Clinical Investigation

The Role of von Willebrand Factor and ADAMTS13 in the No-Reflow Phenomenon

after Primary Percutaneous Coronary Intervention

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We prospectively studied the correlations between plasma levels of von Willebrand factor and its cleaving protease—a disintegrin and metalloproteinase with thrombospondin type I motif, member 13 (ADAMTS13)—in 126 patients who did or did not develop no-reflow phenomenon after primary percutaneous intervention for acute ST-segment–elevation myocardial infarction. Quantitative plasma levels of von Willebrand factor and ADAMTS13 were measured by immunoturbidometric assay.

Angiographic no-reflow was observed in 46 (37%) of the 126 patients. At admission, plasma levels of von Willebrand factor were significantly higher in the no-reflow group (P <0.001), but levels of ADAMTS13 at admission were similar in the 2 groups (P=0.143). At logistic regression, after adjustment for serum creatinine, left ventricular ejection fraction, high-sensitivity C-reactive protein, and N-terminal pro B-type natriuretic peptide, plasma von Willebrand factor level at admission (≥5,531 mU/mL) was still the predictive factor for the no-reflow phenomenon. The area under the receiver operating characteristics curve was 0.785.

Our results suggest that high von Willebrand factor level is related to the no-reflow phenomenon in such a way that it might be a predictor of the phenomenon. ***(Tex Heart Inst J 2011;38(5):516-22)***

Key words: *ADAMTS13 protein, human; angioplasty, balloon, coronary/adverse effects; microcirculation; myocardial ischemia; myocardial reperfusion; no-reflow phenomenon/drug therapy; predictive value of tests; prospective studies; von Willebrand factor*

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In approximately 10% to 40% of cases in which primary percutaneous coronary intervention (PCI) is performed as intervention for ST-elevation myocardial infarction (STEMI), there is a subsequent angiographic "no-reflow" phenomenon, which is associated with a poor clinical prognosis in both the short and long terms.[1-3] The mechanisms that underlie no-reflow are complex and are only partially understood. Neutrophil and platelet plugging, intense vasoconstriction, and external microvascular compression caused by myocardial edema are potential causes of the microvascular obstruction associated with no-reflow.[4-7] Furthermore, in patients treated by primary PCI, distal thrombosis is likely to play a contributory role.

A central molecule in hemostasis, von Willebrand factor (vWF), plays an important role in the microcirculation.[8-11] Meta-analyses of prospective studies have suggested that high levels of circulating vWF are associated with increased risk of coronary heart disease.[12] A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) cleaves the vWF A2 domain, reducing its molecular weight and consequently also its platelet-tethering function.[8] Deficiency of ADAMTS13 promotes vWF-induced platelet aggregation, which can result in thrombotic thrombocytopenic purpura. In mouse models of thrombosis, ADAMTS13 downregulates both platelet adhesion to the exposed subendothelial matrix and thrombus formation in injured arterioles.[13] Consequently, it has been suggested that the circulating levels of ADAMTS13 can influence either the circulating levels of vWF or the function of vWF (or both) and can therefore influence the risk of thrombotic events, such as myocardial infarction, in the general population.

von Willebrand Factor participates in endothelial activation, which is known to play a fundamental role in the no-reflow phenomenon.[3,14,15] Previous study has shown elevated plasma vWF levels in patients with no-reflow.[16] However, we lack data that compare vWF and ADAMTS13 levels with various risk scores—especially in the setting of no-reflow phenomenon after primary PCI. To examine this issue, we pro-

spectively evaluated the relationship between baseline vWF and ADAMTS13 plasma levels and no-reflow in a population of consecutive patients who underwent primary PCI within 12 hours of the onset of chest pain because of STEMI.

Patients and Methods

Study Population

Between August 2008 and December 2009, we studied 126 consecutive patients who underwent PCI as an intervention for STEMI. The inclusion criteria were prolonged chest pain (>30 min), ST-segment elevation greater than 2 mm in at least 2 continuous electrocardiographic leads, and a more than 2-fold increase in serum creatine kinase. We excluded patients with severe chronic heart failure, heart failure of Killip class II or higher on admission, severe valvular heart disease, or a calculated creatinine clearance of less than 80 mL/min/m^2.

