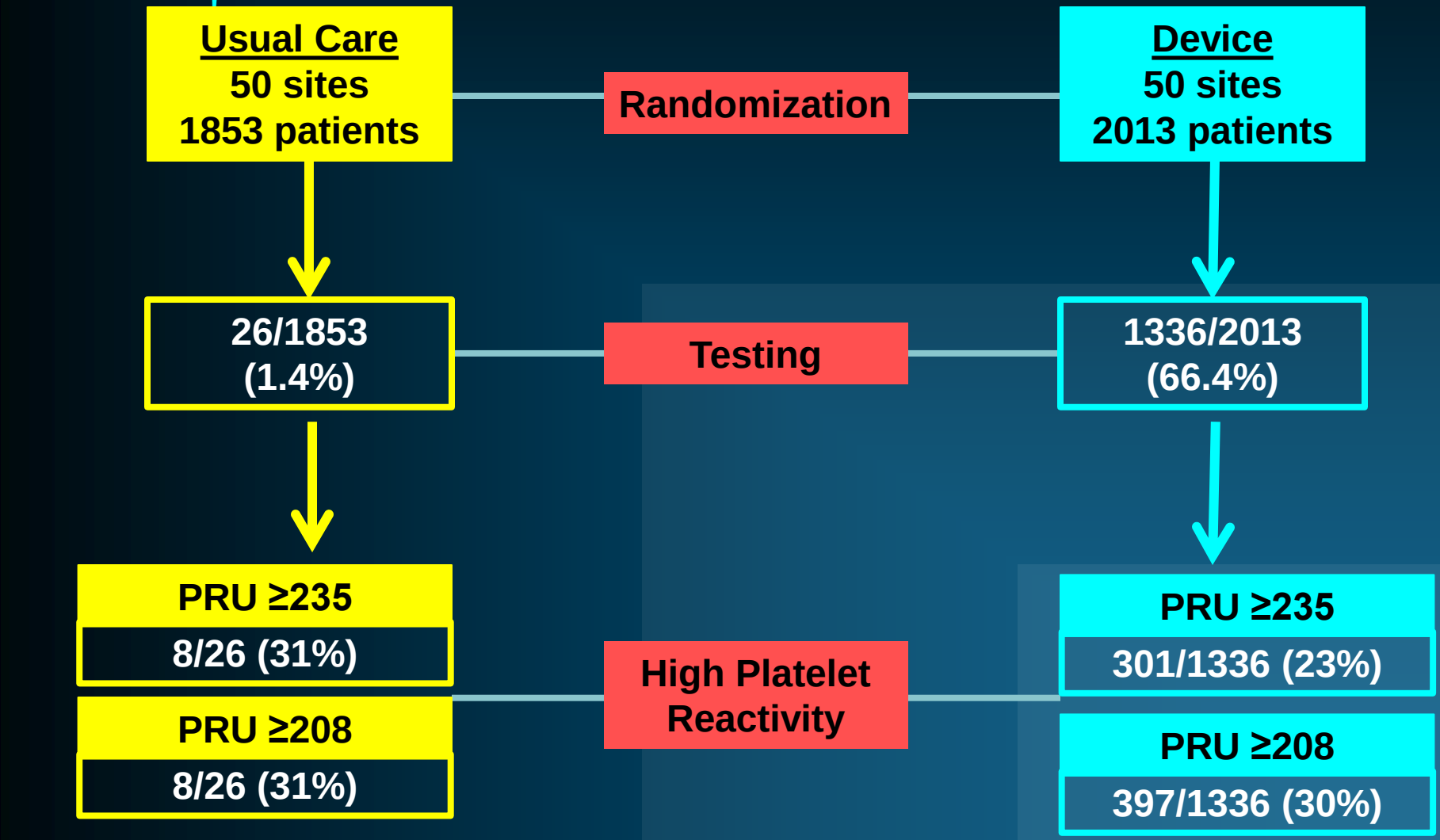
*Comparisons adjusted for correlated responses within site

