

Association Between Platelet Receptor Occupancy After Eptifibatide (Integrilin) Therapy and Patency, Myocardial Perfusion, and ST-Segment Resolution Among Patients With ST-Segment–Elevation Myocardial Infarction

An INTEGRITI (Integrilin and Tenecteplase in Acute Myocardial Infarction) Substudy

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Background—Paradoxically, fibrinolytic agents may systemically activate platelets, which in turn secrete plasminogen activator inhibitor (PAI-1), an antagonist of the fibrinolytic process in proportion to total body platelet mass. We hypothesized that improved epicardial patency, myocardial perfusion, and ST-segment resolution would be associated with higher levels of platelet receptor occupancy (RO) by a glycoprotein IIb/IIIa antagonist in ST-elevation MI (STEMI).

Methods and Results—Patients were drawn from the low-dose tenecteplase plus eptifibatide arm of the INTEGRITI study. Angiographic and platelet RO data were analyzed at 2 independent core laboratories. To take into account the absolute platelet count and receptors available for cross-linking, absolute platelet count was multiplied by percent of available receptors to obtain the index of the absolute number of receptors available (IANRA). Percent RO was higher among patients with a patent artery (TIMI flow grade 2/3; 78.2 ± 9.2 , $n=63$ versus 63.9 ± 29.7 , $n=7$; $P=0.005$), those with TIMI myocardial perfusion grade 2/3 (79.6 ± 9.5 , $n=40$ versus 73.0 ± 16.2 , $n=30$; $P=0.036$), and those with complete ($\geq 70\%$) ST-segment resolution at 60 minutes ($81.3 \pm 8.3\%$, $n=27$ versus $73.1 \pm 17.4\%$, $n=24$; $P=0.034$). The absolute number of glycoprotein IIb/IIIa receptors available for cross-linking was reduced (ie, the IANRA was lower) among patients with a patent artery ($P=0.0015$), patients with TIMI myocardial perfusion grade 2/3 ($P=0.026$), and patients with $\geq 70\%$ ST-segment resolution ($P=0.029$).

Conclusions—This study links restoration of epicardial flow, normal myocardial perfusion, and complete ST-segment resolution with higher levels of platelet glycoprotein IIb/IIIa receptor occupancy after therapy with eptifibatide administered with tenecteplase. (*Circulation*. 2004;110:679-684.)

Key Words: platelets ■ receptors ■ perfusion ■ blood flow

Platelets play a pivotal role in the pathogenesis of acute coronary syndromes. Paradoxically, fibrinolytic agents may lead to the systemic activation of platelets.¹⁻³ These activated platelets in turn secrete plasminogen activator inhibitor (PAI-1), which antagonizes the fibrinolytic process in proportion to total body platelet mass.¹⁻³

The presumed mechanism of enhanced fibrinolysis after the combination of low-dose fibrinolytic therapy with glycoprotein (GP) IIb/IIIa inhibition among patients with ST-segment–elevation myocardial infarction (STEMI) is occupancy of the platelet GP IIb/IIIa receptor by an antagonist.

Identification of the optimal level of receptor occupancy (RO) is likely to be important in maximizing the role of GP IIb/IIIa antagonism in combination with fibrinolysis for STEMI. Initial animal laboratory data have demonstrated that $\geq 80\%$ platelet RO is associated with prevention of platelet-mediated aggregation and thrombosis, with marked prolongation in bleeding times when RO is $>90\%$.⁴⁻⁷

Early human data suggested that platelet RO $\geq 80\%$ was sufficient to reduce platelet aggregation to $<20\%$ of a patient's baseline activity, as assessed by platelet aggregometry, and that this could be maintained with a continuous

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TABLE 1. Baseline Characteristics and Receptors Occupied

