European Heart Journal Supplements (2001) **3** (*Supplement A*), A26–A34

Facilitated percutaneous coronary intervention: results from the SPEED trial

H. C. Herrmann[1], R. H. Li[1] and E. M. Ohman[2]

[1]*Hospital of the University of Pennsylvania, Philadelphia PA, U.S.A.;* [2]*Duke Cardiovascular Research Institute, Durham NC, U.S.A.*

Facilitated percutaneous coronary intervention (PCI) for acute myocardial infarction (MI) combines fibrinolytic therapy, glycoprotein (GP) IIb/IIIa receptor inhibition and early percutaneous intervention to optimize epicardial and microvascular reperfusion. Although fibrinolysis and primary angioplasty were once seen as competing therapies, new evidence indicates that they can be used together safely to improve outcomes. In addition, a new understanding of the role of platelets in acute MI has led to studies demonstrating the benefits of using GP IIb/IIIa receptor inhibitors in combination with fibrinolytic agents. The Thrombolysis in Myocardial Infarction (TIMI) 14 and Strategies for Patency Enhancement in the Emergency Department (SPEED) trials have shown that combination therapy with reduced-dose alteplase or reteplase and full-dose abciximab improves TIMI grade 3 flow by an absolute amount of 10–15% at 60 min, without a significant increase in bleeding. In the SPEED trial of abciximab used with or without low-dose fibrinolytic therapy, the addition of early facilitated PCI resulted in a core laboratory-assessed TIMI grade 3 flow rate of 85% and a normal mean corrected TIMI frame count while retaining the early benefit (between 30 and 60 min) of a pharmacological approach. Facilitated PCI has the potential to improve both very early and later reperfusion; ongoing trials are evaluating the benefits of this approach and the mortality benefit and safety of combination therapy.

(Eur Heart J Supplements 2001; 3 (Suppl A): A26–A34)

Key Words: Facilitated PCI, perfusion, acute MI, lytic, abciximab, SPEED.

Introduction

The rapid restoration of normal blood flow in the infarct-related artery is the key objective in the treatment of patients presenting with acute myocardial infarction (MI). Patency of the infarct-related artery is clearly the most powerful predictor of survival after MI, and normal angiographic flow (Thrombolysis in Myocardial Infarction [TIMI] grade 3) at 90 min correlates with both 30-day[1] and long-term[2] mortality. This goal can be accomplished with either fibrinolytic therapy or primary angioplasty, treatments that are sometimes viewed as competing modalities[3]. In this review, we will discuss various new approaches and combinations of approaches to acute reperfusion in patients with MI.

Pathophysiology of acute MI

The initial event in the formation of an occlusive intracoronary thrombus is the rupture or ulceration of the atherosclerotic plaque[4]. This results in exposure of circulating platelets to the thrombogenic contents of the plaque, such as fibrillar collagen, von Willebrand factor, vitronectin, fibrinogen and fibronectin[5]. The adhesion of platelets to the ulcerated plaque, with subsequent platelet activation and aggregation, then leads to the generation of thrombin, conversion of fibrinogen to fibrin and further activation of platelets as well as vasoconstriction[6]. This prothrombotic milieu promotes the propagation and stabilization of an active thrombus that contains platelets, fibrin, thrombin and erythrocytes[7], resulting in occlusion of the infarct-related artery.

Platelets are a key component in the process of thrombus formation, in modulating the response to fibrinolytic therapy and in mediating reocclusion[5]. Angioscopic studies have shown that intracoronary thrombi in acute coronary syndromes are platelet rich[8,9]. Activation of platelets can occur via multiple pathways, including those mediated by adenosine diphosphate, epinephrine, thrombin and platelet adhesion[5]. This results in the release of prothrombotic substances such as thromboxane A_2, plasminogen activator inhibitor (PAI) and serotonin. Platelet activation also causes exposure and activation of the glycoprotein (GP) IIb/IIIa receptor which, by binding to fibrinogen

Correspondence: Howard C. Herrmann, MD, Hospital of the University of Pennsylvania, 3400 Spruce Street, 9 Founders Pavilion, Philadelphia, PA 19104, U.S.A.

1520-765X/01/0A0026+09 $35.00/0

and von Willebrand factor, results in platelet cross-linking and is therefore the final common pathway leading to platelet aggregation.

The pivotal role of platelets in the pathophysiology of acute MI has provided insights into the problem of 'thrombolytic resistance'[10]. Although the development of fibrinolytic therapy was clearly a major advance in the treatment of MI, a significant proportion of patients do not successfully reperfuse[1]. Proposed mechanisms for this observation include[10]:

- incomplete clot dissolution because fibrinolytics act on only one component of the clot;
- release of PAI-1 and α-2 plasma inhibitor;
- vasoconstriction caused by platelet-derived thromboxane A_2;
- enhanced fibrin activation by exposure of clot-bound thrombin; and
- the direct platelet-activating effect of fibrinolytics.

