Impact of Timing of Eptifibatide Administration on Preprocedural Infarct-Related Artery Patency in Acute STEMI Patients Undergoing Primary PCI

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Abstract

The appropriate timing of eptifibatide initiation for acute ST segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) remains unclear. This study aimed to analyze the impact of timing of eptifibatide administration on infarct-related artery (IRA) patency in STEMI patients undergoing primary PCI. Acute STEMI patients who underwent primary PCI ($n = 324$) were enrolled in this retrospective study; 164 patients received eptifibatide bolus ≤ 30 minutes after emergency department (ED) admission (group A) and 160 patients received eptifibatide bolus > 30 minutes after ED admission (group B). The primary endpoint was preprocedural IRA patency. Most patients in group A (90%) and group B (89%) were late presenters (> 2 hours after symptom onset). The two groups had similar preprocedural thrombolysis in myocardial infarction 2 or 3 flow of the IRA (26 vs. 24%, $p =$ not significant [NS]), similar creatine kinase-MB (CK-MB) levels at 8 hours after admission (339 vs. 281 U/L, $p =$ NS), similar left ventricular ejection fraction (LVEF) (52 vs. 50%, $p =$ NS), and similar 30-day mortality (2 vs. 7%, $p =$ NS). Compared with group B, patients in group A had shorter door-to-device time ($p < 0.001$) and shorter procedural time ($p = 0.004$), without increased bleeding risk (13 vs. 18%, $p =$ NS). Earlier intravenous administration of eptifibatide before primary PCI did not improve preprocedural IRA patency, CK-MB level at 8 hours after admission, LVEF and 30-day mortality compared with patients who received intravenous eptifibatide that was administered later.

Keywords

- glycoprotein IIb/IIIa inhibitor
- timing of administration
- primary PCI

Primary percutaneous coronary intervention (PCI) has become the therapy of choice for the treatment of acute ST segment elevation myocardial infarction (STEMI).^{1–3} However, based on real world practice, application of timely primary PCI

with the recommended door-to-balloon time remains difficult to achieve.⁴ Furthermore, during primary PCI, embolization of atherothrombotic material might occur⁵ which is the most common cause of periprocedural complications.⁶

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Fig. 1 Flowchart of the study. ED, emergency department; IV, intravenous; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Early administration of a glycoprotein IIb/IIIa inhibitor (GPI) has been considered to overcome the delay for receiving mechanical reperfusion,⁷ and GPI administration is also one of the strategies to prevent distal embolization of coronary thrombus during primary PCI.⁸ It is hypothesized that the earlier the GPI is given in the acute phase of an infarction, the earlier platelet aggregation inhibition is achieved, leading to an earlier contribution to opening of the infarct-related artery (IRA). It is known that IRA patency before primary PCI is related to improved left ventricular function⁹ and survival.¹⁰

Until now, the appropriate timing of eptifibatide initiation for acute STEMI patients undergoing primary PCI remains unclear. Therefore, we conducted a study to compare the preprocedural thrombolysis in myocardial infarction (TIMI) flow of the IRA in acute STEMI patients undergoing primary PCI who received earlier eptifibatide infusion in the first 30 minutes after admission and those who received eptifibatide infusion after the first 30 minutes after admission to the emergency department (ED).

Patients and Methods

This study was designed as a retrospective observational study, enrolling 350 acute STEMI patients (≤ 12 hours after onset of symptoms) who underwent primary PCI in National Cardiovascular Center Harapan Kita, Jakarta, Indonesia in the period of April 2011 to October 2012. Overall 324 patients were eligible for analysis and divided into two groups. Group A patients ($n = 164$) received intravenous eptifibatide infusion within 30 minutes after admission to the ED and group B patients ($n = 160$) received eptifibatide infusion after the first 30 minutes after ED admission ($\rightarrow$ Fig. 1).