Initial Treatment

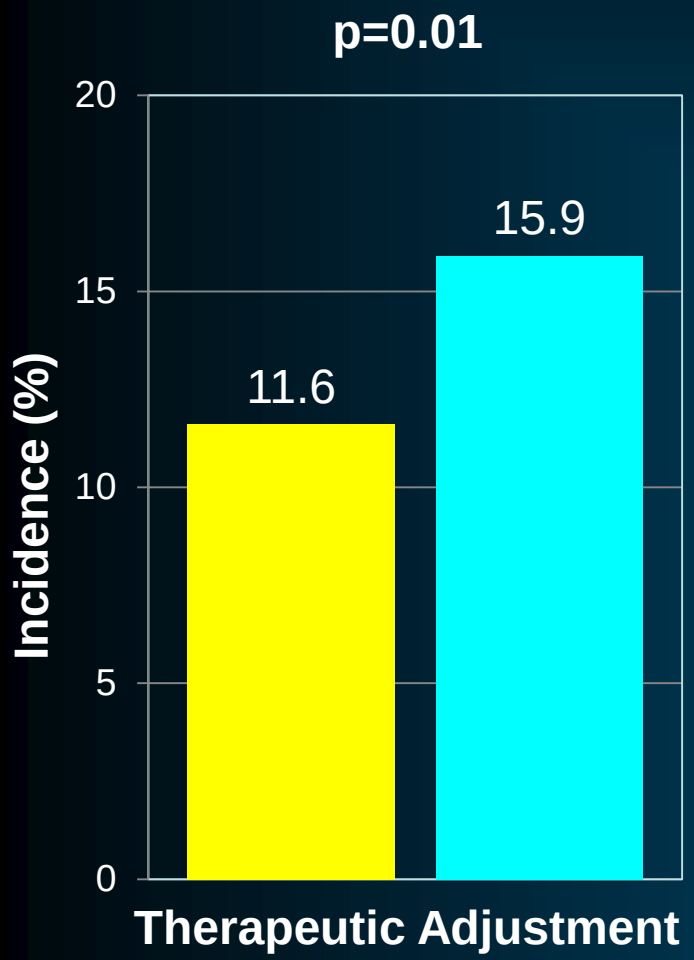
	Usual Care N=1,853		Device N=2,013		P*
Initial ADP receptor inhibitor					0.20
Clopidogrel	1347/1853	(73%)	1518/2013	(75%)	
Prasugrel	506/1853	(27%)	495/2013	(25%)	
Loading dose					
Clopidogrel ≥ 300mg	1197/1347	(89%)	1375/1518	(91%)	0.82
Prasugrel ≥ 60mg	458/506	(91%)	445/495	(90%)	0.70
Initial maintenance dose					
Clopidogrel 75 mg	1278/1347	(95%)	1443/1518	(95%)	0.45
Prasugrel 10 mg	467/506	(92%)	452/495	(91%)	0.29

