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Cost-effectiveness in Clinical Cardiology*

Part 1: Coronary Artery Disease and Congestive Heart Failure

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Abbreviations: ACE=angiotensin-converting enzyme; CCU=coronary care unit; GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries study; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty; QALY=quality-adjusted life year; t-PA=tissue plasminogen activator

Currently, therapeutic recommendations are predominantly determined by our knowledge of the efficacy and safety of specific treatment modalities, eg, medications, devices, and surgery. However, with the health-care costs of the nation reaching 14% of the gross domestic product, medical economics has become an increasing part of our social and professional environment.1 The medical expenses and lost productivity for cardiovascular disease have been estimated at $138 billion, a figure that has focused a great deal of attention on the costs of caring for patients with heart and vascular diseases.2

While the role of the physician may be best performed as a patient advocate independent of cost issues, knowledge of costs is becoming an essential element of our knowledge base. This two-part article will present four patient scenarios with a discussion focused at our current level of knowledge with respect to the cost-effectiveness of cardiovascular interventions. The cases will be preceded by a practical discussion of the general principles of cost-effective-ness analyses. It is important to point out that the most cost-effective modalities may not be the current treatment of choice in general or for a specific patient; conversely, many well-accepted treatments have little or no current cost data available and therefore may not be discussed.

Introduction to Cost-effectiveness Analysis

Despite the analytic and mathematical form of cost-effectiveness data, each element of the analysis is plagued by uncertainties.3 Improvements will occur as the field grows and matures. The key concept is to no longer accept efficacy and safety as sufficient descriptors of therapy but to include the cost of such therapy and its benefit or effectiveness. Cost may be evaluated in a variety of ways. Cost alone may be calculated or it may be related to effectiveness (measured as years of life saved), benefit (measured in dollars), or utility (measured in quality-adjusted life years, ie, QALYs).4,5 A great deal of difficulty arises in assessing effectiveness, especially benefit which requires the equation of life and other outcome variables to dollars (willingness to pay and dollar-year trade-off models are sometimes used). Many of these measures are subjective and a variety of models are used, each with a variety of limitations.3,6 Costs include the direct cost of the illness, indirect costs (eg, income loss), and intangible costs (eg, pain and suffering). The latter two elements are not always included. Furthermore, costs may refer to charges (unreliable with cost shifting), payments (unreliable in that the basis for payment is variable with the payer), or the actual cost of the treatment (infrequently used and more difficult to calculate).4 The total cost or resource consumption equals the unit cost times the number of times of use.

Incremental cost-effectiveness may be used to compare modalities. In this context, net cost is the direct cost plus the cost of adverse events plus the cost of increased longevity minus the savings due to improved health. Two modalities can be compared by the ratio of the change in the net costs to the change in effec-
tivenesses, *eg*, change in dollars to change in years of life saved. An incremental cost-effectiveness ratio (in dollars per QALY) is considered very attractive at less than $20,000; acceptable and consistent with current dialysis funding at $20,000 to $40,000; higher than currently funded at $60,000 to $100,000; and unattractive if more than $100,000. Furthermore, cost and effectiveness must be evaluated over time wherein the value of either may change and must be "discounted." *It is important to understand that the dollars quoted in this review are for the year of publication unless otherwise stated.* A change to current dollars was avoided due to the assumptions inherent in these corrections.

Cost-effectiveness analyses rely on meta-analyses of randomized trials or historic and case-controlled trials when necessary. Often expert opinion is used to fill in the gaps. Only now is the prospective acquisition of cost data being incorporated into large clinical trials. However, when data are collected from clinical trials, the efficacy of the intervention may be biased by patient selection, the highly motivated environment, the academic milieu, and the propensity to publish positive results. Therapeutic effectiveness when applied generally may be less and is now only beginning to be measured. Community-based trials are beginning to emerge to avoid the academic bias. Analyses often use the concepts of decision analysis; to test these models, sensitivity analyses are performed. These concepts and the application of cost-effectiveness analyses will be discussed in part 2.

**Case History 1**

A 52-year-old man with a history of hypercholesterolemia presented to his family physician with recurrent chest tightness while doing yard work during the last 5 weekends. He was referred to a cardiologist who performed stress ECG. The patient developed his typical chest discomfort and 1-mm ST segment depressions after completing stage 3 of a Bruce protocol. He was prescribed aspirin, 81 mg orally in the morning, metoprolol, 100 mg orally bid, and sublingual nitroglycerin, 1/150, as needed, with marked improvement in his symptoms.

Six years later, he was admitted to the coronary care unit (CCU) with 30 min of substernal chest discomfort occurring at rest. Initial and subsequent ECGs and cardiac enzyme levels were normal. Twenty-four hours after hospital admission, he developed persistent chest pain radiating to his left arm and nausea. His ECG showed 2-mm ST segment elevations in leads V2 through V5, and he was treated with an accelerated regimen of tissue plasminogen activator (t-PA) over 90 min followed by a 48-h infusion of heparin. His chest pain and ECG improved.

Aspirin and metoprolol therapy was continued and he was begun on a regimen of captopril, 25 mg orally tid. Five days after hospital admission, he underwent a submaximal thallium stress test. He did not develop chest pain or ischemic ST segment depressions, and his thallium scan showed a moderate-sized fixed defect of the anterior wall without reperfusion on delayed images.

