Economics methods in the Clinical Outcomes Utilizing percutaneous coronary Revascularization and Aggressive Guideline-driven drug Evaluation (COURAGE) trial

William S. Weintraub, MD,[a,b] Paul Barnett, PhD,[c] Shuo Chen, PhD,[c] Pamela Hartigan, PhD,[d] Paul Casperson, PhD,[e] Robert O'Rourke, MD,[e] William E. Boden, MD,[f] Cheryl Lewis, RN,[b] Emir Veledar, PhD,[b] Edmund Becker, PhD,[b] Steven Culler, PhD,[b] Paul Kolm, PhD,[b] Elizabeth M. Mahoney, ScD,[g] Sandra B. Dunbar, DSN,[b] Christi Deaton, PhD,[h] Bernard O'Brien, PhD,[i,✠] Ron Goeree, MA,[i] Gordon Blackhouse, MBA,[i] Robert Nease, PhD,[j] John Spertus, MD, MPH,[k] Stan Kaufman, MD,[l] and Koon Teo, MD[i] ***Decatur and Atlanta, GA; Palo Alto and San Francisco, CA; New Haven and Hartford, CT; San Antonio, TX; Watertown, MA; Manchester, UK; Hamilton, Ontario, Canada; and St. Louis and Kansas City, MO***

Percutaneous coronary intervention (PCI) remains a major therapeutic option for the treatment of chronic coronary artery disease. In the COURAGE trial, 2287 patients with chronic coronary disease were randomized between PCI with medical management and medical management alone. Embedded within the COURAGE trial is a detailed economic analysis being conducted in three health care systems: the US Veterans Administration (VA), Canada, and the US non-VA. Resource use and costs are being collected for each system and overall. Survival is assessed internally in the trial with mean follow-up of 4.5 years. Long-term mean survival will be estimated by projecting survival beyond the trial period by extrapolating the in-trial hazard rates. Utility is being assessed at baseline and at 1, 3, and 6 months and annually thereafter, using a computer-administered standard gamble. Quality-adjusted life years are calculated by multiplying survival by utility. The incremental cost-effectiveness ratio of PCI will be defined as the additional cost of PCI divided by the gain in life years and quality-adjusted life years. The 95% confidence regions of efficacy and costs will be determined by bootstrap over a range of acceptability thresholds, which will then be displayed in the cost-effectiveness plane and as a cost-effectiveness acceptability curve. A multilevel regression model will assess cost-effectiveness from a net benefit perspective. These approaches should provide the most detailed assessment available of the cost-effectiveness of PCI for coronary artery disease. (Am Heart J 2006;151:1180-5.)

COURAGE is a trial of two initial strategies to manage moderate to severe coronary disease, comparing percutaneous coronary intervention (PCI) with the best possible medical therapy to the medical therapy alone. This trial is underway at 45 medical centers in three different health care systems: the US Department of Veterans Affairs (VA), US non-federal hospitals, and Canada. A total of 2287 patients have been randomized and are being followed up for a mean of 4.5 years. Although the primary end point is the composite of death or myocardial infarction, important secondary end points include cost, cost-effectiveness, and quality of life.

Balloon angioplasty has been compared with medical therapy in three previous trials.[1-3] Unfortunately, these small studies enrolled relatively stable patients who might not otherwise have been candidates for PCI. Follow-up medical care was not consistent, and there was no economic evaluation.

COURAGE is much larger trial that involves patients with more severe coronary disease. It has enrolled individuals who would have received PCI and all have received aggressive medical therapy. COURAGE was also designed to assess the cost-effectiveness of PCI with medical therapy versus medical therapy alone.

