UNIVERSITY OF CALGARY

An Economic Evaluation of Sirolimus-eluting Stents with Expanded Consideration of Inputs and Outputs

by

Fiona Shrive

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

APRIL, 2006

UNIVERSITY OF CALGARY
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "An Economic Evaluation of Sirolimus-eluting Stents with Expanded Consideration of Inputs and Outputs" submitted by Fiona Shrive in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

Co-Supervisor, William A. Ghali, Dept. of Community Health Sciences

Co-Supervisor, Braden J. Manns, Dept. of Community Health Sciences

Cam Donaldson, University of Newcastle

Merril Knudtson, Dept. of Cardiac Sciences, Cardiology

John Wong, Dept. of Neurosurgery, Internal Examiner

Konrad Fassbender, University of Alberta, External Examiner

April 20/06
Date

ABSTRACT

Economic evaluations are an important tool for guiding policy. A formal economic evaluation compares the costs and benefits of a particular intervention compared with all potential alternatives. This is particularly useful when new technology becomes available that may offer more benefit to patients at a higher cost than current care.

Clinical restenosis is a major limitation to the long-term success of percutaneous coronary interventions (PCI). Recently, sirolimus-eluting stents have been shown to reduce the clinical restenosis rates. Given that the improvement in outcomes was associated with a significant incremental cost per stent, we performed a traditional economic evaluation of this new, efficacious but expensive technology. Drawing on the Alberta Provincial Project for Outcomes Assessment in Coronary Heart (APPROACH) disease database, we compared the cost per quality-adjusted life year (QALY) of sirolimus-eluting stents to that of bare metal stents in patients undergoing stented PCI.

Recognizing that the cost per QALY rubric may be uninformative to decision-makers, we presented an alternative method for presenting the output of our analysis, considering the costs and benefits of sirolimus-eluting stents. Based on current practice patterns, we projected the number of potentially preventable deaths, second procedures and potential cost increases if sirolimus-eluting stents were adopted. We explored various restricted funding strategies and discuss the complex issues associated with such strategies.

Economic evaluations are the sum of their parts and input values. We explored two different approaches to scoring our quality of life instrument, the EQ-5D; the US- and UK-preference based scoring algorithms. We then proceeded to compare three different costing methods available in Alberta (microcosting and two case grouping methods) to construct

inpatient costs. In each study, we compared the within subject and across subject differences between the methods. We then compared the cost per QALY resulting from the different input values to assess the impact of different methodological choices on economic evaluations.

Economic evaluation is a powerful tool that can be used in a policy realm. This thesis provides insights into how the cost per QALY should be calculated and demonstrates an expanded approach that carefully considers the economic evaluation's inputs and outputs.

ACKNOWLEDGEMENTS

I was supported by a Canada Graduate Scholarship from the Canadian Institutes of Health Research (CIHR) and an Alberta Heritage Foundation for Medical Research (AHFMR) Studentship. I received additional support from a Canadian Cardiovascular Outcomes Research Team (CCORT) Student Research Fellowship which is funded by CIHR and the Heart and Stroke Foundation (HSF) and a Tomorrow's Research Cardiovascular Health Professionals (TORCH) Student Fellowship.

I would like to thank: the APPROACH team for their continued support and use of the data, specifically Diane Galbraith whose patience hasn't failed yet; Cam Donaldson and Merril Knudtson whose encouragement and support has been unfailing; my supervisors, Bill Ghali and Braden Manns, for their kind words of support, inspiration and hard work. You have both gone the extra mile to help me achieve my goals;

Danielle whose friendship is the reason I have laughed so much during this degree; Barry, my best friend, who I love with all my heart; and lastly, I would like thank my parents who have taught me the value of education, love and kindness.

TABLE OF CONTENTS

A. OVERVIEW 1
B. GLOBAL STATEMENT OF THESIS PURPOSE 4
C. CLINICAL BACKGROUND 5
1. General Background 5
2. Stenting 6
3. Drug-eluting Stents 8
4. Sirolimus-eluting Stents 8
D. ECONOMIC EVALUATION 12
1. Background 12
1.1 Economic Evaluation 14
1.2 Approaches to economic evaluations 16
1.3 Decision models 17
1.4 Decision rules 18
2. Methods 19
2.1 Markov Model 20
2.2 Patient Cohorts 21
2.3 Clinical Outcomes 25
2.3.1 Event rates 25
2.3.2 Long-term Survival 26
2.4 Health-Related Quality of life (HRQOL) 27
2.5 Costs 28
2.6 Efficacy of sirolimus-eluting stents 29
2.7 Cost of sirolimus-eluting stents 31
2.8 Economic Analysis 31
2.9 Sensitivity/Scenario Analysis 32
3. Results 34
3.1 Cohort Characteristics 34
3.2 Cost-utility Analysis 36
4. Discussion 41
E. BUDGETARY AND CLINICAL IMPACT ANALYSIS 44
1. Background 44
1.1 Rationale 44
1.2 The Cost of funding Sirolimus-eluting Stents 45
2. The Health benefits from funding Sirolimus-eluting Stents 45
2.1 Funding sirolimus-eluting stents for all patients 45
2.2 Alternative scenarios: Restricted funding for Sirolimus-eluting Stents 47
3. Away From Cost per QALY Rubric 48
3.1 Opportunity Costs 48
3.2 Equity 50
3.3 What else matters when making funding decisions? 52
3.4 Review of new devices and technology within Canada: The Current state 52
4. Future considerations 54

F. THE IMPACT OF HEALTH-RELATED QUALITY OF LIFE VALUATION ON THE RESULTS OF ECONOMIC EVALUATION 56

1. Background 56
1.1 Utility Scores 57
1.2 Direct Elicitation of Utilities 58
1.3 Indirect Elicitation of Utilities 61
1.4 EQ-5D 62
1.4.1 UK Algorithm for the EQ-5D 63
1.4.2 US Algorithm for the EQ-5D 64
1.5 Other Considerations 65

2. Methods 66
2.1 Data Source and Collection 66
2.2 Analysis 67
2.3 Cost-utility Model 67

3. Results 68
3.1 Baseline characteristics of responders 68
3.2 Algorithm Differences 70
3.3 Cost-Utility Ratios 72

4. Discussion 74

G. THE IMPACT OF DIFFERENT METHODS OF COSTING CARE ON THE RESULTS OF ECONOMIC EVALUATION 78

1. Background 78

2. Methods 80
2.1 Overview of the Costing methods 80
2.1.1 Microcosting 80
2.2.2 Diagnosis-related groupers 81
2.2.3 Case-Mix Groupers 83
2.2 Patient Cohort 84
2.3 Implementation of the three costing methods 85
2.3.1 Microcosting 85
2.3.2 RGN-Derived Costs 85
2.3.3 CMG-Derived Costs 85
2.4 Analysis 86
2.5 Cost-Utility Model 86

3. Results 88
3.1 Patient-level Comparisons 88
3.2 Hospitalisation-level Comparisons 90
3.3 Cost-utility Analysis 97

4. Discussion 100

H. GLOBAL CONCLUSIONS 103

1. Relevance of Economic Evaluations 103

2. Limitations of Economic Evaluations 103

3. Translation of Findings 105

4. Methodological Exploration 105

5. Reiteration of Significance 106

K. REFERENCE LIST **108**

L. APPENDIX **123**

LIST OF TABLES

Table 1. Baseline characteristics of APPROACH patients who were treated with a bare metal stent, including mortality and resource use 35

Table 2. Cost-utility of sirolimus-eluting stents, overall and based on age and diabetes status 37

Table 3. Sensitivity Analysis 39

Table 4. Projected Clinical Outcomes and Budget Impact of Funding Sirolimus-eluting Stents in Alberta 46

Table 5. Implications of Restricted Funding Strategies; What Would Happen to Patients in Alberta in Whom Sirolimus-eluting Stents are not Placed 51

Table 6. Comparison of EQ-5D index results using the UK and US scoring algorithms, overall and by subgroup 71

Table 7. Cost-utility ratios resulting from the UK and US scoring algorithm, overall and by subgroup 73

Table 8. 4-year accumulated health care costs 89

Table 9. Hospitalisation costs for the ten most common cardiac RGNs 93

Table 10. Hospitalisation costs for the five most common cardiac CMGs 95

Table 11. Costing estimates used for the economic evaluation, considering the three different costing methods 98

Table 12. Incremental cost-utility ratios resulting from use of costing estimates derived from the three different costing methods, overall and by subgroup 99

LIST OF FIGURES

Figure 1. A stent implanted in a coronary artery 7

Figure 2. The compound structure of Sirolimus 10

Figure 3. Markov Model 23

Figure 4. Decision Model 24

Figure 5. Forest plot of randomized controlled trials included in meta-analysis 30

Figure 6. Scenario analyses 38

Figure 7. US scenario analyses 40

Figure 8. Standard Gamble 59

Figure 9. Time Trade-off 60

Figure 10. Categorized responses ("No problem" versus "Some" or "Severe" problems) for each of the five dimensions of the EQ-5D 69

Figure 11. Scatterplot of microcosts versus RGN-derived costs 91

Figure 12. Scatterplot of microcosts versus CMG-derived costs 92

Figure 13. Distribution of microcosts for specific RGNs 94

Figure 14. Distribution of microcosts for specific CMGs 96

TITLE: An Economic Evaluation of Sirolimus-eluting Stents with Expanded Consideration of Inputs and Outputs

A. OVERVIEW

Coronary heart disease is the leading cause of death in Canada (1). One common treatment option is balloon angioplasty, a procedure where a balloon is inserted into the blocked artery and then inflated to expand the artery. In approximately 85% of angioplasty procedures a stent, a cylindrical mesh-wire tube, is implanted to prop the vessel walls apart (2). If the artery becomes blocked again it is termed "clinical restenosis". Clinical restenosis is a major obstacle in the long-term success of coronary stent implantation. Current estimates are that approximately 14% of stented patients require a repeat revascularization procedure within 1 year of their initial angioplasty (3). This is a cost concern and similarly, a quality of life issue since patients who undergo a second procedure have been shown to have a lower quality of life than those who remain event free post-stenting (4). Additionally, patients who undergo a second procedure are exposed to a small risk of immediate mortality; thus, over time, a reduction in the restenosis rate will be associated with a small reduction in mortality.

The development of drug-eluting stents is a promising step in reducing the rate of restenosis. To date, four randomized control trials have been completed with sirlomus-eluting stents (5-8). All demonstrated significantly lower restenosis rates among patients implanted with a sirolimus-eluting stent. However, sirolimus-eluting stents, as of July 2004, were listed at a cost of five times the cost of a conventional stent ($2900 compared to $500) (9). While promising as a therapeutic intervention, sirolimus-eluting stents now

present a daunting challenge for health system funders and policy makers. A thorough examination of the costs and benefits of sirolimus-eluting stents is required.

This thesis consists of three sub-studies. First, a cost-utility analysis was completed. The results of this analysis help to inform decision makers and policy makers by explicitly weighing the costs of sirolimus-eluting stents against the potential health benefit. The results can then be applied in a priority setting arena. Recognizing that the results of a traditional economic evaluation may not be informative to a decision-maker, we subsequently re-packaged the results into a more informative, concrete budget and clinical impact analysis.