	RO \geq 80% (n=30*)	RO <80% (n=40*)	P
Gender, % male (n)	66.7 (20)	80.0 (32)	0.272
Age, y	58.1 \pm 9.7	59.2 \pm 10.6	0.654
History of hypertension, % (n)	43.3 (13)	22.5 (9)	0.074
History of diabetes, % (n)	6.7 (2)	22.5 (9)	0.100
Hypercholesterolemia, % (n)	36.7 (11)	17.5 (7)	0.098
Prior myocardial infarction, % (n)	23.3 (7)	12.5 (5)	0.338
Prior CHF, % (n)	0 (0)	7.5 (3)	0.255
Cigarette smoking, % (n)	50.0 (15)	60.0 (24)	0.470
Aspirin use at admission, %	23.3 (7)	27.5 (11)	0.786
Clopidogrel use at admission, % (n)	0 (0)	2.5 (1)	1.00
Admission SBP, mm Hg	139.8 \pm 20.1	148.2 \pm 22.7	0.112
Admission DBP, mm Hg	76.8 \pm 13.9 (n=29)	80.6 \pm 14.1	0.272
Admission pulse, bpm	79.3 \pm 13.7	78.9 \pm 22.5	0.929
Weight, kg	84.6 \pm 16.8	80.5 \pm 14.1	0.270
Platelet count, $\times 10^9/L$	264.2 \pm 59.9	260.7 \pm 51.9 (n=39)	0.797

*Unless otherwise noted.

infusion.⁸ Pharmacodynamic modeling of the PRIDE data⁹ led to the double-bolus dosing regimen of two 180- $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ doses 10 minutes apart and a 2- $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion. This modified regimen was associated with a 35% reduction in the composite end point of death, myocardial infarction, or urgent revascularization (6.8% versus 10.5%, $P=0.0034$) compared with antithrombin heparin alone in the Enhanced Suppression of Platelet Receptor IIb/IIIa using Integrilin Therapy (ESPRIT) trial.¹⁰

We hypothesized that in the setting of STEMI, improved epicardial patency, myocardial perfusion, and ECG ST-segment resolution would be associated with higher levels of platelet RO, leaving fewer GP IIb/IIIa receptors available for cross-linking.

Methods

Study Design

A total of 418 patients with STEMI were enrolled in the INTEGRITI (Integrilin and Tenecteplase in Acute Myocardial Infarction) trial.¹¹ Inclusion criteria were presence of ischemic discomfort lasting \geq 30 minutes with onset \leq 6 hours; ST-segment elevation (\geq 0.2 mV in precordial leads, \geq 0.1 mV in limb leads) in at least 2 contiguous leads; and age 18 to 75 years. Standard thrombolytic exclusion criteria were applied. All patients received aspirin (162 to 325 mg oral or 150 to 500 mg IV) followed by daily oral aspirin. The initial heparin bolus dose was 60 U/kg (maximum 4000 U) in all patients. Patients assigned to combination therapy with eptifibatide and tenecteplase (TNK) received a reduced initial heparin infusion of 7 U \cdot kg⁻¹ \cdot h⁻¹ (maximum 800 U/h), whereas patients assigned to TNK monotherapy received the standard initial heparin infusion of 12 U \cdot kg⁻¹ \cdot h⁻¹ (maximum 800 U/h). A nomogram was used to target the activated partial thromboplastin time (aPTT) to \approx 1.5 to 2.5 times control. Patients in part 1 of the dose-finding segment of the study all received eptifibatide 180- $\mu\text{g}/\text{kg}$ bolus, 2- $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion, followed by a 90- $\mu\text{g}/\text{kg}$ bolus 10 minutes later (180/2/90) and were randomized to either half-dose TNK (0.27 mg/kg) or three-quarter-dose TNK (0.40 mg/kg). In part 2 of the dose-finding segment, all patients received half-dose TNK, and patients were randomized to 1 of 2 doses of eptifibatide, 180/2/90 or 180/2/180. The first bolus doses of eptifibatide and TNK were administered

simultaneously, followed by initiation of the eptifibatide infusion. The second bolus of eptifibatide was administered 10 minutes after the first. The eptifibatide infusion was reduced to 1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in patients with renal dysfunction (creatinine 2.0 to 4.0 mg/dL) and could be reduced by 33% in the cases of mild bleeding at the investigator's discretion. The infusion continued for 18 to 24 hours after intervention or 40 to 48 hours in patients not undergoing early percutaneous coronary intervention (PCI).

