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Original Article

Incidence, Predictors and Outcomes of Subacute Stent Thrombosis following Primary Stenting for ST-elevation Myocardial Infarction

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Background/Purpose: Knowledge concerning subacute stent thrombosis (SST) following primary stenting for ST-elevation myocardial infarction (STEMI) is not widely available. We studied the incidence, predictors, and clinical outcomes of SST following STEMI.

Methods: We analyzed data from 455 consecutive patients who underwent primary stenting for STEMI. Baseline clinical characteristics, coronary angiographic features, medication and outcome were compared in patients with and without SST.

Results: SST occurred in 17 patients, and the incidence was 3.7%. Univariate predictors of SST were being a current smoker (53.0% *vs.* 82.4%, $p = 0.01$), Killip class ≥ II (38.4% *vs.* 58.8%, $p = 0.05$), no coronary reflow after stenting (6.2% *vs.* 17.6%, $p = 0.05$) and lack of coprescription with a statin (39.5% *vs.* 5.9%, $p < 0.01$). After multivariate analysis, being a current smoker (odds ratio = 4.76; 95% confidence interval = 1.20–18.95) and using statin therapy (odds ratio = 0.09; 95% confidence interval = 0.01–0.75) were independent correlates of SST. Patients with SST were associated with higher 30-day mortality (37.5% *vs.* 3.1%, $p < 0.01$) and all-cause mortality (23.5% *vs.* 5.3%, $p = 0.01$) at long-term follow-up.

Conclusion: Although SST is rare in patients with STEMI treated by primary stenting, it imparts a significantly higher mortality at short-term and long-term follow-up. Being a current smoker and the lack of coprescription with a statin were associated with higher incidence of SST. Our results suggest initiation of statin therapy in patients with STEMI should be considered before discharge.

Key Words: acute myocardial infarction, statin, stent, thrombosis

In contrast with percutaneous transluminal coronary angioplasty, routine stent implantation for patients with ST-elevation myocardial infarction (STEMI) has been shown to reduce the incidence of target vessel revascularization within 30 days follow-up and to improve late clinical outcomes.[1–3]

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Despite the high procedure success rate, stent placement has its own complications. Subacute sent thrombosis (SST) following primary stenting for STEMI is an infrequent, complicated phenomenon of concern to physicians and is associated with high morbidity and mortality.[4,5] Recently, there have been many changes in pharmacological therapy, stent devices and surgical skills in percutaneous coronary intervention (PCI) for STEMI. Thus it is possible that the incidence, predictors and clinical outcomes may be different from those reported in previous studies. We report our experience of SST following primary stenting for STEMI in 590 consecutive patients.

Methods

Patient characteristics

From January 2000 to December 2006, 590 patients underwent primary PCI for STEMI in our institution. The diagnosis of STEMI was defined as at least two of the following criteria: (1) a typical chest pain lasting at least 20 minutes; (2) serum enzyme elevation at least twice the upper limit of normal; (3) typical electrocardiogram evolving change, including ST segment elevation of 1 mm or more with subsequent evolution of negative T-waves with a depth of 1 mm or more, and evolution of new Q-waves of at least 0.04 seconds in duration or deeper than one fourth of the following R-wave in voltage. For evaluation of the peak serum cardiac biomarker activity, blood samples were obtained every 6 hours for 48 hours or until the activity returned to normal. The reference values for creatine kinase and creatine kinase(CK)-MB were 26–192 IU/L and 7–25 IU/L, respectively. After informed consent, all patients underwent coronary angiography to confirm the diagnosis and for therapeutic intervention. We compared baseline clinical and angiographic characteristics of the study patients with and without SST and assessed independent correlates of SST. Clinical follow-up variables, including unstable angina that required repeat PCI within 1 year, recurrent myocardial infarction and all-cause mortality, were obtained at clinic visits, by telephone conversation and chart review.

