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Antithrombotic Therapy After Myocardial Reperfusion in Acute Myocardial Infarction

VALENTIN FUSTER, MD, FACC, BERNARDO STEIN, MD, LINA BADIMON, PHD, JAMES H. CHESEBRO, MD, FACC*

New York, New York and Rochester, Minnesota

The problem of post-thrombolytic reocclusion can be approached in several ways. 1) Better thrombolytic agents with longer duration of effects and more powerful properties aimed at enhanced clot lysis and anticoagulation are under study. 2) The combination of high dose heparin and low dose aspirin is proposed for all patients with an acute myocardial infarction treated with thrombolytic agents. 3) Peptide inhibitors of thrombin and monoclonal antibodies against platelet glycoprotein receptors and adhesive macromolecules are potentially effective inhibitors of platelet aggregation and thrombus formation during or after thrombolytic therapy.

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One of the most exciting and challenging fields in cardiology over the last few years has been the development of short-term interventions aimed at achieving myocardial reperfusion in patients with acute infarction. Reperfusion can be accomplished pharmacologically with the use of thrombolytic drugs, and mechanically with balloon angioplasty or coronary artery bypass surgery. Thrombolytic therapy has clear advantages over the other two forms of therapy in that it can be administered promptly after the presentation of the patient with acute myocardial infarction, given intravenously and instituted in community hospitals without the need for immediate cardiac catheterization.

One of the problems associated with thrombolysis has been the development of acute coronary reocclusion, which is associated with further myocardial ischemia, extension of infarction and an increased mortality. Over the last 2 years, we have learned a great deal about the causes of reocclusion, and intensive research is now being focused on the development of thrombolytic drugs with associated anticoagulant properties and on more powerful antithrombotic agents. We will analyze 1) the processes of platelet activation and thrombus formation during acute myocardial infarction, 2) the pathophysiologic events that follow thrombolysis and predispose to coronary reocclusion, and 3) future antithrombotic approaches in the prevention of reocclusion.

From the Division of Cardiology, Mount Sinai School of Medicine, New York, New York and the *Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota.

Address for reprints: Valentin Fuster, MD, Division of Cardiology Box 1030, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, New York 10029.

Platelet Activation and Thrombus Formation During Acute Myocardial Infarction

Recent clinical, pathologic and experimental observations have improved our understanding of the pathogenesis of acute coronary syndromes. Postmortem studies (1,2) have demonstrated the presence of atherosclerotic plaque rupture or fissuring with secondary thrombus formation in the majority of fatal cases of unstable angina, myocardial infarction and ischemic sudden death.

Consequences of plaque rupture. After deep vessel wall injury, such as occurs during plaque rupture, fibrillar collagen (particularly type I) is exposed to the circulation. Exposed collagen is a strong stimulus for platelet aggregation and thrombus formation. Experimentally, when type I collagen is exposed to flowing blood in the perfusion chamber designed in our laboratory by Badimon et al. (3), marked platelet deposition occurs. In addition, platelet deposition increases when blood flow is exposed to higher shear rates, similar to those found in coronary stenoses. The platelet thrombus eventually occludes the vessel lumen and is not removed by high blood flow (Fig. 1). This experiment mimics the hemorrheologic conditions that occur during plaque rupture, where exposed collagen and high shear rates promote platelet activation and the rapid growth of platelet thrombi. The deceleration of blood flow that occurs in the poststenotic area produces flow separation and recirculation zones that promote the deposition of fibrin. This leads to the formation of a fixed platelet thrombus in the area of luminal stenosis and a large meshwork of fibrin and trapped red blood cells in the poststenotic area (4). These findings are

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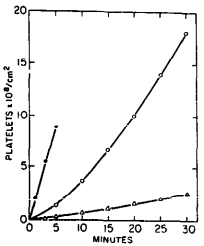


Figure 1. Platelet deposition on type I collagen (which resembles collagen exposed during deep vessel injury) versus exposure time at different shear rates (in seconds^{-1}) solid circles = 3,380; open circles = 1,690; triangles = 212. Note that platelet deposition increases progressively with time and there is no loss of platelets even at high shear rates, which suggests that the thrombus is fixed. (Reprinted with permission from Badimon et al. [3] and the American Heart Association, Inc.)

clinically relevant in the context of the pathogenesis of Q wave myocardial infarction. In these patients, plaque rupture leads to the exposure of vessel wall collagen and to an increase in shear rate, both of which favor the formation of a fixed and occlusive thrombus (5).