The combination of half-dose TNK (0.27 mg/kg) with eptifibatide (180/2/180) was used for direct comparison with standard-dose (0.53 mg/kg) TNK monotherapy in the dose-confirmation phase. Patients in the TNK monotherapy group could receive adjunctive eptifibatide at the time of PCI at the physician's discretion, although a single-bolus regimen (180/2) was recommended in the first 24 hours because of the limited safety experience available with full-dose TNK plus GP IIb/IIIa inhibitor.

Assessment of Coronary Blood Flow and ECGs

The 90-minute TIMI flow grade, corrected TIMI frame count, and TIMI myocardial perfusion grade (TIMI MPG) were assessed by a single observer (CMG), who was blinded to treatment assignment and clinical outcome.¹²⁻¹⁶ The corrected TIMI frame count was converted when necessary to be based on the most common filming speed in the United States of 30 frames/s.^{13,14} Standard 12-lead ECGs were obtained at presentation and 60 minutes before PCI (range 55 to 75 minutes). The degree (continuous value) of and occurrence of complete (ie, \geq 70%) ST-segment resolution on the 12-lead ECG at 60 minutes compared with baseline were assessed. ECGs were read by the electrocardiographic core laboratory, which was blinded to treatment assignment, using previously established techniques.^{17,18}

Assessment of RO

GP IIb/IIIa receptor occupancy was measured in 70 patients randomized to combination therapy by standardized techniques and kits provided by the platelet core laboratory at the University of Tennessee Health Science Center. Blood specimens anticoagulated with PPACK (D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone) were obtained at 60 minutes during infusion of eptifibatide. Platelet GP IIb/IIIa RO was measured by a flow cytometric assay with the phycoerythrin-conjugated D3 monoclonal antibody^{19,20} that binds to a ligand-induced binding site when eptifibatide is bound to the GP IIb/IIIa receptor.^{21,22} The percent of total surface receptors with

TFG at 60 Minutes and Percent of Platelet GP IIb/IIIa Receptors Occupied at 60 Minutes

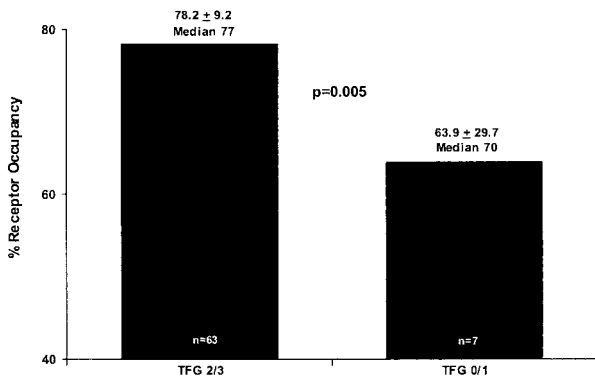


Figure 1. Percent RO among patients with patent artery (TIMI flow grade 2/3) compared with occluded artery (TIMI flow grade 0/1) at 60 minutes ($P=0.005$ by t test, $P=0.13$ by Wilcoxon). TFG indicates TIMI flow grade.

bound eptifibatide (% RO) was calculated by dividing the measured receptors with bound eptifibatide by the total receptors on the platelet surface times 100%.²³ In a second exploratory analysis, a value of 0 was imputed for the percent of receptors occupied in patients treated with TNK monotherapy.

To take into account the absolute platelet count and to better gauge the total body burden of receptors available for cross-linking, the absolute platelet count was multiplied by the percent of available receptors (100% minus percent RO) to arrive at the index of absolute number of receptors available (IANRA). Similarly, an index of the estimated absolute number of receptors occupied was calculated by multiplying the percent RO by the platelet count.

Statistical Analysis

Variables were compared with Fisher’s exact test or the χ^2 test for categorical data. Student’s t test was used for analysis of normally distributed continuous variables. The nonparametric Wilcoxon rank sum test (for 2-way comparisons) or the Kruskal-Wallis test (for 3-way comparisons) was used to compare continuous variables when the data were not normally distributed or when data were imputed.

