

## Projected Cost-Effectiveness of Primary Angioplasty for Acute Myocardial Infarction

TRACY A. LIEU, MD, MPH, R. JAN GURLEY, MD,\* ROBERT J. LUNDSTROM, MD, FACC,  
G. THOMAS RAY, MBA, BRUCE H. FIREMAN, MA, MILTON C. WEINSTEIN, PhD,†  
WILLIAM W. PARMLEY, MD, FACC‡

Oakland and San Francisco, California and Boston, Massachusetts

**Objectives.** This study sought to evaluate the cost-effectiveness of primary angioplasty for acute myocardial infarction under varying assumptions about effectiveness, existing facilities and staffing and volume of services.

**Background.** Primary angioplasty for acute myocardial infarction has reduced mortality in some studies, but its actual effectiveness may vary, and most U.S. hospitals do not have cardiac catheterization laboratories. Projections of cost-effectiveness in various settings are needed for decisions about adoption.

**Methods.** We created a decision analytic model to compare three policies: primary angioplasty, intravenous thrombolysis and no intervention. Probabilities of health outcomes were taken from randomized trials (base case efficacy assumptions) and community-based studies (effectiveness assumptions). The base case analysis assumed that a hospital with an existing laboratory with night/weekend staffing coverage admitted 200 patients with a myocardial infarction annually. In alternative scenarios, a new laboratory was built, and its capacity for elective procedures was either 1) needed or 2) redundant with existing laboratories.

**Results.** Under base case efficacy assumptions, primary angio-

plasty resulted in cost savings compared with thrombolysis and had a cost of \$12,000/quality-adjusted life-year (QALY) saved compared with no intervention. In sensitivity analyses, when there was an existing cardiac catheterization laboratory at a hospital with  $\geq 200$  patients with a myocardial infarction annually, primary angioplasty had a cost of  $< \$30,000$ /QALY saved under a wide range of assumptions. However, the cost/QALY saved increased sharply under effectiveness assumptions when the hospital had  $< 150$  patients with a myocardial infarction annually or when a redundant laboratory was built.

**Conclusions.** At hospitals with an existing cardiac catheterization laboratory, primary angioplasty for acute myocardial infarction would be cost-effective relative to other medical interventions under a wide range of assumptions. The procedure's relative cost-ineffectiveness at low volumes or redundant laboratories supports regionalization of cardiac services in urban areas. However, approaches to overcoming competitive barriers and close monitoring of outcomes and costs will be needed.

(J Am Coll Cardiol 1997;30:1741-50)

©1997 by the American College of Cardiology

Recent randomized, controlled trials (1,2) have shown improved outcomes after primary angioplasty compared with intravenous thrombolysis for acute myocardial infarction. In these research settings, primary angioplasty appeared no more expensive than thrombolysis (3-5). However, the prospect of providing primary angioplasty to general populations poses several dilemmas.

If provided in the community, primary angioplasty may be

less beneficial than in research settings (6,7). Hospitals with a lower volume of procedures have worse outcomes and higher costs (8-11). In addition, 80% of U.S. hospitals are not equipped to provide primary angioplasty, and the costs of the procedure would increase if new cardiac catheterization laboratories needed to be built (12). Regionalization of emergency services for chest pain might be one way of directing patients to high volume hospitals, but any additional transit time needed could reduce the procedure's benefit (13).

Projections of cost-effectiveness under both efficacy and effectiveness assumptions in a variety of settings are needed for decisions about whether primary angioplasty should be more widely adopted, and how services can be most effectively organized. This study evaluated the cost-effectiveness of primary angioplasty relative to thrombolysis and no intervention for a hypothetical cohort of 10,000 patients with acute myocardial infarction under a wide range of assumptions about health outcomes, costs and hospital characteristics.

From the Division of Research, The Permanente Medical Group, Oakland, California; \*San Francisco Department of Public Health, AIDS Office, San Francisco, California; †Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts; and ‡Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, California.

All editorial decisions for this article, including selection of referees, were made by a Guest Editor. This policy applies to all articles with authors from the University of California San Francisco.

Manuscript received January 15, 1997; revised manuscript received July 31, 1997, accepted September 1, 1997.

Address for correspondence: Dr. Tracy A. Lieu, Division of Research, The Permanente Medical Group, 3505 Broadway, Oakland, California 94611. E-mail: tal@dor.kaiser.org.

Abbreviations and Acronyms	
CABG	= coronary artery bypass graft surgery
CMIS	= Cost Management Information System
QALY	= quality-adjusted life-year
t-PA	= tissue-type plasminogen activator

## Methods

### Model Structure

We developed a model to evaluate the health outcomes and costs of primary angioplasty and intravenous thrombolytic treatment of suspected acute myocardial infarction from the societal perspective. The model (Fig. 1) was used to evaluate three clinical policies for treating acute myocardial infarction: primary angioplasty, thrombolysis and no intervention. *No intervention* was defined as all patients receiving neither throm-

**Figure 1.** Decision tree illustrating possible clinical policies for a hypothetical population of patients with an acute myocardial infarction. **Squares** = decision by the clinical policymaker; **circles** = chance events not under the direct control. Under the No Intervention Policy, all patients receive standard hospital treatment for acute myocardial infarction, including heparin and aspirin. Under the Thrombolysis Policy, those patients who are candidates for thrombolysis receive a thrombolytic agent and standard care; those in cardiogenic shock undergo either attempted angioplasty or receive thrombolysis, followed by transport, if possible. Under the Primary Angioplasty Policy, all patients undergo attempted angioplasty, unless they are ineligible because of a nonqualifying electrocardiogram or symptom duration >6 h. \*For a hospital without an existing cardiac catheterization laboratory: 1) under the Primary Angioplasty Policy, a new laboratory would be built; 2) under the Thrombolysis Policy, no new laboratory would be built.

