Myocardial Infarction

A Multicenter, Randomized Study of Argatroban Versus Heparin as Adjunct to Tissue Plasminogen Activator (TPA) in Acute Myocardial Infarction: Myocardial Infarction With Novastan and TPA (MINT) Study

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OBJECTIVES	This study examined the effect of a small-molecule, direct thrombin inhibitor, argatroban, on reperfusion induced by tissue plasminogen activator (TPA) in patients with acute myocardial infarction (AMI).
BACKGROUND	Thrombin plays a crucial role in thrombosis and thrombolysis. In vitro and in vivo studies have shown that argatroban has advantages over heparin for the inhibition of clot-bound thrombin and for the enhancement of thrombolysis with TPA.
METHODS	One hundred and twenty-five patients with AMI within 6 h were randomized to heparin, low-dose argatroban or high-dose argatroban in addition to TPA. The primary end point was the rate of thrombolysis in myocardial infarction (TIMI) grade 3 flow at 90 min.
RESULTS	TIMI grade 3 flow was achieved in 42.1% of heparin, 56.8% of low-dose argatroban (p = 0.20 vs. heparin) and 58.7% of high-dose argatroban patients (p = 0.13 vs. heparin). In patients presenting after 3 h, TIMI grade 3 flow was significantly more frequent in high-dose argatroban versus heparin patients: 57.1% versus 20.0% (p = 0.03 vs. heparin). Major bleeding was observed in 10.0% of heparin, and in 2.6% and 4.3% of low-dose and high-dose argatroban patients, respectively. The composite of death, recurrent myocardial infarction, cardiogenic shock or congestive heart failure, revascularization and recurrent ischemia at 30 days occurred in 37.5% of heparin, 32.0% of low-dose argatroban and 25.5% of high-dose argatroban patients (p = 0.23).
CONCLUSIONS	Argatroban, as compared with heparin, appears to enhance reperfusion with TPA in patients with AMI, particularly in those patients with delayed presentation. The incidences of major bleeding and adverse clinical outcome were lower in the patients receiving argatroban. (J Am Coll Cardiol 1999;33:1879–85) © 1999 by the American College of Cardiology

Thrombolytic therapy represents a major advance in the treatment of acute myocardial infarction (AMI) (1). How-ever, current thrombolytic regimens still have significant shortcomings, including: 1) low optimal reperfusion rate (thrombolysis in myocardial infarction [TIMI] grade 3 flow in 54% (2); 2) time delay to reperfusion averaging 45–120 min (3,4); 3) reocclusion of the infarct-related artery after initial successful reperfusion in 5–10%, which is associated with increased mortality (5) and 4) intracranial bleeding in up to 0.9% of patients treated (6,7).

Abbreviations and Acronyms

AMI	=	acute myocardial infarction
aPTT	=	activated partial thromboplastin time
CABG	=	coronary artery bypass graft surgery
CHF	=	congestive heart failure
CPK	=	creatine phosphokinase
cTFC	=	mean corrected TIMI frame count
GUSTO Trial	=	Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries Trial
MI	=	myocardial infarction
MINT Trial	=	Myocardial Infarction with Novastan and TPA Trial
PTCA	=	percutaneous transluminal coronary angioplasty
TIMI	=	thrombolysis in myocardial infarction
TPA	=	tissue plasminogen activator

These problems in thrombolytic therapy appear to be at least partially related to thrombin activity. In the early phase of thrombolysis, the activity of an exogenous thrombolytic agent is counterbalanced by the continuous, endogenous generation of thrombin and by prothrombinase complex formation from a thrombolytic agent, which prevents and delays a successful recanalization. As thrombolysis progresses, the partially lysed thrombus exposes internal fresh thrombin with activation of platelets and generation of fibrin and thrombolytic agents such as tissue plasminogen activator (TPA) and streptokinase activate platelets, leading to rethrombosis and reocclusion. Early effective inhibition of thrombin will shift the balance away from thrombogenesis toward thrombolysis, thereby increasing the recanalization rate and shortening the time delay to reperfusion. In addition, effective thrombin inhibition will also prevent reocclusion after successful thrombolysis by inhibiting platelets.

