

# Usefulness of Routine Unfractionated Heparin Infusion Following Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction in Patients Not Receiving Glycoprotein IIb/IIIa Inhibitors

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We evaluated the utility of a routine postprocedure course of unfractionated heparin after primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) in patients not receiving glycoprotein IIb/IIIa inhibitors. In the CADILLAC study, 2,082 patients with AMI who underwent primary PCI were randomized to receive stents versus percutaneous transluminal coronary angioplasty (PTCA), each with or without abciximab. In a subset of 976 patients who did not receive abciximab, we compared outcomes of patients who received postprocedural heparin (n = 758; 78%; median duration 2 days) with those who did not. In 421 patients treated with PTCA, postprocedural heparin use was associated with lower in-hospital major adverse cardiac events (MACEs; 5.3% vs 11.4%, p = 0.069), 1-year MACEs (22% vs 31%, p = 0.08), and decreased in-hospital moderate/severe bleeding (2.3% vs 8.9%, p = 0.01). By multivariate analyses, heparin use correlated with freedom from in-hospital and 1-year MACEs in patients after PTCA. In contrast, in 555 patients who underwent stenting, postprocedural heparin use was associated with increased bleeding and hospitalization costs without a decrease in early or late MACEs. In conclusion, in patients with AMI treated with coronary stenting without glycoprotein IIb/IIIa inhibitors, routine postprocedural heparin was not associated with any significant benefits and may be safely omitted. However, in a subset of patients treated with PTCA, postprocedural heparin use was independently associated with fewer in-hospital and 1-year MACEs. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:202–207)

Most previous studies of primary angioplasty and stenting for acute myocardial infarction (AMI) in patients not treated with glycoprotein IIb/IIIa inhibitors have mandated a routine infusion of unfractionated heparin for several days after a successful procedure to decrease the risk of recurrent ischemia and thrombosis.<sup>1–9</sup> However, this practice may increase bleeding, and its utility has never been validated. As a result, current American College of Cardiology/American Heart Association guidelines for the management of AMI are unclear about the need for heparin after primary percutaneous coronary intervention (PCI) when glycopro-

tein IIb/IIIa antagonists are not used.<sup>10</sup> In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, the utility of various interventional reperfusion modalities were studied in patients who underwent PCI for AMI.<sup>11</sup> We therefore examined the CADILLAC database to evaluate the utility of routine heparin administration after primary percutaneous transluminal coronary angioplasty (PTCA) and stenting.

## Methods

**Patient selection and classification:** The CADILLAC trial enrolled 2,082 patients at 76 international centers who presented with AMI within 12 hours of symptom onset. Principal exclusion criteria included cardiogenic shock, saphenous vein graft or left main culprit artery, and other contraindications to bare metal stent implantation.<sup>11</sup> Eligible patients were randomized in a 2 × 2 factorial design to undergo balloon angioplasty (PTCA) alone (n = 518), PTCA plus abciximab therapy (n = 528), stenting alone with the MultiLink stent (Guidant Corporation, St. Paul, Minnesota) (n = 512), or stenting plus abciximab therapy (n = 524). Crossover to abciximab was permitted in patients not initially randomized to abciximab for refractory no-reflow or giant residual thrombus. Postprocedural heparin was not administered to patients receiving abciximab. As in