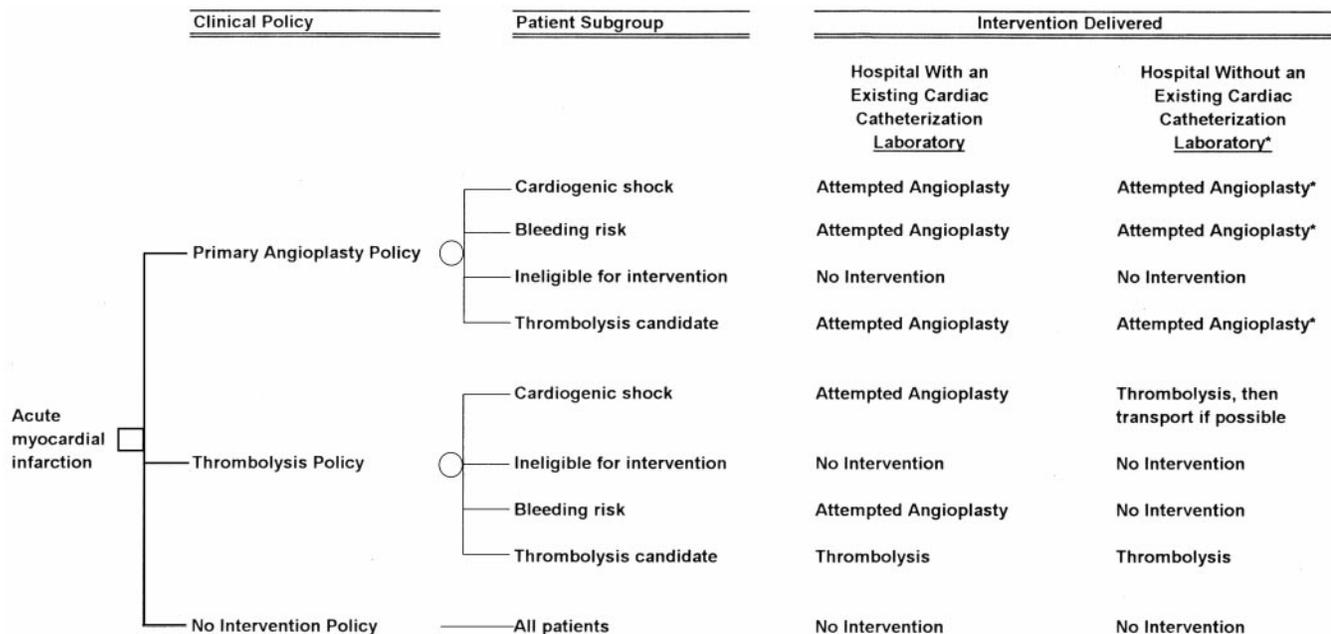
bolysis nor primary angioplasty but still admitted to the hospital for standard care.

**Patient subgroups.** Patients were classified into four subgroups on the basis of clinical characteristics:

1. *Cardiogenic shock*—these patients were considered to always be eligible for primary angioplasty or thrombolysis.
2. *Ineligible for intervention*—other patients presenting >6 h after the onset of symptoms, without  $\geq 1$  mm ST segment elevation in two contiguous electrocardiographic leads, or with complete left bundle branch block, were considered ineligible for thrombolysis or primary angioplasty and would have no intervention.
3. *Bleeding risk factors*—patients with specific risk factors for bleeding, as defined by previous studies (14,15) would be ineligible for thrombolysis but eligible for primary angioplasty.
4. *Candidates for thrombolysis*—the remaining patients were considered eligible for either thrombolysis or primary angioplasty.

**Interventions. Primary angioplasty policy.** Under the primary angioplasty policy, patients with cardiogenic shock, patients with bleeding risk factors and candidates for thrombolysis all would undergo coronary arteriography. Those with potentially treatable lesions would undergo attempted angioplasty without preceding intravenous or intracoronary thrombolytic treatment.

**Thrombolysis policy.** Under the thrombolysis policy, candidates for thrombolysis would receive intravenous infusion of either streptokinase or tissue-type plasminogen activator (t-PA). The choice of intervention for the other patient subgroups would depend on whether the hospital had a cardiac catheterization laboratory. At hospitals with an existing labo-



**Table 1.** Health Outcomes After Interventions for Acute Myocardial Infarction

Outcome	Base Case Estimate (effectiveness estimate) if Treated With			Ref No. or Other Source
	Primary Angioplasty	Thrombolysis	No Intervention	
In-hospital mortality among patient subgroups				
In cardiogenic shock	0.52 (0.71)	0.71	0.85	23-30
Ineligible for intervention	NA	NA	0.10	15, 54-57
With bleeding risk factors	0.12 (0.26)	NA	0.26	31, 32
Thrombolysis candidates	0.04 (0.06)	0.06	0.08	1, 2, 36-38
Among thrombolysis candidates				
Nonfatal disabling stroke	0.0015	0.005	0.002	1, 33, 37
Bleeding requiring transfusion	0.03	0.02	0.005	Expert panel*
1-yr survival rate	0.93 (0.92)	0.92	0.85	4, 14, 15, 35, 36, 38, 40, 58-63
1-yr reinfarction rate	0.10 (0.10)	0.10	0.05	38, 40, 59, 61, 64-66
5-yr survival rate	0.82 (0.82)	0.82	0.77	58, 61, 64, 67
Procedure rates				
CABG during hospital stay	0.10 (0.12)	0.12	0.09	
CABG during next year	0.09 (0.09)	0.09	0.10	
Angioplasty during hospital stay	0.04 (0.05)	0.30	0.18	
Angioplasty during next year	0.15 (0.15)	0.15	0.15	
Average length of hospital stay for uncomplicated myocardial infarction (days)†				
ICU	2.5 (2.5)	3	3.5	
Telemetry unit	2 (2)	2.5	3	
Medical ward	1.5 (1.5)	1.5	1.5	
Total	6 (6)	7	8	
Proportions in CCS classes at 1 yr among candidates for thrombolysis				
I	0.83 (0.68)	0.68	0.68	
II	0.16 (0.25)	0.25	0.25	
III or IV	0.01 (0.07)	0.07	0.07	

\*Seven cardiologists who convened for 1 day to review base case estimates and provide ranges for sensitivity analysis using a modified Delphi process (see Acknowledgments). †Fifty percent of the days saved in the thrombolysis and primary angioplasty groups were assumed to be intensive care unit (ICU) days, and 50% were assumed to be telemetry unit days; for patients with risk factors for bleeding or cardiogenic shock, primary angioplasty and thrombolysis were assumed to not save any hospital days relative to no intervention. CCS = Canadian Cardiovascular Society; CABG = coronary artery bypass graft surgery; NA = not applicable (under the primary angioplasty and thrombolysis policies, patients ineligible for intervention would have no intervention and would have an in-hospital mortality rate of 0.10; under the thrombolysis policy, patients with bleeding risk would have no intervention and would have an in-hospital mortality rate of 0.26); Ref = reference.

ratory, patients with cardiogenic shock or bleeding risk factors were assumed to undergo primary angioplasty as the preferred intervention when the admitting hospital had a cardiac catheterization laboratory. At hospitals without an existing laboratory, patients with bleeding risk would receive no intervention, and those with cardiogenic shock would receive thrombolysis. When possible, patients with cardiogenic shock would be transported to a neighboring hospital for primary angioplasty. Because >50% of the U.S. population lives in metropolitan areas, transport was assumed to be possible for 50% of patients with cardiogenic shock (16).