Heparin may also enhance thrombolysis induced by TPA (8,9). However, heparin is an indirect thrombin inhibitor requiring antithrombin III, and is easily inhibited by acute phase proteins, which are present in AMI. It has been shown to be relatively ineffective for the inhibition of clot-bound thrombin as opposed to free thrombin. Heparin also stimulates platelets and potentiates the effects of various agonists for platelet activation. In addition, it has variable bioavailability with unpredictable effects on activated partial thromboplastin time (aPTT), requiring frequent monitoring, and heparin occasionally induces thrombocytopenia with or without concurrent thrombosis.

Direct thrombin inhibitors, however, have several potential advantages over heparin. They do not require a cofactor to inhibit thrombin, are not inhibited by platelet factor 4 or acute phase proteins and do not activate platelets. They have stable pharmacokinetics, and their effect on the coagulation system is therefore predictable. They do not have the potentially devastating side effect of thrombocytopenia/thrombotic syndrome. In vitro and in vivo studies have shown that these direct thrombin inhibitors are more potent than heparin for the inhibition of thrombin activity (10,11). Despite these theoretical advantages, the direct thrombin inhibitor hirudin failed to show consistent clinical benefit over heparin in patients with acute coronary syndromes (12,13). Another direct thrombin inhibitor, argatroban, has been shown in in vitro experiments to be significantly more potent than hirudin for inhibiting clot-bound thrombin as compared with free thrombin (10,11). A recently completed in vivo study also showed that argatroban, as compared with hirudin, enhances reperfusion with TPA (14). In the rabbit arterial thrombosis model, argatroban, as compared with heparin, improved the reperfusion rate with TPA from 71% to 92% and shortened time delay to reperfusion from 34 to 13 min (15). Furthermore, reocclusion or cyclic flow changes after initial reperfusion were significantly reduced. Argatroban has also been shown to prevent platelet-mediated arterial thrombosis (16,17).

In this study, argatroban was compared with heparin for the enhancement of reperfusion with TPA in patients with AMI.

METHODS

Argatroban. Argatroban, (2R, 4R)-4-methyl-1-[N2-(3-methy-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-1-arginyl]-2-piperidinecarboxylic acid monohydrate, is a small-molecule, synthetic, direct thrombin inhibitor derived from L-arginine that acts by directly and reversibly blocking the active catalytic site of thrombin (18). It has no inhibitory activity against other serine proteases except at concentrations in excess of 100 times those required for thrombin inhibition, and is thus highly selective at clinically useful doses. It inhibits all the physiologic effects of thrombin, including conversion of fibrinogen to fibrin, platelet aggregation and activation of factors V and VIII.

Patient population. Eligible patients included men or nonpregnant women 21 years or older with ischemic chest discomfort lasting at least 30 min with associated ST segment elevation ≥0.2 mV in at least 2 contiguous precordial leads, or at least 0.1 mV ST segment elevation in at least 2 limb leads. The time interval between the onset of chest pain and the initiation of study medication was required to be less than 6 h. Patients considered to be at increased risk of bleeding or with a history of a stroke, hemodynamic instability, recent angioplasty or coronary artery bypass surgery were excluded. Patients who had already received heparin were excluded. The study was approved by the human studies committee from each hospital, and an informed consent was obtained before the enrollment from all patients.

Study design. The Myocardial Infarction with Novastan and TPA (MINT) Trial was a randomized multicenter angiographic trial of 125 patients with AMI who presented within 6 h of pain onset. Patients who met all inclusion and no exclusion criteria were randomized in a single-blind
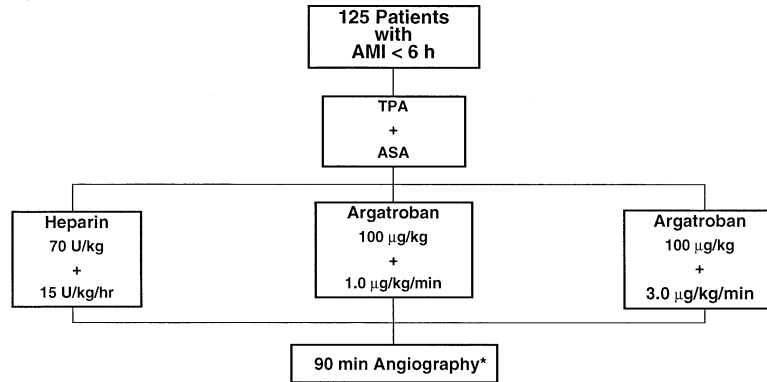
Figure 1. Study design. One hundred twenty-five patients were randomized in a 1:1:1 ratio to heparin, low-dose argatroban and high-dose argatroban therapy. Heparin was administered as a bolus of 70 U/kg over 1 min followed by an infusion of 15 U/kg/h. A bolus of 100 μg/kg of argatroban was given over 1 min followed by an infusion of either 1.0 μg/kg/min or 3.0 μg/kg/min. ASA, aspirin. *TIMI grade 3 flow and corrected TIMI frame count.