In an era when health care budgets are limited, economic evaluations provide a scientific method to find

From the [a]Atlanta VA Medical Center, Decatur, GA, [b]Emory University, Atlanta, GA, [c]VA Palo Alto Health Care System, Stanford University, Palo Alto, CA, [d]VA Connecticut Healthcare System, West Haven, CT, Yale University, New Haven, CT, [e]South Texas Veterans Healthcare System, University of Texas at San Antonio, San Antonio, TX, [f]VA Connecticut Healthcare System, West Haven, CT, Hartford Hospital, Hartford, CT, [g]New England Research Institutes, Watertown, MA, [h]University of Manchester, Manchester, UK, [i]McMaster University, Hamilton, Ontario, [j]Washington University, St. Louis, MO, [k]Mid America Heart Institute, University of Missouri, Kansas City, MO, and [l]San Francisco, CA.

✠Deceased.

Supported by Cooperative Studies Program, Department of Veterans Affairs Office of Research and Development and the Canadian Institute for Health Research.

Submitted March 28, 2005; accepted July 20, 2005.

Reprint requests: William S. Weintraub, MD, Emory Center for Outcomes Research Emory University, Briarcliff Campus Atlanta, GA 30322.

E-mail: wweintraub@christianacare.org

0002-8703/$ - see front matter

© 2006, Published by Mosby, Inc.

doi:10.1016/j.ahj.2005.07.035

the most appropriate allocation of finite resources. The purpose of this paper is to describe the methods associated with the economic study integrated into the design of COURAGE.

Methods

Our primary aim is to determine the incremental cost and effectiveness of PCI in the setting of optimal medical therapy. Comprehensive information on health care used by COURAGE participants will be gathered, including the direct inhospital cost of PCI, other healthcare costs, and indirect costs incurred by patients. This comprehensive approach was adopted because it is difficult to distinguish cardiac from noncardiac events and costs.

We will express health care outcomes using quality-adjusted life years (QALYs), a morbidity-adjusted measure of survival. If one form of therapy is both more effective and more costly, we will calculate the incremental cost-effectiveness in dollars per life year and QALYs gained. For example, if PCI is both more effective and more costly, the resulting ratio will allow health care decision makers to evaluate the cost-effectiveness of PCI versus medical therapy alone and to compare it with other health care choices.

The two arms will be compared using the intention-to-treat principle. The perspective of all analyses will be societal. We will model long-term consequences and estimate cost-effectiveness over a lifetime horizon.

Primary aims of the economic analysis

(1) To compare the total cost of treating patients who have documented coronary artery disease with both PCI and medical management with the total cost of medical management alone over 5 years. Cardiovascular costs are expected to dominate.[4]
(2) To compare health outcomes, using quality of life measures, of patients randomized to each of the two treatment arms over 5 years.
(3) To determine the incremental cost-effectiveness of PCI in dollars per QALY gained both in-trial and extended to lifetime.

Secondary aims

(1) To estimate the differences in types of resource utilization between the two arms, including hospitalizations, procedures, length of stay, time to first hospitalization/procedure, anti-anginal medications, diagnostic procedures, rehabilitation, and outpatient visits.
(2) To determine the cost, effectiveness, and cost-effectiveness of PCI in the three different health care systems (VA, Canada, US non-VA) as well as overall over 5 years.
(3) To compare the cardiac-specific cost of treating randomized patients with coronary artery disease with both PCI and medical management with the cardiac-specific cost of medical management alone over 5 years.

Determination of costs

COURAGE involves sites from three different medical care systems. This diversity of sites was intended so that findings will be widely applicable. However, this presents a challenging economic analysis. Our cost-determination method has features that are common to all three systems, but with adaptations to each. The same measures of health care utilization will be used in each system. The estimates of the cost of services will be specific to the system where care was provided, to provide the best information on the economic cost incurred.

We will study the period from randomization until the end of the follow-up in the trial. When patients are randomized during a hospital stay, we will exclude the costs of the part of the stay that were incurred before randomization.

Medication use during the follow-up period will be obtained from the case report forms. Because the randomized nature of this trial should equilibrate group differences in comorbidities and attendant medication needs, only cardiac-related medications will be included. Medications reported at one visit and at the subsequent visit will be assumed to have been taken for the entire interim period. Otherwise, the medications will be assumed to not have been used during the period. Changes in dosage will be assumed to have occurred midway between reports.

