First Randomized Human Experience with a Ticagrelor Reversal Agent

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Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - **Advisory Board**: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, **PhaseBio**, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, Amarin, Amgen, **AstraZeneca**, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, **PhaseBio**, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda.

This presentation includes investigational uses of PB2452.

This study was sponsored by PhaseBio Pharmaceuticals, Inc.

Background

- Ticagrelor is an oral $P2Y_{12}$ inhibitor used with aspirin to reduce the risk of ischemic events in patients with acute coronary syndromes or prior myocardial infarction, based on the PLATO[1,2] and PEGASUS[3,4] trials.
- As with other antiplatelet drugs, spontaneous major bleeding and bleeding associated with urgent or emergent invasive procedures are concerns.
- The antiplatelet effects of ticagrelor cannot be reversed with platelet transfusion. Therefore, a rapid-acting reversal agent would be useful.

[1]James S, Akerblom A, Cannon CP, et al. *Am Heart J*. 2009;157:599-605.
[2]Wallentin L, Becker RC, Budaj A, et al. *N Engl J Med.* 2009;361:1045-57.
[3]Bonaca MP, Bhatt DL, Braunwald E, et al. *Am Heart J*. 2014;167:437-44.
[4]Bonaca MP, Bhatt DL, Cohen M, et al. *N Engl J Med*. 2015;372:1791-800.

Background

- Currently, no reversal agents for $P2Y_{12}$ receptor antagonists are known.
- Unlike the other oral $P2Y_{12}$ antagonists, ticagrelor is a reversible inhibitor, which makes development of a specific reversal agent for ticagrelor feasible.
- PB2452 is a neutralizing monoclonal antibody fragment (Fab) that binds ticagrelor and its major active circulating metabolite with high affinity.
- We hypothesized that PB2452 could be titrated to reverse rapidly the antiplatelet effects of ticagrelor.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Methods

- In this randomized, double-blind, placebo-controlled, healthy volunteer Phase 1 study, intravenous PB2452 was evaluated as a ticagrelor reversal agent.
- Ten sequential dose cohorts were evaluated.
- Platelet function was assessed using light transmission aggregometry, VerifyNow P2Y12, and vasodilator stimulated phosphoprotein (VASP) assays before and after 48 hours of ticagrelor administration.

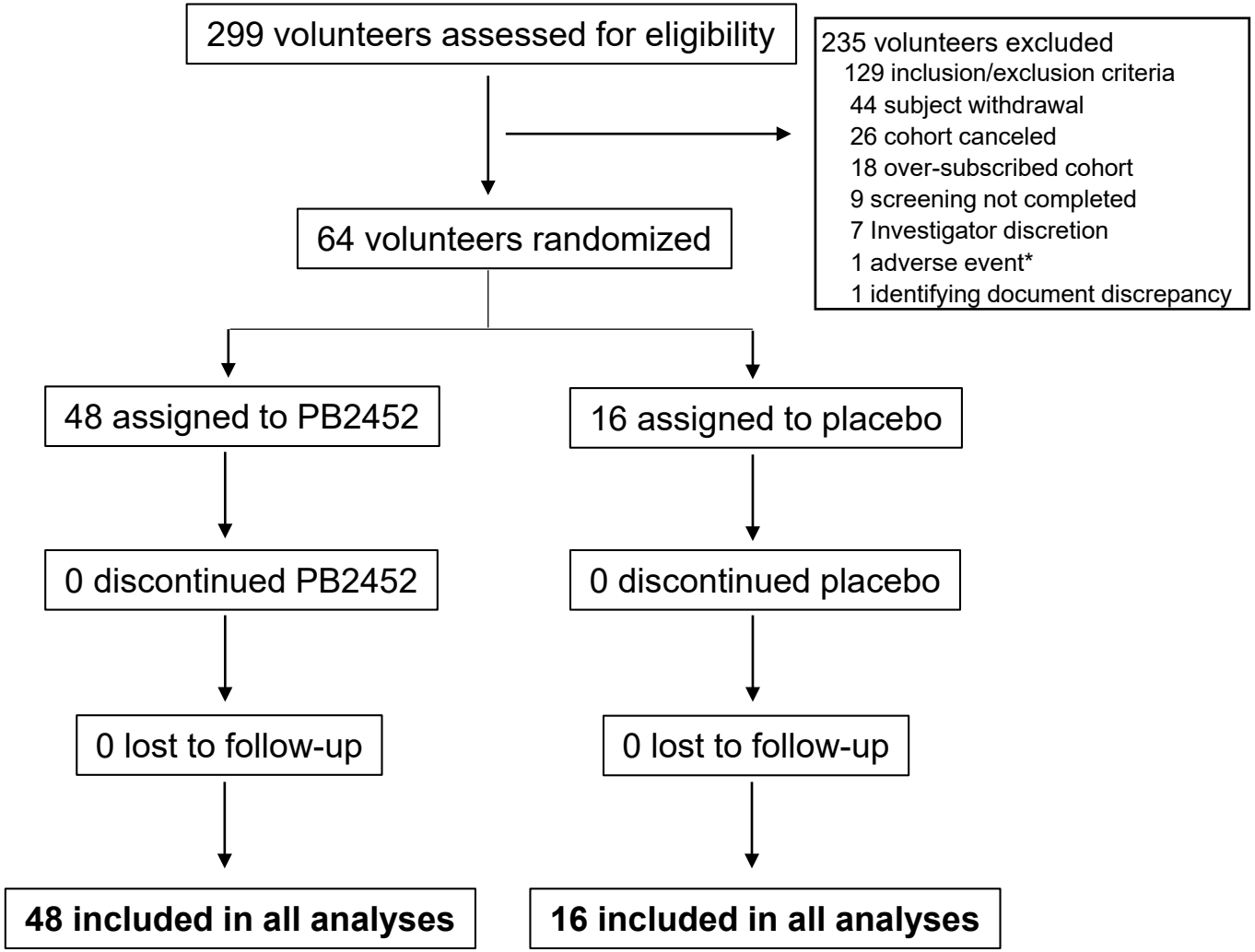
Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Baseline Characteristics

	All Placebo (N=16) n (%)	All PB2452 (N=48) n (%)
Age (years), Mean (SD)	34.0 (8.26)	30.5 (8.76)
Sex, %		
Female	31.3	52.1
BMI (kg/m^2), Mean (SD)	28.6 (3.3)	27.7(4.1)
Ethnicity, n (%)		
Hispanic or Latino	6 (37.5)	22 (45.8)
Race, n (%)		
White	7 (43.8)	27 (56.3)
Black or African American	8 (50.0)	18 (37.5)
Asian	0	1 (2.1)
American Indian or Alaska Native	1 (6.3)	0
Native Hawaiian or Other Pacific Islander	0	1 (2.1)
Multiple	0	1 (2.1)
Platelet count, Mean (SD) (x1000/μL)	239 (52.1)	253 (46.8)
LTA Platelet aggregation, Mean % (SD)	82.1 (7.53)	82.9 (7.49)
VerifyNow P2Y12 PRU, Mean (SD)	226.4 (39.9)	237.7 (36.8)
VASP ELISA PRI, Mean (SD)	89.8 (4.17)	90.2 (3.64)

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Enrollment and Study Flowchart



*One volunteer reported the adverse event of shortness of breath with nausea and vomiting prior to randomization and was withdrawn from the trial.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Study Design

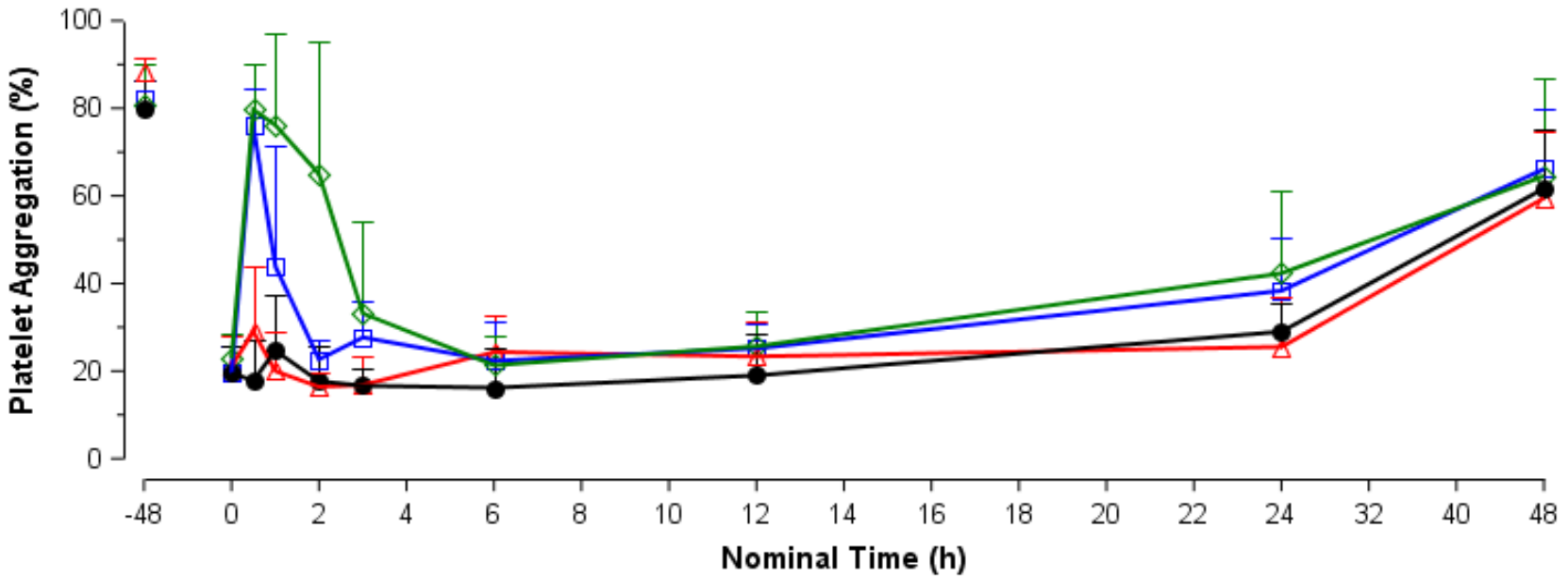
Cohort	Ticagrelor Pretreatment	PB2452 IV regimen	Volunteers Active:Placebo
1	None	0.1g 30 min	3A:1P
2	None	0.3g 30 min	3A:1P
3	None	1g 30 min	3A:1P
4	180mg PO + 90mg BID x 2 days	1g 30 min	6A:2P
5	180mg PO + 90mg BID x 2 days	3g 30 min	6A:2P
6	180mg PO + 90mg BID x 2 days	9g 30 min	6A:2P
7	180mg PO + 90mg BID x 2 days	18g (3g 5 min + 15g 7 hr 55 min)	6A:2P
8	180mg PO + 90mg BID x 2 days	18g (6g 15 min + 6g 3 hr + 6g 8hr 45 min)	6A:2P
9	180mg PO + 90mg BID x 2 days	18g (6g 15 min + 6g 4 hr + 6g 12 hr)	3A:1P
10	180mg PO + 90mg BID x 2 days	18g (6g 10 min + 6g 3 hr + 6g 13 hr)	6A:2P