Four years later, he developed chest pain while walking one block and was referred for coronary angiography. After angiography, revascularization options were discussed with the patient and family.

**Case History 2**

During a routine preemployment evaluation, a 45-year-old man was noted to have cardiomegaly on a chest radiograph. He did not have symptoms of heart failure. The patient had been in good health with no history of hypertension, coronary artery disease, or rheumatic fever. He did not smoke tobacco and rarely drank alcohol. Physical examination revealed a pulse of 78 beats/min and BP of 135/85 mm Hg. No signs of heart failure or valvular disease were present. An echocardiogram revealed enlargement of all four chambers of the heart with global hypokinesis of both ventricles. Valves were structurally normal. Mild mitral and tricuspid regurgitation was detected. During a treadmill exercise test, the patient had normal exercise capacity and thallium images revealed no evidence of ischemia. Diagnosis of idiopathic cardiomyopathy was made. The patient was treated with angiotensin-converting enzyme (ACE) inhibitor, enalapril, 10 mg/d, and he underwent anticoagulation with warfarin.

The patient did well for 2 years. Then he presented to the emergency department with new onset of dyspnea, palpitations, and pedal edema. He was noted to be in atrial fibrillation with rapid ventricular response and congestive heart failure. Digoxin and furosemide therapy was begun and enalapril and warfarin therapy was continued. Heart failure was well compensated with this regimen. Electrical cardioversion of the atrial fibrillation was attempted but was not successful.

Over the next year, the patient suffered heart failure and his condition deteriorated progressively. The patient was hospitalized repeatedly for exacerbations of heart failure and required IV inotropic therapy for improvement. He underwent heart transplantation for refractory symptoms.

**Questions**

Regarding the cost-effective treatment of the first patient:

1. Which of the following strategies for detecting coronary artery disease are cost-effective?
   a. Performing exercise ECG prior to the onset of symptoms.
   b. Performing exercise ECG after he presented with his initial symptoms and proceeding to thallium scintigraphy if abnormal.
   c. Performing exercise ECG after the onset of symptoms and proceeding to coronary angiography if 2-mm or greater ST segment depressions are noted on stress ECG.
   d. Performing stress thallium scintigraphy after the onset of symptoms and if abnormal proceeding to coronary angiography.
   e. Performing coronary angiography after the onset of symptoms.

2. In treating this patient when he presented with 30 min of rest chest pain without ECG changes, which of the following strategies is cost-effective?
   a. Admission to the CCU.
   b. Admission to the intermediate-care or step-down unit with telemetry and resuscitation capabilities.
   c. Admission to routine medical floor.
   d. Admission to a short-stay coronary observation
3. In this patient, which of the following strategies for managing his acute myocardial infarction (MI) are cost-effective?
   a. Reperfusion with streptokinase followed by the Thrombolysis in Myocardial Infarction (TIMI) IIIB conservative strategy.
   b. Reperfusion with t-PA followed by the TIMI IIIB conservative strategy.
   c. Reperfusion with streptokinase followed by the TIMI IIIB invasive strategy.
   d. Reperfusion with t-PA 12 h after the onset of chest pain.

4. In this patient, which of the following post-MI management strategies are cost-effective?
   a. Performing exercise ECG at the time of hospital discharge.
   b. Performing stress thallium scintigraphy at the time of hospital discharge.
   c. Performing coronary angiography at the time of hospital discharge.
   d. Long-term administration of beta-blockers.
   e. Long-term administration of ACE inhibitors.

5. In this patient, cost-effective revascularization strategies include which of the following?
   a. Coronary artery bypass for mild angina and three-vessel disease.
   b. Coronary artery bypass for two-vessel disease (including left anterior descending artery) and severe angina.
   c. Coronary artery bypass for single-vessel disease and mild angina.
   d. Percutaneous transluminal coronary angioplasty (PTCA) for single-vessel disease (type IA lesion) and severe angina.
   e. PTCA with complete revascularization for two-vessel disease and severe angina.
   f. PTCA for single-vessel disease and mild angina.

6. In the treatment of patients with heart failure, which of the following strategies have been demonstrated to be cost-effective?
   a. ACE-inhibitor therapy in patients with asymptomatic idiopathic dilated cardiomyopathy.
   b. Treatment of patients with congestive heart failure with ACE inhibitor.
   c. Providing anticoagulation for patients with heart failure to prevent systemic embolism.
   d. Heart transplantation for patients with refractory heart failure.

   **Answers**

1. *b, c, d, and e*

   The detection and risk stratification of patients with coronary artery disease is a common clinical problem. Several different diagnostic strategies encompassing exercise ECG, stress thallium scintigraphy, coronary angiography, and combinations of these tests are used by clinicians to diagnose and risk-stratify patients with coronary artery disease, and the optimal strategy may vary according to the clinical setting. Several studies using different methods have evaluated the cost-effectiveness of these strategies in asymptomatic patients and patients with atypical and typical angina. These studies have concluded that the cost-effectiveness of all approaches improves as the pretest prevalence of coronary artery disease increases in the population undergoing testing, and the selection of the most appropriate strategy in individual patients depends on the clinically determined pretest likelihood of disease.

