Ticagrelor With AspIrin or ALone In HiGH-Risk Patients After Coronary InTervention: Thrombogenicity Substudy

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Declaration of Interest

The TWILIGHT Trial

Sponsoring organization: Icahn School of Medicine at Mount Sinai, NY

Funded by AstraZeneca

Coordinated by Icahn School of Medicine at Mount Sinai, NY

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Disclosures

Affiliation/Financial Relationship	Company
Advisory board/personal fees	Boston Scientific, AstraZeneca
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Background

- Several trials have shown that monotherapy with a $P2Y_{12}$ inhibitor alone results in similar rates of adverse ischemic events as compared with dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI).[1-4]

- However, most studies were characterized by relatively infrequent[1,2] or lower than expected rates of ischemic events[3,4], thus compromising power to detect signals of harm upon withdrawal of aspirin.

- Examining the direct effect of aspirin withdrawal on human endovascular thrombosis may provide a mechanistic basis for these observations and additional support for a clinical strategy of $P2Y_{12}$ inhibition alone after PCI.

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[1]Hahn et al., JAMA 2019 [2]Watanabe et al., JAMA 2019
[3]Vranckx et al., Lancet 2018 [4]Mehran et al., NEJM 2019

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Objective

To compare the antithrombotic potency of ticagrelor alone versus ticagrelor plus aspirin on ex-vivo whole blood thrombogenicity among high-risk patients undergoing PCI with drug eluting stents (DES)

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Design

- TWILIGHT enrolled patients undergoing PCI with DES discharged on ticagrelor plus aspirin for at least 3 months. Event-free patients were randomized to aspirin or placebo (double-blind) and continued ticagrelor.
- Mechanistic-oriented substudy was nested within TWILIGHT and conducted at a single enrolling site (Mount Sinai Hospital, New York)
- Substudy participants were enrolled after randomization in the main trial, at which time pharmacodynamic studies to establish baseline levels of blood thrombogenicity were performed.
- Patients then commenced randomized therapy and returned 1-6 months thereafter for repeat studies.

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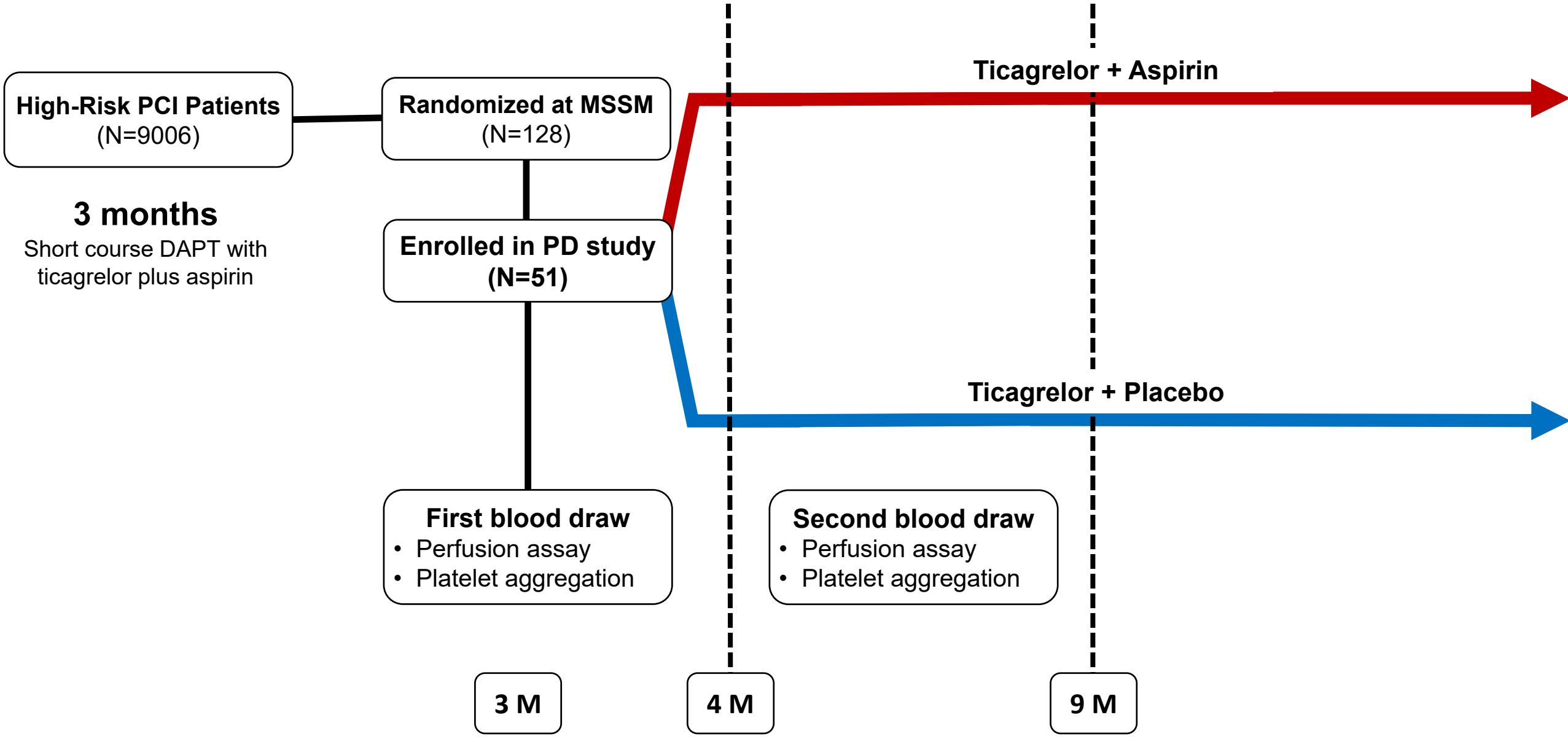
Study Schema