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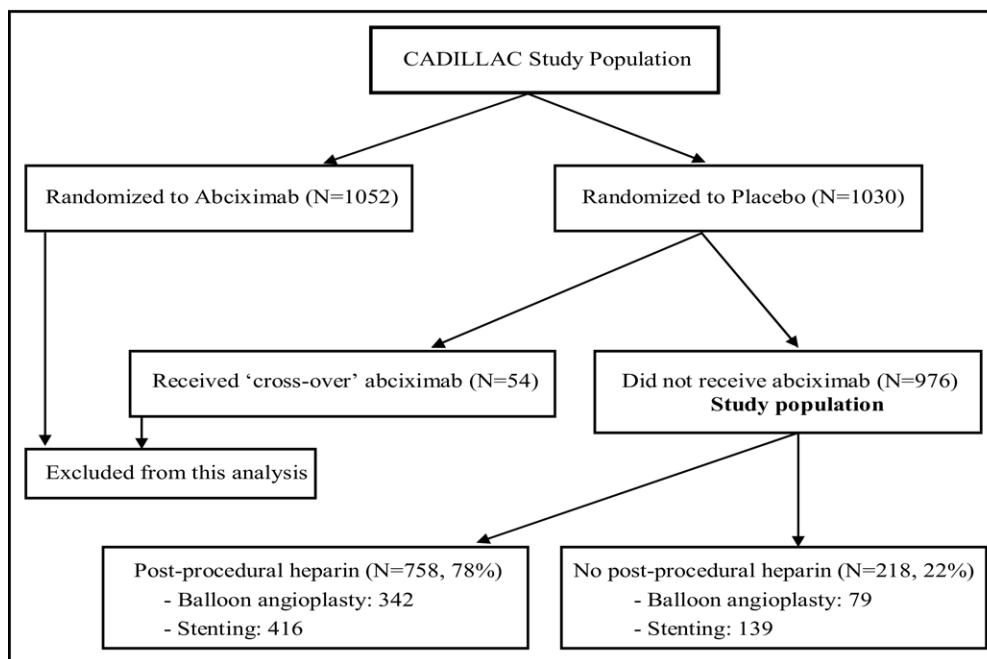


Figure 1. Patient selection for this analysis.

all the previous Primary Angioplasty in Myocardial Infarction (PAMI) trials,<sup>1-9</sup> postprocedural heparin was recommended for 60 hours in patients not receiving abciximab (48 hours at full dose to maintain the activated partial thromboplastin time at 50 to 70 seconds and then 12 hours at 1/2 dose before discontinuation), although heparin use in this setting was left to the operator's discretion.

**Study outcomes:** Clinical follow-up was performed in the hospital, at 1 month, and at 6 and 12 months. The primary end point was the composite major adverse cardiac event (MACE) rate, consisting of death, reinfarction, ischemia-driven target vessel revascularization (TVR), or disabling stroke, as adjudicated by a clinical events committee blinded to treatment assignment and pharmacologic use. The definitions of the components of the primary end point have been previously described.<sup>11</sup> The incidence of moderate or severe bleeding, length of stay, total cost during the index hospitalization, and thrombocytopenia during 30-day follow-up were also assessed. Severe bleeding was defined as intracranial bleeding or hemorrhage resulting in hemodynamic compromise. Moderate bleeding was defined as bleeding requiring blood transfusion but without hemodynamic compromise. Thrombocytopenia was defined as a nadir platelet count <100,000/ml. Procedural success was defined as final Thrombolysis In Myocardial Infarction grade 3 flow with  $\leq 50\%$  diameter stenosis and without any major adverse events within 7 days after the procedure.

**Statistical analysis:** Clinical outcomes as a function of postprocedural heparin use in patients not receiving glycoprotein IIb/IIIa inhibitors were analyzed separately in patients receiving stents versus those managed with PTCA only. Because of the major effect of stents compared with PTCA in decreasing recurrent ischemia and a previous demonstration that clinical outcomes of patients receiving

stents during primary intervention are similar regardless of whether they underwent implantation by intent or for bail out after failed PTCA,<sup>12</sup> device analysis was performed per treatment rather than by intent to treat. Categorical data were compared using Fisher's exact test. Continuous variables are summarized as medians (25th percentile, 75th percentile) and were compared using the nonparametric Kruskal-Wallis test. Clinical outcome estimates were created using the Kaplan-Meier method and compared with log-rank p test. Multiple logistic regression, linear regression, or Cox proportional hazards regression was performed to assess the independent relation of postprocedural heparin use with the occurrence of selected outcome measurements. Variables entered in these models included age, gender, current smoking status, diabetes mellitus, hypertension, hypercholesterolemia, previous myocardial infarction, previous coronary artery bypass graft surgery, estimated creatinine clearance rate <60 ml/min, chest pain onset to hospital arrival time, Killip class, left anterior descending artery infarct vessel, 3-vessel disease, treatment (stent vs PTCA), and postprocedural heparin use.

## Results

**Baseline characteristics:** The study cohort consisted of 976 of the 2,082 patients enrolled in the CADILLAC trial who did not receive abciximab by randomization or cross-over. PTCA without stenting was performed in 421 patients (43%), whereas stents were implanted in 555 patients (57%). Postprocedural intravenous heparin was used in 758 patients (78%), including 342 of 421 patients (81%) treated by PTCA only and 416 of 555 patients (75%) in whom stents were implanted. Figure 1 shows patient selection and study group classification for the present analysis. In patients receiving postprocedural heparin, the median duration (25th, 75th percentile) of heparin therapy was 2 days (range 1, 3) after PCI.

