Ticagrelor versus Clopidogrel in Troponin-negative Patients with Acute Coronary Syndrome Undergoing Ad-Hoc Percutaneous Coronary Intervention: Results of a Prospective, Randomized, Multicenter Pharmacodynamic Study

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Conflicts of interest

- R. Mehran has received research grants from DSI/Eli Lilly, Bristol-Myers Squibb/Sanofi-Aventis, AstraZeneca, and The Medicines Company; and consulting or advisory board fees from AstraZeneca, Bayer, CSL Behring, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Osprey Medical Inc., Regado Biosciences, Inc., The Medicines Company, Watermark Consulting, Abbott Laboratories, Boston Scientific, Covidien, and Sanofi-Aventis
- D.J. Angiolillo has received payment as an individual for: a) Consulting fee or honorarium from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular and PLx Pharma; b) Participation in review activities from CeloNova, Johnson & Johnson, St. Jude Medical, and Sunovion. Institutional payments for grants from Bristol-Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca and Gilead
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- J.M. Sweeny and G. Raveendran have no conflicts of interest to declare
- R. Teng and G. Carlson are employees of AstraZeneca
- Y. Zhao is a consultant to AstraZeneca

Ad-Hoc PCI Study Sites and PIs

15 US sites randomized patients

- Dominick J. Angiolillo: University of Florida, Jacksonville, FL – High Enroller
- Joseph M. Sweeny: Mount Sinai Medical Center, New York, NY
- Barry Bertolet: North Mississippi Medical Center, Tupelo, MS
- Ron Waksman: Washington Hospital Center, Washington, DC
- Thomas Stuckey: LeBauer CV Research Foundation, Greensboro, NC
- Robert Levitt: Sarah Cannon Research Institute, Richmond, VA
- Zakir Sahul: Michigan Heart PC, Ypsilanti, MI
- Ganesh Raveendran: University of Minnesota, Minneapolis, MN
- Zafir Hawa: North Kansas City Hospital, North Kansas City, MO
- Jeffrey Carr: Trinity Medical Center, Tyler, TX
- Frank Iacovone: Clara Maass Medical Center, Belleville, NJ
- Mohamed Effat: University of Cincinnati, Cincinnati, OH
- Mark Sasse: University of Alabama, Birmingham, AL
- Jose Exaire: Oklahoma VA Medical Center, Oklahoma City, OK
- Yerem Yeghiazarians: University of California, San Francisco, CA

Background

- Ticagrelor is an oral, direct-acting, reversible-binding platelet $P2Y_{12}$ receptor inhibitor
- The US Food and Drug Administration approval of ticagrelor for the treatment of ACS patients was based on efficacy in patients pretreated with a $P2Y_{12}$ inhibitor, irrespective of invasive or noninvasive management strategy[1,2]
- Many low-risk, troponin-negative ACS patients do not receive pretreatment with a $P2Y_{12}$ inhibitor
- Over half of all elective PCI procedures in the US are done on an ad-hoc basis in low-risk ACS patients – i.e., immediately after diagnostic coronary angiography[3]
- No previous study has assessed the effect of ticagrelor versus clopidogrel at the time of ad-hoc PCI

1. FDA. July 20, 2011; 2. Wallentin L, et al. *N Engl J Med* 2009;361:1045–1057; 3. Bashore TM, et al. *J Am Coll Cardiol* 2012;59:2221–2305