g = grams, min= minutes, A = active, P = placebo, mg=milligrams, hr=hours, PO=orally, BID= twice per day

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Onset and Duration of Ticagrelor Reversal - LTA

ADP-induced platelet aggregation in the PB2452 and placebo groups (Cohorts 4-6) administered ascending doses of IV PB2452 for 30 minutes



Rapid but transient ticagrelor reversal with 3 g and 9 g of PB2452. Significant reversal was observed at 30 minutes in cohorts 5 and 6. Duration of reversal was dose-dependent, lasting 2 hours with 9 g infusion.

P values by timepoint for each cohort

Cohort	0.5	1	2	3	6	12	24	48
4	1	1	1	1	1	1	1	1
5	0.0216	1	1	0.1515	1	1	1	1
6	0.0216	0.0433	0.0433	0.0866	1	1	0.5844	1

PB2452 1g
PB2452 3g
PB2452 9g
C4-6 Placebo

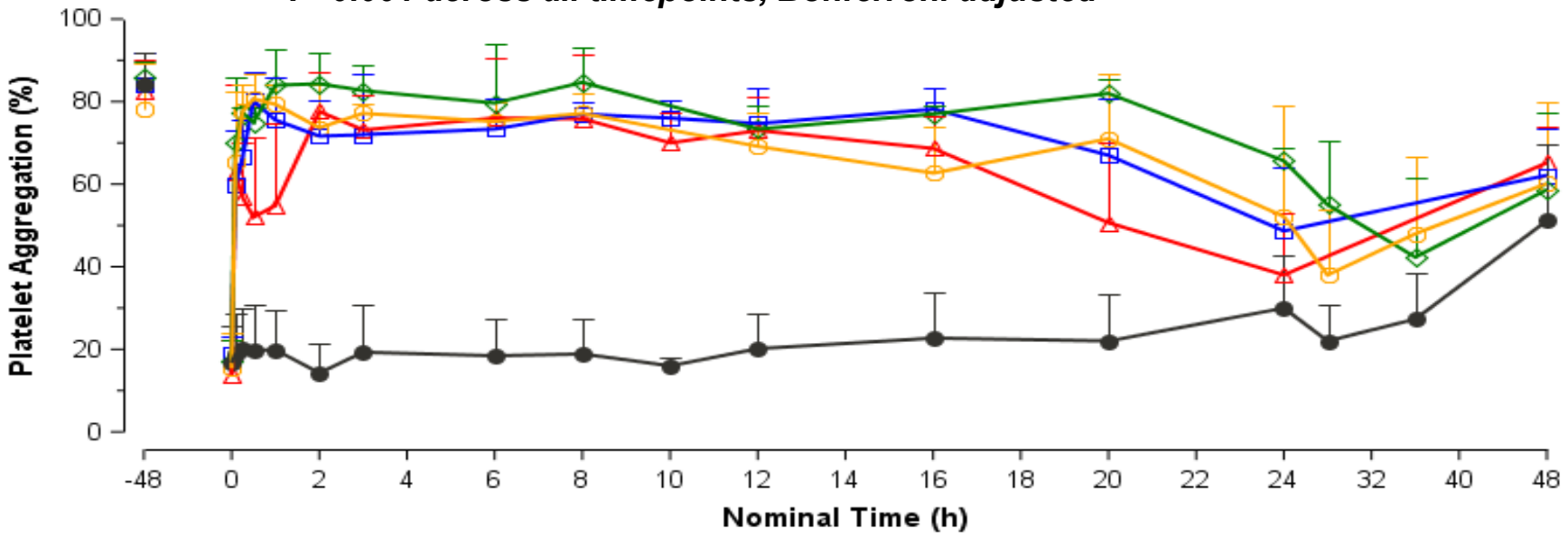
LTA= light transmittance aggregometry; ADP is the agonist

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Onset and Duration of Ticagrelor Reversal - LTA

Volunteers in Cohorts 7-10 were given fixed 18-g doses of PB2452 for 8, 12, and 16 hours in Cohorts 7, 8, and 9/10, respectively

P<0.001 across all timepoints, Bonferroni adjusted

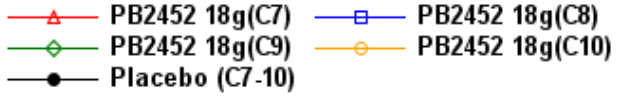


1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion of 18 g PB2452.**

P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h
7	0.040	0.040	0.131	0.037	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.224
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020

Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected. P-values for time point 24 hours or above are not significant.



LTA= light transmittance aggregometry; ADP is the agonist

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Onset and Duration of Ticagrelor Reversal - LTA

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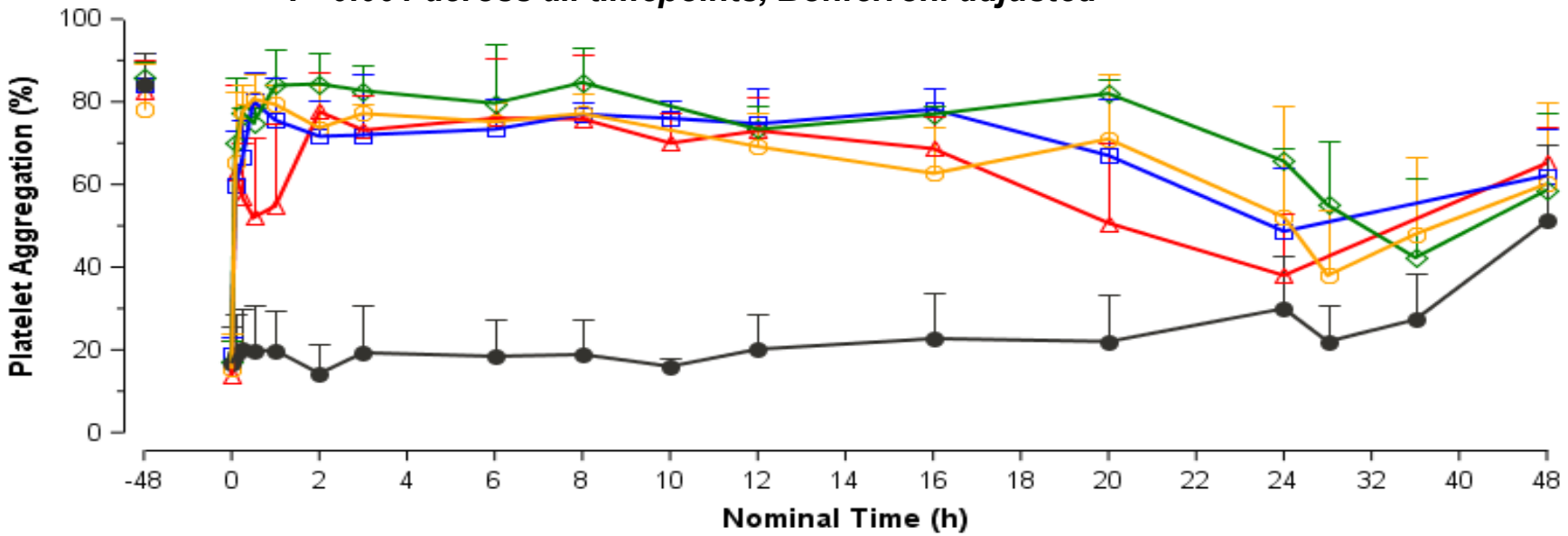
P<0.001 across all timepoints, Bonferroni adjusted



1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion of 18 g PB2452.**
2. **Significant reversal was observed 5 minutes after initiation of PB2452 infusion.**

P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h
7	0.040	0.040	0.131	0.037	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.224
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020

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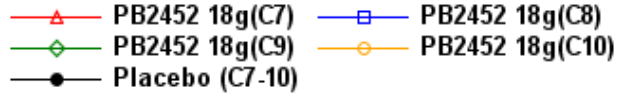