Endpoints and Experimental Methods

- **Primary Endpoint**
  - **Blood thrombogenicity** (platelet-dependent thrombus area) at the post-randomization visit using the Badimon perfusion chamber[5]
  - Validated, *ex-vivo* model that generates thrombus under dynamic flow conditions of shear stress that mimic moderate arterial stenosis (high shear; 1690 sec^{-1}).
  - Native, non-anticoagulated whole blood is perfused over disrupted porcine tunica media, which is then processed and quantified using digital planimetry (μm^2).

- **Secondary Endpoint**
  - Platelet reactivity in whole blood measured with impedance aggregometry (Multiplate Analyzer® DiaPharma - West Chester, OH)
  - Agonists included adenosine diphosphate (ADP), arachidonic acid (AA), collagen and thrombin receptor activator peptide-6 (TRAP).

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[5]*Vilahur et al., Circulation 2004*

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Statistical Methods

- Treatment effect (ticagrelor monotherapy versus ticagrelor plus aspirin) examined using analysis of covariance (ANCOVA)
- Between-group difference in thrombus area was adjusted for baseline values, expressed as a mean difference with 95% CI
- A sample size of 40 was required to provide 80% power to detect at least 2200 μm^2 difference in thrombus area between groups with type I error 0.05 and a within-group standard deviation of 2500 μm^2
- Effective antiplatelet and antithrombotic agents display reductions in thrombus area of at least ~ 2,000 μm^2 [6,7]

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[6]*Lev et al., ATVB 2002; Zafar et al., Thromb Haemost 2017*

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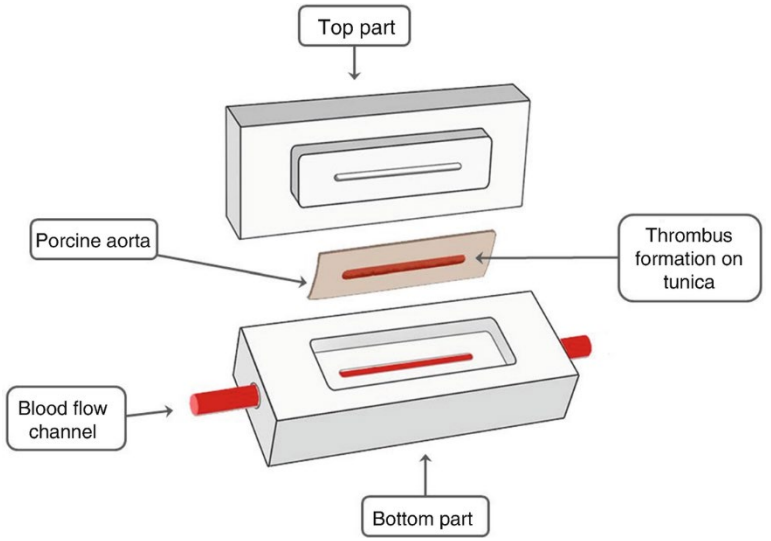
Badimon Perfusion Chamber