Aim and Hypothesis

Aim

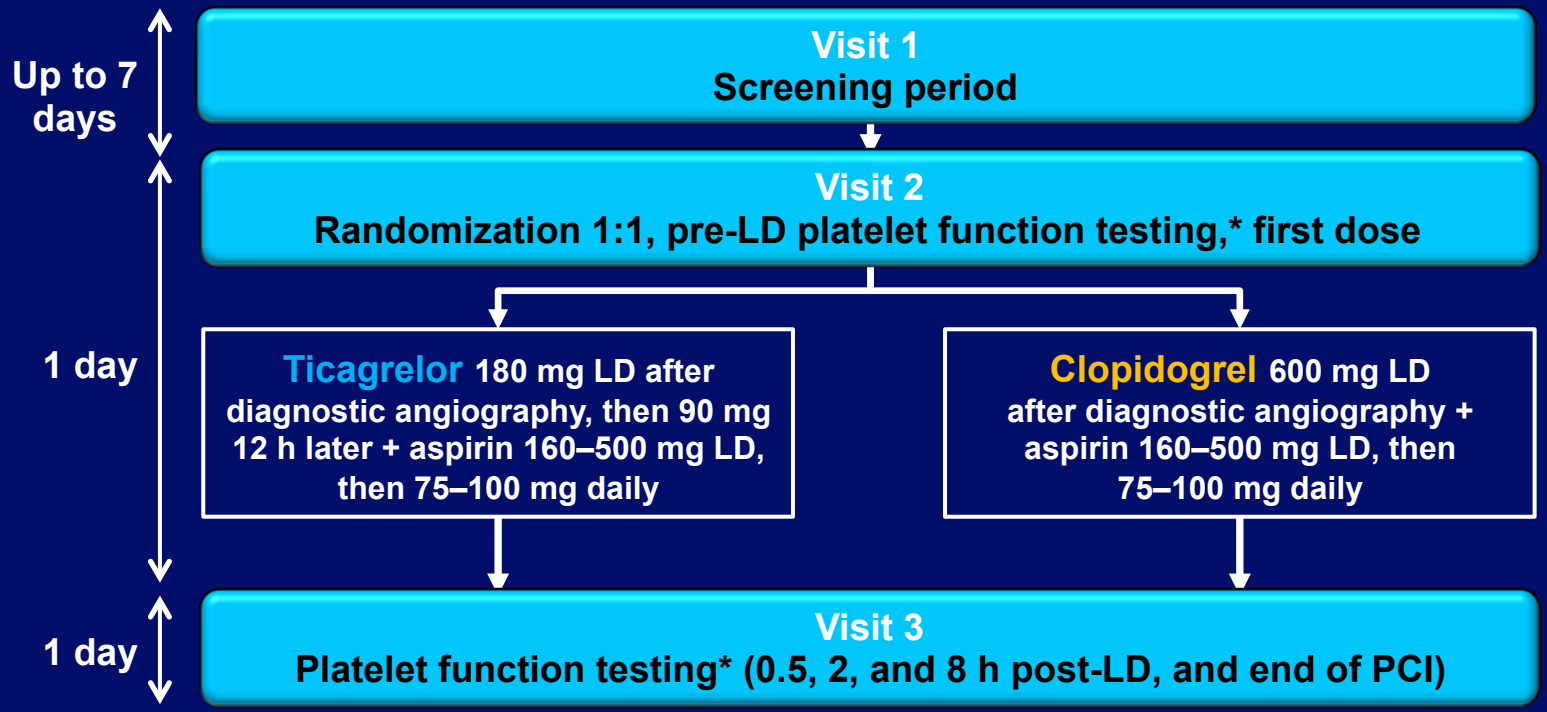
- Evaluate the effect of ticagrelor versus clopidogrel loading dose (LD) on platelet reactivity in troponin-negative ACS patients undergoing ad-hoc PCI

Hypothesis

- Ticagrelor 180 mg LD (standard dose) will result in faster and greater inhibition of platelet reactivity compared with clopidogrel 600 mg LD in this patient population

Study Design

- Prospective, open-label, randomized, multicenter, US, Phase IV study



*Measurement of $P2Y_{12}$ reaction units (PRU) with VerifyNow™

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Inclusion and Exclusion Criteria

Inclusion criteria

- Age ≥18 years
- Women (post-menopausal or surgically sterile) and men
- Documented non-ST-segment elevation ACS
- ≥1 negative troponin test (TnI, TnT or hsTn) 6–48 h after symptom onset
- On aspirin as antiplatelet medication

Key exclusion criteria

- Contraindication to study drug
- Use of any thienopyridine or ticagrelor within 7 days prior to randomization
- Any indication for chronic oral anticoagulation
- Concomitant therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic index, or strong CYP3A inducers

Study Endpoints and Safety Evaluation

Primary endpoint

- Platelet reactivity 2 h after ticagrelor or clopidogrel LD, measured as PRU level using VerifyNow™

Secondary endpoints

- PRU levels at 0.5 h post dose, end of PCI (when guide catheter removed from body), and 8 h post dose
- Percentage reduction from baseline in PRU
- Percentage IPA from baseline

Exploratory endpoint

- Percentage of patients with high on-treatment PRU levels (≥208)

Safety evaluation

- Assessment of AEs (including bleeding), physical examination, and vital signs

IPA, inhibition of platelet aggregation, measured as $P2Y_{12}$ receptor inhibition

Statistical Analysis

Statistical analysis

- The primary analysis of the difference between ticagrelor and clopidogrel in PRUs at 2 hours was analyzed using a two-sample *t*-test. Treatment level means and 2-sided 95% confidence intervals (CIs) were estimated. Tests were evaluated with a 2-sided alpha level of 0.05