Processes by which platelets and clotting factors are activated. After plaque injury, exposed collagen, in addition to other mediators, induces platelet aggregation. Most platelet agonists seem to act through the hydrolysis of platelet membrane phosphatidylinositol by phospholipase C, which results in the mobilization of calcium from the platelet dense tubular system. Calcium, in turn, is an important mediator of platelet activation, which can occur by means of three metabolic pathways: thrombin/collagen-dependent, adenosine diphosphate (ADP)-dependent and arachidonate-dependent (6) (Fig. 2).

In the first pathway, exposed collagen from the vessel wall and thrombin generated by the activation of the coagulation cascade are powerful and independent platelet activators, perhaps through the release of a "platelet-activating factor." The second pathway is mediated by ADP, which may be released from hemolyzed red cells in the area of vessel injury. This agonist stimulates the discharge of calcium from the platelet dense tubular system and promotes the contraction of the platelet, with the subsequent release of its granule contents. Released ADP and serotonin stimulate adjacent platelets, further enhancing the process of platelet activation. Finally, the third pathway is mediated by arachidonate, which is released from the platelet membrane by the stimulatory activity of collagen, thrombin, ADP and serotonin. Arachidonate is converted to thromboxane A_2 by the sequential action of cyclooxygenase and thromboxane synthetase. Thromboxane A_2 not only promotes further platelet aggregation, but also is a potent vasoconstrictor.

Any or all of these three pathways induce the contraction of the platelet, with the subsequent exposure of platelet receptors, namely, the glycoprotein IIb-IIIa (7). Adhesive macromolecules including fibrinogen, von Willebrand factor,

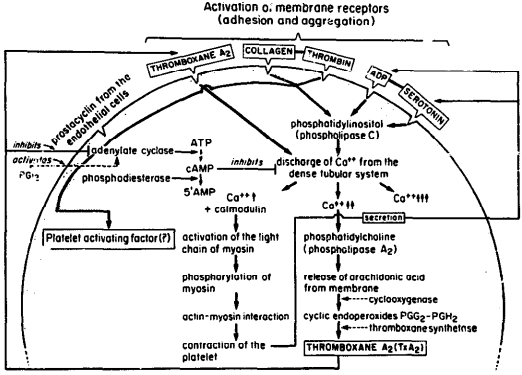
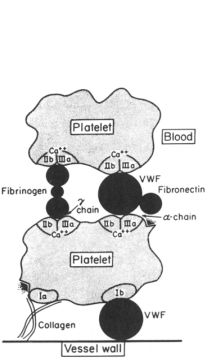
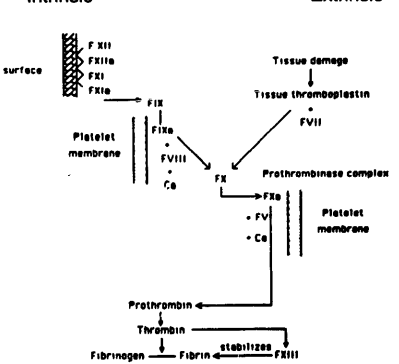


Figure 2. Mechanisms of platelet activation. Most platelet agonists stimulate the mobilization of calcium from the dense tubular system. Calcium is an important mediator of platelet activation, which occurs by means of three metabolic pathways dependent on thrombin-collagen, adenosine diphosphate (ADP) and arachidonate. Cyclic adenosine monophosphate (AMP) inhibits calcium mobilization. Thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) have opposite effects on adenyl cyclase and the level of cAMP. Note that thrombin and collagen can independently activate platelets probably by means of a platelet activating factor (see text). ATP = adenosine triphosphate.





and possibly fibronectin bind to glycoprotein IIb-IIIa and form bridges between neighboring platelets (6,7), thereby playing an essential role in the process of platelet aggregation (Fig. 3).