Results

Baseline Characteristics

There were no statistically significant differences in baseline characteristics among patients with RO $\geq 80\%$ compared with RO $<80\%$ (Table 1).

Sixty-Minute Angiographic and ECG Outcomes and RO

The percent RO was higher among patients with a patent artery (TIMI flow grade 2/3) than among those with an occluded artery (TIMI flow grade 0/1; Figure 1). The percent RO was higher among patients with TIMI MPG 2/3 than among those with delayed or no perfusion (TIMI MPG 0/1; Figure 2). Likewise, the rate of TIMI MPG 2/3 tended to be higher among patients with RO $\geq 80\%$ (Figure 2).

The percent RO was higher among patients with complete ($\geq 70\%$) ST-segment resolution at 60 minutes (Figure 3). Likewise, the rate of complete ($\geq 70\%$) ST-segment resolution at 60 minutes was higher among patients with RO $\geq 80\%$ (Figure 3). Finally, when the percent of ST resolution was analyzed as a continuous variable, the percent ST resolution was higher among patients with RO $\geq 80\%$ (median 91.7%, 25th/75th percentile 57.4%/97.6%, $n=25$ versus median 64.8%, 25th/75th percentile 53.9%/77.7%, $n=26$; $P=0.015$).

Complete restoration of perfusion, defined as the presence of TIMI flow grade 3, TIMI MPG 3, and complete ($\geq 70\%$) ST-segment resolution, was associated with a higher percent RO at 60 minutes (Figure 4). Complete restoration of perfusion was present more than 3 times as frequently among patients with RO $\geq 80\%$ (Figure 4). When patients treated with TNK monotherapy were included in all of the above analyses (an RO of 0 was imputed to these patients), the percent RO remained significantly higher among patients with a patent artery (TIMI flow grade 2/3), patent myocardium (TIMI MPG 2/3), and complete ST-segment resolution ($P<0.05$ for each comparison).

TMPG at 60 Minutes and Percent of Platelet GP IIb/IIIa Receptors Occupied at 60 Minutes

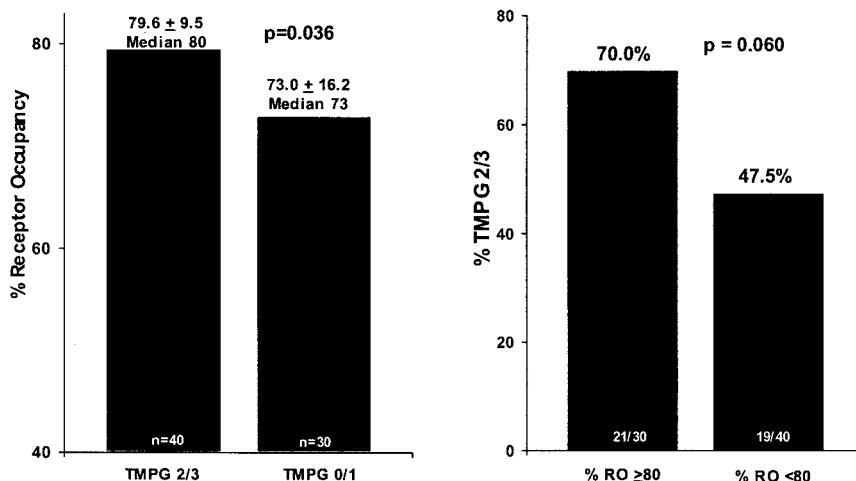


Figure 2. Percent RO among patients with normal myocardial perfusion (TIMI MPG 2/3) compared with delayed or no perfusion (TIMI MPG 0/1) at 60 minutes ($P=0.036$ by t test, $P=0.054$ by Wilcoxon). Among patients with RO $\geq 80\%$, rate of TIMI MPG 2/3 trended higher than in patients with RO $<80\%$. TMPG indicates TIMI MPG.

