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ORIGINAL RESEARCH

Predicting Arterial Thrombotic Events Following Peripheral Revascularization Using Objective Viscoelastic Data

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BACKGROUND: Peripheral artery disease is endemic in our globally aging population, with >200 million affected worldwide. Graft/stent thrombosis after revascularization is common and frequently results in amputation, major adverse cardiovascular events, and cardiovascular mortality. Optimizing medications to decrease thrombosis is of paramount importance; however, limited guidance exists on how to use and monitor antithrombotic therapy in this heterogeneous population. Thromboelastography with platelet mapping (TEG-PM) provides comprehensive coagulation metrics and may be integral to the next stage of patient-centered thrombophrophylaxis. This prospective study aimed to determine if TEG-PM could predict subacute graft/stent thrombosis following lower extremity revascularization, and if objective cut point values could be established to identify those high-risk patients.

METHODS AND RESULTS: We conducted a single-center prospective observational study of patients undergoing lower extremity revascularization. Patients were followed up for the composite end point postoperative graft/stent thrombosis at 1 year. TEG-PM analysis of the time point before thrombosis in the event group was compared with the last postoperative visit in the nonevent group. Cox proportional hazards analysis examined the association of TEG-PM metrics to thrombosis. Cut point analysis explored the predictive capacity of TEG-PM metrics for those at high risk. A total of 162 patients were analyzed, of whom 30 (18.5%) experienced graft/stent thrombosis. Patients with thrombosis had significantly greater platelet aggregation (79.7±15.7 versus 58.5±26.4) and lower platelet inhibition (20.7±15.6% versus 41.1±26.6%) (all $P<0.01$). Cox proportional hazards analysis revealed that for every 1% increase in platelet aggregation, the hazard of experiencing an event during the study period increased by 5% (hazard ratio, 1.05 [95% CI, 1.02–1.07]; $P<0.01$). An optimal cut point of >70.8% platelet aggregation and/or <29.2% platelet inhibition identifies those at high risk of thrombosis with 87% sensitivity and 70% to 71% specificity.

CONCLUSIONS: Among patients undergoing lower extremity revascularization, increased platelet reactivity was predictive of subacute postoperative graft/stent thrombosis. On the basis of the cut points of >70.8% platelet aggregation and <29.2% platelet inhibition, consideration of an alternative or augmented antithrombotic regimen for high-risk patients may decrease the risk of postoperative thrombotic events.

Key Words: graft thrombosis ■ peripheral artery disease ■ personalized medicine ■ platelet aggregation ■ thromboelastography ■ thromboprophylaxis

Peripheral artery disease (PAD) is now considered a global epidemic, with a prevalence of >200 million individuals affected, largely because of worldwide trends toward an aging population.[1] The total number of revascularization procedures has nearly doubled over the prior decade.[2] Yet, despite this increase in operative

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CLINICAL PERSPECTIVE

What Is New?

- The need for antithrombotic therapy for the maintenance of graft patency following surgery for peripheral artery disease is well established, yet how to target those patients at highest risk for major adverse limb events, and their subject-specific response to antiplatelet and anticoagulation medications, remains unanswered.
- This prospective observational study used the emerging point-of-care technology of thromboelastography with platelet mapping to study dual-pathway coagulation dynamics in postoperative patients.
- Despite comparable antiplatelet regimens between groups, the thrombotic event group exhibited significantly greater platelet agreeability.

What Are the Clinical Implications?

- These data imply that a one-size-fits-all approach to thromboprophylaxis in the population with peripheral artery disease is not sufficient.
- Antiplatelet regimens that may be adequate for one patient may not be sufficient for the next, and randomized pharmacologic trials within the population with peripheral artery disease have not been able to address this to date.
- A personalized approach to antithrombotic therapy could be integral to improving rates of limb salvage. Viscoelastic subject-specific monitoring may allow for titration of pharmacologic management to optimize graft patency.

Nonstandard Abbreviations and Acronyms

MA	maximum amplitude
TEG-PM	thromboelastography with platelet mapping

interventions, limb loss remains high. Early bypass graft and/or stent thrombosis is frequent, ranging between 5% and 17%.[3–5] Thrombosis is a leading cause of limb loss, major adverse cardiovascular events, and mortality, with up to 50% of patients dying within 1 year of amputation.[6]

Hypercoagulability is commonly implicated in graft and stent thrombosis. Thus, antithrombotic therapy is a pillar of postoperative maintenance of graft patency.[7] Basic science research has established the highly synchronized and dynamic interplay between platelet activation and the coagulation cascade. Thrombin is a platelet agonist that, through the cleavage of protease-activated receptors and fibrinogen bridges, activates platelets to enhance clot strength. Activated platelets, on the other hand, enhance coagulation through their phospholipid surface on which thrombin generation occurs.[8] This is the basis for evolving antithrombotic strategies within PAD, with direct oral anticoagulants acting to inhibit thrombin-mediated platelet activation, and antiplatelet therapy acting to attenuate thrombin generation.[9,10] Despite our understanding of the molecular biology, there is no level 1A evidence supporting the use of multimodal antithrombotic therapy for PAD.[11–13] Most recommendations are derived from subgroup analysis of randomized trials for patients with coronary and cerebrovascular disease.[13,14] Prior trials examining the use of anticoagulation medications in addition to antiplatelet therapy after revascularization have lacked efficacy, found an unacceptable bleeding risk, or been criticized for a lack of generalizability.[15–17]

This lack of consensus for medical management in postoperative PAD may largely be attributable to the myriad of factors involved in hypercoagulability within this patient population. Medication noncompliance is estimated to be up to 43% in cardiovascular patients.[18] Comorbidities that increase the risk of hypercoagulability, such as diabetes or smoking status, are often categorized as binary variables and not stratified on the basis of severity or chronicity, leading to the potential for covariate analysis to be inaccurate or lack nuance. Following surgery, patients can have temporary hypercoagulable states, because of factors such as blood transfusions, critical illness, and uremia, resulting in a transient thrombotic risk.[19] In addition, nonsensitivity to antiplatelet agents is found in up to 60% to 65% of the population with cardiovascular disease, resulting in significant variability of individual response to therapy unbeknownst to the surgeon.[20] Given the complexities associated with these heterogeneous clinical factors, it has been impossible to quantify the thrombotic risk of an individual patient. Current standards for the assessment of hypercoagulability, such prothrombin time, international normalized ratio, and activated partial thromboplastin time, measure individual steps of the coagulation cascade in a nonphysiologic setting and can poorly reflect in vivo coagulation.[21] In addition, these metrics do not measure for the effectiveness of the most commonly used antithrombotic agents in PAD, such as direct oral anticoagulants or antiplatelet therapy.

