

# Effects of the Early Administration of Heparin in Patients With ST-Elevation Myocardial Infarction Treated by Primary Angioplasty

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**Background** The effect of adjunctive heparin for primary angioplasty in patients with ST-elevation myocardial infarction (STEMI) is not well established, so the authors investigated the effect of early heparin administration in the emergency room (ER) on initial patency of the infarct-related artery (IRA) and on the clinical outcome in STEMI patients.

**Methods and Results** One hundred and twenty consecutive patients who presented with STEMI less than 12 h from pain onset and who were eligible for primary percutaneous coronary intervention were allocated to an early heparin group (heparin administered in ER) or a late heparin group (heparin administered after angiography). In the early heparin group, unfractionated heparin (60 U/kg bolus IV, then 14 U·kg<sup>-1</sup>·h<sup>-1</sup> IV infusion) or enoxaparin (1 mg/kg bolus SC) were administered 144±95 min before angioplasty. No significant differences in baseline characteristics were observed between the early heparin group (n=56) and the late heparin group (n=64). However, initial Thrombolysis In Myocardial Infarction (TIMI) flow grade in the IRA was significantly different between the 2 groups (frequency of TIMI 0/1/2/3; 48/4/7/41% vs 70/8/11/11%, early vs late respectively, p=0.002). TIMI 2 or 3 flow was significantly more frequent in the early heparin group than in the late heparin group (48% vs 22%, p=0.002). However, no significant differences were noted between the 2 groups in terms of in-hospital major adverse cardiac events (7% vs 11%, p=0.472) and TIMI major bleeding (2% vs 3%, p=0.639).

**Conclusions** In STEMI patients, early heparin therapy administered in the ER improves coronary patency, despite not reaching clinical benefit. (*Circ J* 2007; 71: 862–867)

**Key Words:** Acute myocardial infarction; Angioplasty; Heparin; Patency

Primary percutaneous coronary intervention (PCI) is the method of choice for establishing reperfusion in patients with ST-elevation myocardial infarction (STEMI)<sup>1</sup>. Although minimizing treatment delay is important in clinical outcome<sup>2</sup>, some door-to-balloon time is inevitably required to prepare for the PCI procedure, and adjunctive pharmacologic therapy administered during this period may be beneficial in improving initial patency and clinical outcome.

Heparin is an antithrombotic agent that inhibits coagulation at multiple positions in the cascade<sup>3</sup> and enhances fibrinolysis in healthy volunteers<sup>4</sup>. The effects of heparin as an adjunctive therapy to improve reperfusion in STEMI has been previously described in patients who received thrombolytic therapy with tissue-specific type agent<sup>5,6</sup>. However, the role of adjunctive heparin in patients treated with primary PCI is not well established, with the few previous studies showing variable results<sup>7–10</sup>.

Therefore, we investigated the effect of the early admin-

istration of heparin in the emergency room (ER) on both initial infarct-related artery (IRA) patency and clinical outcome in patients with STEMI treated by primary PCI.

## Methods

### Subjects

We retrospectively analyzed the results of 120 consecutive patients who presented with acute STEMI and received heparin either in the ER or in the catheterization laboratory after diagnostic angiography just before primary PCI. We enrolled patients with symptoms of acute myocardial infarction (AMI) with chest pain onset within the previous 12 h and with ECG changes that demonstrated ST-segment elevation >0.1 mV in at least 2 contiguous leads or new left bundle branch block. Patients with chest pain lasting more than 12 h and contraindication to the administration of heparin, aspirin or clopidogrel were excluded. We also excluded patients who had undergone prior coronary artery stenting or coronary artery bypass surgery (CABG). Our institutional review board approved this study and all patients gave written informed consent.

### Study Protocol

According to the timing of heparin administration, patients were allocated to an early or late heparin group. The administration or not of heparin in the ER was decided by the

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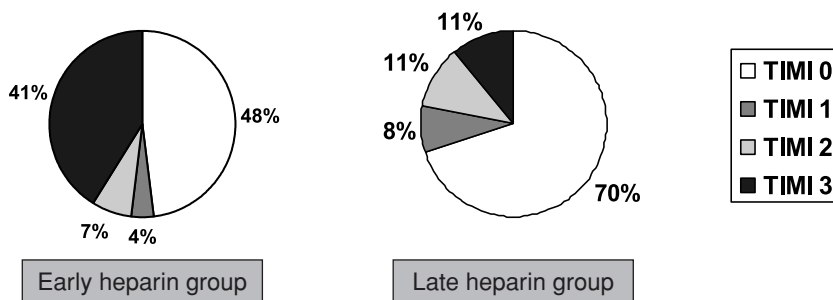
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**Table 1** Baseline Characteristics of Patients

