The rationale for thrombolytic therapy

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Substantial progress has been made toward understanding the pathophysiological processes that lead to acute myocardial infarction. Research has shown that the mechanism of infarction is the rupture of an atherosclerotic plaque with a subsequent thrombogenic response from exposed subendothelial tissue, leading to additional or complete obstruction of the vessel. Myocardial cell death then proceeds in a wavefront fashion from the subendocardium to the epicardium. Time to myocardial reperfusion and the extent of collateral flow are the primary determinants of final infarct area. This knowledge led to the development of therapeutic strategies to achieve early and sustained reperfusion of the infarct-related vessel, the presumption being that this would result in increased myocardial salvage and better residual left ventricular function in addition to reductions in infarct expansion and electrical instability.

The results of several large thrombolytic trials have supported this model, showing that patients who receive thrombolytic therapy derive a constant relative survival benefit when compared with control patients. The largest comparative thrombolytic trial to date has shown that therapies that result in early, more complete reperfusion are indeed associated with lower mortality; however, these therapies may be associated with higher rate of complications such as intracranial haemorrhage and reocclusion. Future evaluations must include assessment of the benefits relative to the risks of newer, more potent thrombolytic regimens.

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Key Words: Acute myocardial infarction, thrombolysis, myocardial reperfusion, open vessel concept, tissue plasminogen activator, streptokinase, heparin.

Introduction

Acute myocardial infarction (AMI) has been a focus of intense research since it became clear that ischaemic heart disease is the leading cause of death in the Western World. Herrick[1] recognized the likelihood that coronary thrombosis was the precipitating event for AMI; however, it is only during the last two decades that fibrinolytic drugs have been used to encourage early reperfusion of the infarcting myocardium with a resulting substantial reduction in morbidity and mortality.

This review considers the basis for administering thrombolytic therapy to patients with AMI, describes the conceptual model for evaluating new approaches to therapy, and details progress being made in the quest for more effective treatment.

What causes acute myocardial infarction?

DeWood and his colleagues were the first to demonstrate that coronary occlusion was typically present in patients with AMI, and this was especially evident when an angiogram was obtained soon after the onset of symptoms and the electrocardiogram (ECG) revealed ST-segment elevation[2]. Intra-operative studies demonstrated that such occlusions were predominantly due to coronary thrombosis[3]. These early observations accelerated interest in the understanding and treatment of AMI and stimulated many subsequent advances.

Coronary thrombosis emanates from a series of events that culminate in a disrupted atherosclerotic plaque. Plaques with large lipid cores and infiltrations of macrophages in the fibrous cap appear to be particularly vulnerable to disruption; these plaques generally cause an angiographically determined stenosis of <50% before the acute event. However, the biological features of plaques that make some vulnerable, while others are at low risk for disruption, remain obscure[3,4].

Besides endogenous factors, the influence of the sympathetic nervous system, physiological events, and other extrinsic factors may transform a vulnerable plaque into a pathological lesion. Psychological or physiological events that precipitate an acute event — so-called ischaemic triggers — include mental stress, sudden exercise, assuming an upright position after reclining, and cigarette smoking. The circadian variation in the risk of AMI appears to result from both a circadian variation in coagulability and the profound
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**Figure 1** A conceptual model relating changes in ejection fraction (ΔEF) from pre-intervention to serial angiography, duration of infarct symptoms, and pre-intervention EF (initial EF). The two key factors are the duration of symptoms before reperfusion and the size of the infarction. (Reprinted from Rentrop et al.\textsuperscript{[10]} with permission.)

...effect of arising from bed after sleep\textsuperscript{[5]}. Whether variation in the balance between coagulation and fibrinolysis at the physiological level has an effect on the response to thrombolysis in the presence of increased exogenous plasminogen activator remains unclear; however, several studies have also described decreased coronary perfusion in the early morning hours\textsuperscript{[6-7]}. When a plaque becomes disrupted, the coronary arterial subendothelial tissues are exposed to the circulation. This results in activation of the coagulation system, probably through the effect of a tissue factor. After this point, a complex series of events occurs, leading to further obstruction or complete occlusion of the vessel and the accompanying clinical sequelae.