The study protocol was approved by the hospital's ethics committee, and patients gave written, informed consent. All clinical data were collected prospectively.

We enrolled 126 patients, 46 (37%) of whom exhibited a Thrombolysis in Myocardial Infarction (TIMI) flow grade of less than 3 within 12 hours after stent deployment. The clinical characteristics in each group are shown in Table I. At baseline, the no-reflow group showed higher levels of serum creatinine (79.26 ± 19.02 vs 64.98 ± 21.74 μmol/L, P=0.002), N-terminal pro B-type natriuretic peptide (NT-pro-BNP) (1,261.77 ± 1,666 vs 354.28 ± 652.9 pg/mL, P=0.001), and high-sensitivity C-reactive protein (hs-CRP) (6.17 ± 3.46 vs 3.14 ± 3.25 mg/L, P <0.001); the no-reflow group also exhibited a lower left ventricular ejection fraction (LVEF) than did the optimal perfusion group (0.58 ± 0.09 vs 0.64 ± 0.93, P=0.002). There were no significant differences between the 2 groups in age, sex, diabetes mellitus, hypertension, total cholesterol, triglycerides, low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C), Gensini score, pre-PCI time, and drugs administered before admission.

Procedures and Medical Treatment

All patients received oral aspirin (300 mg) and clopidogrel (300 mg) immediately after admission, and they received intravenous heparin (5,000 U) before PCI. Low-molecular-weight heparin was continued for the subsequent 5 to 7 days. All patients underwent coronary angiography via the same standard technique. We repeated balloon angioplasty or we implanted stents as needed to reduce the stenosis diameter to under 50%. All stents were deployed at 10 to 16 atm. Angiograms were analyzed by means of a validated quantitative coronary angiographic system (Allura DCI program, Philips Medical Systems; Best, The Netherlands). Angiographic no-reflow after PCI was defined as a TIMI flow of less than 3 immediately after stent implantation, without evidence of dissection or vasospasm.

Blood Sampling

Venous blood samples were obtained at 3 time points from all patients: on admission, at the end of the procedure, and a week after PCI. At the time of sampling, the first 3 mL of blood was obtained for biochemical assessment, and the subsequent 4.5 mL of venous blood was collected in a sequential manner into an evacuated tube containing 0.5 mL of sodium citrate solution (0.13 mol/L, pH 7.5). All blood samples were immediately centrifuged at 3,000 revolutions/min for 10 min at 4 °C, and aliquots of samples were stored at –80 °C until analysis.

Measurement of Plasma von Willebrand Factor and ADAMTS13 Levels

Plasma vWF and ADAMTS13 levels were measured using IMUBIND® vWF ELISA kits (Product Nos. 828 and 813, American Diagnostica Inc.; Stamford, Conn), according to the manufacturer's instructions. The intra- and interassay coefficients of variations for the ELISA kit have been found to be 4% and 7.3%, respectively.

Follow-Up Study

After laboratory samples and angiographic data had been obtained, all patients were monitored for 6 months. The recorded events included heart failure, recurrence of myocardial infarction or unstable angina requiring hospitalization, life-threatening arrhythmia, and death from any cause.

Statistical Analysis

Patients were divided into 2 groups according to the angiographic results after primary PCI: optimal perfusion group (TIMI=3) and no-reflow group (TIMI ≤2). Comparisons between the 2 groups were carried out using the Student t test or Mann-Whitney U test (as indicated) for continuous variables, whereas proportions were compared by use of the Fisher exact test. Data are expressed as mean ± SD (X ± SD), unless otherwise indicated.

All analyses were performed with SPSS statistical software version 15.0 (SPSS Inc., an IBM company; Chicago, Ill). Exploratory analysis was performed in accordance with standard tests, in order to determine differences in vWF and ADAMTS13 plasma levels between patients with no-reflow and those with optimal myocardial perfusion. Receiver operating characteristics (ROC) curve analysis of plasma vWF levels was performed to identify the optimal cutoff value for predicting the no-reflow phenomenon. Multivariate logistic regression analysis was used to identify inde-