Thrombogenic substrate

Thrombus area is quantified

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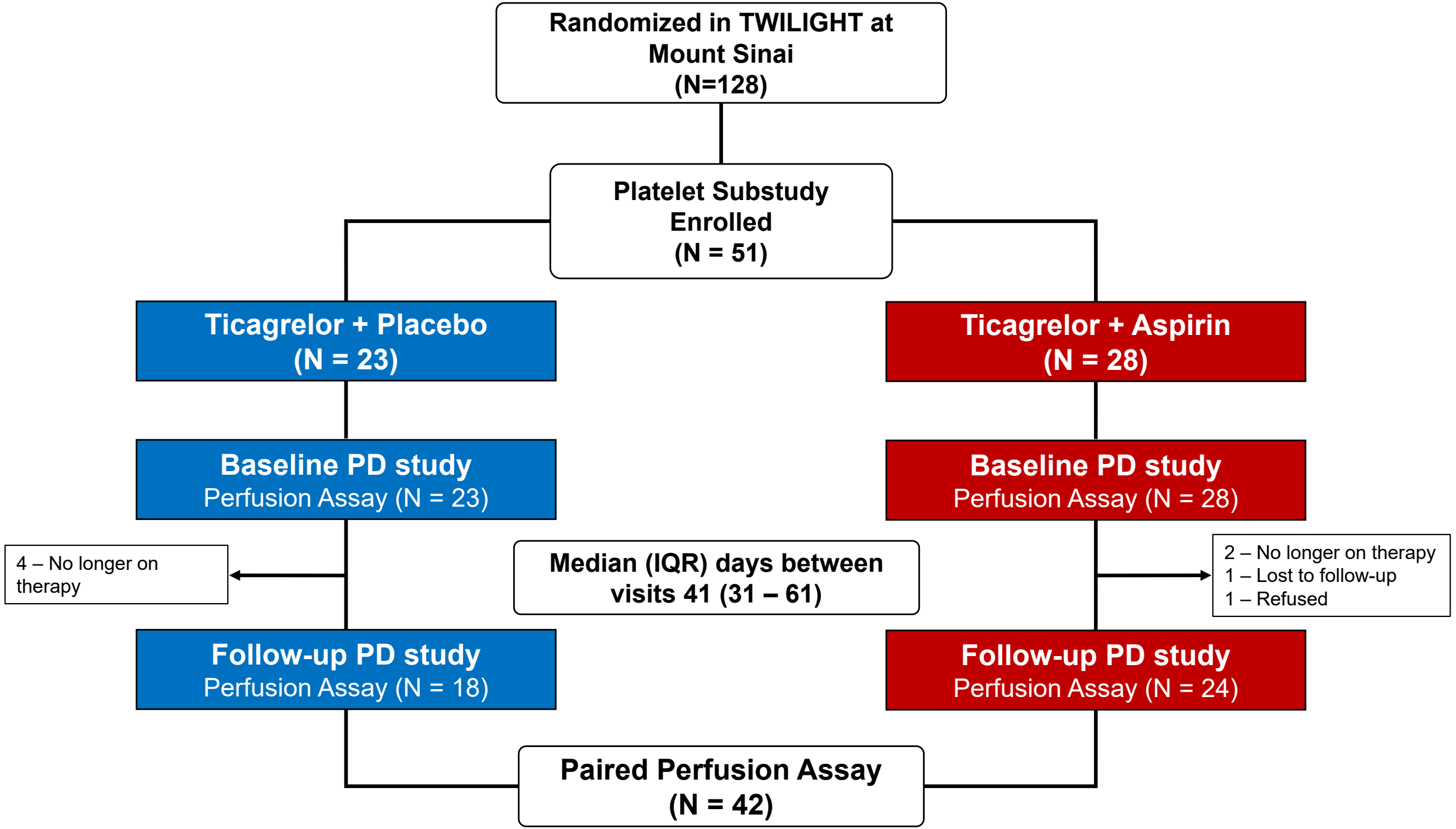

