Cost and Quality of Life: Thrombolysis and Primary Angioplasty

LEE GOLDMAN, MD, FACC
San Francisco, California

In an era of limited health care resources, analyses of the cost-effectiveness of cardiac interventions are becoming increasingly important. By generally accepted cost-effectiveness methodologies, the incremental cost for thrombolysis with streptokinase in patients with acute myocardial infarction ranges from $3,500 to $21,000/year of life saved. The estimated incremental cost-effectiveness of tissue-type plasminogen activator (t-PA) compared with streptokinase ranges from $16,000 to $60,000/year of life saved. Pooled results of three randomized trials suggest that primary angioplasty can reduce mortality by as much as 6% without any increase in cost. This potential benefit is substantial, greater than the 10% to 15% relative mortality rate reduction each hour earlier that thrombolytic therapy is administered or 12% relative benefit suggested for accelerated t-PA compared with that for streptokinase. Large-scale randomized trials are needed to determine whether the cost and mortality of popularized strategies using primary angioplasty are better than strategies that rely on intravenous thrombolysis.

(J Am Coll Cardiol 1995;25[Supplement]:385-4)

Cost-Effectiveness Analysis

In cost-effectiveness analysis, an intervention’s effect on costs is compared with its effect on outcomes (1–3). The result is commonly expressed as a ratio with changes in cost in the numerator and changes in the measure of effectiveness in the denominator.

Costs are commonly measured in dollars and usually refer to the net direct costs of the intervention and the disease-related costs that it may induce or avert. For example, a thrombolytic agent would have its own costs, and its effects on subsequent cardiovascular care, including cardiac procedures and strokes, could be calculated. More complicated analyses would include other medical costs, such as the downstream cost of a cholecystectomy that might eventually be necessary for someone whose life was saved by thrombolysis. Even more ambitious analyses would consider such costs as the estimated effects of the thrombolysis on future custodial care for possible Alzheimer’s disease. Finally, the analysis might consider all medical costs and indirect costs, such as days of work lost, the economic impact of current and future illness on the patient family, and any effects on the social security system. Because many of the assumptions required for these more detailed analyses are so uncertain, most cost-effectiveness analyses concentrate on disease-related costs.

Costs are not the same as prices or charges. Unlike prices, charges, which tend to be reasonably constant regardless of volume, costs vary dramatically with volume. The increment cost of an additional test or procedure may be relatively small because the infrastructure required to provide it is already in place and will have a constant cost regardless of whether the incremental procedure is performed. At some point, however, an increase in volume will require a change in the infrastructure and an increase in fixed costs.

The effectiveness of an intervention is often measured in units such as lives saved, years of life saved or quality-adjusted years of life saved. Any adjustment for quality requires appreciation of how individuals with the condition would value their quality of life. A variety of methods are available to measure such measurements, but none is perfect.

Most studies of cardiac interventions for acute conditions, such as acute myocardial infarction, have relied on analyses that compare costs with years of life saved. Although analysis that consider quality-adjusted years of life would be preferred, empiric data for quality adjustment often have not been reliable enough to be incorporated into such analyses at present time.

In most analyses, immediate costs and effectiveness are measured now, but future costs or promises of benefits are certain. Therefore, cost-effectiveness analyses commonly “count” future costs and future benefits, usually at a rate of about 5% per year. This principle explains why many preventive programs, which must spend dollars now in hope of preventing disease in the future, may not have favor-
cost-effectiveness ratios unless the preventive intervention is inexpensive or the patients are at sufficiently high risk.

In cost-effectiveness analysis, it is not possible to find the greatest possible benefit for the lowest possible cost. The analysis must always strive to determine the resources available and then find the greatest possible effectiveness that can be purchased for these resources, or determine the desired effectiveness and then find the lowest cost way to achieve it. With either approach, a cost-effectiveness ratio can be determined, and it must be compared against what society may be willing to pay. A common benchmark is the $30,000/year of life saved by the end-stage renal disease program. Of note is that this figure has remained constant over the past decade or more, because reimbursements in that program have not increased with inflation (4).

A cost-effectiveness analysis should also include sensitivity analyses in which each of the key assumptions is varied to see if reasonable differences in any of them will have a substantial impact on the overall conclusion of the analysis. Analyses whose conclusions do not vary substantively based on such changes in estimates are much more convincing than those that do.