On admission to the ED, all patients received a single intravenous bolus eptifibatide infusion of 180 $\mu\text{g/kg}$ before primary PCI, followed by a continuous infusion of 2.0 $\mu\text{g/kg/min}$ up to 12 to 18 hours. Patients who received bail-out intracoronary eptifibatide administration ($n = 20$), incomplete clinical variables ($n = 4$), and lost to follow-up ($n = 2$) were excluded.

Primary PCI Procedure

Primary PCI was performed according to the local protocol: standard views were recorded for diagnostic coronary angiography before the PCI procedure, and the TIMI flow of the

IRA was assessed before primary PCI. After a guide-wire has crossed the culprit lesion, manual thrombus aspiration was performed when feasible. The decisions as to predilatation or direct stenting and stent choices between drug eluting or bare metal stent were left to the operator's discretion. Stenting the IRA only was mandatory. Final angiography was performed in a standard view to assess final TIMI flow of the IRA.

Antiplatelet and Anticoagulant Regimen

All patients were pretreated with 160 to 320 mg acetylsalicylic acid and 600 mg clopidogrel orally, followed by a daily administration of 75 mg clopidogrel planned for at least 1 year after discharge and 80 to 100 mg acetylsalicylic acid indefinitely. Before the primary PCI procedure, all patients received an intravenous bolus of unfractionated heparin (50–60 IU/kg). None of the patients received fibrinolytic agents.

Definitions

Acute STEMI was diagnosed by persistent chest pain of more than 20 minutes not relieved by sublingual nitrate and an electrocardiogram with ST-segment elevation in two or more contiguous leads (≥ 2 mm in precordial leads, ≥ 1 mm in limb leads).

Patients in group A received intravenous eptifibatide within 30 minutes after admission, calculated from the time of ED admission to first bolus dose of eptifibatide, whereas patients in group B received eptifibatide after the first 30 minutes.

TIMI flow was graded as follows: TIMI flow grade 0, absent antegrade flow; TIMI flow grade 1, partial contrast penetration beyond an occlusion with incomplete distal filling; TIMI flow grade 2, patent epicardial artery with opacification of the entire distal artery (however, contrast filling and/or washout is delayed); TIMI flow grade 3, patent epicardial artery with normal flow.¹¹

Creatine kinase-MB (CK-MB) level in plasma was measured by immunological UV assay (Roche Hitachi 912, Mannheim, Germany) after arrival in the ED and repeated after 8 hours.

Left ventricular ejection fraction (LVEF) was measured with two-dimensional echocardiography using the modified Simpson rule,¹² performed 1 day after primary PCI.

In-hospital bleeding criteria were defined according to the global utilization of streptokinase and t-PA for occluded coronary arteries (GUSTO) criteria¹³ and are described as

follows¹: Severe or life-threatening bleeding, intracranial bleeding or bleeding that causes substantial hemodynamic compromise requiring treatment²; moderate bleeding, bleeding which needs blood transfusion; and³ minor bleeding, other bleeding, neither requiring transfusion nor causing hemodynamic compromise.

Death was defined as death from all cause within the first 30-days of follow-up. Procedural time was calculated from time of injection of local anesthetics to guide-catheter removal. Door-to-device time was calculated from ED admission to the introduction of first device, being a thrombus aspiration catheter or a balloon catheter into the IRA.

Procedural success was defined as completion of primary PCI without major clinical complications (e.g., stroke, death, or coronary artery perforation).¹⁴

Study Endpoints

The primary endpoint of the study was preprocedural TIMI flow 2 or 3. Secondary endpoints were CK-MB level at 8 hours after admission, LVEF at 1 day after primary PCI, the rate of in-hospital bleeding, and 30-day mortality. Length of stay, procedural time, and door-to-device time were also assessed. Two blinded independent interventional cardiologists verified the TIMI flow in each patient. Clinical events in the first month of follow-up were judged by an independent clinical event committee that was blinded to group allocation of the patients.