*Hospital characteristics.* A base case hospital ("Fully Covered Lab" scenario) was defined as follows: It had an existing cardiac catheterization laboratory that performed elective procedures during weekdays and had cardiovascular surgical backup. Night call for two technical staff members was assumed to be already covered. Primary angioplasty was assumed to be offered 24 h/day, every day. We inferred from two previous studies (17,18) that ~50% of all patients with a

myocardial infarction present to hospitals that treat at least 150 myocardial infarctions/year (17,18). Thus, the base case hospital was assumed to have 200 annual discharges for acute myocardial infarction.

### Data and Assumptions: Health Outcomes

Probabilities of health outcomes (Table 1) were derived from a review of published reports (19), unpublished studies, analyses of Kaiser Permanente data and an expert panel conference. Seven cardiologists (see Acknowledgments) convened in person to review evidence tables that summarized the published reports about each assumption. To derive each final base case estimate, a modified Delphi approach was used in which each panelist submitted initial estimates, then reviewed and adjusted results to reach as much consensus as possible. The base case used efficacy assumptions about health outcomes based on published randomized trials.

**Patient subgroups.** On the basis of published studies (20,21) and a Kaiser Permanente analysis, we assumed that among all patients with an acute myocardial infarction, 3% presented in cardiogenic shock, 65% were ineligible for intervention, and 6% had risk factors for bleeding. The remaining 26% were candidates for thrombolysis (eligible for either thrombolysis or primary angioplasty).

The model took into account that the probability of myocardial infarction among patients within 6 h of chest pain onset and with ST segment was 95% (22). It was assumed that patients without a myocardial infarction would incur treatment costs but would not benefit from thrombolysis or primary angioplasty.

**Survival.** In-hospital mortality rates (Table 1) were taken from published studies and expert panel opinion (23-35). Among candidates for thrombolysis, a published meta-analysis and our expert panel suggested a 4% in-hospital mortality rate after primary angioplasty and a 6% mortality rate after thrombolysis (1,2,36-39). For candidates for thrombolysis, 1-year survival rates were based on randomized studies and a published meta-analysis (4,36,40). It was assumed that survival differences between primary angioplasty and thrombolysis groups were markedly attenuated by 1 year and gone at 5 years.

For patients with cardiogenic shock (41) and bleeding risk, long-term survival rates were assumed to be lower than those of candidates for thrombolysis. Those who survived the hospital period were assumed to have the same life expectancy whether they underwent primary angioplasty or received thrombolysis. For the subgroup with bleeding risk factors, there is no published evidence on long-term survival; they were conservatively assigned a life expectancy equal to patients who were ineligible for intervention. Life expectancy for each subgroup was calculated by combining the appropriate survival rates with estimates of long-term post-myocardial infarction life expectancy from the Coronary Heart Disease Policy Model (42).

**Cardiac procedures and stroke.** For candidates for thrombolysis who underwent primary angioplasty, rates of coronary artery bypass graft surgery (CABG) and angioplasty during the hospital period and the subsequent year were estimated from published data (3,5). Rates of angioplasty and CABG during the subsequent year were assumed to be equal between the primary angioplasty and thrombolysis groups. The rate of nonfatal disabling stroke after thrombolysis was based on the largest available study (33).

**Quality of life.** The quality-adjusted life-year (QALY) saved is a standard outcome measure in cost-effectiveness analyses (43). It takes into account not only the mortality but also the morbidity prevented by an intervention. Candidates for thrombolysis were assumed to have better cardiac functional status after primary angioplasty than after thrombolysis on the basis of published information observed at 1 year after the acute myocardial infarction (4) (Table 1). These health states and their utilities were assumed to apply through the end of life. Survivors with bleeding risk and with cardiogenic shock were conservatively assumed to not derive any advantage in

cardiac quality of life after primary angioplasty, although they derived some advantage from a lower rate of stroke.

Quality of life adjustments were made using utilities from published patient preference studies; community weights for these categories of health states are not available. For Canadian Cardiovascular Society classes, utilities were 0.970 for class I, 0.970 for class II and 0.875 for class III or IV (44). For nonfatal disabling stroke, the utility was 0.10 (45).

### *Data and Assumptions: Costs*

The analysis incorporated costs, including administrative overhead, of the initial hospital period, major cardiac procedures, reinfarction during the subsequent year and future medical expenses through the end of life. We used direct medical costs from the societal perspective in 1993 U.S. dollars. Costs from other years were adjusted to 1993 dollars using the medical component of the Consumer Price Index (16).

**Initial hospital period.** Members of Northern California Kaiser Permanente, a nonprofit health maintenance organization, with an acute myocardial infarction in 1993 were identified using a standard algorithm for International Classification of Diseases, 9th Revision (ICD-9) codes developed by the California Office of Statewide Health Planning Development. Patients with coronary artery bypass graft procedures were identified using diagnosis-related group (DRG) codes. The mean costs of hospital days in the intensive care unit, telemetry unit and regular medical ward were analyzed for these patients using Kaiser Permanente's Cost Management Information System (CMIS).

Using CMIS, length of stay was evaluated for patients discharged in 1993 with a myocardial infarction ( $n = 1,905$ , mean 6.6 days), myocardial infarction with CABG ( $n = 198$ , mean 13 days) and CABG alone ( $n = 372$ , mean 9.5 days). For candidates for thrombolysis, projected lengths of hospital stay were based on these data and on the expert panel's consensus (Table 1).

