An Approach to Evaluating Thrombolytic Therapy in Acute Myocardial Infarction

The ‘Unsatisfactory Outcome’ End Point

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The primary goal of thrombolytic therapy in acute myocardial infarction (AMI) is the early restoration of perfusion and maintenance of viability and function of myocardium that would otherwise undergo necrosis consequent to thrombotic coronary artery occlusion. The salvage achieved by thrombolysis ranges from a minute amount of myocardium of little functional significance to a large mass of heart muscle the necrosis of which could cause death, with an intermediate quantity in most patients. The most dramatic outcome of thrombolytic therapy is reduced in-hospital mortality, but early mortality is a relatively crude end point for measuring variations in the extent to which a given regimen accomplishes the primary goal of thrombolytic therapy defined above. Successful thrombolytic therapy also reduces the frequency of serious complications of AMI such as congestive heart failure and cardiogenic shock. Laboratory measurements reflecting benefit include preservation of left ventricular function and the early reestablishment and subsequent maintenance of patency of the infarct-related coronary artery. The favorable outcome of thrombolytic therapy is in some instances offset by recurrent infarction and by adverse effects, e.g., severe bleeding, including the most serious of all complications—hemorrhagic stroke. These other (nonfatal) outcomes should also be taken into account in assessing thrombolytic therapy.

The favorable effects of thrombolytic therapy have been clearly demonstrated in placebo-controlled trials, and when laboratory measurements such as coronary artery patency or left ventricular function are taken as end points, benefit can be shown in studies comprising only several dozen or a few hundred patients. To compare the effects of thrombolytic therapy and placebo on survival, however, trials involving thousands of patients for each are required. With the exception of special groups of patients, such as those with ST segment depression and those who present relatively late, i.e., more than 6 hours after the onset of symptoms, the benefits of thrombolytic therapy on survival have now been so clearly established that placebo-controlled trials are no longer needed, nor would they be ethical. As currently used, however, thrombolytic therapy is far from optimal in terms of both efficacy and safety; many subgroups of patients with AMI (especially those with advanced age, prior myocardial infarction, diabetes mellitus, and evidence of pump failure at presentation) still do poorly despite this therapy, albeit better than without it. Therefore, the search for the ideal reperfusion strategy continues.

A number of interesting leads currently being explored involve the development of novel thrombolytics, changes in the rate of administration of available thrombolytics, the combination of thrombolytic agents, and the use of thrombolytics coupled to anti-fibrin antibodies. New thrombolytic regimens, as well as conjunctive and adjunctive agents, are becoming available in increasing numbers, and they may be administered in an almost infinite variety of combinations and doses. Although the additional benefits that might be achieved by newer regimens are likely to be considerably smaller than those that have been observed thus far, given the enormous incidence of AMI on a worldwide basis, even relatively small improvements may provide benefit to a very large number of patients in absolute terms, particularly as thrombolytic therapy becomes more widely used.

The Problem

Fortunately, when thrombolytic therapy is used appropriately in patients with AMI suitable for this therapy, mortality occurs less commonly than heretofore, and when early mortality (generally defined as occurring within 7–42 days after AMI) is used as an end point, the number of patients required to compare two or more active treatment regimens is enormous and requires “megatrails” involving tens of thousands of patients. The GISSI-2 trials and International Study Group trials, which compared tissue-type plasminogen activator (t-PA) with streptokinase, enrolled almost 21,000 patients, and the ISIS-3 trial, which compared t-PA, streptokinase, and anisoylated plasminogen streptokinase activator complex, involved more than 46,000 patients. A third megatrial, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) is ongoing and will enroll a total of 41,000 patients. Simple calculations of sample size illustrate the problem: a total of 1,834 patients (917 in each of two arms) is required to demonstrate a mortality reduction from 15% in a placebo group to 10% in an active treatment group at 95% confidence (type I error 5%,
two tailed) and with a power of 90% (type II error=0.10) of detecting this difference, if it exists. In contrast, almost 20 times as many patients, i.e., 36,100 (18,050 in each of two arms), are required to demonstrate a further reduction of mortality from 10% to 9%, with similar errors.