Randomized in TWILIGHT at Mount Sinai (N=128)
Platelet Substudy Enrolled (N = 51)
Ticagrelor + Placebo (N = 23)
Ticagrelor + Aspirin (N = 28)
Baseline PD study Perfusion Assay (N = 23)
Baseline PD study Perfusion Assay (N = 28)
4 – No longer on therapy
Median (IQR) days between visits 41 (31 – 61)
2 – No longer on therapy
1 – Lost to follow-up
1 – Refused
Follow-up PD study Perfusion Assay (N = 18)
Follow-up PD study Perfusion Assay (N = 24)
Paired Perfusion Assay (N = 42)

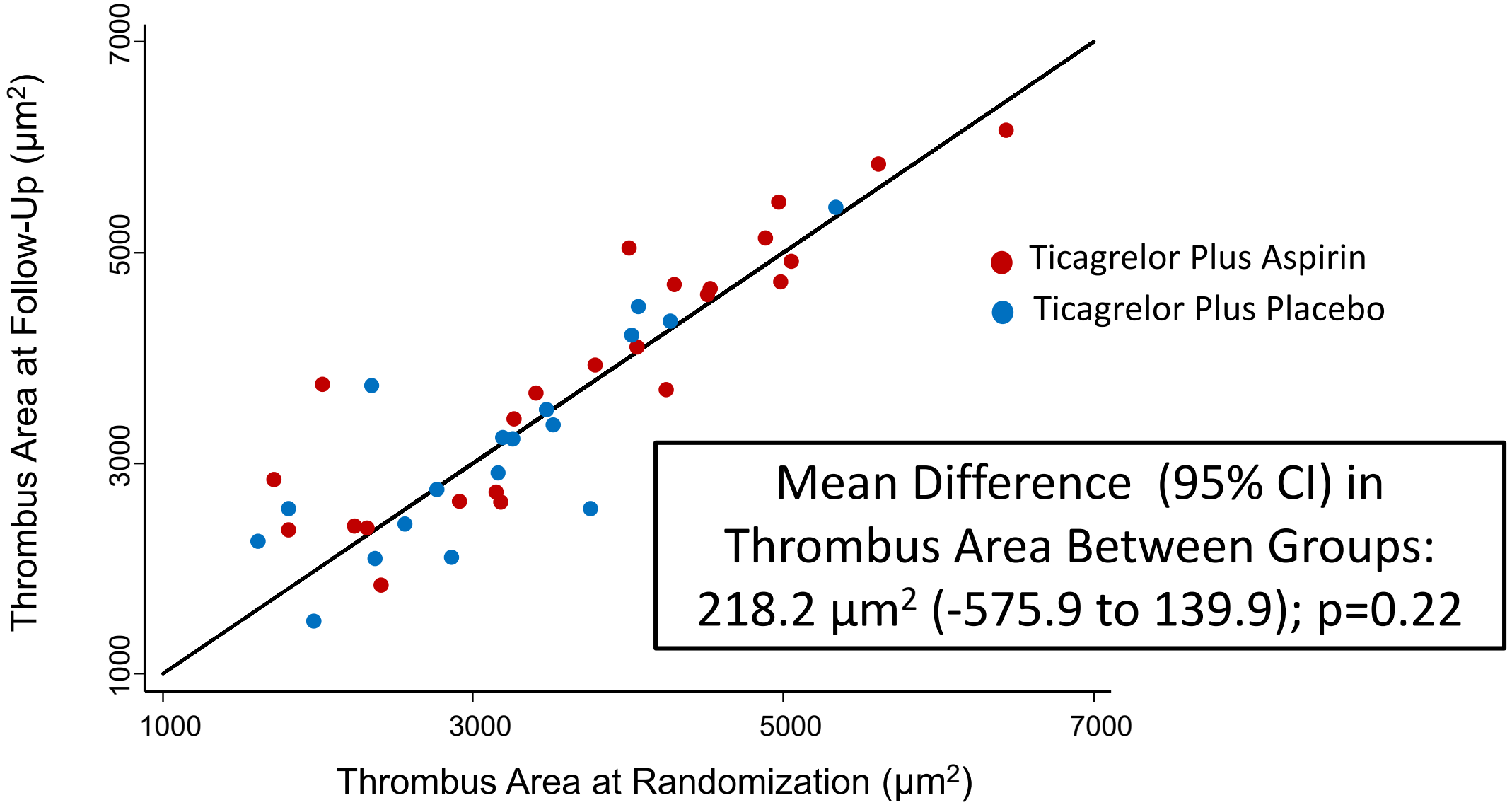
Clinical Characteristics

Variable	Ticagrelor plus Placebo (n=18)	Ticagrelor plus aspirin (n=24)	p-value
Age, years	61.9 ± 9.9	64.6 ± 9.3	0.38
Female Sex	2 (11.1%)	3 (12.5%)	0.89
Nonwhite Race	11 (61.1%)	12 (50%)	0.57
Body mass index, kg/m^2	28.9 ± 4.8	28.5 ± 5.4	0.81
Diabetes Mellitus	5 (27.8%)	10 (41.7%)	0.35
Current Smoker	2 (11.1%)	5 (20.8%)	0.47
Hypercholesterolemia	15 (83.3%)	21 (87.5%)	0.70
Hypertension	18 (100.0%)	21 (87.5%)	0.12
Prior myocardial infarction	1 (5.6%)	5 (20.8%)	0.16
Prior PCI	12 (66.7%)	18 (75.0%)	0.55
Prior coronary artery bypass	2 (11.1%)	2 (8.3%)	0.76
Chronic kidney disease	1 (5.6%)	3 (12.5%)	0.45
Hemoglobin, g/dl	12.9 ± 1.2	13.4 ± 1.9	0.31
Platelet count (x10^3/µL)	243.1 ± 60.2	213.6 ± 56.1	0.11