Definition of SST

Stent thrombosis is classified by the Academic Research Consortium as definite, probable, or possible and as acute (≤ 1 day), subacute (1–30 days), late (31–360 days), or very late (> 360 days). The definition of definite stent thrombosis required the presence of an acute coronary syndrome with angiographic evidence of thrombosis or occlusion of the study stented segment, including the 5-mm proximal and distal margin, which preceded stent thrombosis. Probable stent thrombosis was defined as unexplained deaths within 30 days and possible stent thrombosis included all unexplained deaths occurring at least 30 days after the index procedure.[6] To identify the relationship of coronary angiographic features and stent size with the incidence of SST, only patients with definite stent thrombosis confirmed by coronary angiography were included in the present study.

Cardiac catheterization

All patients received the percutaneous transfemoral approach via an angiography sheath, and standard angioplasty technique was used in these patients.[7,8] Each patient was pretreated with oral acetylsalicylic acid (300 mg), clopidogrel (300 mg) and intravenous heparin (100 U/kg) at the beginning of the procedure, and an additional bolus of heparin was administered to maintain activated clotting time > 300 seconds. Judgment of vessel flow was according to the Thrombolysis In Myocardial Infarction flow grade. Angiography stenosis was defined as a diameter reduction of ≥ 50%. If stent implantation was needed, intravenous heparin infusion was restarted after stenting and was adjusted to maintain the activated partial thromboplastin time at 60–85 seconds for 48 hours. Successful angioplasty was defined as a target vessel at the treatment site with less than 20% residual stenosis and Thrombolysis In Myocardial Infarction 3 flow.

Administration of platelet glycoprotein IIb/IIIa-receptor inhibitor was left to the clinician's

discretion. Post-procedure, all patients were treated with oral acetylsalicylic acid (100 mg) and clopidogrel (75 mg) daily for at least 1 month.

Statistical analysis

Statistical analyses were performed with SPSS version 13.0 (SPSS Inc. Chicago, IL, USA). Quantitative data are expressed as mean ± standard deviation. The χ^2 test with Yates' correction or Fisher's exact test was used to analyze nonparametric data. If the frequency of any cell was < 5, then a Fisher exact test was used. Multivariate analysis was performed with logistic regression to determine the independent predictors of SST. The selection of variables was restricted to those that were *a priori* identified as relevant based on clinical experience and variables with a p value less than 0.1 in the univariate model. A significant odds ratio (OR) was obtained if the 95% confidence interval (CI) exceeded 1 and the p value was less than 0.05. $p < 0.05$ was considered statistically significant. Kaplan-Meier analysis was used to create survival curves for the cumulative incidence of death during follow-up. Log-rank p-test was used to compare survival curves between SST and no-SST groups.

Results

Patients

From January 2000 to December 2006, a total of 590 consecutive patients with STEMI were admitted for primary PCI (Figure 1). After coronary angiography, 486 patients received stent implantation, while 92 (16%) received balloon angioplasty alone and the remaining 12 (2%) did not receive further intervention. Failure to pass the guide wire (7 patients), urgent coronary artery bypass grafting (2 patients), cardio-pulmonary-cerebral resuscitation and death during coronary angiography (2 patients) and self-recanalization of infarct-related artery occurred (1 patient) were reasons why no further intervention was administered. Of the 486 patients receiving stent implantation, 36 patients were excluded because of incomplete follow-up or having expired within 1 month after the index stent implantation. Finally, 455 patients, comprising 384 males and 71 females with a mean age of 60.5 years (range, 30–91 years), were included. Seventeen patients had definite SST confirmed by coronary angiography, and the incidence of SST was 3.7%. All the study