A Possible Solution

The dilemma that we now face is that it is obviously impossible to conduct a megatrial each time an interesting or promising suggestion for an improved thrombolytic regimen or variation in adjunctive or conjunctive therapy is put forward. The need for a more efficient and practical means of evaluation clearly exists. One approach is not to use mortality as the sole end point, but instead to use what we have called the “unsatisfactory-outcome” end point. This consists of two parts: 1) The primary end point involves a composite of events, the occurrence of any of which signifies an unsatisfactory outcome of thrombolytic therapy; and 2) a secondary end point that expresses in each patient the highest score among weighted components of the primary end point.

Primary End Point

The components of the primary end point include death; recurrent myocardial infarction; the development of cardiogenic shock or of severe, sustained congestive heart failure not present at the onset of therapy; and laboratory evidence of severe left ventricular dysfunction before hospital discharge. Failure of the prompt establishment of patency of the infarct-related artery and failure of maintenance of its patency during the hospital course are also considered to be unsatisfactory outcomes of thrombolytic therapy, as is the development of serious adverse reactions to the thrombolytic regimen. The latter consist of severe bleeding, including nonfatal intracranial hemorrhage, and quite rarely, the development of severe anaphylactic shock. The primary end point is expressed as the fraction of patients in a treatment arm in whom the outcome of thrombolytic therapy is unsatisfactory as defined above.

One potential criticism of this approach is that it mixes “apples and oranges,” in that it includes a number of diverse outcomes based on clinical and laboratory observations. However, the unsatisfactory-outcome end point is not unlike other composite end points that have been widely and successfully used in assessing the outcome of cardiovascular (and other) therapies. For example, in comparisons of prosthetic heart valves, a composite end point consisting of the sum of cardiac death, serious valve failure or perivalvular leak requiring reoperation, valve thrombosis or infection, major embolization, and major hemorrhage caused by anticoagulation—all of which may be appropriately regarded as indicators of unsatisfactory outcome of valve replacement—has been used\(^\text{29}\) and is much more sensitive than simple mortality. Perhaps the simplest composite end point in trials of cardiovascular therapy is the sum of death and nonfatal MI, an end point that has been widely used in post-MI trials.\(^\text{29}\) In a subgroup of patients in GISSI-2, the combined end point of death and severe left ventricular dysfunction was used.\(^\text{30}\) In the ongoing TIMI-3 trial on unstable angina, we are using the composite end point of the sum of death, postrandomization myocardial infarction, and recurrent objectively documented myocardial ischemia. Califf et al\(^\text{30}\) have successfully used a combined clinical end point, freedom from adverse clinical events, in a study comparing different thrombolytic and angioplasty strategies.

Each of the individual components of the end point proposed herein may be considered to be an unsatisfactory outcome of thrombolytic therapy of AMI. Death and disabling nonfatal intracranial hemorrhagic stroke obviously represent unsatisfactory outcomes. Recurrent myocardial infarction (diagnosed by the development of new Q waves or enzyme confirmation) in patients who have received thrombolytic therapy is most often a result of coronary reocclusion and usually represents completion of an infarct the progression of which has been temporarily interrupted; thus, it too represents a failure of thrombolytic therapy. The development of severe, sustained heart failure or cardiogenic shock after the onset of therapy and laboratory evidence of severe left ventricular dysfunction late in the patient’s hospital course are complications of massive infarction that should be prevented by successful thrombolytic therapy, and both correlate with poor long-term survival. The benefits of thrombolytic therapy of AMI are predicated on the early achievement and the maintenance of patency of the occluded infarct-related artery.\(^\text{31}\) When thrombolytic therapy fails in this respect, the patient may exhibit a benign clinical course, but the outcome of the therapy may still be considered unsatisfactory. However, there is abundant evidence in patients with AMI—both those who receive thrombolytic therapy\(^\text{32–34}\) and those who do not\(^\text{35}\)—that failure of early reperfusion or of maintenance of coronary artery patency correlates with a poor clinical outcome.\(^\text{36,37}\)

