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Platelet FcγRIIa as a Marker of Cardiovascular Risk After Myocardial Infarction

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ABSTRACT

BACKGROUND A previous single-center study of patients with myocardial infarction (MI) showed that platelet FcγRIIa (pFCG) can distinguish patients at higher and lower risk of subsequent MI, stroke, and death.

OBJECTIVES The authors performed an 800-patient 25-center study to validate the prognostic implications of pFCG.

METHODS Patients with type 1 MI (ST-segment elevation and non–ST-segment elevation) were enrolled in a prospective noninterventional trial during their index hospitalization. Enrolled patients had at least 2 of the following characteristics: age ≥65 years, multivessel coronary artery disease, previous MI, chronic kidney disease, or diabetes mellitus. Flow cytometry was used to quantify pFCG at a core laboratory. A predefined threshold was used to identify high and low pFCG. Patients were queried every 6 months by telephone with a standardized questionnaire. Events were confirmed by review of medical records.

RESULTS Treatment with antithrombotic therapy (aspirin, $P2Y_{12}$ inhibitors, and anticoagulants) was similar in patients with high and low pFCG. The primary composite endpoint (MI, stroke, death) occurred more frequently in patients with high pFCG (HR: 2.09; 95% CI: 1.34-3.26; $P = 0.001$). Among individual components of the composite, both death (HR: 2.57; 95% CI: 1.50-4.40; $P = 0.001$) and MI (HR: 3.24; 95% CI: 1.64-6.37; $P = 0.001$) were more frequent in patients with high pFCG.

CONCLUSIONS Quantifying pFCG identifies patients at higher and lower risk of subsequent cardiovascular events. This prognostic information will be useful in clinical decisions regarding the intensity and duration of antiplatelet therapy. (Assessment of Individual Risk of Cardiovascular Events by Platelet FcγRIIa; NCT05175261) (JACC. 2024;84:1721-1729)

Clinicians must balance the risks of thrombosis and bleeding as they define an antithrombotic strategy after myocardial infarction (MI). Higher intensity and longer duration of antithrombotic therapy reduce ischemic events but are associated with a greater risk of bleeding.[1,2] Bleeding is associated with both morbidity and mortality.[3,4] Although consensus guidelines recommend 12 months of dual antiplatelet therapy (DAPT) after MI,[5] the recognition of the risks associated with bleeding has led to studies on de-escalation of antiplatelet therapy. De-escalation strategies include

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ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

DAPT = dual antiplatelet therapy

GFR = glomerular filtration rate

MI = myocardial infarction

pFCG = platelet FcγRIIa

reduction in DAPT intensity by using less powerful inhibition of $P2Y_{12}$, abbreviating the duration of DAPT by either stopping aspirin or the $P2Y_{12}$ inhibitor, and reducing the dose of $P2Y_{12}$ inhibitor.[6] The STOPDAPT-2 ACS (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent 2 in Acute Coronary Syndrome; NCT03462498) trial demonstrated that shortened DAPT reduced bleeding (HR: 0.46; 95% CI: 0.23-0.94) at the expense of an increased risk of cardiovascular death, MI, any stroke, or definite stent thrombosis (HR: 1.50; 95% CI: 0.99-2.26).[7] Although the 95% CI for ischemic events crosses 1, the wide CI highlights a heterogeneity of treatment effect and the potential value of effective tools to guide individualized treatment. A recent consensus guideline highlighted the need for effective laboratory biomarkers to optimize patient selection for de-escalation as a critical gap.[8]

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We have identified a biomarker that discriminates patients at high and low risk of subsequent ischemic cardiovascular events. FcγRIIa was identified as the low-affinity receptor for the fragment constant (Fc) portion of immunoglobulin G.[9] More recently, a new function of FcγRIIa in platelets has been delineated. During the cytoskeletal rearrangement that accompanies the activation of platelets, FcγRIIa clusters in lipid rafts, is cross-linked, and is phosphorylated.[10,11] This phosphorylation of FcγRIIa amplifies the activation of platelets. Greater platelet expression of FcγRIIa is associated with increased platelet reactivity.[12] Consistent with this observation, greater platelet expression of FcγRIIa markedly enhances thrombus formation when platelets are perfused over a collagen-coated flow chamber under conditions of arterial and venous shear.[13] Thus, FcγRIIa amplifies the activation of platelets, and greater expression o FcγRIIa drives consistently increased platelet reactivity. The role of FcγRIIa as an amplifier of platelet activation is central to its role as a biomarker of thrombotic/ischemic risk.