fashion to receive either one of two doses of argatroban or heparin as adjunctive therapy to TPA and aspirin (Fig. 1). TPA was given as a front-loaded regimen with 15 mg as a bolus followed by 0.75 mg/kg up to 50 mg over the next 30 min, and followed by 0.5 mg/kg up to 35 mg over the next 60 min. All patients received 160–325 mg aspirin orally within 1 h before the beginning of TPA and each day through the 30-day follow-up. Patients were randomized in a 1:1:1 ratio to receive either low-dose argatroban, high-dose argatroban or heparin therapy. A bolus of 100 μg/kg of argatroban was given over 1 min followed by an infusion of either 1.0 μg/kg/min or 3.0 μg/kg/min. Heparin was administered as a bolus of 70 U/kg over 1 min followed by an infusion of 15 U/kg/h (up to 1,500 U/h). Per protocol, TPA and study drug were to begin within 5 min of each other. After the first 6 h, the dose of study medication was adjusted to maintain an aPTT between 50 and 70 s. Other medications, including morphine, beta-adrenergic blocking agents, nitroglycerin or angiotensin-converting enzyme inhibitors, could be used as required for patient management.

These patients underwent acute cardiac catheterization to assess the TIMI grade flow and the corrected TIMI frame counts (19) of the culprit artery at 90 min after TPA administration. Fifty to 100 μg of intracoronary nitroglycerine was administered before angiography. The first 90-min angiography was performed in the right anterior oblique cranial position for the TIMI frame counting on a 9-in. (22.86 cm) or 11-in. (27.94 cm) screen. The second angiography was performed in the same position on a 5-in. (12.7 cm) or 7-in. (17.78 cm) screen. At least two orthogonal views were used to visualize the infarct-related artery. When the 90-min angiogram showed TIMI grade 0 or 1 flow, a rescue angioplasty was recommended. For TIMI grade 2 flow, the decision for an angioplasty was left to the discretion of the investigator. When angioplasty was performed, argatroban was switched to heparin. In those patients who did not require angioplasty, argatroban/heparin infusion was maintained for 48 to 72 h.

The primary end point of the study was the percentage of patients with the TIMI grade 3 flow, and the secondary end point was the mean corrected TIMI frame count (cTFC) at 90 min. The clinical end point was the composite of death, nonfatal recurrent myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft surgery (CABG), shock/new-onset congestive heart failure (CHF), and recurrent ischemia within 30 days. All angiograms were analyzed by two independent reviewers blinded to patient identification at a central angiographic core laboratory. Major bleeding was defined as intracranial bleeding or bleeding associated with a decrease in hemoglobin $\geq$5 g/dl. A transfusion of one unit of blood was considered equivalent to a 1 g/dl fall in hemoglobin. Recurrent MI within 24 h after infarction was defined as recurrent ischemic pain at rest lasting more than 30 min and associated with new ST segment elevation of at least 0.1 mV in two or more contiguous leads. After 24 h, recurrent MI was diagnosed by either cardiac enzyme or electrocardiographic changes. If prior creatine phosphokinase (CPK) MB was in the normal range, enzymatic evidence of MI was defined as CPK MB above the upper limit of normal and ($\geq$3% of total CPK). If the prior level was above the normal range, CPK MB had to be elevated $\geq$30% above the prior level. Electrocardiographic evidence of reinfarction was defined as new significant Q wave (>0.04 s duration or a depth greater than one fourth of the corresponding R wave) in two or more contiguous leads.