Viscoelastic assays, such as thromboelastography, measure the multipathway dynamics of clot formation, strengthening, and breakdown. With time displayed on the *x* axis, the measurements of initial fibrin clot formation (R-time), thrombin "burst" and fibrin cross-linking (K-time and α-angle), fibrin-platelet interactions resulting in maximal clot strength (maximum amplitude

[MA]), and clot disintegration at 30 minutes are the 5 standard outputs on the *y* axis. Platelet function is estimated to result in 80% of the MA, whereas the remaining 20% is derived from fibrin.[22] Thromboelastography with platelet mapping (TEG-PM) not only measures the MA but also used platelet activators, such as ADP, to provide a quantitative analysis of platelet aggregation and inhibition. In this way, TEG-PM provides insight into platelet reactivity, including the effects of antiplatelet medications. Although the use of thromboelastography has become well established as the standard of care in states of hemorrhagic shock because of its efficacy in guiding resuscitation, and its relative ease with a point-of-care model, its use in the prothrombotic space has only recently emerged.[21,23] Promising data for the prediction of clinical outcomes in cerebrovascular disease, for venous thromboembolic events, and even the prothrombotic state associated with surgical site infections and poor wound healing have preceded the use of thromboelastography in arterial thrombosis, despite the intricate relationship between peripheral vascular disease and coagulation.[23,24]

Currently, there are no data examining the use of TEG-PM, or any platelet reactivity assays, in postoperative patients with PAD, nor has the use of these tests been studied in correlation to real-world clinical outcomes in PAD. This prospective, observational study aimed to identify viscoelastic cut points via TEG-PM that may predict thrombosis following named vessel lower extremity revascularization.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Patients scheduled for lower extremity revascularization procedures within the Vascular Surgery department at a single large tertiary institution were prospectively enrolled and followed up clinically between December 2020 and July 2022. Exclusion criteria were inability to provide informed consent, inability to undergo serial blood draws, and pregnancy. If the index procedure did not result in successful revascularization, because of either a lack of a targetable lesion or an inability to endovascularly access a lesion, those patients were excluded from analysis. Study protocol was approved by the institutional review board. Written or electronic informed consent was obtained from each patient or the patient's legally authorized representative if the patient was unable to provide consent. Study protocol was approved by the institutional review board at the Massachusetts General Hospital (Boston, MA).

Procedures

Blood for viscoelastic analysis was collected preoperatively within 24 hours of surgery, and in the postoperative period, daily while inpatient for up to 5 occurrences, at the first outpatient follow-up, and at 3 and 6 months. Whole blood samples were tested with the TEG6 S Haemonstasis Analyzer (Haemonetics Corp, Boston MA). Citrated multichannel cartridges without lysis, measuring time to clot formation (K-time), cloth strengthening (K-time and α-angle), and MA, were chosen to assess for prothrombotic states. PlateletMapping cartridges were assayed with heparinized blood to quantify platelet function in response to ADP agonists. Platelet function quantification with TEG-PM is based on the principle that the difference between the MA and the contribution of fibrinogen to clot strength may be considered an index of platelet contribution to clot strength. The PlateletMapping cartridge consists of dried-in-place reagents to calculate the MA in various scenarios: a standard kaolin-activity thromboelastography, which is considered "best platelet reactivity"; a pure fibrin clot by adding repitlase, which directly converts fibrinogen to fibrin and corresponds to 0% platelet contribution; and an ADP-activated clot to detect platelet reactivity in the presence of aspirin or P2Y12 inhibition. Thus, platelet reactivity (percentage) is calculated as follows: $100\times MA_{ADP}/(MA_{Kaolin}-MA_{Fibrin})$.

All blood was drawn by either physicians or research staff with training for proficiency in research blood draws, as per completion of institutional review board–approved standardized institutional courses. Blood collection was performed either via a peripheral stick or from existing intravenous access following a 10mL discard syringe. Collection using a nongel 4.0-mL sodium heparin Vacutainer tube was performed. A total of 30 minutes of incubation with sample analysis within 2 to 4 hours of the blood draw was executed, as per manufacturer's instructions.

Variables Defined

Age at time of enrollment, sex, race and ethnicity, body mass index, and smoking status were recorded. Medical comorbidities were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*)/*International Classification of Diseases, Tenth Revision* (*ICD-10*), codes and included diabetes, hypertension, hyperlipidemia, coronary artery disease, history of myocardial infarction, and chronic kidney disease.

Complete blood count values were reviewed preoperatively and in conjunction with viscoelastic draws for hemoglobin and platelet count as these metrics can impact platelet aggregation. Values of traditional coagulation studies, international normalized ratio,

prothrombin time, and activated partial thromboplastin time, were also recorded in conjunction with each TEG-PM blood draw from the electronic medical record if available, but not attained if an additional blood draw was needed. Within our institution, it is not routine to obtain coagulation studies at follow-up unless the patient is on a medication that requires routine monitoring, such as warfarin (Coumadin). Nor are other platelet function testing modalities, such as light transmission aggregometry, readily available or routinely used clinically.

The use of antithrombotic medication was closely monitored in association with TEG-PM samples. For each TEG-PM sample, the active antithrombotic medications within the patient's circulation at that time point was recorded. Patients were reported to be on aspirin or clopidogrel if their last dose was within 48 hours of the analyzed TEG-PM sample. Patients were considered to be on full-dose anticoagulation if the last dose was within 24 hours of the analyzed TEG-PM sample, or if associated traditional coagulation parameters reflected therapeutic-dose medication effects. Given the observational nature of this study, antithrombotic regimens were not protocolized across patients, reflecting the real-world variability in prescribing patterns seen in PAD.