	Early-heparin group (n=56)	Late-heparin group (n=64)	p value
Age (years)	61±13	60±14	0.750
Sex (M/F)	48/8	52/12	0.513
Diabetes mellitus	16 (29%)	14 (22%)	0.398
Hypertension	25 (45%)	37 (58%)	0.150
Current smoking	28 (50%)	25 (39%)	0.229
Duration of chest pain (min)	250±212	245±268	0.911
Referral patients	25 (45%)	10 (16%)	0.003
Killip class, I/II/III/IV (%)	68/14/2/16	66/3/4/15	0.514
IRA, LMCA/LAD/LCX/RCA (%)	4/52/5/39	0/52/9/39	0.403

IRA, infarct-related artery; LMCA, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.



**Fig 1.** Initial Thrombolysis In Myocardial Infarction (TIMI) flow grade of infarct-related artery. TIMI flow grade 2 or 3 was observed in 27 of 56 patients (48 %) in the early heparin group versus 14 of 64 patients (22 %) in the late heparin group (p=0.002); TIMI flow grade 3 was observed in 23 (41%) vs 7 (11%) (p<0.001) and TIMI flow grade 0 in 27 (48%) vs 45 (70%) (p=0.014), respectively.

physicians on duty. In the early heparin group, unfractionated heparin (60U/kg IV loading followed by 14U·kg<sup>-1</sup>·h<sup>-1</sup> as an IV infusion until angiography) or enoxaparin (1 mg/kg bolus SC) was initiated in the ER just after ECG interpretation and STEMI diagnosis. In the late heparin group, a 100U/kg bolus of unfractionated heparin was given IV just before the primary PCI procedure. In addition, 300mg of aspirin was given to all patients in the ER and 300mg of clopidogrel was administered just prior to primary PCI in the catheterization laboratory. Other medications, including  $\beta$ -blockers, nitrates, and morphine, were administered at the discretion of the ER duty physician. Glycoprotein IIb/IIIa receptor blockers were given during the interventional procedure as required. Primary PCI was performed in a standard manner. Slow-flow phenomenon was defined as Thrombolysis In Myocardial Infarction (TIMI) grade 2 flow, and no-reflow was defined as TIMI grade  $\leq 1$  flow in the distal IRA in the absence of occlusion at the treatment site or evidence of distal embolization, at the end of the PCI procedure. No additional heparin infusion was given after primary angioplasty. After admission, total creatinine kinase (CK) and CK-MB were measured every 6 h for 24 h, and then on a daily basis until discharge. Transthoracic echocardiography was performed at the time of discharge to evaluate the left ventricular ejection fraction. Bleeding complications fitting the TIMI definition of major bleeding<sup>11</sup> bleeding requiring transfusion and hematomas greater than 5 cm were recorded.

**Study Endpoints**

The primary study endpoint was the initial TIMI ante-grade flow in the IRA graded by coronary angiography<sup>12</sup> TIMI flow grades were scored by 2 cardiologists unaware of the timing of heparin. Secondary endpoints were the angiographic morphologic features of the IRAeg,<sup>13</sup> bleeding complications, and in-hospital major adverse cardiac events

(MACE) including death, recurrent myocardial infarction (MI), and repeat target-vessel revascularization. The angiographic morphologic features used to identify a “high burden thrombus formation” were classified in 7 categories by 2 cardiologists unaware of heparin timing, as described previously<sup>13</sup> In brief, the angiographic features of the IRAs were morphologically classified using the following criteria based on quantitative and qualitative analyses: (1) no visible thrombus in the IRA; (2) incomplete obstruction with the presence of an angiographic thrombus with the greatest linear dimension 3-fold or less of the reference luminal diameter (RLD); (3) incomplete obstruction with the presence of an angiographic thrombus with the greatest linear dimension more than 3-fold that of the RLD; (4) taper pattern (lesion morphology with a tapered end before occlusion); (5) tapered cutoff pattern (lesion morphology with proximal tapering and distal abrupt cutoff pattern filled with some thrombus before the occlusion); (6) cutoff pattern (lesion morphology with an abrupt cutoff without taper before the occlusion); and (7) presence of an accumulated thrombus >5 mm proximal to the occlusion<sup>13</sup> Quantitative coronary angiographic analysis (QCA) of the RLD, minimal luminal diameter, and diameter stenosis were performed by a single experienced angiographer unaware of the timing of heparin. Angiographic measurements were made during end-diastole, using the guiding catheter for magnification calibration.