The hypothesis that platelet activation and aggregation might be a significant contributing factor to thrombolytic resistance led, in part, to the development and testing of platelet GP IIb/IIIa receptor blockers in acute coronary syndromes, including patients who underwent percutaneous coronary intervention (PCI).

In recent years, there have been continuous advances in the medical management of MI with newer fibrinolytic agents, refinement of heparin dosing regimens and development of platelet GP IIb/IIIa receptor inhibitors. Mechanical revascularization with PCI also has improved via better interventional techniques, catheter design and the evolution of intracoronary stenting. These changes, as well as a greater understanding of the pathophysiology of thrombus formation and propagation during acute MI, have led to the recognition that fibrinolytics and primary angioplasty are complementary rather than competing modalities.

Fibrinolysis versus primary angioplasty

Fibrinolytic therapy with streptokinase, alteplase or reteplase is widely available and can be administered without specialized facilities or staff and with minimal time delay. Numerous large clinical trials have shown that fibrinolytics are associated with preservation of left ventricular function, limitation of infarct size and a highly significant reduction in mortality[11–14]. This benefit is partially time-dependent: when administered within 2 h of symptom onset, fibrinolytics are associated with a 30% reduction in mortality, which decreases to an 18% reduction in mortality if given within 6 h[14].

Although fibrinolytics can restore patency in the infarct-related artery in up to 81% of patients by 90 min, failure to achieve TIMI 3 flow, which may occur in 45–70% of patients, is associated with reduced survival[13]. Even after successful reperfusion, reocclusion occurs in up to 20% of patients and reinfarction in 10%[15]. In the end, perhaps only about a quarter of patients treated with fibrinolytics achieve the ideal outcome of rapid and sustained normalization of flow in the infarct-related artery[16]. Finally, fibrinolytic therapy is limited by the contraindications to its use, which can affect up to 10% of patients[3], and the risk of intracranial haemorrhage.

In contrast, primary angioplasty may be more effective than fibrinolytic therapy because it achieves both higher infarct-related artery patency rates and greater TIMI 3 flow[17–20]. Primary angioplasty also has advantages over fibrinolytics in terms of short-term mortality, bleeding complications (including intracranial haemorrhage) and stroke[20,21]. The benefit of primary angioplasty in mortality, reinfarction and recurrent ischaemia appears to be durable over long-term follow-up as well[22]. Early intervention has the additional advantage of angiographic definition of the coronary vessels, which allows early risk stratification and identification of patients at particularly high or low risk[17].

The use of stents in the setting of primary angioplasty may add further benefits, in particular addressing the frequent problem of restenosis and the need for revascularization, which occurs in 20% of patients[23]. The results of several trials comparing primary angioplasty alone and with stenting have shown lower rates of reinfarction and target vessel revascularization compared with angioplasty alone[23–25]. These advantages persisted over 12 months of follow-up[25].

Despite the advantages of primary angioplasty, it has several drawbacks that curtail its usefulness. The availability of primary angioplasty in the U.S.A. is limited by the number of hospitals with catheterization facilities where primary angioplasty can be performed in a timely fashion by experienced operators. In the U.S.A., less than 20% of hospitals are capable of performing angioplasty, and fewer are able to perform the procedure in an emergency situation[3].

Where emergency angioplasty is available, the longer time delay before commencement of therapy with primary angioplasty compared with fibrinolytics also may limit the benefits of this approach. Although the time to treatment in the early angioplasty trials was as short as 60 min[17–19,21], it was much longer in the multicentre Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Angioplasty Substudy (114 min)[20] and in the Myocardial Infarction Triage and Intervention Project Registry (102 min overall, 138 min in low-volume hospitals)[26]. Data from the National Registry of Myocardial Infarction (NRMI-2) show that mortality may increase significantly when door-to-balloon time is greater than 120 min[27]. In addition, most primary angioplasty trials have been performed in centres with motivated, highly experienced operators, and the impressive results of these trials have not yet been replicated in the community hospital setting[26].