Statistical Analysis

For normally distributed continuous variables, data were expressed as mean $\pm$ standard deviation. If not normally distributed, data were expressed as median and interquartile range. Categorical variables were expressed as numbers and percentages. Chi-square tests were used to compare categorical variables. Student's *t*-test or Mann-Whitney *U* test was used to compare numerical variables between the two groups.

Assuming a 33% difference in preprocedural coronary artery patency (TIMI flow 2 or 3) between the two groups,⁹ 95% probability (2-sided) and 80% study power, a minimum of 77 patients was needed per group.

A *p* value of < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 17.0, SPSS Inc., Chicago, IL).

Results

Clinical, Angiographic, and Procedural Characteristics

Most patients in group A (90%) and group B (89%) were late presenters (> 2 hours after onset of symptoms). All characteristics were well balanced between the two groups ($\rightarrow$ Table 1), except for more patients with dyslipidemia in group B than in group A (54 vs. 38%, $p = 0.006$).

The median door-to-eptifibatide initiation time was 30 minutes in all patients. The median (interquartile range) door-to-eptifibatide time in group A and B was 25 (15–30) minutes and 66 (46–105) minutes, respectively. Compared

with group B, patients in group A had shorter median door-to-device time (79 vs. 98 minutes, $p < 0.001$) and shorter median procedural time (35 vs. 40 minutes, $p = 0.004$). Other angiographic and procedural variables were similar between the two groups ($\rightarrow$ Table 2).

Study Endpoints

Both groups did not differ with respect to preprocedural TIMI 2 or 3 flow (26 vs. 24%, $p =$ not significant [NS]) ($\rightarrow$ Fig. 2), CK-MB levels at 8 hours after admission (339 vs. 281 U/L, $p =$ NS), LVEF at 1 day after primary PCI (52 vs. 50%, $p =$ NS), in-hospital bleeding rate (13 vs. 18%, $p =$ NS) and the 30-day mortality (2 vs. 7%, $p =$ NS) ($\rightarrow$ Table 3).

Discussion

The main findings from this study are: (1) Intravenous administration of eptifibatide within the first 30 minutes after admission did not improve preprocedural IRA patency, CK-MB levels at 8 hours after admission, LVEF at 1 day after primary PCI, and 30-day mortality as compared with patients who received eptifibatide after the first 30 minutes after admission; (2) patients who received eptifibatide within the first 30 minutes after admission had shorter door-to-device time and shorter procedural time, without increased bleeding risk, compared with patients who received eptifibatide after the first 30 minutes after admission.

The timing of GPI administration before primary PCI has been analyzed in several studies and showed conflicting results.^{9,15–18} In a meta-analysis by De Luca et al¹⁹ patients who received early abciximab initiation had a better outcome than patients with late initiation of abciximab administration. However, the MISTRAL study found that very early abciximab administration in the ambulance failed to demonstrate a clinical benefit as compared with abciximab administration after admission to the ED.¹⁶ The largest randomized study comparing early and late GPI initiation, the ON-TIME 2 study,¹⁵ has further emphasized the clinical benefit of routine early prehospital initiation with high bolus dose tirofiban without increasing the bleeding risk, as compared with late tirofiban initiation.

The facilitated approach of GPI administration to overcome treatment delay for primary PCI has also been investigated in the FINESSE trial.²⁰ The results of the study showed no advantage of the facilitated PCI (reteplase plus abciximab or abciximab alone) over nonfacilitated PCI for reducing the composite endpoint of all-cause mortality, cardiogenic shock, heart failure or ventricular fibrillation. However, the utilization of the facilitated approach in high-risk patient subgroups such as patients with anterior MI,²¹ or patients in an earlier onset (≤ 2 hours) of an infarction may deserve further studies. Compared with the FINESSE trial, our study utilized eptifibatide in all STEMI patients undergoing primary PCI (mostly patients who presented late) and the GPI was given after hospital admission as a routine protocol before primary PCI.

