Early Stent Thrombosis in Patients Undergoing Primary Coronary Stenting for Acute Myocardial Infarction: Incidence, a Simple Risk Score, and Prognosis

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Background: One of the major concerns remaining in the treatment with stenting of patients with acute myocardial infarction (AMI) is the occurrence of stent thrombosis (ST). The aim of the current study is to investigate the incidence, predictors, and long-term outcomes of early ST after primary coronary stenting for AMI in a large population. Methods: We reviewed 1960 consecutive patients (mean age 56 ± 11.6 years, 1658 males) treated with primary coronary stenting for AMI between 2003 and 2008. All clinical, angiographic, and follow-up data were retrospectively collected. Early ST was defined as thrombosis that occurred in the first 30 days after primary coronary stenting. Results: Early ST was observed in 89 (4.5%) patients. Five variables, selected from the multivariate analysis, were weighted proportionally to their respective odds ratio (OR) for early ST (premature clopidogrel therapy discontinuation [10 points], stent diameter ≤3 mm [5 points], current smoker [4 points], diabetes mellitus [DM; 3 points], and age >65 years [2 points]). Three strata of risks were defined (low risk, score 0-4; intermediate risk, score 5-12; and high risk, score 13-24) and had a strong association with early ST and long-term cardiovascular mortality. Long-term cardiovascular mortality was 5-fold more in patients with early ST than that without ST (24.1% vs 4.7%, respectively, P < .001). Conclusions: Early ST after primary coronary stenting in AMI is strongly related with increased long-term cardiovascular mortality. Premature clopidogrel therapy discontinuation is the most powerful predictor of early ST.

Keywords: stent thrombosis; primary coronary stenting; acute myocardial infarction

Introduction

The superiority of the bare-metal stent over balloon angioplasty in patients with acute myocardial infarction (AMI) treated using primary angioplasty has been well studied.[1,2] One of the major concerns remaining in the treatment with stenting of patients with AMI is the occurrence of stent thrombosis (ST). The clinical sequelae of ST including death and myocardial infarction are grave[3,4] and demand aggressive therapeutic interventions.

The reported incidence of subacute ST after elective stenting ranges from 0.4% to 3.2%[5-9] and can be up to 6% with acute coronary syndromes.[4,10] There are also reports, including the incidence of ST is significantly higher for primary stenting than for elective stenting,[9,11] which suggest that AMI may increase the risk of ST through its association with intracoronary thrombus and any remaining vulnerable plaque, severe inflammation, as well as the insufficient effect of antiplatelet agents because the procedure is performed without premedication.

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Until now, only a few studies have been published on the characteristics and clinical outcomes of patients with early ST after primary coronary stenting for AMI. The aim of this study is to evaluate the incidence, clinical and angiographic predictors, and outcomes of early ST after primary coronary stenting for acute MI in a large population.

Methods

Patient Populations

Between October 2003 and March 2008, primary coronary stenting was performed in 2349 patients admitted with the diagnosis of AMI within 12 hours from the onset of chest pain. The diagnosis of AMI required the presence of at least 2 of the following 3 criteria: (1) ST-segment elevation or new onset of complete left bundle-branch block on an electrocardiogram consistent with AMI, (2) symptoms of myocardial ischemia lasting 20 minutes, and (3) transient increase in cardiac enzymes to more than 2-folds the normal laboratory value. A total of 389 patients were excluded because of unsuccessful procedures (n = 274), death during acute intervention (n = 12), use of drug-eluting stent (n = 64), and cardiogenic shock (n = 39). Therefore, the final study population consisted of 1960 patients. The study protocol was approved by the hospital's Ethics Committee.

Analysis of Patient Data

A clinical history of risk factors such as age, gender, diabetes mellitus (DM), hypertension, hypercholesterolemia, cigarette smoking, family history for coronary artery disease, MI history, primary coronary intervention, or bypass history was determined from medical records. Angina-to-reperfusion time and door-to-balloon time were also determined.