ST Resolution at 60 Minutes and Percent of Platelet GP IIb/IIIa Receptors Occupied at 60 Minutes

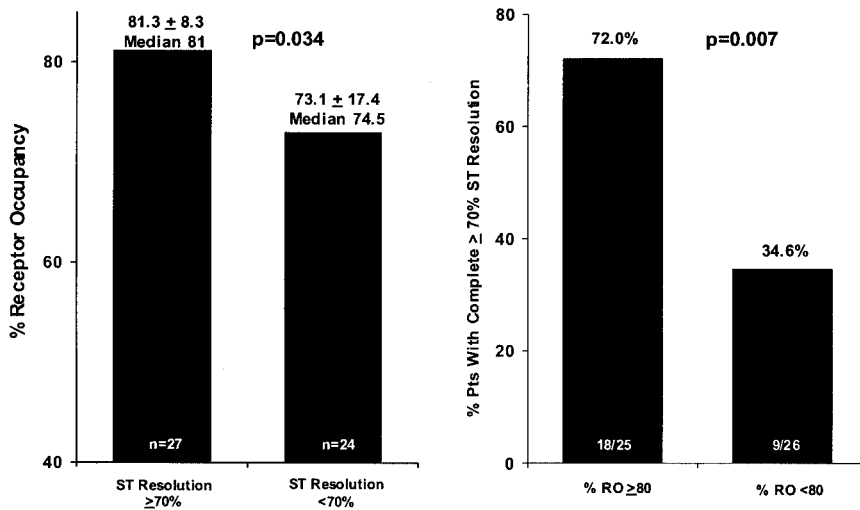


Figure 3. Percent RO was higher among patients with complete ST-segment resolution at 60 minutes ($P=0.034$ by *t* test, $P=0.021$ by Wilcoxon). Among patients with RO $\geq 80\%$, rate of complete ST-segment resolution at 60 minutes was higher than in patients with RO $< 80\%$. Pts indicates patients.

Post-PCI Angiographic Outcomes and RO

The percent RO was higher among patients with TIMI grade 3 flow after PCI (Figure 5). All patients with $\geq 80\%$ RO had post-PCI TIMI flow grade 3 (100%, 19/19 versus 89.3%, 25/28; $P=0.14$).

The percent RO also tended to be higher among patients with TIMI MPG 2/3 after PCI than among those with TIMI MPG 0/1 after PCI (Figure 5). Likewise, among patients with $\geq 80\%$ RO, the rate of TIMI MPG 2/3 after PCI tended to be higher than among patients with RO $< 80\%$ (70.0%, 14/20 versus 44.4%, 12/27; $P=0.081$). When patients in the TNK monotherapy arm were included in the analysis, RO remained higher in patients with an open microvasculature (TIMI MPG 2/3; $41.1 \pm 40.5\%$, median=66, $n=50$ versus $21.1 \pm 34.1\%$, median=0, $n=71$; $P=0.003$ by Wilcoxon).

Absolute Number of Receptors Available for Cross-Linking (IANRA) and Outcomes

The index of the absolute number of GP IIb/IIIa receptors available for cross-linking was reduced (ie, the IANRA was lower) among patients with a patent artery, among patients with improved myocardial perfusion (TIMI MPG 2/3), among patients with $\geq 70\%$ ST-segment resolution, among patients in whom complete reperfusion was achieved, and among patients in whom TIMI MPG 2/3 was achieved after PCI (Table 2). In contrast, there was no difference in the index of the absolute number of receptors occupied for all of the above outcomes (Table 2).

Bleeding and RO

There was no difference in TIMI-defined major or minor bleeding among patients with $\geq 80\%$ RO. Among patients

Complete (TFG 3, TMPG 3, ST Res $\geq 70\%$) Reperfusion at 60 Minutes and Percent Receptor Occupancy