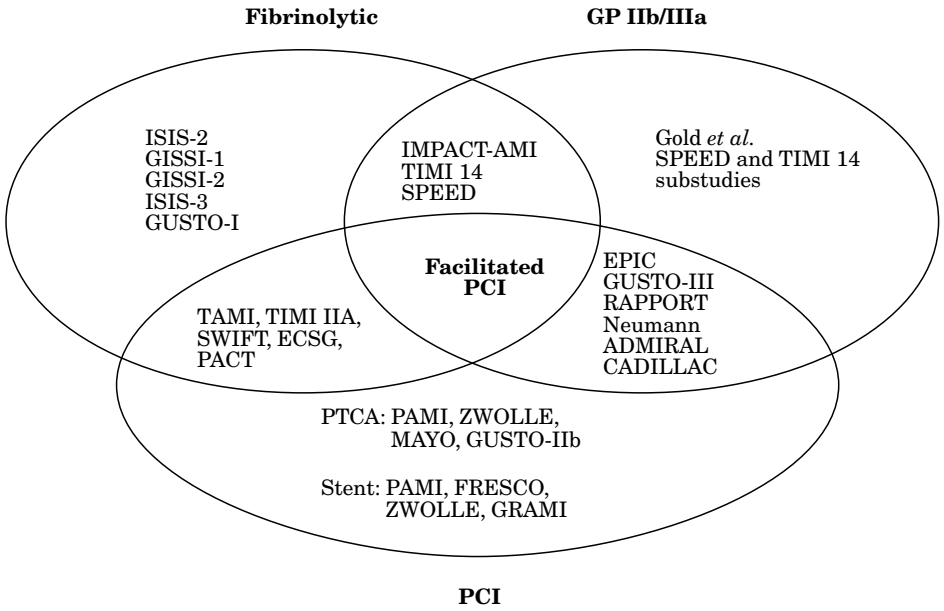

Figure 1 **Diagram of MI studies that evaluated fibrinolytics, GP IIb/IIIa receptor inhibitors and percutaneous coronary intervention (PCI) as monotherapy and in various combinations. (Adapted with permission[28].)**

New approaches to revascularization: triple therapy

The recent advances in our understanding of the contribution of platelet physiology and platelet inhibition in the pathogenesis of acute MI, as well as the advances in mechanical revascularization using stents, have led to new combination approaches to reperfusion in patients with this condition. For instance, all of the binary combinations of fibrinolytic agents, platelet GP IIb/IIIa receptor inhibitors and PCI have now been studied in trials (Fig. 1). In addition, the triple combination of a reduced-dose fibrinolytic and full-dose GP IIb/IIIa receptor inhibitor prior to planned, immediate percutaneous intervention, an approach termed 'facilitated PCI', has now also been evaluated[28].

Combination therapy with fibrinolytics and GP IIb/IIIa receptor inhibitors

A number of studies have examined the combination of fibrinolytic therapy and GP IIb/IIIa receptor inhibition[29–33]. The rationale for this approach stems from the idea that fibrinolytic agents work primarily on fibrin and leave platelets either uninhibited or potentially activated. It was theorized that the use of a GP IIb/IIIa receptor inhibitor at the time of lytic administration could improve the overall reperfusion rate, prevent reocclusion and potentially reduce the risk of intracranial haemorrhage.

The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 pilot trial, which treated 60 MI patients with alteplase, was an early dose-ranging and dose-timing trial of abciximab[29]. This study demonstrated that infarct-related artery patency at day 5 was greater in patients who received abciximab and that abciximab could be combined with alteplase without excessive bleeding complications. In the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial, various doses of the GP IIb/IIIa receptor inhibitor lamifiban were tested in combination with fibrinolytic therapy: lamifiban plus either alteplase or streptokinase[31]. Although there was no difference in the 30-day combined clinical end-point, there was greater ST-segment resolution at 90 min in lamifiban-treated patients than in patients given full-dose lytic alone (80% versus 63%, $P=0{\cdot}005$).

In the Integrilin to Manage Platelet Aggregation to Combat Thrombosis in Acute Myocardial Infarction (IMPACT-AMI) trial, which tested a range of eptifibatide doses given in combination with full-dose alteplase in 132 patients, those receiving high-dose eptifibatide were significantly more likely than those receiving full-dose alteplase (control arm) to achieve the primary end-point of TIMI 3 flow at 90 min (66% versus 39%, $P=0{\cdot}006$)[30]. There was no difference in the combined clinical end-point (death, reinfarction, stroke, revascularization or heart failure) or in severe bleeding between treatment groups in this small study.

In contrast to TAMI 8, PARADIGM and IMPACT-AMI, all of which used full-dose fibrinolytics, two recently published trials tested the hypothesis that abciximab could be combined with reduced doses of fibrinolytic to improve infarct-related artery