A 12-lead electrocardiogram (ECG) was recorded in each patient just after hospital admission, and MI type was also recorded from the ECGs. Global left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiography after primary coronary stenting that was performed using a system V (GE Vingmed Ultrasound, Horton, Norway), with a 2.5-MHz phased-array transducer. The LVEF was measured using modified Simpson's rule.[12]

Coronary Angiography and Stenting

All patients received chewable aspirin (300 mg, unless contraindicated) and clopidogrel (300 mg loading dose) before coronary angiography. Angiographic data of the patients were evaluated from catheter laboratory records. Emergency coronary angiography and stenting were performed by the percutaneous femoral approach. After visualizing the left and right coronary arteries, 2.5 mg of isosorbide dinitrate was selectively injected into the infarct-related artery (IRA) to rule out possible coronary spasm. Angiographic assessments were made at the treating hospital by visual assessment. Infarct-related artery was graded according to thrombolysis in myocardial infarction (TIMI) classification.[13]

Primary coronary stenting was performed only for infarct-related artery. Stents were deployed according to standard techniques. Interventional success at the acute phase is defined as an obstruction and stenosis of the infarct-related vessel having been reduced to <30% stenosis with TIMI flow grade 2 or 3 just after primary angioplasty. All patients received unfractionated heparin intravenously during the procedure (70 U/kg bolus), and heparin infusion (to maintain the activated partial prothrombin time between 80 and 150 seconds) or subcutaneous low-molecular-weight heparin (1 mg/kg twice a day) was restarted immediately after pressure bandage application. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. After stenting, all patients were prescribed a lifelong aspirin (100 mg daily) regimen, and clopidogrel (75 mg daily) was prescribed for at least 1 month. Concomitant medical treatment with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins followed according to the guidelines of American College of Cardiology/American Heart Association (ACC/AHA).

Definition

Stent thrombosis was determined as the occurrence of any of the following events: angiographic proof of stent occlusion, postprocedural MI after successful stent implantation not clearly attributable to another coronary lesion, or unexplained deaths ≤30 days after the procedure. Early ST was defined as thrombosis that occurred in the first 30 days after primary coronary stenting. Early ST was also classified into acute (0-1 days) and subacute (1-30 days). All deaths
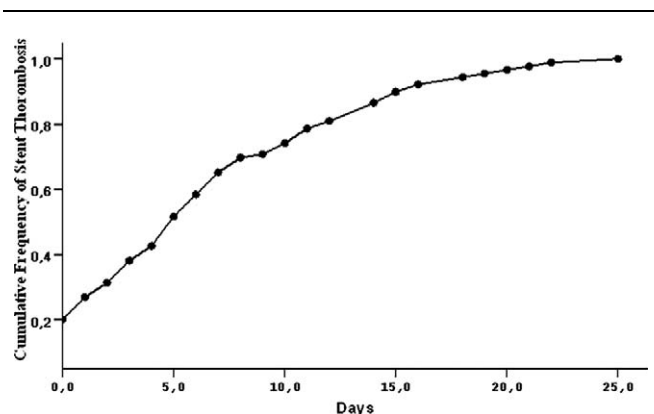
Figure 1.   Cumulative distribution of the time to development of early stent thrombosis.

and MIs were reviewed independently by 2 interventional cardiologists for ST.

Cardiogenic shock was defined as prolonged hypotension (systolic blood pressure <85 mm Hg), with evidence of decreased organ perfusion caused by severe left ventricular dysfunction, right ventricular infarction, or mechanical complications of infarction. Patients were also evaluated according to Killip clinical examination classification.[14] Multivessel disease was defined as a presence of a >50% lesion in 3 major epicardial coronary arteries. Renal failure was defined as a serum creatinine level ≥ 1.5 mg/dL and/or use of dialysis. Patient with DM was defined as the patient with documented DM using either oral hypoglycemic agents or insulin treatment at admission. Hypercholesterolemia was defined as total cholesterol ≥ 200 mg/dL or use of cholesterol-lowering agents.

Follow-Up

Follow-up data were obtained from hospital records or by interviewing with (directly or by telephone) patients, their families, or their personal physicians. Only cardiovascular mortality was recorded. Long-term follow-up was completed in 98% of cases.