**Basic model**

The fundamental understanding of the benefit of myocardial reperfusion resulted from a series of experiments in animals performed by Reimer and associates\textsuperscript{[8]}. Other investigators have corroborated these initial observations. By occluding a coronary epicardial artery in the dog, and releasing the occlusion at different points in time, Reimer et al. were able to simulate the effects of acute thrombotic occlusion followed by reperfusion. Myocardial cell death began within 15 min of coronary occlusion and proceeded in a ‘wavefront’ fashion from the subendocardium out to the epicardium. This ‘inside-out’ cell necrosis was shown to result from the greater metabolic demands of the endocardium, an inevitable flow gradient due to the loss of pressure as the vessels traverse the myocardium, and a paucity of collateral vessels in endocardial tissue compared with the epicardial myocardium. By progressively releasing the occlusion over time, these same investigators demonstrated that myocardial salvage occurs from the epicardium inward, in reverse order from the wavefront.

Other than the time to reperfusion, the only major factor altering the final infarct size in the dog model was the extent of collateral flow to the ischaemic region\textsuperscript{[9]}. With well-developed collaterals, infarction may be almost totally prevented. Indeed, the amount of myocardial salvage differs considerably, from species to species, as a function of the extent of collateral flow.

Despite numerous attempts to develop agents to alter these basic relationships, none has yet been proved to do so. Restoration of coronary blood flow is the only technique that has been demonstrated to be successful in reducing infarct size. Therapies designed to prevent reperfusion injury or to reduce myocardial oxygen demand have not influenced infarct size or the clinical consequences of AMI.

**Clinical model**

A practical approach to the application of thrombolysis in humans was described by Rentrop and his colleagues in 1983\textsuperscript{[10]} (Fig. 1). These authors postulated that the degree of improvement in left ventricular function due to reperfusion would be proportional to the duration of the symptoms and the extent of the myocardium at risk (the greater the region at risk, the larger the amount of anticipated gain). This model presumes that the benefit of thrombolytic therapy is achieved by early reperfusion.
leading to more extensive salvage of myocardium and better residual left ventricular function. Improved left ventricular function should result in lower mortality, fewer complications of infarction, and reduced cost. Of course, this fundamental model is subject to the many vicissitudes of the human condition: variable collateral flow, inability to determine the exact time of coronary occlusion, uncertainty concerning the exact time of reperfusion, and a propensity for reocclusion. Thus, the exact nature of the relationship between determinants is imprecisely reflected in clinical measurements.

Measuring the effect of thrombolytic treatment

To determine an effect of treatment on survival requires an enormous number of patients. Non-fatal end-points are fraught with subjectivity when dependent on clinical observation, and many measurements that could be considered more objective are frequently not available because the patient died, a technical issue prevented adequate acquisition of data, or the patient declined the procedure.

Several concepts are critical in assessing the measured benefits of a therapy such as thrombolyis. The ‘relative’ benefit refers to the proportion of improvement in the treated patients when compared with that of the control patients. The relative benefit of a treatment tends to remain homogeneous across subgroups of a population with a given disease. For example, in the analysis by the Fibrinolytic Therapy Trialists’ (FTT) collaboration, an 18% reduction in death was observed overall for patients with AMI, and only patients with ST-segment depression showed a statistically significant deviation from the estimate. In all other subgroups, the observed mortality reduction included 18% (95% confidence interval) for the estimated treatment effect. The relative benefit, usually expressed as an odds ratio or relative risk, may be considered the best measure of the effects of a treatment.

The ‘absolute’ benefit refers to the absolute difference in rates between the treated group and a control group. In clinical decision making, the absolute benefit is more useful than the relative benefit because it provides an estimate of the number of patients who will experience improvement (a function of the number needed to treat). This concept has been expressed as the number needed to treat (NNT), which is calculated as number of lives saved per number treated divided by 100. In general, since the relative benefit tends to be constant, the absolute benefit increases as a function of the underlying risk of the population. This general observation provides impetus for the ‘no pain, no gain’ theory in clinical therapeutics: patients with the most to gain from an effective therapy are usually those who are the sickest and have the greatest propensity for complications or adverse effects of therapy.

Pathophysiological links

During the first few years after the introduction of thrombolytic therapy, the Rentrop model was assumed to be correct. The critical Second International Study of Infarct Survival (ISIS-2) and Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) trials showed administration of streptokinase to have results superior to those of conservative management of infarction. The ISIS-2 and GISSI trials contributed the majority of patients included in the FTT collaboration, which provided a combined database of individual patient data from all controlled trials of fibrinolytic therapy. A consistent benefit of fibrinolytic therapy is observed with a constant relative benefit, except in patients with ST-segment depression (Fig. 2). With this approximately constant relative benefit, the absolute benefit is greatest in the subgroups at highest risk determined by haemodynamic markers of large infarction or general factors such as advanced age. Smaller, more detailed studies have demonstrated that the degree of ST-segment elevation is another marker for potentially greater benefit, i.e. patients with higher levels of ST-segment elevation achieve more benefit.