VA costs

A cost function will be used to estimate the cost of hospitalization for heart disease. Gross costing will be used to determine other costs. This hybrid approach, applying the most refined method where accuracy is paramount, was recommended in US cost-effectiveness guidelines[5] and by a VA panel.[6]

We will take advantage of Decision Support System (DSS), the cost allocation system adopted by VA, to estimate the cost function. Cost allocation systems are more accurate than cost-adjusted charges, the standard method of characterizing US hospital costs.[7] Yet DSS data are not available for the complete trial and some facilities do not accurately assign cardiac catheterization costs.[8] Facilities with accurate DSS data on cardiac care have been identified. Because a few characteristics explain most of the variation in hospitalization costs,[9] statistical cost functions can simulate costs. They have been used to estimate the cost of VA hospitalizations of patients with leukemia[10] and acute myocardial infarction.[11]

Our cost function will be estimated from DSS cost of cardiac stays at sites with the best DSS practices. Independent variables will be length of stay; days in intensive care; indicators of PCI, CABG, and other procedures; comorbidities; demographics; the Medicare wage index for the hospital location; and indicators of hospital teaching status. The function will be used to estimate the cost of VA cardiac stays, based on these same characteristics. We will consider the need for log transformation of the dependent variable and resulting correction for retransformation bias.[12]

We will use the average cost estimates developed by the Health Economics Resource Center for all other care. Acute hospital costs will be based on cost functions estimated from Medicare data using Diagnosis Related Group (DRG), length of stay, and other characteristics, adjusted to reconcile to actual VA expenditures.[8] Rehabilitation, psychiatric, and long-term hospital costs will be based on length of stay and daily cost

from VA administrative data. Outpatient costs will be estimated by applying Medicare and other charge schedules to the Current Procedural Terminology (CPT) codes recorded in VA outpatient databases and adjusted for VA expenditures.[13] Pharmacy costs will be from the cost schedule of the VA pharmacy benefits management system. We will add to this the mean dispensing cost reported in DSS. Costs that study participants incur outside of VA will be estimated using the methods used for US non-VA sites.

US non-VA costs

We will estimate inpatient hospital costs using information contained in the UB92 formulation of the hospital bill.[4] Charges will be adjusted with whole hospital cost-to-charge ratios from annual Medicare hospital cost reports. We opted not to adjust by department-level ratios because it is not possible to know if charges are consistently mapped into the same departments across hospitals.[14] Furthermore, many departmental cost-to-charge ratios are unavailable. For hospitals that cannot generate UB92s, we will use a billing summary. If none is available, we will use diagnoses data from study forms to assign each visit a DRG and estimate costs using study data from patients whose UB92 bills are available.

Most physician professional costs are not included in the hospital bill. Mitchell[15] analyzed the costs of physician services to inpatients in each DRG and expressed these as a percentage of hospital cost.[15] We will multiply Mitchell's DRG-specific percentages by cost-adjusted charges to estimate physician cost. We will use the DRG recorded on the UB92. If the DRG is not available, we will use the Medicare grouper software to assign a DRG based on diagnoses, procedures, age, sex, and discharge disposition. In the absence of these data, we will assign DRG based on diagnoses recorded on study forms.

We will use Medicare reimbursement rates to estimate the cost of physician office visits, emergency department visits, outpatient procedures, home visiting nurse encounters, and stays in rehabilitation and skilled nursing facilities. A secondary analysis will utilize reimbursement rates for patients <65 years of age reported in the MEDSTAT claims database, which better reflects private insurance.[16]

Medication costs will be estimated from the Red Book average wholesale prices (AWPs). When a price is not available for a particular dosage, we will interpolate prices of other doses. Medications are often sold at discount to AWP; sensitivity analysis will consider a range of discounts.