When conducting an economic evaluation, one must always consider the input values; an economic evaluation is the sum of its parts. Thus, our second study explores the impact of different social weights being applied to the EQ-5D, the measure of health-related quality of life (HRQOL) used in our study. There are two currently published validated algorithms for creating utility scores from the EQ-5D (10;11). One applies British tariffs and most recently, American social tariffs have been developed. Our work is carried out in Canada where no country-specific tariffs have been developed. If applying the various tariffs developed in other countries significantly changes the results of a cost-utility study, we must carefully consider the results of all economic evaluations done in other countries and how to adapt the results to a Canadian setting.

Similarly, when assessing the costs of care, various sources are available to construct the cost profiles. In Alberta, 3 sources of costs are potentially available; microcosting available from the Calgary and Capital Health Regions, case mix groupers available from Alberta Health and Wellness and lastly, case mix groupers available from the Canadian Institute for Health Information. It is conceivable that the cost values derived

from the three different approaches could impact the results in a cost-utility study. Thus, in our last study, a direct comparison of the results of the three approaches to constructing costs of care is completed providing guidance for others when considering which costing source to draw upon.

We then summarize our findings, providing context and a discussion of some of the global issues relating to economic evaluation. Lastly, we discuss the potential implications of our findings and how others could use our results.

B. GLOBAL STATEMENT OF THESIS PURPOSE

1. To complete an economic evaluation of the costs, quality adjusted life-years (QALYs) gained and cost per QALY gained for sirolimus-eluting stents compared to conventional stenting practice. (Main Study)
2. To explore an alternative method of presenting the results of the economic evaluation, rather than the usual cost per QALY rubric, in an attempt to assist decision-makers with the decision as to whether, and for whom, to fund sirolimus-eluting stents. (Main Study)
3. To assess the impact on the cost per QALY of applying the UK preference based tariffs and the US preference based tariffs to the EQ-5D estimates used to inform our economic evaluation. (Health-related Quality of Life Substudy)
4. To assess the impact of using three different methodological approaches to measuring health care costs on the cost per QALY. (Costing Substudy)

C. CLINICAL BACKGROUND

1. General Background

Coronary heart disease is the leading cause of death in Canada (1). Its high prevalence in the general population, and its often devastating consequences have led to a proliferation in the use of cardiac catheterization, a diagnostic procedure that determines the presence and extent of coronary disease in patients who undergo the procedure. Identification of coronary disease is important, because there is opportunity to intervene to improve the health of individuals with coronary heart disease through the use of either invasive cardiac procedures or therapy with a variety of medications that have been shown to be of benefit in patients with coronary disease. Generally speaking, there are currently three treatment options for patients presenting with occluded arteries; coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) and medical management. The former two procedures are often called "revascularization procedures". Over the past 20 years, there has been an increase in the use of revascularization treatment and a shift away from predominantly medical therapy, and this shift has largely arisen from the growing recognition of benefit associated with performance of coronary revascularization when it is technically feasible to do so (2).

In 1968, CABG was introduced (12). CABG is an invasive procedure that reroutes the blood flow around the occlusion using anastomosed saphenous veins or arteries. The vessels are reconnected to the coronary arteries below the occluded site. In several landmark trials, CABG was associated with longer survival and better quality of life than those treated medically in subgroups of patients with multi-vessel and left main disease (13-17).

Given that CABG is highly invasive (i.e., major surgery requiring sternotomy), less invasive revascularization strategies were sought. First used in humans in 1977, PCI has continued to evolve and work in the field has rapidly expanded (18). The procedure involves threading a catheter with a balloon on the tip through an artery either in the groin or the arm to the site of the occlusion. The balloon is then inflated expanding the blocked artery restoring blood flow to the occluded vessel. Increasing experience of the operators, advances in adjuvant drug treatments and new technologies have contributed to the success of the procedure and the low morbidity associated with PCI (19).

There is still much debate about when to proceed with PCI versus CABG versus medical management in patients presenting with coronary artery disease (CAD). The first large-scale randomized controlled trial comparing PCI and CABG found no significant differences in outcomes at 5 years (20). Subsequent trials with varying follow-up periods, similarly, found no difference in mortality between the two treatment groups (21). Subgroup analysis in these trials identified high-risk patient groups in which CABG is more beneficial than PCI. More recently, consensus documents have recommended CABG for patients presenting with left main CAD, triple vessel disease and specifically multivessel disease in those with a low ejection fraction (22).

2. Stenting

In 1994, the FDA approved the first stent, the Palmaz-Schatz stent (23). A stent is a cylinder mesh-wire device (Figure 1) implanted in the artery to buttress the artery walls preventing them from closing in on themselves to occlude the artery, an event termed restenosis. Several large randomized controlled trials showed stents prevented restenosis and their use has increased dramatically since late 1994 (24;25). A meta-analysis including 23 randomized controlled trials comparing stenting with balloon angioplasty found no

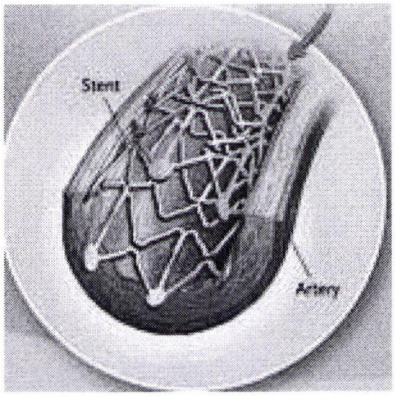


Figure 1. A stent implanted in a coronary artery

(taken from www.cypherusa.com)

significant difference in the mortality rate and non-fatal myocardial infarction rate between the two procedures (26). However, the major adverse cardiac event rate, composed of death, myocardial infarction, target revascularization or stroke, was significantly lower in the patients implanted with a stent (18.2% compared to 25.8%).

As of 2003, an estimated 85% of PCIs performed in Canada involved one or more stents (2). However, restenosis remains a limiting factor to the long-term success of PCI. It is reported that approximately 14% of patients undergoing a PCI implanted with a conventional stent have evidence of restenosis within a year of the index PCI (3).

3. Drug-eluting Stents

Much research has been devoted to the prevention of restenosis and drug-eluting stents have recently emerged as a promising new technology. The concept of using stents as a vehicle for prolonged local administration of drug therapy is appealing. A drug can be administered at the site of the lesion, over an extended period of time and specifically to inhibit proliferation and encourage vascular healing. Heparin coated stents were the first step towards loading medications onto stents (27). Heparin is an antithrombotic agent and as such, the drug release occurs long after deployment of the stent. Several heparin-coated stents are approved for use in Canada. Although, these stents are well-tolerated and seem to have a lower rate of subacute thrombosis than uncoated stents, there has been little evidence published indicating an impact on long-term survival or restenosis (27).

4. Sirolimus-eluting Stents

More recently, the stent device industry has turned its attention to immunosuppressants. Sirolimus is a naturally occurring product discovered in the soil of Easter Island (28). It is isolated from Streptomyces hygroscopicus and is an immunosuppressant agent approved for use in the prevention of renal transplant rejection

by the FDA in 1999. Evidence emerged that sirolimus also inhibits proliferation and migration of vascular smooth muscle cells; two processes central to restenosis (29). These findings encouraged researchers to develop sirolimus-eluting stents.

Sirolimus has a molecular weight of 914 and is comprised of a 31-member macrocyclic lactone (Figure 2). The major intracellular receptor is a small 12-kD protein called FKB12, a member of the immunophilin family of cytosolic binding proteins. Sirolimus prevents cell-cycle progression leading to an arrest in cell growth. In pig models, sirolimus has been shown to inhibit restenosis post-PCI (30).

The human trials have shown significant benefits in the prevention of restenosis. The first human trial, a phase II trial, included 45 patients with CAD and diagnosed angina (31). There were no reports of restenosis, assessed angiograhpically at 4,6,12 and 24 months. The overall major adverse event rate reported was 11.1% at 2 years. These findings lead to the initiation of the Randomized Study With the Sirolimus-eluting Bx Velocity Balloon-expandable stent (RAVEL), a randomized clinical trial comparing sirolimus-eluting stents to uncoated stents (5). 238 patients were included from centres in Europe and Latin America. At 12 months, the sirolimus-eluting stent group had a 0% restenosis rate compared to 23% in the uncoated stent arm. However, the patient population was tightly defined and included only those with unstable or stable angina, a population that may not be at high risk of restenosis. The SIRIUS trial (Sirolimus-coated Bx-Velocity Stent in the Treatment of patients with de Novo coronary artery lesions) had much broader inclusion criteria (6); 1038 patients were enrolled and angiographic follow-up was obtained at 9 months. The results showed a restenosis rate of 5.2% in the sirolimus-eluting arm compared to 20% in the uncoated stent arm. Both these trials showed dramatic reductions in the restenosis rate.

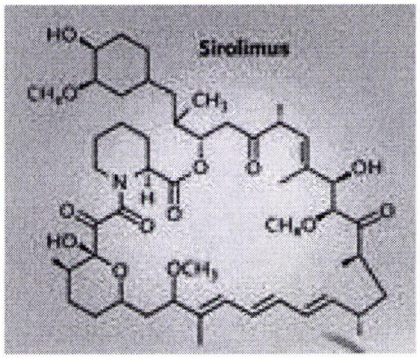


Figure 2. The compound structure of Sirolimus

(taken from www.cypherusa.com)

Of note, both trials reported angiographic restenosis; restenosis detected during a protocol catheterization not necessarily associated with symptomatic presentation. The follow-up periods of the trials were relatively short (one year or less). To date there are limited long-term data available from small registries of patients implanted with sirolimus-eluting stents. In the absence of long-term data, we are unable to determine whether sirolimus-eluting stents simply delay the development of restenosis or prevent the phenomenon.

The results from the two trials lead the FDA to approve, in April 2003, use of sirolimus-eluting stents for de novo lesions with a length of < 30mm and a reference vessel diameter of 2.5-3.5mm. Health Canada quickly followed suit and an estimated 900 sirolimus-eluting stents were implanted in Canada as of July 2003 (32). The use of these new stents is now wide-spread, with approved use occurring in all Canadian provinces although utilization patterns are variable across provinces.

D. ECONOMIC EVALUATION

GLOBAL SUBSTUDY OBJECTIVE: To complete a formal economic evaluation of the costs, quality adjusted life-years (QALYs) gained and cost per QALY gained for sirolimus-eluting stents compared to conventional stenting practice.

1. Background

Resources, both monetary and human, are scarce. Even in wealthy societies there are simply not enough resources to meet all the needs and wants of the citizens. As a result of this scarcity, we must decide which activities to undertake. Each time we use resources to meet one need, those resources are not being used to meet other need. By deciding to use the resources in a particular activity, there is a forgone opportunity by not using those resources in some other activity. In economics, this concept is referred to as opportunity cost; strictly, the opportunity cost is the benefit forgone that could have been derived from allocating resources to the next best alternative (33). In health care, where we have a limited funding envelope, our goal is to achieve maximum health benefits whilst incurring minimal opportunity cost. Choosing programmes whose benefits are greater than their associated opportunity cost will ensure maximum health benefits for minimal opportunity cost.