Table 1  
Baseline clinical characteristics of study groups

Variable	Postprocedural Heparin		p Value
	Yes (n = 758)	No (n = 218)	
US site	85%	70%	<0.0001
Age (yrs)	59 (51, 68)	59 (50, 68)	0.53
Men	72%	73%	0.86
Weight (kg)	82 (73, 93)	80 (69, 91)	0.076
Hypertension	47%	49%	0.70
Diabetes mellitus	15%	18%	0.29
Current smoker	43%	46%	0.39
Dyslipidemia*	35%	44%	0.02
Previous myocardial infarction	12%	14%	0.64
Previous PCI	10.3%	9.6%	0.90
Previous coronary artery bypass grafting	1.5%	1.4%	1.0
Previous cerebrovascular accident	3.6%	2.3%	0.52
Aspirin use before PCI	92%	95%	0.10
Thienopyridine use before PCI	61%	63%	0.75
Initial presentation			
Killip class $\geq$ II	11.1%	7.9%	0.21
Initial electrocardiogram			
STEMI or LBBB	88%	86%	0.56
Non-STEMI	12%	14%	0.56
Creatinine clearance <60 ml/min	17%	20%	0.47
Time from symptom onset to hospital arrival (h)	1.8 (1.0, 3.8)	2.0 (1.0, 3.8)	0.87
Time from arrival at emergency department to first balloon inflation (h)	2.1 (1.5, 2.7)	1.9 (1.3, 3.1)	0.31

\* Total cholesterol level >235 mg/dl.

LBBB = left bundle branch block; STEMI = ST-segment elevation myocardial infarction; US = United States.

As presented in Table 1, most baseline clinical characteristics, including previous use of aspirin and thienopyridine, were similar in patients in whom postprocedural heparin was and was not administered. Patients receiving postprocedural heparin were more frequently enrolled in United States centers and were less likely to have dyslipidemia. Such patients had lower left ventricular ejection fractions, were more likely to have baseline Thrombolysis In Myocardial Infarction grade 0/1 flow, and less likely to have baseline Thrombolysis In Myocardial Infarction grade 3 flow, but had similar postprocedural Thrombolysis In Myocardial Infarction flow rates as patients who did not receive postprocedural heparin (Table 2). Stent use was less common in patients receiving postprocedural heparin. Other baseline and postintervention angiographic characteristics were similar between the 2 groups. Importantly, there were no differences in the rates of angiographic complications after PCI in patients in whom postprocedural heparin was and was not used, including residual thrombus, dissection, no reflow, or distal embolization. In the stent subset, thienopyridine was used after PCI in 99% of patients who received heparin after PCI and in 98% of those who did not (p = 0.70). In the PTCA subset, thienopyridine was used after

Table 2  
Angiographic and procedural characteristics

Baseline angiographic characteristics	Postprocedural Heparin		p Value
	Yes (n = 758)	No (n = 218)	
Ejection fraction (%)	58 (47, 64)	60 (52, 67)	0.078
TIMI flow before intervention*			
0/1	71%	64%	0.065
2	11%	8.4%	0.37
3	19%	28%	0.005
Infarct-related coronary artery*			
Left anterior descending	39%	37%	0.75
Right	45%	46%	0.64
Left circumflex	17%	17%	0.92
No. of narrowed coronary arteries*			
1	52%	48%	0.28
2	33%	36%	0.52
3	15%	17%	0.52
Preprocedure reference diameter (mm)	2.9 (2.6, 3.3)	2.9 (2.6, 3.3)	0.53
Preprocedure minimal luminal diameter (mm)	0.0 (0.0, 0.6)	0.0 (0.0, 0.8)	0.26
Preprocedure diameter stenosis (%)	100 (77, 100)	100 (73, 100)	0.17
Procedural results			
Maximum balloon size (mm)	3.5 (3.0, 3.5)	3.5 (3.0, 3.5)	0.77
Maximum balloon pressure (atm)	12 (9, 15)	12 (10, 16)	0.079
Stent implantation	55%	64%	0.02
Total no. of stents implanted	1 (0, 1)	1 (0, 1)	0.079
Final TIMI grade 3 flow	96%	96%	1.00
Final minimal luminal diameter (mm)	2.4 (2.1, 2.7)	2.5 (2.1, 2.8)	0.21
Final diameter stenosis (%)	19 (10, 28)	17 (9, 26)	0.15
Final thrombus present	5.0%	3.9%	0.58
Final dissection	10.4%	8.9%	0.60
Final no reflow	0.6%	0.5%	1.00
Final distal embolization	1.3%	0.5%	0.47
Intra-aortic balloon pump	10.3%	5.8%	0.15
Procedural success	91%	89%	0.59
Duration of procedure (h)	1.0 (0.8, 1.4)	1.0 (0.8, 1.3)	0.25