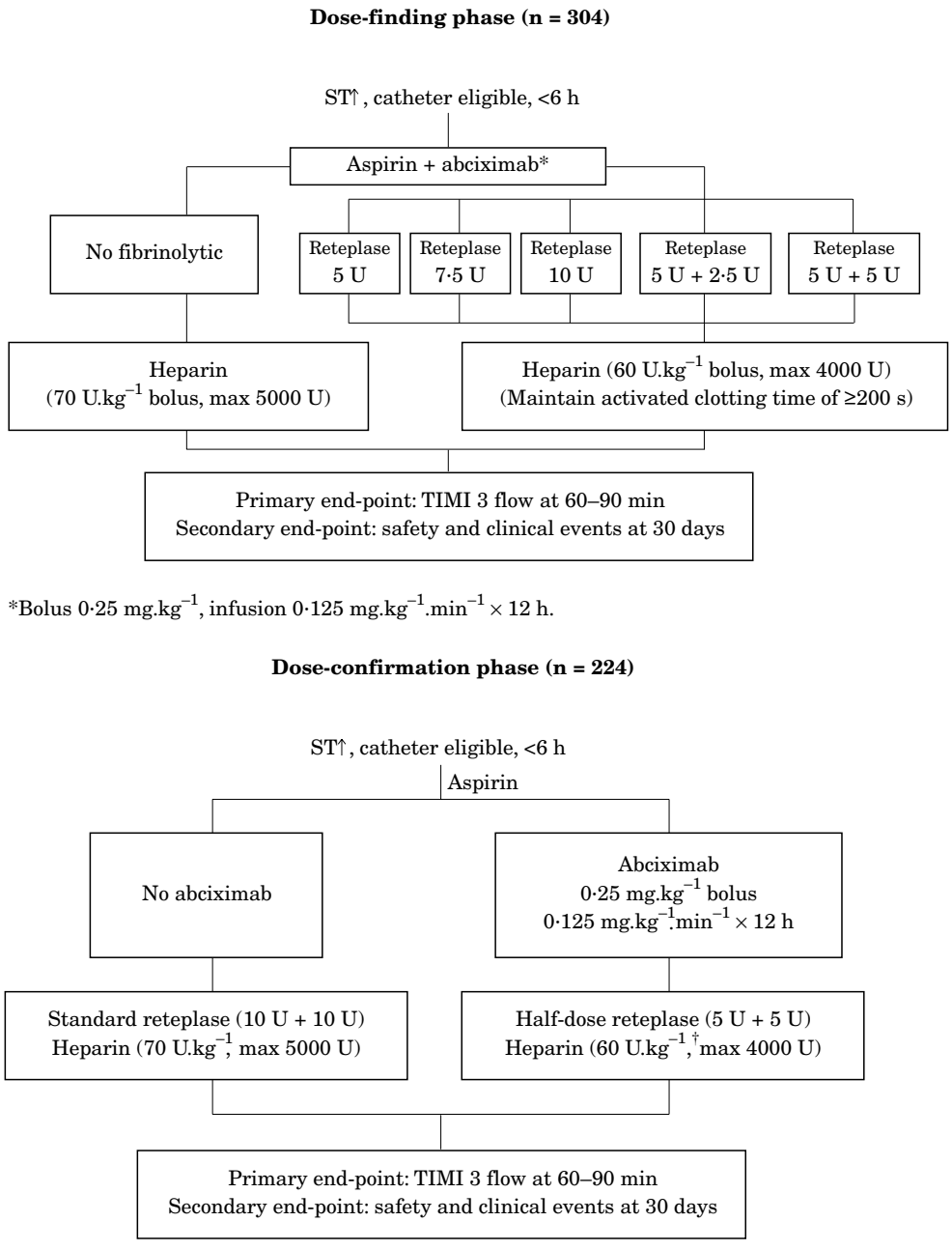

Figure 2 **Design of the SPEED trial: dose-finding phase (top) and dose-confirmation phase (bottom)[33].**

patency[32,33]. The TIMI 14 trial is discussed in E. Braunwald's article in this supplement.

The Strategies for Patency Enhancement in the Emergency Department (SPEED) GUSTO V (formerly known as GUSTO-IV–AMI) pilot trial enrolled 528 patients within 6 h of onset of acute MI. Treatment regimens included abciximab alone, reteplase alone and various combinations of reduced-dosed reteplase with abciximab in a dose-finding phase (Fig. 2) followed by a dose-confirmation phase (Fig. 2)[33]. Angiography was performed at 60 to 90 min (median: 62 min), and PCI was encouraged at the time of the initial angiography. In the dose-finding phase (n=325), half-dose reteplase (5 U+5 U administered 30 min apart) plus abciximab resulted in the highest TIMI 3 flow rates at 60 to 90 min (62%) and was significantly higher than the rate for abciximab alone (27%, $P=0{\cdot}001$).

In the dose-confirmation phase (n=224), standard-dose reteplase (10 U followed by 10 U 30 min later) was compared with half-dose reteplase (5 U+5 U) plus

abciximab. The primary end-point of TIMI 3 flow measured at a median time of 62 min after drug administration was 54% in the half-dose reteplase plus abciximab group and 47% in the reteplase-only group ($P=0{\cdot}32$). However, the TIMI 3 flow rate was higher in the combination therapy group that received the higher dose (60 $U.kg^{-1}$) of heparin compared with the patients who received a lower dose of heparin (40 $U.kg^{-1}$). There was a trend toward a lower composite end-point of death, reinfarction or urgent revascularization for the combination therapy group, although this difference was not statistically significant (6·1% versus 11%, $P=0{\cdot}19$).

There was a trend toward increased major bleeding with half-dose reteplase plus abciximab compared with reteplase only (3·7% versus 9·8%, $P=0{\cdot}11$), but there was no difference in major bleeding with combination therapy in the standard-dose versus low-dose heparin groups (6·3% versus 10·5%, $P=0{\cdot}3$). There also was no difference in intracranial haemorrhage between the combination therapy and the reteplase-only groups (0·86% versus 0·92%).

The TIMI 14 and SPEED trials indicate that combination therapy with reduced-dose alteplase or reteplase plus full-dose abciximab appears to improve both the speed and the degree of reperfusion without a significant increase in bleeding events. However, it has not yet been shown that this improvement in TIMI 3 flow translates into a mortality benefit without increasing bleeding complications. For this reason, the GUSTO V trial has been initiated. This trial has an enrollment goal of 16 600 patients and a primary end-point of all-cause mortality at 30 days.