The classic way in which opportunity cost has been measured within health care is through the use of economic evaluation (discussed below). The type of economic evaluation performed is driven by the type of question being posed. Two levels of questions can be addressed: allocative and technical efficiency questions. Technical efficiency questions are those that pertain to the most efficient way to deliver care to a specific group of patients (33). Technical efficiency assumes that resources have been

allocated to a certain group of patients and is concerned with how to best achieve specified goals within the allocated resources.

Allocative efficiency is a broader concept. In this case, it is not given that resources are allocated to a specific group. The concern is how best to allocate resources among competing groups. Thus, we have groups of patients competing for funding and some will be allocated resources at the expense of the other groups (33).

For example, in Alberta the cardiac services programme is funded through Province Wide Services, an organization responsible for the provision of specialized medical services such as neurosurgery, renal dialysis, major organ transplants, hip and joint replacements and cardiac care. The committee must allocate a certain amount of their annual budget to each of the programmes under its umbrella. Each programme gets a portion of the budget and deciding how large a portion is given to each programme is an allocative efficiency decision. Once a certain amount of resources has been given to the cardiac care programme, the director of the heart health programme at each hospital must decide how best to spend the specified budget. For example, when considering the course of care for cardiac catheterization patients, should the resources be invested in increasing the capacity of the catheterization lab to decrease the wait time for a catheterization or should the resources be used to hire more nurses for the cardiac ward to increase the amount of nursing time the average patient receives while recovering? This is a question of technical efficiency; how best do you deliver cardiac care within a fixed budget?

One of the goals of health economics is to ensure that the benefits forgone by not allocating resources to a certain group (ie: the opportunity cost) are smaller than the health benefits gained from the patient group receiving the resources. Implementing programmes

whose benefits outweigh their opportunity cost will ensure maximum health benefits at minimal cost within a fixed budget.

1.1 Economic Evaluation

Economic evaluation is one tool that can aid decision-makers by weighing the costs and benefits of alternative health strategies. There are three types of economic evaluation: cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). Cost-benefit analysis deals with allocative efficiency whilst the other two forms are primarily concerned with technical efficiency although the results of CUA can be applied within an allocative efficiency framework.

Though costs are generally measured in a similar fashion in each of the forms of economic evaluation, the manner in which clinical effectiveness is measured differs. CEA measures the benefits of a health care intervention in natural units such as life years gained or cases detected. Any alternative strategies considered must be thought to also impact this output though the extent to which they do this may differ. CEA is based on the methods of constrained optimization, to maximize the effectiveness of a program with a restricted health care budget A CEA yields the greatest effectiveness for a given cost; or alternatively, minimum cost for a given effectiveness. CEA is often thought of as a method to determine the best means of delivering care for the same group of patients (34).

Cost minimization analysis is one specific type of CEA. In this case, the two interventions considered are thought to have equivalent health benefits. The programmes differ only by cost, thus, the least costly alternative is the most efficient strategy. Both induced costs and averted costs should be included when estimating the cost to create an overall cost picture. The additional expenditures incurred as well as the costs avoided should be considered.

CUA is a specialized form of CEA. The cost inputs are often identical in both methods, but, the approaches to measuring health benefit differ between the two methods. In CUA health gains are expressed as quality-adjusted life years or another equivalent measure, such as, healthy-year equivalents. When the health programme affects both morbidity and mortality or when health-related quality of life is an important outcome, CUA is the appropriate choice of evaluation. Additionally, CUA incorporates the notion of preference where CEA does not. Utility measures incorporate consumer preference; the outcomes are not only counted but incorporate relative desirability of different outcomes.

CBA differs from the other two methods of evaluation in its method of measuring benefit. CBA requires all consequences to be valued in monetary terms. Intuitively, measuring health benefits in terms of money seems appealing, but, practically it is difficult. There are two approaches that are used; human capital and willingness to pay. The human capital approach values all benefits in terms of future productivity costs lost. One's future productivity costs are valued in terms of labour costs. The major difficulty with this approach is valuing productivity costs for those not in the work force such as retired people, unemployed people or people who choose not to work.

The willingness to pay approach values health benefits based on people's willingness to pay for them. Thus, if people are prepared to pay more to receive a health benefit, we deem that it is more highly valued than another health benefit that they are willing to pay less for. However, willingness to pay is intrinsically linked to ability to pay. The rich have more money and hence are willing to pay more for benefits than a poorer person. This does not necessarily mean that the health benefit is valued less by those poorer. Methodological issues, such as these, associated with the willingness to pay methodology continue to be

researched. While the application of willingness to pay in the health sector is in its infancy, recent research in this area has shown promise.

The scope of CBA is broader than CEA and CUA. CBA can theoretically be used for questions of allocative efficiency where CEA and CUA address primarily technical efficiency and require further judgment to answer the question "Are the costs worth the benefit?." CBA can also be used to assess the value of non-health benefits. For example, CBA can value the process of care, the length of a wait time or the location of care.

1.2 Approaches to economic evaluations

Economic evaluations can be completed in two ways: alongside a clinical trial or using a decision model (35). Incorporating an economic component into a clinical trial allows for "live" data collection. All costs and benefits can be measured prospectively. Patients enrolled in a clinical trial can be followed forward from the time of enrolment with costs being directly measured and gathered. The benefit measure is also collected prospectively. Depending on the measure of benefit, different approaches can be applied. If the benefit is in terms of avoided events or life years gained, patients can be tracked to monitor their health state. If benefit is measured in terms of health-related quality of life, utility instruments can be applied to assess this throughout the study.

While economic evaluation alongside a trial may provide more valid cost and benefit data, there are many cases when this is not an option. Often the clinical trial has been completed without the incorporation of a cost measure. In such circumstances, the economic question has either simply been overlooked, or deferred to future research. Additionally, often clinical trials are not continued for a long enough period of time to gather information on the appropriate health benefits. For example, when considering life years gained as the health outcome patients must be followed long enough to see a

mortality difference in the two treatment groups. Often the 1-year follow-up period of a RCT is simply not long enough to show benefit. Thus, modeling often is needed to compliment the RCT. Lastly, there are some clinical questions that cannot be addressed by carrying out a clinical trial. This could be due to ethical reasons, cost considerations or an inability to establish a reasonable comparator.

1.3 Decision models

Decision analytic modeling is one alternative framework to conduct an economic evaluation. Decision analysis is a systematic tool to aid decision-making (36). It allows for both costs and benefits of treatment strategies to be weighed against each other. Four steps are required to complete a decision analysis (37). First, identify and bound the problem. This involves identifying all alternatives to the problem, gathering clinical information and defining all possible relevant health states of patients.

Secondly, structure the problem over time. The clinical process is modeled over time. Transition probabilities, the probability of patients moving between defined health states, are defined. Costs and benefits associated with each clinical state are identified. Thirdly, the information needed to fill in the decision modeling tree must be characterized. Broadly, the required information can be broken into five categories; transition probabilities, valuation of health outcomes, cost of new treatment, cost of existing treatment and cost of ongoing care. Data sources must be specified and the uncertainty, limits and biases of the data sources should be clearly identified.

Data can come from a variety of sources. Increasingly, published literature is available. However, when using published data caution must be exercised. Any bias within the estimates due to initial study, data collection or interpretation will be carried

through into the economic evaluation. All the input values are only as good as the methodology used to produce them.

The ideal way to get the input values is from a cohort database. Using data from a real cohort of patients enables us to simulate what would have happened had patients been given a different treatment alternative with the relative treatment effect of the new treatment "modeled" from the RCT data available. A cohort, or a group of patients, eliminates some of the sources of bias. Furthermore, sensitivity analysis can be performed to test how robust the model is to various fluctuations in uncertain input values. This also allows for the impact of potential bias within estimates to be evaluated.

Lastly, a preferred course of action should be identified. If one option is less costly and at least as effective as another option, the first option is dominant and should be implemented. The option provides greater benefit at a lower cost. Similarly, a more costly and less effective option should not be implemented; it provides less benefit at a higher cost. If an option is more effective and more costly, judgment and careful consideration of potential tradeoffs is required. Here is the situation where patients have the potential to benefit but additional resources are required.

1.4 Decision rules

Currently, there are three main strategies to guide decisions in the above case. A precedent has been established by the therapies that are currently funded. For example, we fund dialysis which costs approximately $50,000 per QALY thus is seems reasonable to compare other candidates for funding to dialysis. League tables have also been used to incorporate the cost per QALY into decision making. Using a league table approach, all therapies under consideration are listed in rank order from the most cost-effective to the

least and subsequently therapies are funded in the order in which they listed until the budget is exhausted.

Another strategy is to adopt guidelines. Currently, there are three published guidelines. The Gold panel set US $50,000 per QALY as an "acceptable" cost per QALY (38); Laupacis et al proposed CAN $20,000-100,000 per QALY as an acceptable range (39) and more recently, NICE has stated UK £30,000 per QALY as acceptable (40). It is important to note, however, that all the proposed boundaries are arbitrary and may not be founded on economic principles. The cost per QALY can be used as a guide for decisions but simply adopting a treatment strategy if the cost per QALY is within the "acceptable" range does not take into account the other factors that influence health care decisions such as society's "soft-spot" for children's health issues.

Another approach to deciding whether or not to fund a therapy is to return to the notion of opportunity cost. If this particular therapy is funded, what are we giving up? It would only be reasonable to fund a given treatment if the health benefits from funding that treatment exceed the benefits of the intervention(s) selected to lose funding. Explicitly considering the benefits that we are not accruing allows us to discuss whether or not we are willing to give those benefits up in order to gain the proposed benefits.

We now proceed to describe the methods of a cost-utility analysis using observational data and Markov model to derive the cost per QALY of sirolimus-eluting stents compared to that of bare metal stents in patients undergoing stented PCI.

2. Methods

The cost per quality-adjusted life year (QALY) gained with the implantation of a sirolimus-eluting stent compared with a conventional stent was calculated for all patients

undergoing PCI. The calculation was performed for patients overall, by age group and diabetes status. Conventional stents were chosen as the comparison therapy as they represented the current standard of care in Alberta, as well as within Canada, at the time of the analysis. Other therapeutic strategies were considered but were not modeled as they were aimed at different patient populations (medical management), were not widely used (brachytherapy), were not widely available at the time of this analysis (paclitaxel eluting stents) or because no comparative data with sirolimus eluting stents existed (angioplasty without stenting).

All outcome data considered within this analysis was derived from the APPROACH database, a prospective cohort initiative that captures all patients undergoing cardiac catheterization within the province of Alberta, Canada. APPROACH patients are followed forward in time to assess clinical, economic and quality of life outcomes (41). The APPROACH database provided estimates of clinical event rates, costs and HRQOL scores for all conventionally stented patients in Alberta.

2.1 Markov Model

All patients undergoing PCI are potentially eligible, and could benefit to varying degrees, from sirolimus-eluting stents. Our model's goal is to simulate what would have happened to PCI patients over time if implanted with a sirolimus-eluting stent. When considering the model, we wanted the model to be inclusive of all the clinically relevant health states post-PCI but simple enough to be understandable and accessible to general readers. Since patients are followed longitudinally with a time-limited risk of restenosis and then subsequently with a varying risk of death we require a model that allows patients to continually cycle through the same health states. In Markov models, patients are moved between health states by transition probabilities over time periods. This type of model is

particularly well-suited to modeling diseases where patients are exposed to re-occurring risks over time (36). By attaching costs and benefits to health states and transitions, Markov models can be used as decision analysis tools.