**Statistical Analysis**

All statistical tests were performed using the SPSS for Windows® (ver. 10.0, Chicago, IL, USA). Values are expressed as mean  $\pm$  standard deviation or frequencies. Differences in categorical values between the 2 groups were analyzed using the chi-square test, and differences in continuous variables were analyzed using the Student’s t-test. P-values <0.05 were considered statistically significant.

**Table 2** Angiographic Morphologic Features of the Infarct-Related Artery

	Early-heparin group	Late-heparin group
No thrombus	19 (34%)	7 (11%)
Taper pattern	1 (2%)	4 (6%)
Tapered cutoff pattern	14 (25%)	19 (30%)
Thrombus $\leq 3$ of RLD	8 (14%)	7 (11%)
Thrombus $> 3$ of RLD	0 (0%)	3 (5%)
Cutoff pattern	11 (20%)	22 (34%)
Accumulated thrombus	3 (5%)	2 (3%)

RLD, reference luminal diameter.

**Table 3** Procedural Outcomes

	Early-heparin group	Late-heparin group	p value
Door-to-balloon time (min)	125±65	124±53	0.842
Use of glycoprotein IIb/IIIa receptor blocker	5 (9%)	10 (16%)	0.268
No. of stenosed coronary arteries, 1VD/2VD/3VD (%)	30/40/30	28/42/30	0.943
Reference diameter (mm)	3.02±0.45	3.18±0.52	0.175
Minimal luminal diameter (mm)	0.36±0.17	0.46±0.28	0.168
Diameter stenosis (%)	95±7	96±8	0.217
Final diameter stenosis (%)	11±6	9±7	0.220
Final TIMI flow grade 3	52 (93%)	52 (81%)	0.153
No-reflow	0	0	
Slow-flow	3 (5%)	10 (16%)	0.071

VD, vessel disease; TIMI, Thrombolysis In Myocardial Infarction.

**Table 4** In-Hospital Clinical Outcomes

	Early-heparin group	Late-heparin group	p value
Death	4 (7%)	6 (9%)	0.659
Recurrent myocardial infarction	0 (0%)	1 (2%)	0.348
Repeat TVR	0	0	
Major adverse cardiac event	4 (7%)	7 (11%)	0.472
Peak CK (IU/L)	2,929±2,472	3,572±2,467	0.188
Time to peak CK (h)	16.4±11.8	18.0±22.9	0.622
LV ejection fraction (%)	49±12	46±12	0.320

TVR, target-vessel revascularization; CK, creatinine kinase; LV, left ventricular.

## Results

### Patient Characteristics

Among the 120 consecutive patients enrolled, 56 were allocated to the early heparin group and 64 to the late heparin group. In the early heparin group, 36 patients received unfractionated heparin and 20 patients received enoxaparin, 144±95 min before angioplasty. Of the 120 patients, 35 (29%) patients were transferred from other hospitals. Baseline clinical and angiographic characteristics were similar in the 2 groups (Table 1).

### Initial TIMI Flow Grade and Angiographic Morphologic Features of the IRA

The primary endpoint of the initial TIMI flow grade in the IRA was significantly different between the 2 groups (Fig 1). In the early heparin group, TIMI 3 flow was significantly more frequent (41% vs 11%), and conversely TIMI 0 flow was significantly less frequent (48% vs 70%). Of the 56 patients in the early heparin group, 27 (48%) had TIMI 2 or 3 flow, versus 14 (22%) of the 64 patients in the late heparin group (p=0.002).

The angiographic morphologic features of the IRA differed in the 2 groups (Table 2). Of note, the frequency of the cutoff pattern in the IRA, accumulated thrombus (>5 mm)

proximal to the occlusion, and incomplete obstruction with presence of accumulated thrombus more than 3-fold that of RLD of the IRA, which have been reported to be indicators of a “high-burden thrombus formation”, were significantly lower in the early heparin group (25% vs 42%, p=0.048). Moreover, the proportion of patients with no visible thrombus was higher in the early heparin group (34% vs 11%, p=0.002).

### Procedural Outcomes

Procedural outcomes are compared in Table 3. Mean door-to-balloon times were similar in the 2 groups. The use of glycoprotein IIb/IIIa receptor blockers was not significantly different in the 2 groups, and stent implantation was performed in all cases. Final TIMI 3 flow of the IRA, confirmed after the PCI procedure, was achieved in 93% of the early heparin group and in 81% of the late heparin group, without statistical significance. No intraprocedural deaths or emergency CABG occurred. Final diameter stenosis measured by QCA was not significantly different in the 2 groups, and the no-reflow phenomenon did not occur in either group. However, the frequency of the slow-flow phenomenon tended to be lower in the early heparin group (5% vs 16%, p=0.071).