LTA= light transmittance aggregometry; ADP is the agonist

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Onset and Duration of Ticagrelor Reversal - LTA

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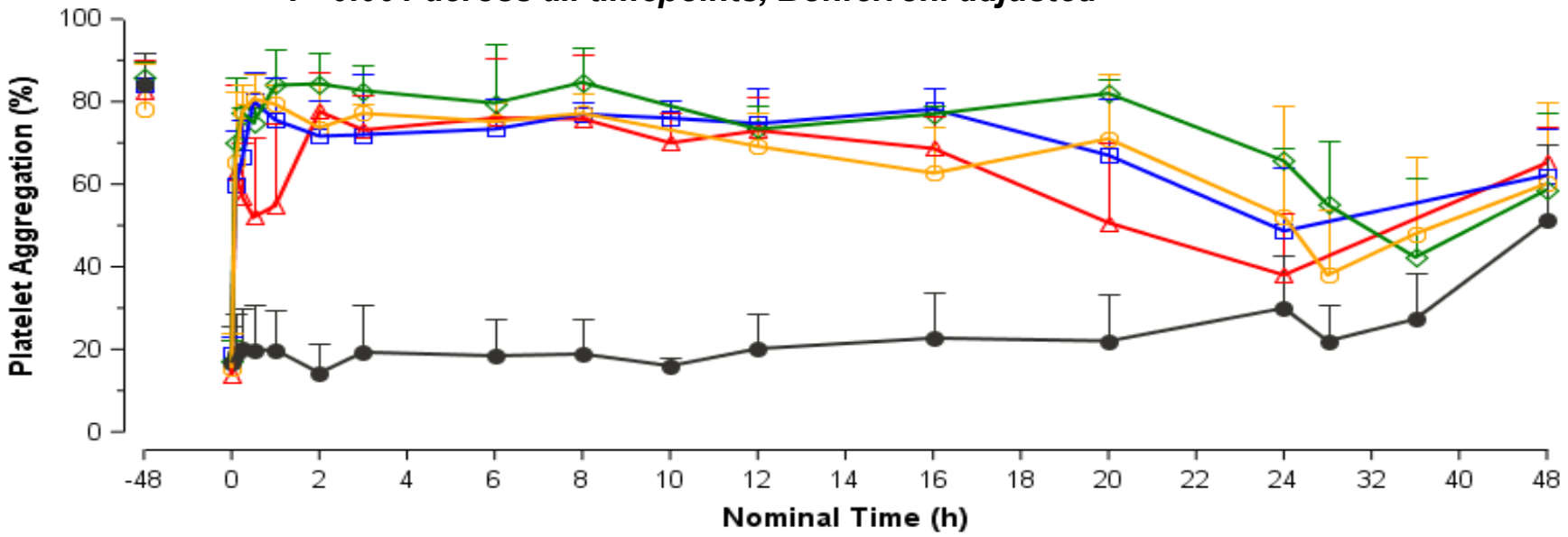
P<0.001 across all timepoints, Bonferroni adjusted

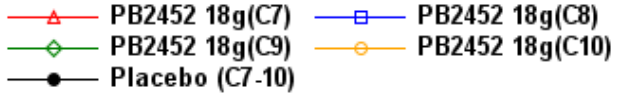


1. **Immediate and sustained ticagrelor reversal with bolus + prolonged infusion of 18 g PB2452.**
2. **Significant reversal was observed 5 minutes after initiation of PB2452 infusion.**
3. **Duration of reversal was infusion-time dependent, lasting 20-24 hours with a 16-hour infusion.**

P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h
7	0.040	0.040	0.131	0.037	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.224
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020

Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected. P-values for time point 24 hours or above are not significant.

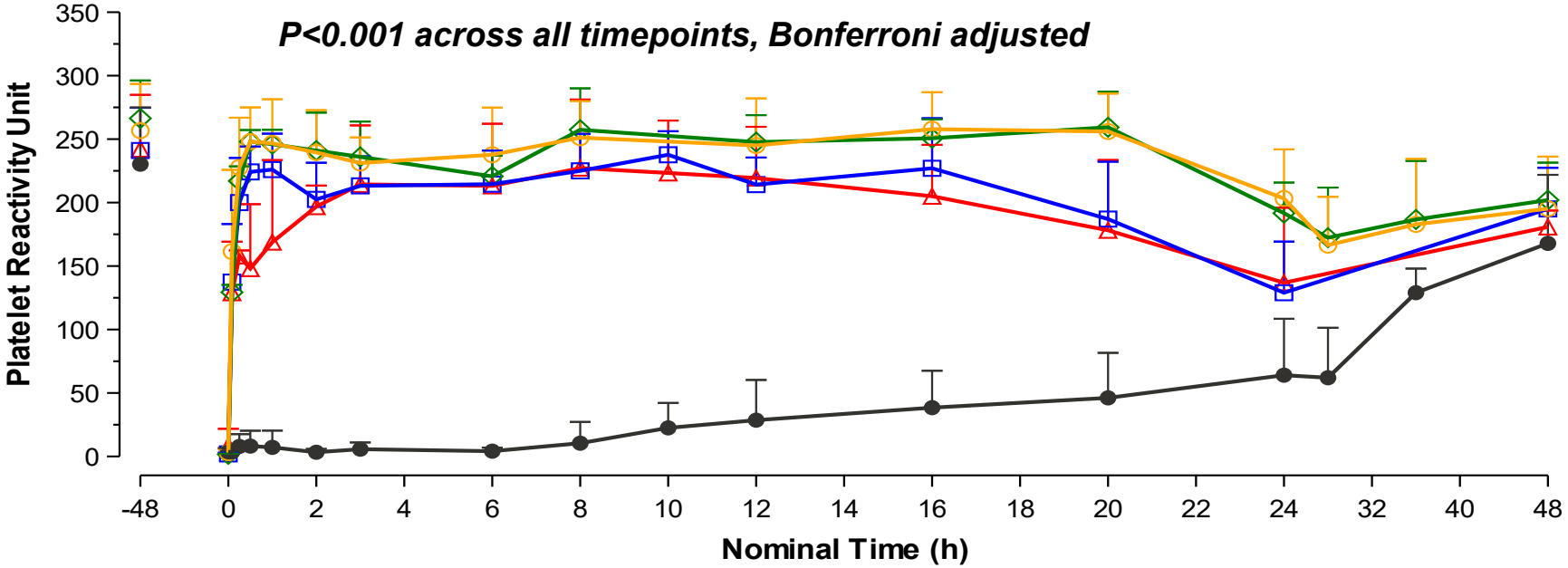


LTA= light transmittance aggregometry; ADP is the agonist

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Onset and Duration of Ticagrelor Reversal – VerifyNow P2Y12 (PRU)

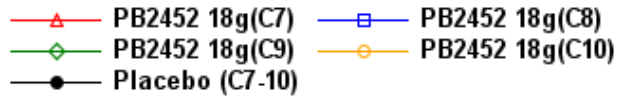
Platelet aggregation as observed in the PB2452 and placebo groups (Cohorts 7-10)



Immediate and sustained ticagrelor reversal with bolus + prolonged infusion of 18 g PB2452 as assessed by the VerifyNow P2Y12 assay.

P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h	24h
7	0.040	0.040	0.097	0.019	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.019	0.559
8	0.019	0.040	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019	0.485
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020	0.020



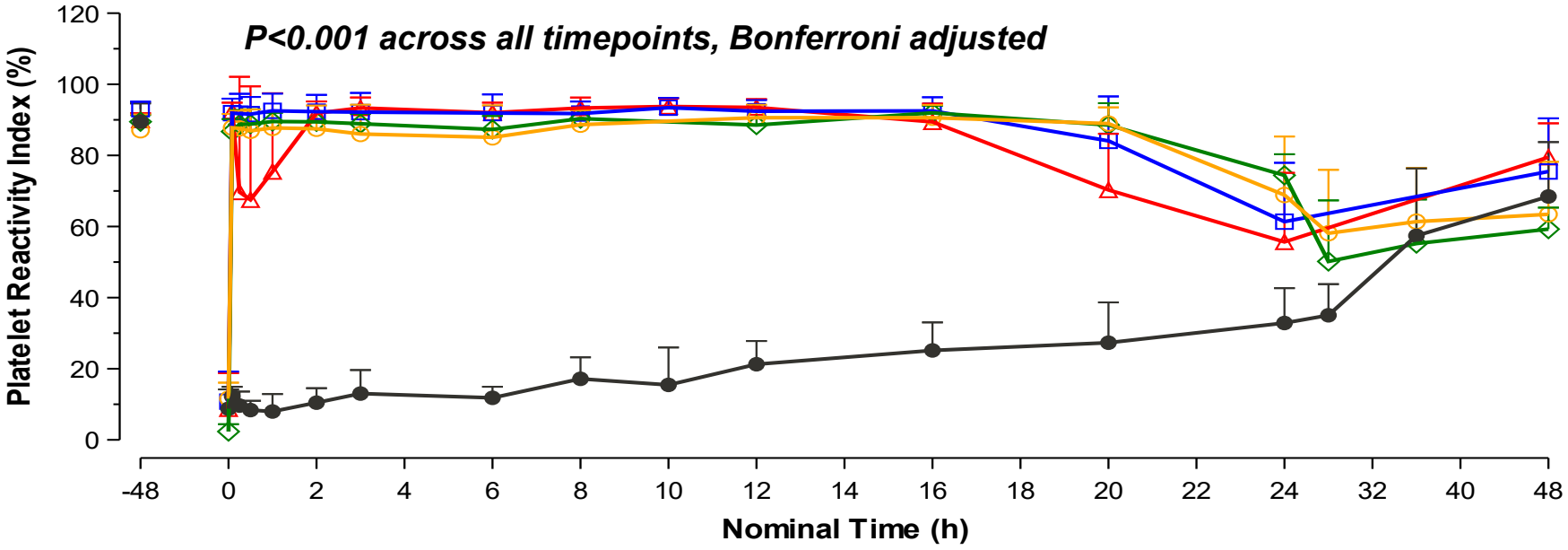
Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected.
P-values post time point 24 hours are not significant.