Not all possible events that can occur after AMI are included in the unsatisfactory-outcome end point. For example, the need for performance of mechanical revascularization (percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery) is not regarded as an unsatisfactory outcome, because these procedures may be needed by unstable patients to ensure long-term maintenance of myocardial perfusion that has been successfully initiated by thrombolytic therapy. Thus, the need for revascularization does not necessarily imply that thrombolytic therapy has been unsuccessful; indeed, when an infarct-related coronary artery remains occluded and the infarct has been completed, the patient is far less likely to exhibit recurrent ischemia than is a patient with AMI in whom the occluding thrombus has been lysed but who is left with a critical stenosis. Also, because the decision to perform mechanical revascularization is not usually based on absolute criteria but requires physician judgment, it is not a “hard” end point, making it difficult to exclude observer bias. Recurrent transient ischemia also is not considered to be an unsatisfactory-outcome end point because, like the need for mechanical revascularization, it may be a direct consequence of successful reperfusion and myocardial salvage and is not a permanent event such as reinfarction or severe left ventricular dysfunction. Similarly, ventricular fibrillation per se does not qualify as an unsatisfactory-outcome end point, because most patients with early, primary ventricular fibrillation do well after prompt resuscitation, whereas patients with secondary ventricu-
lar fibrillation generally manifest or develop one of the components of the end point, such as severe heart failure, cardiogenic shock, or death. Similar considerations apply to the development of atrioventricular or intraventricular conduction disturbances.

Secondary End Point

The unsatisfactory-outcome end point described above, i.e., the primary end point, is dichotomous in that each patient either reaches it or not by the time of hospital discharge or at a specified time after AMI. Because the clinical consequences of reaching different components of this end point vary enormously, however, it also appears desirable to weight the individual components by use of a scale such as that shown in Table 1. Each patient is assigned a score that represents the single most serious outcome (not the sum of all outcomes). Each event is scored according to its severity up to 1.0, and patients who do not achieve the unsatisfactory-outcome end point are assigned a score of zero. The event that has the highest score, regardless of other events that may occur, becomes the score for that individual patient. The average score in a group of similarly treated patients is then used as the secondary end point. Califf et al.88 have considered a similar approach but prefer a ranking of outcomes and have compared this ranking in different groups by use of an ordinal logistic model.89

It is acknowledged that the weighting shown in Table 1 represents the judgment of the authors and is somewhat arbitrary; it could probably be improved by being subjected to a consensus panel. However, it is based on the consideration that pump failure,40 reduced left ventricular ejection fraction,41 recurrent infarction, coronary reocclusion, and failure to sustain or achieve coronary artery patency32,37 during initial hospitalization correlate with later mortality in approximately the order listed, and the outcomes are scored in the same order; i.e., the development of severe, sustained heart failure after thrombolytic therapy (score of 0.8) denotes a more serious prognosis than failure to achieve reperfusion at 90 minutes after the onset of therapy (score of 0.2). Additional studies are needed, however, to determine with greater precision the prognostic significance of each of these outcomes, and such studies could help to refine the scoring system.

The event rates of both the primary and secondary end points are high enough to allow comparison of thrombolytic regimens in a moderate number of patients. Thus, preliminary results in two of the ongoing TIMI trials in which this approach is used in a group of patients with AMI who receive currently available thrombolytic therapy reveal that approximately 47% reach an unsatisfactory outcome as defined above (the primary end point), and the average score is 0.22±0.03 (SEM) (secondary end point). A trial comparing two thrombolytic regimens using only 500 patients (250 in each group) could detect, with a type I error of 5% (p<0.05, two-tailed) and a power of 85%, a 28% reduction in the composite unsatisfactory-outcome end point, i.e., the primary end point (from 47% to 34%) and a 23% reduction in the average score from 0.22 to 0.17.