\* Sum of numbers in each column may not equal 100 due to rounding. TIMI = Thrombolysis In Myocardial Infarction.

PCI in 54% of patients who received heparin after PCI and 65% of those who did not (p = 0.10).

**Clinical outcomes in all patients:** As presented in Table 3, in-hospital death, reinfarction, disabling stroke, and MACE rates were similar between patients who did and those who did not receive postprocedural heparin. However, postprocedural heparin was associated with a nonsignificant trend toward lower rates of in-hospital ischemic TVR. However, by multivariate analysis, postprocedural heparin use did not impart an independent benefit on in-hospital TVR (adjusted odds ratio 0.56, 95% confidence interval 0.26 to 1.22, p = 0.14). At 1-year follow-up, the incidence of clinical events was nearly identical in the 2 groups.

Table 3  
Clinical outcomes in all patients

Outcome	Postprocedural Heparin		p Value
	Yes (n = 758)	No (n = 218)	
<b>In-hospital events</b>			
Death	1.8%	1.4%	0.78
Reinfarction	0.4%	0.9%	0.31
Ischemic TVR	2.9%	5.5%	0.09
Disabling stroke	0.0%	0.0%	—
MACEs*	4.7%	6.9%	0.23
Subacute thrombosis	1.1%	1.8%	0.32
<b>1-yr events</b>			
Death	3.9%	3.7%	0.91
Reinfarction	2.1%	2.3%	0.78
Ischemic TVR	14%	15%	0.65
Disabling stroke	0.3%	0.5%	0.65
MACEs*	18%	19%	0.66
Subacute thrombosis	1.4%	2.3%	0.30

\* Death, reinfarction, ischemia-driven TVR, or disabling stroke.

**Clinical outcomes in patients undergoing PTCA versus stenting:** In patients treated with PTCA alone, postprocedural heparin was associated with nonsignificant decreases in in-hospital and 1-year rates of MACEs (Table 4). By multivariate analysis, heparin use showed a weak independent correlation with lower in-hospital (odds ratio 0.47, 95% confidence interval 0.20 to 1.10,  $p = 0.08$ ) and 1-year (odds ratio 0.66, 95% confidence interval 0.41 to 1.04,  $p = 0.07$ ) MACEs. In patients who underwent stenting (Table 4), no significant differences in in-hospital or 1-year outcomes were present between study groups. Target vessel thrombosis was not decreased by prolonged heparin usage in the PTCA or stent cohorts.

**In-hospital bleeding, thrombocytopenia, length of hospitalization, and costs:** As presented in Table 5, in the entire study population, the decision to use postprocedural heparin had no effect on in-hospital bleeding rates, thrombocytopenia, length of hospitalization, or costs. In the PTCA subset, the incidence of moderate bleeding (2.0% vs 7.6%,  $p = 0.02$ ) and the combined risk of moderate or severe bleeding (2.3% vs 8.9%,  $p = 0.01$ ) were paradoxically lower in patients who received postprocedural heparin than in those who did not, and rates of thrombocytopenia were similar. Length of hospital stay also tended to be shorter in the heparin group, but hospitalization costs were similar between groups. In contrast, in patients receiving stents, heparin use after PCI was associated with an increase in moderate or severe bleeding and a longer and more expensive hospital stay. By multivariate analysis, postprocedure heparin use was an independent correlate of a shorter hospital stay in the PTCA group ( $p = 0.0004$ ) but not in the stent group.