For eptifibatide, some small to moderate scale studies^{17,18,22,23} have shown an improvement of preprocedural epicardial flow, which was not reflected in our study.

Table 1 Baseline characteristics

Characteristics	Group A ^a (N = 164)	Group B ^b (N = 160)	p-Value
Demographic characteristics			
Age, y	54 ± 9	56 ± 8	NS
Male gender	141 (86%)	136 (85%)	NS
Body mass index, kg/m ²	25 (15–36)	25 (18–35)	NS
Risk factors			
Hypertension	89 (54%)	89 (56%)	NS
Dyslipidemia	63 (38%)	86 (54%)	0.006
Diabetes mellitus	41 (25%)	48 (30%)	NS
Smoker	113 (69%)	103 (64%)	NS
Location of MI			
Anterior wall	83 (51%)	82 (51%)	NS
Onset of infarction			
≤ 2 h	17 (10%)	18 (11%)	NS
2–6 h	92 (56%)	87 (54%)	
6–12 h	55 (33%)	55 (34%)	
Vital sign			
Systolic BP, mm Hg	130 (62–208)	132 (61–217)	NS
Diastolic BP, mm Hg	78 (38–121)	81 (44–152)	NS
Heart rate, bpm	75 (16–146)	75 (31–160)	NS
Risk stratification			
Killip class > 1	43 (26%)	32 (20%)	NS
TIMI risk score ≥ 4	80 (49%)	81 (51%)	NS
Laboratory parameter at admission			
Hemoglobin, mg/dL	14 ± 1.7	15 ± 8.4	NS
Creatinine, mg/dL	1.1 ± 0.4	1.2 ± 1.0	NS
Blood glucose, mg/dL	145 (85–559)	158 (68–597)	NS
Leukocyte count, /μL	12,725 (6,070–22,000)	12,005 (1,623–39,650)	NS
Length of stay, d	5 (1–28)	5 (2–38)	NS

Abbreviations: BP, blood pressure; bpm, beats per minute; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction risk variables; NS, not significant.

^aGroup A: patients who received intravenous eptifibatide within 30 minutes after emergency department admission.

^bGroup B: patients who received eptifibatide bolus after the first 30 minutes of emergency department admission.

Two conditions might explain the negative results of our study. First, most of the patients in group A (90%) and group B (89%) arrived at the ED relatively late (> 2 hours after onset of symptoms), a finding that agrees well with one of our previous reports.⁴ It is postulated that the concept of “the earlier the better” for GPI administered before primary PCI might be true only in patients who were admitted to the ED within 2 hours after onset of symptoms, probably related to the integrity of the thrombus. Hassan et al⁹ and Van't Hof et al¹⁵ have shown beneficial effect of prehospital GPI initiation, as compared with GPI initiation after admission.

Second, in our study, we used a single bolus of eptifibatide. The guideline advocates a double bolus of eptifibatide with a

class IIa indication.²⁴ However, our population had a smaller body weight compared with a western population, shown by a median body mass index of 25 kg/m² in both groups (►Table 1). Lower body weight is associated with increased bleeding risk.²⁵ To minimize the bleeding risk in our population, we used a single bolus of eptifibatide, but whether a single bolus dose is less effective than a double bolus dose in our population deserves further investigation.

The classification used to define “early” and “late” GPI initiation in STEMI patients undergoing primary PCI differs among studies. The description “early” was given to GPI administration in ED,¹⁸ or in-ambulance,^{9,15,16} whereas GPI administration was “late” if given in the catheterization