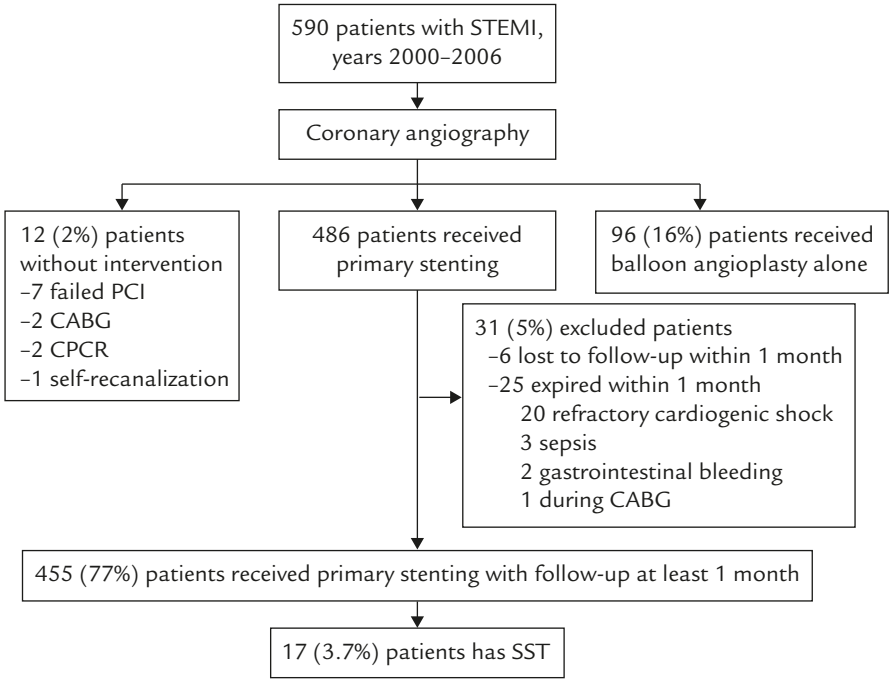

Figure 1. Study patient enrollment. STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CPCR = cardio-pulmonary-cerebral resuscitation; SST = subacute stent thrombosis.

patients received bare metal stents. None of patients in the study discontinued dual anti-platelet therapy prematurely. Patient characteristics are presented in Tables 1 and 2.

Patients with SST

Of the 17 patients with SST, eight patients (47.1%) presented within the first week, four (23.5%) during the second week and five (29.4%) during the third or fourth week after index stent implantation (Table 3). The mean time to SST was 11.2 ± 8.7 days. Sixteen (94.1%) patients with SST presented as myocardial reinfarction and one (5.9%) as unstable angina. All the patients with SST in our study had reocclusion of the stent in the infarct-related vessel confirmed by coronary angiography. These vessels included the left anterior descending in 13 patients (76.5%), the left circumflex in one patient (5.9%) and right coronary artery in three patients (17.6%).

Predictors of SST following primary stenting for STEMI

The differences in the patient characteristics with or without SST are described in Tables 1 and 2. Univariate analysis demonstrated that patients with SST had a significantly higher incidence of current smoking, Killip class ≥ II at presentation, no coronary reflow after stenting, and lack of co-prescription with a statin compared with those without SST. Logistic regression analysis demonstrated that being a current smoker (OR = 4.76; 95% CI = 1.20–18.95), and statin therapy (OR = 0.09, 95% CI = 0.01–0.75) were independent correlates with SST following primary stenting for STEMI (Table 4).

Table 1. Comparison of patient characteristics between those with and without subacute stent thrombosis*

	All patients (n = 455)	No SST (n = 438)	SST (n = 17)	p
Age (yr)	60.5 ± 12.2	60.5 ± 12.3	60.7 ± 11.5	0.94
Sex, male	384 (84.4)	368 (84.0)	16 (94.1)	0.22
BMI (kg/m^2)	25.7 ± 3.9	25.7 ± 3.8	26.1 ± 4.7	0.72
Hypertension	252 (55.4)	241 (55.7)	11 (64.7)	0.22
Diabetes mellitus	139 (30.5)	131 (29.9)	8 (47.1)	0.07
Current smoker	246 (54.1)	232 (53.0)	14 (82.4)	0.01
Heart failure	43 (9.5)	39 (8.9)	4 (23.5)	0.06
COPD	19 (4.2)	17 (3.9)	2 (11.8)	0.15
LVEF ≤ 50%	102 (22.4)	98 (22.4)	4 (23.5)	0.56
Presentation				
Typical angina	399 (87.9)	385 (88.1)	14 (82.4)	0.34
Killip class ≥ II	178 (39.1)	168 (38.4)	10 (58.8)	0.05
WBC ≧ 10,000/μL	255 (56.0)	245 (55.9)	10 (58.8)	0.41
Hb ≦ 10 mg/dL	10 (2.2)	10 (2.3)	0 (0)	0.68
Creatinine ≥ 1.4 mg/dL	102 (22.4)	98 (22.4)	4 (23.5)	0.55
CK (IU/L)	2764.9 ± 2240.7	2761.9 ± 2227.1	2845.1 ± 2667.0	0.88
CK-MB (IU/L)	257.4 ± 195.8	258.5 ± 196.5	228.2 ± 178.9	0.54
T-CHO > 160 (mg/dL)	333 (74.5)	319 (74.0)	14 (87.5)	0.18
TG > 150 (mg/dL)	145 (32.4)	139 (32.2)	6 (37.5)	0.33
HDL < 40 (mg/dL)	117 (42.4)	113 (42.3)	4 (44.4)	0.58
LDL > 100 (mg/dL)	299 (73.0)	194 (73.2)	6 (66.7)	0.46