Several baseline characteristics provide some evidence of possible deviation from the general principle of constant proportional benefit. In all these instances, large numbers of patients are required to reach statistical certainty of a differential treatment effect.

Location of infarction

Patients with anterior infarction who received thrombolytic therapy demonstrated a 30% reduction in mortality compared with 15% in those with inferior infarction. These proportional differences, coupled with the higher baseline risk in anterior infarction, resulted in an NNT of only 31 in anterior infarction compared with an absolute difference of 0-9% (NNT>100) for inferior infarction. Yet the 95% confidence limits for the benefit of treatment broadly overlap.

Treatment effect and age

The relationship between treatment effect and age raises some interesting questions. Patients younger than 55 years have a very low risk of death without thrombolytic therapy; thus, they have only a small absolute benefit. The absolute benefit increases incrementally with age until the age of 75 years, after which the relative benefit seems to decrease. Again, these results are not definitive, and whether there is a true diminution in effect in patients older than 75 years or whether those results represent random occurrence remains uncertain.

Timing and treatment benefit

Most pertinent to the paradigm is the relationship between time to treatment and subsequent benefit. An
A fibrin-specific agent, t-PA had ample documentation that it was superior to streptokinase in providing early benefit, and GISSI-2 and ISIS-3 studies were designed to compare two thrombolytic agents, streptokinase and tissue plasminogen activator (t-PA) [16-17]. Developed as a fibrin-specific agent, t-PA had ample documentation that it was superior to streptokinase in providing early benefit. Many investigators anticipated that this superior early patency would result in greater myocardial salvage, improved left ventricular function, and lower mortality.

The combined results of the GISSI-2 and ISIS-3 studies, which demonstrated no difference in mortality, led to a re-examination of the entire paradigm [116,117]. Several possibilities could explain the lack of mortality difference between treatment groups in these two large trials. The previous perfusion data could have been incorrect; however, the number of angiographic observations was sufficient to make this explanation unlikely. Because of the large number of patients in the ISIS-3 and GISSI-2 international studies, random chance could not be invoked. Neither trial used intravenous heparin with t-PA, a practice supported by the results of several randomization trials [18-20]. The ISIS-3 trial used duteplase, a different form of t-PA with little published perfusion or outcome data; this explanation does not pertain to the GISSI-2 international study, however.

### Comparative studies to establish benefits of thrombolytics

The GISSI-2 and ISIS-3 studies were designed to compare two thrombolytic agents, streptokinase and tissue plasminogen activator (t-PA) [16,17]. Developed as a fibrin-specific agent, t-PA had ample documentation that it was superior to streptokinase in providing early patency. Many investigators anticipated that this superior early patency would result in greater myocardial salvage, improved left ventricular function, and lower mortality.

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### Table: Presentation features