To address the potential confounders of disease severity and intervention type, given the diversity of vascular procedures included, operative details were compared between groups. Procedure type was categorized as open surgery, including bypass or endarterectomy; endovascular, including balloon angioplasty, mechanical thrombolysis, or stent procedures; and hybrid open and endovascular surgery. Target lesion location was categorized as proximal (including the popliteal artery) or distal (below the popliteal artery) as distal lesions are commonly considered higher risk for postoperative thrombosis. For patients undergoing infrainguinal bypass surgery, conduit type of native vein versus prosthetic graft was assessed, as prosthetic grafts are also generally considered higher risk for postoperative thrombosis.

Angiographic findings assessing the patency of the anterior tibial, posterior tibial, and peroneal arteries as they diverge below the distal popliteal artery are commonly evaluated during endovascular or hybrid procedures to characterize distal blood outflow to the foot. In patients with <3-vessel flow, or "runoff," the risk of thrombosis increases because of potential stagnation of blood with fewer available through-ways. For patients undergoing endovascular procedures, fluoroscopic images were reviewed to determine distal extremity runoff in the operative limb at the end of the procedure and then categorized as 3, 2, 1, or 0 vessels. If completion runoff was unavailable, then preintervention runoff was used.

Primary Outcome and Comparison Groups

Patients were followed up clinically for up to 1 year. The primary end point of thrombosis was defined as a composite outcome of graft/stent thrombosis, which included radiographic evidence of graft/stent failure, reintervention to reestablish patent arterial flow, or major limb (above or below the knee) amputation. The metric of TEG-PM analysis in the nonevent group was the sample from the last postoperative clinic visit ("last known well"). In the thrombosis group, the closest TEG-PM sample that was at least 10 days before the diagnosis of the event was analyzed to reasonably assess for the predictive nature of these data. Preoperative TEG-PM analysis was also compared between groups to assess baseline platelet reactivity and explore any variability in response to medications between groups.

Statistical Analysis

Inferential analysis was performed initially to assess for any significant differences between groups. Student *t*-test was used for continuous variables, and Fisher exact test was used for binary variables.

For regression analysis, a proportional hazards model was selected given the variability in time to event. The proportional hazards assumption was first assessed for any evidence of violation via Schoenfeld residuals both overall and for each predictor variable. The time-to-event variable corresponded to the number of days from surgery to either experiencing thrombosis or being administratively censored, which was uniform throughout the study population. Univariate Cox proportional hazards regression analysis was performed to explore if viscoelastic, demographic, and clinical covariates could predict thrombosis.

Next, a multivariate regression model was then constructed with clinical consideration of pertinent and statistically significant covariates in the univariate model and using Bayesian information criterion to create a parsimonious model fit. The variance inflation factor was used to assess for multicollinearity within the final multivariate model.

For cut point analysis to determine what qualifies a "high-risk" patient, receiver operating characteristic (ROC) curves were created. The area under the ROC curve was reported, with >0.7 suggesting good discrimination. The demarcation point corresponding to the maximum of the Youden index (sensitivity and 1–specificity) was used to determine the viscoelastic values of those patients considered to be high risk for thrombosis.

Kaplan-Meier curves were then constructed by patients above and below these cut points to visually assess the probability of thrombosis over time by platelet inhibition and platelet aggregation value.

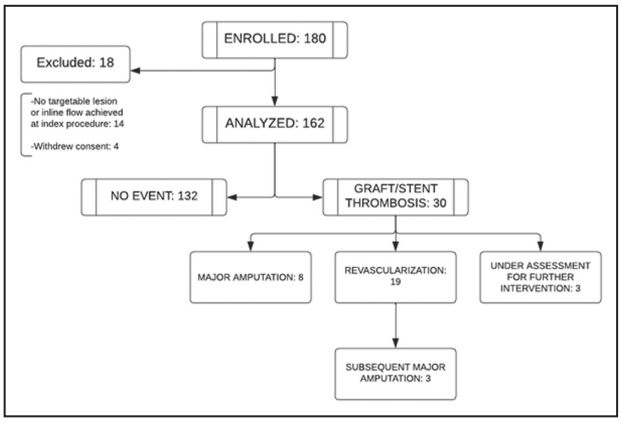

Figure 1. Study population.

RESULTS

Study Population and Follow-Up

A total of 180 patients were enrolled. Eighteen patients were excluded after enrollment: 14 were not successfully revascularized at the index procedure because of a lack of a targetable arterial lesion or an inability to endovascularly access the pathology; and 4 patients withdrew consent. The remaining 162 patients were followed up for the primary outcome of thrombosis for up to 1 year. The average follow up was 302.2 days. During the follow-up period, 30 patients (18.5%) experienced a thrombotic event (Figure 1).

The average time to a thrombotic event was 71.4 days. TEG-PM analysis was, on average, 38.5 days before the diagnosis of the event (Figure 2).

Demographics and Comorbid Conditions

Baseline demographics, including age at time of enrollment, sex, and race and ethnicity, did not differ significantly between groups. In the event group, there was a significantly higher prevalence of diabetes (70.0% versus 49.2%; P=0.04). Other comorbidities, including hypertension, hyperlipidemia, coronary artery disease, prior myocardial infarction, and chronic kidney disease, did not differ significantly in prevalence between groups (Table 1).

Operative Details

Procedure type, including open surgical, endovascular, or combined procedures, was not significantly associated with events. Distal anatomic target (defined as below the popliteal artery), a combined proximal and distal target, prior intervention on the index limb, and infrainguinal bypass conduit type were not significantly associated with events. Angiographic findings at the completion of endovascular or hybrid procedures in terms of distal extremity runoff was also not significantly different between groups (Table 1).

Preoperative Analysis of Medication, Laboratory Values, and TEG-PM Parameters

There were no significant differences between those with thrombosis and those without events in terms of preoperative antiplatelet or anticoagulation medication regimens (Table S1). Overall, the use of preoperative antiplatelet therapy was lower compared with postoperative antiplatelet therapy. In the nonevent group, mono-antiplatelet therapy use was only 49.2% and dual-antiplatelet therapy use was only 16.7%. In the event group, mono-antiplatelet therapy use was 43.3% and dual-antiplatelet therapy use was 23.3%.

Traditional coagulation test metrics, including international normalized ratio, prothrombin time, and activated partial thromboplastin time, as well as hemoglobin and platelet count values, at the preoperative time point also did not differ significantly between groups (Table S1).