Statistical analysis. Data were analyzed using the intention to treat approach. A p value <0.05 was considered statistically significant. The comparability of the three treatment groups was determined for the demographic and baseline variables. Treatment differences for categorical variables measured on a nominal scale (e.g., gender) were analyzed using the Fisher exact test. Continuous variables (e.g., age) were analyzed using analysis of variance (ANOVA) with effects for treatment. For the achievement

Table 1. Baseline Characteristics

Groups	Heparin	Low-dose Argatroban	High-dose Argatroban	p Value
Patients	40	38	47	
Age (yrs)	60 ± 1.5	59 ± 1.7	56 ± 1.8	0.17
Male (%)	82.5	73.7	85.1	0.40
Weight (kg)	78.5 ± 2.2	80.7 ± 2.3	81.5 ± 2.1	0.60
SBP (mm Hg)	135 ± 3	135 ± 4	135 ± 3	0.98
HR (beats/min)	76 ± 2	80 ± 2	75 ± 2	0.16
Time delay to TPA from pain onset (h)	2.7 ± 0.2	3.0 ± 0.2	3.1 ± 0.2	0.30
Culprit vessel				0.61
LAD	11	12	11	
RCA	18	15	28	
LCX	7	8	5	
Ramus	2	2	2	

Values are expressed as mean ± SEM.

HR = heart rate; LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery; SBP = systolic blood pressure; TPA = tissue-type plasminogen activator.

of TIMI grade 3 flow at 90 min, the occurrence of an "adverse outcome" within 30 days and the incidence of major and minor bleeding, the normal approximation test (two-sided) was used to compare each argatroban dose with heparin. Corrected frame counts were analyzed using the Kruskall-Wallis test. If the overall effect for treatment was significant (p < 0.05), tests comparing each argatroban dose to heparin were performed.

RESULTS

A total of 125 patients were enrolled by 27 (11 U.S., 14 Argentine, 2 Brazilian) investigators in three countries (see Appendix). Four patients did not have 90-min TIMI flow grade measured: one patient in the high-dose argatroban group died before the 90-min angiography and one patient in the low-dose argatroban group had normal coronary angiogram. Two films belonging to the heparin group could not be found. The baseline characteristics of the patients are shown in Table 1. Age, gender distribution, weight and hemodynamic status were comparable among the groups. The time delay from the pain onset to the administration of TPA was 2.7 ± 0.2 h in the heparin group, 3.0 ± 0.2 h in the low-dose argatroban group and 3.1 ± 0.2 h in the high-dose argatroban group. No significant difference was observed in the distribution of the infarct-related artery among the groups.

The results of TIMI grade 3 flow at 90 min are shown in Figure 2. TIMI grade 3 flow was observed in 42.1% (16/38) of patients randomized to heparin, 56.8% (21/37) of those with low-dose argatroban (p = 0.20 vs. heparin) and 58.7% (27/46) of those with high-dose argatroban (p = 0.13 vs. heparin). Although the differences did not reach a statistically significant level, this represents a 39% relative improvement of TIMI grade 3 flow in the high-dose argatroban patients as compared with heparin patients. No

significant difference was observed in the combined TIMI grade 2 and 3 flow between the groups: 81.6% (31/38) in the heparin group, 78.4% (29/37) in the low-dose argatroban group and 78.3% (36/46) in the high-dose argatroban group. When the patients were divided depending on the time delay from the pain onset, no significant difference was observed between heparin and either argatroban groups in TIMI grade 3 flow for patients presented within the first 3 h: 56.5% (13/23) of heparin patients, 61.9% (13/21) of low-dose argatroban and 58.3% (14/24) of high-dose argatroban patients (p > 0.7). However, for the patients who presented late, between 3 and 6 h from the pain onset, TIMI grade 3 flow was achieved significantly more frequently in the high-dose argatroban group as compared with the heparin group: 20.0% (3/15) of heparin, 50.0% (8/16) of low-dose argatroban and 57.1% (12/21) of high-dose argatroban patients (p = 0.03 vs. heparin) (Fig. 3). Of note, the total number of patients with delayed presentation was small (52 patients).