**Data presented as n (%) or mean ± standard deviation. SST = Subacute stent thrombosis; BMI = body mass index; CK = creatine kinase; COPD = chronic obstructive pulmonary disease; Hb = hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; T-CHO = total cholesterol; TG = triglyceride; WBC = white blood cell.*

Outcome of SST

Among those who developed SST following primary stenting, three patients died because of cardiogenic shock at 2, 10 and 17 days after the SST event, respectively. The 30-day mortality of patients with SST was higher than that of those without SST (37.5% *vs.* 3.1%, $p<0.01$, Table 2). During mean follow-up periods of 37.8±26.1 and 29.0±25.9 months ($p=0.17$) in patients with and without SST, respectively, there were no differences between the two groups in rates of unstable angina that required repeat PCI in 1 year (31.3 % *vs.* 29.4, $p=0.45$) and recurrent myocardial infarction (3.4% *vs.* 0%, $p=0.56$). However, patients with SST had higher all-cause mortality than those without SST at clinical follow-up (23.5% *vs.* 5.3%, $p=0.01$). Using Kaplan Meier analysis, the survival rate was significantly lower in the group with SST ($p<0.001$ by log-rank test, Figure 2) than in those without.

Table 2. Angiographic characteristics, medication and outcome of the study patients and comparisons between those with or without subacute stent thrombosis*

	All patients ($n=455$)	No SST ($n=438$)	SST ($n=17$)	p
Door to balloon time (min)	95.8±32.1	97.5±32.7	97.5±32.7	0.87
Coronary angiographic features				
Multiple-vessel disease	300 (65.9)	289 (66.0)	11 (64.7)	0.45
Total occlusion	330 (72.5)	320 (73.1)	10 (58.8)	0.11
Infarct-related vessel				0.57
LAD	258 (56.7)	245 (55.9)	13 (76.5)	
LCX	34 (7.5)	33 (7.5)	1 (5.9)	
RCA	160 (35.2)	157 (35.8)	3 (17.6)	
Left main	1 (0.2)	1 (0.2)	0 (0)	
Intermediate artery	2 (0.4)	2 (0.5)	0 (0)	
Stent diameter (mm)	3.1±0.5	3.1±0.5	3.0±0.6	0.19
Stent length (mm)	21.8±7.7	21.9±7.7	18.8±5.5	0.10
No reflow	30 (6.6)	27 (6.2)	3 (17.6)	0.05
Medication				
Heparin	444 (97.6)	428 (97.7)	16 (94.1)	0.35
Glycoprotein IIb/IIIa receptor inhibitor	50 (11.0)	47 (10.7)	3 (18.8)	0.25
Nitrates	141 (31.0)	134 (30.6)	7 (41.2)	0.18
β-Blockers	156 (34.3)	148 (33.8)	8 (47.1)	0.14
Calcium antagonists	12 (2.6)	11 (2.5)	1 (5.9)	0.37
ACEI/ARB	298 (65.5)	286 (65.3)	12 (70.6)	0.34
Statin	174 (38.2)	173 (39.5)	1 (5.9)	<0.01
Acetylsalicylic acid	426 (93.6)	409 (93.4)	17 (100)	0.32
Clopidogrel	378 (83.1)	362 (82.6)	16 (94.1)	0.19
Outcome				
Death in 30 d	17 (3.7)	14 (3.1)	3 (37.5)	<0.01
Repeat PCI in 1 yr	142 (31.2)	137 (31.3)	5 (29.4)	0.45
Recurrent MI	15 (3.3)	15 (3.4)	0 (0)	0.56
All-cause mortality	27 (5.9)	23 (5.3)	4 (23.5)	0.01
Follow-up (mo)	37.5±26.2	37.9±26.1	27.6±26.8	0.11

