I
n Part I of this series, we reviewed some key concepts and tools of medical economics. In this concluding article, we use case studies of contemporary cardiovascular technologies to demonstrate the application of these principles. Three different types of therapies are considered: expensive one-time therapies (eg, coronary revascularization), the costs of which occur predominantly in the present and the benefits of which may stretch years into the future; prevention therapies, which must be applied to large populations for many years to prevent future complications; and maintenance therapies, which are applied to a chronic illness (such as heart failure) to improve longevity and functional status and to decrease complications.

Coronary Revascularization
Vigorously medical innovation over the past 30 years has transformed cardiovascular medicine from a largely noninvasive diagnostic discipline to one that employs a substantial armamentarium of procedures and devices, many of them invasive and expensive. Coronary revascularization is one of the most commonly performed procedures in the United States today, with 686 000 percutaneous coronary revascularizations (PCIs) and 366 000 coronary artery bypass graft surgeries (CABGs) performed in 1997. Because CABG typically costs >$30 000 per procedure, and PCI ~$12 000 per procedure (including hospital and physician costs), the total direct cost for coronary revascularization in the United States alone exceeds $20 billion per year.

With such huge expenditures on coronary revascularization, skeptics might well ask whether society is receiving a good value for all the money spent. There is no simple answer to this question because coronary revascularization is applied to many different subpopulations of patients, and the balance of cost and benefit depends on patient selection and the alternative treatments available for that population. The very same procedure can provide superb value in one group of patients yet be a wasteful extravagance in a different clinical setting. Thus, there is no single answer to the question, “Is coronary revascularization cost-effective?” Instead, a specific form of revascularization should be evaluated in a specific patient population and compared with the next best alternative management strategy. For example, coronary stenting may be compared with either medical therapy or bypass surgery, and this comparison may be performed in patient subsets with different extents of coronary disease and either stable or unstable symptoms. Because all economic analysis is incremental, the clinical context (eg, the patient population, the alternative therapy) must be considered. To define the incremental health benefits and costs of a particular revascularization strategy means that we must carefully inventory all the outcomes and costs that would occur if the new strategy were used and would not have occurred if the alternative therapy were applied.

Coronary Artery Bypass Surgery
Randomized clinical trials that compared CABG with medical therapy found that patients with significant left main disease have an increase in life expectancy with CABG of 19.3 months over a 10-year follow-up, whereas patients with 3-vessel disease average a 5.7-month increase in life expectancy and patients with 1- or 2-vessel disease average an extra 1.8 months. Because the cost of performing bypass surgery is roughly the same, irrespective of the severity of the underlying coronary disease, CABG for left main disease is clearly more economically attractive than CABG for 1-vessel disease (4-fold greater benefit for the same cost). These results are consistent with early economic analyses of CABG, which found that its use for left main disease had a cost-effectiveness ratio of $3800 per added life-year, a very economically attractive result. A more modern analysis of coronary revascularization confirmed that CABG is most economically attractive when applied to high-risk patients (such as those with severe multivessel disease and depressed left ventricular function) in whom the procedure significantly enhances life expectancy.

Even when bypass surgery does not significantly enhance survival, it may be economically attractive when it significantly improves quality of life. Relief of angina improves quality of life both through the elimination of patient suffering and through better physical functioning and psychological well-being. In an analysis that assigned patient preferences (utilities) to different anginal states, CABG in patients with severe angina was found to be economically attractive, even when mortality was not altered, whereas CABG in patients...
with mild angina fell in the gray zone of cost-effectiveness ratios.\(^6\)