Facilitated PCI

Initial experience with the combination of fibrinolysis and early percutaneous transluminal coronary angioplasty (PTCA) was not favourable. The TAMI trial tested whether immediate angioplasty improved the results of 386 acute MI patients treated with alteplase compared with deferred angioplasty (5 to 10 days later). In this trial, patients who underwent immediate intervention experienced higher mortality, as well as a greater need for emergency coronary artery bypass graft (CABG) surgery and repeat angioplasty[34]. Higher rates of mortality, reinfarction, bleeding and emergency CABG also were reported by the TIMI IIA investigators, who compared early intervention with delayed angioplasty (18 to 24 h) or conservative care[35]. The results of these and other[36,37] trials demonstrating the absence of benefit to early intervention in the setting of fibrinolytic therapy led to the abandonment of this strategy[38,39].

Over the last decade, there have been many improvements in both the medical and the interventional care of MI patients. The pivotal role of platelets in the prothrombotic milieu of acute MI has led to the development of new potent platelet antagonists. There also have been improvements in interventional techniques, equipment and operator experience. For instance, the Plasminogen-activator Angioplasty Compatibility Trial (PACT) demonstrated an improvement in safety of early PCI in this more current time period, that is, in which stents and platelet GP IIb/IIIa receptor inhibitors are available[40].

In the SPEED trial of abciximab with or without low-dose fibrinolytic therapy, all of the patients had early angiography and PCI was encouraged. This study design allowed for a reexamination of the utility of early PCI after thrombolysis in a contemporary setting. Although the term 'facilitated PCI' has been used to describe a number of management strategies that aim to use pharmacological agents to improve the outcome of early PCI in acute MI, we have used the term to describe the administration of reduced-dose fibrinolytic therapy and GP IIb/IIIa receptor inhibitors in the setting of planned, immediate PCI. We hypothesized that facilitated PCI incorporating stents and GP IIb/IIIa receptor inhibition would be safe and would improve the angiographic and procedural outcomes of patients with acute MI.

A total of 323 patients (61%) underwent PCI at the time of initial angiography, a median of 63 min after reperfusion therapy began[41]. Cineangiograms were reviewed by a blinded core laboratory. Ischaemic events, bleeding, angiographic results and clinical outcomes were compared between early PCI and no-early-PCI patients (n=162), between patients with TIMI grade 0 or 1 flow before PCI versus TIMI grade 2 or 3 flow, and among three treatment regimens.

The procedural success rate in early PCI patients was 88%, and 78% received intracoronary stents. Major cardiovascular events by 30 days occurred in 5·6% of the study population and included death (3·4%), reinfarction (1·2%) and urgent revascularization for severe ischaemia (1·6%)[41]. In the 162 patients who did not undergo early PCI, there were no significant differences from early PCI patients in clinical characteristics, but the rates of reinfarction, urgent revascularization and the composite of ischaemic events were substantially higher (Fig. 3)[41]. The clinical success rate, defined as freedom from death, reinfarction and urgent revascularization by 30 days, was 94·4% for early PCI patients and 83.8% for those not undergoing early PCI ($P<0{\cdot}001$) (Fig. 4)[41].

TIMI flow grade was assessed in 294 patients undergoing early PCI with evaluable angiograms. The percentage of patients who achieved TIMI grade 2 or 3 flow increased from 66% before PCI to 98% after early PCI ($P<0{\cdot}001$). A similar improvement was noted in the corrected TIMI frame count. Interestingly, in the entire SPEED trial, patients with TIMI grade 0 or 1 flow before PCI were more likely to undergo intervention. Similarly, early PCI was performed more often in patients receiving abciximab alone (without a fibrinolytic), probably reflecting the lower initial rate of TIMI 3 flow. In patients who received combination therapy with abciximab and reduced-dose reteplase, post-PCI TIMI

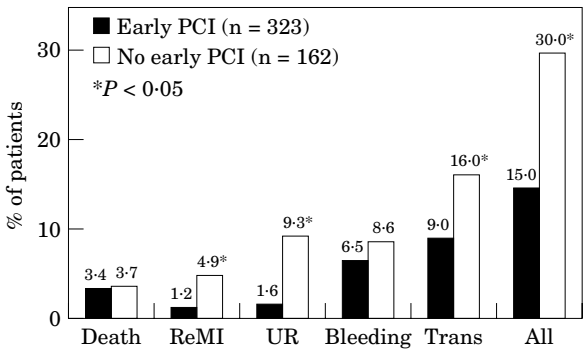

Figure 3 **SPEED trial end-point events are shown at 30 days for the early PCI group compared with the group that did not undergo early PCI. There were significant differences in the rates of reinfarction (ReMI), urgent target vessel revascularization (UR), transfusion (Trans) and the composite of ischaemic events. (Adapted with permission[41].)**