**Cardiac procedures and reinfarction.** The initial cost of primary angioplasty was estimated using a previously described model (11) that took into account four factors: 1) whether cardiac catheterization laboratories already existed at a hospital; 2) whether the laboratory's technical personnel were already paid for night call; 3) how cardiovascular surgical backup would be provided; 4) the hospital's annual number of discharges for myocardial infarction. Using the base case hospital's characteristics, the initial cost of a primary angioplasty procedure was \$2,068, including physician costs.

The cost of an elective angioplasty procedure was calculated by adding the costs of cardiologist time, supplies, wages for technical and clerical personnel and cardiac catheterization laboratory maintenance and depreciation. Elective angioplasty was assumed to require a hospital admission of 2 days. Reinfarction in the subsequent year was assumed to require a hospital admission of 7 days.

**Table 2.** Costs Used in Analysis of Interventions for Acute Myocardial Infarction

Service	Cost (U.S. 1993 \$)	Ref No. or Other Source
ICU day	1,845	CMIS*
Telemetry unit day	955	CMIS*
Medical ward day	700	CMIS*
CABG procedure†	9,160	KP‡
Elective angioplasty procedure†	2,068	KP‡
Primary angioplasty procedure§	2,068 (varies)	11
Streptokinase	320	68
t-PA	2,750	68
Transport to neighboring hospital	500	KP**
Transfusion (2 U of packed RBCs)	225	KP**
Nonfatal disabling stroke		
Initial rehabilitation	21,216	CMIS*
Outpatient physical therapy	1,248	CMIS*
Future nursing home care (400 days)	34,232	47, 48
Average annual medical costs from 1-yr anniversary of MI to end of life	11,133	18, 49

\*Estimate is from analysis of cases in Cost Management Information System (CMIS) of Northern California Kaiser Permanente. †Professional time and procedure costs (e.g., operating room, cardiac catheterization laboratory and supplies) only; estimate includes overhead but does not include costs of hospital stay; the cost of a coronary artery bypass graft surgery (CABG) procedure was estimated on the basis of cardiovascular surgeons' and anesthesiologists' time allocated for each procedure and the cost of cardiovascular operating room time, which included technical personnel, room and equipment costs; after including hospital costs, the total costs of an elective bypass surgery procedure would be \$23,000. ‡Estimate is based on analyses of Kaiser Permanente (KP) administrative data. §Base case analysis estimate of \$2,068 assumed an existing cardiac catheterization laboratory and cardiovascular surgical backup; night call for technical staff would be already covered, and the hospital would discharge 200 patients with myocardial infarction (MI)/year; costs under alternative scenarios were \$4,453 in the "Add Night Call" scenario, \$5,140 in the "Add Needed Lab" scenario and \$9,393 in the "Add Redundant Lab" scenario. RBCs = red blood cells; t-PA = tissue-type plasminogen activator; other abbreviations as in Table 1.

**Other costs.** The base case used the cost of t-PA for thrombolysis (Table 2). Treatment for bleeding complications was assumed to include transfusion of 2 U of packed red cells and two additional days in the cardiac care unit (46). The costs of nonfatal disabling stroke were based on Kaiser Permanente CMIS data and on estimates from the National Nursing Home Survey (47,48). The estimated annual average cost of medical care from the 1-year anniversary of the myocardial infarction to the end of life (Table 2) was calculated on the basis of published estimates from the National Medical Expenditure Survey (49) and the Coronary Heart Disease Policy Model (18).

### Outcome Measures

An Excel spreadsheet was used to calculate health outcomes, costs and cost-effectiveness ratios from the societal perspective for a hypothetical cohort of 10,000 patients admitted to the hospital with an acute myocardial infarction. This

cohort included 1,000 patients/year for 10 years. Results were expressed in net present value averaged over the 10-year period. In the base case, per current recommendations, future costs and life-years to the end of each patient's life were discounted at 3%/year (43).

*Incremental cost-effectiveness ratios* were defined as the additional cost per additional health benefit of primary angioplasty compared with thrombolysis and of thrombolysis compared with no intervention. *Primary angioplasty* was defined as having dominance when it was both more effective and cost saving than thrombolysis and having extended dominance when its incremental cost effectiveness ratio was lower than that of thrombolysis. When dominance or extended dominance existed, it was appropriate to calculate the cost-effectiveness of primary angioplasty compared with no intervention (43).

### Sensitivity Analyses

Uncertainty surrounds the assumptions in every decision analysis. We varied four major factors both individually and simultaneously, as follows: 1) the effectiveness of primary angioplasty; 2) the hospital scenarios in which it might be offered; 3) the volume of services; and 4) the time to treatment. Sensitivity analyses were also conducted for individual assumptions, including in-hospital mortality, long-term survival, subsequent cardiac quality of life, the cost of thrombolysis, the cost of future medical care for survivors and the discount rate.

**Effectiveness assumptions.** The base case analysis used efficacy assumptions about health outcomes from randomized, controlled trials in optimal settings. We conducted an alternative analysis that used effectiveness assumptions from community-based observational studies of primary angioplasty and thrombolysis (6,7). In the effectiveness assumptions, primary angioplasty had no advantages over thrombolysis in in-hospital mortality or future survival for any of the patient subgroups. It was also assumed the primary angioplasty and thrombolysis groups had identical rates of CABG during the initial hospital period and rates of CABG and elective angioplasty during the next 12 months. The only advantages that primary angioplasty retained over thrombolysis were a shorter hospital stay and lower rates of nonfatal disabling stroke and bleeding requiring transfusion. When the volume of annual myocardial infarctions was varied, assumptions about health outcomes were changed only when explicitly stated.

**Hospital scenarios.** The initial cost of primary angioplasty was varied on the basis of 10 alternative sets of assumptions about the admitting hospital, as previously described; three are presented here (11). The "Add Night Call" scenario was identical to the base case hospital ("Fully Covered Lab" scenario), except that night call for two technical staff members was a new expense.

The "Add Needed Lab" scenario assumed that the admitting hospitals were in a geographic area where there had been elective procedures going unperformed for want of a cardiac catheterization laboratory. Thus, part of the new laboratories' costs were apportioned to 100 elective angioplasty and 700

elective angiography procedures per year. In contrast, in Northern California and many other urban areas, excess capacity for elective angioplasty and angiography already exists. For this reason, the "Add Redundant Lab" scenario assumed that the economic cost of building and equipping the new laboratories was attributable entirely to primary angioplasty. When a new laboratory was built, it was assumed that cardiovascular surgical backup would be provided by transport to a neighboring hospital.

