Fibrinolytic Therapy
Past, Present, and Future

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HISTORICAL PERSPECTIVE

In 1933 it was first reported by Tillet and Garner that Lancefield Group A beta-hemolytic streptococci isolated from patients produced a fibrinolytic substance (1). Subsequently, MacLeod and Christensen called this substance streptokinase and defined the mechanisms of streptococcal fibrinolysis (2). In 1950, Sherry began to report the clinical potential and applications of this finding (3). Then, the first report of a prolonged infusion of streptokinase appeared in 1958(4) followed but followed by several small studies that found no convincing evidence support the use of fibrinolytic therapy for acute myocardial infarction. During that same period of time, the role of the thrombus was debated and viewed as an inconsistent finding in acute myocardial infarction (5). This contributed significantly to the lack of enthusiasm and widespread interest in pursuing these significant findings.

The quest for arterial patency would need to await the crucial findings of De Wood (6). The identification of the thrombus as the proximate cause of myocardial infarction rekindled the interest in factors that precipitated coronary fibrinolysis and treatments that impeded propagation and facilitated clot lysis. Several clinical trials followed. But these were small by today' standards. Rentrop demonstrated that local infusion of streptokinase into the infarct artery could promptly recanalize the vessel and reestablish flow (7). Observations consistently found a high rate of spontaneous recanalization - but too little, too late. Schroder however introduced and demonstrated the efficacy of a high-dose brief duration intravenous infusion of streptokinase in achieving early recanalization of the infarct vessel (8,9). Finally, tissue plasminogen activator was isolated and found to be effective in clinical trials.

MEGATRIALS

European investigators perceptively recognized that simple large clinical trials with intravenous agents would be necessary for widespread adoption of both the concept and efficacy of fibrinolytic agents. The safety and an appropriate risk-benefit assessment would be important as it was increasingly recognized that intracerebral hemorrhage was a small but clear and definite risk of coronary thrombolysis with a high mortality and residual disability.

The mortality efficacy of streptokinase was evaluated in four large placebo controlled trials. The seminal first GISSI and second ISIS trails clearly established intravenous fibrinolytic therapy as an effective mode for coronary reperfusion(10,11) (Figure 1). Streptokinase is an indirect plasminogen activator and early concerns involved allergic reactions, a hypotensive effect, a systemic hypocoagulable state, and repeat administration. Natural t-PA is produced by vascular endothelium. A theoretical advantage of t-PA was its lack of antigenicity and less fibrinogen depletion. Also, t-PA was found to be more fibrin specific and had the ability to lyse more highly cross-linked fibrin. This presented the theoretical advantage with an ability to increase patency in patients presenting later after symptom onset. A theoretical disadvantage was the need for heparin therapy to sustain patency and prevent reocclusion in the absence of a systemic hypocoagulable state.