<table>
<thead>
<tr>
<th>Presentation features</th>
<th>Percent of patients dead</th>
<th>Odds ratio &amp; CIs</th>
<th>Chi-square test of odds ratios in different patient categories:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Fibrinolytic</td>
<td>Control</td>
<td>Odds ratio &amp; CIs</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td>-O-E</td>
</tr>
<tr>
<td>Normal</td>
<td>18.7%</td>
<td>23.6%</td>
<td>2.45</td>
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<tr>
<td>ST elev, anterior</td>
<td>13.2%</td>
<td>16.9%</td>
<td>12.0</td>
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<tr>
<td>ST elev, inferior</td>
<td>7.5%</td>
<td>8.4%</td>
<td>3.71</td>
</tr>
<tr>
<td>ST elev, other</td>
<td>10.6%</td>
<td>13.4%</td>
<td>2.42</td>
</tr>
<tr>
<td>ST depression</td>
<td>15.2%</td>
<td>16.8%</td>
<td>1.29</td>
</tr>
<tr>
<td>Other abnormality</td>
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<td>5.6%</td>
<td>0.95</td>
</tr>
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<td>Normal</td>
<td>3.0%</td>
<td>2.3%</td>
<td>3.4</td>
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<td>Hours from onset</td>
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<td>-O-E</td>
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<tr>
<td>0-1</td>
<td>9.5%</td>
<td>13.0%</td>
<td>2.93</td>
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<td>2-3</td>
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<td>4-6</td>
<td>9.7%</td>
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</tr>
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<td>7-12</td>
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<td>12.7%</td>
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</tr>
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<td>13-24</td>
<td>10.0%</td>
<td>10.5%</td>
<td>1.11</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>-O-E</td>
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<tr>
<td>&lt; 65</td>
<td>3.4%</td>
<td>4.6%</td>
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<td>65-74</td>
<td>7.2%</td>
<td>8.8%</td>
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<tr>
<td>75+</td>
<td>24.3%</td>
<td>25.3%</td>
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<td>Gender</td>
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<tr>
<td>Male</td>
<td>8.2%</td>
<td>10.1%</td>
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<tr>
<td>Female</td>
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<td>16.0%</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<td>&lt; 100</td>
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<td>35.1%</td>
<td>3.38</td>
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<td>100-149</td>
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<td>11.5%</td>
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<td>7.2%</td>
<td>8.7%</td>
<td>0.56</td>
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<tr>
<td>175+</td>
<td>7.2%</td>
<td>8.2%</td>
<td>1.10</td>
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<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td>-O-E</td>
</tr>
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<td>&lt; 60</td>
<td>7.2%</td>
<td>8.5%</td>
<td>0.83</td>
</tr>
<tr>
<td>60-99</td>
<td>9.2%</td>
<td>11.3%</td>
<td>0.85</td>
</tr>
<tr>
<td>100+</td>
<td>17.4%</td>
<td>20.7%</td>
<td>0.51</td>
</tr>
<tr>
<td>Prior MI</td>
<td></td>
<td></td>
<td>-O-E</td>
</tr>
<tr>
<td>Yes</td>
<td>12.5%</td>
<td>14.1%</td>
<td>0.43</td>
</tr>
<tr>
<td>No</td>
<td>8.9%</td>
<td>10.9%</td>
<td>0.22</td>
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<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>-O-E</td>
</tr>
<tr>
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<td>13.6%</td>
<td>17.3%</td>
<td>0.41</td>
</tr>
<tr>
<td>No</td>
<td>8.7%</td>
<td>10.2%</td>
<td>0.14</td>
</tr>
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<table>
<thead>
<tr>
<th>ALL PATIENTS</th>
<th>2820/29315</th>
<th>3357/29285</th>
<th>-269.5</th>
<th>1377.4</th>
<th>18% SD 2 odds reduction</th>
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<tbody>
<tr>
<td></td>
<td>0.6%</td>
<td>11.3%</td>
<td></td>
<td></td>
<td>2P&lt;0.00001</td>
</tr>
</tbody>
</table>

Figure 2 Proportional effect of fibrinolytic therapy on mortality during days 0–35, subdivided by presentation features. 'Observed minus expected' (0–E) number of events among fibrinolytic-allocated patients (and its variance) is given for subdivisions of presentation features, stratified by trial. This is used to calculate odds ratios (ORs) of death among patients allocated to fibrinolytic therapy compared with that among those allocated to control. ORs (black squares with areas proportional to amount of 'statistical information' contributed by the trials) are plotted with their 99% confidence indexes (CIs, horizontal lines). Squares to the left of the solid vertical line indicate benefit (significant at 2P<0.01 only where entire CI is to left of vertical line). Overall result and 95% CI is represented by the diamond, with overall proportional reduction in the odds of death and statistical significance given alongside. Chi-square tests for evidence of heterogeneity of, or trends in, size of ORs in subdivisions of each presentation feature are also given. (Reprinted from FTT Collaborative Group [111] with permission.)
Finally, the dosing regimen in both trials was prolonged in an effort to prevent reocclusion.

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial was designed to test the concept that early and sustained reperfusion in MI would reduce mortality\[21\]. The thrombolytic regimens selected included accelerated dosing with alteplase, a regimen that produced a very high early perfusion rate, and streptokinase with either intravenous or subcutaneous heparin. The streptokinase regimens were the standard regimens in worldwide practice at the time of the study. To develop the links between perfusion, left ventricular function, and survival, a 2400-patient angiographic substudy was built into the trial design\[22\]. The substudy design called for half the patients to undergo angiography at 90 min and 7 days; the remainder of the patients were randomized to angiography at 3 h, 24 h, or 7 days.

The main trial and the angiographic substudy produced some expected and some unexpected results. The accelerated t-PA regimen was associated with superior perfusion and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow compared with either streptokinase regimen. Multiple measures demonstrated better left ventricular systolic function after the accelerated t-PA regimen. In addition, mortality rates at 30 days and 1 year were lower — by 10 to 11 lives per 1000 patients treated — in patients randomized to accelerated t-PA\[23\].