**Table 5 Bleeding Complications**

	Early-heparin group	Late-heparin group	p value
TIMI major bleeding	1 (2%)	2 (3%)	0.639
Bleeding requiring transfusion	1 (2%)	4 (6%)	0.222
Hematoma	2 (4%)	6 (9%)	0.204

Abbreviation see in Table 3.

**Table 6 Subgroup Analysis: Non-Referred Patients (n=85)**

	Early-heparin group (n=31)	Late-heparin group (n=54)	p value
Initial TIMI flow grade			<0.001
0	16 (52%)	41 (76%)	
1	0 (0%)	5 (9%)	
2	1 (3%)	4 (7%)	
3	14 (45%)	4 (7%)	
Death	1 (3%)	4 (7%)	0.430
Recurrent myocardial infarction	0 (0%)	1 (2%)	0.446
Major adverse cardiac event	1 (3%)	5 (9%)	0.296

Abbreviation see in Table 3.

### In-Hospital Clinical Outcomes and Infarct Size

During in-hospital follow-up ( $8.6 \pm 5.0$  days), MACE occurred in 4 patients in the early heparin group and in 7 in the late heparin group, which was not significant (Table 4). Four deaths occurred in the early heparin group and 6 in the late heparin group. One death caused by hypovolemic shock from massive bleeding occurred in each group, and the other deaths were all caused by cardiac events. Recurrent MI occurred in 1 patient in the late heparin group. No cases of repeat target-vessel revascularization occurred, and infarct sizes as determined by peak CK value were similar in the 2 groups. Pre-discharge left ventricular ejection fractions measured by echocardiography were similar in the 2 groups.

### Bleeding Complications

TIMI major bleeding occurred in 1 patient in the early heparin group and in 2 in the late heparin group, which was not significant (Table 5). No cases of hemorrhagic stroke occurred in either group. The occurrence of bleeding requiring transfusion and the frequency of hematoma formation were not significantly different in the 2 groups.

### Subgroup Analysis

To exclude the possibility of selection bias among referral patients, we performed subgroup analysis on the 85 patients who directly visited the study hospital (Table 6). In this subgroup of non-referred patients, initial TIMI flow of grade 2 or 3 was observed in 48% in the early heparin group and in 14% in late heparin group ( $p=0.001$ ).

## Discussion

The major findings of the present study are that the initial TIMI flow grade and angiographic thrombus burden of the IRA were improved in patients who received heparin early in the ER as compared with patients who were administered heparin in the catheterization laboratory after diagnostic angiography. Moreover, these benefits resulted in a tendency for less occurrence of slow-flow during the primary angioplasty procedure. No significant difference was observed between the 2 study group in terms of bleeding complications or in-hospital clinical outcomes.

### Adjunctive Heparin in Patients With STEMI Treated by Primary PCI

The ACC/AHA guidelines for the management of patients with STEMI recommends that patients undergoing percutaneous or surgical revascularization should receive unfractionated heparin as ancillary therapy to reperfusion therapy.<sup>14</sup> However, no specific indications are given concerning the exact timing or dosage of this adjunctive therapy. The same guidelines also recommend weight-adjusted boluses of heparin of 70–100 U/kg when primary PCI is chosen as the route of reperfusion, which does not differ from the recommendation for routine PCI. At the time of patient enrolment, the study hospital had 2 methods of heparin administration (ie, in the ER or after diagnostic coronary angiography) because of concerns that the preparation time for primary PCI is greater when heparin is administered in the ER. The decision as to which method to adopt was made by the physicians responsible at the time of the patient's presentation in the ER. In the present study, analysis of 120 consecutive cases showed that good initial patency results were obtained for patients who received heparin in the ER.

### Effect of Early Heparin on Initial IRA Patency

Several reports have been published on the effects of heparin on initial IRA patency. In a pilot study, high-dose (300 U/kg) IV bolus heparin administered in the ER produced promising initial patency results,<sup>7</sup> but a subsequent randomized trial failed to confirm this benefit.<sup>8</sup> However, the door-to-balloon time in that study was too short (median time to first balloon 71 min) for the administered heparin to have improved patency.<sup>8</sup> Another observational study showed higher initial patency rates of the IRA in patients who were administered aspirin and heparin ( $\geq 5,000$  IU IV) pre-hospital than in patients administered this combination in-hospital, which was mainly attributed to difference in the time interval from aspirin and heparin administration to angiography,<sup>9</sup> which supports the results of the present study. However, the groups that have classified patients only according to the route of admission (ie, referred vs non-referred) are not suitable for direct comparison. Recently, a prospective study of pre-hospital enoxaparin (0.5 mg/kg IV followed by 1 mg/kg SC) revealed a promising initial

patency rate, but did not have a control group.<sup>10</sup> In the present study, sufficient time (144 min) was allowed for heparin to affect IRA patency. Moreover, the proportion of patients transferred from other hospitals was relatively small (29%), and thus avoids selection bias from the route of admission, as was supported by our subgroup analysis of non-referred patients.