**Data presented as n (%) or mean±standard deviation. ACEI=Angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; LAD=left anterior descending artery; LCX=left circumflex artery; MI=myocardial infarction; PCI=percutaneous coronary intervention; RCA=right coronary artery; SST=subacute stent thrombosis.*

Table 3. Characteristics of the patients with subacute stent thrombosis*

	Frequency (%)
Patients without SST	438 (96.3)
Patients with definite SST	17 (3.7)
Length of index hospital stay, mean (d)	
Time to SST	9.9 ± 4.7
Within 1st wk	8 (47.1)
Within 2nd wk	4 (23.5)
Within 3rd and 4th wk	5 (29.4)
Mean (d)	11.2 ± 8.7
Presentation of SST	
Recurrent myocardial infarction	16 (94.1)
Unstable angina	1 (5.9)
Infarct-related vessel	
LAD	13 (76.5)
LCX	1 (5.9)
RCA	3 (17.6)

**Data presented as n (%) or mean ± standard deviation. LAD = Left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; SST = subacute stent thrombosis.*

Table 4. Multivariate analysis of subacute stent thrombosis

	Odds ratio	95% CI	*p*
Age (yr)	1.00	0.96–1.05	0.87
Sex, male	2.70	0.28–25.99	0.39
Killip class ≥ II	2.06	0.71–5.96	0.18
Diabetes mellitus	2.45	0.67–8.93	0.10
Heart failure	2.45	0.67–8.93	0.17
Current smoker	4.76	1.20–18.95	0.03
Statin use	0.09	0.01–0.75	0.03

CI = Confidence interval.

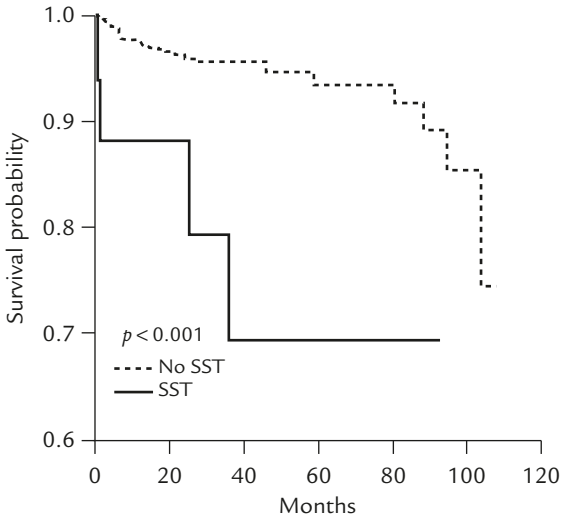

Figure 2. Survival curve produced by Kaplan Meier analysis. Cumulative survival was significantly higher in the group without subacute stent thrombosis (SST; $p < 0.001$ by log-rank test).

Discussion

The present study assessed the incidence, risk factors and outcomes of angiography-proven SST in a cohort of STEMI patients undergoing primary stenting. SST after STEMI treated with primary stenting is relatively rare. Previous studies had shown that 0.4–4.1% of patients had SST after primary PCI for STEMI.[2–4,9,10] The incidence of SST in the present study was 3.7%. Our study appeared to have a similar incidence of SST as compared with previous studies.

The etiology of SST is multifactorial. Clinical variables associated with SST reported in previous studies include an emergently placed stent, stent malposition, the use of a longer stent, intravascular thrombus, Killip classification on admission, and left ventricular systolic dysfunction.[5,9–13] In the present study, being a current smoker, Killip class ≥ II on admission, no coronary reflow after stent implantation and lack of coprescription of statin therapy were associated with a probability of SST following primary stenting for STEMI. By using logistic regression analysis, current smoker and no use of statins were independent predictors for SST. To our knowledge, the present study is the first to show that statin therapy could prevent SST following primary stenting during STEMI. Most previous studies have not provided the data of statin therapy for their patient groups.[5,9–13]

Smoking is a well-known preventable risk factor for coronary artery disease.[14] Although the exact pathophysiology of smoking has not been well described, smoking produces superoxide anions, reduces production of nitric oxide, and causes endothelial dysfunction, platelet retention and

adhesion that subsequently cause arterial thrombosis.[15,16] By means of comparison with nonsmokers, Rea et al demonstrated that smoking was associated with an elevated risk for recurrent coronary events after incident myocardial infarction.[17] Also, in the present study, patients with SST had higher prevalence of current smoking habits compared with those without SST.