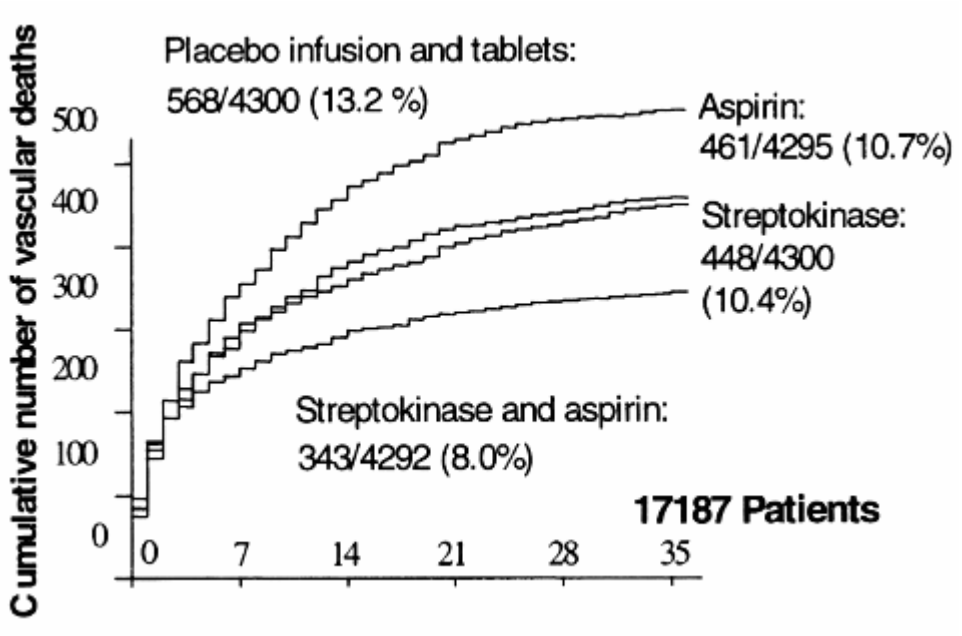

Figure 1: Results from the ISIS-2 trial comparing aspirin and streptokinase alone and in combination with AMI. Aspirin was effective in reducing mortality alone and was additive when given to streptokinase. From ISIS-2 Collaborative Group. Lancet. 1988;2:349-360

Finally, the initial large clinical trials confirmed the importance of early reperfusion. Reimer had demonstrated in dogs that a wavefront phenomenon of myocardial cell death occurred (12) . The absolute 35-day mortality in clinical trials interesting correlated with Reimer's earlier animal experiments. (Figure 2) Early intervention was felt necessary to prevent myocardial necrosis and preserve left ventricular function. A meta-analysis of the early fibrinolytic trials confirmed the importance of early administration as well as efficacy in a broad number of patient subgroups (13) (Figure 3).

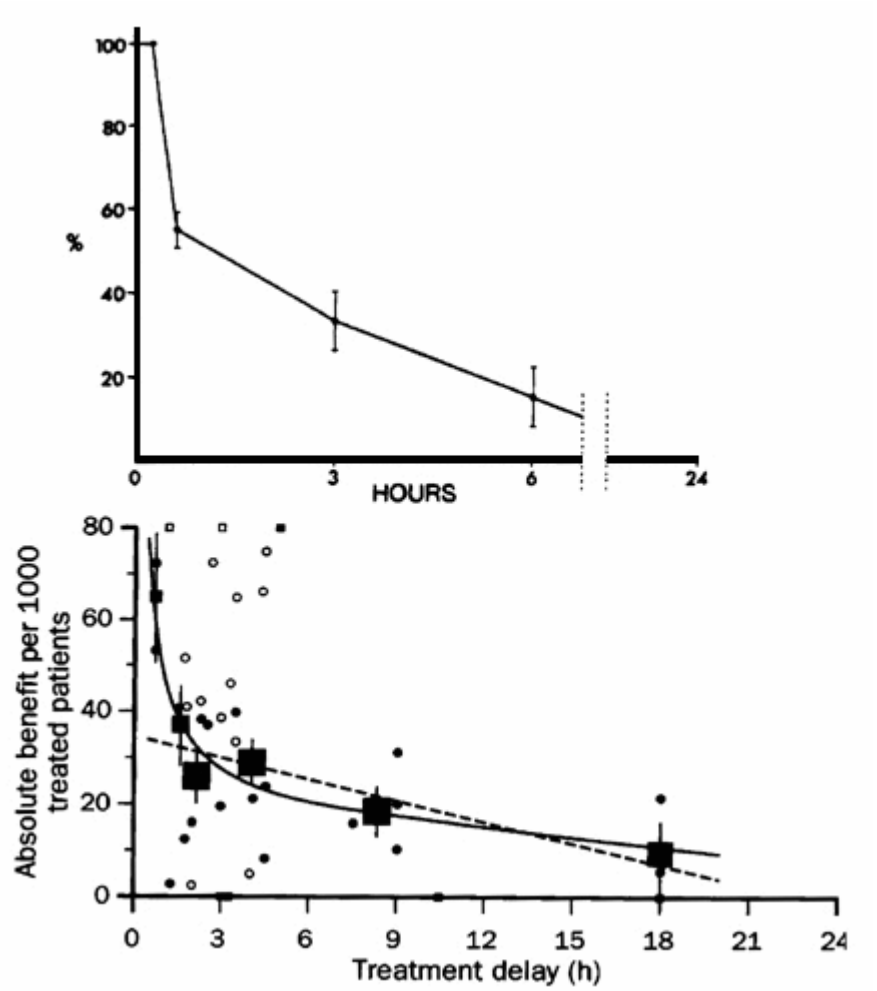

Figure 2: Top Panel. Proportion of ischemic muscle that is viable and potentially salvageable as a function of time after coronary occlusion. From Reimer. Circulation 1977;56:786-94. Bottom Panel. Absolute 35-day mortality plotted as a function of time to treatment. From Boersma, Lancet;1996:771-775