Table 2 Angiographic and procedure-related characteristics

Characteristics	Group A (N = 164)	Group B (N = 160)	p-Value
Access site			
Transradial approach	58 (35%)	42 (26%)	NS
Procedure during primary PCI			
Use of IABP	4 (2%)	4 (2%)	NS
Thrombus aspiration	98 (60%)	95 (59%)	NS
Direct stenting	48 (29%)	33 (21%)	NS
Predilation before stenting	116 (71%)	127 (79%)	NS
DES implantation	55 (33%)	57 (36%)	NS
Infarct-related coronary artery			
LM	0 (0)	1 (0.6%)	NS
LAD	84 (51%)	92 (57%)	NS
LCX	8 (5%)	5 (3%)	NS
RCA	69 (42%)	56 (35%)	NS
Number of diseased vessels			
Single vessel	62 (38%)	55 (34%)	NS
Multivessel	102 (62%)	105 (66%)	
Door-to-device time, min	79 (29–248)	98 (24–366)	< 0.001
Initial TIMI flow grade			
0/1	122 (74%)	122 (76%)	NS
2	19 (12%)	17 (11%)	
3	23 (14%)	21 (13%)	
Final TIMI flow grade			
0/1	4 (2%)	1 (1%)	NS
2	12 (7%)	13 (8%)	
3	148 (90%)	146 (91%)	
Procedural time, min	35 (12–94)	40 (16–163)	0.004
Procedural success	164 (100%)	160 (100%)	NS

Abbreviations: DES, drug eluting stent; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; NS, not significant; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

(cath)-laboratory^{9,18} or in a coronary care unit.¹⁰ In our study population, 30 minutes is the median time of door-to-first bolus dose of eptifibatide time. To date, standard criteria of timing of GPI administration in acute STEMI patients are lacking; in this study 30 minutes is taken as the cut off time to differentiate the timing of administration between the groups.

Eptifibatide, one of the approved GPIs, is a small hepta-peptide that is highly selective and rapidly dissociates from its receptor after cessation of therapy.²⁶ In Indonesia, eptifibatide is the only available GPI and since several studies have shown the noninferiority of eptifibatide compared with abciximab,^{27–30} intravenous eptifibatide administered in the ED has been used as a routine protocol in our institution for STEMI patients undergoing primary PCI since 2011.

In our study, the door-to-device time and the procedural time were shorter in group A patients (eptifibatide within the first 30 minutes), which might reflect an increased awareness of the ED staff to react and activate the cath-laboratory more promptly. It was shown that early activation of the cath-laboratory is associated with a reduced door-to-balloon time.³¹ Door-to-device time has been shown to be associated with mortality.³² It should be noted that the shorter door-to-device time found in group A patients was probably related to patient selection bias rather than to an effect of treatment. Further studies are needed to investigate whether patients who receive earlier eptifibatide administration have lower risk of periprocedural complications leading to a smoother and faster completion of the procedure compared with late administration. Furthermore, both groups had similar LVEF, probably due to similar infarct sizes in both groups. However,

Fig. 2 Primary endpoint: Pre-PCI TIMI flow 2 or 3 by the treatment group. Group A: patients who received intravenous eptifibatide within 30 minutes after emergency department admission; group B: patients who received eptifibatide bolus after the first 30 minutes of emergency department admission. NS, not significant; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

if GPI was given in the prehospital phase, beneficial effects as to infarct size and LVEF were observed, as compared with in-hospital GPI administration.⁹ Another important finding of the current study is that the bleeding risk was not increased in both groups, suggesting a good safety profile of early eptifibatide administration. But this favorable safety profile did not lead to any significant clinical benefit.

Although, our study failed to find any clinical benefit in patients with preprocedural TIMI flow 2 or 3, LVEF tended to be slightly higher in patients with initial TIMI flow 2 or 3 than in patients with initial TIMI flow 0 or 1 (53 vs. 50%, $p = \text{NS}$).

In this study, all patients were pretreated with 600 mg clopidogrel orally, thus the result of this study cannot be applied in centers that are using ticagrelor or prasugrel in addition to acetylsalicylic acid. Further studies are needed to observe the efficacy of the novel oral antiplatelet agents, and to assess the bleeding risk when the novel oral antiplatelet agents are used in combination with routine eptifibatide administration in STEMI patients undergoing primary PCI.