   Screening asymptomatic patients for coronary artery disease by exercise ECG was prohibitively expensive in two studies. However, targeting high-risk populations for screening improved cost-effectiveness, e.g., screening asymptomatic 45-year-old men with three additional coronary risk factors cost $11,271 to $17,489 per patient diagnosed as having coronary artery disease. In this study, thallium scintigraphy was more cost-effective than exercise ECG because of the high incidence of false-positives associated with exercise ECG. In contrast, economic analyses of strategies for diagnosing coronary artery disease in patients with atypical angina have found all diagnostic approaches to be cost-effective. These results are not surprising because according to Bayes’ theorem, noninvasive tests have their most significant effect on changing the pretest likelihood of coronary artery disease in patients with an intermediate probability of coronary disease such as patients with atypical chest pains. Four strategies, exercise ECG, stress thallium scintigraphy, initial coronary angiography, and sequenced exercise ECG leading to stress thallium scintigraphy, were evaluated in middle-aged men with atypical angina and found to be highly cost-effective ($5,300 to $6,300 per patient diagnosed as having coronary artery disease in the cost-utility study and $9,000 to $10,000/yr of life saved in the cost-effectiveness study). The differences among the four diagnostic strategies were small. In the cost-utility study, initial stress thallium scintigraphy was the most cost-effective, while in the cost-effectiveness study, exercise ECG was the most cost-effective. In another study of middle-aged men with atypical angina, exercise ECG using 1-mm or greater ST segment depression as a threshold to select patients for subsequent coronary angiography was more cost-effective than strategies of initial angiography or exercise ECG using a 2- or 3-mm cutoff.

   Although patients with typical angina have a greater...
than 80% prevalence of coronary artery disease and the power of noninvasive testing to impact the pretest likelihood of disease is diminished compared to patients with atypical angina, economic analyses of patients with typical angina have found all noninvasive and invasive strategies used for stratifying risk and identifying suitable candidates for bypass surgery to be cost-effective.9-12 However, the ranking order of cost-effectiveness among the different diagnostic approaches varied in these studies. In a cost-utility study of middle-aged men with typical angina, exercise ECG, stress thallium scintigraphy, initial coronary angiography, and sequential exercise ECG leading to thallium scintigraphy were all highly cost-effective with a range of $3,300 to $4,600 per coronary artery disease diagnosis.

Initial coronary angiography was the most cost-effective strategy because the consequences of misdiagnosis due to false-negative and nondiagnostic noninvasive studies is avoided. In contrast to patients with atypical angina, exercise ECG was more cost-effective than stress thallium scintigraphy because there are fewer false-positives with exercise ECG in this subset of patients compared to subsets with lower disease prevalence.9 In another study of middle-aged men with angina that evaluated the same four diagnostic strategies, all four approaches were again highly cost-effective with little difference among approaches ($8,700 to $8,800/yr of life saved).10 In another study of middle-aged men with typical angina, a policy of initial coronary angiography was more cost-effective than exercise ECG using 1-, 2-, or 3-mm ST segment depression as a threshold for performing angiography. A fourth study compared five diagnostic strategies for detecting left main coronary artery disease in patients with mild stable angina. The strategies were conservative therapy (no diagnostic testing unless symptoms progressed), initial coronary angiography, and exercise ECG using different levels of ST segment depression (1, 2, or 3 mm) to screen patients for angiography. In contrast to the previously mentioned studies, coronary angiography was dominated by exercise ECG. Although the 1-mm threshold resulted in the largest improvement in life expectancy, a strategy using a 2-mm threshold had the most favorable incremental cost-effectiveness ratio.12

Stress echocardiography has been shown to be superior to exercise ECG for diagnosing coronary disease and is competitive with thallium scintigraphy as a stress-imaging modality. Although economic analyses of stress echocardiography are limited, a recent study suggested that stress echocardiography as an initial diagnostic test for coronary artery disease in women is less expensive than exercise ECG because fewer unnecessary coronary angiograms are performed following stress echocardiography.13

In our patient with typical angina, although screening prior to symptom onset would not be cost-effective, all of the strategies are cost-effective after symptoms occurred. Although several studies suggest initial coronary angiography is the most cost-effective approach, defining the optimal strategy awaits further study.

2. b, d

The efficacy of CCUs in the treatment of patients with acute MI is both intuitive and well documented. CCUs allow the rapid diagnosis and treatment of serious arrhythmias, hemodynamic monitoring of patients with significant left or right ventricular dysfunction, and a controlled environment for implementation of reperfusion strategies. However, the suboptimal accuracy of the initial clinical evaluation of chest pain combined with the dire consequences of misdiagnosis of MI has resulted in a policy of admitting large numbers of patients with chest pain in the absence of infarctions to the CCU, severely diluting the cost-effectiveness.14,15