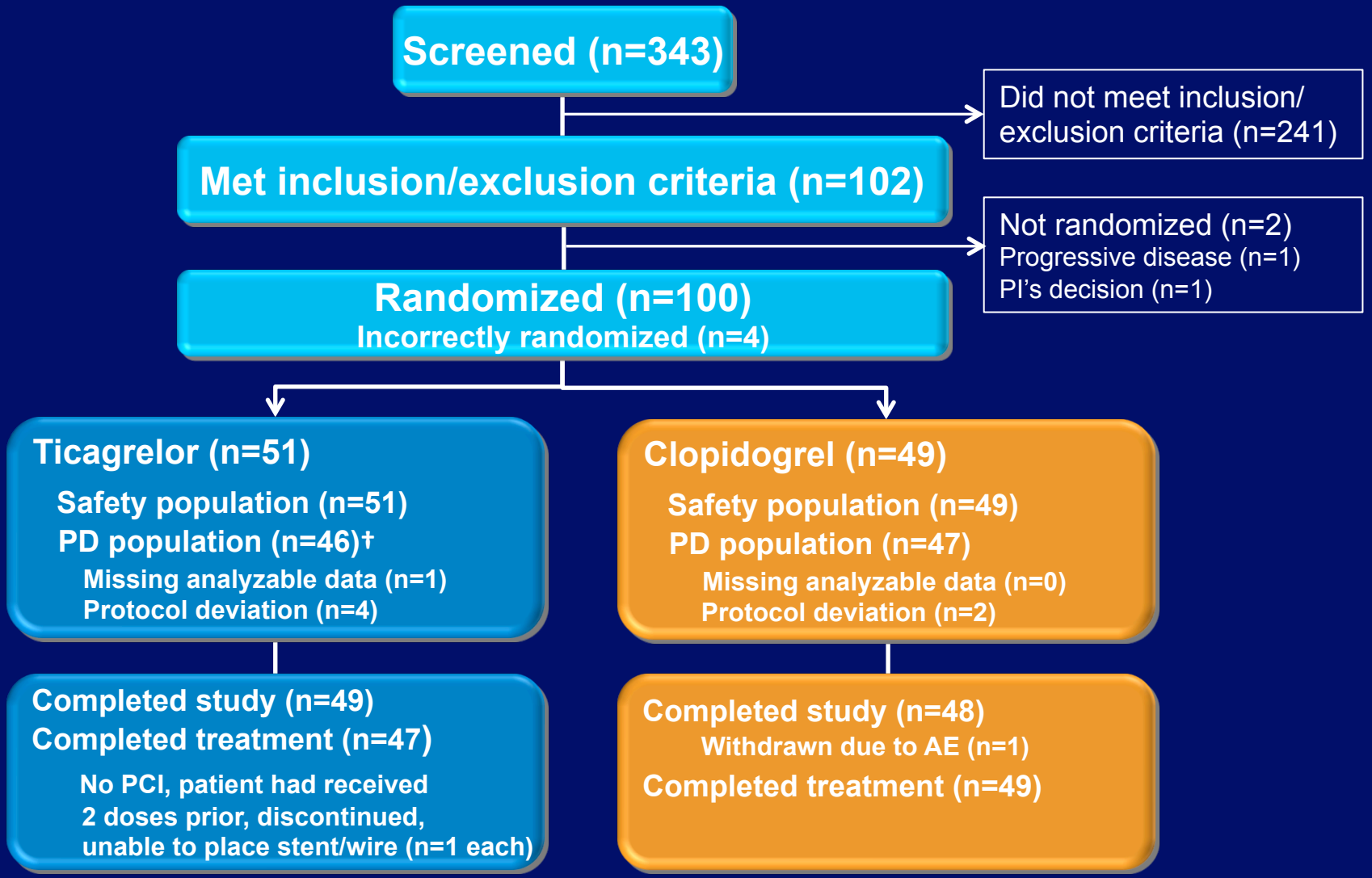
Sample size

- Calculations using 90% power, detection of a difference of 100 PRUs, and a 2-sided alpha of 0.05 yielded a required sample size of 40 completed patients, with 20 per treatment group. This assumed a standard deviation (SD) of 93 PRUs based on a previous study. However, the administration of study treatment in a supine position was assumed to incur a 2- to 3-fold increase in variability, resulting in a sample size of approximately 100 patients

Results

Patient Disposition and Characteristics

Patient Disposition



†One patient with pre-dose PRU <150 was excluded from primary and secondary endpoint analyses (n=45)