#### *Morphologic Thrombus Burden and Slow-Flow Phenomenon*

Cura et al demonstrated that the angiographic presence of a visible thrombus is 1 of the independent predictors of slow-flow after primary PCI in patients with AMI.<sup>5</sup> Moreover, Yip et al morphologically classified the angiographic features of the IRA, and showed that the angiographic features of "high burden thrombus formation" (ie, the cutoff pattern, accumulated thrombus proximal to the occlusion; incomplete obstruction with presence of accumulated thrombus more than 3-fold that of the RLD of the IRA; presence of a floating thrombus; persistent dye stasis distal to the obstruction; and RLD of the IRA  $\geq 4$  mm) are independent predictors of slow-flow or no-reflow after primary PCI.<sup>3</sup> In the present study, the early heparin group had a significantly lower frequency of "high burden thrombus formation" and significantly higher frequency of "no visible thrombus" on the baseline angiogram. Moreover, these morphologic features tended to reduce the frequency of slow-flow phenomenon in the early heparin group, as previously suggested.<sup>13,15</sup>

#### *Clinical Outcomes*

In the present study, observed benefits in terms of initial patency, the morphologic features of thrombus burden, and the tendency to reduce the prevalence of the slow-flow phenomenon did not reduce mortality or MACE. This lack of an observed clinical outcome benefit may be attributed to the presence of many other important variables that affect the clinical outcome of STEMI patients after primary PCI. In a previous report, the independent predictors of death in AMI patients treated by primary PCI were age, multivessel disease, a final TIMI flow grade  $\leq 2$ , and cardiogenic shock,<sup>16</sup> and in the PAMI trial, the independent predictors of mortality after primary PCI were old age, Killip class, tachycardia ( $>100$  beats/min), diabetes, and anterior MI or left bundle branch block.<sup>17</sup> Recently Halkin et al suggested a risk score system for predicting mortality after primary PCI, which includes advanced age, Killip class, baseline left ventricular function, anemia, renal insufficiency, triple-vessel disease, and postprocedural TIMI flow grade.<sup>18</sup> Although the slow-flow phenomenon (ie, final TIMI grade 2 flow), which showed a reducing tendency in the present study, was included in the previous studies as 1 of the independent predictors, there are many other variables evidently affecting the clinical outcome after primary PCI.

#### *Bleeding Complications*

Three TIMI major bleeding episodes occurred in the present study, 1 (2%) in the early heparin group and 2 (3%) in the late heparin group, which is not significantly higher than in previous reports that heparin was administered with thrombolytic therapy<sup>5,6</sup> or with primary PCI.<sup>7-10</sup> Of these 3 patients, 2 who had been treated with abciximab experienced profuse bleeding in the oral cavity or at a tracheostomy site, and both required a massive blood transfusion after

PCI, but finally succumbed to hypovolemic shock. The other patient, who had not been treated with abciximab, developed retroperitoneal hematoma and recovered from transient hypovolemic shock after a blood transfusion.

#### *Study Limitations*

Because of its non-randomized, retrospective nature, significant unknown differences may have existed between the 2 study groups, even though no significant difference was observed between the 2 in terms of baseline clinical and angiographic characteristics. However, unlike randomized trials, the present study included high-risk patients (eg, patients with cardiogenic shock) who are typically excluded from randomized trials. Another limitation concerns the mixed use of unfractionated heparin or enoxaparin in the early heparin group, as there may be some differences in the action times and efficacies of unfractionated heparin and low-molecular-weight heparin. However, no data are available on this topic in STEMI patients treated by primary PCI, and thus we view the mixed use of unfractionated heparin and enoxaparin as being representative of actual practice rather than being a serious shortcoming.

## Conclusion

The present study demonstrates the benefits of early heparin administration on initial patency of the IRA and on a tendency of less occurrence of slow-flow during primary angioplasty. Moreover, these benefits were achieved without increasing bleeding complications, although were not found to reduce in-hospital adverse cardiac events.

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