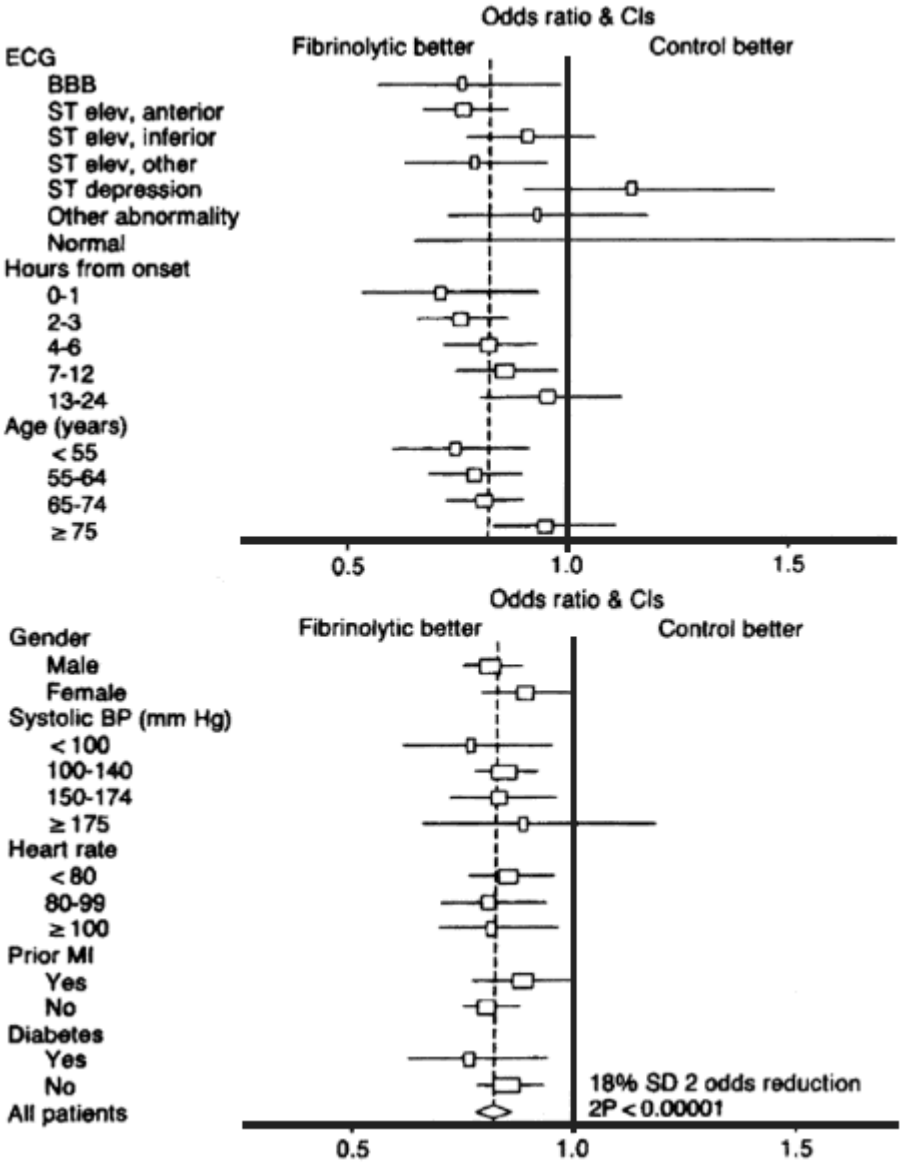

Figure 3: Proportional effects of fibrinolytic therapy and mortality rates in the Fibrinolytic Trialists Collaborative Group (FTT) meta-analysis. In this analysis of 9 major fibrinolytic trials with over 1000 patients, treatment was demonstrated in a wide subgroup of patients including women, diabetics and the elderly. Note the risk of harm in patients with ST-segment depression. Fibrinolytic Trialist. 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. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet. 1994;343:311-22.

