reviews

Current Status of Thrombolysis in Acute Myocardial Infarction*

Part III. Optimization of Adjunctive Therapy After Thrombolytic Therapy

Gabriel B. Habib, MD, FCCP

(CHEST 1995; 107:809-16)

Key words: adjunctive therapy; myocardial infarction; thrombolysis

Despite the well-recognized salutary effects of thrombolytic post acute myocardial infarction (AMI),1 about 20 to 30% of patients fail to reperfuse following thrombolysis;2,3 moreover 10 to 25% of patients experience reocclusion despite successful thrombolysis.4,6 Thus, as we are now beginning to realize the limitations intrinsic to all forms of thrombolytic therapy, the role for “adjunctive strategies” after thrombolysis is beginning to assume increasing importance in the management of patients who have suffered AMI. The principal goals of adjunctive therapy in patients with AMI receiving thrombolytic therapy are as follows: (1) maintenance of coronary artery patency by preventing late reocclusion (open artery hypothesis); (2) prevention of ventricular remodeling (dilatation); (3) reduction of myocardial ischemia by improving coronary blood flow, or decreasing myocardial oxygen demands, or both; and (4) reduction of myocardial infarct size.

Since the advent of thrombolytic therapy for AMI, a number of pharmacologic and mechanical interventions have been advocated as adjunctive therapy.

As will be discussed below, some of these adjunctive strategies have clearly proven benefits, whereas other strategies remain unclear or even unhelpful. Accordingly, to clarify the role of adjunctive therapy following thrombolysis, part 3 of this review will address the rationale for and against a number of adjunctive therapeutic modalities in the treatment of patients with AMI receiving thrombolysis. We would like to emphasize at the outset that this review is not intended to serve as an all-inclusive review of adjunctive strategies following AMI, but rather those strategies that have been used in concert with thrombolytic therapy.

THE ROLE OF ANTIPLATELET AGENTS

Should All Survivors of AMI Receive Aspirin Regardless of the Concomitant Use of Thrombolytic Therapy?

Experimental and clinical studies implicate platelet thrombus formation as a major contributor to reocclusion due to rethrombosis after successful thrombolysis. The importance of aspirin therapy in patients with AMI was shown in a large-scale multicenter clinical trial, the Second International Study of Infarct Survival (ISIS-2).7 In this trial, aspirin therapy, 160 mg/d, started immediately at presentation and continued thereafter reduced 5-week vascular mortality by 23% and early nonfatal reinfarction by 49% compared with placebo.7 This clinical benefit of aspirin therapy administered alone was not accompanied by an increased risk of major hemorrhage and reduced nonfatal stroke rate by about 50%.

Clinical benefit of aspirin therapy was consistently shown in patients with suspected AMI regardless of whether streptokinase was given.7 As adjunctive treatment to streptokinase, aspirin reduced 5-week mortality an additional 19%. This synergistic effect of aspirin and streptokinase is attributed to the different mechanisms of cardioprotection with these two

*From the Cardiology Section of the Department of Medicine, Veterans Affairs Medical Center, and Baylor College of Medicine, Houston.
Reprint requests: Dr. Habib, V.A. Medical Center, Section of Cardiology, #3C-330D, 2002 Holcombe Blvd., Houston, TX 77030

AMI=acute myocardial infarction; aPTT=activated prothrombin time; ISIS=International Study of Infarct Survival; MIAMI=metoprolol in acute myocardial infarction; MILIS=Multicenter Investigation for the Limitation of Infarct Size; TIMI=thrombolysis in myocardial infarction; t-PA=tissue plasminogen activator

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21710/ on 06/21/2017
drugs: thrombolysis promotes lysis of an occluded intracoronary clot and aspirin prevents reocclusion secondary to rethrombosis. Moreover, aspirin reduces the procoagulant activity of thrombolytic drugs, a phenomenon thought to be in part mediated by platelet activation.8,9

Conclusion and Recommendation: Aspirin therapy, 160 mg daily, should be started immediately in patients with suspected AMI regardless of whether thrombolysis is administered and should be continued thereafter.

THE ROLE OF THROMBIN INHIBITORS
What Is the Rationale for Using Thrombin Inhibitors as Adjunctive Therapy Following Thrombolytic Therapy?