Canadian costs

Canadian hospitals are funded through governmental global budgets. As a result, hospital billing records for patients are generally not available. Recently, several Canadian hospitals have developed integrated, sophisticated costing and inpatient resource information systems. These hospitals have the capability to provide details of both resource use and resource costs for individual inpatient episodes. This information is primarily used to produce price weights for inpatient episodes by Case Mix Group (a Canadian system that characterizes hospital discharges by diagnosis similar to Medicare DRGs).

For patients recruited at hospitals participating in the Ontario Case Costing Project (OCCP), patient-level hospital costs will be available.[17] For patients recruited at hospitals not participating in OCCP, we will estimate costs for measured items of resources used based upon the study case report forms. Our strategy is to use data from OCCP hospitals to create a Canadian-specific regression model of hospitalization costs for patients in the COURAGE trial.[18] For each patient in COURAGE in whom costs are directly measured, total per patient hospital cost will be used as the dependent variable. Independent variables will include utilization data collected in the hospitalization case report form (total length of stay, ICU days, catheterization, PCI, CABG, MRI, Holter monitor, etc) along with other demographic covariates (sex, age) and hospital characteristics (teaching status, hospital size, urban/rural location).

Physician reimbursement in Canada is reported separately from hospital accounts. Physicians submit claims directly to provincial Ministries of Health. These claims are based on billings specified in "fee schedules." Fee schedule(s) will be used to estimate billings for the physician services provided to the COURAGE trial participants.[19] Physician service utilization information for patients will be obtained from the study research data forms. In addition to diagnostic and surgical procedures, physicians can claim reimbursement for consultations and assessments given to patients while they are in the hospital.

For outpatient procedures, we will obtain a standard cost for each test/procedure from an OCCP teaching hospital and an OCCP non-teaching hospital. For pharmaceuticals standard unit costs based on an Ontario-wide formulary (Drug Benefit Formulary) will be used.

Patient-incurred (indirect) costs

Lost wages will be estimated using data from follow-up forms (time missed from work, work effectiveness, and classification of employment). Fully effective days of work lost for each follow-up period will be calculated by multiplying the number of days worked by one minus the effectiveness during that period and adding to that quantity the number of days missed from work. The dollar value of lost work will be calculated using the average wage of workers in similar employment classifications. For US participants, we will use average hourly earning reported in the US Bureau of Labor Statistics, Office of Compensation and Working Conditions. For Canadian participants, we will use Statistics Canada data on Canadian salaries and earnings. Whether to include indirect costs of medical care within the numerator as part of cost or within the measurement of utility is acknowledged to be controversial. Analyses will be offered with and without indirect costs.

Trial-wide costing

The system specific analyses above do not provide an overall analysis of costing or cost-effectiveness analysis. The trial-wide costing will apply an overall costing method based on US health care costs, to test the cost-effectiveness hypothesis from the point of view of decision makers in the US health care system.

All hospitalizations will be assigned a DRG. Costs will be assigned using the average cost for by DRG from Medicare for the appropriate year.[20] The intent is to include costs incurred after randomization. These are difficult to assess if the patient was randomized in the hospital. Stays in which a participant was randomized will be assigned a cost only if there was PCI and only the cost associated with PCI. This will

generally be the cost of a DRG for PCI without catheterization: DRG 517 (without stent) or 518 (with stent). Physician costs will be estimated by the method of Mitchell.[15] As alternative, costs will be estimated from MEDSTAT and a blend with MEDSTAT below age 65 and Medicare age 65 and above. Outpatient office visits and procedures will be assigned a CPT code and then cost will be estimated from the Medicare fee schedule. Medications will be priced using Red Book AWP, with sensitivity analyses for discounting medications, as above. Indirect costs will be estimated using the methods for US non-VA costing.