The corrected TIMI frame count was 39.0 ± 4.6 (mean ± SEM) in the heparin group, 30.4 ± 3.4 in the
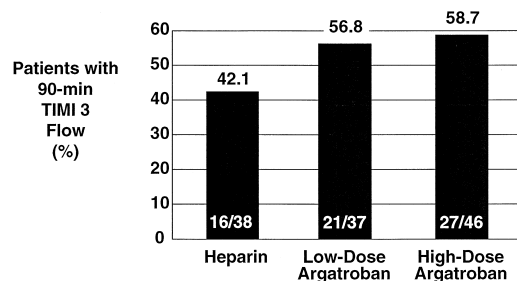

Figure 2. TIMI grade 3 flow at 90 min. TIMI grade 3 flow was observed in 42.1% (16/38) of heparin patients, 56.8% (21/37) of low-dose argatroban (p = 0.20 vs. heparin) and 58.7% (27/46) of high-dose argatroban patients (p = 0.13 vs. heparin patients).
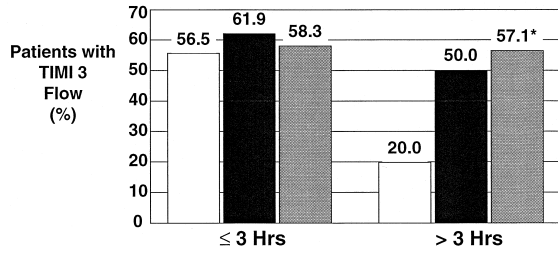
Figure 3. TIMI grade 3 flow at 90 min in patients presented ≤3 h and >3 h. For the patients who presented late, between 3 and 6 h from the pain onset, TIMI grade 3 flow was achieved significantly more frequently in the high-dose argatroban group as compared with the heparin group: 20.0% of heparin, 50.0% of low-dose argatroban and 57.1% of high-dose argatroban patients (p = 0.03 vs. heparin). **White bars,** heparin; **black bars,** low-dose argatroban; **gray bars,** high-dose argatroban.

Table 2. Adverse Clinical Outcome at 30 Days

Groups	Heparin	Low-dose Argatroban	High-dose Argatroban
Patients	40	38	47
Death	3 (8%)	3 (8%)	2 (4%)
Reinfarction	2 (5%)	0	1 (2%)
Shock	3 (8%)	1 (3%)	0
CHF	3 (8%)	2 (5%)	1 (2%)
PTCA	7 (18%)	5 (13%)	6 (13%)
CABG	1 (3%)	2 (5%)	2 (4%)
Recurrent ischemia	3 (8%)	2 (5%)	1 (2%)
Composite	15 (37.5%)	12 (31.6%)	12 (25.5%)

CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

low-dose argatroban and 28.0 ± 2.4 in the high-dose argatroban group. There was no significant difference among the treatment groups (p = 0.19). The cTFC showed the same pattern: in those with early presentation, cTFC was 30.9 ± 3.7 (mean ± SEM) in the heparin, 28.3 ± 4.7 in the low-dose argatroban and 29.9 ± 3.6 in the high-dose argatroban group. There was no significant difference among the treatment groups (p = 0.74). In those patients with late presentation, between 3 and 6 h from the pain onset, mean cTFC was significantly lower in the high-dose argatroban group as compared with the heparin group: 54.4 ± 9.7 in the heparin group, 32.9 ± 4.9 in the low-dose argatroban and 26.6 ± 3.2 in the high-dose argatroban group (p = 0.01 vs. heparin).

Major bleeding was observed in 10.0% (4/40) of heparin patients, 2.6% (1/38) of low-dose argatroban (p = 0.18 vs. heparin) and 4.3% (2/47) of high-dose argatroban patients (p = 0.29 vs. heparin). The rate of minor bleeding was 67.5% (27/40) in the heparin group, 65.8% (25/38) in the low-dose argatroban group and 55.3% (26/47) in the high-dose argatroban group (p = 0.25 vs. heparin). Although not statistically significant, the combined incidence of major and minor bleeding was lower in high-dose argatroban patients as compared with heparin patients: 59.6% versus 77.5% (p = 0.07).

The median (range) aPTT 6 h after the start of bolus was 100 (32 to 300) s in the heparin group, 55.5 (28 to 126) s in the low-dose argatroban group and 75 (28 to 180) s in the high-dose argatroban group. At 12 h, aPTT was 65.1 (22 to 129.4), 50 (32.4 to 150) and 77 (44 to 180) s, respectively. The median (range) peak CPK level was 1,071 (52 to 10,566) U/L in the heparin group, 1,073 (78 to 4,992) U/L in the low-dose argatroban group and 1,515 (118–7,003) U/L in the high-dose argatroban group.