In the last few years, we have witnessed increasing interest in various adjunctive antithrombotic modalities. This interest is justified for two reasons: (1) the high (10 to 25%) rate of reocclusion despite initially successful thrombolysis,4-6,10 and (2) adverse impact of reocclusion on recovery of left ventricular function, reinfarction rate, and short- and long-term survival.11,12 Reocclusion after thrombolysis is due to heightened thrombogenicity following thrombolytic therapy. The latter is thought to be mediated by the persistent luminal stenosis and the presence of a residual thrombus in a large percentage of treated patients.13 Since rethrombosis postthrombolysis is mediated by activation of platelets13 and of the coagulation cascade,14 adjunctive antithrombotic therapy is intended to inhibit thrombin production, platelet activation, aggregation, and deposition.

Should All Patients Treated With a Thrombolytic Drug Receive Heparin as Adjunctive Therapy?

A total of four clinical trials consisting of 1,073 patients assessed the role of intravenous heparin as adjunctive therapy after thrombolysis by evaluating coronary artery patency at varying intervals after treatment.15-19 All four studies compared a standard intravenous heparin dosing regimen widely used in the United States (5,000 IU intravenous bolus followed by a continuous intravenous drip starting at 1,000 IU/h and titrated to maintain an activated prothrombin time (aPTT) of 1.5 to 2 times control) to either placebo17-19 or to low-dose aspirin.15,16 In all four studies, intravenous heparin consistently increased coronary artery patency regardless of whether coronary patency rates were evaluated at 18 h,15,16 57 h,17 or 2 to 5 days18,19 after treatment. This increased coronary patency rate was associated with a lower rate of recurrent ischemia or infarction in some of these studies17 but not others.15 The addition of intravenous heparin was not accompanied by an increased rate of bleeding complications.15

An important issue related to the use of heparin as adjunctive therapy in AMI is the adequacy of heparinization. Based on suboptimal anticoagulation and marked individual variability in response to the currently advocated fixed dose subcutaneous heparin dosing in European trials,20,21 as well as the difficulty of achieving effective heparinization in the initial 24 h after AMI,22 the currently recommended adjunctive heparin regimen after thrombolysis consists of an initial intravenous heparin bolus of 5,000 IU given as soon as the clinical diagnosis of AMI is suspected, followed by a continuous intravenous heparin drip at 1,000 IU/h.23 The maintenance dose of heparin should be titrated to maintain an aPTT of 1.5 to 2 times control. In the first 24 h, it is desirable to avoid decreasing heparin maintenance dose to <1,000 IU/h even if aPTT exceeds two times baseline level since the risk of rethrombosis is highest in the first 24 h.

Conclusion and Recommendation: Heparin is recommended routinely as adjunctive antithrombotic therapy in patients with AMI treated with a thrombolytic agent, particularly a fibrin-specific short-acting thrombolytic drug such as tissue plasminogen (t-PA) activator in order to maintain coronary patency and to minimize the risk of reocclusion due to rethrombosis.

Should All Patients Receive Intravenous Heparin Therapy Regardless of the Type of Thrombolytic Agent Used?

It is widely accepted that reocclusion and rethrombosis are more common after t-PA than with streptokinase.13 This may be due to the shorter half-life of t-PA and the lack of systemic fibrinogenolysis with the use of this fibrin-specific agent.8,21 Thus, unlike streptokinase, t-PA requires immediate and effective intravenous heparinization. It is conceivable that delayed initiation (4 and 12 h, respectively) and ineffective heparinization with subcutaneous heparin in GISSI-224 and ISIS-325 may explain the failure of these studies to show a significant difference in mortality between patients treated with t-PA and those treated with streptokinase as was recently reported in the Global Utilization of Streptokinase and Tissue Plasminogen Activator in Occluded Coronary Arteries (GUSTO) trial2 in which all patients treated with t-PA received intravenous heparin immediately at presentation. In contrast, it is presently unclear whether intravenous heparin is superior to subcutaneous heparin in patients with AMI treated with
streptokinase. In the GUSTO trial,² 30-day mortality and coronary artery patency were similar in patients treated with streptokinase in combination with either intravenous or subcutaneous heparin therapy. However, since reocclusion rate is lower in patients who received intravenous heparin,²,6 it is generally desirable to use intravenous heparin in all patients with AMI treated with streptokinase.²³

**Conclusion and Recommendation:** Heparin should be administered intravenously with an immediate bolus of 5,000 IU followed by a heparin infusion at a rate of at least 1,000 IU/hr titrated to achieve a prolongation of aPTT to 1.5 to 2 times control. This intravenous heparin regimen is recommended in all patients with AMI treated with t-PA and is generally desirable in those treated with streptokinase.