A Markov process was used to model the cost and clinical outcomes for stented patients post-PCI in 6-month time intervals. Patients progressed through five Markov health states based on the health state transitions that may occur after an initial PCI: 1) alive with no clinical restenosis (i.e. event free), 2) clinical restenosis as determined by the need for a subsequent CABG, 3) clinical restenosis as determined by the need for repeat PCI, 4) repeat catheterization with no subsequent revascularization and 5) death (Figure 3). The decision tree is shown in Figure 4. Restenosis was only considered to occur in the first year after the initial PCI (3). Beyond the first year, patients continue to progress in the event-free, post CABG, post repeat PCI, and post catheterization with no revascularization health states, with an ongoing long-term risk of death as described below.

2.2 Patient Cohorts

Three patient cohorts from APPROACH were used to inform our economic evaluation. Patients undergoing PCI procedures with conventional stents between 1998 and 2000 (N = 7334) were used to estimate event rates and HRQOL. This cohort of patients represents the largest group of patients available in APPROACH after glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa inhibitors), an anti-platelet therapy which has been shown to reduce mortality post-PCI, became widespread standard therapy. Thus the 1998-2000 cohort is the largest cohort available with similar rates of GPIIb/IIIa inhibitor use across the selected years allowing for stable event rate estimates to be produced.

An expanded APPROACH cohort was used to calculate the 30-day mortality rates. The 1995-2000 stented PCI (N=8528) was used since it provides larger numbers of patients to ensure stability in the 30-day mortality estimates across all subgroups.

Costing data were not available for either of the above described cohorts. Therefore the 1995-1997 APPROACH cohort (N=1824) of PCI patients treated with conventional stents was used to estimate health care costs.

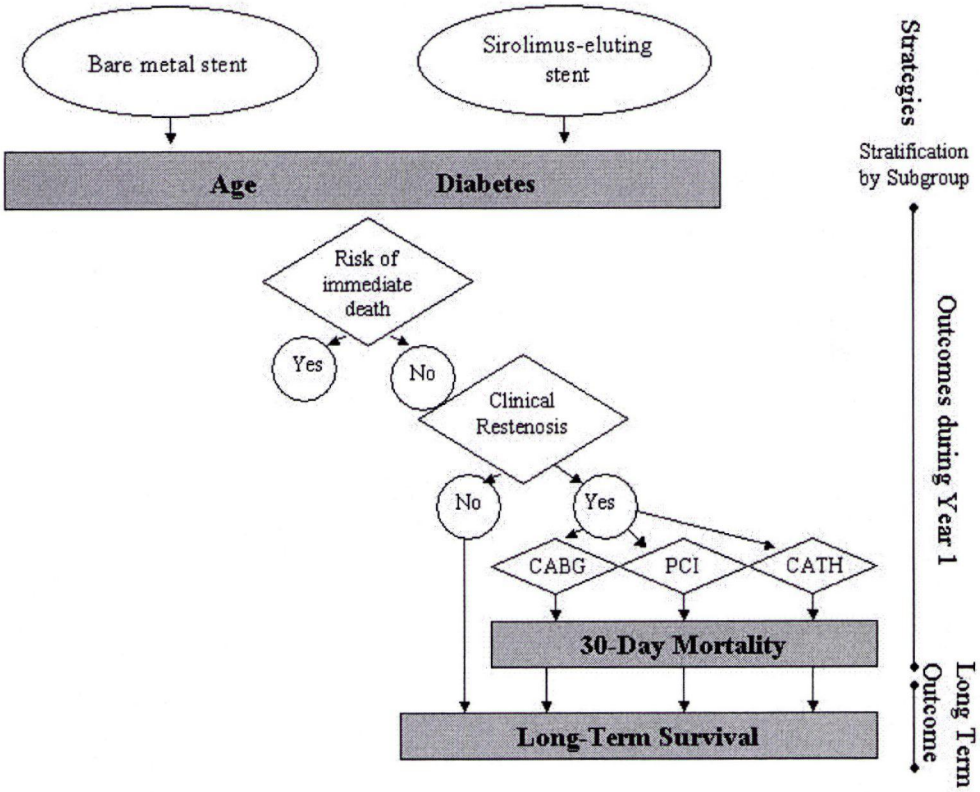


Figure 3. Markov Model

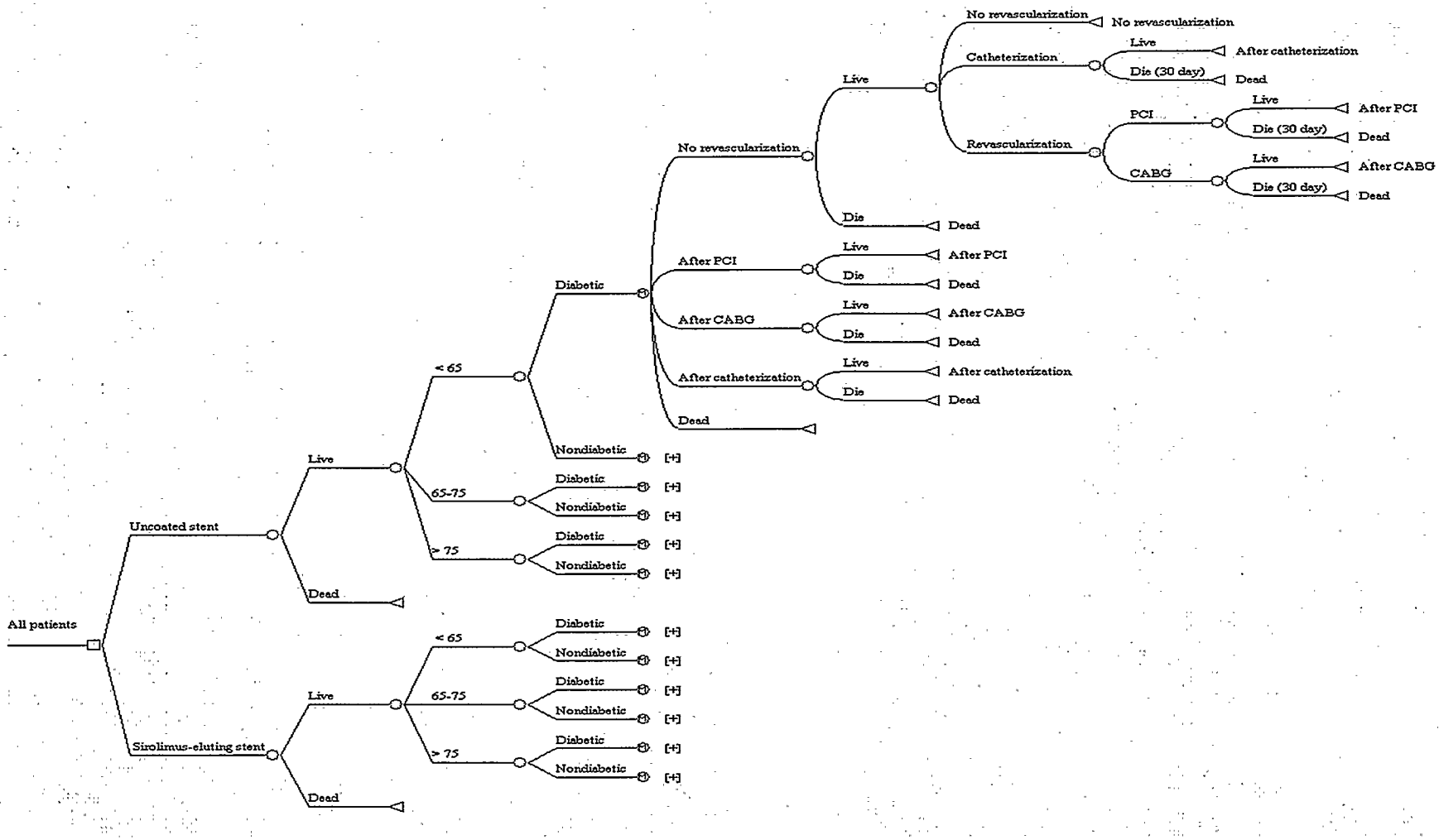


Figure 4. Decision Model

2.3 Clinical Outcomes

2.3.1 Event rates

One-year clinical restenosis and death rates in conventionally stented patients were taken from the 1998-2000 APPROACH cohort. A hierarchy of events was used to classify patients: CABG, PCI, repeat catheterization with no subsequent revascularization and lastly death. If none of these events occur, then patients continue in the "event-free" state. Additionally, once a patient has an event they move into the respective post-state and continue to cycle exposed to a risk of death. Any CABG, regardless of the artery targeted, was considered a failure of the initial PCI. CABG is the most invasive and highest risk of the possible procedures, thus any patient undergoing a CABG within the 6-month window was counted as a CABG event regardless of the other procedures a patient may have undergone (ie: if a patient undergoes a second PCI and then a CABG, the patient was counted as having a CABG). Only target vessel PCIs were included in the definition of clinical restenosis. Any PCI with another vessel as the target was included as a repeat catheterization with no subsequent revascularization.

A repeat catheterization without subsequent revascularization was defined as a patient undergoing a repeat catheterization with no procedure (i.e. target vessel PCI or CABG) occurring in the ensuing 3 months. This is a relatively common event in clinical practice that relates to either the lack of radiographic restenosis in the target vessel (thus no revascularization indicated) or it may be seen in patients with true restenosis for whom no revascularization is performed due to feasibility considerations (e.g. patient or vessel-related reasons) or due to provider and/or patient preference. For all repeat catheterizations that were performed where no PCI or CABG was subsequently done, a case-by-case review of the coronary anatomy at the time of repeat coronary angiography revealed that the target

vessel from the index PCI was greater than 50% occluded in 49.5% of cases. Thus, in our baseline analysis, 49.5% of repeat catheterizations that were not followed by PCI or CABG were assumed to be avoidable by sirolimus-eluting stents.

The 1998-2000 APPROACH cohort was used to calculate an immediate 7-day mortality risk associated with the index PCI. This was applied before patients enter the Markov model to eliminate those patients who are likely to die regardless of which stent is implanted. Thirty-day mortality rates after CABG, repeat PCI and repeat catheterization requiring no revascularization were taken from the expanded 1995-2000 APPROACH cohort. A larger cohort ensures stable death rates across all subgroups. Any death within thirty days of the second procedure was included and the 30-day death rate remained constant over all modeled time-periods.

2.3.2 Long-term Survival

During the first 6 months, the risk of death was determined using the 1998-2000 APPROACH patients undergoing PCI with conventional stents. To increase the precision of our estimates for long-term survival after specific events, data on death rates between six months and 4 years were taken for patients in each of the predefined health states, stratified by age and diabetes, from the expanded cohort of APPROACH patients undergoing conventional stenting from 1995-2000. Given the small numbers of patients in some of the age and diabetes stratified health states, a Cox proportional hazard model was used to derive hazard ratios (relative risks) for mortality in specific patients groups (under 65 with diabetes, 65-75 with diabetes, 65-75 no diabetes, >75 with diabetes, >75 no diabetes) during the subsequent three and a half years, compared with the death rate for patients under the age of 65 without diabetes. The 6-month risk of death in the under 65 non-diabetic subgroup was calculated by converting, using the rate-risk conversion formula, the

three and half year rate of death observed in the under 65 non-diabetic subgroup. To account for increasing age-related mortality, after 4 years, the hazard ratios for each of the patient subgroups was multiplied by the age-specific increment in mortality risk of the Canadian population (42).