Statistical Analysis

Quantitative variables were expressed as mean value $\pm$ SD, and qualitative variables were expressed as percentage (%). Comparison of parametric values between 2 groups was performed by means of 2-tailed Student *t* test. Categorical variables were compared by the likelihood ratio χ^2 test or Fisher exact

test. Backward stepwise multivariate Cox regression analysis that included variables with $P < .1$ was performed to identify independent predictors of early ST. Premature clopidogrel therapy discontinuation, Killip class 2/3, postprocedural TIMI flow grade 2, percutaneous coronary intervention (PCI) history, stent diameter ≤ 3 mm, stent length ≥ 20 mm, MI history, current smoker, predilatation before stenting, age >65 years, and DM were entered into the model. The cumulative survival curves for cardiovascular mortality were constructed using the Kaplan-Meier method with differences assessed using the log-rank test. A *P* value <.05 was considered statistically significant. All statistical studies were carried out with SPSS program (version 15.0, SPSS, Chicago, Illinois).

Results

Incidence of ST and Patient Characteristics

The overall incidence of early ST was 4.5% (n = 89), of which 0.9% (n = 19) were acute ST and 3.5% (n = 70) were subacute ST in our 1960 study patients (mean age 56 $\pm$ 11.6, years, 1658 males). The median time to development of ST was day 5 after stent implantation. The cumulative distribution of time to development of early ST within the first 30 days is shown in Figure 1. The baseline characteristics in 2 groups are summarized in Table 1. Patients developing ST were significantly older, current smoker, and more commonly had DM, history of PCI and MI, and advanced Killip class. Mean LVEF after primary coronary stenting was similar in the 2 groups.

Angiographic and Procedural Characteristics

Angiographic and procedural characteristics are depicted in Table 2. When patients with early ST were compared to the group without ST, total stent length was longer (21.56 $\pm$ 8.27 vs 18.96 $\pm$ 6.29, respectively, $P < .001$) and smaller (2.98 $\pm$ 0.29 vs 3.12 $\pm$ 0.34, respectively, $P < .001$) in patients with early ST. The patients with ST had higher rate of predilatation before stenting and less rate of postprocedural TIMI flow grade 3. The use of glycoprotein IIb/IIIa inhibitors was found to be similar in both groups

Table 1.   Baseline Characteristics of Study Patients

Variable	ST (n = 89)	No ST (n = 1871)	*P* Value
Age, years (SD)	59 ± 13.7	55.8 ± 11.4	.01
Male, n (%)	75 (84.2)	1582 (84.6)	.9
DM, n (%)	27 (30.3)	423 (22.6)	.09
Current smoker, n (%)	66 (74.1)	1160 (62)	.02
Hypertension, n (%)	42 (47.2)	730 (39)	.1
Hypercholesterolemia, n (%)	30 (33.7)	688 (36.8)	.6
Family history, n (%)	12 (13.4)	331 (17.7)	.3
PCI history, n (%)	10 (11.2)	99 (5.3)	.01
Bypass history, n (%)	2 (2.2)	46 (2.5)	.8
MI history, n (%)	14 (15.7)	172 (9.2)	.03
Renal failure, n (%)	4 (4.5)	80 (4.3)	.8
Killip class 2/3, n (%)	16 (17.8)	78 (4.2)	<.001
Anterior MI, n (%)	48 (53.9)	885 (47.3)	.2
LVEF (%)	45 ± 8	47 ± 8	.1
Angina-to-perfusion time, hours (SD)	3.8 ± 2.8	3.2 ± 2.3	.08
Door-to-balloon time, minutes (SD)	34 ± 20	32 ± 25	.6

NOTES: DM = diabetes mellitus; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

Table 2.   Angiographic and Procedural Characteristics of Study Patients

	ST (n = 89)	No ST (n = 1871)	*P* Value
Pre-PCI Variables			
TIMI flow in culprit artery, n (%)			
0-1	73 (82)	1616 (86,4)	.24
2	10 (11,2)	170 (9,1)	.5
3	6 (6,7)	84 (4,5)	.32
Multivessel disease, n (%)	22 (24,7)	441 (23,6)	.81
PCI Variables			
Infarct-related artery location, n (%)			
LAD	48 (53,9)	888 (47,5)	.23
CX	8 (8,9)	237 (12,7)	.31
RCA	33 (37,1)	728 (38,9)	.72
Other[a]	0 (0)	18 (0,9)	.33
Predilatation before stenting, n (%)	70 (78,6)	1266 (67,7)	.03
Stent length			
Total, mm (SD)	21.56 ± 8.27	18.96 ± 6.29	<.001
≥20 mm, n (%)	41 (46)	561 (30)	.001
Stent diameter, mm (SD)	2.98 ± 0.29	3.12 ± 0.34	<.001
≤3 mm, n (%)	72 (80,9)	1230 (65,7)	.003
Post-PCI Variables			
TIMI flow in culprit artery, n (%)			
2	7 (7,9)	65 (3,5)	.03
3	82 (92,1)	1806 (96,5)	.03
Glycoprotein IIb/IIIa inhibitors use, n (%)	52 (58,4)	952 (50,9)	.135
Premature clopidogrel therapy discontinuation, n (%)	15 (16,9)	58 (3,1)	<.001

NOTES: CX = circumflex coronary artery; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction; ST = stent thrombosis.
[a] Left main, saphenous vein graft, or intermediate artery.