Activation of clotting mechanism. During plaque rupture, in addition to platelet deposition in the injured area, the clotting mechanism is activated by the exposure of the deendothelialized vascular surface (intrinsic pathway) and the release of tissue factor (extrinsic pathway) (Fig. 3). The activation of the coagulation cascade leads to the generation of thrombin which, as mentioned before, is a powerful platelet activator that also catalyzes the formation and polymerization of fibrin. Fibrin is essential in the stabilization of the platelet thrombus and allows it to resist removal by high intravascular pressure and shear rate. These basic concepts have clinical relevance in the context of myocardial infarction, where plaque rupture exposes collagen, which activates platelets and the coagulation system and results in the formation of a fixed and occlusive platelet/fibrin thrombus.

Coronary Reocclusion After Thrombolysis

The goal of thrombolytic therapy is to restore myocardial perfusion through a previously occluded vessel in the shortest possible time to prevent or limit myocardial necrosis. The ideal thrombolytic agent would produce the highest rate of reperfusion and the lowest incidence of complications, namely, bleeding and rethrombosis (8). We will analyze the pathogenetic mechanisms underlying rethrombosis after thrombolysis.

The incidence of rethrombosis after successful coronary thrombolysis is approximately 5 to 20% (9). To date, two

Figure 3. Left, Scheme of the binding of adhesive macromolecules to platelet membrane glycoproteins. Fibrinogen binds to the glycoprotein IIb-IIIa–Ca^{++} complex (gamma chain) constituting the essential reaction in platelet aggregation. Von Willebrand factor (VWF) can either bind to glycoprotein Ib or IIb-IIIa–Ca^{++} complex (alpha chain) in association with fibronectin, thus contributing to both platelet adhesion and aggregation. Collagen may bind to glycoprotein Ia and possibly participate in the process of adhesion. **Right,** Scheme of the biochemical activation of the coagulation system. F = factor. (Modified from Davis JA, McNichol G. Haemostasis and thrombosis. In: Weatherall DJ, Ledingham JEE, Warell DA, eds. *Oxford Textbook of Medicine*. Oxford, New York. Oxford Press, 1983:19.)

main contributing factors for the development of rethrombosis have been identified: 1) altered hemorrheologic conditions associated with the persistent luminal stenosis caused by the residual thrombus (10), and 2) persistence of a strong thrombogenic stimulus caused by the residual thrombus itself.

Residual luminal stenosis. To investigate the altered hemorrheology seen in cases of significant coronary stenosis, we used the perfusion chamber mentioned previously (3), in which we exposed arterial blood from a pig's carotid artery to different substrates and at different degrees of wall shear rate and luminal stenosis. Using stripped tunica media as the exposure substrate and allowing the arterial blood to circulate through conduits with different degrees of luminal stenosis, we were able to demonstrate a marked increment in platelet deposition when higher degrees of stenosis were used (Fig. 4) (5,11). The reason for this phenomenon is that, in a system with a mild obstruction to flow, the shear rate, which is the difference in fluid velocity (or gradient) between

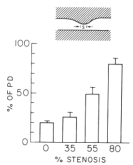


Figure 4. Using the perfusion chamber, blood from the carotid artery of pigs was exposed to injured arterial tissue at various degrees of eccentric stenosis. The percent of platelets deposited (PD) at the peak area of stenosis (S) was compared with the total platelets deposited in the exposed tissue. Note the significant increase in deposited platelets at higher degrees of luminal stenosis. (Reproduced with permission from Fuster et al. [5] and the American Heart Association, Inc.)

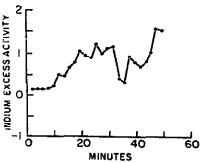


Figure 5. Using the same model as in Figure 4, a continuous scintigraphic image of the events that occurred during perfusion of an area with 80% stenosis. The ordinate corresponds to the peak area of stenosis and is expressed as indium-111 excess activity with respect to blood. Note that at 30 min of perfusion, there is an abrupt decrease in indium counts followed by a rapid increase. This suggests spontaneous thrombolysis or platelet disaggregation followed by massive platelet deposition in the affected area (see text). (Reproduced with permission from Fuster et al. [5] and the American Heart Association, Inc.)

the center and the periphery of the circulating mass, is low. However, with higher degrees of stenosis, the shear rate is markedly increased. This facilitates the interaction of platelets and the vessel wall and promotes platelet deposition on the exposed surface (12). In addition, it appears that under high shear rate conditions, red blood cells contribute to the delivery of platelets to the injured area by forcing them to travel in the periphery of the circulating mass (12).