A 1984 study evaluated the incremental cost-effectiveness of four increasingly expensive management strategies of patients presenting to the emergency department with chest pain with a low (5%) probability of having an acute MI. The four strategies in order of increasing expense were outpatient care, admission to a routine-care floor, admission to an intermediate-care unit with capabilities of administering prophylactic lidocaine and rapidly performing cardiac resuscitation, and admission to a CCU. If infarction was documented in patients being treated in one of the first three settings, transfer to the CCU would occur. Although this study included routine lidocaine prophylaxis, a practice no longer advocated, and does not reflect the advances associated with the thrombolytic era, the conclusions are still instructive. Although admission to the CCU resulted in the most lives saved, CCU care was expensive with a cost of $2,000,000 per life saved and $139,000/yr of life saved. Admission to an intermediate-care unit cost $570,000 per life saved and $43,000/yr of life saved. Routine floor care and outpatient care were less cost-effective than an intermediate-care unit. Sensitivity analysis was instructive as to how to improve the efficiency of the CCU. By increasing the probability of MI to 10%, cost-effectiveness of the CCU improves to $970,00 per life saved and $66,000/yr of life saved, and by increasing the probability to 20%, cost-effectiveness improved to $485,000 per life saved and $33,000/yr of life saved.16 Therefore, improving patient selection by improved initial diagnostic methods will lead to a more cost-effective utilization of the CCU. Current research into more rapid and accurate
biochemical markers of myocardial necrosis, 99mTc sestamibi imaging, and emergency department-based chest pain centers is expected to achieve this goal. Clinical outcomes and costs for patients with chest pain and a low probability of acute MI admitted to a short-stay coronary observation unit were compared with those of low-risk patients conventionally triaged to the CCU, intermediate-care unit, routine medical floor, or home care. No differences in clinical outcomes were observed. Median costs were significantly lower for patients treated in the short-stay unit ($1,900) than for patients treated in the CCU ($9,200), intermediate-care unit ($4,000), and routine floor ($4,700).

In our patient who presented with chest pain and no ECG evidence of infarction, admission to the intermediate-care unit or short-stay coronary observation unit would be cost-effective while the other strategies would be expensive.

3. a and b

Reperfusion therapy with thrombolytic drugs or primary PTCA improves survival in acute MI and has become a standard of treatment. The efficacy of these therapies varies significantly with multiple factors, including infarct size, time interval between the onset of infarction and reestablishment of blood flow, pharmacologic agent or modality used to achieve reperfusion, patient age, and the postreperfusion management strategy to prevent or treat reocclusion. Several studies using different methods have demonstrated that reperfusion therapies are highly cost-effective, and that the cost-effectiveness is dramatically affected by the same variables as efficacy.

A decision analysis model was used to evaluate the cost per life saved of four reperfusion strategies: IV streptokinase or t-PA with conservative postreperfusion management, IV streptokinase or t-PA with aggressive postreperfusion management, intracoronary streptokinase, and primary PTCA. Cost per year of life saved could not be assessed because long-term survival data with reperfusion were not available at that time. This study demonstrated that several reperfusion strategies were extremely cost-effective in many clinical settings. Marked variations in cost-effectiveness were noted according to infarct size, time to reperfusion, and postreperfusion management strategies. As an example, the cost per life saved in large infarctions with streptokinase and a conservative postreperfusion management strategy was $7,000 if the drug was administered at the start of the infarction, $12,000 if administered 2 h later, and $27,000 if administered 4 h after the infarction started. In moderate-sized infarctions, the comparable figures are $40,000, $59,000, and $171,000. In general, cost per life saved varied by a multiple of 7 to 15 according to infarct size, by a multiple of 3 to 7 according to the time elapsed between infarct onset and initiation of therapy, and by a multiple of 3 to 6 according to the postreperfusion strategy selected. Therefore, the cost per life saved varied from $7,000 for large infarcts treated early and conservatively to $2,733,000 for small infarcts treated late and aggressively.

A decision analysis model was used to evaluate the cost to Medicare per life saved of seven management strategies in acute MI: standard care; IV streptokinase with conservative management, immediate or delayed cardiac catheterization; and IV t-PA with conservative management, immediate or delayed cardiac catheterization. The cost to Medicare per life saved ranged from $53,000 to $57,000 with the two IV agents and a conservative follow-up. However, aggressive follow-up protocols using immediate or delayed diagnostic cardiac catheterization increased the cost to Medicare per life saved to $200,000 to $323,000. An ancillary finding of this study was that thrombolytic therapy will increase the volume of cardiac catheterizations, PTCA, and bypass operations performed because of the increased incidence of incomplete infarction with residual stenosis and potential ischemia. A decision analysis model was also used to evaluate the cost per life saved of streptokinase compared with standard care in MI according to infarct location. Streptokinase was cost-effective although the cost per life saved was six times greater for inferior wall MIs compared with anterior wall MIs. The cost per life saved was $9,900 for anterior wall MIs, $56,600 for inferior wall MIs, and $28,400 for other infarctions.

A decision analysis model compared the incremental cost-effectiveness of IV streptokinase with standard care in the elderly. The cost per year of life saved by administering IV streptokinase to an 80-year-old patient was $21,200.

In contrast to the four studies discussed above that used model-based analysis, a matched-pair analysis prospectively evaluated the cost-effectiveness of thrombolytic therapy relative to standard care. Total charges were not significantly higher in the patients receiving thrombolytics despite the added expense of the thrombolytic drugs and increased use of procedures, possibly because of a more benign course in the group treated with thrombolytics. The cost per life saved by the thrombolytics was $34,600.