PRU= Platelet Reactivity Units

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Onset and Duration of Ticagrelor Reversal – VASP PRI

Platelet aggregation observed in the PB2452 and placebo groups (Cohorts 7-10)



Immediate and sustained ticagrelor reversal with bolus + prolonged infusion of 18 g PB2452 as assessed by the VASP assay.

P values by timepoint for each cohort

Cohort	5min	0.25h	0.5h	1h	2h	3h	6h	8h	10h	12h	16h	20h	24h
7	0.040	0.040	0.019	0.019	0.040	0.019	0.019	0.019	0.152	0.019	0.019	0.019	0.354
8	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.019	0.152	0.019	0.019	0.019	0.283
10	0.043	0.020	0.020	0.020	0.020	0.020	0.020	0.020	N/A	0.020	0.020	0.020	0.040

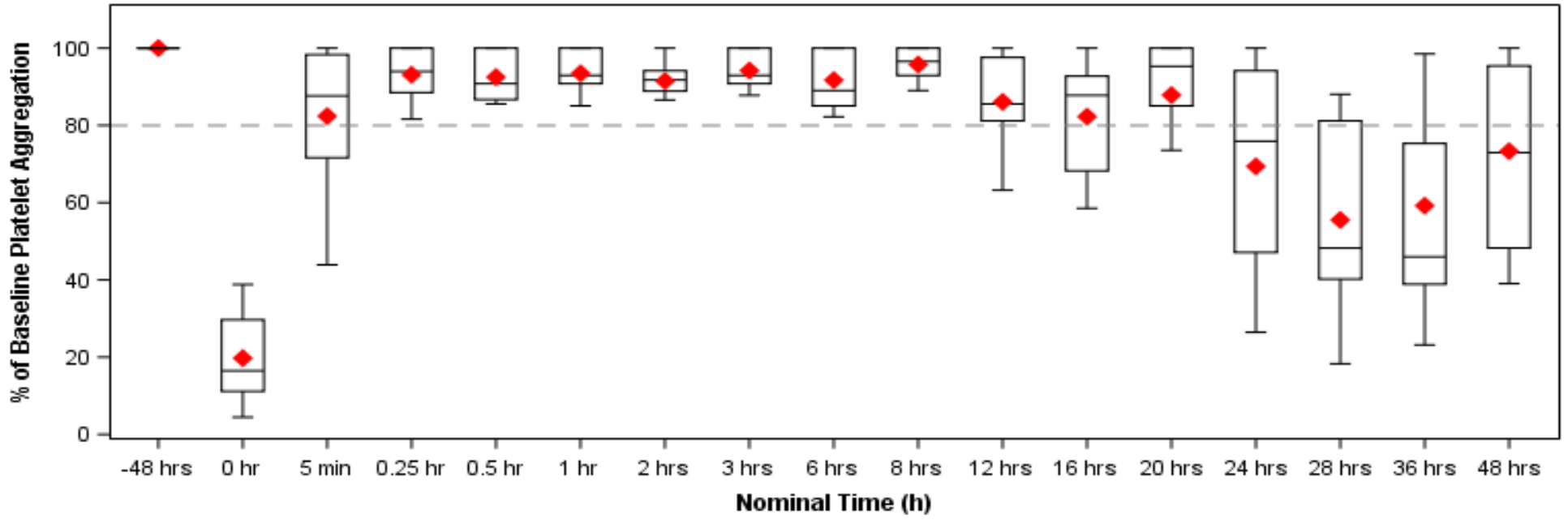
Due to the small sample size for cohort 9 (n=3), statistical testing was not performed. For Cohorts 9 and 10, no 10-hour timepoint was collected.
P-values post time point 24 hours are not significant.

VASP PRI= vasodilator stimulated phosphoprotein platelet reactivity index

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Platelet Function After Ticagrelor Reversal - LTA

Normalization of platelet response to ADP was assessed by whether reversal of ticagrelor achieved a normal range of platelet function



1. **Normal platelet function post-reversal was considered to be ≥ 80% of baseline, indicated by the dashed line.**

LTA= light transmittance aggregometry

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

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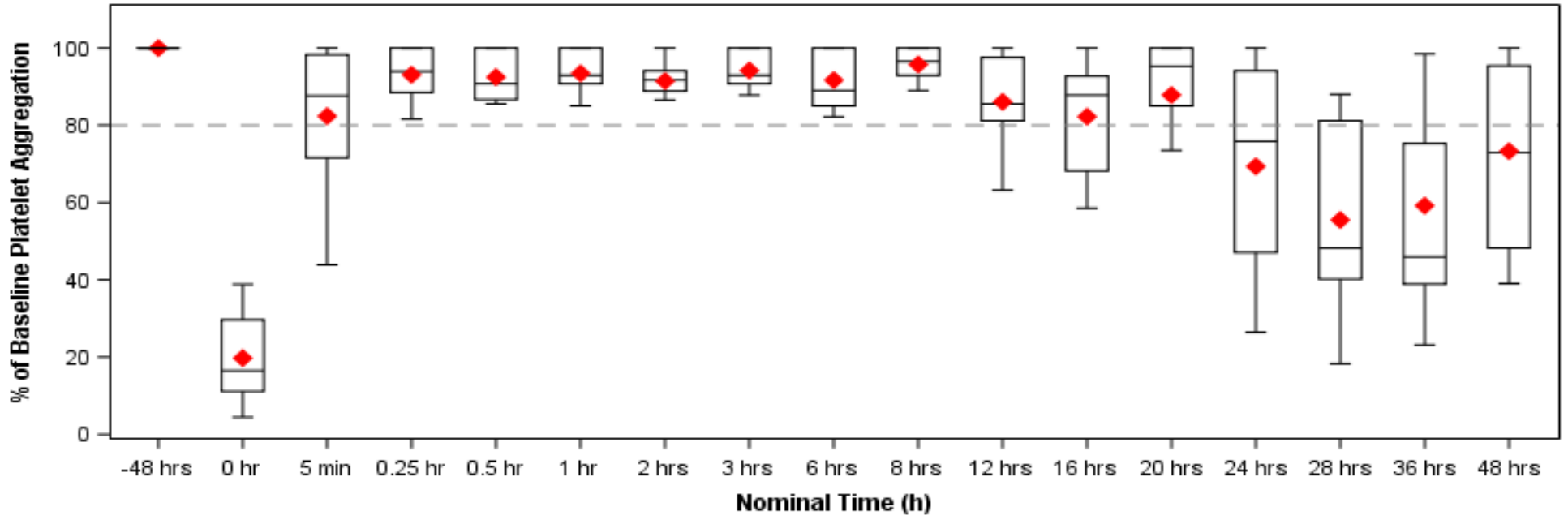


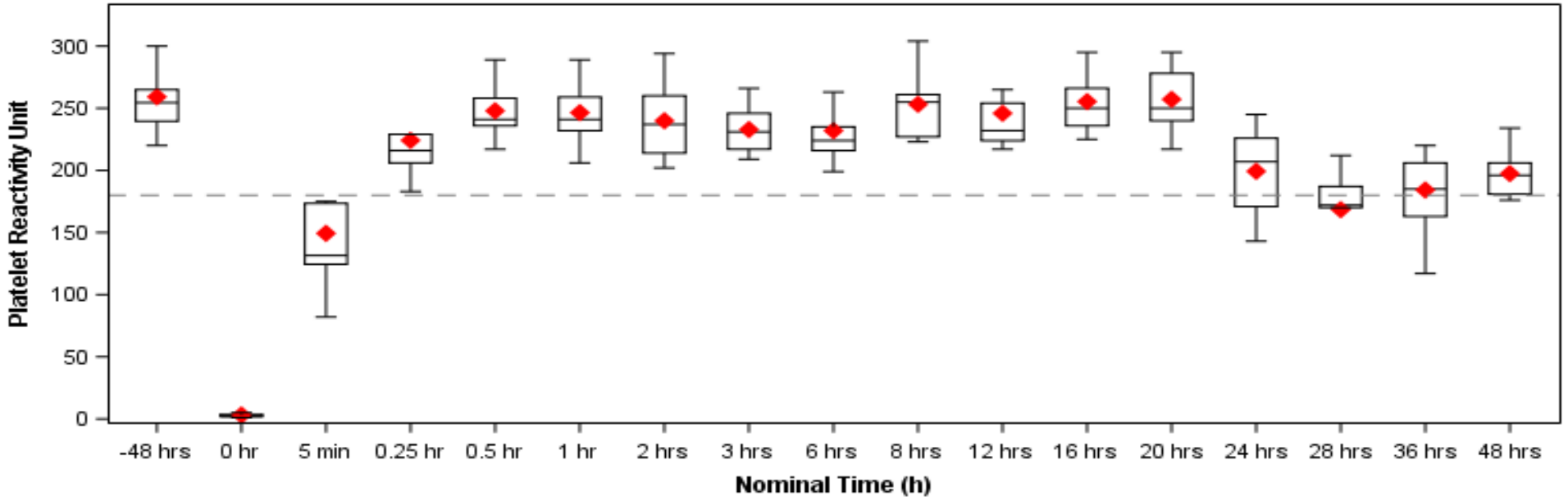
1. **Normal platelet function post-reversal was considered to be ≥ 80% of baseline, indicated by the dashed line.**
2. **Within 5 minutes, this was achieved and sustained for at least 20 hours.**