Baseline Characteristics

	Ticagrelor (n=51)	Clopidogrel (n=49)
Age, years; mean (SD)	60.1 (10.7)	63.0 (9.1)
Women, n (%)	17 (33.3)	13 (26.5)
Race, n (%)		
White	33 (71.7)	33 (71.7)
Black or African American	11 (23.9)	11 (23.9)
Other†	2 (4.4)	2 (4.3)
Body mass index >30 kg/m^2, n (%)‡	24 (48.0)†	24 (49.0)
CV risk factors, n (%)		
Dyslipidemia	38 (74.5)	42 (85.7)
Hypertension	44 (86.3)	48 (98.0)
Diabetes mellitus	20 (39.2)	16 (32.7)
Chronic kidney disease, GFR <60 mL/min/1.73m^2	7 (13.7)	7 (14.3)
Prior CVD and CV procedures, n (%)		
Congestive heart failure	5 (9.8)	2 (4.1)
Peripheral arterial occlusive disease	1 (2.0)	1 (2.0)
Stroke, ischemic	0	1 (2.0)
Prior myocardial infarction	9 (17.6)	16 (32.7)
Prior PCI	19 (37.3)	22 (44.9)
Prior coronary artery bypass graft,	5 (9.8)	14 (28.6)

GFR, glomerular filtration rate †Asian, American Indian, or Alaskan Native ‡Data missing for one patient