The small survival benefits of an accelerated t-PA regimen relative to the administration of streptokinase that was demonstrated in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study (GUSTO) has raised questions about whether this small survival advantage is worth the added expense of using t-PA. A prospective economic analysis was incorporated into the GUSTO study strengthening the validity of the cost-
effectiveness analysis. The cost per year of life saved with accelerated t-PA relative to the streptokinase protocol was $32,700. Subgroup analysis demonstrated that the incremental cost-effectiveness of t-PA exceeded $50,000/yr of life saved in patients younger than 40 years with anterior wall MIs and patients younger than 60 years with inferior wall infarctions.24

Because the cost of aspirin is negligible, to our knowledge, there has been no formal study to demonstrate the cost-effectiveness of the early administration of aspirin in patients with acute MI. In an editorial, Hennekens et al25 estimated that the cost-effectiveness of a 1-month course of aspirin therapy initiated soon after infarction onset was $13 per life saved. Cost-effectiveness data on primary PTCA in acute MI await the publication of the economic analyses of the Primary Angioplasty in Myocardial Infarction Study and GUSTO II trials. Nevertheless, preliminary studies suggest that the costs of hospitalization for patients undergoing primary PTCA were comparable or lower than those of patients receiving thrombolitics.26

In the patient discussed, IV thrombolytic therapy followed by elective cardiac catheterization for an ischemic end point (TIMI II B conservative strategy) would be cost-effective.

4. a, d, and e

The 1-year mortality rate of survivors of acute MI is between 6% and 10% and the incidence of reinfarction is between 4% and 12%, with most events occurring in the first 6 months.27 Some of the patients at increased risk can be identified by clinical variables during hospitalization such as congestive heart failure, hypotension, and recurrent ischemia. These patients, who make up 20% of the survivors, are often referred for coronary angiography and possible revascularization. A significant percentage of the remaining 80% of survivors are also at increased risk and the identification and treatment of these patients cost-effectively is an important goal.28 Exercise ECG, stress thallium scintigraphy (more recently stress echocardiography), and coronary angiography are used in various combinations to stratify risk in these patients. The cost-effectiveness of these diagnostic tests was evaluated in an analysis that compared seven different management strategies. The strategies studied were standard medical care, exercise ECG as the initial screening test (with stress thallium scintigraphy reserved for indeterminate results), stress thallium scintigraphy as the initial screening test, and coronary angiography as the initial evaluation. The model evaluated two different criteria for bypass surgery for each of the three screening options. With the first criterion, bypass surgery was performed for left main disease or a strongly positive noninvasive study. With the second criterion, which was less stringent, bypass surgery was performed for three-vessel disease or one- or two-vessel disease with a significant amount of myocardium at risk, in addition to the indications of criterion 1. Results were reported in 1987 dollars as cost per life saved. Although using stress thallium scintigraphy or coronary angiography as the initial screening procedure resulted in more lives saved, exercise ECG was the most cost-effective procedure, $217,000 per life saved. The incremental cost of using initial coronary angiography instead of exercise ECG was $360,670 per life saved and for stress thallium scintigraphy the incremental cost was $206,000 per life saved. It should be pointed out that the cost per life saved was significantly higher for all three diagnostic strategies if the more stringent criteria for bypass surgery were applied because survival did not improve significantly.29

The efficacy of β-adrenergic blocking agents in the secondary prevention of cardiac death and reinfarction for survivors of acute MI has been established in randomized placebo-controlled trials involving more than 20,000 patients.30 The early IV administration of beta-blockers followed by long-term therapy for 2 years or longer is recommended for all patients with MI who have no contraindications to beta-blockers. The cost-effectiveness of long-term beta-blocker therapy was studied in a model of male MI survivors aged 45 to 65 years who received beta-blocker therapy for 6 years. The survivors were further classified as low, medium, or high risk for future adverse events based on clinical and noninvasive variables. In the model, a 25% relative reduction in mortality for years 1 to 3 and a 7% relative reduction for years 4 to 7 was assumed for long-term beta-blocker therapy. The cost per year of life saved in 55-year-old male survivors of infarction was $13,000 for low-risk patients, $3,600 for medium-risk patients, and $2,400 for high-risk patients. Therefore, beta-blockers were extremely cost-effective in high- and medium-risk patients. Long-term beta-blocker therapy was also moderately cost-effective in low-risk patients, although this conclusion was sensitive to varying the baseline assumptions.31

Most trials that have studied the effects of ACE inhibitors in acute MI have shown that ACE inhibitors are beneficial, although questions regarding the timing of drug administration and appropriate patient selection remain unanswered.32 Using data from the Survival and Ventricular Enlargement trial, the cost-utility of the long-term administration of captopril initiated in the convalescent phase of acute MI (day 3 to 16) was evaluated in patients with acute MI and asymptomatic left ventricular dysfunction. In this select group of patients, cost-utility ranged from $60,500/QALY gained.
in 50-year-old patients to 3,600/QALY in 80-year-old patients. Long-term anticoagulation of survivors of MI has been reported to be a dominant strategy achieving improved outcomes at reduced costs compared with a strategy of no antithrombotic therapy. The cost savings associated with fewer recurrent ischemic events in the anticoagulated patients offset medication and monitoring costs. Secondary prevention of coronary heart disease with long-term aspirin therapy following MI has been reported to be a dominant strategy in women and has a cost-effectiveness of $563/yr of life saved in men.