2.4 Health-Related Quality of life (HRQOL)

To date, the RCTs of sirolimus-eluting stents have not reported any impact on the mortality rate other than possibly that associated with eliminating the immediate mortality risk associated with undergoing a second procedure (ie: CABG, repeat PCI, or repeat catheterization). The main benefit of sirolimus-eluting stents, therefore, may be seen as avoiding the costs associated with repeat procedures and possibly improved HRQOL since repeat procedures may be associated with a reduction in a patient's quality of life (4).

HRQOL estimates were determined from the APPROACH 1998-2000 stented PCI cohort, based on self-reported EUROQOL EQ-5D index scores at one year after catheterization. HRQOL estimates were available for 1,954 patients. Based on the published validated algorithm (10), mean utility scores were calculated for patients in each subgroup. It has been reported that patients undergoing repeat procedures report similar reductions in HRQOL regardless of the type of procedure that they have undergone; preliminary analyses found similar results in our cohort. Thus, the procedure specific scores were combined to produce a "combined event" utility score applied to each of the clinical event states described above. Given that it seems unlikely for long term HRQOL to be impaired by a short-term procedure, patients who undergo a second procedure received the "combined event" utility score for the first year only in our base case analysis. After year one, HRQOL for patients in all of the health states were assumed to be equal. The impact of this assumption was tested in a sensitivity analysis.

2.5 Costs

Data on costs were obtained from Alberta Health and Wellness (the sole payer for hospitalisation and physician care in Alberta) for the 1995-1997 APPROACH cohort. Costs were categorized as hospitalisation, ambulatory care, home care, physician claims and medication costs and were available to March 2001. APPROACH patients were merged to the hospitalisation data based on their personal health number (PHN) and the index PCI procedure data recorded in APPROACH. If the PHN matched, the hospitalisation date +/- 7 days was then matched to the admission and discharge date recorded in APPROACH. Only those patients that were successfully matched to an index PCI hospitalisation record were included in the subsequent annual costs (N=1824).

Ambulatory care costs were restricted to cardiac care. All available home care, physician claims and drug costs were included. During the first year, costs were calculated for those that are event free for each age and diabetic subgroup. The procedural costs of CABG, repeat PCI and repeat catheterization with no follow-up procedure were included as transitional costs and remain constant for each subgroup. In the post-states for the same time period as above, the costs were calculated for each health state overall regardless of age and diabetic status. This modeling approach was used to avoid overly skewed costs in the smaller subgroups. Costs for subsequent years for all health states were calculated by age and diabetic subgroup regardless of health state.

Costs were converted to 2002 dollars by applying a yearly inflation factor calculated from the consumer price index (43). Given that we see a trend of fairly constant costs during year 3 and 4, we assumed that yearly costs remained constant after the 4-year period, an assumption that was tested in sensitivity analyses.

2.6 Efficacy of sirolimus-eluting stents

Four clinical trials were identified by a comprehensive review of the published literature on sirolimus-eluting stents. The reduction in the restenosis rate due to sirolimus-eluting stents was estimated by combining, using meta-analysis, the results of the RAVEL and SIRIUS studies (5-8). The RAVEL study included 238 patients with unstable and stable angina, while the SIRIUS study had broader inclusion and exclusion criteria and enrolled 1510 patients in the three arms. Given that we are interested in the effectiveness of sirolimus-eluting stents, our analysis focused on the reduction in "clinical restenosis"; those procedures that resulted from symptomatic presentation as opposed to procedures undertaken for asymptomatic angiographic restenosis. Since all studies had protocol angiograms, we concluded from the published results that 17 events in the conventional stent arm (14.4% restenosis rate) and no events in the sirolimus arm were considered to be "clinical restenosis" in the RAVEL study, and that 87 events in the conventional stent arm (16.6% restenosis rate) and 21 events in the sirolimus arm (3.9% restenosis rate) were due to "clinical restenosis" in the SIRIUS study. C-SIRIUS reported 9 clinically driven events in the conventional arm (18% restenosis rate) and 3 events in the sirolimus arm (6% restenosis rate). Similarly, E-SIRIUS reported 40 events in the conventional stent arm (22.6% restenosis rate) and 7 in the sirolimus arm (4% restenosis rate) due to clinical restenosis (8).

Data from the four trials were pooled. A forest plot (Figure 5) was produced to visually assess the heterogeneity of the 4 trials. Heterogeneity of the trials determines which type of model, random or fixed, to apply when combining the results or indeed if the results of various trials should be combined (44).

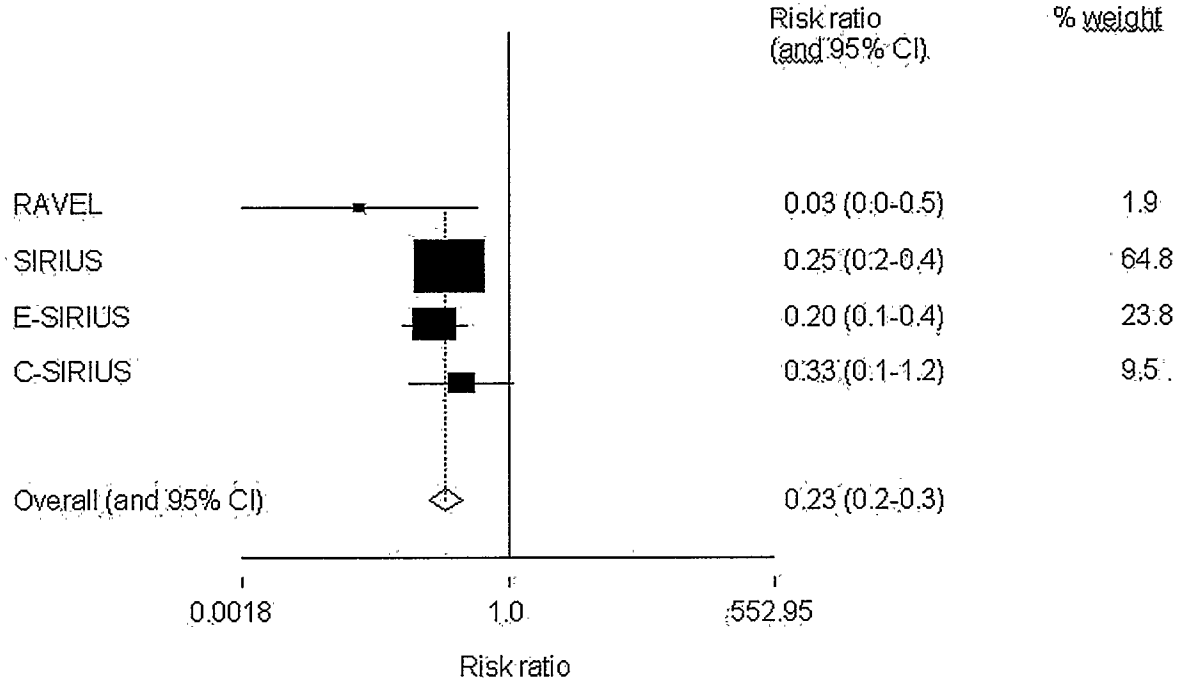


Figure 5. Forest plot of randomized controlled trials included in meta-analysis

Essentially, homogeneity implies that the results of all trials considered report a consistent treatment effect (i.e. all trials report a similar positive, negative or neutral effect of the treatment, though the magnitude of the effect across trials can vary). If the trials are very heterogeneous, whether pooling the results from all trials is appropriate should be considered. In some cases, instead of reporting pooled results, an investigation into the differences between the trials should be presented. If it is deemed appropriate to pool the results, a random effects model should be applied to take into account the variability seen in the treatment effect across the trials. In our case, the test for heterogeneity produced a non-significant χ^2 statistic ($p=0.38$). However, we applied a DerSimonian- Laird random effects model due to the small number of trials and the in-balance seen between the trials.

2.7 Cost of sirolimus-eluting stents

We estimated the cost, based on the published list price, for a sirolimus-eluting and conventional stents as CAN$2900 and CAN$500, respectively. Based on the number of conventional stents used per patient in the APPROACH cohort, an average of 1.4 stents per PCI was modeled in the base case analysis. The cost of care during the initial hospitalisation was otherwise assumed to be equal to that of patients undergoing conventional stenting. Future health care costs for patients receiving sirolimus-eluting stents are likely to be reduced as a result of fewer second procedures, the cost of which was assumed to be equal for patients originally treated with a conventional and sirolimus-eluting stents.

2.8 Economic Analysis

We adopted a health care payer perspective within this study. The outcomes considered are costs and QALYs over a patient's lifetime. Costs and outcomes were discounted using an annual rate of 3 percent following the Gold panel recommendation.

Costs are presented in 2002 CAN dollars. SAS, version 8.1, was used for the data modeling. All decision analysis modeling was done in DATA 4.0.

2.9 Sensitivity/Scenario Analysis

To examine the impact of the various assumptions required to run the Markov model, various scenario and sensitivity analyses were completed. The results are described as "sensitive" if the cost per QALY changes substantially while varying the estimates within plausible ranges. The 30-day mortality rates associated with second procedures were varied by a relative amount of +/-50% to account for different rates of mortality that might be seen in other centres/countries (45-47). To account for practice variations in the preference for use of PCI or CABG to treat patients with clinical restenosis, the probability of receiving a CABG, as opposed to a PCI, was varied by +/-25%.

The effect of varying the baseline estimate of clinical restenosis seen with conventional stents to reflect the restenosis rates reported in the individual RCTs and in other clinical settings was also assessed by applying the clinical restenosis rate reported in RAVEL and subsequently the combined arms of SIRIUS (5-8). Additionally, various patient subgroups are at higher risk of restenosis, particularly those with complex high-risk lesions. Unfortunately, there is no standard definition of a "complex" lesion and within our database we were unable to compute the risk of restenosis specifically in those patients with complex lesions. Thus, we varied the clinical restenosis rate by up to 100% to simulate a clinical restenosis rate that may be seen in patients with more complex coronary lesions (48).

Since the introduction of sirolimus-eluting stents is quite recent, there are limited data available on how the introduction of sirolimus-eluting stents has affected practice patterns and re-intervention thresholds. To simulate one of the possible variations in

practice patterns due to the widespread use of drug-eluting stents, we considered a scenario with all patients undergoing a second PCI being implanted with a sirolimus-eluting stent. Additionally, we considered a scenario where only patients initially implanted with a sirolimus-eluting stent were implanted with a sirolimus-eluting stent if they undergo a second PCI: patients initially implanted with a conventional stent were implanted upon a second PCI with a conventional stent.

The extent to which the occurrence of catheterization with no subsequent revascularization would be reduced by sirolimus-eluting stents is uncertain. In the base case analysis, we assumed that only 49.5% of catheterizations with no subsequent restenosis were potentially preventable (to which we applied a relative risk of 0.23 for sirolimus-eluting stents). We compared this to two different scenarios, one where sirolimus-eluting stents would not prevent repeat catheterizations with no revascularization (relative risk of 1.0) and one where all repeat catheterizations with no subsequent revascularization were considered "potentially preventable" with sirolimus-eluting stents (a relative risk of 0.23 applied to 100% of the repeat catheterizations with no repeat revascularization).