A single center study on patients with MI demonstrated that platelet FcγRIIa (pFCG) can distinguish patients at higher and lower risks of a composite of subsequent MI, stroke, and death (HR: 3.9; $P = 0.007$).[14] We performed an 800-patient 25-center study to validate the prognostic implications of pFCG. This prospective cohort study was designed to evaluate outcomes after 80 ischemic events (MI, stroke, death) and after the last enrolled patient completed 18 months of follow-up. We report results after accrual of 80 ischemic events.

METHODS

PATIENTS. Adults were enrolled in this prospective observational noninterventional study after providing written informed consent. Sites were allowed to use their Institutional Review Boards or a central review board. Patients were enrolled during hospitalization for type 1 MI (ST-segment elevation or non-ST-segment elevation). Most frequently, patients were enrolled shortly before discharge after therapeutic interventions were completed and clinical judgment was used to determine whether the MI was type 1. Inclusion criteria required that participants had at least 2 of the following characteristics: age ≥65 years, multivessel coronary artery disease, previous MI, chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), and diabetes mellitus. These criteria were used to target a higher-risk patient group that would have an estimated risk of ~10% for the composite endpoint of MI, stroke, and death.[15] This study focused on patients treated with antiplatelet therapy, but a limited number (n ≈ 100) of patients treated with long-term anticoagulants were permitted. Patients were excluded if they were enrolled in another trial in which the subject could receive anticoagulant or antiplatelet treatment as part of the trial intervention and if noncardiovascular conditions, in the judgment of the investigator, would limit survival to <2 years. After enrollment, subject data were recorded in a central database (REDCap Cloud).

QUANTIFICATION OF pFCG. Citrate anticoagulated blood was taken at each clinical site within 2 weeks of enrollment. Before samples were shipped to a core laboratory, platelets were fixed with formaldehyde within 24 hours after phlebotomy. After samples arrived at the core laboratory, they were processed within 5 days of fixation, because preliminary studies demonstrated that pFCG expression was stable for that interval. Before performing the assay, platelets were washed 3 times (platelets were pelleted by centrifugation and resuspended in phosphate-buffered saline solution). Subsequently, pFCG was quantified by exposure of platelets to CD42b conjugated with phycoerythin-CY5 (BD Biosciences) and an antibody that binds to pFCG, 5G1. 5G1 was developed to bind with high affinity to pFCG on platelets that have been previously fixed. 5G1 was labeled in a 1:1 molar ratio with phycoerythrin. Flow cytometry was used to quantify pFCG. Platelets were identified by their size and expression of CD42b. The flow

cytometry output (mean fluorescence intensity) was converted to molecules of pFCG/platelet with the use of standardized beads (Quantibrite; BD Biosciences). In our first study,[14] Bangs Beads (Bangs Laboratories) were used for standardization of flow output. Shortly before initiation of this multicenter study, Bangs Laboratories changed the calculation template (formula that translates flow output to molecules/platelet). This change substantially reduced the molecules of pFCG/platelet. Quantibrite beads were subsequently adopted for use. Results with Bangs Beads with the updated formula yielded results similar to those obtained with Quantibrite beads. Thus, the change represented a "unit" change rather than a complete revision of the translation of mean fluorescence intensity into molecules/platelet. Results from the original study were analyzed with the use of the Quantibrite formula to relate results obtained using the previous Bangs Laboratories formula with the formula used with Quantibrite beads. A nearly perfect fit was obtained with log-transformation of the data. The prespecified threshold (11,000 molecules/platelet) defined for the first study[14] was translated to 1,750 molecules/platelet and used to identify high and low pFCG in this study.

OUTCOMES. The primary endpoint was a composite of MI, stroke, and all-cause death. A secondary endpoint was the incidence of clinically significant bleeding according to the Bleeding Academic Research Consortium (BARC) scale type 2 to 5.[16] Telephone follow-up was performed every 6 months and used a standardized questionnaire. Patient-reported events were confirmed by medical record review. Investigators identified clinical events (MI, stroke) by the combination of symptoms plus biomarkers (MI) or imaging (stroke). Redacted documentation of events was uploaded to REDCap Cloud.