LTA= light transmittance aggregometry

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Platelet Function After Ticagrelor Reversal – VerifyNow P2Y12 PRU

Normalization of platelet response was assessed by whether reversal of ticagrelor normalized platelet reactivity



1. **Normal platelet function post-reversal was considered to be ≥ 180 PRU, indicated by the dashed line.**

PRU= Platelet Reactivity Units

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Platelet Function After Ticagrelor Reversal – VerifyNow P2Y12 PRU

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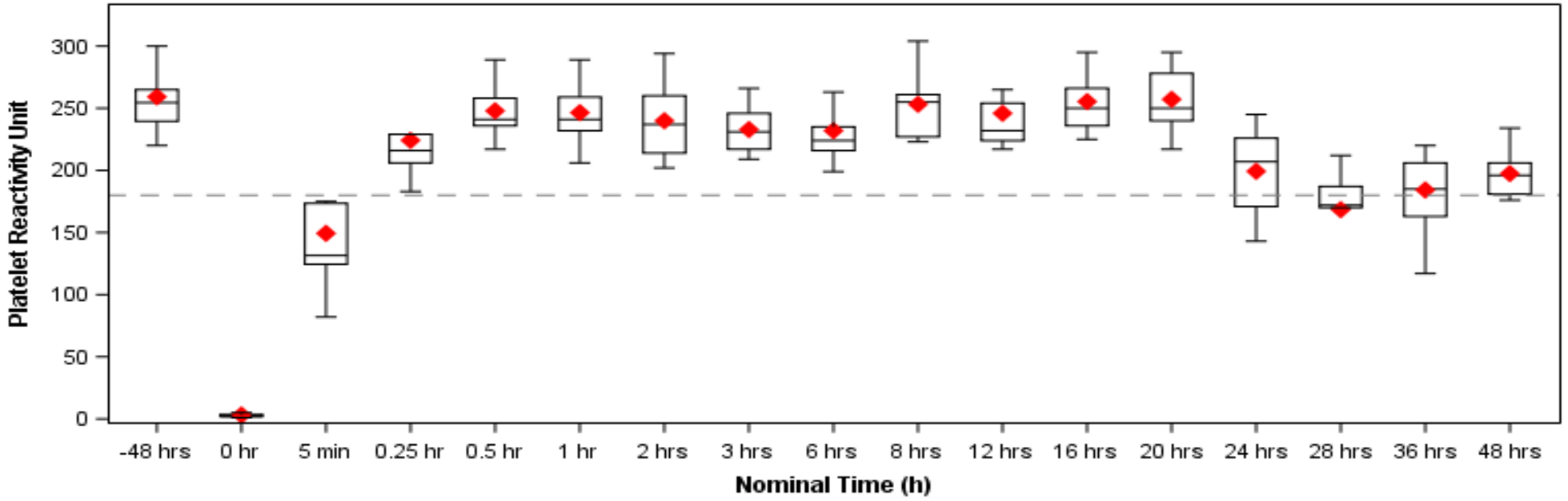

1. **Normal platelet function post-reversal was considered to be ≥ 180 PRU, indicated by the dashed line.**
2. **Essentially the same pattern for onset and offset of reversal was seen using the VerifyNowP2Y12 assay.**

PRU= Platelet Reactivity Units

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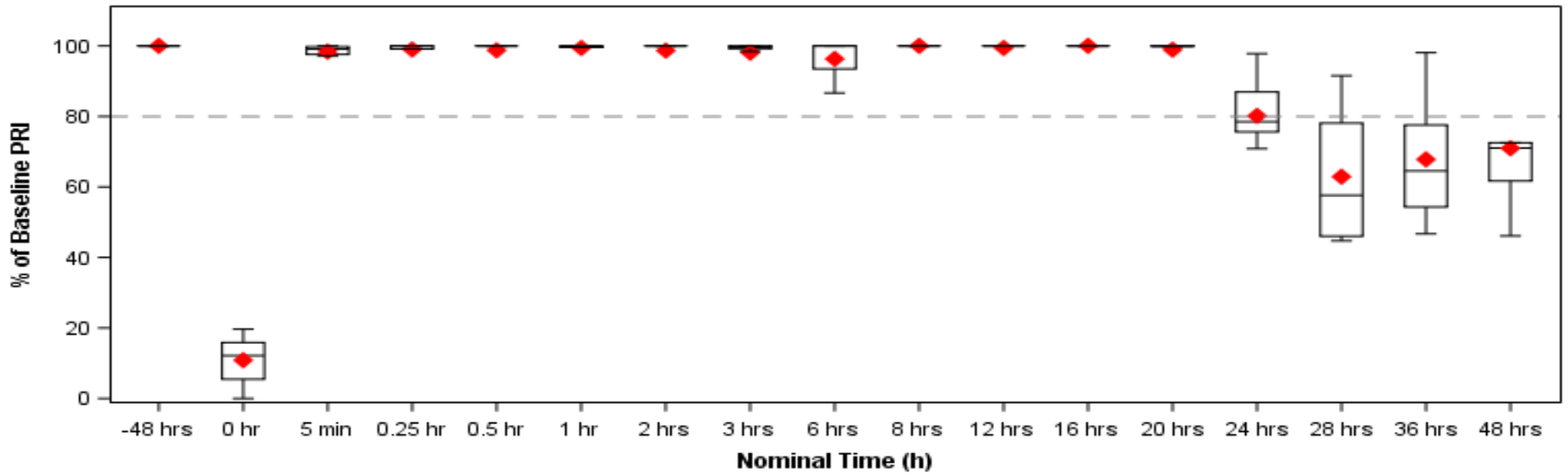
Platelet Function After Ticagrelor Reversal – VASP PRI

Normalization of platelet response was assessed by whether reversal of ticagrelor achieved a normal range of platelet function



Normal platelet function post-reversal was considered to (dashed line)

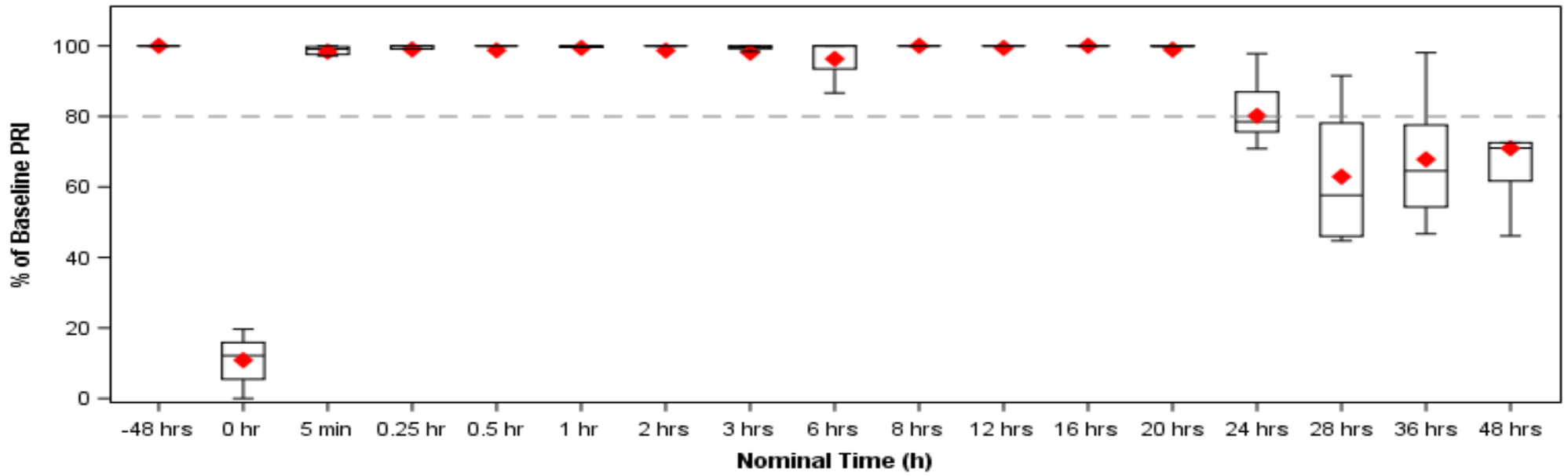
1. **Normal platelet function post-reversal was considered to be ≥ 80% of baseline PRI, indicated by the dashed line.**

VASP PRI= vasodilator stimulated phosphoprotein platelet reactivity index

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Platelet Function After Ticagrelor Reversal – VASP PRI

Normalization of platelet response was assessed by whether reversal of ticagrelor achieved a normal range of platelet function



Normal platelet function post-reversal was considered to (dashed line)