Thrombolysis
The relative benefit of thrombolytic therapy varies directly with the delay between the onset of symptoms and the institution of therapy. Pooled data suggest about a 32% reduction in mortality if treatment is instituted in the first 2 to 3 h after the onset of symptoms, a 25% reduction in mortality if therapy is instituted within about 2 to 6 h after the onset of symptoms and a 15% reduction in mortality if therapy is instituted between 6 and 12 to 24 h after the onset of symptoms (5).

The first major cost-effectiveness analysis of thrombolysis (6) noted that the approximate cost for each additional person who would survive 1 year or more with thrombolysis was very reasonable for large and moderate-sized myocardial infarctions but less convincing for small infarctions. The projected cost-effectiveness depended on the amount of jeopardized myocardium, the time since onset of symptoms, the time from treatment to the achievement of reperfusion and the type of postthrombotic treatment the patients were to receive. This and another early analysis (7) did not try to calculate a cost per year of life saved, the most common metric for cost-effectiveness analyses, because data were not yet available regarding long-term outcomes after thrombolysis.

More recently, another analysis (5) found that thrombolysis with streptokinase had an estimated cost-effectiveness ratio of about $21,000/year of life saved in patients as old as 80 years of age, and it would be more attractive in younger subjects. Although the elderly receive less relative benefit from thrombolysis than younger patients with myocardial infarction, their absolute risk of death from myocardial infarction is much higher. A reduced relative benefit multiplied by a higher absolute risk yields a rather similar absolute immediate bene-

fit from thrombolysis. Nevertheless, because the elderly have a shorter life expectancy than younger patients, the cost-effectiveness ratio is still not quite as good.

This analysis also demonstrated that the cost-effectiveness of thrombolysis was relatively independent of whether the rate of stroke was as high as 2% and did not change substantially based on varying assumptions about the costs of the stroke, the risk of other bleeding complications, or the cost of bleeding complications. However, if the thrombolytic agent cost $2,000/patient rather than the $200 average cost of streptokinase, and the increased costs were not associated with any changes in clinical outcomes, the cost-effectiveness ratio would increase to about $45,000/year of life saved when compared with no thrombolysis (5). The cost-effectiveness of thrombolysis also depends on the location of the infarct and the degree of certainty that the patient is having an acute myocardial infarction with an occluded vessel (8).

If accelerated tissue-type plasminogen activator (t-PA) results in an additional 12% relative reduction in mortality compared with that for streptokinase (9) because of higher reperfusion rates (10), this incremental benefit would be accompanied by an increment of $1,800 in costs (5,11), which would approximately double the cost of thrombolytic treatment, including all induced cardiovascular costs. The additional 12% relative benefit from substituting accelerated t-PA for streptokinase would provide an absolute incremental benefit that is about one-third as great as the absolute incremental benefit that results from the 27% relative benefit that is achieved by adding streptokinase to routine care.

The estimated incremental cost-effectiveness ratio of streptokinase in nonelderly patients with acute myocardial infarction ranges from $23,500 (10) to $21,000 (5) per year of life saved. The estimated incremental cost-effectiveness ratio of t-PA compared with that for streptokinase ranges from $16,000 to $60,000/year of life saved (12).

Any estimate of the relative cost-effectiveness of accelerated t-PA compared with streptokinase depends critically on whether the benefits in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial are replicable. On the basis of experimental evidence regarding the improvement in patency rates with such treatment both in GUSTO (13) and in other studies (14), it seems likely that this new regimen does, in fact, confer such benefit. In patients with smaller myocardial infarctions or in patients treated long after the onset of symptoms, the incremental cost-effectiveness ratio of accelerated t-PA would be higher than in other patients.

Primary Angioplasty
The three most recent randomized controlled trials of primary angioplasty (15-17) suggest a striking 65% reduction in early mortality rates among patients treated with this strategy compared with routine thrombolysis (Table 1). Of note is that this relative reduction in mortality was greater than the 35% or so relative reduction reported in studies of
Table 1. The Three Most Recent Randomized Controlled Trials of Immediate Coronary Angioplasty Versus Thrombolysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Early Mortality Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angioplasty Thrombolysis</td>
</tr>
<tr>
<td>Gibbons et al. (15)</td>
<td>1/47 (2.1%) 0/6</td>
</tr>
<tr>
<td>Grines et al. (16)</td>
<td>5/192 (2.6%) 13/200 (6.5%)</td>
</tr>
<tr>
<td>Zijlstra et al. (17)</td>
<td>0/72 4/72 (6%)</td>
</tr>
<tr>
<td>Average</td>
<td>1.9% 5.2% 63% reduction</td>
</tr>
</tbody>
</table>

Numbers in parentheses are reference numbers.