**How Long Should Heparin Be Continued After Thrombolysis in Uncomplicated AMI?**

The optimal duration of heparin therapy in patients with AMI has been evaluated in several studies. In a pilot study,²⁶ 50 patients with uncomplicated AMI were randomized to a brief (≤24 h) or prolonged (>72 h) intravenous heparin infusion after successful reperfusion with a thrombolytic drug (t-PA, streptokinase, or urokinase), or coronary angioplasty, or both. Coronary artery patency rates were similar at 1 week and bleeding complications were more frequent in the patients who received prolonged heparin therapy.²⁶ In another study,²⁷ 241 patients with AMI treated with t-PA and a 24-h heparin infusion were randomized to aspirin and dipyridamole therapy or to a continuation of heparin infusion for 7 to 10 days. Coronary patency rates, left ventricular function, reinfarction, and recurrent chest pain during 7 to 10 days were similar in both groups.

**Conclusion and Recommendation:** Heparin therapy should be continued for 24 to 72 h in patients with uncomplicated AMI and for several days in patients who have continuing evidence of myocardial ischemia during hospitalization. It should be emphasized that precise guidelines for the optimal timing of heparin therapy withdrawal have not been clearly established in the literature.

**Should All Patients Recovering From AMI Receive Long-term Oral Anticoagulation?**²

A total of 10 placebo-controlled prospective randomized clinical trials have evaluated the effect of aspirin or warfarin (Coumadin) on cardiovascular events in AMI survivors. Overall, aspirin in daily doses ranging between 300 and 1,500 mg has been shown to reduce vascular events by 25% over a mean follow-up period of 2 years in six clinical trials.²⁸ There was no clear relationship between aspirin dose and extent of reduction of vascular events. In another four multicenter randomized clinical trials in 3,222 patients with AMI,²⁹-³³ warfarin therapy reduced all-cause mortality by about 32% over a 3 to 6-year follow-up period (Table 1).

Until recently, to our knowledge, no studies have compared the effects of aspirin and warfarin therapy on survival post-AMI. Recently, a large-scale randomized controlled clinical trial sponsored by the Veterans Affairs Cooperative Studies Program was designed to compare aspirin with low-dose warfarin therapy in survivors of AMI. While awaiting the results of this and other studies comparing aspirin with warfarin therapy post-AMI, it is widely recommended that aspirin, rather than warfarin, be used routinely in patients recovering from AMI,²³,³⁴ primarily because of its greater safety and simplicity and lower cost. Aspirin therapy, 160 to 325 mg daily, should be continued indefinitely in these patients. Because of the higher risk of mural thrombus formation and of systemic thromboembolism in patients with a large anterior infarct, particularly if it involves the apex, oral anticoagulation with warfarin may be recommended in these patients for the first 3 months after hospital discharge.²⁸ The use of aspirin should be postponed in these patients until oral anticoagulation is discontinued. The combination of aspirin and warfarin should be avoided in any patient with AMI because of the increased risk of bleeding and unproven benefit compared with either drug alone.

**Table 1—Summary of the Results of Four Clinical Trials of Long-term Warfarin Therapy After Recovery From AMI**

<table>
<thead>
<tr>
<th>Study, yr</th>
<th>Patients</th>
<th>Follow-up, yr</th>
<th>Decrease in Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC,²⁹ 1964</td>
<td>383</td>
<td>3</td>
<td>30 (NS)</td>
</tr>
<tr>
<td>VA COOP,³⁰,³¹ 1965/69</td>
<td>747</td>
<td>3</td>
<td>33*</td>
</tr>
<tr>
<td>SIXTY-PLUS,³² 1980</td>
<td>878</td>
<td>6</td>
<td>43†</td>
</tr>
<tr>
<td>WARIS,³⁵ 1990</td>
<td>1,214</td>
<td>3</td>
<td>24†</td>
</tr>
<tr>
<td>Pooled</td>
<td>3,222</td>
<td>5-6</td>
<td>32</td>
</tr>
</tbody>
</table>

*p<0.01.
†p<0.02.
‡p<0.03 compared with the control group.
Conclusion and Recommendation: Aspirin therapy (160 to 325 mg daily) is recommended routinely in all survivors of AMI. It should be started immediately at presentation in patients with suspected AMI and should be continued indefinitely. At present, oral warfarin therapy is recommended in patients recovering from an anterior wall myocardial infarction for the first 3 months after myocardial infarct onset, after which aspirin therapy should be started and continued indefinitely. The combination of aspirin and warfarin may be associated with an increased risk of bleeding and, at the time of this writing, has not been shown to be more beneficial than either therapy alone. Accordingly, the routine administration of both aspirin and warfarin should be avoided in patients with AMI.