There was no significant difference between groups in terms of preoperative TEG-PM analysis, including R-time, K-time, α-angle, MA, platelet aggregation, or platelet inhibition (Table S2).

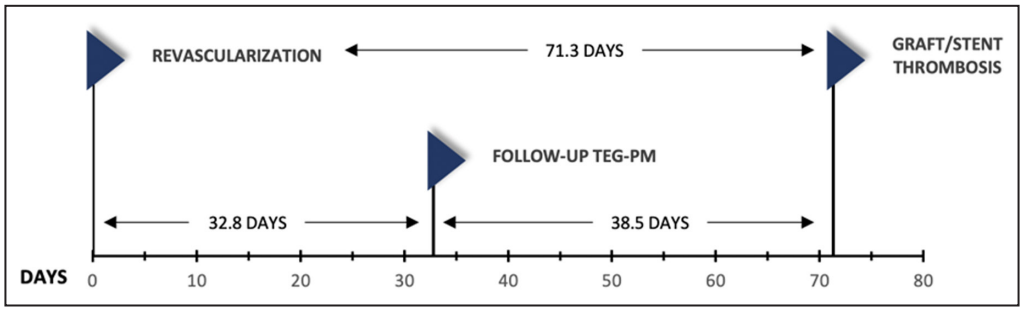

Figure 2. Procedure, analysis, and event timeline for patients with thrombosis.
TEG-PM indicates thromboelastography with platelet mapping.

Table 1. Patient and Operative Characteristics Between Nonevents and Those With Thrombosis

Characteristic	No event, N/mean (%/SD)	Thrombosis, N/mean (%/SD)	*P* value
Total patients	132	30	
Age at enrollment, y	67.1 (±13.0)	66.3 (±11.9)	0.75
Men	86 (65.2)	20 (66.7)	1.00
Non-Hispanic White race and ethnicity	112 (84.9)	23 (76.6)	0.28
Body mass index, kg/m^2	27.5 (±6.3)	27.2 (±4.1)	0.81
Ever smoker	107 (81.1)	23 (76.6)	0.61
Hypertension	115 (87.1)	28 (93.3)	0.53
Hyperlipidemia	87 (65.9)	22 (73.3)	0.52
Diabetes	65 (49.2)	21 (70.0)	0.04
Coronary artery disease	59 (44.6)	16 (53.3)	0.42
Prior myocardial infarction	21 (15.9)	8 (26.6)	0.18
Chronic kidney disease	39 (29.5)	9 (30.0)	1.00
Prior intervention on the index limb	59 (44.7)	15 (50.0)	0.67
Procedure type			
Open	49 (37.1)	7 (23.3)	0.14
Endovascular	61 (46.2)	18 (60.0)	0.22
Hybrid	22 (16.6)	5 (16.6)	1.00
Anatomical target			
Proximal	89 (67.4)	19 (63.3)	0.67
Distal*	25 (18.9)	6 (20.0)	1.00
Proximal+distal	18 (13.6)	5 (16.7)	0.77
Infrainguinal bypass conduit type†			
Vein	14 (66.7)	3 (42.9)	0.38
PTFE	7 (33.3)	4 (57.1)	0.38
Completion angiogram findings‡			
3-Vessel runoff	29 (34.9)	5 (21.7)	0.31
2-Vessel runoff	20 (24.1)	5 (21.7)	1.00
1-Vessel runoff	18 (21.7)	5 (21.7)	1.00
0-Vessel runoff	2 (2.4)	0 (0.0)	1.00
Not performed	14 (16.9)	8 (34.8)	0.08

PTFE indicates polyTetraFluoroEthylene.
*Distal target defined as below the popliteal artery.
†Subset analysis of the 28 patients who underwent infrainguinal bypass revascularization.
‡Subset analysis of the 106 patients who underwent endovascular/hybrid revascularization.

Antithrombotic Therapy, Traditional Coagulation Tests, and Blood Count Values Associated With Subacute Thrombotic Events

The use of antithrombotic medication was closely monitored in associated with TEG-PM samples analyzed, which was the time point before the diagnosis of an event in the thrombosis cohort and the last postoperative visit in the nonevent cohort. Patients were only considered to be on a medication if they had taken it within the time frame of their TEG-PM sample (see "Variables Defined" in the "Methods" section). There were no patients on novel P2Y12 inhibitors, such as ticagrelor, in this cohort. Most patients (84.6%) were on antiplatelet therapy, with 63.6% on mono-antiplatelet therapy regimens and 21.0% on dual-antiplatelet therapy regimens. There was no statistically discernable difference in the use of antiplatelet regimens between groups. In the thrombosis group, there was a significantly greater use of anticoagulation compared with the nonevent group (56.7% versus 33.3%), including direct oral anticoagulant medications (40.0% versus 18.2%) (all $P<0.05$) (Table 2).

A total of 70.0% of patients had concomitant coagulation assays drawn on the same day of the TEG-PM sample used for event analysis, as it is not routine within our department to perform coagulation tests unless there is a clear clinical indication. Mean values of these traditional coagulation tests did not differ significantly between groups. Pertinent complete blood count values, including hemoglobin and platelet count, at the time of the event in the thrombosis group compared with the last follow-up visit in the nonevent group also did not differ significantly (Table 2).

Table 2. Postoperative Medication and Laboratory Analysis Before Diagnosis of Event in the Thrombosis Group and "Last Known Well" in the Nonevent Group: Antithrombotic Therapy, Traditional Coagulation Assay, and Blood Count Metrics

Variable	No event, N/mean (%/SD)	Thrombosis, N/mean (%/SD)	*P* value
Total patients	132	30	
Antiplatelet therapy			
Aspirin	97 (73.5)	23 (76.7)	0.82
Clopidogrel	43 (32.6)	8 (26.7)	0.66
MAPT	84 (63.6)	19 (63.3)	1.00
DAPT	28 (21.2)	6 (20.0)	1.00
Anticoagulation therapy			
Any anticoagulation	44 (33.3)	17 (56.7)	0.02
Direct oral anticoagulant	24 (18.2)	12 (40.0)	0.01
Traditional coagulation assay values*			
INR	1.4 (±0.7)	1.2 (±0.2)	0.30
PT	16.5 (±6.4)	15.1 (±2.3)	0.37
aPTT	51.2 (±31.9)	58.3 (±26.3)	0.43
Pertinent CBC values			
Hemoglobin	11.1 (±2.3)	11.6 (±2.0)	0.99
Platelet count	249 (±117)	287 (±117)	0.12

aPTT indicates activated partial thromboplastin time; CBC, complete blood cell; DAPT, dual-antiplatelet therapy; INR, international normalized ratio; MAPT, mono-antiplatelet therapy; and PT, prothrombin time.
*Subset analysis of 113 patients with available preoperative metrics.