*Comparisons adjusted for correlated responses within site

Study Intervention



Primary End Point
Therapeutic Adjustment



Usual care Device

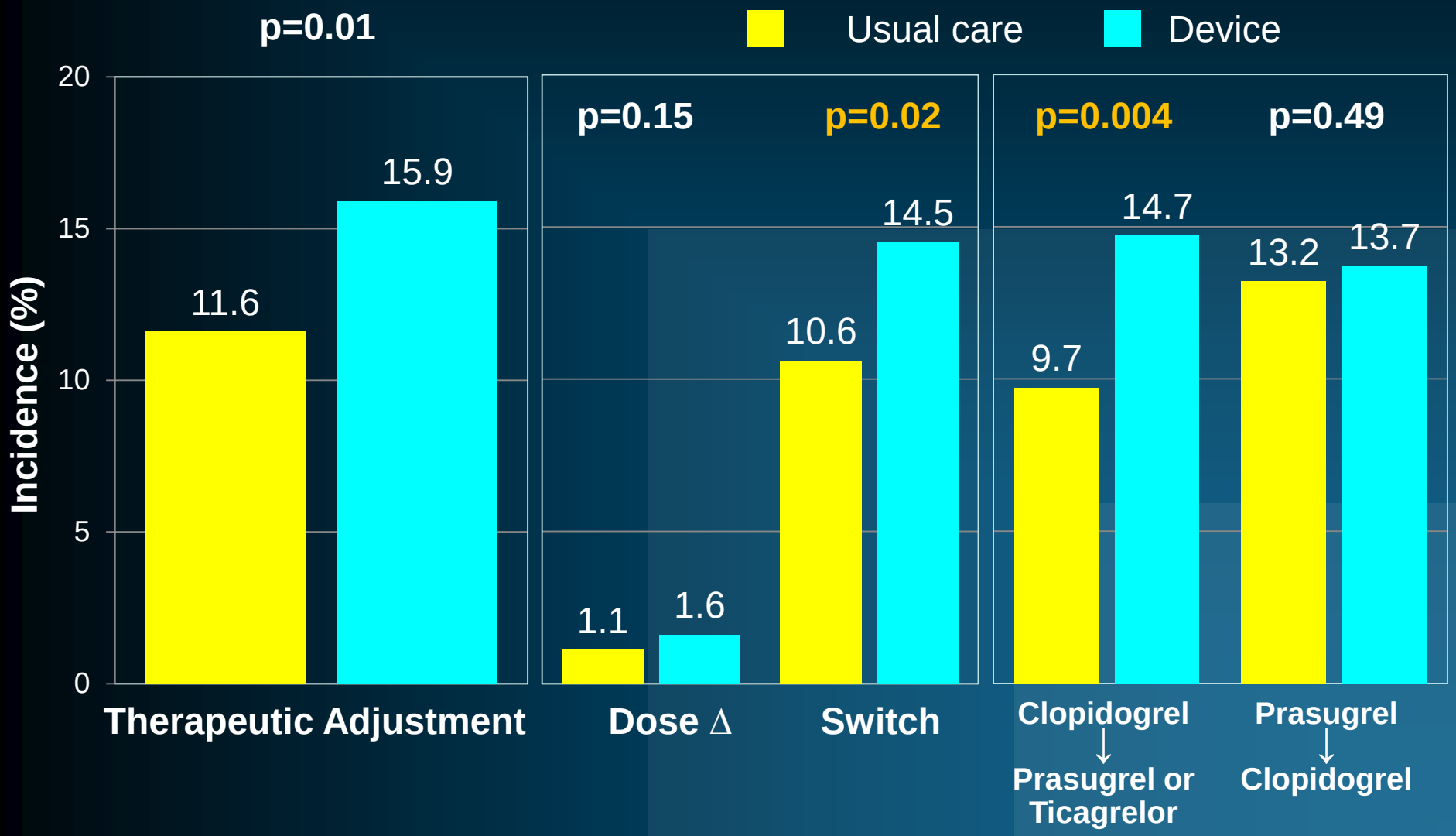
Device vs. Usual Care

OR 1.55, 95% CI 1.11-2.17