Table 3.   Univariate Predictors of Early Stent Thrombosis

Univariate Predictors	Odds ratio	95% CI	P Value
Premature clopidogrel therapy discontinuation	6.33	2.90-13.82	<.001
Killip class 2/3	5.02	2.47-10.2	<.001
Postprocedural TIMI flow grade 2	2.37	1.05-5.33	.03
PCI history	2.28	1.14-4.54	.01
Stent diameter ≤3 mm	2.21	1.29-3.78	.004
Stent length ≥20 mm	1.99	1.29-3.05	.002
MI history	1.86	1.03-3.36	.04
Current smoker	1.77	1.07-2.94	.02
Predilatation before stenting	1.73	1.03-2.9	.03
Age >65 years	1.67	1.05-2.65	.02
DM	1.49	0.93-2.37	.09

NOTES: CI = confidence interval; DM = diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

Table 4.   Independent Predictors and Risk Score for Early Stent Thrombosis

Multivariable Predictors	Odds Ratio	95% CI	P Value	Risk score
Premature clopidogrel therapy discontinuation	9.53	3.43-26.5	<.001	10
Stent diameter ≤3 mm	5.41	1.57-18.55	.007	5
Current smoker	4.39	1.6-12.02	.004	4
Diabetes mellitus	2.99	1.4-6.38	.004	3
Age >65 years	2.26	0.97-5.26	.05	2

NOTE: CI = confidence interval.

and time to development of ST was not delayed by using this inhibitor (median 5 vs 6 days, $P = .2$). In addition, premature clopidogrel discontinuation was significantly too higher in patients with ST (16.9% vs 3.1% $P < .001$).

Predictive Factors for ST and Risk Scoring

We performed a univariate and multivariate analysis to determine the factors that were associated with early ST (Tables 3 and 4). The following were considered independent variables: premature clopidogrel therapy discontinuation (OR 9.53, 95% confidence interval [CI] 3.43-26.5; $P < .001$), stent diameter ≤3 mm (OR 5.41, 95% CI 1.57-18.55; $P = .007$), current smoker (OR 4.39, 95% CI 1.6-12.02; $P = .004$), DM (OR 2.99, 95% CI 1.4-6.38; $P = .004$), and age >65 years (OR 2.26, 95% CI 0.97-5.26; $P = .05$). Using these variables as risk indicators, we developed a simple risk scoring system. The independent predictors of early ST were assigned a risk score based on their ORs and the total risk score was calculated for each patients with a range of 0 to 24 points (Table 4). For simplicity, 3 risk strata were defined (low risk, score 0-4; intermediate risk, score
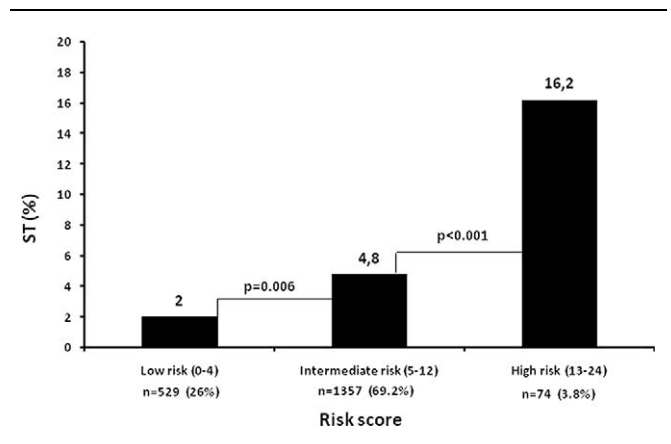

Figure 2.   Incidence of early stent thrombosis (ST) in study patients according to the risk score.