In the base case, a HRQOL decrement was applied for one year to the post-procedure health states. To assess how this assumption affected the results, scenarios with a sustained HRQOL decrement (ie: patients with a second procedure maintained the lower HRQOL score for their entire lifetime) and a scenario where no HRQOL decrement was associated with a procedure were also evaluated. The latter is equivalent to an analysis considering life years gained instead of QALYs.

We also determined the cost per QALY of sirolimus-eluting stents in patients with different clinical indications for PCI such as stable/unstable angina, acute myocardial infarction and emergent acute myocardial infarction by varying the clinical event and 30-

day mortality rates after second procedures that were observed in patients with the above noted indications for the index PCI. The APPROACH cohort was divided into subgroups based on the above noted clinical indications. Subsequently the event rates, 7-day mortality rates and 30-day procedural mortality rates were calculated within each subgroup. This analysis did not consider age and diabetic subgroup.

The impact of varying the cost of sirolimus-eluting stents by 50% was also evaluated.

Finally, recognizing that our source data for this economic evaluation were obtained from a Canadian cardiac registry, we completed supplementary analyses in which specific assumptions were modified to reflect the US health care situation. Consistent with reports comparing the cost of health care between Canada and the United States, health care costs were increased to 150% (49). Restenosis rates were increased to reflect published US estimates and the apparent lower threshold for reintervening with a repeat revascularization procedure after an initial PCI procedure; CABG and PCI 30-day mortality rates were varied to reflect published US estimates (50).

3. Results

3.1 Cohort Characteristics

Table 1 displays the baseline characteristics, clinical outcomes, including mortality rates and HRQOL, and costs of care for the APPROACH cohort of conventionally-stented patients. The mean age of the overall cohort was 61.5 years and 18% of the cohort reported diabetes. As expected, mortality rates increased with age and diabetes status. EQ-5D index scores were higher for event-free patients (0.85), compared with patients who have a second procedure to manage restenosis (0.77, $p<0.001$).

Table 1. Baseline characteristics of APPROACH patients who were treated with a bare metal stent, including mortality and resource use

	Overall Cohort	Age groups			Diabetes Status	
Baseline Characteristics (1998-2000 Cohort)	*N = 7334*	< 65 *N=4439*	65-75 *N=2005*	> 75 *N=900*	No Diabetes *N= 6015*	Diabetes *N= 1319*
Mean age (SD)	61.5 (11.6)	53.9 (7.7)	70.2 (2.8)	79.6 (3.2)	61.2 (11.7)	63.0 (11.2)
Male Sex (%)	70.9	80.9	68.3	58.2	67.7	76.2
Diabetes (%)	18.0	16.7	20.2	19.4	-	-
Indication						
Acute Myocardial Infarction (%)	46.9	48.6	43.2	46.7	47.2	45.7
Unstable Angina (%)	27.3	25.5	26.1	33.1	26.9	29.3
Stable Angina (%)	19.9	20.1	20.1	14.2	19.9	20.1
Use of GPIIB/IIIA Inhibitors (%)	46.4	47.6	46.0	41.1	46.2	46.9
Event rates						
7-day mortality after initial PCI (%)	1.1	0.6	1.2	3.1	1.0	1.4
Repeat Catheterization with Revascularization for restenosis within 12months of Index PCI (%)	8.2	8.5	8.1	7.0	7.8	9.9
Proportion of revascularized patients with CABG as second procedure (%)	28.0	21.9	32.1	17.4	28.1	27.9
Repeat Catheterization with no revascularization performed (%)	12.2	12.6	11.6	11.2	11.9	13.5
Mortality in first 6 months (%)	1.4	0.8	1.8	3.6	1.3	1.7
For patients with Repeat catheterization:						
30-day mortality post CABG (%)	3.1	1.8	3.6	5.6	2.9	3.8
30-day mortality post repeat PCI (%)	1.4	0.7	1.8	3.3	1.2	2.0
30-day mortality post repeat cath.with no revasc. performed (%)	1.8	0.9	2.0	4.7	1.5	3.0
Subsequent annual mortality (%)*	1.4	0.7	2.0	3.4	1.5	3.1
EQ-5D utility scores (1998-2000 Cohort)						
Event**	0.77	0.77	0.79	0.74	0.78	0.72
Event free	0.85	0.86	0.84	0.78	0.86	0.78
Mean Costs in 2002 CAN dollars (IQR) (1995-1997 Cohort)	*N =1812*	*N=1134*	*N=508*	*N=170*	*N= 1551*	*N=261*
Year 1						
Event-free	5195 (2079-5733)	4297(1773-4648)	6168(2737-6515)	8047(3400-8787)	4948(2055-5379)	6736(2459-7426)
CABG***	32009(20750-40072)	-	-	-	-	-
Repeat PCI***	15569(8870-17343)	-	-	-	-	-
Repeat Cath. without revasc.***	12591(5603-15114)	-	-	-	-	-
Year 2	3226 (401-3142)	2634 (244-2376)	4224 (1136-4229)	4188 (1290-4560)	2860 (371-2903)	5398 (778-5173)
Year 3	2337 (336-2525)	1819 (211-1957)	3354 (977-3144)	2756 (911-3557)	2141 (306-2355)	3502 (809-3628)
Year 4	1775 (231-2189)	1410 (158-1672)	2295 (756-2762)	2662 (766-2820)	1651 (223-2031)	2516 (293-2938)

*estimated within our model by multiplying the baseline mortality by the appropriate Cox proportional hazard ratio

**defined as need for repeat catheterization, whether revascularization occurred or not

***Year 1 costs are estimated by health state. Subsequent years are estimated based on age and diabetic status

3.2 Cost-utility Analysis

The results of the baseline analysis are presented in Table 2. The cost per QALY gained by implanting a patient with a sirolimus-eluting stent, compared with a conventional stent, was CAN $58,721. The use of sirolimus-eluting stents was more economically attractive in older patients and in patients with diabetes, due in part to a higher risk of mortality associated with second procedures in these patient subgroups (Table 2).

Our analysis was robust to plausible alternative scenarios (Figure 6). However, when we considered a scenario where sirolimus-eluting stents do not reduce the frequency of repeat catheterizations with no revascularization, the cost per QALY gained rose to $108,340. When we completed an analysis considering life years not QALYs a cost of $55,890 per life year gained resulted.

The results of the other one-way sensitivity analyses are shown in Table 3. The cost per QALY of sirolimus-eluting stents varied with the estimate of effectiveness; when the efficacy estimate of sirolimus-eluting stents was varied within a plausible range (relative risk ranging from 0.01 to 0.55), the cost per QALY ranged from $39,777 to $119,280 (Table 3). When the baseline clinical restenosis rate was increased by 50% and subsequently by 100% the cost per QALY improved to $33,723 and $21,312, respectively. The cost per QALY also improved when the cost of sirolimus-eluting stents was decreased by 25% ($35,082 per QALY) or 50% ($11,443 per QALY).

Figure 7 presents the results of a scenario analysis simulating more closely a US health care setting. When the costs of care were increased by 150% and the restenosis rate was varied, the cost per QALY gained decreased to CAN $23,831. Additionally, when considering 30-day mortality rates associated with CABG and PCI that have been reported in US settings, the cost per QALY gained decreased to $17,741.

Table 2. Cost-utility of sirolimus-eluting stents, overall and based on age and diabetes status

Group of Patients	Incremental Cost * ($CAN)	Incremental Utility (QALY)	Incremental cost-utility ratio ($CAN/QALY)
Overall	2,500	0.04	58,721
Age < 65	2,600	0.04	72,464
Age 65-75	2,400	0.05	47,441
Age > 75	2,600	0.07	40,129
No Diabetes	2,500	0.04	63,383
Diabetes	2,400	0.06	44,135

* The incremental cost is the average additional cost per patient over the patient's lifetime (discounted at 5% per year) associated with implanting a sirolimus-eluting stent compared to implanting a conventional bare metal stent. The costs considered include the immediate cost of the stent and procedure, and future health care costs incurred by patients in the two treatment strategies. Incremental utility is the average quality-adjusted life year gained per patient. The incremental cost-utility ratio is the additional expenditure required to gain one quality-adjusted life year.