Table 3. Postoperative TEG-PM Assay Analysis Before Diagnosis of Event in the Thrombosis Group and "Last Known Well" in the Nonevent Group

Variable	No event, N/mean (%/SD)	Thrombosis, N/mean (%/SD)	*P* value
Total patients	132	30	
Thromboelastography values			
R-time	7.3 (±3.0)	8.8 (±4.0)	0.02
K-time	1.9 (±1.3)	1.8 (±1.2)	0.44
α-Angle	68.5 (±10.2)	67.5 (±13.3)	0.63
MA	61.0 (±10.4)	64.7 (±8.8)	0.07
Platelet mapping values			
% Platelet aggregation	58.5 (±26.4)	79.7 (±15.7)	0.0001
% Platelet inhibition	41.1 (±26.6)	20.7 (±15.6)	0.0001

MA indicates maximum amplitude; and TEG-PM, thromboelastography with platelet mapping.

Association of TEG-PM Parameters With Subacute Thrombotic Events

The R-time, or time to clot formation, reflected the greater use of anticoagulation medications observed within the event group as it was significantly longer at 8.8±4.0 minutes versus 7.3±3.0 minutes in the nonevent group (*P*=0.02). The MA, or platelet-fibrin clot strength in millimeters, was higher in the thrombosis group, although this did not reach statistical significance (64.7±8.8 versus 61.0±10.4 mm; *P*=0.07). The K-time and α-angle did not differ significantly between groups (Table 3).

Patients with thrombotic events demonstrated consistently greater platelet reactivity compared with the nonevent group. Percentage platelet aggregation was significantly higher in those with thrombosis (79.7%±15.7% versus 58.5%±26.4%; *P*=0.0001) (Figure 3A). Percentage platelet inhibition was significantly lower in the thrombotic event group compared with the nonevent group (20.7%±15.6% versus 41.1%±26.6%; *P*=0.0001) (Figure 3B).

Predictors of Thrombotic Events With a Cox Proportional Hazards Model

Univariate Cox proportional hazards regression analysis found that for every 1% increase in platelet aggregation, the hazard of experiencing an event during the study period increased by 5% (hazard ratio [HR], 1.05 [95% CI, 1.03–1.08]; *P*<0.001). Similarly, for every 1% decrease in platelet inhibition, the hazard of experiencing an event during the study period also increased by 4% (HR, 0.95 [95% CI, 0.93–0.98]; *P*<0.001). In the univariate analysis, diabetes was also found to be a significant predictor of events (HR, 2.57 [95% CI, 1.17–5.61]; *P*=0.01). No other demographic, comorbid, or clinical covariates were found to be significant predictors of events (Table 4).

A pairwise Pearson correlation matrix found platelet aggregation and platelet inhibition to be collinear (*P*<0.001); thus, only platelet aggregation was used in the multivariate model (Table S3).

For multivariate modeling, covariates were chosen on the basis of assessment of our univariate analysis *P* values and with clinical consideration of potentially pertinent covariates and included diabetes, open procedure type, MA, and platelet aggregation. On the basis of a Bayesian information criterion diagnostic of ≤2, a final model was created. Platelet aggregation was again found to be a significant predictor of thrombotic events (HR, 1.05 [95% CI, 1.02–1.07]; *P*<0.001).

Although not significant on its own, the maximum clot amplitude contributed positively to model fit, with a greater MA increasing the hazard of experiencing an

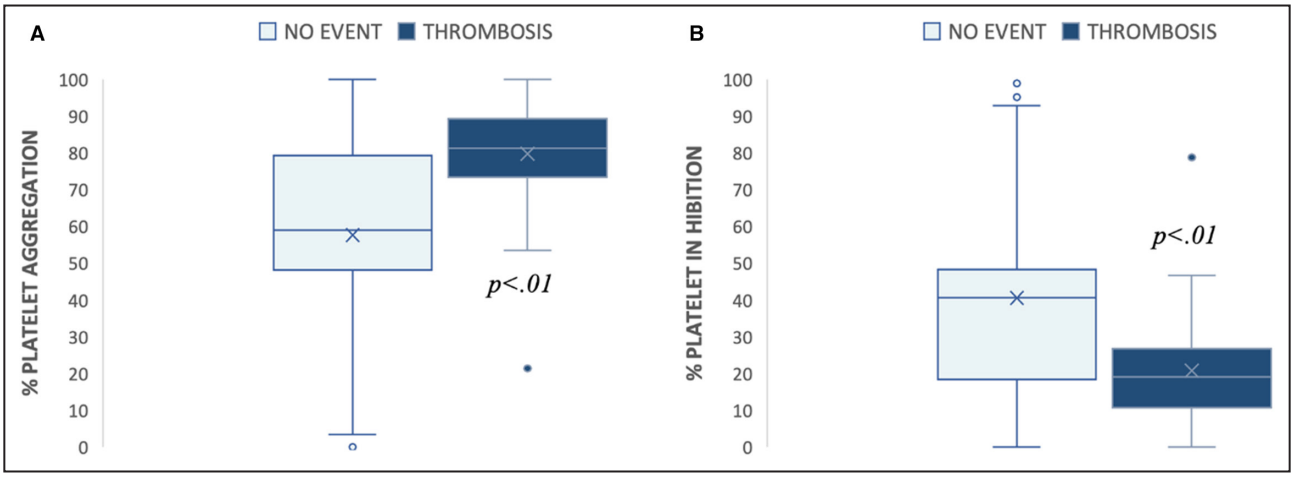

Figure 3. Differences in platelet aggregation and inhibition between patients who had a thrombotic event and those that did not have an event.
Box-and-whisker distribution of platelet mapping values between nonevents and those with thrombosis: platelet aggregation (**A**) and platelet inhibition (**B**).