This study was not powered by design to show significant clinical benefit. However, the incidence of composite end point of death, recurrent MI, shock/heart failure, revascularization and recurrent ischemia at 30 days was highest in the heparin group and lowest in the high-dose argatroban group (Table 2): 37.5% (15/40) in the heparin group, 31.6% (12/38) in the low-dose argatroban group and 25.5% (12/47) in the high-dose argatroban group (p = 0.23).

DISCUSSION

Despite theoretical advantages, recent studies failed to show a consistent clinical benefit of hirudin over heparin in patients with acute coronary syndromes (12,13). However, another direct thrombin inhibitor, hirulog, showed a significant benefit over heparin in patients with AMI (20,21), indicating that any benefits of direct thrombin inhibitors may be agent specific, and "thrombin hypothesis" may still need to be properly tested.

Argatroban-treated patients demonstrated a trend towards improved TIMI grade 3 flow as compared with those treated with heparin, in combination with TPA and aspirin. Although there was a trend showing argatroban is associated with lower incidence of adverse clinical outcome and major bleeding complication, these findings should be interpreted with caution, because the study was not powered to demonstrate clinical benefit. Considering the safety profile of argatroban, it is conceivable that the efficacy could have been more marked, had a higher dose been used. The doses of 1.0 and 3.0 µg/kg/min were chosen on the basis of a pilot experience, which showed prolongation of aPTT to 1.5 and 2.0 times the baseline at steady state (12 h), respectively (data on file; Texas Biotechnology Corporation, Houston, Texas). These relatively low doses were selected in order to maintain an aPTT below 90 s based on the experience with the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries Trial (GUSTO) IIa (22) and TIMI 9A (23) Trials. These two doses provide an opportunity not only to evaluate the dose-response effect of argatroban with TPA in acute MI, but also to prove the existence of the "thrombin paradox" (24). In previous studies using hirudin and hirulog, there were suggestions that a low-dose, direct thrombin inhibitor may be more effective than a high dose (20,25), which can be explained by preservation of thrombomodulin and protein C pathway (24). Seeing clear dose-response efficacy results, the doses

chosen in the study were still on the up slope of the dose-response curve, and better efficacy can probably be expected with a higher dose. One may be concerned with further prolongation of the aPTT and consequent increased bleeding risk at higher doses. However, as shown in this study, the current doses appear to be safe despite prolongation of aPTT up to 77 s. In the Hirulog Early Reperfusion/Occlusion (HERO) study (21), the dose of hirulog that prolonged aPTT over 90 s was not associated with increased risk for bleeding. These findings suggest that aPTT may not be a good parameter to predict bleeding, when these short-acting direct thrombin inhibitors are used.

An intriguing observation is that argatroban did not lose its efficacy in patients with delayed presentation (between 3 and 6 h from the pain onset), which indicates that the small-molecule, direct thrombin inhibitor may still be effective even when a thrombus is partially organized. This is in contrast to another recently published study, which demonstrated the lower efficacy of hirulog in combination with streptokinase in patients presenting between 3 and 6 h as compared with those presenting within the first 3 h (22). This difference may be explained by the ability of argatroban to inhibit clot-bound thrombin more effectively than other thrombin inhibitors. A short time delay between TPA and argatroban administration, as compared with other studies with direct thrombin inhibitors in which there was a significant time delay between lytic agent and a thrombin inhibitor, might have contributed to the persistent benefit. In any case, this result should be interpreted with caution, because this was a post hoc analysis based on a small sample size.

Although argatroban appears to be better than heparin as an adjunct to TPA, the difference of 16.6% in TIMI grade 3 flow at 90 min may not be sufficient to expect significant clinical benefit. It was shown that an approximately 25% increase in TIMI grade 3 flow is required to achieve the absolute mortality reduction by 1% (4). Several approaches can be considered to further improve the efficacy. One is to increase the dose of argatroban considering its safety profile. A second approach is to add a glycoprotein IIb/IIIa receptor antagonist to a thrombolytic agent as it is being actively evaluated (Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-Acute Myocardial Infarction [IMPACT-AMI], TIMI 14 and Strategies for Patency Enhancement in the Emergency Department [SPEED]). Another potential approach would be the combination of TPA, argatroban and glycoprotein IIb/IIIa receptor antagonist. If the trend toward better safety profile is confirmed in larger trials, argatroban may be the preferred thrombin inhibitor for this triple combination.