## Discussion

The principal findings of the present report follow. (1) In patients with AMI who underwent emergency coronary stenting without glycoprotein IIb/IIIa inhibitors, the routine use of long-term postprocedural unfractionated heparin does

not confer any benefit and may be safely omitted. (2) In patients who underwent PTCA without stenting, postprocedural heparin was associated with strong univariate and multivariate trends toward lower in-hospital and 1-year MACE rates. The slight benefit in in-hospital TVR rates shown in the postprocedural heparin group in the total study population (Table 3) was primarily driven by the beneficial effect of heparin in the PTCA group. (3) In the entire study population, a 60-hour postprocedural heparin course was not associated with increased bleeding, thrombocytopenia, prolonged hospitalization, or excessive costs. However, in this regard, differences were present in the angioplasty and stent cohorts. Contrary to expectations, hemorrhagic complications were decreased in patients with PTCA treated with a prolonged heparin course, and length of hospitalization was significantly shortened. In contrast, a prolonged heparin course in patients who received stents served only to increase hemorrhagic complications and prolong the duration and cost of hospitalization.

Because of conflicting data regarding the utility of glycoprotein IIb/IIIa inhibitors in AMI<sup>11,13-15</sup> and the desire to minimize attendant costs and complications, wide geographic, hospital-based and operator-specific variabilities exist in the use of these agents in the primary PCI setting. However, previous studies in which excellent outcomes of primary PCI were obtained with unfractionated heparin alone without glycoprotein IIb/IIIa inhibitors (such as those reported in the PAMI and CADILLAC trials) incorporated a 60-hour to 1-week postangioplasty course of intravenous heparin to minimize ischemic complications.<sup>1-9</sup> This practice has never been validated, and whether it is necessary in the era of thienopyridine and stents (which decrease recurrent ischemia) has not been investigated. The results of the present study suggest that a 60-hour routine postprocedure course of heparin may offer value if PTCA alone is performed, but is not necessary, and may be deleterious if the infarct lesion is stabilized by stent implantation.

The 2.6% absolute decrease in ischemic TVR noted in the present study with prolonged heparin is comparable to the 2.4% decrease in TVR rates between the abciximab and no-abciximab groups in the CADILLAC trial.<sup>11</sup> The 4.5% absolute benefit in in-hospital TVR rates in patients with PTCA treated with prolonged heparin is even more notable, with this benefit persisting at 1-year follow-up. It is likely that the modest sample size prevented this finding from reaching statistical significance by univariate or multivariate testing. Parallel to this decrease in TVR, routine postprocedure heparin use in patients after PTCA was associated with absolute decreases of 6.1% in in-hospital MACEs and 8.9% in 1-year MACEs. In contrast, there was no persistent benefit from postprocedure heparin in terms of preventing ischemic TVR in the stent subgroup, and MACE rates were not favorably affected in this cohort.

Contrary to expectation, a routine prolonged postprocedure heparin course in patients after PTCA was associated with fewer hemorrhagic complications and shorter length of stay. It is likely that this effect is merely due to chance because there were only 79 patients in the PTCA group who did not receive postprocedural heparin. It is conjectural that lower bleeding rates in patients with PTCA who received postprocedural heparin may be secondary to fewer in-hos-

Table 4  
Clinical outcomes in balloon angioplasty and stent cohorts

Outcome	Balloon Angioplasty Only		p Value	Stent Implanted		p Value
	Postprocedural Heparin			Postprocedural Heparin		
	Yes (n = 342)	No (n = 79)		Yes (n = 416)	No (n = 139)	
<b>In-hospital events</b>						
Death	0.9%	2.5%	0.24	2.6%	0.7%	0.31
Reinfarction	0.3%	0.0%	1.00	0.5%	1.4%	0.26
Ischemic TVR	4.4%	8.9%	0.15	1.7%	3.6%	0.19
Disabling stroke	0.0%	0.0%	—	0.0%	0.0%	—
MACEs*	5.3%	11.4%	0.069	4.3%	4.3	1.00
Subacute thrombosis	1.2%	2.5%	0.31	1.0%	1.4%	0.64
<b>1-Year events</b>						
Death	3.9%	7.8%	0.14	3.9%	1.5%	0.17
Reinfarction	1.8%	1.3%	0.78	2.3%	2.9%	0.65
Ischemic TVR	19%	24%	0.25	10.5%	10.4%	0.99
Disabling stroke	0.3%	0.0%	0.63	0.3%	0.8%	0.43
MACEs*	22%	31%	0.08	15%	12%	0.55
Subacute thrombosis	1.8%	2.6%	0.64	1.0%	2.2%	0.28

\* Death, reinfarction, ischemia-driven TVR, or disabling stroke.