Table 4. Univariate Cox Proportional Hazards Regression Analysis Assessing the Impact of Postoperative Viscoelastic Parameters, Demographics, and Operative Covariates on Experiencing Thrombosis During the Study Period

	Hazard ratio	95% CI	*P* value
Univariate analysis			
Platelet aggregation	1.05	1.03–1.08	<0.001
Platelet inhibition	0.96	0.93–0.98	<0.001
Age	1.00	0.97–1.02	0.81
Men	1.04	0.49–2.22	0.92
BMI	0.99	0.93–1.05	0.74
Non-Hispanic White race and ethnicity	0.74	0.30–1.82	0.51
Ever smoker	0.87	0.37–2.04	0.76
Diabetes	2.57	1.17–5.61	0.01
CAD	1.14	0.56–2.35	0.71
CKD	0.98	0.45–2.14	0.96
Hyperlipidemia	1.09	0.50–2.37	0.84
Aspirin	1.27	0.55–2.97	0.58
Clopidogrel (Plavix)	0.75	0.33–1.69	0.49
MAPT	1.10	0.52–2.32	0.80
DAPT	0.93	0.38–2.29	0.88
Prior intervention	1.42	0.69–2.91	0.34
Open procedure	0.47	0.20–1.10	0.08
R-time	1.09	1.00–1.20	0.06
K-time	0.93	0.68–1.28	0.66
α-Angle	0.99	0.96–1.02	0.59
MA	1.04	0.99–1.09	0.13

BMI indicates body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; MA, maximum amplitude; and MAPT, mono-antiplatelet therapy.

event during the study period (HR, 1.04 [95% CI, 0.99–1.10]; *P*=0.10). Similarly, the presence of diabetes also contributed to the multivariate model fit by increasing the hazard of experiencing an event (HR, 2.05 [95% CI, 0.93–4.50]; *P*=0.08) (Table 5). The variance inflation factor of the multivariate model was found to be 1.02, suggesting low suspicion for multicollinearity within the model.

Cut Point Analysis of Platelet Mapping Metrics to Predict Those at High Risk for Thrombosis

ROC curves were created for platelet aggregation and platelet inhibition to assess the diagnostic viability of using these metrics for the prediction of thrombosis. For platelet aggregation, the area under the ROC curve was 0.769 (95% CI, 0.684–0.853), suggesting good discrimination. Using the Youden index, the optimal cutoff percentage for platelet aggregation was 70.8%, above which patients were considered high risk, with a sensitivity of 87% and a specificity of 70% for catching

Table 5. Multivariate Cox Proportional Hazards Regression Analysis With Consideration of Clinically Relevant Predictors to Assess Impact of Postoperative Viscoelastic Parameters, Demographics, and Operative Covariates on Experiencing Thrombosis During the Study Period

Multivariate analysis			
	Hazard ratio	95% CI	*P* value
Platelet aggregation	1.05	1.02–1.07	<0.001
MA	1.04	0.99–1.10	0.10
Diabetes	2.05	0.93–4.50	0.08

MA indicates maximum amplitude.

a thrombotic event during the study period (Figure 4A). A Kaplan-Meier curve was then created to visually assess the probability of thrombosis over time. Patients with <70.8% platelet aggregation (low risk) were compared with those with ≥70.8% platelet aggregation (high risk) (Figure 4B).

For platelet inhibition, the area under the ROC curve was 0.756 (95% CI, 0.670–0.841), suggesting good discrimination. On the basis of the Youden index, the optimal cutoff percentage for platelet inhibition was 29.2%, below which patients were considered high risk, with a sensitivity of 87% and a specificity of 71% for catching a thrombotic event during the study period (Figure 4C). Kaplan-Meier curve analysis compared patients with >29.2% inhibition (low risk) with those with ≤29.2% inhibition (high risk) (Figure 4D).

DISCUSSION

The risks faced by patients with PAD after revascularization are high and include major adverse limb events. The prognosis following major adverse limb events demonstrates the substantial frailty of this population, with an increase in the risk of death by 3-fold, and an increase in the risk of subsequent amputation by 200-fold.[25] Most efforts to prevent thrombosis after surgery for PAD rely on standard "one-size-fits-all" recommendations, which are then inconsistently, and somewhat subjectively, altered at the discretion of the surgeon based on intervention subtype or concomitant risk factors.[13]

There is large variability within the population with PAD, ranging from asymptomatic, to lifestyle-limiting claudication, to the sickest patients with critical limb ischemia. Diversity in natural history and disease progression is compounded further by a range of comorbid risk factors as well as variation in intervention type. A significant weakness in any "protocolized" pharmacologic approach, as encountered in previous randomized trials on the topic, is the inability to accurately provide an evidence-based algorithm for all PAD