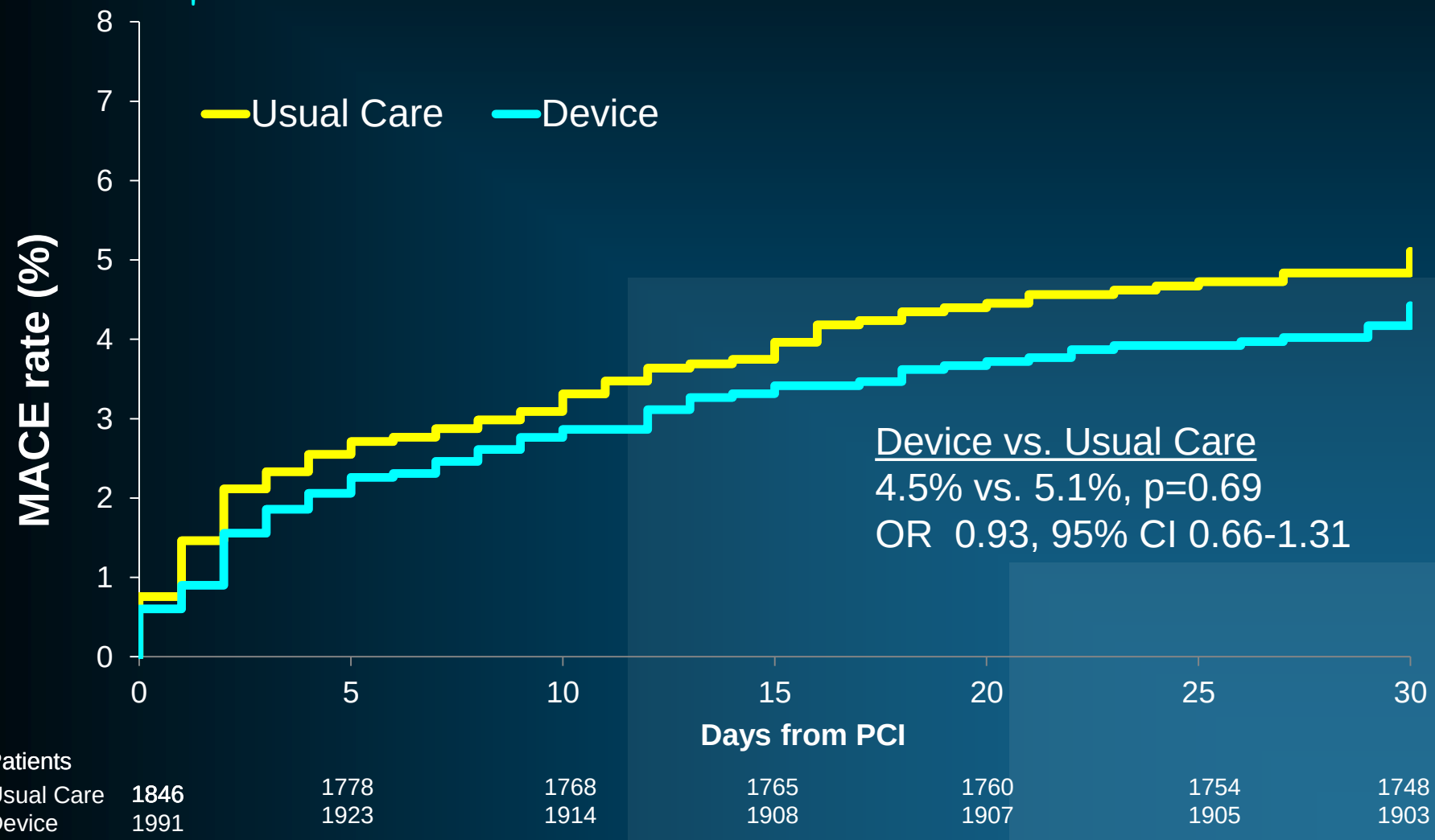
In the device arm, therapeutic adjustments occurred in:

- 31% patients with PRU ≥ 235
  (vs. 14% PRU <235, p<0.001)
- 29% patients with PRU ≥ 208
  (vs. 13% PRU <208, p<0.001)