What Is the Present and Future Role of the Newer More Potent Thrombin Inhibitors as Adjuvant Therapy After Thrombolysis in AMI?

Thrombin inhibitors include heparin, selective thrombin inhibitors such as hirudin, and various synthetic hirudin analogues such as hirugen, argatroban (MCI-9038), and MD-805. During thrombus formation, thrombin binds to fibrin and is incorporated into the growing thrombus. Both free thrombin and thrombus-bound thrombin stimulate further thrombin generation by activating clotting factors V and VIII and by activating platelets. Heparin inhibits thrombin activation primarily by binding with antithrombin III and potentiating the inhibition of free thrombin by antithrombin III. Heparin's antithrombotic efficacy is limited by its minimal inhibition of fibrin-bound thrombin that continues to activate platelets despite the presence of heparin.

Compared with heparin, hirudin is a more potent and effective antithrombotic agent in patients with AMI because it does not need to complex with antithrombin III to achieve thrombin inhibition and has a more sustained antithrombotic activity due to inactivation of both free and fibrin-bound thrombin. Hirudin, a natural protein produced by leeches, is now produced in large quantities by recombinant technology. It is the most extensively evaluated new thrombin inhibitor in patients with AMI. In the Thrombolysis in Myocardial Infarction (TIMI) 5, hirudin was effective in preventing reocclusion without increasing the rate of spontaneous bleeding. Coronary arteriography at 18 to 36 h after treatment revealed a reocclusion rate of 1% with hirudin compared with a 7% reocclusion rate with heparin in 214 patients with AMI treated with t-PA. In another pilot study conducted in Germany, hirudin was at least as effective as heparin in preventing reocclusion after thrombolysis with front-loaded t-PA in 40 patients with AMI. A larger clinical trial sponsored by the National Heart, Lung, and Blood Institute, TIMI 9, has been designed to compare hirudin and heparin as an adjunctive antithrombotic therapy in patients with AMI treated with any of the presently commercially available thrombolytic drugs, t-PA, streptokinase, or anistreplase (APSAC).

Conclusion and Recommendation: Until the results of the TIMI 9 clinical trial are known, hirudin, a new more potent and selective thrombin inhibitor than heparin, is not routinely recommended as adjunctive antithrombotic therapy in patients with AMI treated with a thrombolytic drug.

The Role of Coronary Angioplasty in AMI
Should Angioplasty Be Performed Routinely After Successful Thrombolysis?

After thrombolysis, most patients have a high-grade residual stenosis with or without an intracoronary clot. Since early reinfarction is mediated by rethrombosis and is primarily due to the thrombogenic potential of a residual high-grade lesion and of a residual clot, routine coronary angioplasty after successful thrombolysis seems to be a reasonable approach aimed at reducing reinfarction. In the last decade, ten prospective randomized clinical trials compared two strategies in 5,492 patients with AMI who had successful reperfusion with a thrombolytic drug: (1) an anatomically driven strategy (also referred to as an invasive strategy) consisting of routine coronary angioplasty of any anatomically significant lesion in the infarct-related artery or (2) a clinically driven strategy (referred to as a conservative strategy) consisting of coronary angioplasty in patients with recurrence of angina or with inducible ischemia on a submaximal treadmill exercise test.

The above studies differed in the timing of the coronary angiography and angioplasty: coronary angioplasty was performed immediately in three studies, within 1 or 2 days in five studies, and in 3 to 14 days in the remaining two studies. However, despite these differences, all ten studies consistently reported no difference in clinical outcome (death and nonfatal reinfarction) between the invasive (anatomically driven) strategy and the conservative (clinically driven) strategy. Thus, coronary angiography followed by angioplasty is not recommended routinely in patients who have been successfully treated with a thrombolytic drug and have recovered from AMI without spontaneous angina or inducible ischemia during stress testing.
Conclusion and Recommendation: Routine coronary angiography and coronary angioplasty are not recommended in all patients with AMI treated with thrombolysis. However, patients with spontaneous or provokable ischemia are candidates for coronary angiography and angioplasty if technically feasible or coronary artery bypass surgery.