This analysis will also provide for sensitivity analyses considering the impact of drug-eluting stents. The DRG for drug-eluting stents can be used and then the costs related to restenosis decreased by 75%.[21]

Utility determination

Years of survival will be adjusted using health care utility, a measure of health status that varies from a low of zero, representing death, to high of one, representing ideal health. Health utilities allow quality of life to be compared with length of life. For example, 2 years of life in a health state with 0.5 utility equates to 1 year in ideal health.

The standard gamble is a widely accepted utility measure. This technique originated with von Neumann and Mogenstern.[22] The patient is presented with a choice between continuing with current health and a treatment that would restore ideal health, but with a specified risk of immediate death. The assessment systematically varies the amount of risk until the patient is indifferent to the alternatives. Utility is one minus the amount of risk the patient is willing to accept to be restored to ideal health. For example, if a patient is indifferent between continuing with her current health and taking a 5% chance of immediate death to attain ideal health, her utility for current health is 0.95 (= 1 − 0.05).

Standard gamble assessments are time-consuming and cognitively challenging. To overcome these obstacles, an efficient and reproducible assessment has been developed. COURAGE is using the U-Titer computer program,[23] embedded within an Epimetrics-designed application, to conduct the SF-36 and the Seattle Angina Questionnaire and to assess utilities. Use of the program standardizes quality of life assessment across sites. The program summarizes patients' responses to the SF-36 and Seattle Angina Questionnaire. The summary is used to present the current health anchor in the standard gamble assessment.[24] Utility is assessed at randomization and again at 1, 3, and 6 months and annually to the end of the trial. Assessments were scheduled more frequently at the beginning of the trial to capture any early differences caused by the intervention.

Patients will be followed up for a minimum of 3 years and as long as 7 years. The first 2 weeks of patients' post-randomization course will be assigned the baseline utility. The subsequent period until 2 months post-randomization will be assigned the utility measured at 1 month. The period until 4.5 months after randomization will be characterized by the 3-month utility. We will use the midpoints between assessments to define subsequent periods. For example, months 4.5 to 9.0 will be assigned the 6-month utility. Quality-adjusted life years will be calculated by multiplying the duration of the period by assessed utility. Missing utility values will be estimated by multiple imputation.[25]

Cost-utility analyses

Costs will be adjusted for inflation using the all goods component of US Consumer Price Index.[26] Costs will be discounted at 3% per year to reflect the lower economic value of deferred expenses.[27] Quality-adjusted life years will be discounted at the same rate to reflect the greater value of near-term quality of life.

If one form of therapy is both more effective and more costly, we will calculate the incremental cost-effectiveness in dollars per QALY gained. Cost-utility analysis determines the incremental cost of achieving an additional QALY by adopting the intervention.[28,29] We will find the point estimate of the incremental cost-effectiveness ratio (ICER) for the more effective therapy by finding the increased mean cost (ΔCOST) and dividing it by the increase in mean QALYs (ΔQALY). We will estimate the 95% confidence region around this point by bootstrap.[30] We will report the percentage of bootstrap replicates where PCI is dominant, where PCI is dominated, and where PCI is cost-effective over a range of thresholds. The results will be displayed in the cost-effectiveness plane and as cost-effectiveness acceptability curves, showing the probability that PCI is significantly cost-effective over the range of acceptability thresholds.

The net benefit method compares the ICER to the maximum amount (λ) that society is willing to pay to gain a QALY, or $\Delta\text{COST} / \Delta\text{QALY} < \lambda$.[31] The cost-effectiveness decision can be formulated as a question of whether the net-monetary-benefit (NMB) is greater than zero at a given willingness-to-pay threshold. The NMB is defined as λ^* (ΔQALY − ΔCOST). Alternatively, it can be formulated as the question of whether the net-health-benefit (NHB) is greater than zero. NHB is defined as (ΔQALY − ΔCOST) / λ.