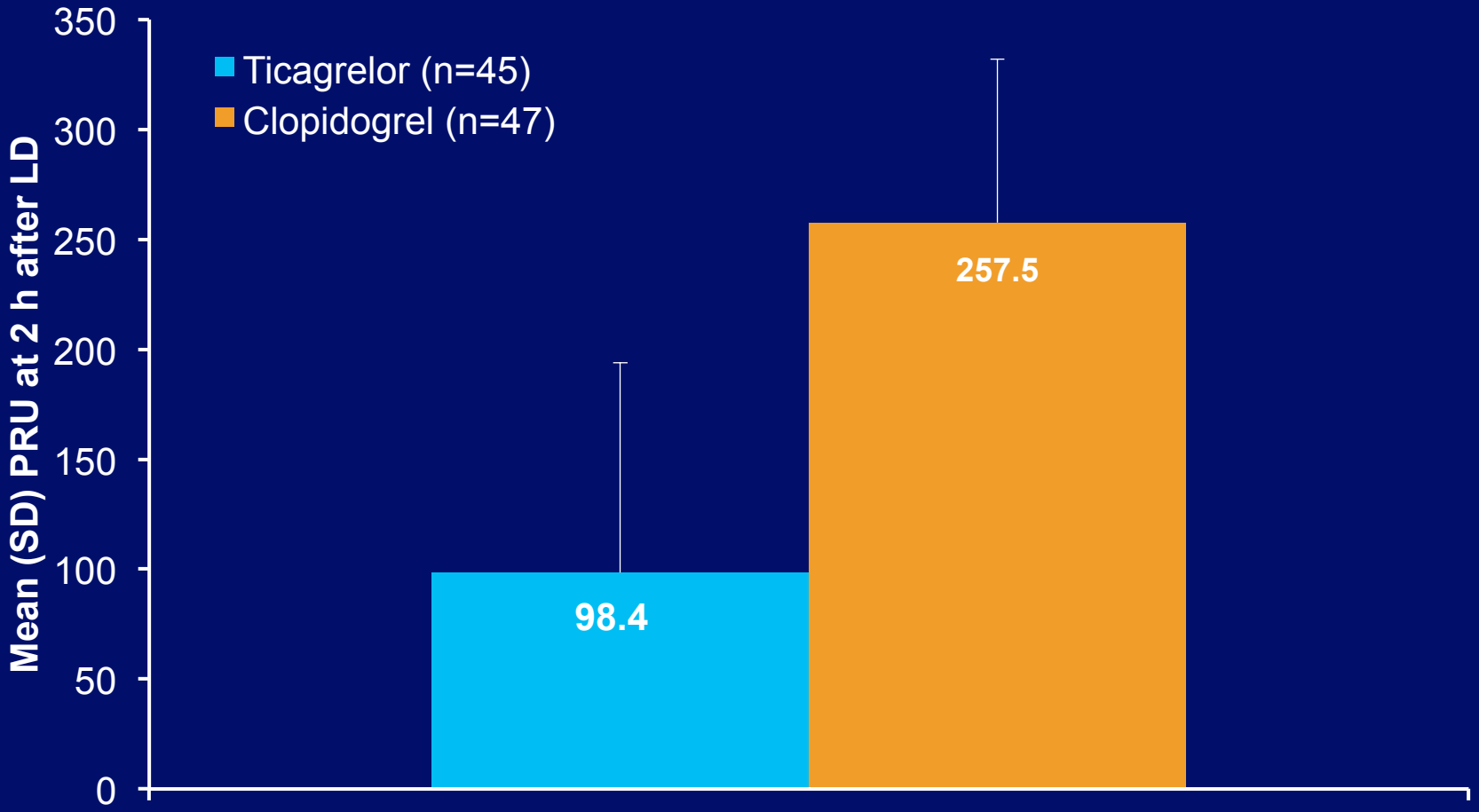
Results

Primary Endpoint

PRU at 2 h after LD

PD Population

Treatment difference (95% CI): -159.1 (-194.7, -123.5); p<0.001

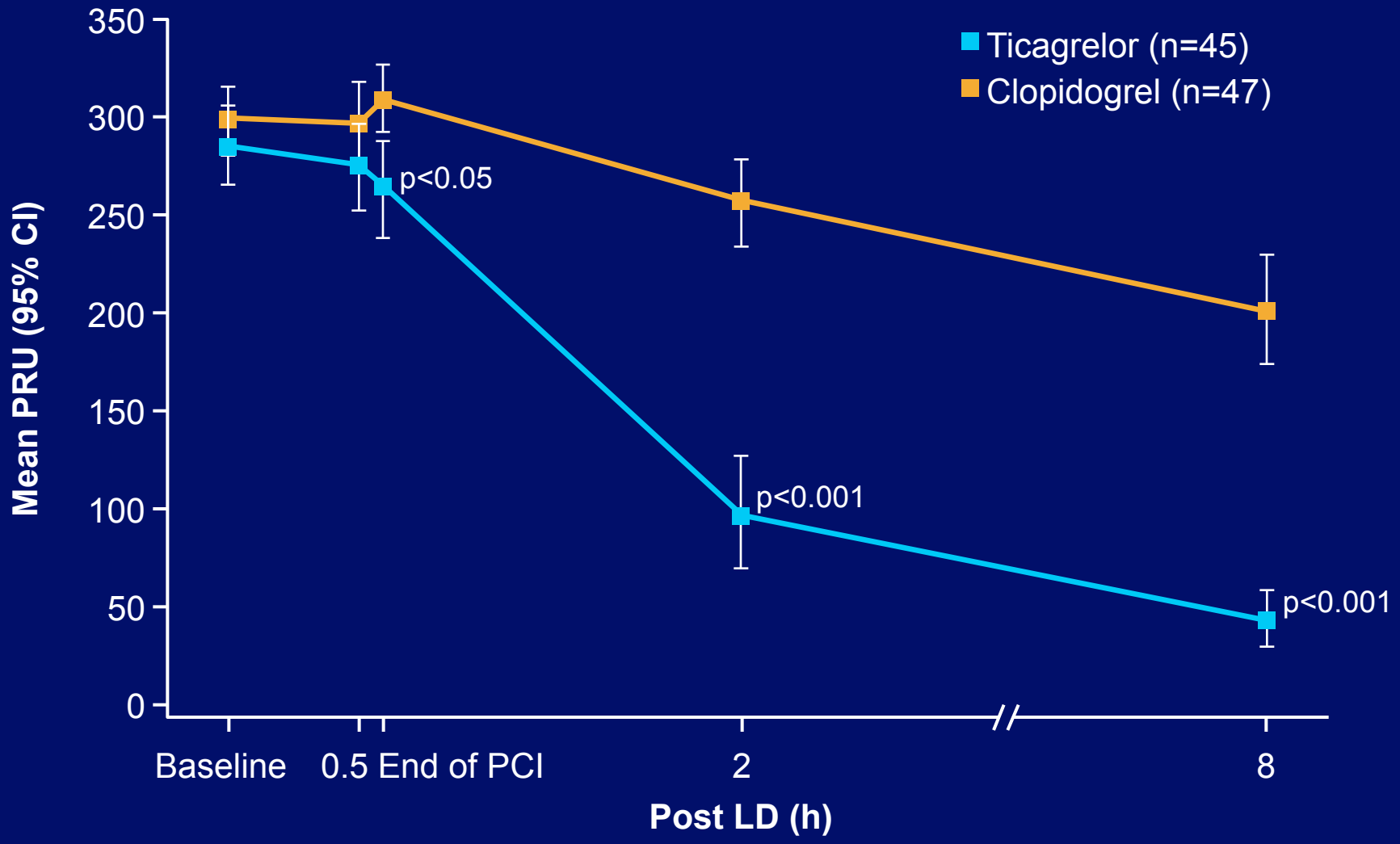


Results

Secondary Endpoints

Time Course of PRU

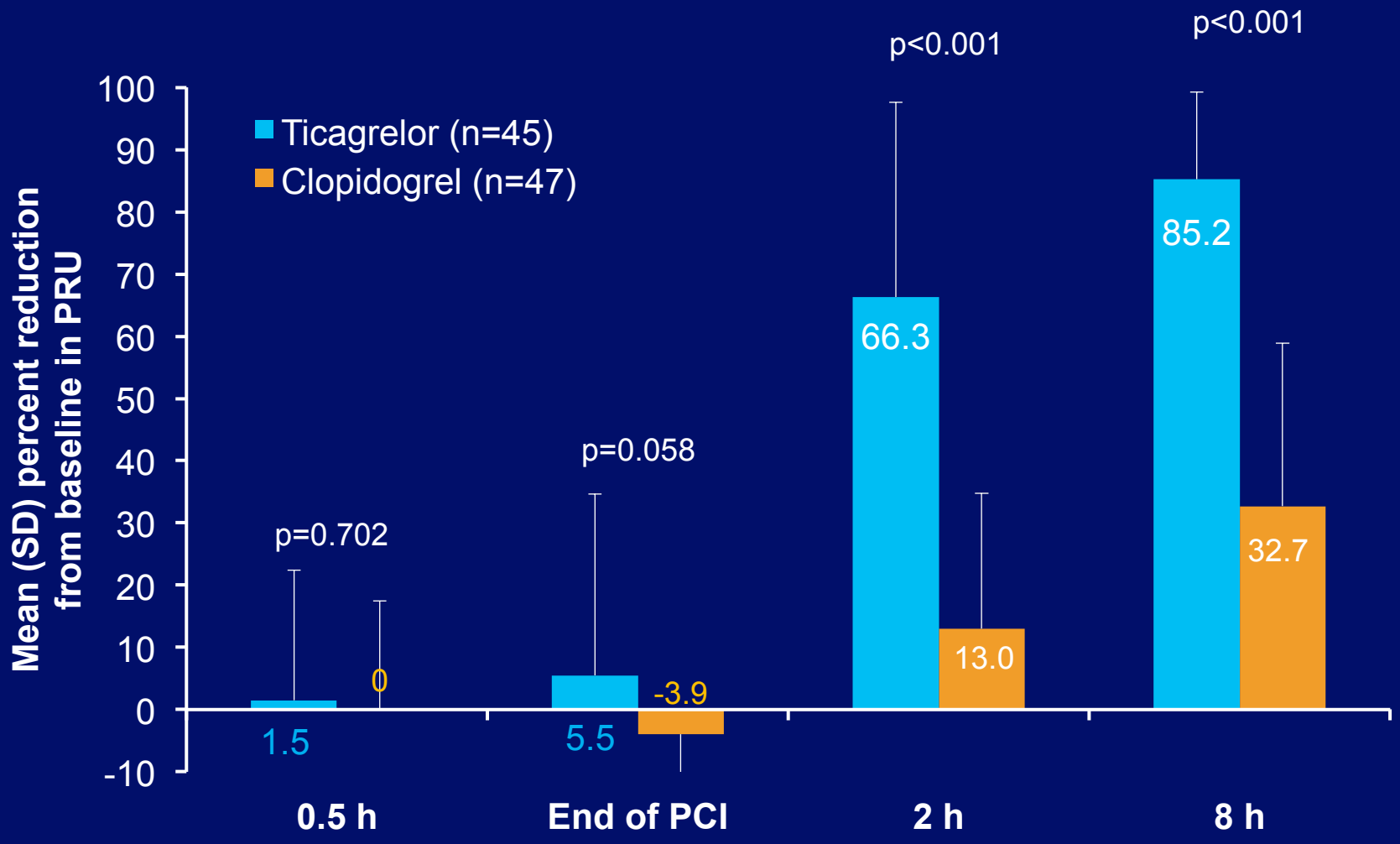
PD Population



Mean time to end of PCI 0.6 h

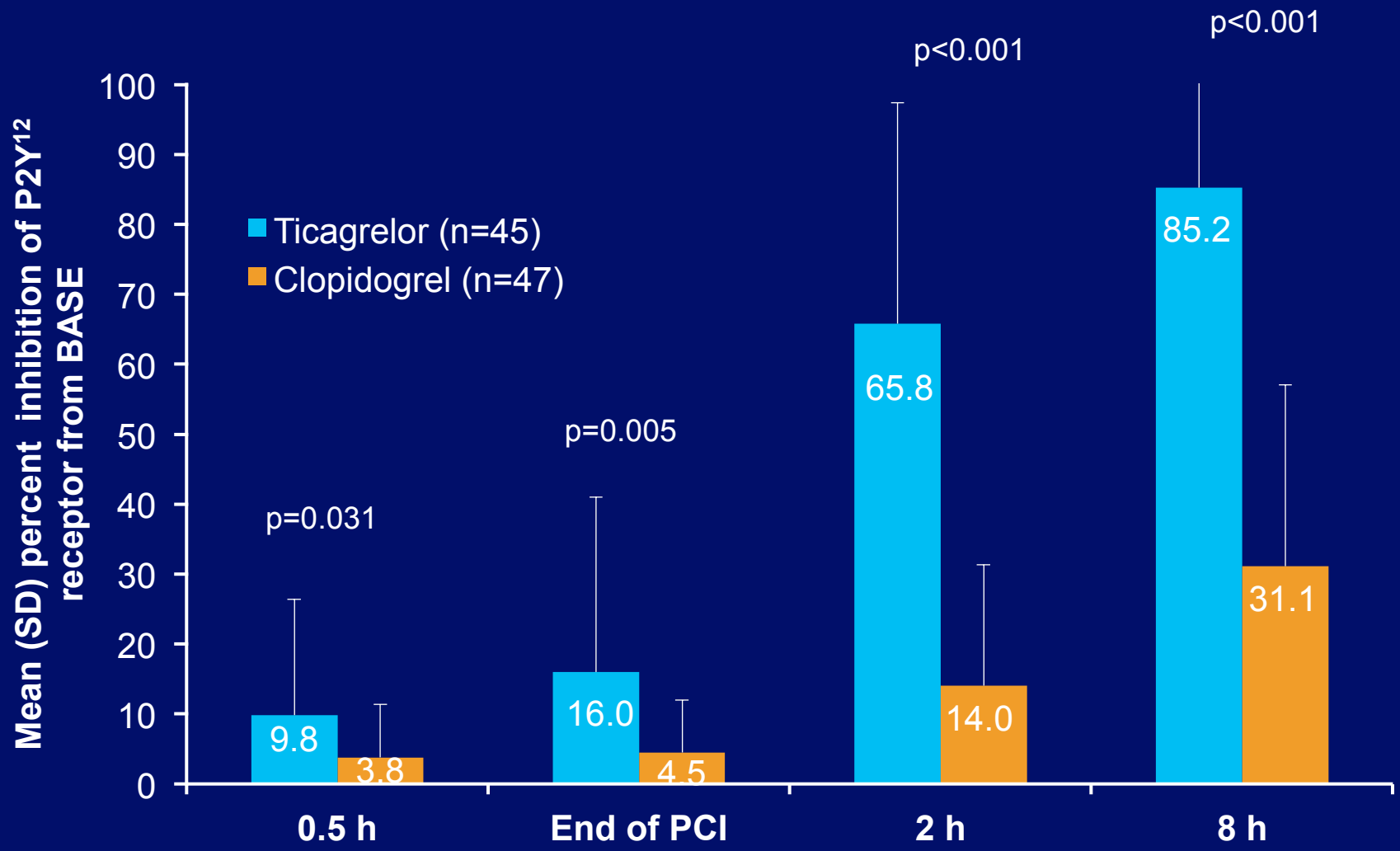
Percent Reduction from Baseline in PRU

PD Population



Device-defined IPA†

PD Population



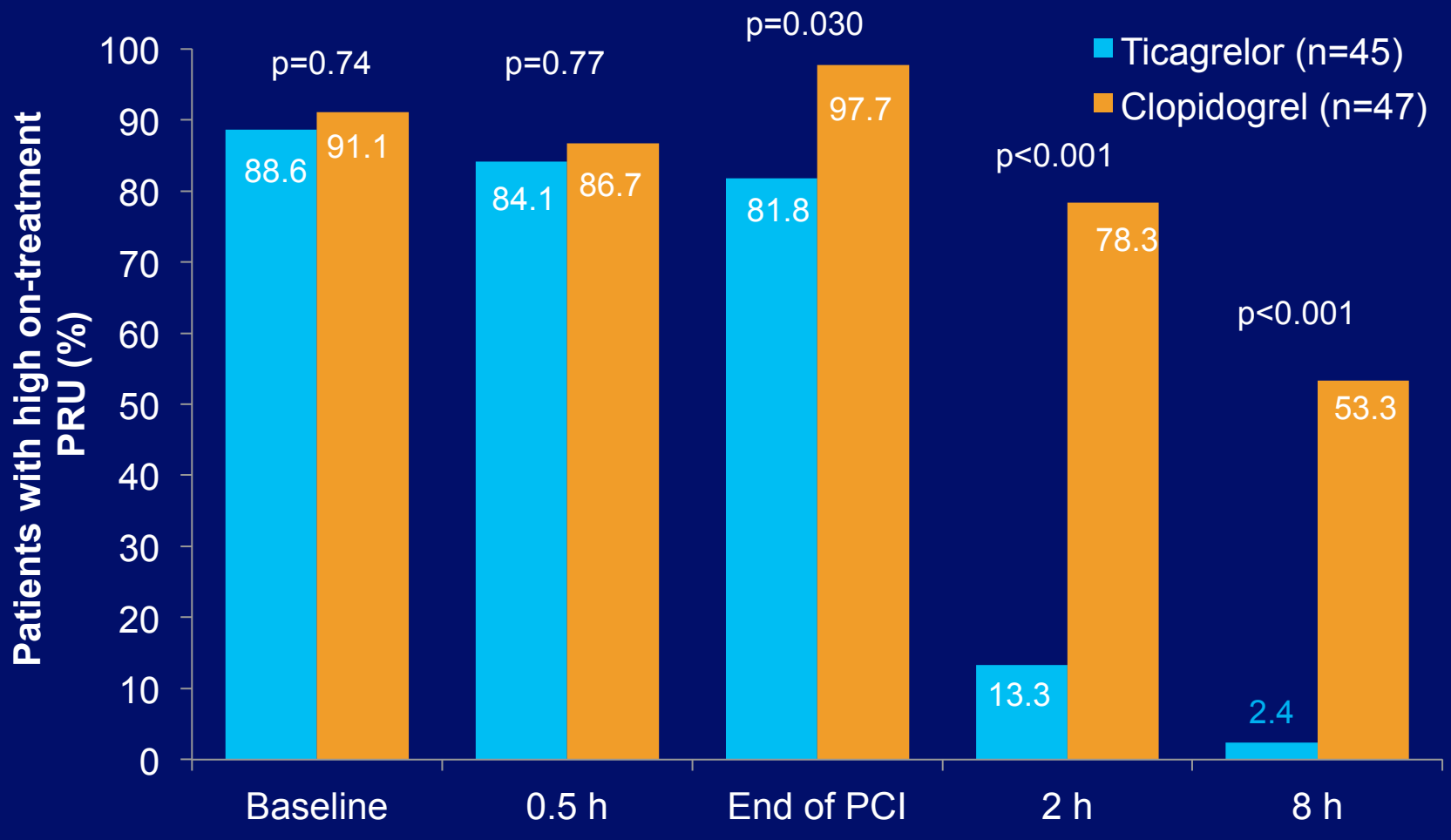