TABLE I. Baseline Characteristics of the Patients Enrolled in the Study

Characteristic	No-Reflow Group (n=46)	Optimal-Perfusion Group (n=80)	*P* Value
Age, yr	66.47 ± 9.24	63.4 ± 10.17	NS
Male sex	26 (56.5)	47 (58.8)	NS
Coronary risk factors, %			
Active smoker	34.9	31	NS
Diabetes mellitus	18.6	27.9	NS
Hypertension	12.3	14.7	NS
LVEF	0.58 ± 0.09	0.64 ± 0.09	0.002
HbA1c, mg/dL	6.26 ± 0.43	6.15 ± 0.58	NS
Serum creatinine, μmol/L	79.26 ± 19.02	64.98 ± 21.74	0.002
NT-pro-BNP, pg/mL	1,261.77 ± 1,666	354.28 ± 652.9	0.001
hs-CRP, mg/L	6.17 ± 3.46	3.14 ± 3.25	0
Total cholesterol, mmol/L	6.51 ± 1.04	6.2 ± 0.59	NS
Triglycerides, mmol/L	2 ± 2.76	2.28 ± 3.31	NS
LDL-C, mmol/L	2.95 ± 0.78	2.83 ± 0.67	NS
HDL-C, mmol/L	1.16 ± 0.3	1.18 ± 0.46	NS
No. diseased vessels			NS
1	14 (30.4)	25 (31.3)	
2	20 (43.5)	27 (33.7)	
3	12 (26.1)	28 (35)	
Gensini score	57.71 ± 28.41	79.96 ± 52.14	NS
Drugs before admission			NS
ACEI or ARB	33 (72)	56 (70)	
β-Blockers	26 (56.5)	38 (47.5)	
Statins	27 (58.7)	47 (58.8)	
Long-acting calcium antagonists	15 (32.6)	26 (32.5)	
Nitrates	17 (37)	25 (31.2)	

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HbA1c = hemoglobin A1c; HDL-C = high-density-lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density-lipoprotein cholesterol; LVEF = left ventricular ejection fraction; NS = not significant; NT-pro-BNP = N-terminal pro B-type natriuretic peptide

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ is considered statistically significant.

pendent predictors for the development of the no-reflow phenomenon. Variables included in the multivariable model were those showing a significant association with no-reflow at univariate analysis. Correlations between 2 continuous variables were evaluated using linear regression analysis. $P < 0.05$ was always required for statistical significance.

As a further characterization of the relationship between vWF plasma levels and no-reflow, patients were divided into 3 groups according to tertiles of vWF levels, and the presence or absence of no-reflow was compared across groups.

Results

All patients with a TIMI flow grade of less than 2 were treated with 100 to 200 μg nitroglycerin via intracoronary administration; if perfusion did not improve, we then administered intravenous tirofiban (a loading dose of 0.5 mg, followed by an infusion at 0.01 mg/kg/hr). At the end of the procedure, the last angiograms showed a TIMI flow grade of 2 or greater in all patients.

Plasma von Willebrand Factor and ADAMTS13 Levels

Elevated vWF concentrations were found in patients with no-reflow phenomenon, regardless of whether the samples had been collected on admission, just after stent deployment, or a week after PCI ($P < 0.01$) (Fig. 1). However, there were no significant differences in the plasma levels of ADAMTS13 between the 2 groups except for the samples collected a week after PCI, which showed a clear elevation in the no-reflow group (Fig. 2).

As a further characterization of the relationship between vWF and no-reflow, all 126 patients were divided into 3 groups according to tertiles of vWF plasma levels on admission, and the presence or absence of no-reflow was compared across groups. Figure 3 shows the percentage of patients with no-reflow according to tertiles of vWF plasma levels (1st vs 2nd tertile, $P < 0.01$; 2nd vs 3rd tertile, $P < 0.01$; and 3rd vs 1st tertile, $P < 0.01$).

An ROC curve analysis was performed to evaluate the predictive power of vWF for the no-reflow phenomenon. The area under the ROC curve for vWF was 0.785 (Fig. 4). A vWF concentration ≥5,531 mU/mL showed a sensitivity of 88.4% and a specificity of 65.1%.