NMB and NHB will be calculated at the patient level. We will use standard parametric regression methods to compare the means in PCI and medical therapy groups.[32] Because of the multisite design of the trial, economic data will be clustered, that is, data specific to a given site may be correlated. Multilevel (hierarchical) regression models will be used to account for the intracluster correlation. An empirical Bayesian shrinkage factor will be applied to estimate site-specific cost-effectiveness. These will be applied using a range of willingness-to-pay thresholds.[32,33]

Time horizon

We will consider cost-effectiveness over the first 5 years after randomization using data from the trial. We will also consider cost-effectiveness over the long-term. The cost of PCI is incurred immediately after randomization, but potential benefits may be realized beyond the end of the trial. We will construct a model to estimate the health care cost and QALYs beyond the end of the trial.

Expected survival for each patient beyond the in-trial period will be estimated from the Saskatchewan Health Database.[16,34] Death hazards will be estimated for phases in which hazard rates are relatively constant.[35] This method accounts for covariate data and in-trial events, including acute myocardial infarction and coronary surgery. Utility will be carried forward from the last available data. It will be assumed that there are no differences in cost in any period between the treatment arms after the in-trial period. If there is a difference in survival, then an estimate of the additional cost due to prolonged survival will

be made based on discounted in-trial costs.[36] As a sensitivity analysis, the costs in the last 2 years of follow-up will be carried forward for 5 years, after which we will assume no difference in direct costs, except for additional cost due to prolonged survival. The ICER and its distribution, as well as net benefit, will be estimated as described above.

Significance

Percutaneous coronary intervention is a common and expensive form of therapy with >500 000 procedures performed annually in the United States. The COURAGE trial will be the first trial to enroll a sufficient number of appropriate participants, assessing PCI in patients who would otherwise undergo this intervention. COURAGE has sufficient power to assess the hard outcomes of death or myocardial infarction. The economic component of COURAGE will assess both the additional cost and cost-utility of PCI. The cost-utility analysis will be crucial to assessing if one of the therapeutic approaches offers a better clinical outcome at higher cost. The economics study has a number of critical features. First of all, it is thoroughly embedded within the trial structure. The major questions have been developed a priori, exactly as in the clinical component. Costs will be measured from patient level resource use, not simulated from summary tables. The utility of participants is being assessed directly, using the standard gamble. The size of the COURAGE trial and duration of follow-up will provide adequate statistical power for the economic component, which parallels the primary clinical outcome measure. COURAGE is also being conducted in three distinct health care systems, which will allow assessment of generalizability of cost-effectiveness. The COURAGE trial will provide crucial clinical and economic information to help guide both medical decision making and public policy.