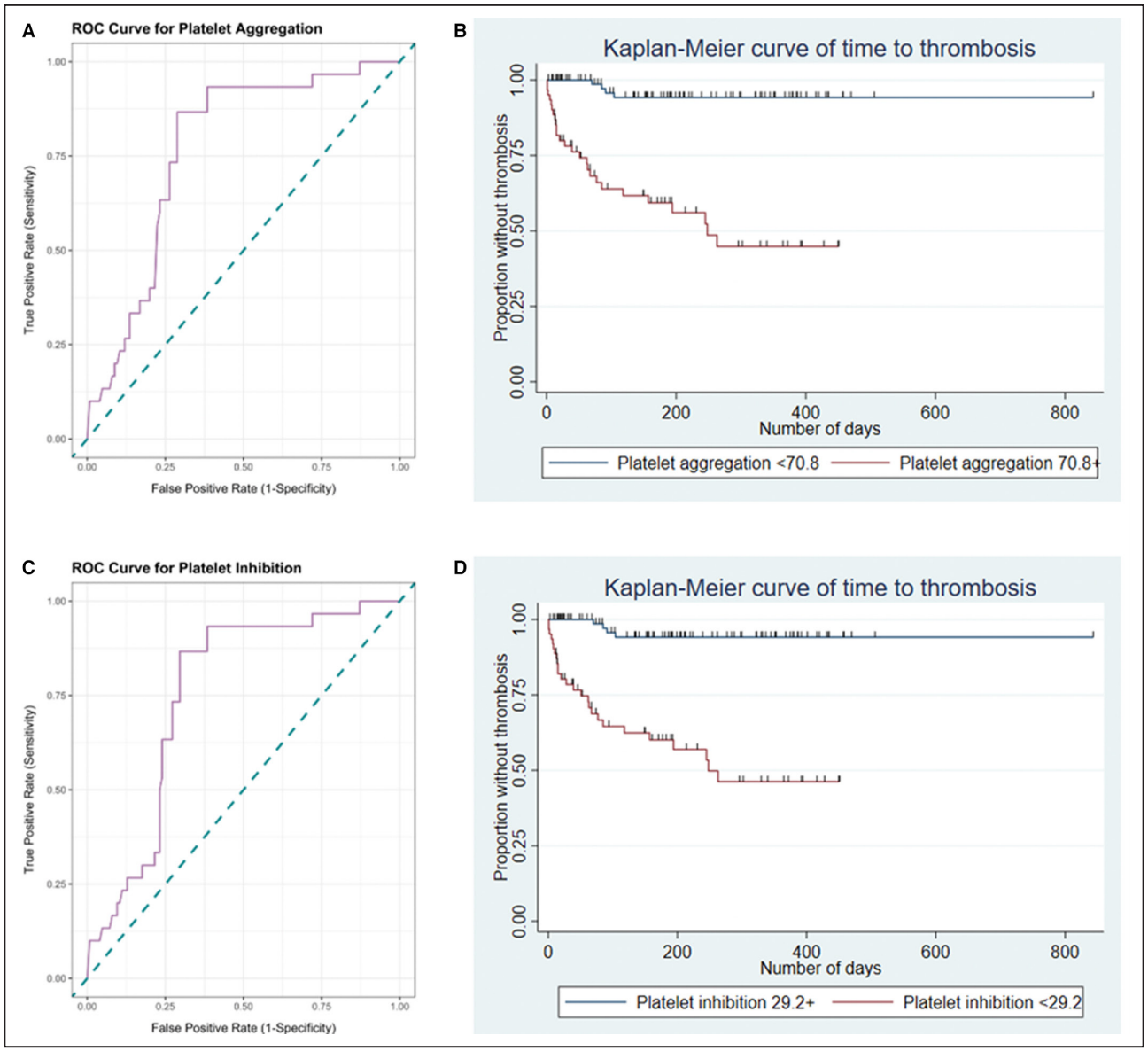

Figure 4. Cut point analysis detailing the platelet aggregation and platelet inhibition levels associated with thrombosis. Cut point analysis for platelet aggregation (receiver operating characteristic [ROC] curve analysis [area under the ROC curve {AUC}, 0.769 {95% CI, 0.684–0.853}]) (**A**) with Kaplan-Meier visualization of thrombotic risk for >70.8% aggregation over time (**B**) and platelet inhibition (ROC curve analysis [AUC, 0.756 {95% CI, 0.670–0.841}]) (**C**) with Kaplan-Meier visualization of thrombotic risk for <29.2% inhibition over time (**D**).

stages where the risks of major adverse limb events, mortality, and bleeding should be weighted differently for each individual patient.

A viscoelastic-based model provides an opportunity to assess real-time thrombotic potential on an individual basis and tailor therapy through a personalized approach, thus maximizing thromboprophylactic potential. This could address the nuance of treating such a heterogeneous population with a distinct range of surgical techniques.

Several other assays have been developed in the past to measure platelet function and the effects of antiplatelet agents, including light transmittance aggregometry and impedance aggregometry. These modalities have been criticized because of poor standardization, expense, and time-consuming nature.[26] In addition, although prior studies using these modalities have demonstrated statistically reportable data, such as high on-treatment platelet reactivity with aspirin and dipyrone use, and increased spontaneous platelet aggregation in the population with PAD as a whole, there has been no link of these metrics to arterial thrombosis, and thus it is unclear how to apply these findings.[27,28]

Thromboelastographic analysis with the adjunct of platelet mapping, on the other hand, is a point-of-care

technology that is increasingly available in tertiary centers and the first to be linked to real-world clinical outcomes in patients with PAD.[24] The important benefit of using TEG-PM is the ability to concurrently assess the coagulation and platelet pathways, offering the potential to study the additive, confounding, or null effect that anticoagulation management has on platelet function, which is yet to be established. Our data leverages this comprehensive capacity by uncovering a series of impactful findings:

1. Platelet mapping demonstrates that postoperative platelet reactivity is significantly higher in those with events, before the diagnosis of thrombosis, and despite comparable antiplatelet management between groups.
2. Thromboelastography reveals a trend toward increased fibrin-platelet clot strength, MA, in association with events (P=0.07). This trend is supported by optimization of model fit when adding the MA to a multivariate Cox proportional hazards regression analysis, with a CI closely approaching >1.00 (0.99–1.10). In other words, in patients with high platelet aggregation, the presence of concomitant high fibrin-platelet clot strength furthers the risk of postoperative graft/stent thrombosis.
3. Thromboelastography also demonstrated that the R-time, or time to clot formation, was paradoxically greater in those with thrombosis (P=0.02). These viscoelastic findings are consistent with the increased postoperative anticoagulation use in the thrombosis group. But these findings provoke consideration that the desired pharmacologic effect may not be translating to a clinical lack of thrombosis within this patient population.

The most important value of these findings arises from the comparable use of antiplatelet medications at the time of TEG-PM analysis, indicating that it is only a subset of patients who may require an augmented approach. Although most patients in either group were on antiplatelet therapy, none was on novel P2Y12 inhibitors, such as prasugrel and ticagrelor, which are less affected by drug-drug interactions and polymorphisms within the cytochrome P450 system or PGY12 gene.[29–31] This reflects a possible underuse of potentially efficacious antiplatelet therapy with lower resistance and nonresponsiveness.[32,33]

The clinical implications of these data are notable, in that all viscoelastic analysis took place at least 10 days before the diagnosis of a thrombotic event, and on average, even longer at 38.5 days before the diagnosis of an event. This indicates a strong predictive potential for the use of viscoelastic monitoring in postoperative graft/stent surveillance. The real-world implication of this lead time is providing clinicians with a potential opportunity to intervene.