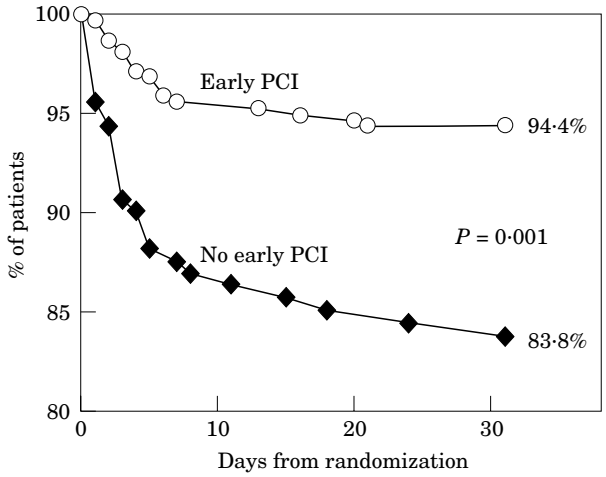

Figure 4 **The clinical success rate at 30 days for patients in the SPEED trial who underwent early PCI compared with those who did not. For success defined as freedom from death, reinfarction and urgent revascularization by 30 days, the rates were 94·4% versus 83·8%, respectively ($P<0·001$).**

grade 3 flow was present in 86% of patients at an estimated 90 min after treatment began. In these patients there also was a trend toward improved clinical outcome, with a composite rate of death, MI and urgent revascularization of 5·9% compared with rates of 8·1% and 7·1% in patients receiving abciximab or reteplase alone, respectively[41].

Thus, early PCI in this setting appears to be both safe and effective. Some of the likely reasons for the better results in the present trial include use of abciximab, use of intracoronary stents, optimization of heparin anticoagulation and increased interventional operator experience. Several trials have shown that abciximab can improve the results of primary angioplasty in acute MI patients[42]. Stent usage has also been shown to improve the short-term results of primary angioplasty, particularly when combined with abciximab[43]. Finally, the specific lytic agent used — in this case, reteplase — also may have contributed to the improved outcome. Reteplase has been shown to produce greater early TIMI 3 flow rates compared with alteplase, and in patients undergoing rescue angioplasty in the GUSTO-III trial, patients who received abciximab had improved outcomes when randomized to reteplase compared with randomization to alteplase[44].

Combining treatment with reduced-dose fibrinolytics, GP IIb/IIIa receptor inhibition and early PCI has a number of potential benefits. These include: (1) potential for more rapid restoration of TIMI 3 flow due to the more ready availability of pharmacological therapy, (2) more complete final restoration of TIMI 3 flow provided by early PCI, (3) improvements in PCI outcomes due to pre-treatment with fibrinolytics and GP IIb/IIIa receptor inhibitors as well as greater patient stability due to an open artery, and (4) improvements in tissue-level perfusion as indicated by ST-segment resolution and coronary flow reserve. For instance, Brodie and colleagues recently detailed the many benefits of an open artery during PCI[45]. In 1490 consecutive patients treated with primary angioplasty from 1984 to 1997, TIMI 0 or 1 flow was present initially in 81·7% of patients and TIMI 2 or 3 flow was present in 18·3% of patients. Patients with initially patent arteries (TIMI 2 or 3 flow) were less likely to experience cardiogenic shock (1·8% versus 9·4%, $P<0·0001$) and severe left ventricular dysfunction (12·6% versus 19·9%, $P=0·007$) and had greater procedural success (97·4% versus 93·8%, $P=0·02$) than patients who presented with closed arteries. It should be noted that the clinical course in the catheterization laboratory was also less morbid, as patients with open arteries had less ventricular fibrillation (3·3% versus 9·7%, $P=0·0006$) or cardiopulmonary arrest (2·9% versus 6·3%, $P=0·03$) and were less likely to require intra-aortic balloon pumping (8·1% versus 15·7%, $P=0·001$) or temporary pacing (12·9% versus 22%, $P=0·007$).

In addition, treatment with combination therapy, by maximizing patency of the infarct-related artery, may facilitate the performance and outcome of PCI. de Lemos and colleagues have presented data on 105 patients (12%) in the TIMI 14 trial who underwent PCI after 90-min angiography[46]. Using ST-segment resolution as a marker for tissue-level reperfusion, the relationships between PCI, combination therapy with low-dose alteplase plus abciximab, and TIMI flow were explored. In patients who underwent PCI, there was a greater rate of ST-segment resolution in those who had received combination therapy with alteplase plus abciximab compared with those who had received fibrinolytics alone (49% versus 8%, $P=0·002$). This difference was even more marked in patients who had TIMI 3 flow prior to PCI (57% versus 1%, $P=0·04$). Likewise, in patients who received combination therapy and who had TIMI 3 flow, ST-segment resolution was greater in those who underwent early PCI than in those who did not (57% versus 24%, $P=0·006$)[47]. These results suggest that