Primary End Point



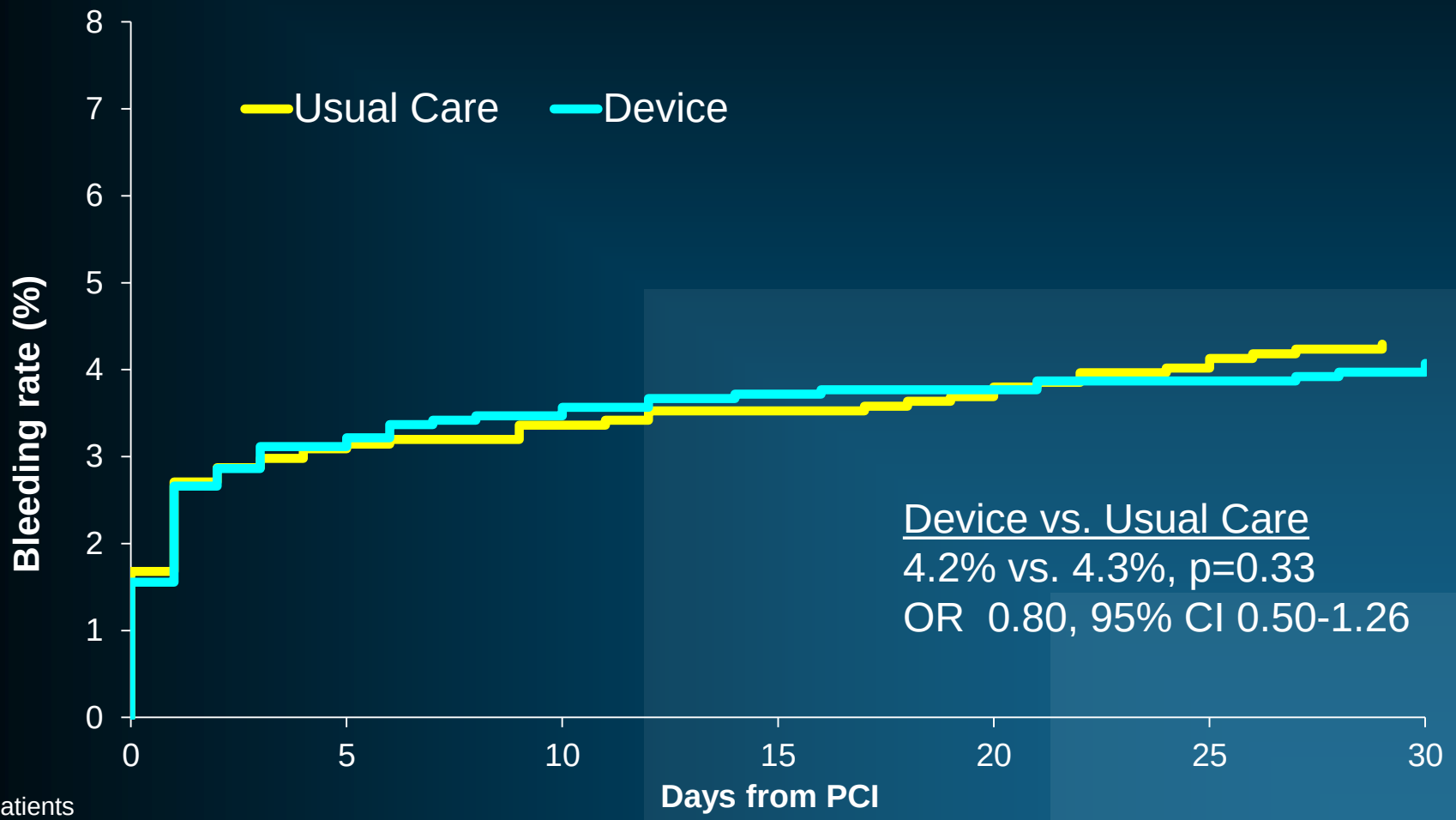
Major Adverse Cardiovascular Events



1.4% lost to follow-up through day 30

MACE = composite of death, MI, stroke, or unplanned revascularization

GUSTO Bleeding



Device vs. Usual Care
4.2% vs. 4.3%, p=0.33
OR 0.80, 95% CI 0.50-1.26

Patients							
Usual Care	1846	1776	1768	1765	1760	1754	1748
Device	1991	1923	1914	1908	1907	1905	1903