Thrombolysis as compared with randomized controlled patients (4). It also compares very favorably with the ~17% relative mortality reduction achieved by giving thrombolysis in the prehospital setting compared with the in-hospital setting, which results in about a 1-h reduction in the delay between the onset of symptoms and the administration of thrombolysis (18) (Table 2).

The trials of primary angioplasty have found about a 1-h delay between hospital arrival and the angioplasty. If a 1-h difference in the time to reperfusion correlates with about a 17% mortality difference, primary angioplasty would be expected to be better than intravenous thrombolytic therapy even if the delay were increased from 1 h to 2 or 3 h.

In the three most recent randomized trials of primary angioplasty, the procedure resulted in coronary reperfusion in 93% to 98% of patients (15–17). The success rate from primary angioplasty in these randomized trials was substantially higher than in small randomized trials performed in the United States in 1984 (19) and in Brazil in 1989 (20), probably because of improvements in angioplasty techniques. The Thrombolysis in Myocardial Infarction (TIMI) grade 3 perfusion rate with direct angioplasty was higher than with t-PA (21), and it was achieved quickly and without the risk of thrombolysis-related bleeding. Success rates of 88% to 98% (22–25) have been achieved in other recent nonrandomized U.S. studies. Improved reperfusion apparently explains the reduction in mortality, especially in the highest risk patients.

Patients treated with primary angioplasty tended to have shorter hospital stays and lower in-hospital and 6-month follow-up costs (15,26). However, the analysis of costs did not assume that new facilities, systems, or other resources would be required if the strategy of primary angioplasty were to be extended beyond the small number of institutions that currently could perform it on an emergent, around-the-clock basis to the large number of institutions that now rely on thrombolysis as the preferred treatment.

If primary angioplasty can achieve a 63% relative reduction in mortality at no increase in costs, then recommendations regarding its use do not require any sophisticated calculations. Pending additional data, it is hard to argue against primary angioplasty as the treatment of choice in situations in which it is a practical extension of an existing system that provides high-quality angioplasty and on-site coronary artery bypass surgery.

If current data can be extrapolated, our national health care system should consider the possibility of transfer for primary angioplasty rather than on-site thrombolysis if such a strategy resulted in no more than a 1- to 2-h delay, especially in the highest risk patients. However, such a strategy would require empiric testing through a randomized controlled trial before it could be widely recommended. A more difficult issue is whether the capabilities for a primary angioplasty should be extended to the large number of institutions that currently cannot provide such care. It was recently estimated that only 18% of hospitals in the United States can perform angioplasty (27), and even fewer can both perform it on an emergent basis and provide backup coronary artery bypass surgery. Primary angioplasty may be performed in some hospitals without on-site coronary artery bypass surgery with success rates and survival rates that are similar to what is accomplished at sites that have available on-site surgery (22). However, much larger studies would be required before such an approach could become national policy.

The incremental expense of developing these facilities and training their staff would be far different from the costs incurred at sites where these capabilities already exist. Furthermore, the success rate of primary angioplasty is critically dependent on the skill and the volume of the operator, and there is no evidence that the results found in the high quality centers that have participated in the published trials could be extended to all institutions.

Where Are We Now?

In my opinion, the existing randomized trials demonstrate the benefit of primary angioplasty under ideal circumstances. Future randomized trials should assess whether the delay required for transfer to appropriate facilities is warranted, at least among high risk patients with myocardial infarction. The alternative, which would be to provide such services routinely in all hospitals, is less likely to be a cost-effective alternative to the current policy, which is to administer thrombolysis as rapidly as possible.

How about thrombolysis? If accelerated t-PA is truly better than the t-PA regimens used in previous randomized trials (28,29), its cost-effectiveness ratio relative to streptokinase will be reasonable (30), especially in higher risk patients and those
with more favorable ratios for all types of thrombolysis. If the incremental benefit of t-PA is uncertain (31,32), its incremental cost may seem overwhelming. However, even assuming the best from a clinical standpoint, the price of t-PA will remain a deterrent, because it represents up to 50% of the incremental costs of the entire thrombolytic strategy. Would a patient with an acute myocardial infarction be willing to pay out of pocket for the incremental cost of accelerated t-PA even if it has the projected benefit? Should our health care system be willing to pay this price, or should a national system be able to negotiate for a price reduction? Stay tuned.

References