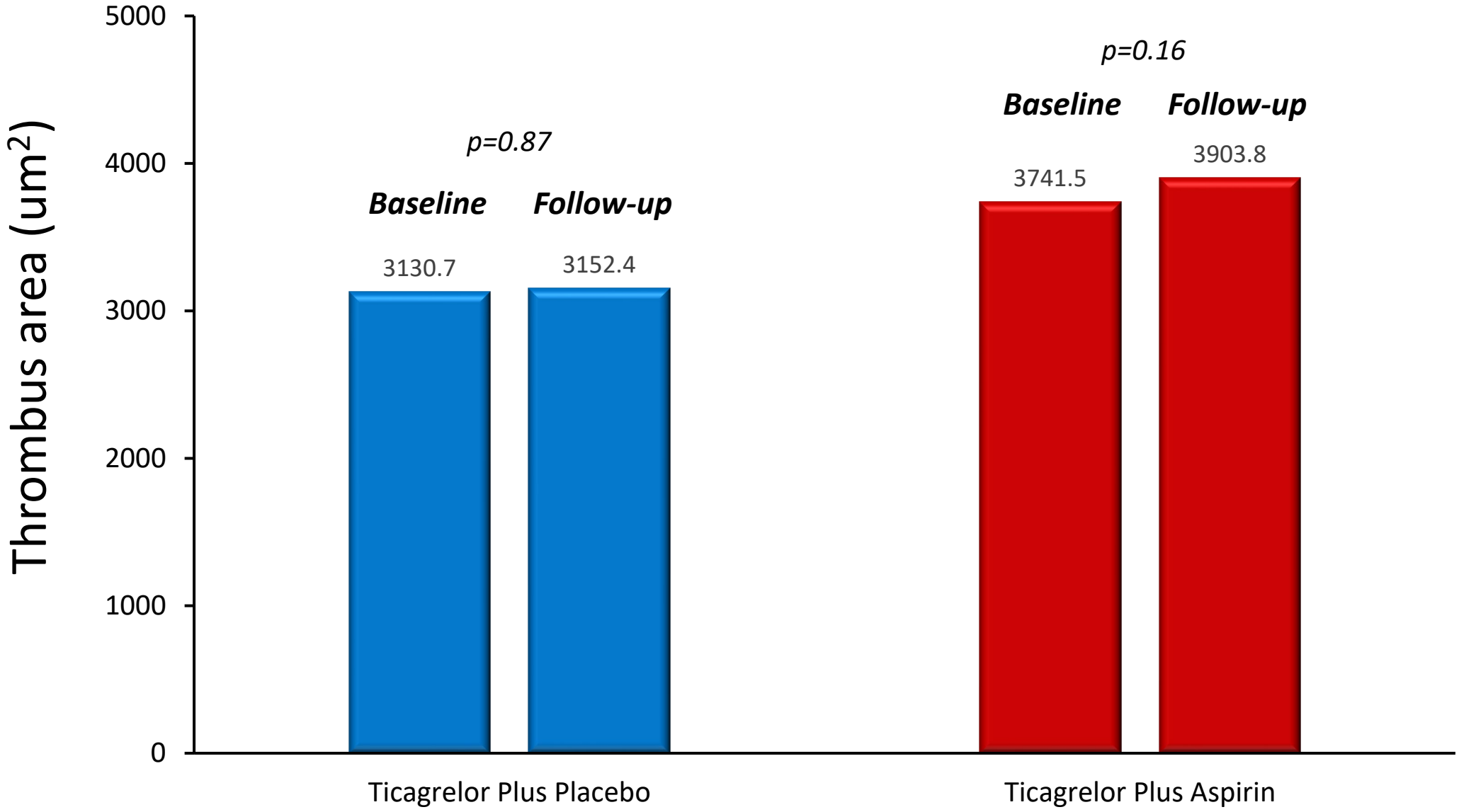
Procedural Characteristics

Variable	Ticagrelor plus Placebo (n=18)	Ticagrelor plus aspirin (n=24)	p-value
Indication for PCI			
Stable angina	6 (33.3%)	10 (41.7%)	0.58
Acute coronary syndrome	9 (50%)	14 (58%)	0.59
Multivessel CAD	12 (66.7%)	11 (45.8%)	0.18
Number of lesions treated	1.7 ± 0.8	1.6 ± 0.8	0.86
LAD	6 (33.3%)	11 (45.8%)	0.41
RCA	8 (44.4%)	8 (33.3%)	0.46
LCx	8 (44.4%)	8 (33.3%)	0.46
Stent length (mm)	35.8 ± 24.5	35.1 ± 21.9	0.92
Target lesion morphology			
Thrombus (%)	2 (11.1%)	4 (16.7%)	0.61
Calcification, moderate or severe (%)	3 (16.7%)	11 (45.8%)	0.047
Any bifurcation (%)	6 (33.3%)	5 (20.8%)	0.83