THE QUEST FOR OPTIMAL ARTERIAL PATENCY AND THE BEST FIBRINOLYTIC AGENT

The open artery hypothesis links early patency and reduced mortality with improved ventricular function. The TIMI phase one trial compared the effectiveness of streptokinase vs. rt-PA in opening occluded arteries. This study demonstrated that t-PA was superior to streptokinase with twice the rate of open arteries at 90 minutes (70% vs 43%) independent of the baseline angiogram (14). The European Study Group reported similar results (15). However, GISSI-2 and ISIS-3 compared the mortality of the two regimens. In these studies, no mortality benefit was identified(16,17). Several reasons for this were enthusiastically debated. Then, GUSTO-1 reported a higher survival rate (11 patients saved per 1,000 patients treated) and linked this survival to early arterial patency through an angiographic substudy (18). In perspective, a more aggressive accelerated protocol for alteplase and early IV heparin in GUSTO-1 contrasted with the 3 hour infusion of alteplase and duteplase and subcutaneous heparin likely provided the improved results. The open artery hypothesis appeared alive and well, as did the superiority of rt-PA (19).

In recent years, the alternative strategy of direct percutaneous intervention has taken on increasing importance. Angioplasty has been shown to have superior patency rates, less reocclusion, lower intracerebral hemorrhage and equal cost analysis (20-22). The wider appeal of fibrinolytic therapy is attributed to the limited availability and complexity of PCI. However, in the U.S., the current demographic distribution of PCI facilities positions 70% of MI patients within a 45 minute radius of most patients. Additionally, the concept of facilitated PCI (see below) and a renewed interest in "rescue" angioplasty for failed fibrinolysis is again on discussion (23).

Since clinical trials have clearly shown the benefit of initiating fibrinolytic therapy early in numerous patient subgroups, earlier prehospital or in-home administration of thrombolysis (whatever the agent) was a logical concept. In fact, fibrinolytic therapy given in the community as a very early intervention has been demonstrated to improve survival, but results have been variable and confounded. A meta-analysis by European investigators found a 17% improvement in survival (24). In general, the prehospital administration of fibrinolytics improves survival when transport times are long or emergency department administration delayed. Reviewing this information, the recently published AHA International ECC Guidelines recommends consideration of prehospital fibrinolysis when transport time will exceed 60 minutes or a skilled physician is present, e.g. home or health care facility. (25) The issue of prehospital fibrinolysis is again under review with the availability of newer bolus fibrinolytics.

THE OPEN ARTERY HYPOTHESIS AND THE ILLUSION OF REPERFUSION. A NEW PERSPECTIVE, AN ADDITIONAL PROBLEM

The initial focus of therapy for acute coronary syndromes was the epicardial artery - find them, streptokinase them, and then stretch (angioplasty) them. Visual quantification of epicardial flow was proposed by the TIMI investigators and has become widely accepted: grade 0-no perfusion; grade 1- contrast penetration of the thrombus without distal perfusion; grade 2- partial perfusion with slow entry of dye into the distal bed (compared to other arteries; grade 3- complete normal flow into the distal coronary circulation (26). Initially, successful perfusion was felt to occur if patency and blood flow was reestablished to the distal coronary circulation, e.g. TIMI 2 and TIMI 3 flow. Investigators soon realized however that TIMI 2 flow did not represent effective reperfusion of the myocardium and a patent epicardial artery might only represent an illusion of reperfusion (27).

Microvascular flow has important implications in both unstable angina and ST-segment elevation myocardial infarction. Clinically, the TIMI flow classification scheme was modified and standardized (TIMI frame count) and faster flow was correlated to improved clinical outcomes. More recently, Gibson has used myocardial blushing as a further index of microvascular flow and myocardial perfusion.(28) Even in patients with normal TIMI 3 flow, the myocardial blush grade can define a low and high risk patient group. (Figure 4) These parameters of microvascular flow have been correlated with ST-segment resolution allowing for evaluation and monitoring of a clinically useful tool to assess risk and prognosis following intervention.