### Percutaneous Coronary Intervention

Balloon coronary angioplasty initially was regarded as an alternative to CABG, a way to achieve coronary revascularization less traumatically, at less cost and with a much shorter rehabilitation period. During the past 2 decades, it has become clear that angioplasty largely serves as an expensive alternative to medical therapy rather than an inexpensive alternative to CABG. Unfortunately, there are only 6 trials of angioplasty versus medical therapy, and they randomized a total of fewer than 2000 patients.\(^7\) The Angioplasty Compared to MEDicine (ACME) trial found a modest improvement in angina, treadmill time, and quality of life for 1-vessel disease patients treated with angioplasty.\(^8\) An economic analysis of ACME found that, although initial 6-month angioplasty costs were higher, the costs added by angioplasty in comparison with the medical arm diminished progressively over the next 4.5 years.\(^9\) The Second Randomized Intervention Treatment of Angina trial (RITA-2) compared medical therapy and angioplasty in 1018 patients in the United Kingdom and Ireland. Angioplasty produced greater symptomatic improvement, especially among patients who were more symptomatic at baseline.\(^10\) Relief of cardiac symptoms in RITA-2 was associated with improved physical functioning, vitality, and general health, but after 1 year, only 33\% of the angioplasty patients and 22\% of the medical group rated their health as much improved.\(^11\) The Atorvastatin Versus Revascularization Treatments (AVERT) trial randomized 341 low-risk stable patients with coronary disease to angioplasty or medical therapy including a statin.\(^12\) Over an 18-month follow-up period, the medical therapy group had a marginally significant reduction in need for revascularization or hospitalization for worsening angina.

There have been no trial-based analyses of the cost-effectiveness of angioplasty relative to medical therapy. A model of coronary revascularization found angioplasty to be economically attractive when applied to patients with severe angina but not when applied to patients with few or no symptoms.\(^6\)

### CABG Versus PTCA

Angioplasty and surgery are both reasonable alternatives for patients with multivessel disease that is not extensive. During the 1990s, a series of trials were conducted to compare balloon coronary angioplasty and coronary bypass surgery in this patient population. Meta-analyses of these trials show a consistently greater reduction in angina with bypass surgery as well as a trend toward reduction in mortality for bypass surgery.\(^13\) The largest of these, the Bypass Angioplasty Revascularization Investigation (BARI), recently reported that at the end of a 7-year follow-up there was a significant survival advantage for patients randomized to CABG relative to angioplasty (84\% versus 81\%, \(P=0.04\)).\(^14\) Several of these trials have included economic analyses, with the results consistently showing that balloon angioplasty initially costs one half to two thirds the cost of bypass surgery, but that this early cost advantage was largely lost during the subsequent follow-up period as a result of repeat revascularization procedures in patients initially treated with angioplasty. BARI found that, after an average 5-year follow-up, the total medical costs averaged 4\% to 6\% lower in angioplasty patients than in CABG patients.\(^15\) Cost-effectiveness analysis based on these data suggested that bypass surgery was more economically attractive than angioplasty for patients with 3-vessel disease, although angioplasty maintained a significant cost advantage in the 2-vessel disease population, albeit with lower relief of anginal symptoms.

### Recent Developments in PCI

Percutaneous coronary revascularization has evolved substantially over the last decade. Procedures done in the early 1990s consisted of balloon angioplasty by itself with periprocedural heparinization as the primary adjunct. During the past 5 years, the use of coronary stenting has grown to include >80\% of procedures in many laboratories. In addition, the adjunctive use of glycoprotein IIb/IIIa inhibitors has grown substantially and recent figures suggest that >80\% of PCI procedures involve the use of 1 of the 3 agents currently approved for this use.\(^16\) In the recently completed Evaluation of IIb/IIIa Platelet Inhibitor for STENTing (EPISTENT) trial, the average hospital cost plus professional fees for 1 year of stent strategy alone was \(\approx\$17\,000\); for balloon angioplasty plus abciximab it was \(\$17\,400\), and stent plus abciximab was \(\approx\$18\,000\).\(^17\) Projecting the 1-year outcomes to a lifetime perspective, the stent plus abciximab group had an incremental life expectancy (compared with the balloon angioplasty plus abciximab arm) of 0.11 years and an incremental cost-effectiveness ratio of \$5300 per added life-year. Compared with the stent alone arm, the stent plus abciximab group had an incremental life expectancy of 0.15 years and an incremental cost-effectiveness ratio of \$6200 per added life-year. In this study, therefore, the primary stent strategy had equivalent 1-year clinical outcomes and costs compared with balloon angioplasty, whereas the combination of abciximab and stenting had better outcomes and higher costs and was more economically attractive.