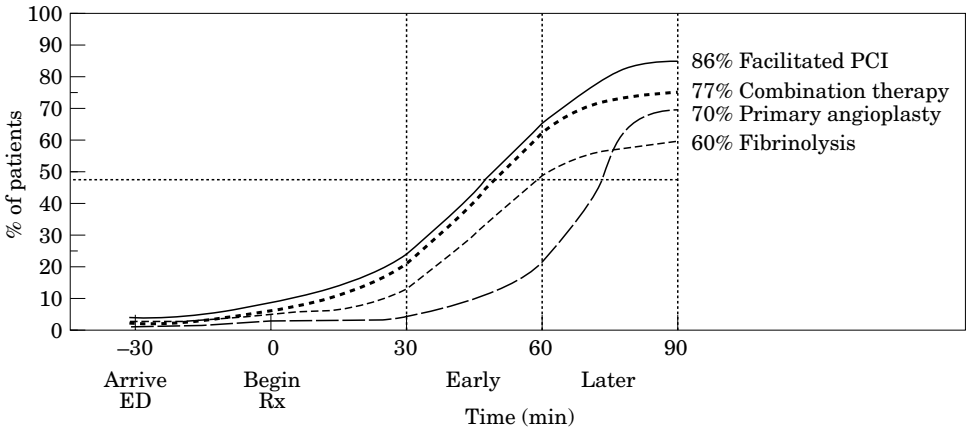

Figure 5 **TIMI 3 flow rate comparisons for treatment of acute MI. Facilitated PCI includes a fibrinolytic, a GP IIb/IIIa receptor inhibitor, and early percutaneous intervention. Combination therapy includes a fibrinolytic plus a GP IIb/IIIa receptor inhibitor. (Adapted with permission[41].)**

combination therapy facilitates tissue-level reperfusion in patients who undergo early PCI even in the setting of TIMI 3 flow prior to intervention.

Conclusions

In summary, facilitated PCI for acute MI involves the combination of fibrinolytics, GP IIb/IIIa receptor inhibitors and early percutaneous intervention to maximize the degree of reperfusion to both epicardial vessels and the microvasculature for optimum clinical benefit. Although early studies showed no benefit and increased risk of performing early PCI in a fibrinolytic milieu, there is a growing body of evidence indicating not only that these treatment modalities can be used together safely, but that both angiographic and clinical outcomes may be enhanced with their combination.

Although previous discussion has frequently focused on whether fibrinolysis or primary PTCA provides the best outcome based on the incidence of TIMI 3 flow at 90 min, the time at which normal flow is achieved is equally important[48]. The combination pharmacological approach of abciximab and reduced-dose reteplase or alteplase can improve TIMI grade 3 flow by an absolute amount of 10–15% at 60 min[32,33]. Primary angioplasty can achieve higher patency rates but generally at later time points[23,48]. The addition of early facilitated PCI in the SPEED trial resulted in an extremely high core laboratory-assessed TIMI grade 3 flow rate (86%) and a normal mean corrected TIMI frame count, without sacrificing the early benefit (between 30 and 60 min) of a pharmacological approach (Fig. 5)[41]. Combination therapy has the potential to improve both very early and later reperfusion. However, the mortality benefit and safety of combined therapy must first be validated in a large trial, such as the current GUSTO V trial. Similarly, the benefits of facilitated PCI should be confirmed in a prospective, randomized trial. Two such trials, one called Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) using reteplase and abciximab and another using tenecteplase and tirofiban, are planned.

References

[1] Simes RJ, Topol EJ, Holmes DR Jr *et al.* Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. Circulation 1995; 91: 1923–8.
[2] Ross AM, Coyne KS, Moreya E *et al.* Extended mortality benefit of early postinfarction reperfusion. Circulation 1998; 97: 1549–55.
[3] Lange RA, Hillis LD, Grines CL. Should thrombolysis or primary angioplasty be the treatment of choice for acute myocardial infarction? N Engl J Med 1996; 335: 1311–7.
[4] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). N Engl J Med 1992; 326: 242–50.
[5] Coller BS. Platelets and thrombolytic therapy. N Engl J Med 1990; 322: 33–42.
[6] Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (2). N Engl J Med 1992; 326: 310–8.
[7] Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995; 92: 657–71.
[8] Mizuno K, Satomura K, Miyamoto A *et al.* Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. N Engl J Med 1992; 326: 287–91.
[9] Van Belle E, Lablanche JM, Bauters C *et al.* Coronary angioscopic findings in the infarct-related vessel within 1 month of acute myocardial infarction: natural history and the effect of thrombolysis. Circulation 1998; 97: 26–33.
[10] Cannon CP. Overcoming thrombolytic resistance: rationale and initial clinical experience combining thrombolytic therapy and glycoprotein IIb/IIIa receptor inhibition for acute myocardial infarction. J Am Coll Cardiol 1999; 34: 1395–402.
[11] Gruppo Italiano per lo Studio Della Sopravivenza nell'Infarto Miocardico. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Lancet 1990; 336: 65–71.