Finally, network organization is essential to optimize patient care at the acute stage of an acute myocardial infarction.³³ Thus, the benefit of intravenous administration of antiplatelet agents might be seen best in the 1st hour after onset of an infarction (golden hours), and it might be initiated immediately after the first medical contact. Larger multicenter randomized trials are needed to observe the proper timing of eptifibatide initiation in a real world acute STEMI population that is arriving at the ED relatively late. Until then, the recent 2012 European Society of Cardiology (ESC) guideline has indicated the routine use of GPI as an adjunct to primary PCI with a class IIb recommendation,²⁴ and the 2011 ACCF/AHA/SCAI PCI guideline with a class III recommendation.³⁴

Limitations

Several limitations should be addressed. First, this is a non-randomized study, in which we included almost all consecutive patients undergoing primary PCI reflecting a true real world practice. Second, we did not evaluate the myocardial blush grade, TIMI frame count, and ST-segment resolution after primary PCI. However, preprocedural TIMI flow was assessed in all patients to assess epicardial flow and microvascular perfusion, both immediately before and after primary PCI. At last, we administered a single bolus of

Table 3 Endpoints of the study

Endpoints	Group A (N = 164)	Group B (N = 160)	p-Value
Primary endpoint			
Preprocedural TIMI flow 2/3	42 (26%)	38 (24%)	NS
Secondary endpoints			
Baseline CK-MB, U/L	43 (6–499)	48 (9–894)	NS
Serial CK-MB, U/L	339 (12–1672)	281 (15–2,400)	NS
LVEF, %	52 (17–76)	50 (14–80)	NS
In-hospital bleeding ^a			
Severe	0 (0)	0 (0)	NS
Moderate	5 (3%)	3 (2%)	NS
Mild	17 (10%)	26 (16%)	NS
Mortality within the first 30 d	4 (2%)	11 (7%)	NS

Abbreviations: CK-MB, creatine kinase-MB; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; NS, not significant; TIMI, thrombolysis in myocardial infarction.

^aGUSTO bleeding criteria.

eptifibatide due to a lower body weight of our population than generally present in western studies.

Conclusion

From this study, which mostly enrolled late STEMI presenters, intravenous administration of eptifibatide within the first 30 minutes after admission did not improve the preprocedural IRA patency, CK-MB level, LVEF, and 30-days mortality than patients who received intravenous eptifibatide, which was administered after the first 30 minutes after admission.

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Note

This is an original article, and is not being submitted elsewhere.

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Conflict of Interest

None.