The prognostic importance of residual stenosis after thrombolysis has been clearly demonstrated by a number of clinical studies (13–17). A residual stenosis >75% luminal diameter (13) or a cross-sectional area <0.4 mm^2 (14) was associated with an increased risk of early rethrombosis. Furthermore, Badger et al. (15) showed that a residual luminal diameter <0.6 mm or a Thrombolysis in Myocardial Infarction (TIMI) perfusion grade 1 or 2 (partial perfusion) (18) was associated with higher angiographic reocclusion at 5 weeks and a higher 1 year mortality rate. These clinical observations are supported by data from our laboratory (3,11), which show that higher degrees of luminal stenosis and higher shear rates are both associated with increased platelet deposition and thrombus formation (Fig. 1 and 4).

Thrombogenicity of the residual thrombus. With regard to the persistence of a thrombogenic stimulus after lytic therapy, we have found that the presence of a residual thrombus, which is common after thrombolysis (10), is one of the most powerful thrombogenic surfaces ever encountered in the laboratory. In the ex vivo model using the perfusion chamber, we measured the degree of deposition of indium-111–labeled platelets on stripped tunica media exposed to different degrees of stenosis (Fig. 5) (11). When the stenosis was severe (80% of luminal diameter), platelet deposition increased with time as a result of the increased shear rate. After 30 min of perfusion, platelet deposition and associated fibrin formation abruptly decreased, probably because of spontaneous thrombolysis or platelet disaggregation. This was followed immediately by a rapid increase in platelet deposition in the affected area, which suggests that the thrombus that remains after spontaneous lysis or platelet disaggregation is markedly thrombogenic and stimulates the massive deposition of platelets on its surface (5). With continued perfusion, a recurrent cycle of platelet disaggregation followed by massive platelet deposition was observed. This finding is supported by clinical studies (13,19) that have shown an increased risk of rethrombosis when a residual thrombus is seen angiographically after thrombolysis as compared with cases without evidence of a residual thrombus.

There have been recent provocative experimental and clinical studies (20–24) that have suggested an increase in platelet activation and thrombin activity after the administration of streptokinase or recombinant tissue plasminogen activator (rt-PA). Fitzgerald et al. (20) observed a marked elevation in plasma and urinary metabolites of thromboxane A_2 after the administration of streptokinase in patients with acute myocardial infarction. This effect was not seen in patients pretreated with aspirin. In another study, Eisenberg et al. (21) showed an increase in fibrinopeptide A (which is released by the action of thrombin on fibrinogen) immediately after thrombolytic therapy with streptokinase in patients with acute myocardial infarction. Although these elegant studies suggest a direct stimulatory effect of streptokinase on platelet and thrombin activity, their conclusions must be interpreted with caution. We believe that these prothrombotic events seen after thrombolysis may reflect the powerful thrombogenic effects exerted by the residual thrombus on both platelets (11) and thrombin activity (25) and by the altered hemorrheologic conditions, as described earlier. The clinical implications of the studies just mentioned in terms of post-thrombolysis reperfusion and rethrombosis remain to be defined.

Antithrombotic Therapy After Thrombolysis

After the preceding discussion on the potential factors that lead to rethrombosis, an important question remains. What is the best antithrombotic approach for preventing reocclusion? As we stated before, in spite of high rates of reperfusion achieved with different thrombolytic agents, the incidence rate of acute reocclusion is about 5 to 20%, and it occurs even in patients on full anticoagulant therapy (26). Active research is being done to develop a better antithrombotic regimen that will be able to reduce the rate of rethrombosis and its associated morbidity and mortality. New approaches in the prevention of reocclusion include 1) improvement in thrombolytic agents, 2) use of currently available antithrombotic drugs, and 3) peptide inhibitors of thrombin and monoclonal antibodies directed against platelet receptors and adhesive macromolecules.

Improvement in thrombolytic agents. Currently available thrombolytic agents act directly or indirectly as activators of plasminogen (8). These agents are streptokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), urokinase, rt-PA and recombinant single chain urokinase plasminogen activator (scu-PA). These compounds have different pharmacologic properties and hematologic effects. Although they are associated with a high (60 to 70%) rate of reperfusion if used early after myocardial infarction, the failure rate in terms of clot lysis is still between 20 and 40% (8).