This brief overview shows that expensive drugs and procedures may provide good value for the money spent when applied appropriately—that is, when life expectancy can be substantially prolonged or when symptoms are severe. Significantly increasing either the quantity or quality of life can provide incremental quality-adjusted life-years (QALYs) and justify the high costs. Nevertheless, revascularization is not economically attractive in all clinical subgroups.

The analyses of stents and abciximab also highlight the point that a research study defining a particular therapy as “economically attractive” does not necessarily make such a therapy the standard of care. Just as one would not feel obligated to buy a new automobile simply because Consumer Reports had declared it a “best buy,” a health system will not necessarily provide all economically attractive therapies. The primary reason for this is that if there is not enough money available, a healthcare system may not be able to pay for a new therapy, regardless of how cost-effective the therapy is. For example, for every 1000 patients undergoing PCI, adopting one of the newer strategies tested in EPISTENT would
increase initial healthcare costs by between $600 000 and $900 000. This additional expenditure may not be affordable, especially if the higher costs cannot be recovered by increased reimbursements.

**Prevention of Cardiovascular Disease**

Therapies to prevent cardiovascular disease may be used both to prevent the development of clinical disease (primary prevention) in those subjects who are believed to be disease free and to prevent progression or complications (secondary prevention) in patients with established disease. Primary prevention is logical and attractive; it seems obvious that preventing disease should be more economically attractive than the use of expensive procedures to treat a clinical disease after it has developed. In actual practice, however, two aspects of preventive therapies may negate these apparent advantages. First, it is difficult to identify the disease-free individuals who will progress to have clinically important diseases in the future. Even with risk stratification algorithms, many patients must be treated for years to prevent a cardiac event, so the cost of treating many patients for years must be weighed against the benefit of preventing 1 event, such as a myocardial infarction. Second, the cost of preventive therapy is typically a lifelong expense. Although some prevention may be applied at a single point in time (eg, an immunization or a smoking intervention), most preventive regimens require lifetime therapy. Thus, many patients must be treated for a long period of time to prevent disease from developing in a few. From these general considerations, it follows logically that the return on investment for prevention is inversely proportional to both the number of patients who need to be treated to prevent 1 event and to the duration of therapy. Thus, “patient-years” of preventive therapy are generally lower in secondary prevention than in primary prevention because the number needed to treat is lower and the results of treatment are seen sooner. In the primary prevention setting, treatment is more cost effective for higher-risk cases.

**Secondary Prevention**

Two major studies have examined cholesterol-lowering therapy for secondary prevention. The Scandinavian Simvastatin Survival Study (4S) randomized 4444 patients aged 35 to 60 years with a history of angina or prior myocardial infarction and total cholesterol levels between 210 and 310 mg/dL to either adjusted-dose simvastatin or placebo. Simvastatin reduced all-cause mortality by 30% ($P=0.003$). The clinical benefits in this secondary prevention trial were much greater in absolute magnitude than those in primary prevention studies (Table). Although the cost of the drug therapy and laboratory monitoring was similar to that of primary prevention studies, it was offset to a larger extent ($3900 per patient) because of reduced cardiac hospitalizations. Thus, the net cost of the statin arm in 4S was $≈$780 per patient, corresponding to a cost-effectiveness ratio of $5800 per life-year.

The results of the Cholesterol And Recurrent Events (CARE) trial were quite similar (Table). In a cost-effectiveness model based on trial findings, the cost-effectiveness ratio for pravastatin therapy in CARE ranged between $16 000 and $31 000 per added life-year.