Although improved survival has not been definitively demonstrated in individual randomized trials, two meta-analyses have shown that comprehensive cardiac rehabilitation, including exercise and risk factor counseling following MI, results in a 20 to 25% reduction in mortality. The cost-utility of 8 weeks of cardiac rehabilitation initiated within 6 weeks of infarction in patients with mild to moderate anxiety or depression was $9,200/QALY.

5. a, b, d, and e

Three large prospective randomized trials, a meta-analysis, and a task force position paper have led to a consensus that coronary artery bypass surgery definitely improves outcomes in patients with left main coronary artery disease and three-vessel disease associated with any degree of left ventricular dysfunction, and may possibly improve outcomes in patients with normal left ventricular function, severe angina, and three-vessel disease or two-vessel disease, including proximal left anterior descending artery involvement. However, because of the volumes of bypasses performed annually (468,000 in 1992) accounting for a significant proportion of the total national health-care expenditure, the role of bypass surgery is prominent in the current health-care debate. In spite of this, only one major economic analysis comparing medical therapy and bypass surgery performed in 1982 has been undertaken. Despite the obvious limitations of applying the results of a 1982 study to current practice, this rigorous analysis is still respected and quoted. The study was a cost-utility analysis that evaluated quality-adjusted life expectancy. The analysis utilized results from the Veterans Administration Cooperative Study and the European Coronary Surgery Study Group. Results of the Coronary Artery Surgery Study, which detected less favorable benefits for surgery in patients with two-vessel and three-vessel disease in contrast to the European study, were not available at that time for inclusion.

This study found that coronary artery bypass surgery was cost-effective in subsets of patients in whom surgery improved symptoms or survival. Focusing on middle-aged men, this study found that cost per QALY gained to be $470,000 for one-vessel disease with mild angina, $30,000 for one-vessel disease and severe angina, $30,000 for two-vessel disease and mild angina, $14,000 for two-vessel disease and severe angina, $7,500 for three-vessel disease and mild angina, and $2,800 for left main disease. In one-, two-, and three-vessel disease, left anterior descending artery involvement improved the cost-utility ratio. Several sensitivity analyses were performed to test the robustness of the results of this analysis. One sensitivity analysis involved looking only at survival as opposed to quality of life (cost-effectiveness analysis). Surgery for single-vessel disease was not cost-effective and the cost-effectiveness of two-vessel disease rose to $47,000/year of life saved when quality of life was not taken into account.

The use of PTCA in the United States has increased steadily since its introduction (approximately 400,000 procedures annually) despite the scarcity of randomized trials comparing PTCA with medical therapy and bypass surgery. The one published prospective randomized trial comparing PTCA and medical therapy in single-vessel disease reported that PTCA was superior to medical therapy in relieving angina and improving exercise tolerance. At the present time, six randomized trials comparing PTCA with surgery are underway and expected to improve our understanding of the indications for both methods of revascularization. American Heart Association/American College of Cardiology Task Force Guidelines published in 1993 stated that PTCA was justified in patients with single-vessel and multivessel disease if they had significant symptoms (Canadian Cardiovascular Society class 2 to 4 angina) or severe ischemia demonstrable noninvasively and low- to moderate-risk lesions for PTCA, ie, type A or B coronary artery lesions. However, the task force also acknowledged the gaps in our knowledge by pointing out that even in the clinical and angiographic subsets given a class 1 indication, other modes of therapy were acceptable.

Information about the cost-effectiveness of PTCA is also limited. Although the costs of initial PTCA are lower than bypass surgery, because of the higher rate of symptom recurrence and need for repeat procedures, the cost of PTCA catches up to coronary artery bypass grafting. At 5 years, savings associated with PTCA were only 17%. In an extensive study published in 1989, a clinical decision and cost-utility analysis was used to compare the efficacy and cost-effectiveness of medical therapy, PTCA, and bypass surgery. In general, PTCA was found to be cost-effective in those clinical and angiographic subsets in which there is a consensus regarding its indication. In patients with
one-, two-, and three-vessel disease, type A lesions, and severe angina, PTCA was highly cost-effective. The cost per QALY gained ranged from $6,000 to $11,000. In patients with mild angina, cost-effectiveness was marginal to ineffective. Sensitivity analysis demonstrated that increasing complexity of lesions and incomplete revascularization reduced cost-effectiveness.46

The high rate of restenosis following PTCA limits the long-term efficacy of PTCA and leads to significant additional costs. Primary coronary stenting is one of several strategies that has been developed to deal with this problem. Primary coronary stenting has a lower incidence of acute occlusion and restenosis compared with PTCA but also incurs higher initial costs and is associated with more vascular complications. In patients with symptomatic single-vessel disease, a strategy of initial coronary stenting had an incremental cost-utility ratio of $23,600/QALY compared with PTCA. This ratio improves in high-risk candidates for PTCA and is less favorable in low-risk candidates.47

In this patient, if angiography demonstrated one- or two-vessel disease and type A or B lesions, PTCA would be highly cost-effective treatment. Because of the severity of his symptoms, coronary artery bypass surgery would also be a cost-effective treatment option, especially if the lesions were less suitable for angioplasty and if the proximal left anterior descending artery was involved. However, if the patient had only mild angina, neither PTCA or bypass surgery would be cost-effective for one- or two-vessel disease. However, coronary artery bypass surgery would be highly cost-effective if left main disease or three-vessel coronary artery disease (especially with left anterior descending artery involvement) was demonstrated independent of the severity of his symptoms.