STATISTICS. The trial design was event driven. Enrolled patients (~800 subjects) were planned to be followed until at least 80 ischemic events had occurred. Assuming a roughly 50-50 split between high and low pFCG, this number of events provided at least 95% power to detect a 2.3-fold greater incidence of the primary endpoint (MI, stroke, and death) among patients with high compared with low pFCG at a 2-sided significance level of 0.05. An observed HR of 1.9 would result in a lower bound of the 95% CI of approximately 1.2. For the secondary endpoint (bleeding), presuming that 5% of subjects would experience a bleeding event, the number of events provided a 95% power to detect an HR of 3.1 assuming a 2-sided α of 0.05.

TABLE 1 Clinical Characteristics

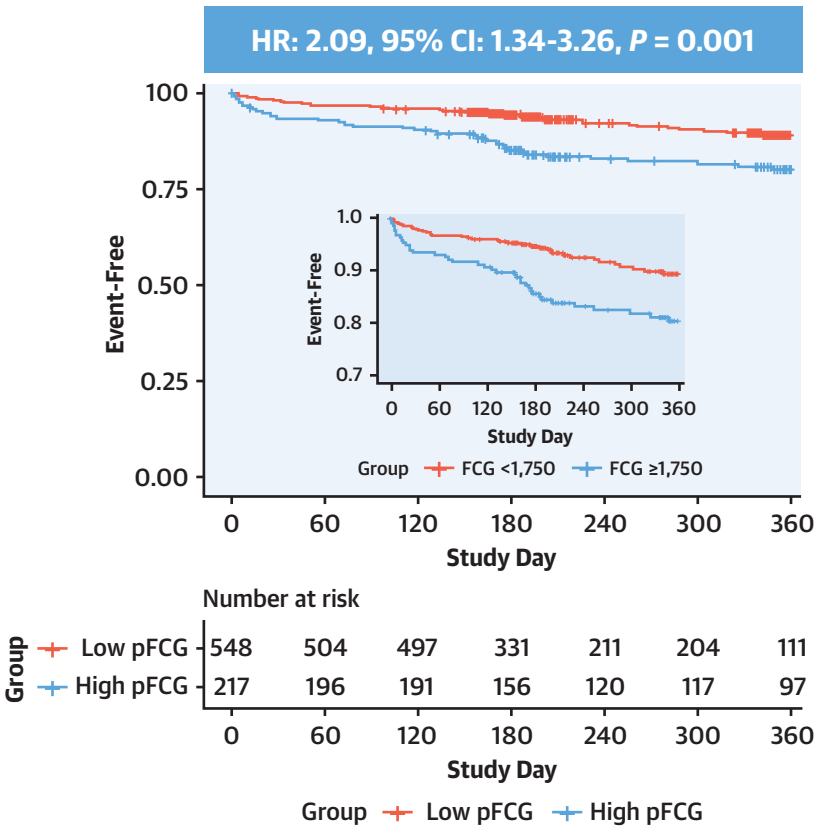
	All Patients (N = 764)	Low pFCG (n = 547)	High pFCG (n = 217)	*P* Value
Age, y	69 ± 10	69 ± 10	69 ±10	0.847
Male	68 (519)	68 (372)	67 (145)	0.932
MI type				
STEMI	29 (222)	29 (159)	29 (63)	0.930
NSTEMI	71 (542)	71 (388)	71 (154)	0.930
HTN	87 (665)	86 (470)	89 (173)	0.288
DM	57 (435)	57 (312)	59 (128)	0.686
Insulin treatment	26 (199)	24 (131)	30 (65)	0.120
Active smoker	22 (168)	23 (125)	19 (41)	0.284
Hyperlipidemia	74 (565)	74 (404)	76 (165)	0.521
Previous MI	28 (214)	26 (142)	32 (69)	0.108
Previous CABG	14 (107)	12 (66)	17 (37)	0.078
Previous PCI	36 (275)	36 (197)	35 (76)	0.802
PAD	12 (92)	11 (59)	15 (33)	0.083
Previous stroke	10 (76)	8 (44)	14 (30)	0.021[a]
Chronic kidney disease				
eGFR <60 mL/min/1.73 m^2	31 (237)	28 (153)	39 (84)	0.006[a]
ESRD	4 (30)	2 (11)	7 (15)	0.003[a]
Medications				
Aspirin	93 (711)	93 (509)	93 (202)	1.000
Clopidogrel	55 (420)	57 (312)	52 (113)	0.227
Ticagrelor	24 (183)	25 (137)	22 (48)	0.511
Prasugrel	7 (53)	6 (33)	8 (17)	0.348
Anticoagulant	14 (107)	14 (77)	14 (30)	0.908
β-Blocker	88 (672)	88 (481)	89 (193)	0.625
CCB	21 (160)	20 (109)	24 (52)	0.282
Nitrates	33 (242)	34 (186)	30 (651)	0.393
ACEI/ARB	55 (91)	55 (43)	54 (48)	0.850
Diuretic	39 (22)	37 (6)	42 (16)	0.217
Lipid lowering	94 (718)	95 (519)	92 (199)	0.134