†VerifyNow™-determined percent inhibition from the reference base channel

Results

Exploratory Endpoint

High On-treatment PRU (≥208)

PD Population



Mean time to end of PCI 0.6 h

Results

Safety Evaluation

Safety Summary

- No deaths or AEs leading to discontinuation of study drug
- Most frequently occurring AEs with ticagrelor vs clopidogrel were
  - Chest pain (4 vs1 patient)
  - Unstable angina (0 vs 3 patients)
  - Hypotension (3 vs 0 patients)
  - Dyspnea (2 vs 1 patient)
  - Hematoma (2 vs 0 patients)
- All except 3 AEs (all in the ticagrelor group) and all except one SAE (duodenitis in 1 patient in the ticagrelor group) were considered unrelated to study drug
- Bleeding events considered related to study drug occurred in 3 (5.9%) ticagrelor patients, all of mild intensity, and 0 clopidogrel patients
- No notable findings for vital signs or physical examination
- No new clinically meaningful safety findings

Conclusions

- In low-risk ACS patients undergoing ad-hoc PCI, platelet reactivity as measured by VerifyNow™ was decreased to a greater extent at 2 h after ticagrelor LD, compared with clopidogrel LD, and was maintained up to the 8-h time point
- The number of patients with high on-treatment PRU at 2 h was significantly lower with ticagrelor ($p<0.001$)
- Ticagrelor was well tolerated, with no notable safety findings, as assessed by AEs, bleeding events, physical examination, and vital signs
- These findings suggest that a ticagrelor LD may be more effective than clopidogrel for inhibition of platelet activity in low-risk, troponin-negative ACS patients undergoing ad-hoc PCI