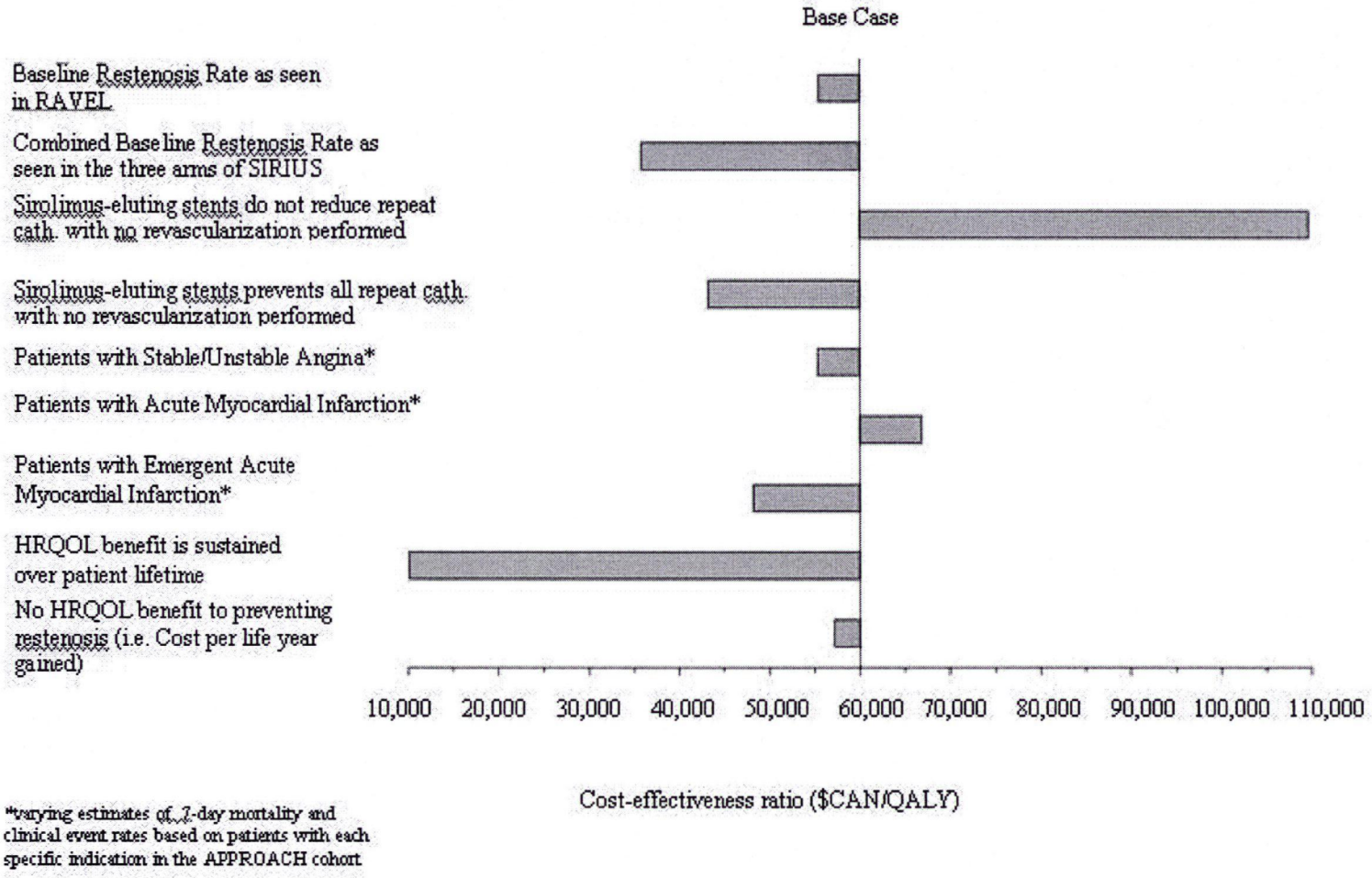


Figure 6. Scenario analyses

Table 3. Sensitivity Analysis

Variables used in analysis	Incremental Cost per QALY Gained ($ CAN/QALY)
Base Case	58,721
30-day mortality after second procedure	
Increased by 50%	40,838
Decreased by 50%	106,445
Procedure rates	
Increased CABG rates by 25%	55,379
Decreased CABG rates by 25%	62,309
Clinical restenosis rates (base case – 14.2%)*	
Decreased by 25% (10.7%)	83,801
Increased by 50% (21.3%)	33,723
Increased by 100% (28.4%)	21,312
Assuming patients undergoing a second PCI are implanted with a sirolimus-eluting stent	56,187
Difference in EQ-5D scores between event and event free groups	
Increased by 50%	55,169
Decreased by 50%	62,760
Subsequent mortality	
Upper 95% CI limit	62,507
Lower 95% CI limit	55,398
Efficacy of Sirolimus-eluting stents	
Relative risk resulting from meta-analysis using a fixed effects model (RR=0.21)	56,996
Lower 95% CI in RAVEL (0.01)	39,777
Upper 95% CI in SIRIUS (0.55)	119,280
Cost of Sirolimus-eluting stents	
Increased by 25%	82,359
Reduced by 25%	35,082
Reduced by 50%	11,443
Average number of stents per procedure	
Increased by 25%	78,284
Decreased by 25%	39,157
Discount rates	
No discounting	44,691
Discount rate of 5%	68,573
Discount rate of 6%	73,582

* Restenosis rate (PCI/CABG) of 8.2% combined with a repeat catheterization with no subsequent revascularization rate of 12.0% of which 49.5% were considered preventable (8.2% + 6.0% = 14.2%)

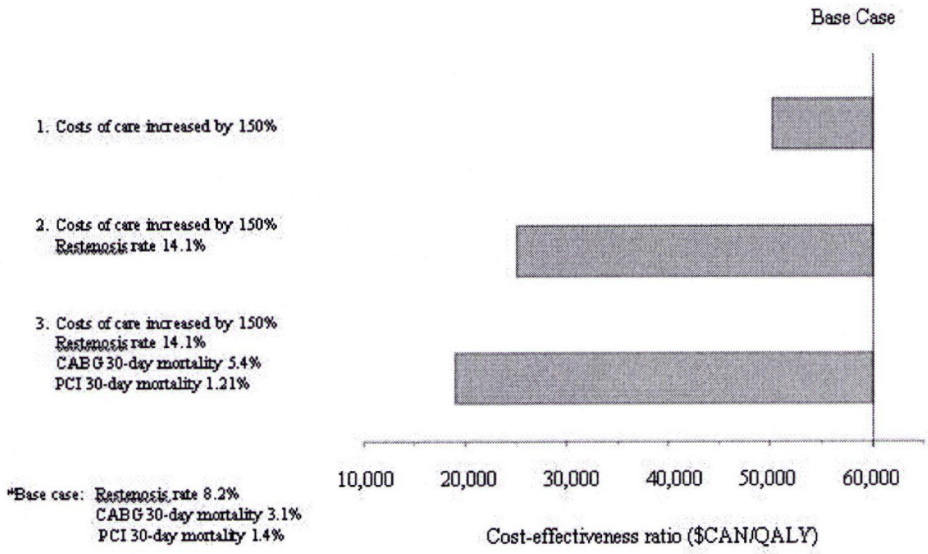


Figure 7. US scenario analyses

4. Discussion

We estimated the cost per QALY gained with the implantation of sirolimus-eluting stents in all patients undergoing PCI and for subgroups of patients based on age and the presence of diabetes. In the base case, the overall cost per QALY gained was $58,721 with the cost per QALY varying from $40,129 to $72,464 among the age and diabetes subgroups. The use of sirolimus-eluting stents appeared more economically attractive in older patients and in those with diabetes, due to a combination of factors, the most important of which was the higher 30-day mortality rates associated with second procedures in these subgroups; this finding is consistent with the results from a preliminary short-term cost-effectiveness analysis performed in the US setting (51). When the clinical restenosis rate was increased by 50% and 100%, risks that may be seen in patients with more complex lesions (3), the cost per QALY was reduced to $33,723 and $21,312, respectively.

It seems reasonable to consider the cost per QALY associated with use of sirolimus-eluting stents in relation to other commonly funded therapies. Published estimates for coronary artery bypass surgery range from CAN $13,200 to $100,000 per QALY gained (52-54), cardiac defibrillators when implanted in cardiac arrest survivors with a low ejection fraction are an estimated CAN $75,000 per QALY gained (52;55), and intensive glycemic control in patients with Type 2 Diabetes is an estimated $41,384 per QALY (56). Our analysis shows the cost per QALY of sirolimus-eluting stents (CAN $58,721) is comparable with these accepted therapies, though higher than many economically efficient medical therapies (i.e. intensive hypertension control in patients with Type 2 Diabetes (-$1959 per QALY))(56).

Our analysis was sensitive to the estimate considered for the efficacy of the sirolimus-eluting stent, suggesting more research is needed into the effectiveness of these stents at preventing "clinical restenosis". In addition, our analysis was sensitive to whether sirolimus-eluting stents prevent repeat catheterizations that are not followed by revascularization. When we assumed that such procedures were not prevented by sirolimus-eluting stents, the cost per QALY increased to CAN $108,340.

Since we could not derive actual outcomes associated with complex lesions from our patient cohort, our sensitivity analysis presented a scenario with estimated clinical restenosis rates similar to those reported for patients with complex lesions (57). The cost per QALY improves to $21,312 when only patients with complex lesions are considered. This raises the possibility of selected use of sirolimus-eluting stents for only those patients with complex lesions – a strategy that anecdotal reports suggest may already be operating in some centres. If such a policy were to be formally implemented explicit criteria for defining "complex" lesions would need to be derived and also possibly audited.

Consistent with the 2006 CADTH Economic evaluation guidelines, our analysis considered a payer's perspective. This seems reasonable for several reasons including the fact that significant methodological controversy exists in the measurement of indirect costs. Moreover, in our case, the inclusion of indirect costs (i.e., taking a societal perspective) would have been unlikely to change the results of our analysis since the difference in indirect costs between the two treatment arms would likely have been small. For instance, although the lost labour costs associated with a second procedure would result in a difference in indirect costs between the two arms, since our cohort had a mean age of 61.5 years, most patients would have had minimal lost labour costs.

If all patients were contributing to the work force (an unrealistic assumption), assuming a hypothetical cohort of 100 patients and 1 month of lost work for each second procedure, the conventional stent arm would be associated with approximately 10 months of additional lost labour (approximately 14% of patients would undergo a second procedure when implanted with a conventional stent compared to 4% when implanted with a sirolimus-eluting stent). Assuming a wage of $3000 per month the additional cost would be $300 per patient, which represents < 12% of the total incremental direct cost for the sirolimus eluting stent strategy, compared to a conventional stenting strategy. As such, considering a societal perspective would have been unlikely change the results of our analysis.

Drug-eluting stents are a promising technological advance in reducing restenosis after PCI. However, given the large potential population of eligible patients, and the high cost of sirolimus-eluting stents, it is important to consider their impact on both clinical outcomes and costs. These data will inform decisions on reimbursement, and the selection of patients in whom the use of sirolimus-eluting stents is most efficient. The use of sirolimus-eluting stents in PCI patients, particularly in patients who are at higher risk of restenosis or a high risk of mortality if a second revascularization procedure were to be required, is associated with a cost-effectiveness ratio similar to other accepted medical therapies. Their use is, of course, associated with an incremental cost, and in the absence of a budget increase will require resources from other health care sectors.

E. BUDGETARY AND CLINICAL IMPACT ANALYSIS

GLOBAL SUBSTUDY OBJECTIVE: To explore an alternative method of presenting the results of the previously described economic evaluation, rather than the usual cost per QALY rubric, in an attempt to assist decision-makers with the decision as to whether, and for whom, to fund sirolimus-eluting stents

1. Background

1.1 Rationale

As described in the previous chapter, we performed a traditional economic evaluation comparing sirolimus-eluting and bare metal stents in patients undergoing percutaneous coronary intervention (PCI). Overall, for each patient implanted with a sirolimus-eluting stent, there was, on average, an incremental cost of $2,500 and an incremental effectiveness gain of 0.04 quality adjusted life years (QALY) resulting in an overall incremental cost per QALY of CAN$58,721. It should be noted, though, that the cost per QALY varied by patient subgroup in our analysis; the use of sirolimus-eluting stent was most economically attractive in patients with complex coronary lesions ($21,312 per QALY). This finding was consistent with the results of a recently published British economic analysis comparing drug eluting stents and bare metal stents, which noted the cost per QALY to be £15,000 (£1=CAN$2.27) for non-diabetic patients with long coronary lesions (58).

But what do these cost per QALY values represent, and what do they mean? For many reasons, health care decision-makers, and clinicians, may have difficulty applying this traditional cost per QALY framework within their everyday decision-making. In this paper, we explore an alternative method of presenting the results of our economic evaluation, rather than the usual cost per QALY rubric, in an attempt to assist decision-makers with the decision as to whether, and for whom, to fund sirolimus-eluting stents. We

then discuss several issues that decision-makers and providers may wish to take into consideration when making such funding decisions.

1.2 The Cost of funding Sirolimus-eluting Stents

Drawing on the Alberta Provincial Project for Outcomes Assessment in Coronary Heart disease (APPROACH) database, we are able to project the potential budgetary implications of funding sirolimus-eluting stents. In 2003, 2772 stented index PCI procedures were performed in Alberta. An average of 1.4 stents per procedure were used each associated with an immediate additional upfront expenditure of $2400 ($2900 for a sirolimus-eluting stent compared to $500 for a bare metal stent). Therefore, if all patients in Alberta were to have sirolimus-eluting stents, the cardiac stent budget would increase by CAN $9.3 million (M). Projecting this to all of Canada (approximately 20,000 PCIs were performed in 2000), an additional $67.2 M expenditure would be expected (47).

2. The Health benefits from funding Sirolimus-eluting Stents

2.1 Funding sirolimus-eluting stents for all patients

We examine the implications of funding sirolimus-eluting stents in Table 4. Firstly, we highlight a strategy of funding these stents in all patients in terms of the impact on clinical outcomes, expressed as the number of deaths and second procedures (PCI, CABG and repeat catheterizations with no subsequent procedure) expected in year 1. It is important to note that while the existing clinical trials comparing drug-eluting and bare metal stents have shown no difference in short-term patient survival (5-8), our model assumes that therapies which prevent clinical restenosis, thereby avoiding the need for revascularization procedures which carry a definite mortality penalty, will reduce mortality to a limited extent.