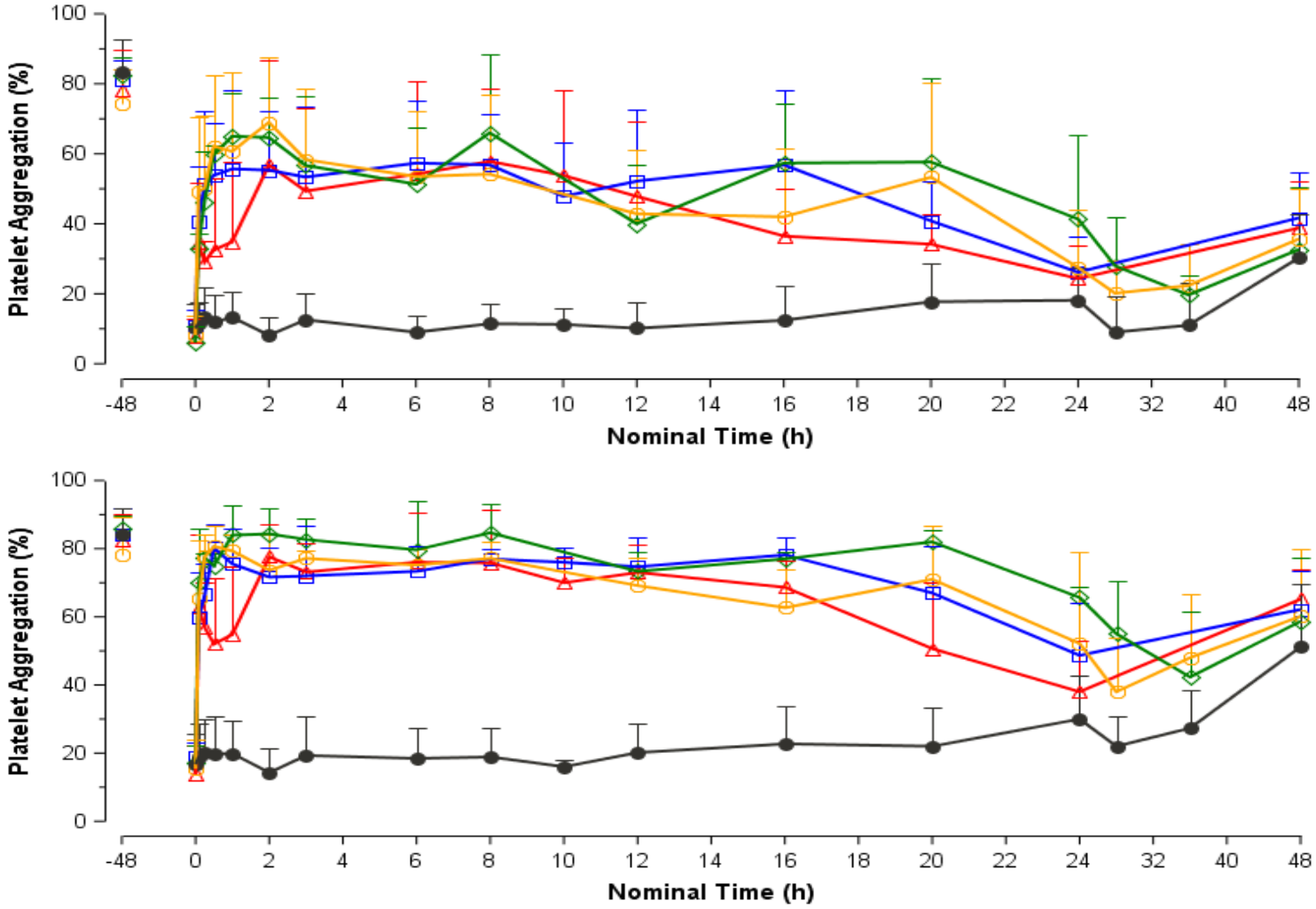
1. **Normal platelet function post-reversal was considered to be ≥ 80% of baseline PRI, indicated by the dashed line.**
2. **Essentially the same pattern for onset and offset of reversal was seen using the VASP assay.**

VASP PRI= vasodilator stimulated phosphoprotein platelet reactivity index

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Platelet Aggregation with Low- and High-Dose ADP

Mean platelet aggregation by LTA using 5 μM ADP (top) or 20 μM ADP (bottom) as agonist



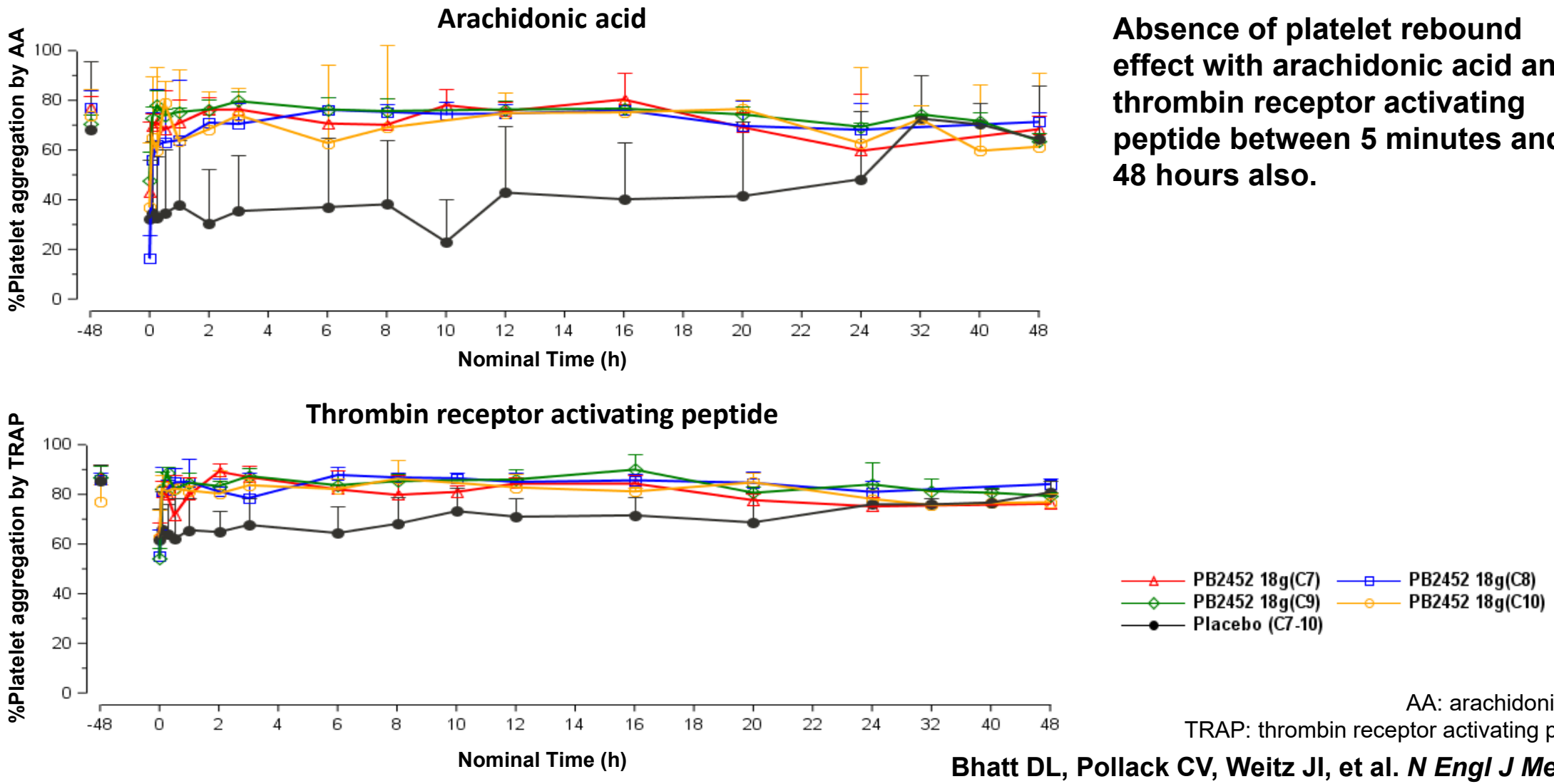
Platelet hyper-reactivity, or rebound, between 5 minutes and 48 hours was ruled out by the response to low-dose ADP versus high-dose ADP.

LTA: light transmission aggregometry;
ADP: adenosine diphosphate

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Platelet Aggregation with AA and TRAP

Mean platelet aggregation by LTA using AA (top) or TRAP(bottom) as agonist



Absence of platelet rebound effect with arachidonic acid and thrombin receptor activating peptide between 5 minutes and 48 hours also.

AA: arachidonic acid;
TRAP: thrombin receptor activating peptide

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Summary

- Of the 64 volunteers randomized, 48 received PB2452,16 received placebo.
- After 48 hours of ticagrelor, platelet aggregation was suppressed by ~80%.
- Compared with placebo, PB2452 administered as a 10-minute IV bolus, followed by 16-hour infusion, significantly restored platelet function as measured by multiple assays.
- Onset of reversal occurred within 5 minutes and was sustained for over 20 hours ($P<0.001$, Bonferroni-adjusted across all time points for all assays).
- There was no evidence of rebound in platelet activity after drug cessation.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Treatment-emergent Serious Adverse Events

None study-related per blinded investigator

Preferred Term	All Placebo (N=16) n (%)	All PB2452 (N=48) n (%)
Total Number of SAEs	0	2
PB2452-related SAEs	0	0
Unrelated SAEs*	0	2 (4.2)
Alcohol intoxication	0	1 (2.1)
Acute Respiratory Failure	0	1 (2.1)

*Both SAEs occurred in the same individual 4 days after discharge from the clinical site

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Treatment-emergent Adverse Events

Preferred Term	All Placebo (N=16) n (%)	All PB2452 (N=48) n (%)
Total Number of TEAEs	3	27
Number of volunteers with at Least 1 TEAE	2 (12.5)	17 (35.4)
Infusion site bruising	0	4 (8.3)
Medical device site reaction	0	3 (6.3)
Infusion site extravasation	0	2 (4.2)
Vessel puncture site bruise	0	2 (4.2)
Abdominal pain	0	1 (2.1)
Acute respiratory failure	0	1 (2.1)
Alcohol poisoning	0	1 (2.1)
Blood urine present	0	1 (2.1)
Conjunctivitis	0	1 (2.1)
Contusion	1 (6.3)	0
Dizziness	0	1 (2.1)
Eyelid irritation	1 (6.3)	0
Gastroenteritis	0	1 (2.1)
Hematuria	0	1 (2.1)
Infusion site reaction	0	1 (2.1)
Musculoskeletal chest pain	1 (6.3)	0
Nasopharyngitis	0	1 (2.1)
Oropharyngeal pain	0	1 (2.1)
Pharyngitis streptococcal	0	1 (2.1)
Pneumonia aspiration	0	1 (2.1)
Skin abrasion	0	1 (2.1)
Upper limb fracture	0	1 (2.1)

Mostly limited to mild injection site issues.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Limitations

- We studied healthy volunteers and not patients with atherosclerosis.
- The sample size was modest, although it was well-powered for pharmacodynamic endpoints, and all platelet assay results were consistent and highly significant.
- This study was not designed to evaluate the impact of PB2452 on clinical bleeding events.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Conclusion

- Using multiple assays in healthy volunteers, PB2452, a specific reversal agent for ticagrelor, provided immediate and sustained reversal of ticagrelor's antiplatelet effects.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Conclusion

- Using multiple assays in healthy volunteers, PB2452, a specific reversal agent for ticagrelor, provided immediate and sustained reversal of ticagrelor's antiplatelet effects.