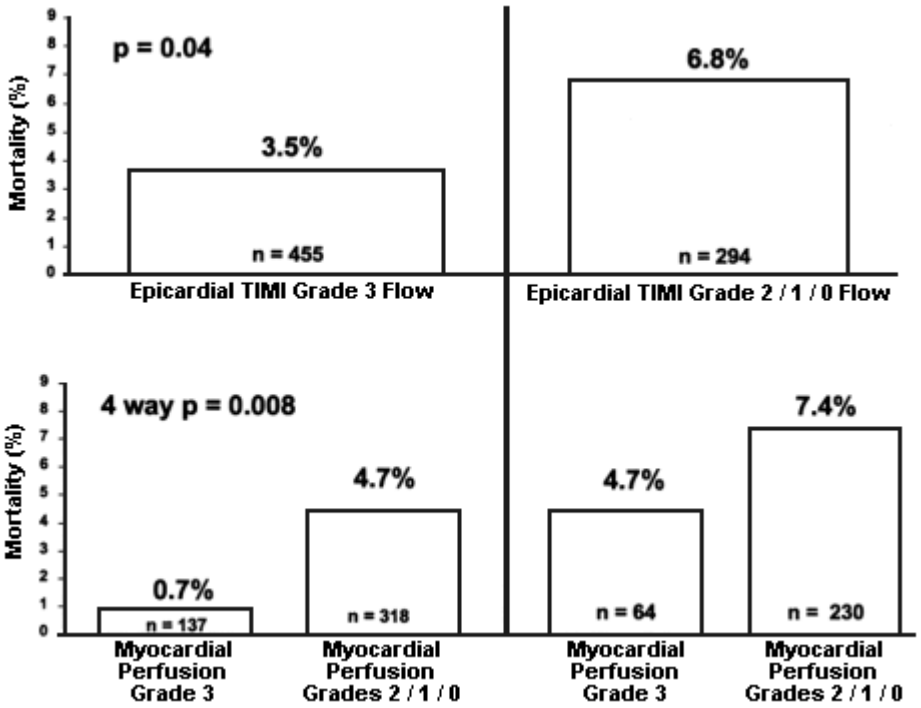

Figure 4: Top Panel. Mortality as a function of TIMI perfusion grade. TIMI Grade 3 Flow confers a 50% reduction in mortality. Bottom Panel. Mortality as a function of myocardial perfusion grade. A normal myocardial perfusion grade predicts reduced mortality even in those patients with normal epicardial TIMI 3 flow. Conversely, TIMI 3 flow may not imply myocardial perfusion-" the illusion of reperfusion" From Gibson, Circulation 2000; 101:125-130

Current and future fibrinolytic strategies must take into account not only sustained early patency, but microvascular perfusion at the myocardial cell level.

BOLUS ADMINISTRATION. QUICKER IS BETTER?

Reteplase (r-PA) was one of the first bolus lytics and mutant variations of wild-t-PA to undergo large clinical testing. Dosing studies and observations suggested the maximal efficacy of r-PA occurred when two 10U boluses were given thirty minutes apart. The INJECT trial evaluated 30 day mortality and found that r-PA was at least equivalent to streptokinase (29). Two angiographic trials compared reteplase with alteplase. The RAPID-1 and RAPID-2 trails evaluated TIMI grade 3 flow at 90 minutes and found that r-PA was superior (30,31). Although mortality was less in the RAPID trials, this observation required confirmation in a larger clinical trial. This clinical trial was GUSTO-3, designed as a superiority trial with 30 day mortality as the primary end-point. Over 15,000 patients presenting within 6 hours were randomized within 6 hours of symptom onset. The mortality endpoint was achieved in 7.47% of r-PA patients and 7.24% of alteplase patients32. Thus, superiority of r-PA was not achieved.

Tenecteplase or TNK-tPA is a deletion mutant of naturally occurring t-PA which can be administered as a single bolus. TNK-PA is more fibrin specific than alteplase or reteplase. A slower plasma clearance allows for single bolus administration. Clinical testing of TNK-tPA began with the TIMI-10A and ASSENT-1 trials (33,34). Initial rates of intracranial hemorrhage and severe bleeding were increased but, importantly, were reduced with an adjustment of heparin dosage. TNK-tPA was compared to alteplase in ASSENT 2, a large randomized equivalency study (35). Equivalency was observed in mortality with a relative risk of 1.00 for 30 day mortality. This equivalence persisted in subgroup analysis. Interestingly, patients treated after 4 hours had improved outcomes with TNK-tPA, a theoretical benefit attributed to the greater fibrin specificity of TNK-tPA. An analysis of the GUSTO-3 trial found similar effects with alteplase more effective than r-PA. A thrombus may be more resistant the longer it matures with fibrin cross-linking.

Lanoteplase (n-PA) is another deletion mutant of naturally occurring t-PA. Initial testing demonstrated a trend towards high TIMI-3 flow rates. The IN-TIME -2 trial was a large randomized equivalency trial testing

120KU/kg of lanoteplase with accelerated alteplase. The 30-day mortality rates were similar between the two agents, but intracranial hemorrhage was significantly higher with n-PA (1.13% vs 0.62% p < [less than] 0.003) (36). As a result, the agent is not presently being developed for clinical use.