**Time to intervention.** If primary angioplasty services were regionalized, there might be delays in intervention due to either increased travel time by emergency medical services or time required for transfer if the patient initially presented to a hospital without primary angioplasty. Data from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) (50) trial were used to estimate the proportions of candidates for thrombolysis ready for intervention at 0 to 2 h (20%), 2 to 4 h (50%) and 4 to 6 h (30%) after symptom onset. The absolute decrease in benefit from a 1-h delay in reperfusion at 0 to 2 h (2%), 2 to 4 h (0.5%) and 4 to 6 h (none) was nonlinear and was estimated from a summary of recent thrombolysis trials (51). Combining these data, we assumed that a 1-h delay in primary angioplasty would result in an average 0.65% absolute increase in mortality for candidates for thrombolysis. Only candidates for thrombolysis who had undergone attempted angioplasty under the primary angioplasty policy were assumed to have the 1-h delay; those treated under the thrombolysis policy were assumed not to have a delay.

## Results

**Health outcomes.** For the hypothetical cohort of 10,000 patients with an acute myocardial infarction, under the base case (efficacy) assumptions, primary angioplasty was predicted to save 22% more lives and to reduce nonfatal disabling strokes by one-third compared with thrombolysis (Table 3). The improvement in survival was 741 undiscounted QALYs (514 discounted QALYs) relative to thrombolysis.

**Costs and cost-effectiveness.** The primary angioplasty policy would save \$7.2 million in short-term costs compared with thrombolysis (Table 3). This was due to the primary angioplasty procedure's slightly lower cost than that of t-PA and the projected savings in hospital days. Even after the costs of lifetime medical care for hospital survivors were included, primary angioplasty would lead to cost savings of \$1.9 million relative to thrombolysis.

Primary angioplasty dominated thrombolysis because it had both superior health outcomes and lower costs. In this situation, it was appropriate to express the cost/QALY saved by primary angioplasty compared with no intervention, which was \$12,000.

**Sensitivity analyses.** *Effectiveness assumptions and hospital scenarios.* For the base case hospital with an existing, fully staffed laboratory, using effectiveness rather than efficacy assumptions resulted in only a slight increase in the cost/QALY

saved by primary angioplasty, still \$12,000. Likewise, primary angioplasty continued to have a cost/QALY saved of <\$30,000 under alternative hospital scenarios, provided that efficacy assumptions were used and the hospital's annual volume of myocardial infarctions was  $\geq 200$  (Fig. 2).

However, when effectiveness assumptions were combined with alternative hospital scenarios, primary angioplasty appeared much less cost-effective. Under effectiveness assumptions and at an annual volume of 200 myocardial infarctions, the cost/QALY saved increased to \$72,000 in the "Add Needed Lab" scenario and to \$330,000 in the "Add Redundant Lab" scenario (Fig. 2).

*Procedure volume.* Under the "Add Night Call," "Add Needed Lab" and "Add Redundant Lab" scenarios, the cost/QALY saved by primary angioplasty increased sharply as the annual number of patients with an acute myocardial infarction admitted to the hospital decreased (Fig. 2). When effectiveness assumptions were used and the hospital admitted <150 patients with a myocardial infarction/year, the cost/QALY saved increased to >\$100,000 in all hospital scenarios except the base case hospital.

*Time to intervention.* Under base case efficacy assumptions, increasing the time to intervention by 1 h reduced the undiscounted QALYs saved by the primary angioplasty policy to 3,986 relative to no intervention (a 5% reduction) and 544 relative to thrombolysis (a 26% reduction). However, primary angioplasty was still cost saving compared with thrombolysis and had a cost/QALY saved of \$12,000 compared with no intervention. In contrast, under effectiveness assumptions, increasing the time to intervention by 1 h resulted in higher total mortality than thrombolysis, rendering this an ineffective strategy no matter what the cost.

*Other sensitivity analyses.* For the base case hospital, the "Add Night Call" scenario, and the "Add Needed Lab" scenario, primary angioplasty always had a cost/QALY saved of <\$20,000 when individual assumptions (e.g., in-hospital mortality, long-term survival, subsequent cardiac quality of life) were varied over plausible ranges. When the cost of thrombolysis was changed to that of streptokinase (\$320), primary angioplasty's cost/QALY was \$7,000 compared with thrombolysis, still less than that of thrombolysis compared with no intervention. When future medical costs were not included, the cost/QALY saved compared with no intervention ranged from \$400 for the base case hospital to \$18,000 for the "Add Redundant Lab" scenario. At a discount rate of 5% rather than 3%, primary angioplasty still had projected cost savings compared with thrombolysis and a cost of \$12,000/QALY saved compared with no intervention.

## Discussion

**Main findings.** From a societal perspective, primary angioplasty for acute myocardial infarction would have reasonable cost-effectiveness under a wide range of assumptions if provided by hospitals that already have fully supported cardiac catheterization laboratories. Under base case assumptions, the

**Table 3.** Projected Outcomes of Primary Angioplasty and Thrombolysis Policies for a Hypothetical Cohort of 10,000 Patients With Acute Myocardial Infarction

	Clinical Policy		
	Primary Angioplasty	Thrombolysis	No Intervention
<b>Health outcomes</b>			
Deaths	982	1,034	1,269
Survivors	9,018	8,966	8,731
Nonfatal disabling strokes	16	25	17
Relative to no intervention			
Lives saved	287	235	NA
Life-years saved (undiscounted)	4,310	3,626	NA
QALYs saved (undiscounted)	4,183	3,442	NA
Relative to thrombolysis			
Lives saved	52	NA	NA
Life-years saved (undiscounted)	684	NA	NA
QALYs saved (undiscounted)	741	NA	NA
<b>Costs [U.S. \$ in thousands (% of total costs)]*</b>			
Initial intervention	6,500 (1)	8,100 (1)	NA
Initial hospital stay	102,000 (14)	107,000 (15)	108,000 (16)
Reinfarction and procedures in subsequent 12 mo	30,000 (4)	30,000 (4)	29,000 (4)
Subtotal for 12 mo	138,000 (19)	145,000 (20)	137,000 (20)
Future health costs of survivors	585,000 (81)	581,000 (80)	553,000 (80)
Total	724,000 (100)	726,000 (100)	690,000 (100)
Incremental 12-mo cost (savings)†	(7,200)	8,300	NA
Incremental total cost‡	(1,900)	36,000	NA
<b>Cost-effectiveness ratios‡</b>			
Vs. thrombolysis			
\$/life saved	Savings	NA	NA
\$/life-year saved	Savings	NA	NA
\$/QALY saved	Savings	NA	NA
Vs. no intervention§			
\$/life saved	120,000	150,000	NA
\$/life-year saved	11,000	14,000	NA
\$/QALY saved	12,000	15,000	NA