After primary stenting for STEMI, intravascular stents are metallic and thrombogenic.[13] Additionally, Sianos et al emphasized that large thrombus burden during STEMI increased risk of stent thrombosis.[18] Therefore, instead of proper stent deployment, intense anticoagulation and antiplatelet therapy were needed in prevention of more thrombus formation after primary stenting for STEMI. Furthermore, the statin-associated pleiotropic effects, independent of its lipid-lowering effect, have been described to reduce plaque thrombogenicity, improve endothelial function, and inhibit vascular inflammatory response and free-radical production in the vascular wall.[19] Thus we believe that early coprescription of statin therapy might play an additional role in protection of patients with STEMI from developing more thrombus formation and thereby decrease the prevalence of SST in the present study. Rondina et al also demonstrated that early statin therapy in patients with STEMI reduced the risk of adverse cardiovascular events in the weeks and months following index myocardial infarction.[20] Furthermore, guidelines from the American College of Cardiology and the American Heart Association recommended that patients with STEMI should be treated earlier with statin therapy before discharge.[21,22] However, only about 40% of the study patients received statin therapy before discharge from the index hospitalization, whereas up to 70% of the study patients had dyslipidemia. Early statin therapy in patients with STEMI is still underused in clinical practice, which might be due to lack of awareness, inertia of previous practice and limitation of reimbursement guidelines used by the national Bureau of National Health Insurance.[23]

In the present study, about half of the patients developed SST more than 1 week after the index stent implantation. It was usually impossible to rapidly restore coronary arterial flow because patients had been discharged from the hospital during the development of SST. In the Primary Angioplasty in Acute Myocardial Infarction studies, 1-month reinfarction was independently predictive of death and revascularization at 6 months.[5] In the present study, there was no significant difference in repeat PCI and reinfarction between patients with and without SST. However, we found SST to be strongly associated with increased mortality rates at short-term and long-term follow-up.

The present study has shown that patients with SST had higher 30-day and all-cause mortality rates during clinical follow-up. The pleiotropic effects of statin therapy might provide protection from SST in those receiving primary stenting for STEMI. Recent studies have demonstrated cardiovascular morbidity and mortality benefits in patients with acute coronary syndrome who were prescribed with statin therapy within hours to days of their events.[20] However, statin therapy during the index hospitalization is still underused in real world practice. Clinical physicians should be aware of this information, and early statin therapy might be considered in patients with STEMI prior to hospital discharge.

There were several limitations in this study. First, this was a retrospective analysis, which may have inherent shortcomings. Second, smoking status was based on patients' self report as documented in medical records and was not verified by biochemical assay. Our finding may underestimate the rate of smoking that attenuated the accuracy of association between smoking and risk for recurrent coronary events. Third, it is possible that some patients visited other hospitals due to SST and were missed by our hospital record review. Furthermore, we obtained angiographic follow-up only in those patients who returned with acute coronary syndrome. The incidence of SST may be underestimated, because SST could occur silently. Fourth, β-blockers, as well as statins, were underused in the present study, which may have influenced the outcome of the patients. Finally, the present study was performed before drug-eluting

stents were widely used in patients with STEMI, because drug-eluting stents might alter the incidence of SST. However, recent studies had shown that there were no differences in the incidence of SST between patients receiving drug-eluting stents and non-coated stents for myocardial infarction.[24,25]

In summary, SST in the era of primary stenting for STEMI is rare. However, patients with SST following primary stenting for STEMI have significant higher mortality rate at short-term and long-term follow-up. We found that being a current smoker and the lack of coprescription with a statin were associated with higher SST risk. Statin therapy, which is still underused in clinical practice, might be considered in patients with STEMI prior to hospital discharge.

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