References

1. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. N Engl J Med 1992;326:10-6.
2. RITA-2 Trial Participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. RITA-2 trial participants. Lancet 1997;350:461-8.
3. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med 1999;341:70-6.
4. Weintraub WS, Mauldin PD, Becker E, et al. A comparison of the costs of and quality of life after coronary angioplasty or coronary surgery for multivessel coronary artery disease. Results from the Emory Angioplasty Versus Surgery Trial (EAST). Circulation 1995;92:2831-40.
5. Luce B, Manning J, Siegel J, et al. Estimating costs in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russel LB, et al, editors. Cost-effectiveness in health and medicine. New York: Oxfore University Press; 1996. p. 176-213.
6. Swindle R, Lukas CV, Meyer DA, et al. Cost analysis in the Department of Veterans Affairs: consensus and future directions. Med Care 1999;37(4 Suppl Va):AS3-8.
7. Shwartz M, Young DW, Siegrist R. The ratio of costs to charges: how good a basis for estimating costs? Inquiry 1995; 32:476-81.
8. Barnett PG, Lin P, Wagner TH. Estimating the cost of cardiac care provided by the hospitals of the U.S. Department of Veterans Affairs. In: Weintraub WS, editor. Cardiovascular health care economics. Totowa: Humana Press; 2003. p.15-29.
9. Kukull WA, Koepsell TD, Conrad DA, et al. Rapid estimation of hospitalization charges from a brief medical record review. Evaluation of a multivariate prediction model. Med Care 1986;24:961-6.
10. Welch HG, Larson EB. Rapid estimation of hospital charges in patients with leukemia. Validation of a multivariate prediction model. Med Care 1989;27:900-4.
11. Barnett PG, Chen S, Boden WE, et al. Cost-effectiveness of a conservative, ischemia-guided management strategy after non–Q-wave myocardial infarction: results of a randomized trial. Circulation 2002;105:680-4.
12. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ 2001;20:461-94.
13. Phibbs CS, Bhandari A, Yu W, et al. Estimating the costs of VA ambulatory care. Med Care Res Rev 2003;60(3 Suppl):54S-73S.
14. Ashby J. The accuracy of cost measures derived form Medicare Cost Report data. Hosp Cost Manage Account 1992;3:1-8.
15. Mitchell J, Burge R, Lee A, et al. Per case prospective payment for episodes of hospital care. Springfield (Va): US Department of Commerce National Technical Information Service. [Report No.: Publication PB95226023]; 1995.
16. Weintraub WS, Mahoney EM, Lamy A, et al. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. J Am Coll Cardiol 2005;45:838-45.
17. Ontario Case Cost Project. Ontario Case Cost Project (OCCP): Ontario guide to case costing, version 1.1. September ed. Ottawa: Ontario Case Cost Project; 1995.
18. Willan AR, O'Brien BJ. Cost prediction models for the comparison of two groups. Health Econ 2001;10:363-6.
19. Ontario Ministry of Health. Schedule of benefits: physician services under the Health Insurance Act, 2005. Toronto (Ontario): Queen's Printer; 2005.
20. Mahoney EM, Jurkovitz CT, Chu H, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non–ST-segment elevation myocardial infarction. JAMA 2002;288:1851-8.
21. Cohen DJ, Bakhai A, Shi C, et al. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial. Circulation 2004;110:508-14.
22. Von Neumann J, Mogenstern O. Theory of games and economic behaviour. Princeton: Princeton University Press; 1944.
23. Nease Jr RF, Kneeland T, O'Connor GT, et al. Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic Heart Disease Patient Outcomes Research Team. JAMA 1995; 273:1185-90.
24. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional

status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-41.
25. Rubin D. Multiple imputation after 18+ years. J Am Stat Assoc 1996;91:473-89.
26. Weintraub WS, Mahoney EM, Ghazzal ZM, et al. Trends in outcome and costs of coronary intervention in the 1990s. Am J Cardiol 2001;88:497-503.
27. Libscomb J, Weinstein MC, Torrance GW. Time preference. In: Gold MR, Siegel JE, Russell LB, et al, editors. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
28. Weinstein MC, Fineberg HV. Clinical decision analysis. Philadelphia: WB Saunders; 1980. p. 214-46.
29. Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ 1986;5:1-30.
30. Efron B, Tibshirani R. An introduction to the bootstrap. New York: Chapman and Hall; 1993.
31. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making 1998;18(2 Suppl):S68-S80.
32. Manca A, Rice N, Sculpher MJ, et al. Assessing generalisability by location in trial-based cost-effectiveness analysis: the use of multilevel models. Health Econ 2004;14:471-85.
33. Willan AR, Pinto EM, O'Brien BJ, et al. Country specific cost comparisons from multinational clinical trials using empirical Bayesian shrinkage estimation: the Canadian ASSENT-3 economic analysis. Health Econ 2005;14:327-38.
34. Caro J, Migliaccio-Walle K, Ishak KJ, et al. Estimating life-years lost due to atherothrombotic events: flexible survival functions to use in disease modeling. J Am Coll Cardiol 2004;43:425A [abstract].
35. Blackstone EH, Naftel DC, Turner MEJ. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assoc 1986;81: 615-24.
36. Weintraub WS, Zhang Z, Mahoney EM, et al. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. Circulation 2005;111:1106-13.