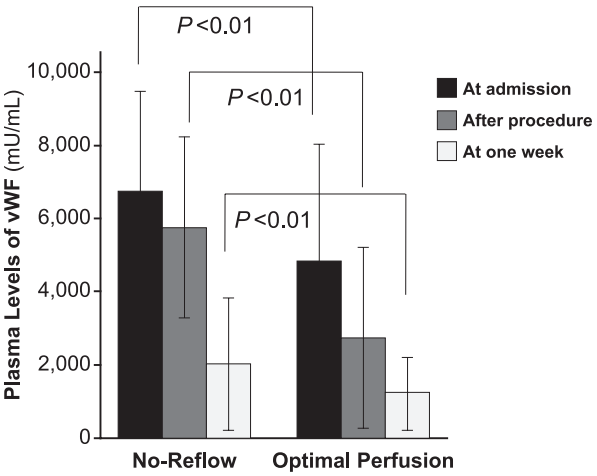

Fig. 1 *The mean plasma levels of von Willebrand factor (vWF), at the same point of time, were higher in the no-reflow group than in the optimal-perfusion group. At a* P *value <0.01, the differences were statistically significant.*

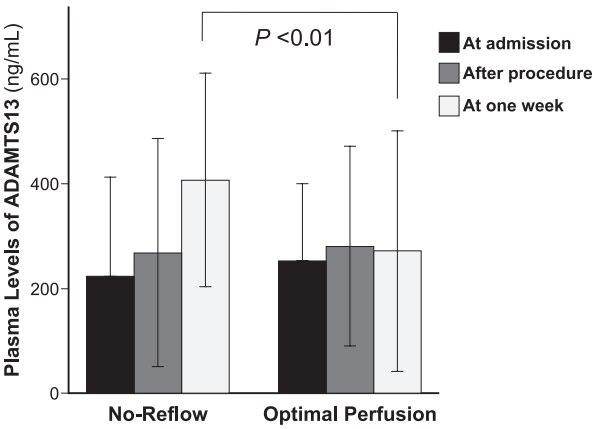

Fig. 2 *The mean plasma levels of ADAMTS13 in the 2 groups are shown at different points of time. At 1 week after PCI, the level in the no-reflow group increased markedly over that in the optimal-perfusion group, for a significant difference (*P *<0.01).*

ADAMTS13 = a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13

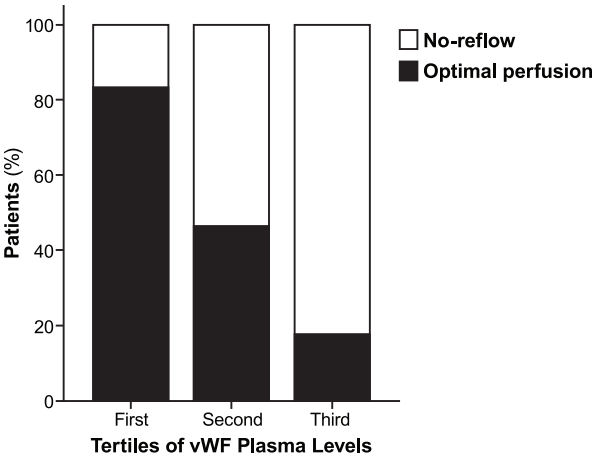

Fig. 3 *Percentages of patients with angiographic no-reflow, by tertiles of von Willebrand factor (vWF) plasma levels on admission. Patients were divided into 3 groups according to tertiles of vWF plasma levels on admission, and the presence or absence of no-reflow was compared across groups (1st vs 2nd tertile,* P *<0.01; 2nd vs 3rd tertile,* P *<0.01; and 3rd vs 1st tertile,* P *<0.01).*