5-12; and high risk, score 13-24). The incidence of early ST and long-term cardiovascular mortality significantly increased with score (Figures 2 and 3).

Long-Term Prognosis

The median follow-up time was 22 months. Follow-up data after discharge were not obtained for 34 (1.8%) patients without ST and 4 (2.2%) patients
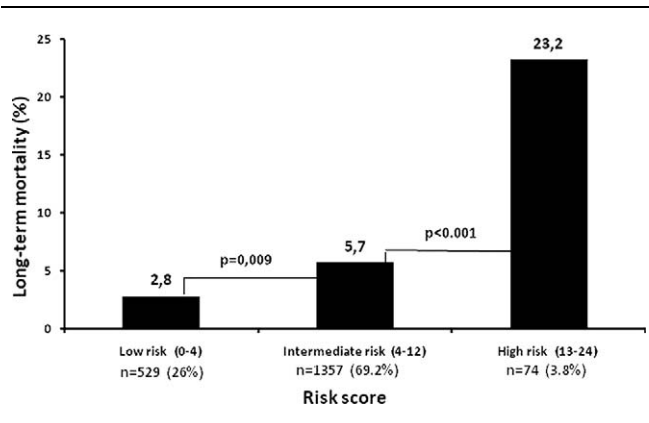
Figure 3.   Long-term mortality in study patients according to the risk score.

Figure 4.   Kaplan-Meier curve for long-term cardiovascular mortality in patients with stent thrombosis (ST) versus without ST.

with ST. The Kaplan-Meier survival plot for cardiovascular mortality in both groups is presented in Figure 4. Patients with ST had significantly higher incidence of long-term cardiovascular mortality than patients without ST (24.1% vs 4.7%, respectively, $P < .001$). Independent predictors of long-term cardiovascular mortality were determined by multivariate Cox regression analysis. Stent thrombosis was found to be a powerful independent predictor of long-term mortality (OR 7.1, 95% CI 2.6-19.2; $P < .001$).

Discussion

The main findings of the current study are (1) after primary coronary stenting in AMI, early ST can be simply predicted using 5 clinical and angiographic variables readily available at the time of intervention; (2) premature clopidogrel therapy discontinuation and small size stent were the most powerful predictors of early ST; and (3) early ST showed a strong association with long-term cardiovascular mortality.

In patients with acute coronary syndrome, the reported incidence of subacute ST after elective stenting ranges from 0.4% to 3.2%[5-9] and can be up to 6%.[4,10,15] Consistent with the results from these trials, the overall incidence of early ST was 4.5%. There are also reports suggesting that the incidence of ST is significantly higher for primary coronary stenting than for elective stenting[9,11] because of the delayed inhibition of platelet aggregation by unplanned antiplatelet therapy for the marked increase in platelet reactivity in AMI.[16]

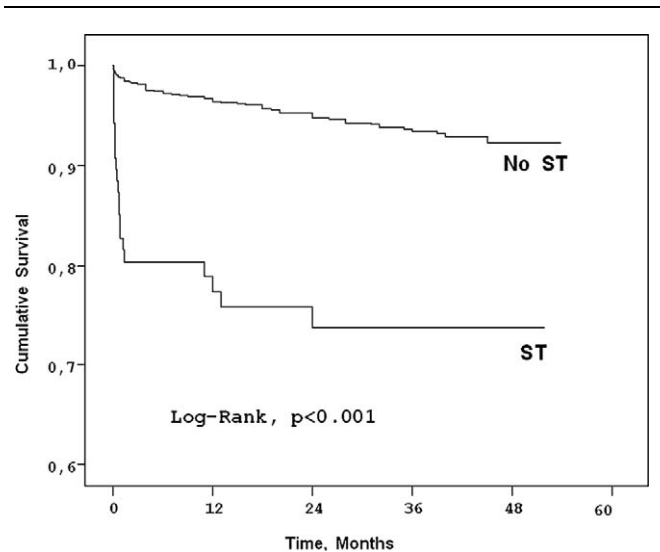Dual antiplatelet therapy consisting of acetylsalicylic acid (ASA) and thienopyridines has been shown to be superior to aspirin alone and oral anticoagulation in the prevention of death and nonfatal MI following coronary stenting.[17-19] In the era of bare-metal stents, it has been customary to prescribe dual antiplatelet therapy for at least 1 month after the coronary stenting. In agreement with these reports, our risk score identified that premature clopidogrel discontinuation was the most powerful predictor of early ST and accounted for 10 of the total 24 points.