When the GUSTO results were examined to evaluate the relationship between perfusion and mortality, an interesting relationship was observed\[24\]. From the perspective of TIMI flow grade regardless of thrombolytic assignment, the link between perfusion and survival is clear\[24\]. Patients with TIMI 3 flow on the initial angiogram had a mortality rate half that of patients with TIMI 0–1 flow. This relationship explains >90% of the variability in mortality in the comparison of drug regimens in GUSTO. A variety of mechanisms could be proposed to explain this finding. A review of previous trials reporting angiographic findings found almost identical results in the aggregated data\[25\]. When non-fatal complications reflecting left ventricular dysfunction were evaluated, better clinical outcomes were again associated with better coronary artery flow.

The open vessel concept

Expansion or stretching of the infarcted myocardium leads to the progressive dilatation of the ventricle with resultant larger diastolic volume and myocardial fibre length\[26\]. As part of this process of 'remodelling', the non-infarcted zone also tends to expand. This process results in a progressive increase in the incidence of congestive heart failure over time, as observed in the Framingham Study\[27\].

Although many of the benefits of thrombolytic therapy result from early reperfusion, a variety of observations have led to the concept that other critical mechanisms may play a role. Studies of the pathophysiological and clinical effects of sustained coronary reperfusion have led to the emergence of the 'open vessel' concept, which holds that outcome is improved by an open vessel independent of (and additive to) early perfusion\[28\–30\].

Of numerous studies of infarct healing, the rat occlusion studies of Hochman and Choo provide the most graphic results\[31\]. Compared with permanent occlusion, reperfusion of an occluded artery at 2 h resulted in substantial myocardial salvage. Whereas later reperfusion did not salvage myocardium, it resulted in a different healing process, allowing the myocardium to be protected from infarct expansion (Fig. 3). The resulting healing process yielded smaller left ventricular volumes.

Reperfusion can cause alterations in infarct expansion through a variety of mechanisms. By decreasing the size of the infarction, perfusion reduces the extent to which the infarct zone expands and, therefore, the extent to which it stretches the non-infarcted zone. Even in the absence of such reduction in infarct size, preservation of the epicardial rim of myocardium may buttress the infarct zone to limit expansion. The manner in which the infarcted myocardium heals may be as critical as initial infarct size reduction. The late reperfusion of ischaemic myocardium produces contraction band necrosis, leading to greater tensile strength of the myocardium\[32\].

Finally, reperfusion may reduce the risk of electrical instability. Most immediate post-myocardial infarction deaths are sudden, the result of ventricular fibrillation. Detailed studies have shown that patients treated with reperfusion therapy are less likely to have ventricular arrhythmias induced at electrophysiological study\[33,34\] and that they less often have abnormal after-depolarizations on the signal-averaged ECG\[35,36\].

Although it is reasonable to expect the sequence of reperfusion to infarct size reduction to improved survival, a variety of factors should be considered when evaluating deviations from a linear relationship between early perfusion and mortality. For perfusion to be beneficial, it must be not only early, but also sustained. The GUSTO trial was notable for identical reocclusion rates in the treatment arms. Reocclusion is associated with a doubling of mortality risk, essentially eliminating the initial treatment benefit\[37\]. Differences between specific thrombolytic agents in reocclusion rates are difficult to establish and require large sample sizes.

Unexpected adverse events must also be contemplated. A major question confronting new thrombolytic regimens is whether improved reperfusion may result in a higher rate of intracranial haemorrhage. The higher rate associated with fibrin-specific agents compared with streptokinase suggests that the incidence of intracranial haemorrhage could be a serious adverse problem with more specific agents. GUSTO IIa, TIMI9, and the third Hirudin for the Improvement of Thrombolysis (HIT-3) trial provide an example of this difficulty: more aggressive adjunctive regimens led to an unacceptable rate.
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Figure 3 Infarct size (percentage of left ventricular muscle mass), transmurality (percentage of transmural necrosis from endocardium to epicardium), and expansion index as a function of timing of reperfusion vs permanent occlusion. Despite similar infarct size and transmurality of infarction between 2 h reperfusion and permanent occlusion, the expansion index was significantly reduced after delayed resumption of coronary flow. (Adapted from Hochman and Choo with permission.)

of intracranial haemorrhage. Moreover, different patient populations may obscure differences in outcome. Selective inclusion of patients treated late, the very elderly, patients with inferior MI, or those with minimal ST-segment elevation could be expected to reduce the apparent incremental gain of a regimen otherwise associated with a higher rate of TIMI 3 perfusion.

Conclusion

Re-establishing patency in acutely occluded coronary arteries has a sound basis in pathophysiological reasoning, basic experimentation, and clinical outcome data. The simplicity of the basic model must be modified by consideration of reocclusion and adverse outcomes not directly related to myocardial reperfusion. Intracranial haemorrhage is the most common example; however, the possibility of other adverse outcomes must be considered in the evaluation of future therapies.

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