**Primary Prevention**

The value of lipid-lowering therapy in primary prevention was evaluated by 2 major studies, the West of Scotland Coronary Prevention Study (WOSCOPS) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS). Each included an economic analysis. WOSCOPS randomized 4159 middle-aged males without overt coronary artery disease who had LDL cholesterol levels $\geq 155$ mg/dL to either pravastatin (40 mg/d) or placebo. The pravastatin arm had significantly fewer cardiac events than the placebo/usual care arm (Table). The pravastatin therapy cost $≈$3700 to treat 1 subject for 5 years, which was only slightly offset by $100 by the prevention of adverse events. Thus, pravastatin therapy in WOSCOPS did not pay for itself, even over the long run, but it did increase life expectancy by 0.10 years. The resulting cost-effectiveness ratio was $32 600 per life-year saved, so that by conventional benchmarks, pravastatin therapy for patients eligible for WOSCOPS (high-risk, predominantly asymptomatic middle-aged men) would qualify as an economically attractive therapy. The findings of AFCAPS/TEXCAPS were similar (Table).

In contrast to the findings of WOSCOPS, a recent model-based analysis of primary prevention found that statin therapy had cost-effectiveness ratios ranging from $54 000 to $1.4 million per QALY, depending on the population selected.
prevention would be used in lower-risk patient populations, in which clinical benefits are fewer.

The empirical results of these primary and secondary prevention trials clearly show the interrelationship of treatment costs, cost offsets, and absolute levels of benefit in determining the cost-effectiveness of statin treatment. The cost of drug therapy in all trials was comparable, but the cost savings in secondary prevention populations was much greater, producing a lower net cost of treatment. Meanwhile, the absolute levels of benefit were much higher in the secondary prevention populations. With greater benefits at lower cost, it is more economically attractive to treat high-risk patients.

Heart Failure
Heart failure is the prototype of a chronic medical illness in which a variety of medical therapies are used both to improve functional status and to prolong life expectancy. The course of the disease is characterized by frequent regular contacts with the medical system punctuated by episodes of decompensation requiring unplanned emergency department visits and hospitalizations. Thus, the cost of caring for heart failure patients can be divided into the costs of routine maintenance care and those additional elements required to treat episodes of decompensation. (A third set of costs is related to therapies designed to reverse the heart failure state, including heart transplantation and left ventricular assist devices. At present, these other therapies are only applicable to a small proportion of the total heart failure population.) Heart failure has been increasing in prevalence over the last decade and there are now ≈550,000 new cases diagnosed each year. The 5-year mortality rate is ≈50%, and the annual cost to the US healthcare system is ≈$19 billion.

Pharmacological Therapy
Angiotensin-converting enzyme (ACE) inhibitors reduce mortality in patients with heart failure, and their use has been subjected to economic analyses in several studies. Glick and coworkers used data from the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial (which enrolled patients with mild to moderate heart failure and ejection fractions <35%) to model the cost-effectiveness of enalapril therapy. They estimated that the study patients had a life expectancy of ≈6.5 to 7 years and that treatment with enalapril would add 0.3 discounted life-years. Because heart failure patients have impaired quality of life, the incremental life expectancy was equivalent to 0.21 QALYs. During the 4 years of the trial, the enalapril patients averaged $11840 in hospitalization and medical costs, whereas the placebo patients averaged $12560, thus providing a savings of $720 per patient. Projecting these figures to the lifetime of the study cohorts, the enalapril patients were estimated to have costs of ≈$22,000, versus $21,975 for placebo patients. In this model, then, enalapril had a lifetime incremental cost of $25 per patient. The corresponding cost-effectiveness ratios were $80 per added life-year and $115 per added QALY. These data suggest that ACE inhibitor therapy for symptomatic patients with heart failure is highly cost-effective and may even be a dominant therapy.