Values are mean ± SD or % (n). [a]Significant difference.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass surgery; CCB = calcium-channel blocker; DM = diabetes mellitus; ESRD = end stage renal disease; eGFR = estimated glomerular filtration rate; HTN = hypertension; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; pFCG = platelet FcγRIIa; STEMI = ST-segment elevation myocardial infarction.

The primary analysis of the primary endpoint used a Cox proportional hazards model. The dependent variable was the number of days from enrollment to the occurrence of a primary endpoint, with censoring at the last day of complete follow-up. Independent variables included pFCG, age, history of diabetes mellitus, previous revascularization, multivessel coronary artery disease defined as ≥2 vessels or left main with a stenosis ≥50%, chronic kidney disease defined as eGFR <60 mL/min/1.73 m^2, previous MI, hypertension, tobacco use, previous stroke or transient ischemic attack, and peripheral arterial disease. For the secondary analysis of bleeding, independent variables (selected from those associated with greater risk of bleeding[17]) included pFCG, age, hypertension,

FIGURE 1 Freedom From Myocardial Infarction, Stroke, and Death



Kaplan-Meier plot of freedom from composite endpoint of MI, stroke, and death. The inset graph shows the same results with a limited *y* scale (0.7-1.0). pFCG = platelet FcγRIIa.

end-stage renal disease, and previous stroke. Significance was defined as $P < 0.05$.

To determine whether the pFCG test augments assessment of cardiovascular risk beyond that provided by clinical characteristics, ROC analysis was performed. Clinical characteristics from the Cox regression model were used to stratify patients into low-risk and high-risk groups. The additive value of pFCG results (used as a continuous variable) was assessed by means of ROC analysis, and significance was assessed with the use of bootstrap analysis.

RESULTS

Clinical characteristics are presented in Table 1. Patients with high pFCG were more likely to have previous stroke and renal disease (eGFR <60 mL/min/1.73 m^2). Treatment with antithrombotic therapy (aspirin, $P2Y_{12}$ inhibitors, and anticoagulants) was similar in patients with high and low pFCG. Management strategies were defined by the treating clinician and included percutaneous coronary intervention (63%), medical management (22%), and coronary artery bypass surgery (15%).

Similarly to our previous results, a broad range of expression (nearly 13-fold) of pFCG was seen: 591-7,640 molecules/platelet. The prespecified threshold of 1,750 molecules/platelet) identified 71% of patients as having low pFCG. The primary composite endpoint (MI, stroke, death) occurred more frequently in patients with high compared with low pFCG (Figure 1) (HR: 2.09; 95% CI: 1.34-3.26; $P = 0.001$). The composite of death and MI (Table 2) was similarly more prevalent in patients with high pFCG (HR: 2.71; 95% CI: 1.73-4.25; $P < 0.001$). Among individual components of the composite (Table 2), both death (HR: 2.57; 95% CI: 1.5-4.4; $P < 0.001$) and MI (HR: 3.24; 95% CI: 1.64-6.37; $P < 0.001$) were more frequent in

TABLE 2 HRs for Ischemic Endpoints

	Ischemic Events				
	All	Low pFCG	High pFCG	HR (95% CI)	*P* Value
Composite	80	41	39	2.09 (1.34-3.26)	0.001
MI or death	76	37	39	2.71 (1.73-4.25)	<0.001
MI	34	15	19	3.24 (1.64-6.37)	<0.001
Death	54	26	28	2.57 (1.50-4.40)	<0.001
Stroke	8	6	2	0.83 (0.17-4.12)	0.823

MI = myocardial infarction; pFCG = platelet FcγRIIa.