Table 5  
In-hospital bleeding, thrombocytopenia, length of stay, and cost of hospitalization

Outcome	Postprocedural Heparin		p Value
	Yes (n = 758)	No (n = 218)	
Severe bleeding	0.3%	0.5%	0.53
Moderate bleeding	2.1%	2.8%	0.60
Moderate/severe bleeding	2.4%	3.2%	0.47
Thrombocytopenia	2.2%	2.3%	1.00
Length of stay (h)	92 (70, 125)	90 (69, 145)	0.93
Cost of hospitalization (\$)	11,214 (8,889, 14,422)	11,052 (9,047, 13,790)	0.82
<b>Balloon angioplasty cohort</b>			
No. of patients	342	79	
Severe bleeding	0.3%	1.3%	0.34
Moderate bleeding	2.0%	7.6%	0.02
Moderate/severe bleeding	2.3%	8.9%	0.01
Thrombocytopenia	1.8%	2.5%	0.64
Length of stay (h)	93 (72, 125)	97 (74, 166)	0.07
Cost of hospitalization (\$)	9,628 (8,007, 12,731)	10,111 (7,697, 13,832)	0.58
<b>Stent cohort</b>			
No. of patients	416	139	
Severe bleeding	0.2%	0.0%	1.00
Moderate bleeding	2.2%	0.0%	0.12
Moderate/severe bleeding	2.4%	0.0%	0.07
Thrombocytopenia	2.6%	2.2%	1.00
Length of stay (h)	91 (70, 125)	81 (67, 122)	0.26
Cost of hospitalization (\$)	12,004 (10,149, 15,065)	11,160 (9,593, 13,790)	0.035

pital TVR events (4.4% vs 8.9%) compared with patients with PTCA who did not receive postprocedural heparin. In contrast, recurrent ischemia was rare in patients with stents (in whom thienopyridine was also used in 99% of patients), and postprocedure heparin in this setting served only to increase the rate of hemorrhagic complications, prolong hospitalization, and increase costs.

Before the present report, only 1 study had investigated the role of prolonged heparin use after reperfusion therapy in AMI. Kander et al<sup>16</sup> randomized 50 patients with AMI

who underwent successful pharmacologic or mechanical reperfusion to receive a brief infusion of intravenous heparin for  $\leq 24$  hours or a prolonged infusion for  $\geq 72$  hours. Angioplasty was performed in 20 patients in each group, and 29 received thrombolytic therapy. At 1-week follow-up, 2 documented reocclusions occurred in each group. Significant bleeding complications occurred in no patient after the brief infusion and 6 patients (24%) after the prolonged infusion. The relevance of this trial is limited by its small size, use of preceding thrombolytic therapy,

and its performance before the routine use of stents or thienopyridine.

Our post hoc analysis is subject to selection bias and confounding. Specifically, prolonged heparin use might have been favored for those with suboptimal angiographic results. However, no obvious differences in procedural success rates or angiographic complications were present in patients receiving prolonged heparin versus those receiving it. Second, although the present study is by far the largest investigation to examine the issue of postprocedural heparin after primary PCI, the point estimates for benefit (or lack thereof) would have been narrower had more patients been enrolled. Third, on the basis of the CADILLAC<sup>11,12</sup> and other studies, stents have supplanted balloon angioplasty during primary PCI for AMI, except in small vessels. Although it is likely that recurrent ischemic rates are even greater after PTCA only in small vessels<sup>17</sup> (and thus postprocedural heparin may be of benefit), not enough small vessels were studied in the CADILLAC trial to definitively address this issue. Fourth, subsets of patients who may be most likely to benefit from postprocedural heparin, such as those with cardiogenic shock and severe left ventricular dysfunction, are not well represented in this study. Patients with cardiogenic shock were excluded, and the median left ventricular ejection fraction was 59%. Fifth, our study does not address the role of low-molecular-weight heparin<sup>18,19</sup> or direct thrombin inhibitors<sup>20,21</sup> in the setting of primary PCI.

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