One approach for the prevention of reocclusion is the use of drugs that produce a long proteolytic state. An agent that offers certain advantages over the others is APSAC because it can be administered as an intravenous bolus, has a long half-life and is associated with a lower rate of rethrombosis (about 10%), perhaps owing to its long duration of action (9,27,28). Moreover, a recent large randomized double-blind placebo-controlled trial of APSAC in acute myocardial infarction (29) showed a remarkable 47% reduction in the 30 day mortality rate, which was maintained in the 1 year follow-up study. Alternatively, a prolonged maintenance infusion of rt-PA (for an additional 4 to 6 h) has been used in an attempt to reduce the reocclusion rate, but the results are controversial and the number of patients studied is small (30,31).

A second approach to preventing reocclusion is focused on the development of more effective thrombolytic agents that can achieve enhanced clot lysis and vessel patency. A method that is evolving is the use of synergistic combinations of thrombolytic agents with different mechanisms of fibrin specificity, such as rt-PA and scu-PA (32).

A third approach is the development of long-acting lytic agents that also create an antithrombotic environment in the area of the residual thrombus. In fact, streptokinase, which is not as fibrin-specific as rt-PA, causes fibrinogenolysis with the associated production of fibrinogen degradation products. As a result of these effects, platelet aggregation is impaired (fibrinogen is necessary for normal platelet aggregation) and the degradation products have anticoagulant and polymerization-inhibiting activities (9). The benefits and risks of the use of long-acting lytic agents with strong antithrombotic properties need to be explored further.

Currently available antithrombotic agents. As mentioned earlier in this report, platelet activation in the area of clot lysis, which is secondary to altered hemodynamics and high shear rates and to the exposure of a residual thrombogenic surface, is an important contributor to thrombus formation and vessel occlusion (8). Therefore, platelet inhibitors may play a role in the prevention of reocclusion (5). Compelling data come from the recently completed Second International Study of Infarct Survival (ISIS-2) trial (33). In this study, more than 17,000 patients with suspected acute myocardial infarction were randomized to aspirin or intravenous streptokinase, the combination of both or placebo within 24 h of the onset of symptoms. This impressive study showed a reduction in 5 week vascular mortality rate of 23% in the aspirin-treated group, 25% in the streptokinase-treated group and 42% in patients treated with both agents. Aspirin probably acts by preventing rethrombosis after spontaneous or streptokinase-induced vessel reperfusion. It is also of interest that streptokinase was effective even when given after 6 h and up to 24 h from the onset of symptoms, although its maximal effectiveness was obtained when given in the first 3 h after the onset of infarction. Although the explanation for this finding is only speculative, the generalized fibrinogenolytic and antithrombotic effects of streptokinase may contribute to the maintenance of vessel patency and the prevention of reocclusion (34). In addition, the reduction in blood viscosity induced by streptokinase (35) may improve coronary blood flow and thus limit the extent of myocardial necrosis. Two smaller studies (36,37) have shown a reduction in early rethrombosis after streptokinase administration with the use of aspirin alone or in combination with dipyridamole.

With regard to anticoagulation, we recommend systemic heparinization in all patients undergoing thrombolysis. In the study by Guerci et al. (38), a low incidence rate (<6%) of recurrent ischemia was found in patients who received rt-PA for acute myocardial infarction. This low incidence of early ischemia was possibly a result of adjunctive therapy with high dose heparin, aimed at an activated partial thromboplastin time of two to three times control, which may prevent reocclusion by inhibiting thrombin activity. Moreover, in a group of patients treated with streptokinase and maintained on heparin therapy, recurrent ischemia was observed shortly after the discontinuation of heparin (39). The benefits of heparin are supported experimentally (40) in a pig model of deep arterial injury, in which we found an inverse relation between platelet deposition and the dose of heparin used.