Is Coronary Angioplasty Recommended After Failed Thrombolysis (Rescue Angioplasty)?

“Rescue” coronary angioplasty refers to coronary angioplasty in patients who have failed to reperfuse after thrombolysis. In the only (to our knowledge) large randomized clinical trial comparing immediate angiography and rescue angioplasty in 287 patients with delayed coronary angiography after 5 days in 288 patients, rescue angioplasty was associated with a significant reduction in adverse clinical events (defined as death, stroke, reinfarction, reocclusion, heart failure, or recurrent ischemia) from 45 to 33% (p=0.004) and a small nonsignificant increase in mortality from 4 to 6%. A review of a pooled analysis of 560 patients in 12 nonrandomized clinical trials showed an angiographic success rate of 71 to 92% (mean, 80%) and an overall mortality of about 11%, but no overall beneficial effect on left ventricular function. Moreover, mortality in patients who failed to reperfuse after rescue angioplasty was substantially elevated (25 to 39%) and reocclusion rates were as high as 29% (on average 24% reocclusion rate with t-PA, and 14% reocclusion rate with nonfibrin-specific drugs such as streptokinase). Thus, it is not clear at present whether rescue coronary angioplasty should be performed routinely in all patients who fail thrombolysis. A large clinical trial, the Randomized Evaluation of Salvage Angioplasty With Combined Utilization of End Points (RESCUE), may provide further evidence about the efficacy and safety of rescue angioplasty in such patients.

Conclusion and Recommendation: Rescue coronary angioplasty in patients who fail to reperfuse after thrombolytic therapy for AMI is not recommended routinely. However, in patients with persistent ischemia or cardiogenic shock despite optimal medical therapy, rescue coronary angioplasty may be considered since the benefits of rescue angioplasty in these patients might outweigh its expected risks.

**Intravenous Beta-blockers as Adjunctive Therapy Following Thrombolysis**

In the mid-1970s, beta-blockers were used in the treatment of coronary heart disease, primarily for the symptomatic relief of angina pectoris. Experimental studies using the dog model of acute coronary occlusion suggested that intravenous beta-blockers reduce myocardial ischemia and limit infarct size. These experimental observations led to a number of clinical studies designed to test the efficacy and safety of beta-blockers in survivors of AMI. In the early 1980s and before the widespread use of thrombolysis in AMI, four multicenter, placebo-controlled, and randomized clinical trials evaluated the effect of intravenous beta-blocker therapy on myocardial infarct size and hospital mortality. The results of these clinical trials conducted in more than 20,000 patients with AMI constitute an important foundation for current guidelines for the use of intravenous beta-blockers in patients with AMI. The results of these trials suggested that delay to beta-blocker therapy is a critical determinant of treatment benefit. This concept is best illustrated by comparing the timing of beta-blocker therapy in these studies (Table 2).

Two clinical trials evaluated the effect of beta-blockers on myocardial infarct size: the Norwegian intravenous timolol trial and the Multicenter Investigation for the Limitation of Infarct Size (MILIS). In the Norwegian intravenous timolol trial in which all enrolled patients received timolol (a nonselective beta-blocker) within 4 h of infarct symptom onset (mean, 3 h), there was a significant 30% reduction in infarct size. In contrast, in the MILIS study, in which only 2% of the 269 enrolled patients received the drug within 4 h of infarct symptom onset (mean, 9 h), there was no change in infarct size or left ventricular function.