A disadvantage of the unsatisfactory-outcome end point is that it requires complete or nearly complete ascertainment of multiple end points in each patient. Coronary arteriography is, of course, the most accurate technique now available for assessing coronary arterial patency, but it is expensive and limits the trial to institutions in which this procedure can be carried out. However, noninvasive techniques such as perfusion scintigraphy (with sestamibi42) and creatine kinase isoenzyme subforms for detecting coronary reperfusion43,44 are promising alternatives that may allow accurate, relatively inexpensive, noninvasive assessment of the unsatisfactory-outcome end point.

A second potential disadvantage of this approach, and one it shares with all clinical trials, is that the end points can be influenced both by the baseline characteristics of the patients and the therapy other than the thrombolytic regimen that is administered. In trials involving several hundreds of patients in each treatment arm, the randomization process can be expected to prevent gross imbalances in baseline characteristics, or if they occur, they can be dealt with by appropriate statistical adjustment. Randomization should also minimize the differences in the therapy other than that being tested. However, clear, prospectively agreed-upon guidelines for such adjunctive therapy can aid in reducing the possibility of introducing bias on this basis.

Conclusions

If mortality remains the principal end point of thrombolytic trials of AMI, it will be impossible to test more than a small fraction of the new, innovative thrombolytic regimens now being developed. Megatrials involving tens of thousands of patients require herculean efforts; only a very limited number of such trials can be carried out simultaneously on a worldwide basis, and each can test only a limited number of hypotheses. Therefore, despite the obvious importance of mortality, insistence on its use as the only principal end point in trials of thrombolytic therapy of AMI may inhibit future progress of this important aspect of cardiovascular therapeutics. The approach described herein, i.e., the use of the unsatisfactory-outcome end point, should make it possible to compare innovative thrombolytic regimens in much smaller trials. In the final analysis, these two

<table>
<thead>
<tr>
<th>Event</th>
<th>Score</th>
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<tbody>
<tr>
<td>Death</td>
<td>1.0</td>
</tr>
<tr>
<td>Intracranial hemorrhage with severe permanent neurological deficit</td>
<td>1.0</td>
</tr>
<tr>
<td>Development of severe, sustained CHF or cardiogenic shock</td>
<td>0.8</td>
</tr>
<tr>
<td>Ejection fraction &lt;40% (or &lt;30% for second MI)</td>
<td>0.6</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0.5</td>
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<tr>
<td>Occlusion or reocclusion of the IRA 1–7 days after AMI</td>
<td>0.4</td>
</tr>
<tr>
<td>Major spontaneous hemorrhage: hematocrit drop &gt;15% or intracranial hemorrhage without severe or permanent neurological deficit</td>
<td>0.3</td>
</tr>
<tr>
<td>Failure of early recanalization of IRA up to 2 hours after onset of therapy</td>
<td>0.2</td>
</tr>
<tr>
<td>None of the above</td>
<td>0.0</td>
</tr>
</tbody>
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CHF, severe congestive heart failure; MI, myocardial infarction; IRA, infarct-related artery; AMI, acute myocardial infarction.
different end points (mortality and unsatisfactory outcome) are not mutually exclusive and could, in fact, be used in a complementary fashion. Thus, after a new thrombolytic regimen has been shown to be particularly promising, as judged by the unsatisfactory-outcome end point, it could then become a candidate for testing in a megatrial the principal end point of which is mortality.

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KEY WORDS • thrombolytic therapy • Point of View
An approach to evaluating thrombolytic therapy in acute myocardial infarction. The 'unsatisfactory outcome' end point.

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Circulation. 1992;86:683-687
doi: 10.1161/01.CIR.86.2.683

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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