More recently, β-blocker therapy has been shown to improve survival in patients with heart failure. Two major trials have demonstrated that β-blocker therapy reduces both mortality and need for hospitalization in heart failure: the METoprolol CR/XL Randomised Intervention Trial in congestive Heart Failure (MERIT-HF) and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). Economic analysis of both studies is planned. Economic analysis has been performed for the smaller US Carvedilol Heart Failure Trials Program. This analysis employed a Markov model to simulate the long-term outcomes and costs for a hypothetical cohort of heart failure patients on the basis of the major findings reported in the 4 clinical trials of carvedilol. For patients on usual therapy, life expectancy was projected to be 6.7 years, whereas life expectancy for patients in the carvedilol arm was ≥7 years. The lifetime costs of heart failure–related care was projected to be $29,000 for conventional therapy and $39,000 for carvedilol therapy. The cost-effectiveness ratio for carvedilol was $13,000 per life-year saved.

Disease Management
Two randomized trials have evaluated the use of a disease management strategy to improve the quality of care for heart failure patients. Rich and colleagues enrolled 182 elderly, hospitalized heart failure patients who were judged to be at high risk for readmission to either an experimental intervention (consisting of education by a registered nurse and a dietitian, review and simplification of the medical therapy by a geriatric cardiologist, and intensive follow-up through telephone and home visits) or a control group of usual heart failure care. During the 90-day follow-up period, the intervention patients had a 44% reduction in hospitalizations (P=0.04) and a significant improvement in quality of life. Economic analysis demonstrated that this intervention was associated with a net savings of $460 per patient.

A second trial of disease management was conducted at 9 Veterans Administration medical centers and involved 1296 patients hospitalized with diabetes, chronic obstructive lung disease, or congestive heart failure. The interventional strategy in this trial was intensive primary care intervention delivered by a physician and a nurse initiated before discharge and continuing for 6 months. In contrast to the previous trial, this interventional strategy produced significantly higher rates of readmission (P=0.005); although no clinical benefits were observed from the intervention, the intervention patients were significantly more satisfied with their care.

Cost-Effectiveness in Clinical Practice
Economic evaluations aim to assist clinical decisions and provide a rational basis for policy. They are an extension of evidence-based medicine to a more broad set of outcomes than the traditional measures of morbidity and mortality. These forms of analyses have limitations at both a practical and theoretical level.

Economic evaluations typically focus on one intervention and compare it with an alternative—for example, use of ACE inhibitors as secondary prevention after myocardial infarc-
tion. In practice, however, clinical decisions are more complex, and the clinician may be considering several interventions, with many possible permutations and combinations. To the extent that each intervention acts independently and additively, conventional evaluations of clinical effectiveness and cost-effectiveness generally can be applied. There may well be diminishing returns to each additional therapy, however, which could reduce the clinical effectiveness and cost-effectiveness of an intervention. When there are diminishing benefits, the principles of economic evaluation suggest the therapy with the most favorable cost-effect ratio be applied first, and further therapies be added to the extent that they produce incremental, additional benefit at an acceptable cost.

Economic evaluation aids in the efficient use of medical resources, but decisions also involve ethical considerations. In critically ill patients, for instance, individual clinicians have obligations that may require use of expensive resources with small, unexpected gains. We do not believe the clinician should compromise his or her role as the patient’s advocate to ration care at the bedside. Although additional economic data could help us to better understand and quantify the magnitude of expenditures in this population, the solution lies outside of economics. The proper use of resources in these situations should be discussed at the societal level and implemented in guidelines for care.

**Medical Economics: Future Directions**

The economic analysis of medical practices is a relatively young discipline. The methodology will be refined and improved as it is applied to difficult, real-world problems. In particular, methods to marry evidence-based medicine, clinical trials, and economic models will be developed, allowing us to perform a greater range of analyses. This synthesis will be important because therapies are rarely, if ever, cost-effective for everyone (and are sometimes cost-effective for no one). Rather, there are gradations of clinical efficacy, cost, and cost-effectiveness across different patient subsets. Thus, cost-effectiveness data will be best used as part of clinical guidelines that help to identify the patient groups most likely to benefit from new technology.

**References**


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