\*U.S. 1993 dollars, discounted at 3%/year over 10 years; numbers are rounded to two or three significant digits and thus do not always add to total. †Incremental costs are primary angioplasty versus thrombolysis and thrombolysis versus no intervention. ‡Costs and benefits discounted at 3%/year. §Primary angioplasty is considered economically preferable to thrombolysis by the principle of extended dominance, because the cost/quality-adjusted life-year (QALY) saved of primary angioplasty relative to thrombolysis is lower than that of thrombolysis relative to no intervention; thus, the cost/QALY saved of primary angioplasty relative to no intervention is given. NA = not applicable.

procedure was projected to save costs compared with thrombolysis and to cost \$12,000/QALY saved compared with no intervention. The latter ratio is lower than those of many other accepted medical interventions. These findings are in accord with empirical studies (3-5) suggesting that the cost-effectiveness of primary angioplasty under ideal conditions is better than or equal to that of thrombolysis.

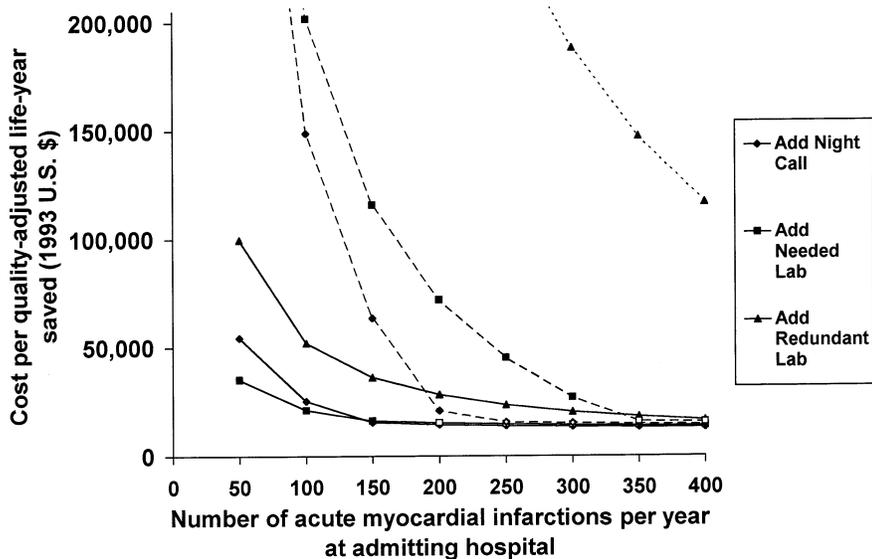
However, these results also underscore the potential cost-ineffectiveness of primary angioplasty if provided in settings where health outcomes are similar to those in observational community-based studies and where the procedure's costs are higher or volumes are lower. Under effectiveness assumptions and at low volumes, the cost/QALY saved under most hospital scenarios rapidly increased beyond \$100,000, out of the range of most accepted medical interventions.

**Policy implications.** Our findings suggest that regionalization of cardiac services would be desirable from a societal

perspective. Providing primary angioplasty cost-effectively will depend on using existing cardiac catheterization laboratories and maximizing hospitals' volumes of procedures. Without regionalization, the procedure might be offered by hospitals with a lower volume or less experienced operators, which tends to lead to worse angioplasty outcomes (6,8,10).

The present study was conducted to inform health policy decisions rather than to direct individual bedside decisions. The results suggest that primary angioplasty would have reasonable cost-effectiveness if optimal costs and outcomes could be achieved, even if the average time to intervention increased by 1 h. In urban areas, where ~80% of the U.S. population resides, regionalization might be achieved by having emergency medical services triage symptomatic patients to high volume hospitals with primary angioplasty capability.

In reality, the conflicting perspectives of the various stakeholders in health care may pose a barrier to optimal use of



**Figure 2.** Cost/QALY saved by using a policy of primary angioplasty, depending on procedure volume (based on the number of acute myocardial infarctions/year at the admitting hospital). **Solid lines** = cost/QALY saved under the three alternative hospital scenarios given base case (efficacy) assumptions about health outcomes; **dashed lines** = cost/QALY saved under the three alternative hospital scenarios, given effectiveness assumptions estimated from community-based observational trials; **solid symbols** = analyses where primary angioplasty is compared with thrombolysis; **open symbols** = analyses where primary angioplasty had dominance or extended dominance over thrombolysis and is thus compared with no intervention. When volume is varied, assumptions about health outcomes are not changed, except as depicted using the **dashed lines** for effectiveness assumptions. The cost/QALY saved by primary angioplasty under the base case hospital ("Fully Covered Lab" scenario) was not depicted and remained at \$12,000 compared with no intervention under both efficacy and effectiveness assumptions regardless of volume. Using low volumes and effectiveness assumptions about health outcomes, the cost/QALY saved was >\$100,000 under most hospital scenarios.

primary angioplasty. In the United States, decisions about health services are usually made at the level of the individual hospital or health plan, and this poses competitive barriers to regionalization. An individual hospital in a competitive market may seek to maximize revenue and market share by providing profitable services such as invasive cardiac procedures, even if they duplicate those of neighboring hospitals and preclude cooperation.

A large health maintenance organization may need to contract with outside hospitals to provide primary angioplasty services and would most likely face higher charges for primary angioplasty than the optimal cost of ~\$2,000 in our base case, possibly closer to the \$5,000 cost in our "Add Needed Lab" scenario. In addition, most patients with chest pain do not actually have an acute myocardial infarction. If emergency medical services triaged all patients with chest pain to regional centers without attempting to select those with an acute myocardial infarction, costs to a third-party payer could increase even more. Thus, if regional triaging is considered, close monitoring of actual costs and outcomes will be warranted to avoid providing primary angioplasty in a cost-ineffective manner.