[12] The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329: 673–82.
[13] 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.
[14] 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 randomised trials of more than 1000 patients. Lancet 1994; 343: 311–22.
[15] Ohman EM, Califf RM, Topol EJ *et al*. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. Circulation 1990; 82: 781–91.
[16] Lincoff AM, Topol EJ. Illusion of reperfusion: does anyone achieve optimal reperfusion during acute myocardial infarction? Circulation 1993; 88: 1361–74.
[17] Grines CL, Browne KF, Marco J *et al*. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993; 328: 673–9.
[18] Zijlstra F, de Boer MJ, Hoorntje JC *et al*. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993; 328: 680–4.
[19] Gibbons RJ, Holmes DR, Reeder GS *et al*. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993; 328: 685–91.
[20] The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997; 336: 1621–8.
[21] Weaver WD, Simes RJ, Betriu A *et al*. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997; 278: 2093–8.
[22] Zijlstra F, Hoorntje JC, De Boer MJ *et al*. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999; 341: 1413–9.
[23] Grines CL, Cox DA, Stone GW *et al*. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999; 341: 1949–56.
[24] Antoniucci D, Santoro GM, Bolognese L *et al*. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction: results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. J Am Coll Cardiol 1998; 31: 1234–9.
[25] Saito S, Hosokawa G, Tanaka S, Nakamura S. Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the Primary Angioplasty Versus Stent Implantation in Acute Myocardial Infarction (PASTA) trial. Cathet Cardiovasc Interv 1999; 48: 262–8.
[26] Every NR, Parsons LS, Hlatky M *et al*. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. N Engl J Med 1996; 335: 1253–60.
[27] Cannon CP, Gibson M, Lambrew CT *et al*. Relationship of time to treatment and door-to-balloon time to mortality in 27 080 patients with acute myocardial infarction treated with primary angioplasty (Abstr). Circulation 1999; 100 (Suppl I): I-360.
[28] Herrmann HC. Triple therapy for acute myocardial infarction: combining fibrinolysis, platelet IIb/IIIa inhibition, and percutaneous coronary intervention. Am J Cardiol 2000; 85 (Suppl): 10C–16C.
[29] Kleiman NS, Ohman EM, Califf RM *et al*. Profound inhibition of platelet aggregation with monoclonal antibody 7E3 Fab after thrombolytic therapy: results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 pilot study. J Am Coll Cardiol 1993; 22: 381–9.
[30] Ohman EM, Kleiman NS, Gacioch G *et al*. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction: results of a randomized, placebo-controlled, dose-ranging trial. Circulation 1997; 95: 846–54.
[31] The PARADIGM Investigators. Combining thrombolysis with the platelet glycoprotein IIb/IIIa inhibitor lamifiban: results of the Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction (PARADIGM) trial. J Am Coll Cardiol 1998; 32: 2003–10.
[32] Antman EM, Giugliano RP, Gibson CM *et al*. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis In Myocardial Infarction (TIMI) 14 trial. Circulation 1999; 99: 2720–32.
[33] The Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000; 101: 2788–94.
[34] Topol EJ, Califf RM, George BS *et al*. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987; 317: 581–8.
[35] The TIMI Research Group. Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction: TIMI IIA results. JAMA 1988; 260: 2849–58.
[36] Simoons ML, Arnold AE, Betriu A *et al*. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. Lancet 1988; i: 197–203.
[37] SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. BMJ 1991; 302: 555–60.
[38] Ryan TJ. Angioplasty in acute myocardial infarction: is the balloon leaking? N Engl J Med 1987; 317: 624–6.
[39] Cheitlin MD. The aggressive war on acute myocardial infarction: is the blitzkrieg strategy changing? JAMA 1988; 260: 2894–6.
[40] Ross AM, Coyne KS, Reiner JS *et al*. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT Trial. J Am Coll Cardiol 1999; 34: 1954–62.
[41] Herrmann HC, Moliterno DJ, Ohman EM *et al*. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction: results from the SPEED (GUSTO-4 Pilot) Trial. J Am Coll Cardiol 2000; 36: 1489–96.
[42] Brener SJ, Barr LA, Burchenal JEB *et al*. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998; 98: 734–41.
[43] Montalescot G, Barragan P, Wittenberg O *et al*. Abciximab associated with primary angioplasty and stenting in acute myocardial infarction: the ADMIRAL study, 30 day final results (Abstr). Circulation 1999; 100 (Suppl I): I-87.
[44] Miller JM, Smalling R, Ohman EM *et al*. Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction (results from the GUSTO-III trial). Am J Cardiol 1999; 84: 779–84.
[45] Brodie BR, Stuckey TD, Hansen C *et al*. Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. Am J Cardiol 2000; 85: 13–18.

[46] de Lemos JA, Antman EM, Gibson CM *et al*. Abciximab improves both epicardial flow and myocardial reperfusion in ST-elevation myocardial infarction: observations from the TIMI 14 trial. Circulation 2000; 101: 239–43.
[47] de Lemos JA, Gibson CM, Antman EM *et al*. Abciximab improves microvascular perfusion after rescue PCI: a TIMI 14 substudy (Abstr). J Am Coll Cardiol 2000; 35 (Suppl A): 40A.
[48] Gibson CM. Primary angioplasty compared with thrombolysis: new issues in the era of glycoprotein IIb/IIIa inhibition and coronary stenting. Ann Intern Med 1999; 130: 841–7.