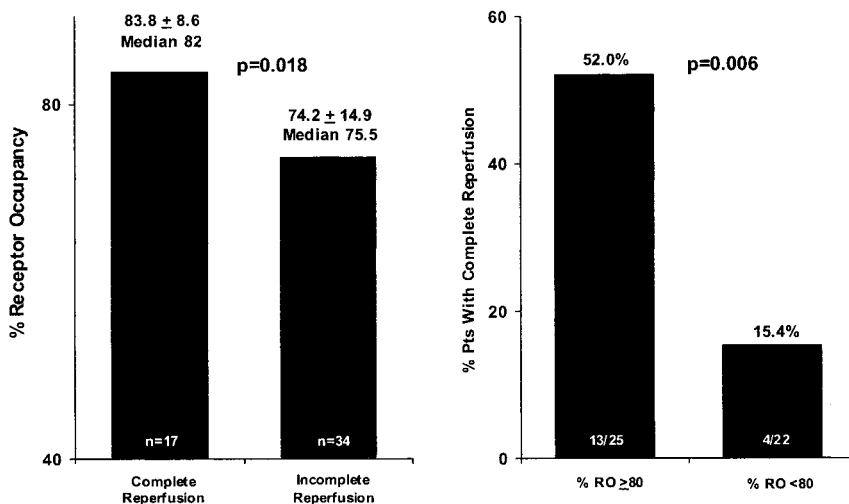


Figure 4. Percent RO was higher among patients with complete reperfusion (defined as TIMI flow grade 3, TIMI MPG 3, and complete ST-segment resolution) at 60 minutes ($P=0.018$ by *t* test, $P=0.004$ by Wilcoxon). Among patients with RO $\geq 80\%$, rate of complete reperfusion at 60 minutes was higher than in patients with RO $< 80\%$. TFG indicates TIMI flow grade; TMPG, TIMI MPG; Res, resolution; and Pts, patients.

TFG and TMPG post-PCI and Percent of Platelet GP IIb/IIIa Receptors Occupied at 60 Minutes

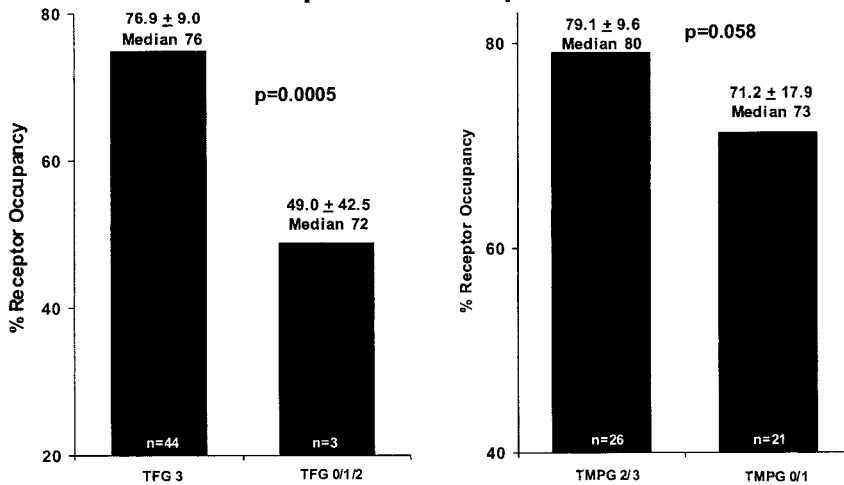


Figure 5. Percent RO tended to be higher among patients with TIMI flow grade 3 than among those with TIMI flow grade 0/1/2 after PCI ($P=0.0005$ by t test, $P=0.21$ by Wilcoxon). Percent RO tended to be higher among patients with open microvasculature (TIMI MPG 2/3) than among those with closed microvasculature (TIMI MPG 0/1) after PCI ($P=0.058$ by t test, $P=0.108$ by Wilcoxon). TFG indicates TIMI flow grade; TMPG, TIMI MPG.

with $\geq 80\%$ RO, 20.0% had major or minor TIMI bleeding compared with 17.5% of patients with RO $< 80\%$ ($P=NS$). Likewise, TIMI-defined major bleed rates did not differ (3.3% versus 2.5%, $P=NS$).