On the basis of these data and while awaiting the completion of two large trials (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico [GISSI]-2 and ISIS-3), we recommend the use of a high dose intravenous bolus

of heparin (100 U/kg) after thrombolysis, followed by a maintenance infusion of about 1,000 U/h for approximately 5 days (aimed at an activated partial thromboplastin time of 2 to 2.5 times control). This regimen may be followed by subcutaneous administration of heparin at a dose of about 10,000 U twice daily. In addition, we recommend concomitant therapy with aspirin at a dose of 80 mg/day. Such a low dose is recommended to reduce the risk of gastrointestinal bleeding. If revascularization is not done, the patient can be discharged on aspirin therapy (160 to 325 mg/day) if he or she is at low risk for recurrent thrombotic events. This risk can be assessed by certain clinical and angiographic variables that include the patency of the infarct-related artery, the presence or absence of a residual thombus or the early recurrence of ischemia. High risk patients may benefit from a short-term (4 to 6 weeks) combination of low dose aspirin and warfarin. Such a combination seemed to be beneficial in our short-term pilot study of unstable angina (unpublished data) and, if the final results confirm our preliminary impression, this recommendation may be extended to postinfarction patients treated with thrombolytic agents.

Future approaches. In addition to the thrombolytic and antithrombotic approaches already mentioned for the prevention of postlysis reocclusion, active investigation is currently underway in the development of powerful antithrombotic agents or a combination of agents that work through different mechanisms. According to preliminary data obtained in our laboratory, recombinant peptide inhibitors of thrombin appear to be very promising in the prevention of reocclusion (unpublished data). This approach is aimed at the inhibition of thrombin, which is one of the most important platelet activators.

Golino et al. (41) demonstrated a reduction in the incidence of reocclusion with the simultaneous use of inhibitors of thromboxane A_2 and serotonin in an animal model. Although these results are interesting, these agents only inhibit the thromboxane- and serotonin-dependent pathways of platelet activation, leaving intact the most important pathway that is dependent on thrombin and collagen. Therefore, it remains to be proved whether these agents are more effective in terms of platelet-inhibitory effects than aspirin alone.

Gold et al. (42) studied the combined effects of rt-PA and monoclonal antiplatelet glycoprotein IIb-IIIa antibody in an animal model. In their elegant study, reperfusion with rt-PA was followed rapidly by reocclusion and cyclic periods of reflow and reocclusion. When rt-PA was given in combination with a monoclonal antibody [7E3-F(ab')$_2$] directed against the platelet glycoprotein IIb-IIIa receptor, the time to reperfusion was shortened and reocclusion was prevented. As stated, glycoprotein IIb-IIIa binds fibrinogen and von Willebrand factor and is essential in the process of platelet aggregation. Therefore, whereas rt-PA or other thrombolytic agents lyse the existing thrombus, a glycoprotein IIb-IIIa blocker produces marked inhibition of platelet aggregation by agonists such as thrombin and collagen (43). As a result, platelet/fibrin thrombus formation is inhibited and the risk of vessel reocclusion is reduced. The clinical applicability of this approach remains to be defined.

Another approach to the problem of platelet activation associated with vessel wall injury consists of the use of blockers of adhesive glycoproteins. In one study (44), heparinized carotid blood from pigs was exposed to collagen type I at shear rates typical of stenotic arteries and the degree of platelet deposition was determined using indium-111–labeled platelets. Animals pretreated with aspirin had a 30% reduction in platelet deposition as compared with control. When animals with severe von Willebrand's disease were used, we found a 90% reduction in platelet deposition. Furthermore, when normal pigs were treated with a monoclonal antibody directed against porcine von Willebrand factor, an 81% reduction in platelet deposition was seen. In these experimental conditions, the pharmacologic inhibition of von Willebrand factor produced a marked reduction in platelet deposition, not seen with any of the currently available platelet inhibitors. Whether or not this approach has clinical utility remains to be elucidated.

Conclusion. The problem of post-thrombolysis reocclusion is of paramount clinical importance and is associated with significant morbidity and, perhaps, mortality. This issue can be approached through several avenues. First, better thrombolytic agents with longer duration of effects and more powerful antithrombotic properties aimed at enhanced clot lysis are needed. While completion of the GISSI-2 and ISIS-3 trials is awaited, the combination of high dose heparin and low dose aspirin is proposed for all patients who do not have a contraindication to these drugs. Finally, peptide inhibitors of thrombin and monoclonal antibodies against platelet glycoprotein receptors and adhesive macromolecules (such as von Willebrand factor) may prove to be powerful, effective inhibitors of platelet aggregation and thrombus formation and, therefore, may greatly improve the efficacy of thrombolytic therapy.

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