6. b and c

The cost-effectiveness of ACE-inhibitor therapy in patients with asymptomatic idiopathic dilated cardiomyopathy has not been adequately studied. The SOLVD prevention trial48 evaluated the effectiveness of enalapril in reducing cardiovascular morbidity and mortality among patients with asymptomatic left ventricular dysfunction. Patients with left ventricular ejection fractions of 0.35 or less, who were not receiving drug treatment for heart failure, were randomly assigned to receive either placebo (n=2,117) or enalapril (n=2,111). A significant reduction in total or cardiovascular mortality was not observed. Enalapril, compared with placebo, significantly reduced the development of heart failure (20.7% vs 30.2%), hospitalizations for heart failure (2.7% vs 4.8%), and death or development of heart failure (29.8% vs 38.6%). To our knowledge, however, cost-effectiveness analysis of enalapril has not been performed. In the SAVE study,49 within 3 to 16 days after MI, 2,231 patients with ejection fractions of 0.40 or less but without overt symptoms of heart failure or myocardial ischemia were randomly assigned to receive either placebo or captopril and were followed up for an average of 42 months. In the captopril group, there was a significant reduction in overall mortality (20% vs 25%), death from cardiovascular causes (17% vs 21%), development of congestive heart failure (11% vs 16%), and recurrent MI (12% vs 15%). The cost-effectiveness of captopril therapy was evaluated in the SAVE study.39 Since it is not known whether the benefits of captopril therapy would persist beyond 4 years, two sets of analyses were made; one assumed that the survival benefits associated with captopril therapy would persist beyond 4 years (persistent-benefit analysis) and the other assumed that captopril therapy incurred costs but no survival benefit beyond 4 years (limited-benefit analysis). In the persistent-benefit analysis, the incremental cost-effectiveness ranged from $3,700 to $5,600/QALY for patients 60 to 80 years old and $10,400/QALY for 50-year-old patients. In the limited-benefit analysis, cost-effectiveness was similar to persistent-benefit analysis for 80-year-old patients at $3,600/QALY. Since 50-year-old patients have more years of life remaining, cost would be much higher at $60,500/QALY if the benefits of captopril are not persistent. Effectiveness of reducing the annual cost of captopril therapy will depend on the age of the patient and whether the benefit of captopril is limited or persistent. The cost-effectiveness of captopril therapy compares favorably with many other cardiac interventions, eg, $3,200 to $18,400/yr of life saved with β-adrenergic blockers after MI,41 $21,200 to $22,400/yr of life saved with streptokinase for suspected acute MI in elderly patients.22 Thus, ACE-inhibitor therapy is cost-effective in patients with asymptomatic left ventricular dysfunction following an acute MI. It is not known whether these findings could be extrapolated to patients with asymptomatic left ventricular dysfunction secondary to idiopathic cardiomyopathy.

Three randomized multicenter trials have evaluated the role of vasodilator and ACE-inhibitor therapy in patients with congestive heart failure. In the V-HeFT I trial,50 642 men with congestive heart failure who were taking digoxin and a diuretic were randomly assigned to receive additional double-blind treatment with placebo, prazosin, or the combination of hydralazine and isosorbide dinitrate. The mortality in the prazosin group was similar to that in the placebo group. The group receiving hydralazine and isosorbide dinitrate had a 36% risk reduction by 3 years and improvement in left ventricular ejection fraction. In the SOLVD treatment trial,51 patients with congestive...
heart failure receiving conventional treatment were randomly assigned to receive either placebo (n=1,284) or enalapril (n=1,285). When compared with placebo, enalapril significantly reduced total mortality (39.7% vs 35.2%), death due to progressive heart failure (19.5% vs 16.2%), and hospitalization for cardiovascular causes (63% vs 57%). The V-HeFT II trial\textsuperscript{52} compared the effects of hydralazine and isosorbide dinitrate with those of enalapril in 804 men receiving digoxin and diuretic therapy for congestive heart failure. Mortality after 2 years was significantly lower in the group receiving enalapril than the group receiving hydralazine and isosorbide dinitrate (18% vs 25%). The data from these three major trials have been used to evaluate the cost-effectiveness of vasodilator therapy for heart failure. A decision analysis model was used to evaluate the cost-effectiveness of adding hydralazine-isosorbide dinitrate combination or enalapril to standard therapy with digoxin and diuretics.\textsuperscript{53} Incremental cost-effectiveness was calculated as the cost of the new treatment per unit of improved outcome, compared with usual standard of care.\textsuperscript{3} An incremental expense of $5,600/yr of life saved was required for a patient receiving hydralazine-isosorbide dinitrate therapy and $9,700 for enalapril therapy. These costs compare favorably with other accepted preventive measures, ie, $25,000/yr of life saved with the treatment of hypertension\textsuperscript{54} and $3,200 to $18,400/yr of life saved with β-adrenergic blocker therapy after MI. Paul et al\textsuperscript{55} were of the opinion that the additional cost for enalapril therapy could be justified by the additional number of lives saved. Sensitivity analysis on drug costs revealed that when the cost of enalapril therapy is less than 1.6 times the cost of hydralazine-isosorbide therapy, hydralazine-isosorbide therapy becomes inappropriately costly. The cost ACE-inhibitor drugs is falling and they can be considered vasodilator drugs of choice. After analyzing the Munich Mild Heart Failure Trial, it was concluded that captopril therapy was cost-effective in the treatment of heart failure.\textsuperscript{55} However, details of the method of the cost-effectiveness analysis were not provided. Some large randomized trials of ACE inhibitors (SMILE, TRACE, ACHIEVE) are still in progress and will shed further light on the cost-effectiveness of this class of drugs.