Smoking may result in a hypercoagulable state and provoke thrombosis by oxidative stress, endothelial dysfunction, and platelet activation.[20,21] Previous studies have demonstrated that smokers with AMI have a higher incidence of platelet-rich thrombus, which may theoretically increase the likelihood of early reinfarction.[22] However, previous primary PCI trials have found similar or lower rates of reinfarction after primary PCI in current smokers compared with nonsmokers.[23,24] In contrast to these previous reports, smoking was also associated with a higher early ST incidence in the current study.

In addition to independent predictors mentioned above, the other predictors of early ST in our study patients were old age, DM, and small-size stent. We were unable to identify certain factors such as stent length and renal failure that have previously been identified as predictors of ST.[3,25] This may be related to the inclusion criteria of our study as well as other differences between our and other published reports' study population.

In our study, in contrast to the Controlled Abciximab and Device Investigation to Lower Late

Angioplasty Complications (CADILLAC) trial,[8] the use of glycoprotein IIb/IIIa inhibitors at the time of stenting (in addition to dual antiplatelet therapy) was neither found to lower the ST incidence nor found to significantly delay time for ST development. Besides, in the subgroup analysis, the use of glycoprotein IIb/IIIa inhibitors did not reduce acute ST incidence as well. In our opinion, this may be related to more frequent use of prophylactic glycoprotein IIb/IIIa inhibitors in patients who have high risk for ST development due to the fact that having not randomized the usage of the drug but instead left to physician's own discretion. Another reason the glycoprotein IIb/IIIa inhibitors did not decrease early ST incidence may be that in our study, we used tirofiban in contrary to abciximab that had been used in CADILLAC trial. Moreover, consistent with the result of this study, ACC/AHA guidelines recommend tirofiban use during primary Percutaneous Transluminal Coronary Angioplasty (PTCA) as class IIb.[26] However, according to On-TIME 2, which was published very recently and randomized, double-blind, placebo-controlled trial, routine prehospital initiation of high bolus dose tirofiban improved clinical outcomes after primary coronary intervention. In contrast to our study, high-dose tirofiban along with 600 mg bolus clopidogrel was used in that trial.[27]

We found that early ST was strongly associated with increased long-term cardiovascular mortality. Those presenting with 1-month ST had a 5-fold increased cardiovascular mortality than patients without ST at long-term. These findings are in accord with several trials that show strong associations between ST and cardiovascular mortality.[3,4,28] This increased mortality underscores the need for identification of high-risk patients for early ST. Therefore, we developed a simple risk score in our study to predict early ST using clinical and angiographic variables readily available at the time of intervention. The current risk score showed a strong association with early ST and long-term cardiovascular mortality. Consequently, in the knowledge of this poor overall outcome, patients at high risk for early ST can be simply identified during primary coronary intervention. Thus, more intense and prolonged monitoring can be done to these patients in-hospital and long-term follow-up.

Study Limitations

Several limitations need to be kept in mind when interpreting the results of this study. First, this study carries the well-known limitation of the retrospective design. Second, intravascular ultrasound was not routinely used in patients with ST. This precluded the analysis for mechanical causes of ST such as inappropriate stent expansion and insufficient stent overlap. Third, the use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the individual operator. Selection bias in the use of this medication might have influenced the outcomes of our study. Fourth, bare-metal stent was used in all patients, but we did not classify according to brands. So, we cannot analyze the effect of different stent brands on ST. Fifth, this study was done as a teamwork, which means there are different applicators for angiographic procedures. So, there may be minor differences between operators, but in our high-volume center (>3000 PCIs/year, and >500 primary PCIs/year), primary PCI was performed by experienced operators performing >75 elective PCIs/year. We think that operator experience surpasses practical differences. Finally, this study did not include drug-eluting stents.

Clinical Implications

This study shows that early ST after primary coronary stenting in AMI is strongly associated with increased long-term cardiovascular mortality and can be simply predicted by using clinical and angiographic variables readily available at the time of intervention. We should not forget that premature clopidogrel therapy discontinuation is the most powerful predictor of early ST. As an inevitable consequence of this, the clinical significance of using clopidogrel should be explained insistently especially to the high-risk patients for ST.

Acknowledgment

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