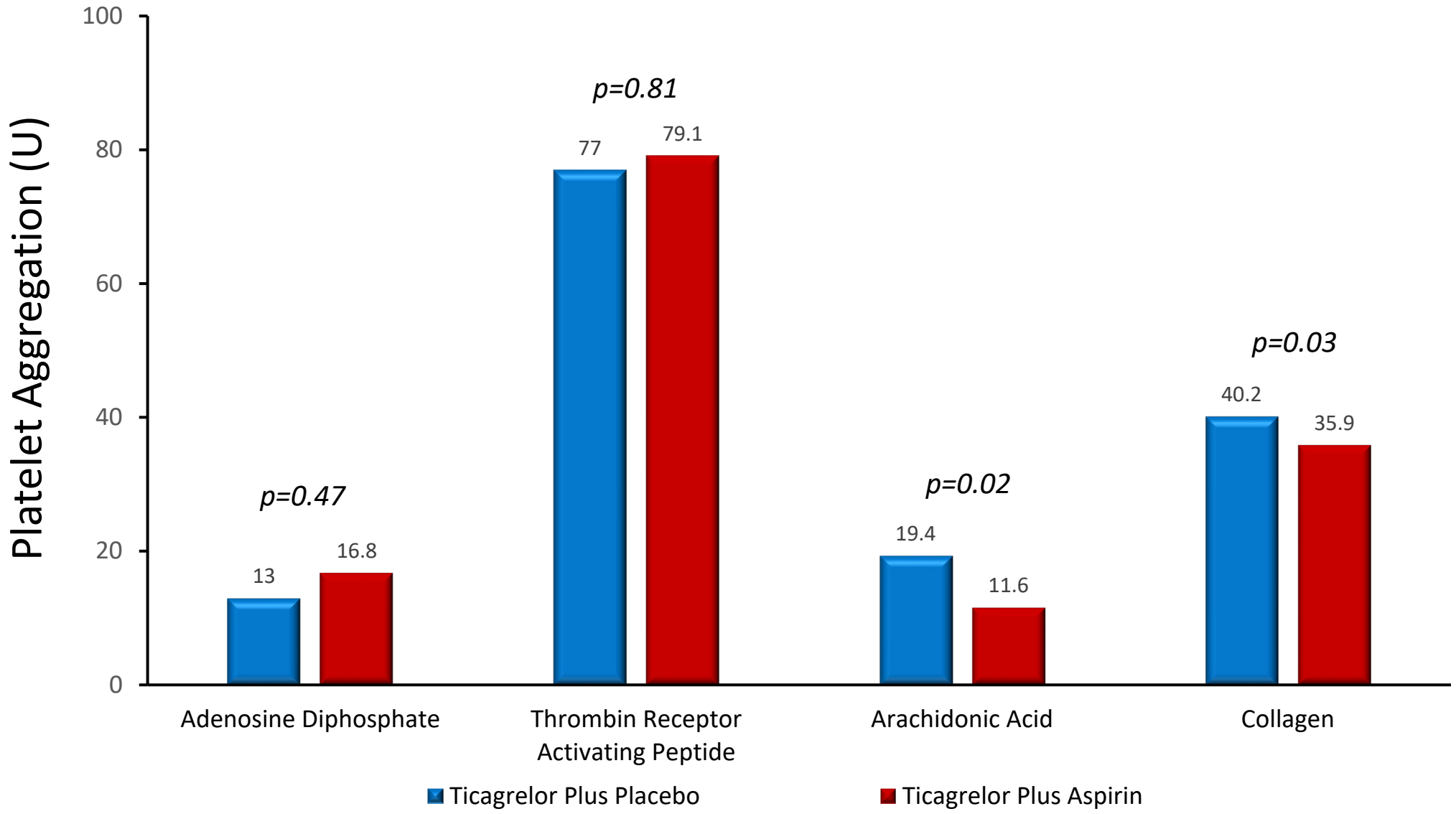
Ex-vivo Thrombus Area by Treatment Group



Within-Group Changes in Thrombus Area



Post-Randomization Platelet Reactivity by Treatment Group



Limitations

- Baseline differences in parameters that can influence thrombotic potential. However, thrombus was generated under uniform conditions using a common substrate, partially isolating the treatment effect from confounding.

- Given the study design, inferences regarding $P2Y_{12}$ inhibition with prasugrel or clopidogrel with respect to blood thrombogenicity are not possible

- Patients were assessed after 3 months of DAPT; earlier time points after PCI may have yielded different results

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Conclusions

- Ticagrelor monotherapy provides a similar antithrombotic effect to that of ticagrelor plus aspirin as assessed by *ex-vivo* platelet-dependent thrombus formation.

- Platelet reactivity to collagen and AA is increased in the absence of aspirin while aggregation to ADP and thrombin is unchanged with or without aspirin.

- These findings suggest that aspirin withdrawal does not modulate *ex-vivo* blood thrombogenicity in the presence of strong $P2Y_{12}$ blockade with ticagrelor and ***corroborates the clinical observations of no incremental ischemic risk upon aspirin withdrawal seen in TWILIGHT***

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