The decision to provide anticoagulation for a patient rests on a tradeoff between the benefits of preventing systemic or pulmonary emboli and risks of hemorrhage caused by anticoagulant. Most clinically recognized emboli result in cerebrovascular accidents that may cause permanent disability or death. Most bleeding complications are not life threatening and even major bleeds usually do not cause permanent sequelae except when the cerebrovascular circulation is involved. To our knowledge, there has been no randomized trial of anticoagulant therapy in patients with heart failure. To evaluate cost-effectiveness of anticoagulation in patients with heart failure, the incidence of systemic embolism and the risks of bleeding from warfarin therapy must be established.\textsuperscript{56} The risk of embolism is affected by various factors in heart failure. Atrial fibrillation increases the risk of embolism. The risk of embolism in the presence of mitral stenosis and atrial fibrillation is 12 to 20%/yr; 2 to 3% in the presence of a mechanical valve with anticoagulation.\textsuperscript{57} In MI, the risk of embolism is high during the first 12 weeks after which time it declines.\textsuperscript{57} In a retrospective study, the incidence of embolism was noted to be 4%/yr in patients with dilated cardiomyopathy.\textsuperscript{56} Emboli are more likely to occur within the 6 months of onset of atrial fibrillation and soon after a previous embolism.\textsuperscript{56}

Risks of anticoagulation are also variable. Anticoagulation aimed at an international normalized ratio of 2 to 3 results in a serious bleeding rate of approximately 2%/yr. More intense anticoagulation used in patients with prosthetic valves results in 5.2%/yr incidence of serious bleeding.\textsuperscript{59} Several studies have shown that the risk is not cumulative and tends to level off after 2 years of therapy. Patient reliability, comorbid conditions, and availability of anticoagulation clinics modify the risk.\textsuperscript{57}

The cost-effectiveness of anticoagulant prophylaxis in patients with heart disease was evaluated.\textsuperscript{56} The costs of administering warfarin, and sequelae of bleeding and embolism were established in 1991 dollars. The cost-effectiveness of anticoagulation will depend on the risk of embolism. In a 35-year-old woman with mitral stenosis and atrial fibrillation, the presumed rate of systemic embolism was 4.7%/yr. Anticoagulation was calculated to provide an increase in life-expectancy of 4.5 QALYs. The marginal cost-effectiveness ratio was $2,700/QALY, meaning that each QALY is purchased at a cost of $2,700. Discounting, a technique used to correct for uncertainties of projecting into the future, increased the cost-effectiveness to $3,700/QALY.\textsuperscript{56} In young women with mild mitral stenosis in sinus rhythm, the risk for embolism is lower at 1.4%/yr. In this case, anticoagulation would provide an increase in life expectancy of 0.31 QALY with a cost-effectiveness ratio of $43,000/QALY without discounting.\textsuperscript{56} In a patient with atrial fibrillation and recent embolism, risk of recurrent embolism is 9.6%/yr. In this case, anticoagulation would increase life expectancy by 7.1 QALYs at a cost of $1,600/QALY and is offset by little by discounting.\textsuperscript{56} Anticoagulation to prevent systemic embolism can be expected to be cost-effective in the second patient when he developed heart failure and atrial fibrillation. However, various factors that affect the rate of embolism and risk of bleeding should be taken into consideration.
Cost-effectiveness of heart transplantation has not been investigated adequately. The economic aspects of transplantation have been reviewed. In one report, the average charge was $209,100 for the first year and an additional $60,000 for the next 4 years in 1993 dollars, but the costs vary in different institutions. Many patients who are evaluated for transplantation are rejected or die while waiting for a donor heart. Among patients who receive a heart, 25% die in the first 5 years. Only 32 to 50% return to work, although 60% report that they are able to do so. However, it should be noted that cost of caring for a patient with refractory heart failure is also very high; in addition, prognosis is dismal and quality of life poor. Cost-effectiveness of heart transplantation has not been studied extensively but since it is a life-saving procedure, the cost per year of life saved is likely to compare favorably with many other accepted treatment modalities that were discussed earlier, eg, CCU monitoring for suspected MI, thrombolytic therapy for inferior wall infarction, and treatment of hypertension.

Again, we emphasize that the above discussions are focused on cost-effectiveness and not necessarily on current first-choice treatment modalities. The data are limited by the scope and methods of the available analyses. In the second part of this article, cost-effectiveness in preventive cardiology and in antiarrhythmic therapy will be presented.

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