The importance of early initiation of intravenous beta-blocker therapy was also evident in the beta-blocker mortality trials: ISIS-1 (First International Study of Infarct Survival) and MIAMI (Metoprolol in Acute Myocardial Infarction). Hospital mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Delay to Treatment, h</th>
<th>Primary End Point</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwegian</td>
<td>&lt;4</td>
<td>Infarct size</td>
<td>Positive*</td>
</tr>
<tr>
<td>MILIS</td>
<td>&lt;18</td>
<td>Infarct size</td>
<td>Negative</td>
</tr>
<tr>
<td>ISIS-1</td>
<td>&lt;12</td>
<td>Mortality</td>
<td>Positive</td>
</tr>
<tr>
<td>MIAMI</td>
<td>&lt;24</td>
<td>Mortality</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*A “positive” study result indicates a favorable clinical outcome, that is, a significant reduction in infarct size or in hospital mortality, whereas a “negative” study result indicates no change in infarct size or hospital mortality with beta-blocker therapy compared with placebo.
was significantly reduced (from 4.6 to 3.9%, p<0.02) in the ISIS-1 trial in which the beta-blocker therapy was started within the first 12 h (mean, 5h).51 and was unchanged in the MIAMI trial in which it was given throughout the first 24 h after infarct symptom onset (mean, 7 h).52 Thus, intravenous beta-blockers appear to reduce infarct size and decrease hospital mortality in patients with AMI who were treated within the first 4 to 6 h of AMI symptom onset. This is consistent with experimental studies showing no further myocardial necrosis after coronary occlusion for longer than 3 to 4 h, suggesting that myocardial salvage may be possible only in the first few hours of infarct evolution.

Is There a Role for Intravenous Beta-blockers as Adjunctive Therapy In Thrombolytic Therapy?

Given that the above four clinical trials were conducted before the widespread use of thrombolysis in AMI, the extrapolation of the results of these studies to patients with AMI treated with thrombolysis has remained unsettled. It is conceivable that the favorable impact of thrombolysis on clinical outcome of patients with AMI made intravenous beta-blocker therapy obsolete. Thus, the efficacy of early beta-blockade in patients with AMI who received a thrombolytic drug was evaluated in a recently completed multicenter randomized clinical trial, the TIMI (Thrombolysis in Acute Myocardial Infarction) IIB trial.5 In this study, all patients received t-PA (with or without intravenous metoprolol) within 4 h of infarct symptom onset. A total of 1,390 patients were randomized to immediate treatment with intravenous metoprolol (15 mg) followed by oral metoprolol, or delayed oral metoprolol started on day 6 post-AMI. Nonfatal reinfarction and recurrent ischemic events occurred less frequently in patients who received intravenous metoprolol compared with patients who received deferred oral metoprolol (p=0.02 and p=0.005, respectively).

Intravenous beta-blockers (metoprolol, 15 mg, or atenolol, 10 to 20 mg) are now approved by the Food and Drug Administration as prophylactic therapy to reduce the risk of death and nonfatal reinfarction in patients with AMI. It is recommended that patients with AMI, including those receiving thrombolytic therapy, with tachycardia or systolic hypertension or both and without decompensated heart failure or other contraindications to beta-blockade should receive early intravenous beta-blockade.23

Conclusion and Recommendation: Intravenous beta-blockers reduce infarct size and hospital mortality when initiated within the first 4 h after AMI symptom onset, particularly in patients with sinus tachycardia, or systolic hypertension, or both. In patients receiving thrombolytic therapy, metoprolol (15 mg) or atenolol (10 to 20 mg) is recommended as routine adjunctive therapy for patients with AMI presenting within the first 4 h after symptom onset. Furthermore, intravenous beta-blocker therapy can be recommended regardless of concomitant thrombolysis.

Conclusion

In the previous section, we have reviewed the rationale for the optimal utilization of adjunctive therapy to maximize the salutary effects of thrombolysis. It is clear from the above discussion that the benefits of thrombolytic therapy can be maximized by the judicious use of adjunctive therapies. However, it is important to recognize the importance of individualizing the decision to start an adjunctive therapy after thrombolysis and to weigh the expected benefits against any anticipated risks. Recommendations outlined in this and parts 1 and 2 of this review should not substitute for a careful assessment of the risk to benefit ratio in the individual patient.

References
6 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
Sherry Aguirre, 23
Trutgill 25
ISIS-3 18
De 17
Hsia J, 27
EM, myocardial infarction: ventricular dial infarction: DC, Coll 83:31-46
12:78A-84A
15 Hsia J, 20
1991; 324:1218 1993;
67:3A-11A

40 Prins MH, Hirsh J. Heparin as an adjunctive treatment after thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1991; 67:3A-11A
46 SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. SWIFT Trial of delayed elective intervention vs conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. BMJ 1991; 302:555-60
49 Ellis SG, Mooney MR, George BS, et al. Randomized trial of late elective angioplasty versus conservative management for patients with residual stenoses after thrombolytic treatment of