In summary, argatroban, as compared with heparin, appears to improve reperfusion with TPA in patients with AMI. Argatroban does not lose its efficacy in patients with delayed presentation. The incidences of major bleeding and adverse clinical outcome were lower in the patients treated with argatroban. These promising results need confirmation in a larger clinical trial.

APPENDIX

REFERENCES

1. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? [Editorial] Circulation 1989;79:441–4.
2. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–22.
3. Neuhaus K-L, von Essen R, Tebbe U, et al. Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: results of the rt-PA-APSAC Patency Study (TAPS). J Am Coll Cardiol 1992;19:885–91.
4. Cannon CP, McCabe CH, Diver DJ, et al. Comparison of front-loaded recombinant tissue-type plasminogen activator, antistreplase and combination thrombolytic therapy for acute myocardial infarction: results of the Thrombolysis is Myocardial Infarction (TIMI) 4 Trial. J Am Coll Cardiol 1994;24:1602–10.
5. Ohman EM, Califf RM, Topol EF, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. Circulation 1990;82:781–91.
6. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;1:397–402.
7. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.
8. Hsia J, Hamilton WP, Kleiman N, et al. A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1990;323:1433–7.
9. Bleich SD, Nichols TC, Schumacher RR, et al. Effect of heparin on coronary arterial patency after thrombolysis with tissue plasminogen activator in acute myocardial infarction. Am J Cardiol 1990;66:1412–7.
10. Berry CN, Girardot C, Lecoffre C, Lunven C. Effects of the synthetic thrombin inhibitor argatroban on fibrin- or clot-incorporated thrombin: comparison with heparin and recombinant hirudin. Throm Haemost 1994;72:381–6.
11. Lunven C, Gauffeny C, Lecoffre C, et al. Inhibition by argatroban, a specific thrombin inhibitor, of platelet activation by fibrin clot-associated thrombin. Thromb Haemost 1996;75:455–8.
12. GUSTO IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775–82.
13. Antman EM for the TIMI 9B Investigators. Hirudin in acute myocardial infarction. Thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. Circulation 1996;94:911–21.
14. Boeve TJ, Reed GL, Carias de Oliveria N, et al. Comparison of argatroban and hirudin for the reperfusion of thrombotic arterial occlusion by tissue plasminogen activator. J Thromb Thrombol 1998;5:103–8.
15. Jang IK, Gold HK, Leinbach RC, et al. In vivo thrombin inhibition enhances and sustains arterial recanalization with recombinant tissue-type plasminogen activator. Circ Res 1990;67:1552–61.
16. Jang IK, Gold HK, Ziskind AA, et al. Prevention of platelet-rich arterial thrombosis by thrombin inhibition. Circulation 1990;81:219–25.
17. Jang IK, Gold HK, Leinbach RC, et al. Persistent inhibition of arterial thrombosis by a one hour intravenous infusion of argatroban, a selective thrombin inhibitor. Coron Artery Dis 1992;3:407–14.
18. Kikumoto R, Tamao Y, Tezuka T, et al. Selective inhibition of thrombin by (2R, 4R)-4 methyl-1-[N2-(3-methy-1,2,3,4-tetrahydro-8-quinolinesulfony)-1-arginyl]-2-piperidinecarboxylic acid. Biochemistry 1984;23:85–90.
19. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count. A quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
20. Theroux P, Perez-Villa F, Waters D, Lesperance J, et al. Randomized double-blind comparison of two doses of hirulog with heparin as adjunctive therapy to streptokinase to promote early patency of the infarct-related artery in acute myocardial infarction. Circulation 1995;91:2132–9.
21. White HD, Aylward PE, Frey MJ, et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Circulation 1997;96:2155–61.
22. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. A randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. Circulation 1994;90:1631–7.
23. Antman EM, for the TIMI 9A investigators. Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. Circulation 1994;90:1624–30.
24. Griffin JH. Blood coagulation: the thrombin paradox. Nature 1995;378:337–8.
25. Topol EJ, Fuster V, Harrington RA, et al. Recombinant hirudin for unstable angina pectoris. A multicenter, randomized angiographic trial. Circulation 1994;89:1557–66.