TABLE 3 Univariate (Unadjusted) Multivariate (Adjusted) Analysis of Pimary Endpoint (MI, Stroke, Death)

	Univariate Analysis		Multivariate Analysis	
	HR	*P* Value	HR	*P* Value
High pFCG	2.09	0.001[a]	1.84	0.010[a]
Age	1.12	0.303	1.14	0.306
Diabetes	1.57	0.059	1.33	0.260
Hypertension	4.28	0.013	2.05	0.238
Renal disease	3.17	<0.001[a]	2.62	<0.001[a]
Active smoker	1.05	0.861	1.69	0.078
Previous revascularization	2.82	<0.001[a]	2.09	0.010[a]
Previous MI	2.21	<0.001[a]	1.33	0.309
Multivessel CAD	0.70	0.18	0.70	0.237
PAD	1.98	0.014[a]	0.94	0.824
Previous stroke	3.46	<0.001[a]	2.32	0.002[a]

[a]Significant difference.

CAD = coronary artery disease; MI = myocardial infarction; pFCG = platelet FcγRIIa; PAD = peripheral artery disease.

patients with high pFCG. Low pFCG identified patients at low risk of recurrent MI (event rate 2.7/100 patient-years) compared with high pFCG (event rate 7.0/100 patient-years). Although uncommon, the combination of MI plus death (as a surrogate for fatal MI) was strongly predicted by high pFCG (12 subjects; HR: 4.23; 95% CI: 1.25-14.28; $P = 0.020$). Stroke was uncommon (8 events) and not independently predicted by pFCG.

Multivariate analysis was performed (Table 3). This analysis demonstrated that pFCG independently predicted risk (HR: 1.84; $P = 0.01$). Other factors independently associated with risk included renal disease (eGFR <60 mL/min/1.73 m^2), previous revascularization, and previous stroke.

To determine whether the pFCG test augments assessment of cardiovascular risk beyond that provided by clinical characteristics, ROC analysis was performed. Specifically, linear predictors were created from 2 Cox regression models, one including a set of clinical characteristics alone and another that added the pFCG test results. These linear predictors were used to generate ROC curves. The clinical characteristics alone exhibited a c-statistic of 0.75. The results of the pFCG test had a modest impact on risk assessment, increasing the c-statistic to 0.77 (the pFCG result in the full Cox model was statistically significant: $P = 0.006$). To further assess the potential contribution of the pFCG test, enrolled patients were stratified into low risk and high risk based on clinical characteristics from a Cox regression model. The low- and high-risk groups were divided so that each group had an equal number of events. For the composite endpoint, the event rates were 6.4% (40 events in 627 subjects) in the low-risk group and 29.2% in the high-risk group (40 events in 137 subjects). Once again, ROC analysis was performed to assess the additional impact of the pFCG test. The ROC analysis (Figure 2) demonstrates that pFCG distinguished patients at higher and lower risk among patients categorized as either high or low risk based on clinical characteristics. The additive value was evident for both the composite endpoint ($P = 0.008$ for low-risk group; $P = 0.00003$ for high-risk group) and the combination of death or MI ($P = 0.001$ for low-risk group; $P = 0.00007$ for high-risk group). For these analyses, pFCG was used as a continuous variable. Thus, the pFCG test is capable of discriminating higher and lower risk among patients deemed to be at high risk based on clinical characteristics.