Discussion

This study links the magnitude of platelet RO to angiographic and ECG outcomes in acute myocardial infarction. The present study builds on the GOLD (AU-Assessing Ultegra Multicenter Data) study, which demonstrated a relationship between platelet aggregation and clinical outcomes in the setting of planned coronary intervention.²⁴ The present study demonstrates that in the setting of STEMI, higher levels of platelet GP IIb/IIIa RO after therapy with eptifibatid (Integrilin) administered in combination with TNK are associated with improved measures of epicardial flow, myocardial perfusion, and complete ST-segment resolution. Furthermore, the achievement of TIMI grade 3 flow and improved myocardial perfusion (TIMI MPG 2/3) after rescue/adjunctive PCI was also associated with higher levels of RO. Finally, it was the IANRA and not the absolute number of receptors occupied or neutralized that was associated with the angiographic and ECG improvements.

Platelet function and activation are critical in the pathogenesis of acute myocardial infarction.^{25–28} Patients with acute coronary syndromes have been shown to have higher platelet volumes than healthy control subjects and patients with stable angina.²⁹ Increased platelet volume has also been associated with risk of myocardial infarction, outcomes after myocardial infarction, and sudden cardiac death.^{30–35} The mechanism of action of fibrinolytic agents is the degradation of fibrin, which in turn increases thrombin exposure and activation. This paradoxically leads to increased platelet activation and consequent aggregation in the newly formed thrombus.^{36,37} In turn, these activated platelets secrete large amounts of PAI-1, which antagonizes the fibrinolytic process. This antagonization is in direct proportion to the platelet mass.^{1–3} Finally, after local platelet activation, there may be systemic platelet activation and higher PAI-1 expression proportional to total body platelet mass.

Whereas prior studies documented the association of RO and clinical efficacy in the elective PCI setting, the present study extends these observations to the STEMI setting. In the present study, $< 80\%$ platelet RO was associated with poorer epicardial and myocardial perfusion after rescue/adjunctive

TABLE 2. IANRA vs Angiographic and ECG Outcomes

Outcome	Success	Failure	P^*
Pre-PCI TIMI flow grade 2/3	55.9 ± 26.0 (55.7) n=62	106.4 ± 96.7 (77.9) n=7	0.0015
Pre-PCI TIMI MPG 2/3	51.5 ± 26.3 (55.2) n=39	73.3 ± 52.2 (65.4) n=30	0.026
Pre-PCI ST-segment resolution $\geq 70\%$	46.8 ± 20.7 (46.1) n=27	74.5 ± 59.6 (71.8) n=23	0.029
Pre-PCI TIMI flow grade 3, TIMI MPG 2/3, and ST-segment resolution $\geq 70\%$	39.1 ± 19.5 (43.6) n=17	70.1 ± 50.6 (64.9) n=33	0.019
Post-PCI TIMI MPG 2/3	51.2 ± 24.8 (54.0) n=26	79.6 ± 58.4 (67.8) n=21	0.03

Values shown for IANRA are mean ± SEM × 10³ (median × 10³) and number of patients.

* P values shown are ANOVA values. Corresponding P values by nonparametric Wilcoxon rank sum test are pre-PCI TFG 2/3 $P=0.065$; pre-PCI TIMI MPG 2/3 $P=0.03$; pre-PCI ST-segment resolution $\geq 70\%$ $P=0.035$; pre-PCI TIMI flow grade 3, TIMI MPG 2/3, ST-segment resolution $\geq 70\%$ $P=0.002$; and post-PCI TIMI MPG 2/3 $P=0.01$.

PCI. Whether the ratio, absolute number of unbound receptors, or density per unit surface area correlates best to clinical outcomes is a question for further work. Measurement of RO is a highly specialized technique, whereas the extent of platelet aggregation, although a technique with its own shortcomings, is presently more practical from a clinical viewpoint. Further studies are needed to determine whether patients with low percent platelet RO might be candidates for an additional supplemental dose of GP IIb/IIIa inhibition at the time of PCI.

Study Limitations

These data were drawn from a substudy of a randomized trial, are retrospective in nature, and could be influenced by both identified and unidentified confounders. Although the IANRA adjusts for the absolute platelet count and the percent of receptors occupied, it does not take into account the number of receptors on each platelet. The study may have been underpowered to detect differences in bleeding as a function of RO.

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