Conclusions

- A substantial proportion of MI patients have an inadequate response to antiplatelet treatment
- Yet, access to testing had only a modest impact on ADP receptor inhibitor selection and/or dosing
- No observed impact on early MACE or bleeding outcomes, investigation of long-term outcomes is ongoing

Study Strengths

- Cluster-randomized trial within observational registry framework permits unique insight into how platelet function testing is integrated into routine practice
- Design allowed clinicians to personalize response to test results for patients
  - Choice of PRU threshold and response not protocol-driven
  - Pragmatic intent as clinicians often required to make decisions based on patients' needs and capabilities

Limitations

- Platelet function testing performed only at a single time point during the index hospitalization
- Only 100 of 150 planned sites randomized due to termination of enrollment in parent study
- 66% penetrance of platelet function testing among device arm patients
- Study underpowered to detect significant differences in early MACE or bleeding events

Clinical Implications

Routine platelet function testing had only a modest impact on antiplatelet therapy adjustment

- Higher upfront prasugrel use
- Medication changes may have occurred after discharge
  - Switch by 6 weeks: 4.6% device vs. 3.0% usual care (p=0.09)
- No randomized studies showing testing-guided antiplatelet treatment improves outcomes in acute MI population
- Current US practice still strongly favors generic clopidogrel

Acknowledgments

TRANSLATE-ACS Steering Committee

David J. Cohen
Mid America Heart Institute
Kansas City, MO

Gregg C. Fonarow
Ahmanson-UCLA
Los Angeles, CA

Timothy D. Henry
Minneapolis Heart Institute
Cedars Sinai Medical Center

John C. Messenger
University of Colorado
Denver, CO

Mandeep Singh
Mayo Clinic
Rochester, MN

Gregg W. Stone
Cardiovascular Research Foundation
New York, NY

TRANSLATE-POPS Working Group

Dominick J. Angiolillo
University of Florida
Jacksonville, FL

Peter B. Berger
Geisinger Health System
Danville, PA

Thank you to all TRANSLATE-POPS Investigators

Top 20 Enrollers

Timothy Henry, MD
Minneapolis Heart Institute
Minneapolis, MN

Michael Chang, MD
Mercy General Hospital
Sacramento, CA

Mark Kozak, MD
Penn State University
College of Medicine
Hershey, PA

Stephen Lewis, MD
Bethesda North Hospital
Cincinnati, OH

Dorian Beasley, MD
Trinity Medical Center
Rock Island, IL

Harry Wallner, MD
Trinity Medical Center
Rock Island, IL

David Roth, MD
Kalispell Regional Medical
Kalispell, MT

Matthew Gibb, MD
Carle Physicians Group/Carle
Foundation Hospital
Urbana, IL

H.Vernon Anderson, MD
Memorial Hermann Hospital
Houston, TX

Chowdhury Ahsan, MD
University Medical Center of
Southern Nevada
Las Vegas, NV

Joel Carver, MD
Washington Regional Medical
Center, Fayetteville, AR

Richard Webel, MD
University of Missouri Health
System, Columbia, MO

Bina Ahmed, MD
University of New Mexico
Hospitals, Sacramento, CA

David Roberts, MD
Sutter Heart and Vascular
Institute, Sacramento, CA

Mark Koenig, MD
Saint Thomas Hospital
Nashville, TN

Arsenio Rodriguez, MD
Florida Hospital
Orlando, FL

Christopher Allen, MD
University of Pittsburgh
Medical Center, Pittsburgh,
PA

Jean Foucauld, MD
Cardiology Partners
Clinical Research Institute,
LLC, Wellington, FL

Michael Del Core, MD
The Cardiac Center of
Creighton University
Medical Center, Omaha,
NE

Larry Weathers, MD
Mercy Medical Center
Northwest Arkansas
Rogers, AR