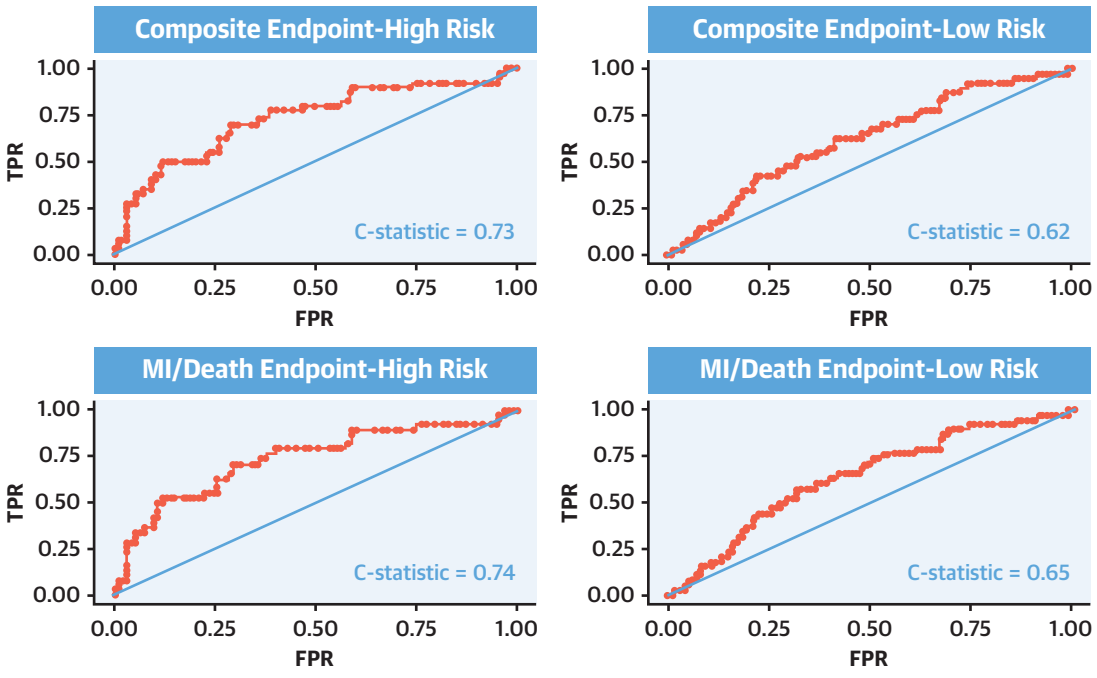
Bleeding events (BARC ≥2; n = 31) tended to be more frequent in patients with high pFCG (HR: 1.84; 95% CI: 0.98-4.05; $P = 0.095$). In multivariate analysis (Table 4), no characteristic was associated with a greater risk of bleeding. The majority of bleeding events were BARC ≥3 (n = 23).

DISCUSSION

Our results show that pFCG discriminates patients at higher and lower risk of subsequent MI, stroke, and death. The pFCG test effectively identified patients at higher and lower risk of the combination of death or MI as well as death alone and MI alone. The results of this multicenter study validate results previously seen in a single-center study.[14] The pFCG test bridges a critical gap identified by a recent consensus statement[8] and identifies risk of ischemic events independently from clinical risk factors. Accordingly, identification of patients who are at low risk of recurrent MI will support clinical decision making, particularly in patients judged to be at increased risk of bleeding.

Although pFCG is a surface receptor, the prognostic implications of pFCG are unlikely to be mediated

FIGURE 2 ROC Analysis



ROC analysis of patients deemed to be at low risk (n = 627; event rate 6.4%) and high risk (n = 137; event rate 29.2%) based on clinical characteristics used in the Cox regression models. The top 2 panels assessed the composite endpoint of myocardial infarction (MI), stroke, and death, and lower 2 panels assessed the MI or death endpoint. FPR = false positive rate; TPR = true positive rate.

primarily by the receptor function, because a second function of pFCG is the amplification of platelet activation.[10,11] Amplification is mediated by clustering of pFCG in signaling domains during platelet activation. Thus, greater expression of pFCG is associated with increased platelet reactivity, which has been consistently associated with a higher cardiovascular risk.[18] Unlike platelet function tests used to identify increased platelet reactivity, quantifying pFCG does not require activation of platelets and thus substantially reduces test variability. An additional important difference is that high pFCG reflects increased platelet reactivity to any agonist. Platelet function tests determine platelet activation in response to a specific concentration of a single agonist or combination of agonists. Megakaryocyte production of FcγRIIa determines pFCG. Thus, pFCG expression would be stable for the circulating life of platelets.

In our single-center study, approximately 50% of the patients exhibited high pFCG. We observed that pFCG was higher in older patients as well as patients with diabetes and previous revascularization.[14] In the present study, approximately 70% of patients exhibited low pFCG. An important difference between the studies is the enrollment criteria for the present study, which included age ≥65 years, diabetes, previous MI, and renal disease. The greater prevalence of these characteristics in the present study may have influenced categorization of patients into high- and low-risk categories as well as the association of pFCG with risk. The prevalence of patients categorized as low risk by pFCG can be expected to be 50% to 70%.