**Limitations of the study.** In this study, primary angioplasty did not result in long-term cost savings compared with no intervention, in part because increased survivorship led to higher costs of future lifetime medical care. Including these costs presents the most accurate picture of a policy's effects (52). When future medical costs were not included, the costs/QALY saved by primary angioplasty appeared to be 50% to 90% lower. Estimates from other studies, such as the \$33,000/

life-year saved by t-PA versus streptokinase, usually have not included such costs (53).

Although we did not include work-loss costs, this would not have changed our conclusions because patients who undergo primary angioplasty have at least equal and possibly better cardiac functional status than those who receive thrombolysis (4). This analysis used the wholesale price of t-PA, which may be higher than the true cost to society of manufacturing the medication. However, the results did not change when the lower price of streptokinase was used. New thrombolytic agents or other technologies under development may have lower stroke rates or superior effectiveness than t-PA, but this analysis showed that primary angioplasty would be cost-effective relative to thrombolysis even without any advantage in stroke rates.

**Conclusions.** Primary angioplasty for patients with an acute myocardial infarction is likely to be cost-effective at hospitals that already have fully supported cardiac catheterization laboratories operating at high volumes. The procedure's relative cost-ineffectiveness at low volumes supports regionalization of cardiac services in urban areas. However, if primary angioplasty services are to be effectively regionalized in the United States, creative approaches to overcoming competitive barriers and close monitoring of outcomes and costs will be needed.

We are grateful to the cardiologists who joined two of the authors (R.J.L. and W.W.P.) for the expert panel conference: Cindy Grines, MD, J. Ward Kennedy, MD, Dean Mason, MD, Guy Reeder, MD and Thomas Ryan, MD. We appreciate the contributions of Karen Kuntz, ScD and Lee Goldman, MD

through the Coronary Heart Disease Policy Model. We thank Thomas Thom, PhD for advice on calculation of the nursing home costs of stroke survivors and Menko Jan deBoer, MD and Felix Zijlstra, MD, who shared advance data on cardiac functional status after primary angioplasty. We thank Michael Sorel, MPH, who initiated the programming and analysis, and many others with Kaiser Permanente, including Laura Finkler, MPH, Gary Salyer, MDiv, Lyn Wender, Marie Miller, PhD, John Mosher, MBA, Agnes Cronin, MBA and Matt Kaplan, MBA. We are indebted to Dr. Reeder and to Joe Selby, MD for thoughtful reviews of the manuscript and to Jay Crosson, MD for sponsoring the study.

## References

- Grines CL, Brown 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.
- Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfensperger MR, Gersh BJ. 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.
- Reeder GS, Bailey KR, Gersh BJ, Holmes DR, Christianson J, Gibbons RJ. Cost comparison of immediate angioplasty versus thrombolysis followed by conservative therapy for acute myocardial infarction: a randomized prospective trial. *Mayo Clin Proc* 1994;69:5-12.
- de Boer MJ, van Hout BA, Liem AL, Suryapranata H, Hoorntje JCA, Zijlstra F. Cost-effectiveness analysis of primary coronary angioplasty vs. thrombolysis for acute myocardial infarction. *Am J Cardiol* 1995;76:830-3.
- Stone GW, Grines CL, Rothbaum D, et al. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the Primary Angioplasty in Myocardial Infarction (PAMI) trial. *J Am Coll Cardiol* 1997;29:901-7.
- Every NR, Parson LS, Hlatky M, Martin JS, Weaver WD. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. *N Engl J Med* 1996;335:1253-60.
- Rogers WJ, Dean LS, Moore PB, et al. Comparison of primary angioplasty versus thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1994;74:111-8.
- Ritchie JL, Phillips KA, Luft HS. Coronary angioplasty: statewide experience in California. *Circulation* 1993;88:2735-43.
- Jollis JG, Peterson ED, DeLong ER, et al. The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. *N Engl J Med* 1994;331:1625-9.
- Kimmel SE, Berlin JA, Laskey WK. The relationship between coronary angioplasty procedure volume and major complications. *JAMA* 1995;274:1137-42.
- Lieu TA, Lundstrom RJ, Ray GT, Fireman BH, Gurley RJ, Parmley WW. The initial cost of primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1996;28:882-9.
- Weaver WD, Litwin PE, Martin JS, et al. Use of direct angioplasty for treatment of patients with acute myocardial infarction in hospitals with and without on-site cardiac surgery. *Circulation* 1993;88:2067-75.
- Goldman L. Cost and quality of life: thrombolysis and primary angioplasty. *J Am Coll Cardiol* 1995;25 Suppl:38S-41S.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). 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.
- ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;335:349-60.
- Graves EJ. Summary: National Hospital Discharge Survey. Advance data from Vital and Health Statistics, No. 264. Hyattsville (MD): National Center for Health Statistics, 1995.
- McClellan M, McNeill BJ, Newhouse JP. Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. *JAMA* 1994;272:859-66.
- Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB, Goldman L. Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. *Am J Public Health* 1987;77:1417-26.
- Lieu TA, Gurley RJ, Lundstrom RJ, Parmley WW. Primary angioplasty and thrombolysis for acute myocardial infarction: an evidence summary. *J Am Coll Cardiol* 1996;27:737-50.
- Krumholz HM, Friesinger GC, Cook EF, Lee TH, Rouan GW, Goldman L. Relationship of age with eligibility for thrombolytic therapy and mortality among patients with suspected acute myocardial infarction. *J Am Geriatr Soc* 1994;42:127-31.
- Althouse R, Maynard C, Cerqueira MD, Olsufka M, Ritchie JL, Kennedy JW. The Western Washington myocardial infarction registry and emergency department tissue plasminogen activator treatment trial. *Am J Cardiol* 1990;66:1298-303.
- The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1989;320:618-27.
- Hibbard MD, Holmes DRJ, Bailey KR, et al. Percutaneous transluminal coronary angioplasty in patients with cardiogenic shock. *J Am Coll Cardiol* 1992;19:639-46.
- Gacioch GM, Ellis SG, Lee L, et al. Cardiogenic shock complicating acute myocardial infarction: the use of coronary angioplasty and the integration of the new support devices into patient management. *J Am Coll Cardiol* 1992;19:647-53.
- Yamamoto H, Hayashi Y, Oka Y, et al. Efficacy of percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction complicated by cardiogenic shock. *Jpn Circ J* 1992;56:815-21.
- Lee L, Bates ER, Pitt B, Walton JA, Laufer N, O'Neill WW. Percutaneous transluminal coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. *Circulation* 1988;78:1345-51.
- Lee L, Erbel R, Brown TM, et al. Multicenter registry of angioplasty therapy of cardiogenic shock: initial and long-term survival. *J Am Coll Cardiol* 1991;17:599-603.
- Brodie BR, Weintraub RA, Stuckey TD, et al. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. *Am J Cardiol* 1991;67:7-12.
- Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. *Am J Cardiol* 1967;20:457-64.
- Scheidt S, Ascheim R, Killip T. Shock after acute myocardial infarction: a clinical and hemodynamic profile. *Am J Cardiol* 1970;26:556-64.
- Cragg DR, Friedman HZ, Bonema JD, et al. Outcome of patients with acute myocardial infarction who are ineligible for thrombolytic therapy. *Ann Intern Med* 1991;115:173-7.
- Himbert D, Juliard J-M, Steg G, et al. Primary coronary angioplasty for acute myocardial infarction with contraindication to thrombolysis. *Am J Cardiol* 1993;71:377-81.
- 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.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343:1115-22.
- ISIS-4 Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
- Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. *Circulation* 1995;91:476-85.
- Zijlstra F, de Boer MJ, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680-4.
- Ribeiro EE, Silva LA, Carneiro R, et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. *J Am Coll Cardiol* 1993;22:376-80.
- Simari RD, Berger PB, Bell MR, Gibbons RJ, Holmes DR. Coronary angioplasty in acute myocardial infarction: primary, immediate adjunctive, rescue, or deferred adjunctive approach? *Mayo Clin Proc* 1994;69:346-58.
- Nunn C, O'Neill W, Rothbaum D, et al. Primary angioplasty for myocardial infarction improves long-term survival: PAMI-1 follow-up [abstract]. *J Am Coll Cardiol* 1996;25 Suppl:153A.
- Goldberg RJ, Gore JM, Alpert J, et al. Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community-wide perspective, 1975 to 1988. *N Engl J Med* 1991;325:1117-22.