- The ability to reverse ticagrelor's antiplatelet effects rapidly could distinguish it from other antiplatelet drugs.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Conclusion

- Using multiple assays in healthy volunteers, PB2452, a specific reversal agent for ticagrelor, provided immediate and sustained reversal of ticagrelor's antiplatelet effects.

- The ability to reverse ticagrelor's antiplatelet effects rapidly could distinguish it from other antiplatelet drugs.

- PB2452 may be a useful way to treat or prevent bleeding complications due to ticagrelor.

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

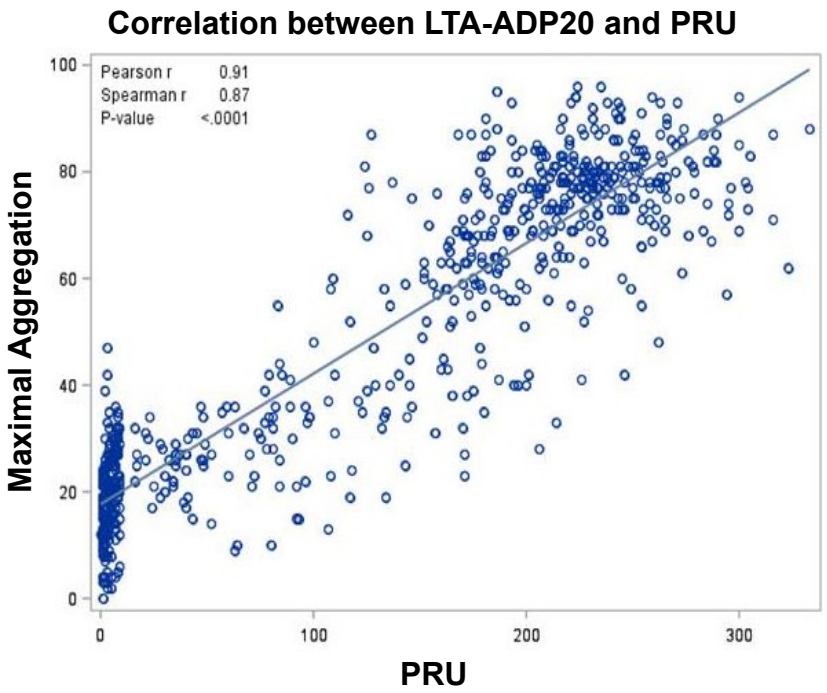
Antibody-Based Ticagrelor Reversal Agent in Healthy Volunteers

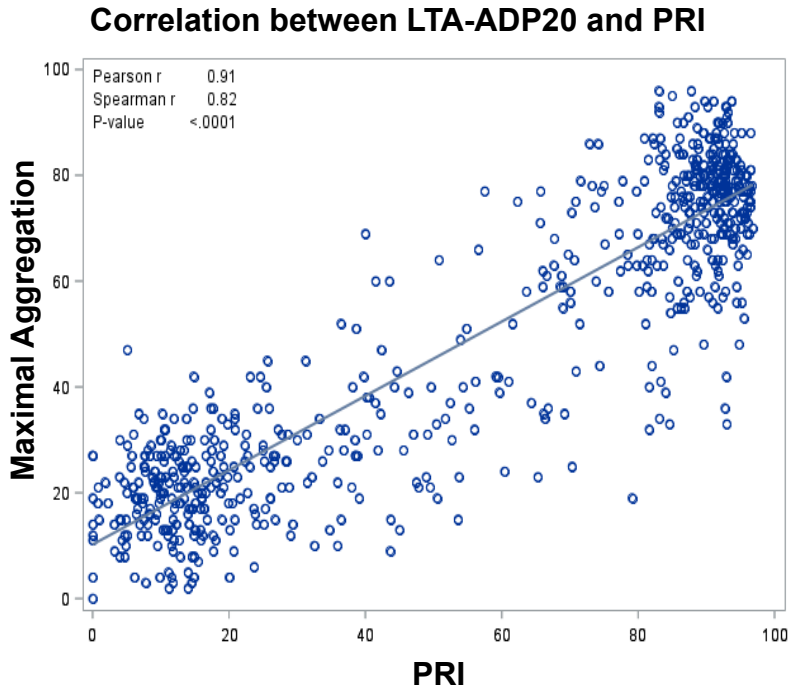
Deepak L. Bhatt, M.D., M.P.H., Charles V. Pollack, M.D., Jeffrey I. Weitz, M.D., Lisa K. Jennings, Ph.D., Sherry Xu, Ph.D., Susan E. Arnold, Ph.D., Bret R. Umstead, M.S., Michael C. Mays, B.S., and John S. Lee, M.D., Ph.D.

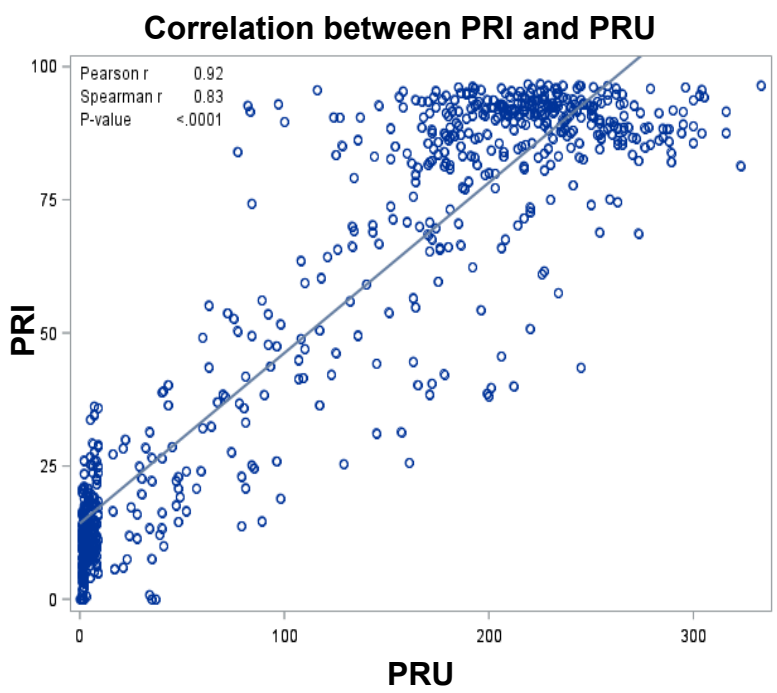
Article available at https://www.nejm.org
Slides available for download at https://www.ACC.org

Correlation Between Platelet Function Assays

LTA, VerifyNow P2Y12 PRU, and VASP PRI





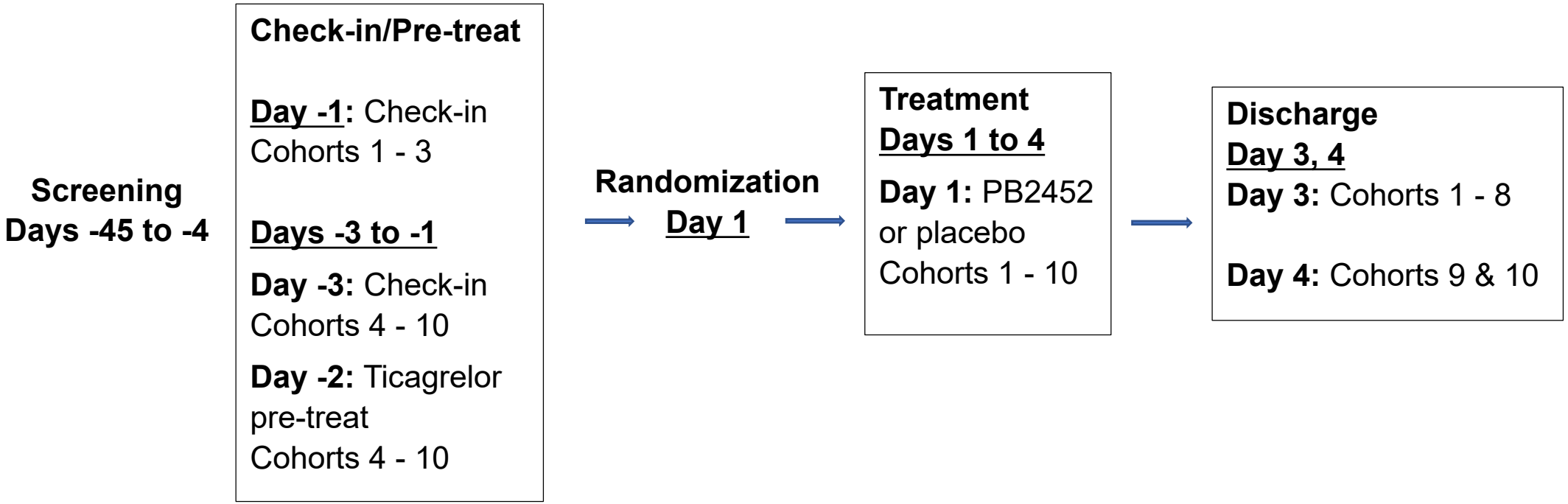


Pearson and Spearman correlation analyses were performed between platelet function assays, r values represent correlation coefficients. P < 0.0001 for all analyses.