TABLE 4 Analysis of Bleeding Events (BARC ≥2)

	Univariate Analysis		Multivariate Analysis	
	HR	*P* Value	HR	*P* Value
High pFCG	1.84	0.095	1.73	0.138
Age ≥65 y	1.06	0.876	1.06	0.891
Hypertension	1.58	0.447	1.38	0.600
ESRD	1.95	0.360	1.51	0.583
Previous stroke	2.66	0.031[a]	2.17	0.097

[a]Significant difference.

BARC = Bleeding Academic Research Consortium; ESRD = end-stage renal diseae; pFCG = platelet FcγRIIa.

Higher pFCG was seen in patients with previous stroke and in those with renal disease. An association between pFCG with age and diabetes has been reported previously.[19,20] We have reported that interferon-γ increases pFCG expression by augmenting megakaryocyte production.[21] More extensive atherosclerotic vascular disease is associated with greater expression of interferon-γ.[22-25] Similarly, diabetes[26] and renal disease[27] are associated with greater expression of interferon-γ. Thus, conditions associated with higher pFCG are associated also with greater expression of interferon-γ. This observation leads us to hypothesize that interferon-γ is a key driver of megakaryocyte production of FcγRIIa and thereby pFCG.

A key goal of this multicenter study was to validate the prognostic implications of the pFCG test. Inclusion criteria were used to ensure that a sufficient number of events were accrued. Our first study[14] did not use inclusion criteria and was more reflective of the broad range of clinical risk encountered in the care of patients with MI. As in this multicenter study, the pFCG test discriminated risk in patients at high and low clinical risk.[28] In aggregate, these studies demonstrate that the pFCG test can identify patients with MI who are at higher and lower risk of subsequent ischemic events across a broad range of clinical risk.

We observed a trend toward a positive association between pFCG and bleeding events. Because pFCG increases platelet reactivity,[10,11] this association was not anticipated. The association of pFCG with older age,[19,20] renal disease, and stroke may be the causal connection between pFCG and a greater risk of bleeding. Consistent with this hypothesis, the association between pFCG and bleeding was weaker after multivariate analysis that included recognized risk factors for bleeding. In patients with non–ST-segment elevation myocardial infarction who were medically managed, platelet reactivity assessed by means of the VerifyNow device was not significantly associated with the long-term risk of major bleeding events.[29] Those authors concluded that that low on-treatment platelet reactivity does not independently predict serious bleeding risk. The relationship between pFCG and bleeding will require further evaluation with a greater number of bleeding events to determine whether this is a true association that is clinically meaningful, the play of chance, or the association between pFCG and clinical characteristics associated with greater risk of bleeding.

Both the multivariate analysis and the ROC analysis demonstrate that pFCG discriminates risk independently from clinical characteristics. Future research will assess the prognostic implications of a risk score that combines selected clinical characteristics plus pFCG. Results from this multicenter study will be used to develop the risk score, which will be validated in subsequent studies.

STUDY STRENGTHS AND LIMITATIONS. Strengths of this study include the size of the study and the number of centers, as well as inclusion of patients treated with percutaneous coronary intervention, coronary artery bypass surgery, and medical therapy alone. Consistency of pFCG test results was ensured by using a core laboratory. Limitations of this study include the following: 1) it does not demonstrate whether multiple laboratories can perform this test with similar results; 2) the inclusion criteria selected patients at higher risk rather than patients at both lower and higher risk; 3) the study did not enroll patients with types 2, 4, and 5 MI; 4) it did not evaluate changes in pFCG expression over time; and 5) compared with the predictive implications of clinical characteristics, the incremental predictive value of the pFCG test is modest, although the value of a single blood test over aggregating numerous other risk factors is clear. Future directions include: 1) assessment of changes in this biomarker over time; 2) assessment of this biomarker in patients with stable coronary disease; and 3) assessment of this biomarker in a larger cohort of patients treated with anticoagulants. An interventional study assessing outcomes in patients whose treatment is guided by this biomarker will be necessary to establish this test as a precision tool.

CONCLUSIONS

pFCG stratifies patients at higher and lower risk of subsequent cardiovascular events. The prognostic implications are independent from clinical characteristics, and the use of pFCG can refine risk as defined by clinical characteristics.

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