References

- 1 Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;341(19):1413–1419
- 2 Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation* 2003;108(15):1809–1814
- 3 Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet* 2006;367(9510):579–588
- 4 Dharma S, Juzar DA, Firdaus I, Soerianata S, Wardeh AJ, Jukema JW. Acute myocardial infarction system of care in the third world. *Neth Heart J* 2012;20(6):254–259
- 5 Dharma S, Kedev S, Jukema JW. Thrombus management in the catheterisation laboratory in the setting of primary percutaneous coronary intervention: what is the current evidence? *Heart* 2013;99(4):279–284
- 6 Henriques JPS, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J* 2002;23(14):1112–1117
- 7 Kiernan TJ, Ting HH, Gersh BJ. Facilitated percutaneous coronary intervention: current concepts, promises, and pitfalls. *Eur Heart J* 2007;28(13):1545–1553
- 8 Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;359(9302):189–198
- 9 Hassan AKM, Liem SS, van der Kley F, et al. In-ambulance abciximab administration in STEMI patients prior to primary PCI is associated with smaller infarct size, improved LV function and lower incidence of heart failure: results from the Leiden MISSION!
- acute myocardial infarction treatment optimization program. *Catheter Cardiovasc Interv* 2009;74(2):335–343
- 10 Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 2001;104(6):636–641
- 11 Bekkers SCAM, Yazdani SK, Virmani R, Waltenberger J. Microvascular obstruction: underlying pathophysiology and clinical diagnosis. *J Am Coll Cardiol* 2010;55(16):1649–1660
- 12 Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography. . American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2(5):358–367
- 13 The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993;329(10):673–682
- 14 Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006;47(1):e1–e121
- 15 Van't Hof AW, Ten Berg J, Heestermaans T, et al. Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Pre-hospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008;372:537–546
- 16 Ohlmann P, Reydel P, Jacquemin L, et al. Prehospital abciximab in ST-segment elevation myocardial infarction: results of the randomized, double-blind MISTRAL study. *Circ Cardiovasc Interv* 2012;5(1):69–76, S1
- 17 Aquilina M, Varani E, Balducci M, Vecchi G, Frassinetti V, Maresta A. Administration of eptifibatide during transfer for primary PCI in patients with STEMI: effect on Pre-PCI TIMI flow and its correlation with pain-to-therapy time. *J Invasive Cardiol* 2009;21(3):115–120
- 18 Gibson CM, Kirtane AJ, Murphy SA, et al; TIMI Study Group. Early initiation of eptifibatide in the emergency department before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: results of the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 trial. *Am Heart J* 2006;152(4):668–675
- 19 De Luca G, Bellandi F, Huber K, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results (EGYPT-ALT) cooperation: individual patient's data meta-analysis. *J Thromb Haemost* 2011;9(12):2361–2370
- 20 Ellis SG, Tendera M, de Belder MA, et al; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med* 2008;358(21):2205–2217
- 21 Ellis SG, Tendera M, de Belder MA, et al; FINESSE Investigators. 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. *JACC Cardiovasc Interv* 2009;2(10):909–916
- 22 Zeymer U, Zahn R, Schiele R, et al. Early eptifibatide improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized integrilin in acute myocardial infarction (INTAMI) pilot trial. *Eur Heart J* 2005;26(19):1971–1977

- 23 Cutlip DE, Cove CJ, Irons D, et al. Emergency room administration of eptifibatide before primary angioplasty for ST elevation acute myocardial infarction and its effect on baseline coronary flow and procedure outcomes. *Am J Cardiol* 2001;88(1):A6, 62–64
- 24 Steg PG, James SK, Atar D, et al; Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33(20):2569–2619
- 25 Van de Werf F, Barron HV, Armstrong PW, et al; ASSENT-2 Investigators. Assessment of the Safety and Efficacy of a New Thrombolytic. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: a comparison of TNK-tPA and rt-PA. *Eur Heart J* 2001;22(24):2253–2261
- 26 Zeymer U. The role of eptifibatide in patients undergoing percutaneous coronary intervention. *Expert Opin Pharmacother* 2007;8(8):1147–1154
- 27 De Luca G, Ucci G, Cassetti E, Marino P. Benefits from small molecule administration as compared with abciximab among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-analysis. *J Am Coll Cardiol* 2009;53(18):1668–1673
- 28 Akerblom A, James SK, Koutouzis M, et al. Eptifibatide is non-inferior to abciximab in primary percutaneous coronary intervention: results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2010;56(6):470–475
- 29 Ottani F, La Vecchia L, De Vita M, Catapano O, Tarantino F, Galvani M. Comparison by meta-analysis of eptifibatide and tirofiban to abciximab in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Am J Cardiol* 2010;106(2):167–174, e1
- 30 Zeymer U, Margenet A, Haude M, et al. Randomized comparison of eptifibatide versus abciximab in primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction: results of the EVA-AMI Trial. *J Am Coll Cardiol* 2010;56(6):463–469
- 31 Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med* 2006;355(22):2308–2320
- 32 Rathore SS, Curtis JP, Chen J, et al; National Cardiovascular Data Registry. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ* 2009;338:b1807
- 33 Danchin N. Systems of care for ST-segment elevation myocardial infarction: impact of different models on clinical outcomes. *JACC Cardiovasc Interv* 2009;2(10):901–908
- 34 Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2012;79(3):453–495