LTA= light transmittance aggregometry, PRU= Platelet Reactivity Units,
VASP PRI= vasodilator stimulated phosphoprotein platelet reactivity index

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

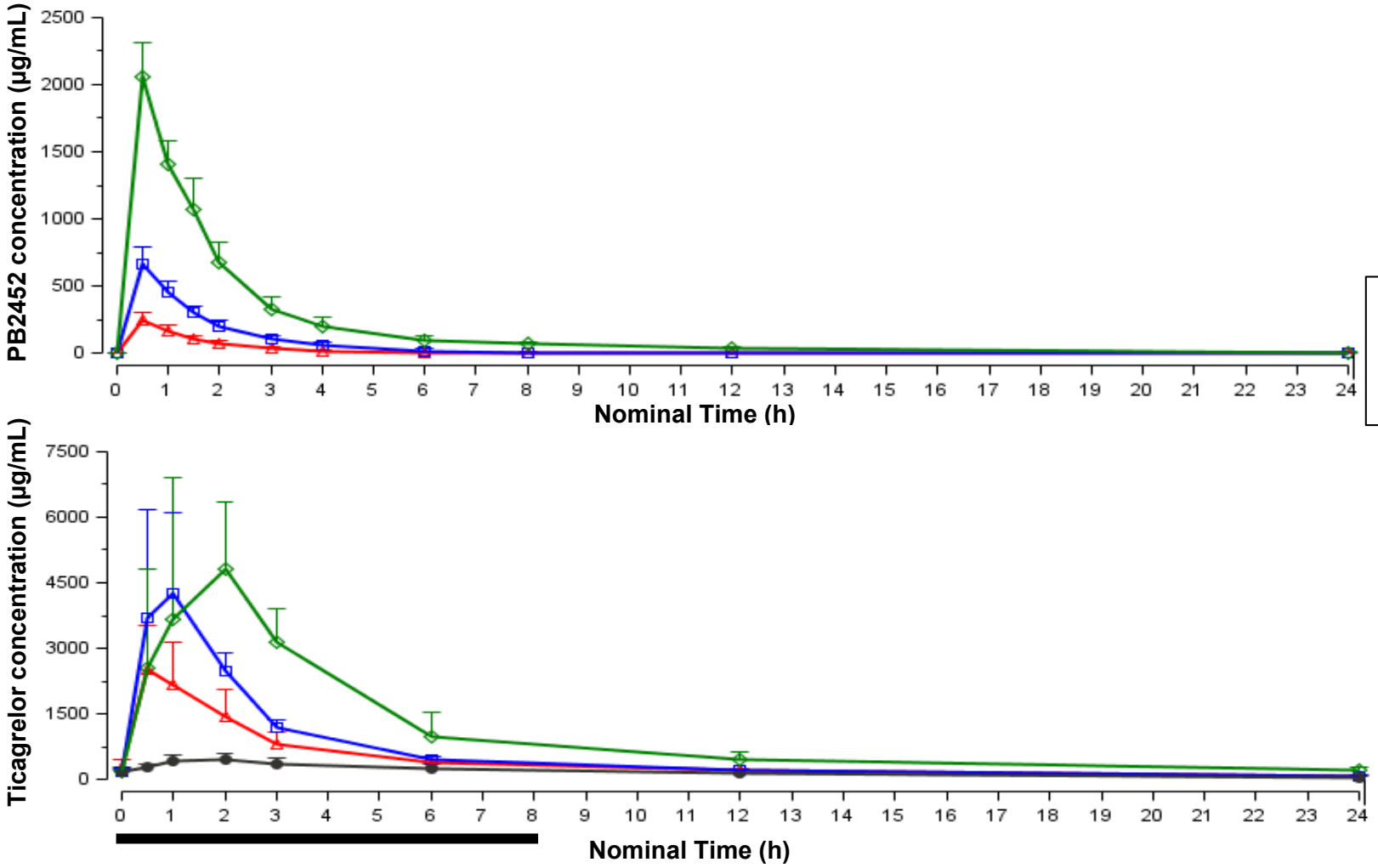
Study Timeline



Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Pharmacokinetics of PB2452 and Ticagrelor

Circulating drug concentrations of ascending doses of PB2452 over time (top) and of total ticagrelor in Cohorts 4, 5, and 6



Cohort | treatment

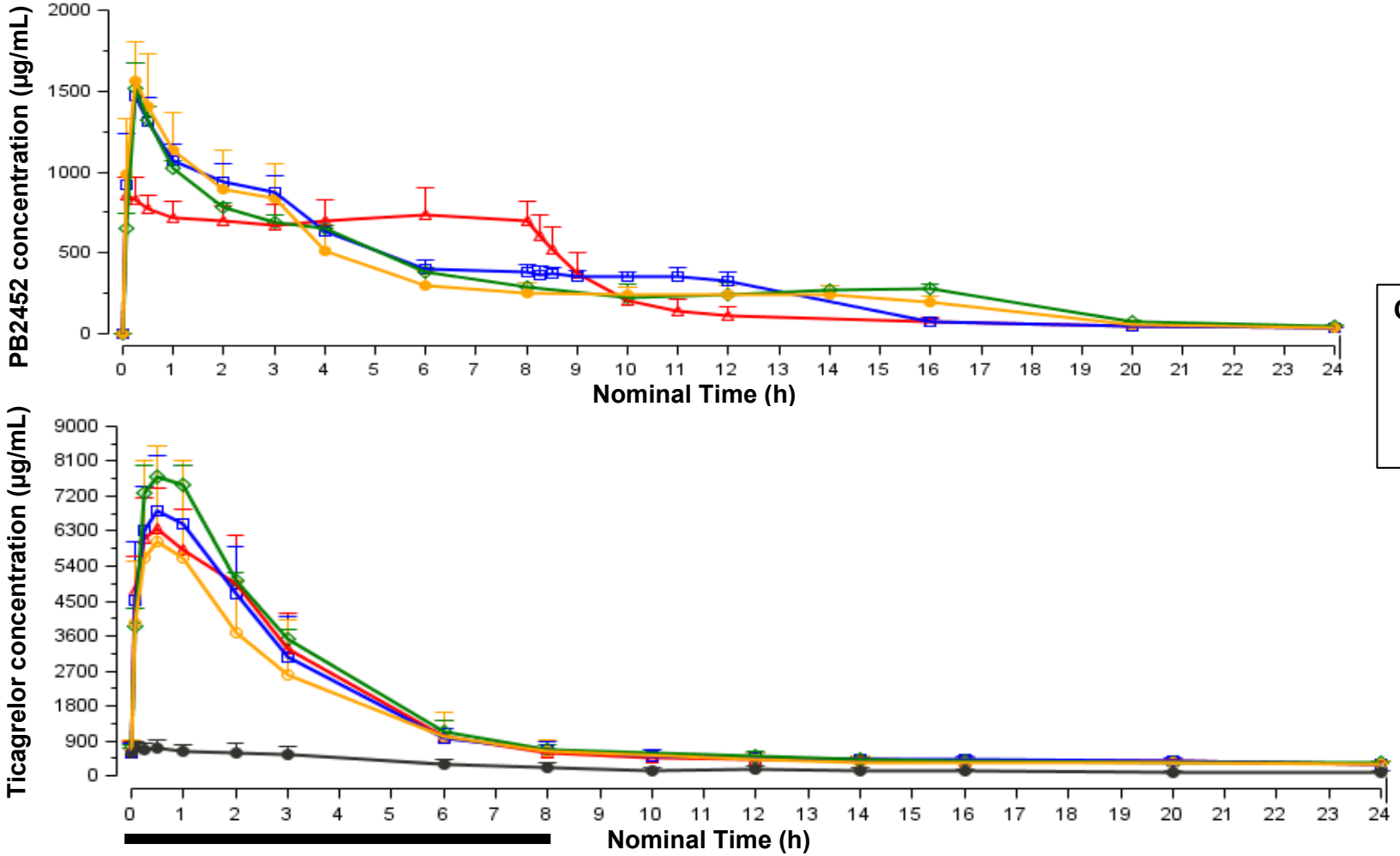
- C4 | 1 g PB2452
- C5 | 3 g PB2452
- C6 | 9 g PB2452
- C7—C10 Placebo

Solid black line shows the period of ticagrelor redistribution induced by circulating PB2452

Bhatt DL, Pollack CV, Weitz JI, et al. *N Engl J Med*. 2019.

Pharmacokinetics of PB2452 and Ticagrelor

Circulating drug concentrations over time of fixed 18 g doses of PB2452 with extended infusion times and of total ticagrelor in Cohorts 7-10



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