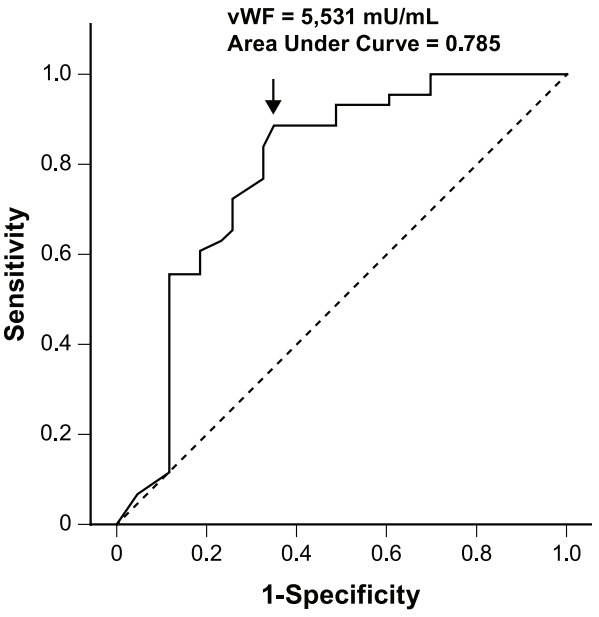

Fig. 4 *Receiver operating characteristic curve analysis of von Willebrand factor (vWF) for predicting the angiographic no-reflow phenomenon. The number on the curve indicates the cutoff value of the point.*

Predictors of the No-Reflow Phenomenon

A multivariable logistic regression analysis (Table II) was performed to determine the independent factors related to the development of the no-reflow phenomenon. Along with the plasma levels of vWF on admission, the variables included in the multivariable model were those that showed a significant association with no-reflow at univariate analysis: NT-pro-BNP, LVEF, serum creatinine, and hs-CRP. A vWF of 5,531 mU/

TABLE II. Multivariable Logistic Regression Analysis for the No-Reflow Phenomenon

Variable	Odds Ratio	*P* Value	95% CI
NT-pro-BNP	1.001	0.058	1.000–1.001
High-sensitivity C-reactive protein	1.164	0.109	0.967–1.401
Left ventricular ejection fraction	1.032	0.404	0.959–1.111
Serum creatinine	1.021	0.272	0.984–1.059
von Willebrand factor ≥5,531 mU/mL	6.087	0.024	1.264–29.319

CI = confidence interval; NT-pro-BNP = N-terminal pro B-type natriuretic peptide

The variables included in the multivariable model were those showing a significant association with no-reflow at univariate analysis. If we set von Willebrand factor ≥5,531 mU/mL as a predictor of no-reflow phenomenon, the odds ratio was 6.087 and the 95% confidence interval was 1.264–29.319, *P*=0.024.

mL or greater was the potent predictor of no-reflow at multivariable analysis (odds ratio; 6.087; 95% confidence interval, 1.264–29.319; *P*=0.024), when adjusted by hs-CRP, NT-pro-BNP, serum creatinine, and LVEF.

Correlation on Admission between von Willebrand Factor and ADAMTS13 Levels (and Other Variables)

At the time of admission, the vWF levels correlated negatively with ADAMTS13 levels (r= –0.433; P <0.001) and with LVEF (r= –0.411; P <0.001), but correlated positively with hs-CRP (r=0.39; P <0.001), serum creatinine (r=0.254; P=0.018), and NT-pro-BNP (r=0.235; P=0.029). On admission, the ADAMTS13 levels correlated negatively with hs-CRP (r=–0.282; P=0.009), LVEF (r=0.014; P=0.898), serum creatinine (r=–0.210; P=0.052), and NT-pro-BNP (r=0.072; P=0.511).

Six-Month Clinical Outcomes

Short-term adverse sequelae occurred in 5 members of the no-reflow group and in 8 members of the optimal perfusion group (10.9% vs 10%, P >0.05); these included hematoma and minor bleeding at the puncture site and limitations on lower-extremity activity, but all patients recovered within 1 month.

During 6 months after primary PCI, there were no significant differences between the no-reflow group and the optimal perfusion group in terms of mortality rate (1 [2.2%] vs 0, *P*=0.365), recurrent acute myocardial infarction or unstable angina pectoris (4 [8.7%] vs 1 [1.3%], *P*=0.059), life-threatening arrhythmia (3 [6.5%] vs 1 [1.3%], *P*=0.138), and heart failure requiring hospitalization (4 [8.7%] vs 3 [3.8%], *P*=0.257). In the combined analysis, the incidence of major adverse cardiovascular events was significantly higher in the no-reflow group than in the optimal-perfusion group (12 [26.1%] vs 5 [6.3%], *P*=0.003).