Although prior trials exploring the use of platelet function testing to optimize outcomes among patients with acute coronary syndromes and cardiac stents failed to correlate with decreased complications, a similar study examining serial testing in the postoperative population with PAD has never been done.[34–36] On the basis of our analysis, we would consider enhanced observation with serial TEG-PM monitoring for those patients considered high thrombotic risk via viscoelastic cut points (platelet aggregation >70.8% and/or platelet inhibition <29.2%). And we would encourage future research exploring the utility of antithrombotic medication titration based on TEG-PM analysis in patients undergoing lower extremity revascularization.

Limitations

Although these data are novel and represent the only available quantitative analysis linking platelet function metrics to thrombosis in the postoperative population with PAD, there is significant variability within this cohort in terms of lesion location, intervention type, and antithrombotic regimens. Given the vast range in patient characteristics and management options for PAD, this issue is commonly encountered within peripheral vascular research. We opted to include all patients as not to limit the generalizability for this initial hypothesis-generating work, and aimed to thoroughly assess for any potential confounding factors through detailed reporting of all major comorbid, anatomic, and operative covariates (Table 1). However, to affect practice patterns and validate these data, a randomized approach, in which selection criteria are uniform and antithrombotic regimens are standardized, will be needed.

CONCLUSIONS

In this study of 162 patients undergoing lower extremity revascularization, platelet aggregation of >70.8% and platelet inhibition of <29.2% were predictive of postoperative graft/stent thrombosis, with 87% sensitivity and 70% to 71% specificity. A quantitative and personalized antithrombotic approach is integral to improving rates of limb salvage, and a viscoelastic model may provide that opportunity.

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Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Preoperative medication and lab analysis between nonevents and those with thrombosis: antithrombotic therapy, traditional coagulation assay and blood count metrics

	No event N/mean (%/SD)	**Thrombosis N/mean (%/SD)**	***P***
Total patients	132	30	
Antiplatelet therapy			
Aspirin	87 (65.9)	17 (56.7)	.40
Clopidogrel	22 (16.7)	9 (30.0)	.12
MAPT	65 (49.2)	13 (43.3)	.68
DAPT	22 (16.7)	7 (23.3)	.43
Anticoagulation therapy			
Any Anticoagulation	34 (25.8)	9 (30.0)	.65
Direct Oral Anticoagulant	17 (12.9)	6 (20.0)	.38
Traditional coagulation assay values[a]			
INR	1.3 (±0.6)	1.3 (±0.6)	.75
PT	16.0 (±5.7)	15.9 (±6.0)	.93
aPTT	40.9 (±21.5)	44.4 (±21.5)	.66
Pertinent CBC values			
Hemoglobin	12.0 (±2.3)	11.6 (±2.4)	.45
Platelet count	262 (±105)	254 (±89)	.73

Table S2. Preoperative TEG-PM assay analysis between nonevents and those with thrombosis

	No event N/mean (%/SD)	**Thrombosis N/mean (%/SD)**	***P***
Total patients	132	30	
TEG values			
R time	6.8 (±3.2)	7.4 (±4.0)	.53
K time	2.1 (±1.5)	2.1 (±1.4)	.92
α-angle	67.6 (±11.7)	67.3 (±12.6)	.92
MA	58.4 (±11.3)	59.4 (±11.9)	.73
Platelet Mapping values			
% Platelet aggregation	76.6 (±20.1)	74.5 (±18.7)	.72
% Platelet inhibition	23.1 (±24.3)	25.5 (±18.7)	.74

Abbreviations used: MA, maximum amplitude; TEG, thromboelastography

Table S3. Correlation matrix using Pearson's correlations for pairwise relationships between continuous variables, point-biserial for one continuous and one binary variable, and phi for two binary variables

	Platelet agg.	Platelet inh.	Age	Male sex	BMI	NH White	Ever smoker	DM	CAD	CKD	HLD	Aspirin	Plavix	MAPT	DAPT	AC	Prior interv.
Platelet inhibition	-0.997 ***																
Age	-0.007	0.018															
Male sex	0.020	-0.032	0.062														
BMI	-0.041	0.046	-0.194 *	0.059													
Non-Hispanic White	0.039	-0.053	-0.183 *	0.061	0.011												
Ever smoker	0.082	-0.081	0.049	0.162 *	0.050	0.310 ‡											
DM	-0.181 *	0.172 †	0.040	0.070	-0.140	-0.047	-0.162 *										
CAD	0.013	-0.016	-0.099	0.229 †	0.032	0.190 *	0.066	0.191 *									
CKD	0.096	-0.096	-0.183 *	0.025	-0.043	0.074	-0.025	0.041 †	0.108								
HLD	-0.152	0.150	-0.159 *	0.025	-0.011	0.074	-0.025	0.041	0.260 †	0.033							
Aspirin	0.041	-0.036	0.008	0.053	-0.128	0.026	0.128	-0.097	0.068	-0.164 *	0.132						
Plavix	0.083	-0.085	-0.067	0.030	0.000	0.122	0.087	0.047	0.010	0.113	0.133	-0.091					
MAPT	-0.040	0.045	-0.008	-0.183	0.050	-0.005	0.060	-0.048	0.048	-0.230 †	-0.051	0.373 ‡	-0.451 ‡				
DAPT	0.065	-0.066	-0.024	0.139	-0.118	0.086	0.063	0.034	0.030	0.130	0.160 *	0.234 †	0.785 ‡	-0.651 ‡			
Anticoagulation	-0.164 *	0.172 *	-0.047	0.052	0.026	-0.080	-0.140	0.130	0.272 †	0.102	0.089	-0.119	0.120	-0.036	0.041		
Prior intervention	-0.040	0.046	-0.139	-0.190 *	0.085	0.132	0.104	0.065	-0.013	0.114	0.087	0.007	0.271 †	-0.073	0.217 *	0.044	
Open procedure	0.054	-0.055	0.027	0.102	0.004	0.092	0.092	-0.245 †	0.058	-0.252 †	-0.053	0.124	-0.173 *	0.157	-0.125	-0.027	-0.172

* $p<0.05$; † $p<0.01$; ‡ $p<0.001$

Abbreviations used: Platelet agg, platelet aggregation; Platelet inh, platelet inhibition; BMI, body mass index; NH White, non-Hispanic White; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; HLD, hyperlipidemia; MAPT, mono-antiplatelet therapy; DAPT, dual-antiplatelet therapy; AC, anticoagulation; Prior interv, prior intervention