THE IDEAL FIBRINOLYTIC AGENT

An ideal fibrinolytic agent would achieve 100% patency in a short time period and have minimal bleeding complications. This agent would be easily administered as a bolus, have a prolonged half-life and slow plasma clearance. It would bed highly fibrin specific with little or no fibrinogen depletion. In addition, it would improve microvascular function and flow.

Despite general perceptions, treatment outcomes with fibrinolytic therapy are even far from optimal. Current fibrinolytic regimens restore patency in approximately half the patients treated with present day regimens. New information and data have focused attention on the importance of microvascular function and myocellular perfusion. Full myocardial perfusion is absent in a significant number of patients, leaving only 30%-45% of patients with optimal myocardial flow. At issue also is a reocclusion rate of 10-15% over time.

Efforts to improve vessel patency with more potent regimens or increased fibrin specificity have resulted in unacceptable rates of intracerebral bleeding. This has resulted in the impression that a "ceiling" persists for vessel patency. Two concepts have been proposed to improve reperfusion based on results from clinical trials and an accumulating appreciation of the mechanisms involved in the complex pathophysiology of thrombosis and myocellular function. First, fibrinolytic therapy is more appropriately fibrinolytic therapy. In additional to fibrinolysis, other important targets involve antiplatelet and antithrombin therapy. The second concept recognizes that fibrinolytic therapy and direct percutaneous intervention are not exclusive therapies. In patient subgroups, in fact, they may be complementary and facilitate synergistic outcomes.

FACILITATED FIBRINOLYSIS AND PERCUTANEOUS INTERVENTION

The importance of platelet function and the lack or paradoxic effect of fibrinolytic therapy on platelet activation and aggravation provided the stimulus and rationale for combining GPIIb/IIIa inhibitor therapy with fibrinolytic agents. Initial studies provided promising results and included IMPACT-AMI (alteplase/eptifibatide), TIMI 14 (SK, alteplase, reteplase and abciximab), and SPEED (reteplase and abciximab)(37-39). In aggregate, these trials demonstrated that combination therapy improved TIMI-3 flow and patency at 60 or 90 minutes. These trials were not powered to evaluate major bleeding or mortality.

The GUSTO-V trial randomized 16, 588 patients within the first 6 hours of an evolving ST-elevation infarction to standard dose reteplase or half-dose reteplase and full dose abciximab. In this trial, no difference in 30-day mortality was observed between the two regimens. Of note, the mortality was extremely low in this clinical trial (5.9% reteplase vs 5.6% combined regimen) (40). There was however a reduction in secondary endpoints, including reinfarction and recurrent ischemia albeit at an apparent increase in major non-intracranial bleeding.

The ASSENT-3 trial compared three fibrinolytic adjuncts with tenecteplase. Full- dose tenecteplase and weight adjusted unfractionated heparin was compared with half-dose tenecteplase and weight-adjusted low-dose unfractionated heparin or full-dose tenecteplase and enoxaparin (41). Composite endpoints for safety and safety plus efficacy were reviewed. The tenecteplase plus enoxaparin or abciximab regimens reduced the frequency of ischemic complications. The enoxaparin group had fewer bleeding complications and is more convenient to use. The trial investigators concluded that the enoxaparin regimen was an attractive alternative warranting further study.

The use of percutaneous coronary intervention is a superior reperfusion modality compared to current fibrinolytic regimens and is preferred when an experienced operator and facility is available. PCI will be discussed in another paper in this Congress. However, the addition of GP IIb/IIIa inhibitors appears

promising in addressing microvascular dysfunction limiting the efficacy of PCI.

SUMMARY AND CONCLUSIONS

The reperfusion era has demonstrated that sustained early patency of the infarct artery is paramount to the efficacy of fibrinolytic regimens. Major intracerebral hemorrhage and other bleeding complications have limited attempts at increased efficacy in the context of low trial mortality rates, confounding variable undoubtedly due to other adjunctive therapies. We now realize that fibrin lysis is only one component of the reperfusion challenge. New data have also emphasized the role of the microvasculature and the importance of microvascular function. Major advances will come in the areas of targeted antiplatelet and antithrombotic therapy and the appropriate use of facilitated and "rescue" PCI with appropriate risk-stratification of patient subgroups. At this time, earlier patient presentation does not seem feasible. However, the largest improvement in numbers of lives saved will not come from a new agent or regimen, but from broader application of existing strategies to all eligible patients in an expedient manner.

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