Discussion

After the onset of STEMI, primary PCI is a life-saving emergency procedure. The benefit comes from myocardial reperfusion in a short time. However, this benefit can be offset by the no-reflow phenomenon, which is a pathologic process arising from multiple factors, such as diabetes mellitus, hyperlipidemia, ischemic preconditioning, long ischemic duration, and thrombosis. Before performing primary PCI, one should evaluate the patient for the risk of no-reflow phenomenon. Although no direct pathophysiologic role has been verified, there have been suggestions that white blood cell count and levels of glucose, cholesterol, and inflammatory markers (such as hs-CRP) independently predict no-reflow.[17-19]

In our study, the incidence rate of no-reflow after primary PCI was 37%, which is similar to the incidence reported by others.[15] There were no significant differences between the 2 groups in the presence of active smoking and diabetes, but there were clear differences in LVEF and in the levels of serum creatinine, HDL-C, and hs-CRP.

Our study showed not only that there is a correlation between plasma vWF levels on admission and the no-reflow phenomenon after primary PCI for STEMI, but that this correlation is sufficient to be predictive of no-reflow. In the ROC curve analysis (using a plasma vWF level ≥5,531 mU/mL), the sensitivity of 88.4% was excellent, but the specificity was only 65%. This relatively low specificity can be attributed to the wide variety of stimuli that cause endothelial cells to produce and release vWF: these include hypoxia, inflammatory cytokines, thrombin, leukocyte elastase, histamine, endotoxin, adrenaline,[20] and other conditions associated with vascular damage, including primary pulmonary arterial hypertension and diabetic angiopathy.[21] In the multivariable logistic regression analysis, we found that patients with high vWF levels on admission (≥5,531 mU/mL) had a 6.087-fold higher rate of no-reflow after

PCI than those with lower vWF values (<5,531 mU/mL), after adjusting for LVEF and levels of serum creatinine, HDL-C, and hs-CRP. This finding implies that vWF levels on admission correspond with TIMI flow grade after primary PCI.

At admission, we did not find significant differences between the groups in plasma ADAMTS13 levels, but at a week after PCI the plasma levels of ADAMTS13 in the no-reflow group increased significantly. This suggested that abnormal increase of vWF, rather than lack of ADAMTS13, is the direct reason for no-reflow.

The no-reflow phenomenon is important not only because it correlates with infarct size but also because it provides additional prognostic information. Patients with the no-reflow phenomenon are in the highest risk subgroup of patients who undergo reperfusion, with increased associated risks of early and more protracted congestive heart failure and of death.[1-3] As a result, the focus of reperfusion therapy is shifting toward improving the patency of the wider vasculature in the affected area rather than the patency merely of the target vessel. Although the preventive effects of embolic protection and some mechanical thrombectomy devices have been disappointing in the setting of STEMI,[22-24] the preventive administration of some drugs before PCI may be helpful. For example, the use of GPIIb/IIIa inhibitor reduced the rate of no-reflow,[25,26] and intracoronary thrombolytics or adenosine infusion before PCI was beneficial in the prevention of no-reflow in small studies.[27,28]

Limitations. Our study has some limitations. First, the techniques used to evaluate no-reflow may be somewhat inadequate in comparison with contrast echocardiography of the myocardium or magnetic resonance perfusion imaging, which are now considered the gold standard for that purpose. Second, we cannot exclude the possibility that the small sample size underpowered the study. Third, the number of diseased vessels does not precisely indicate the extent of the myocardial necrosis. The present study did not include objective data regarding the size of the infarct-related necrosis.

Conclusion

In clinical practice, the identification of no-reflow predictors will assist in determining which patients are at high risk. In this study, all patients with a TIMI flow grade of less than 2 were treated with intracoronary injection of nitroglycerin or tirofiban (or both), after which a TIMI flow grade or 2 or greater was restored in every case. Although in the combined analysis, the incidence of major adverse cardiovascular events was significantly higher in the no-reflow group than in the optimal-perfusion group, there were no significant differences between the groups in the prevalence of heart failure, recurrence of myocardial infarction or angina, life-threatening arrhythmia, or death for any reason during the 6-month follow-up period. Our result was much better than the outcomes observed in other studies,[29,30] and it implies that a vWF-guided approach can be useful in identifying patients at high risk of no-reflow after primary stent implantation for STEMI. Consequently, we might be able to give more intensive treatment to patients at higher probable risk, in order to improve their clinical outcomes.

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