42. Hunink MG, Goldman L, Tosteson AN. The recent decline in mortality from coronary heart disease, 1980-1990: the effect of secular trends in risk factors and treatment. *JAMA* 1997;277:535-42.
43. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, 1996.
44. Nease RJ, Kneeland T, O'Connor GT, et al. Variation in patient utilities for outcomes of the management of chronic stable angina. *JAMA* 1995;273:1185-90.
45. Solomon NA, Glick HA, Russo CJ, et al. Patient preferences for stroke outcomes. *Stroke* 1994;25:1721-5.
46. Krumholz HM, Pasternak RC, Weinstein MC, et al. Cost effectiveness of thrombolytic therapy with streptokinase in elderly patients with suspected acute myocardial infarction. *N Engl J Med* 1992;327:7-13.
47. National Center for Health Statistics. *The National Nursing Home Survey* DHHS Publication No. (PHS) 89-1758. Hyattsville (MD): U.S. Department of Health and Human Services, 1989.
48. National Center for Health Statistics. *Health United States 1994*. Hyattsville (MD): U.S. Department of Health and Human Services, 1995.
49. Hahn B, Lefkowitz D. Annual expenses and sources of payment for health care services (AHCPR Pub. No. 93-0007). *National Medical Expenditure Survey Research Findings 14*, Agency for Health Care Policy and Research. Rockville, MD: Public Health Service, 1992.
50. Newby LK, Rutsch WR, Califf RM, et al. Time from symptom onset to treatment and outcomes after thrombolytic therapy. *J Am Coll Cardiol* 1996;27:1646-55.
51. Boersma E, Maas ACP, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;348:771-5.
52. Meltzer D. Accounting for future costs in medical cost-effectiveness analysis. *J Health Econ* 1996. In press.
53. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med* 1995;332:1418-24.
54. The Thrombolysis Early in Acute Heart Attack Trial Study Group. Very early thrombolytic therapy in suspected acute myocardial infarction. *Am J Cardiol* 1990;65:401-7.
55. Kennedy JW, Martin GV, Davis KB, et al. The Western Washington intravenous streptokinase in acute myocardial infarction randomized trial. *Circulation* 1988;77:345-52.
56. Simoons ML, Serruys PW, VanDenBrand M, et al. Early thrombosis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;7:717-28.
57. ISIS Pilot Study Investigators. Randomized factorial trial of high-dose intravenous streptokinase, of oral aspirin and of intravenous heparin in acute myocardial infarction. *Eur Heart J* 1987;8:634-42.
58. Cerqueira MD, Maynard C, Ritchie JL, Davis KB, Kennedy JW. Long-term survival in 618 patients from the Western Washington Streptokinase in Myocardial Infarction trials. *J Am Coll Cardiol* 1992;20:1452-9.
59. Arnold AER, Simoons ML, Van de Werf F, et al. Recombinant tissue-type plasminogen activator and immediate angioplasty in acute myocardial infarction: one-year follow-up. *Circulation* 1992;86:111-20.
60. AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. *Lancet* 1990;335:427-31.
61. Simoons ML, Vos J, Tijssen JGP, et al. Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989;14:1609-15.
62. Califf RM, Topol EJ, George BS, et al. One-year outcome after therapy with tissue plasminogen activator: report from the Thrombolysis and Angioplasty in Myocardial Infarction trial. *Am Heart J* 1990;199:777-85.
63. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Effects of alteplase in acute myocardial infarction: 6-month results from the ASSET study. *Lancet* 1990;335:1175-8.
64. O'Murchu B, Gersh BJ, Reeder GS, Bailey KR, Holmes DR. Late outcome after percutaneous transluminal coronary angioplasty during acute myocardial infarction. *Am J Cardiol* 1993;72:634-9.
65. Terrin ML, Williams DO, Kleiman NS, et al. Two- and three-year results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II clinical trial. *J Am Coll Cardiol* 1993;22:1763-72.
66. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987;2:871-4.
67. Mori T, Nosaka H, Kimura T, Nobuyoshi M. Long-term follow-up of patients treated with intracoronary thrombolysis or percutaneous transluminal coronary angioplasty for acute myocardial infarction. *J Cardiol* 1991;21:323-36.
68. Anonymous. 1993 Drug Topics Red Book. Montvale (NJ): Medical Economics Data, 1993.