Table 4. Projected Clinical Outcomes and Budget Impact of Funding Sirolimus-eluting Stents in Alberta

Strategy	Upfront cost of stent	Averted cost due to reduction in second procedures	Overall cost	Incremental cost	Expected deaths in year 1 (N=2772)	Incremental deaths in year 1	Second procedures in year 1	Incremental second procedures in year 1
Do not fund	-	-	33.6 M	-	67 (2.4 %)	-	394	-
Fund for all (N=2772,100%)	9.3 M	2.5 M	40.4 M	+ 6.8 M	61 (2.2%)	- 6	93	- 301
Fund for patients with Diabetes (n = 579, 21%)	2.0 M	0.6 M	35.0 M	+ 1.4 M	65 (2.3%)	- 2	276	- 118
Fund only for patients > age 75 (n = 437, 16%)	1.5 M	0.4 M	34.7 M	+ 1.1 M	65 (2.3%)	- 2	353	- 39
Fund only for patients with complex lesions (n = 693, 25%)	2.3 M	1.9 M	34.0 M	+ 0.4 M	62 (2.2%)	- 5	237	-157

If sirolimus-eluting stents were funded for all PCI patients in a province like Alberta, 6 deaths and 301 second revascularization procedures would be avoided corresponding to a number needed to treat (NNT) of 462 to prevent one death and a NNT of 9 to prevent one second procedure. The NNT associated with death indicates that, unlike some therapies that are "cost-effective", sirolimus-eluting stents have relatively little impact on mortality. Their health benefits are predominantly related to avoidance of a second procedure and thus improved quality of life.

2.2 Alternative scenarios: Restricted funding for Sirolimus-eluting Stents

Given the large budget impact, provinces and/or health regions may consider funding these stents for selected patients, who may be at higher risk of clinical restenosis or who, if they develop restenosis, may be at higher risk of dying during the subsequent revascularization procedure (i.e. PCI or CABG). In fact, such a strategy has been advocated by the National Institute for Clinical Excellence (NICE) in the United Kingdom, who released the following guidance to the National Health Service (NHS) (the public provider of health care in the UK): "the use of either a Cypher (sirolimus-eluting) or Taxus (paclitaxel-eluting) stent is recommended in PCI for patients with symptomatic coronary artery disease, in whom the target artery is less than 3mm in calibre (internal diameter) or the lesion is longer than 15mm"(40). We model the potential implications, both on costs and clinical outcomes, of restricting the use of drug-eluting stents to selected patient groups using data from a cohort of APPROACH patients with symptomatic coronary artery disease.

Given that patients with diabetes and those over the age of 75 have higher baseline risks of clinical restenosis and mortality, Table 4 presents the impact of funding strategies that restrict the use of sirolimus-eluting stents to patients with these characteristics.

Restricting funding to patients with diabetes would cost an additional $1.4 M (compared to $6.8 M if all patients were treated), avoid 2 of 6 of the potentially avoidable deaths (33%) and avoid 118 of 301 (39%) potentially preventable second procedures. Similarly, restricted funding for those over the age of 75 would cost an additional 1.1 M; prevent 2 deaths but only 39 (13%) second procedures. Perhaps most interestingly, a funding strategy confining sirolimus-eluting stent use to patients with complex coronary lesions, using type "C" of the ACC/AHA classification scheme as one indicator of complexity (59), prevents 5 of the 6 potentially avoidable deaths (83%) and 157 of 301 the preventable second procedures (52%) for only an $0.4 M increase in expenditures (Table 4). The role of lesion complexity is further supported by a recent publication from the SIRIUS investigators reporting lower costs per avoided procedure when the vessel diameter is less than 2.5 mm and/or lesion length is greater than 20 mm. As noted, our findings are consistent with the results of the UK economic analysis noted above (58), the results of which were the basis of NICE's recommendation to the NHS

3. Away From Cost per QALY Rubric

3.1 Opportunity Costs

Although the cost per QALY for the use of sirolimus-eluting stents overall (CAN$58,721) is within what many would consider an "acceptable" range (39), the use of sirolimus-eluting stents, which are very expensive at current quotations (CAN $2900) (9), creates a large budgetary impact. More importantly, the "acceptable" range of $20,000 to $100,000 per QALY is arbitrary and not necessarily consistent with basic economic principles. For instance rather than considering the cost per QALY in isolation, it is more important to consider the opportunity cost associated with the adoption of a new technology (60). In fact, many have suggested that funding for all agents considered to be

"cost-effective", by conventional criteria, is not sustainable within the current Medicare system (61;62).

The cardiac services portfolio within many provinces is administered by a centralized decision-making body, such as the Cardiac Care Network in Ontario or the Province Wide Services Committee in Alberta. As such, the budget for the majority of procedural cardiac care is allocated from one source. Within that budget, one of the goals is to achieve the maximum health benefits. Within this system, assuming that the cardiac services budget remains constant, funding sirolimus-eluting stents will decrease the funds available to support other elements of cardiac care that are currently funded. It would only be reasonable to fund sirolimus-eluting stents if the health benefits from funding these stents exceed the benefits of the intervention(s) selected to lose funding. If additional resources are available, one must still ask whether switching to sirolimus-eluting stents constitutes the optimal use of marginal funds. An example of a competing cardiac treatment also currently being considered is the use of implantable cardiac defibrillators (ICD) in patients at high risk of sudden cardiac death who have left ventricular ejection fraction of less than 35%. Recent economic evaluations have suggested that their use in this setting is associated with a cost per life-year gained between $40,000 and $110,000 depending on the patients' risk of sudden death (63;64).

To this point, we have only considered allocation of resources for cardiac care. Taking a broader perspective, it is important to note that funds allocated to sirolimus-eluting stents (assuming the cardiac care budget is increased to cover the additional expenditure) reduces funds available to other health care areas (e.g., chemotherapy treatments for cancer patients or public health expenditures). Even more broadly, increases in the health care budget decreases funds available for other publicly funded sectors (i.e.,

Education, Transportation, Social assistance). Again, the opportunity cost of funding sirolimus-eluting stents must be considered.

3.2 Equity

When adopting restrictive criteria for reimbursement of new technologies, it is important to also consider the impact of such strategies on equity. For instance, what about the patients who will not receive the new technology? Do the efficiency gains that result from directing the new therapy to patients who have a greater need and ability to benefit from the sirolimus-eluting stent outweigh the potential equity concerns (65)? There is no universally accepted definition of equity. Some define it as equal treatment for all; others have put forth the concept of equal treatment for equal need, sometimes qualified to mean equal treatment for equal need for those who have equal capacity to benefit (66). Depending on the definition adopted, restricted funding strategies need not violate the principle of equity. For example, restricting funding to patients at highest risk of clinical restenosis or death following clinical restenosis (i.e. those who would benefit most from the new technology), could assist cardiac services programmes in maximizing clinical benefit within their allotted budget. This strategy may enable unused funds to be spent on other cost-effective therapies.

An optimal funding strategy would minimize adverse clinical outcomes in patients who will not receive the new technology whilst minimizing total expenditures. As such, in Table 5, we consider what we are giving up, in health outcomes, and the savings (i.e. costs avoided) that result from not funding the new technology in all patients.

Table 5. Implications of Restricted Funding Strategies; What Would Happen to Patients in Alberta in Whom Sirolimus-eluting Stents are not Placed

	Number of patients not funded (%, N = 2772)	Incremental Costs Averted	Preventable deaths occurring	Preventable second procedures occurring
Fund for all	0	0	0	0
Fund for patients with Diabetes	2193 (79%)	5.4 M	4	183
Fund only for patients > age 75	2335 (84%)	5.7 M	4	262
Fund only for patients with complex lesions	2079 (75%)	6.4 M	1	144

3.3 What else matters when making funding decisions?

When considering new technologies, it is clear that the cost per QALY of the therapy is not the only element considered by decision-makers. There is a growing literature attempting to identify other characteristics that should be considered. These include 1) whether an intervention is immediately life saving and less so the expected gain in life expectancy, 2) the impact on quality of life, 3) the number of people eligible for treatment, 4) the age of the potentially treatable patients (younger versus older), 5) whether the treatment was for people with good or poor underlying baseline health, 6) the likelihood of the treatment being successful, and 7) its impact on equality of access to therapy (67;68).

Applying this checklist to our proposed case, one might argue that funding of sirolimus-eluting stents is somewhat attractive given that the majority of these patients are middle-aged, are likely to have a lower quality of life if not treated (4) and are highly likely to recover from the procedure (although it could be argued that the likelihood of recovery is also quite high with conventional stents). However, when comparing sirolimus-eluting stents to, for example, ICDs, another competing innovation in cardiac care, the case for sirolimus-eluting stents might be considered less attractive. Both technologies are aimed at similar patients and both are associated with a high cost per QALY. However, the type of health gains are very different. The gains associated with ICDs are more notably in lives saved as opposed to quality of life gains (quality-adjusted life years) for sirolimus-eluting stents.

3.4 Review of new devices and technology within Canada: The Current state

Currently, while there is considerable health technology assessment capacity in Canada, there is no widely accepted or transparent set of criteria for deciding which innovations should be funded, and in what circumstances. For pharmaceuticals, the

Common Drug Review (CDR) has recently been mandated to review new drugs and provide formulary listing recommendations to participating drug plans in Canada. With no such review body for new device technologies in existence, there is diversity across the country in their adoption and implementation. In fact, the decision to cover new devices is often made at a local level in a non-systematic fashion. An organized approach could aid local decision-makers by providing guidance to those responsible for the implementation of new technologies which would make decisions more transparent and evidence-based. Given different competing demands for funding in different jurisdictions and contexts, the decisions would still need to be made locally, taking into account the notion of opportunity costs. Several approaches have been proposed to assist with such local health care decision-making, one of the most common being programme budgeting and marginal analysis (69).

Another factor that distinguishes device-funding decisions from pharmaceutical funding decisions is that while non-funded drugs can still be purchased 'off-formulary' by informed patients, non-funded devices may be difficult to purchase independently. This heightens the complexity of device funding decisions; equity considerations must be balanced against the rights of individuals to seek optimal care.

Currently, the Canadian health care system is a "price-taker" with heavy reliance on competition within the market place as a means to improve medical device quality and to provide downward cost pressure. Purchase prices of new technology are set by the company marketing it and purchasers have, by and large, made their buying decisions assuming that there is only limited bargaining room available. Another potential advantage of having a central organized body reviewing new innovations could be to shift the health care system into a "price-setter" role that both creates a common front for negotiating and purchasing, and signals to innovators that if they want the health care system to adopt their

technology, it may mean accepting a price that produces an "acceptable" cost-effectiveness ratio.

4. Future considerations

It is important to note that the economic impact of sirolimus-eluting stents may be mitigated by price reductions in the future; indeed, anecdotal evidence suggests that market competition with the availability of other drug coatings has softened prices and some hospitals may currently be paying less for sirolimus-eluting stents than is quoted here. In fact, our sensitivity analyses yielded significantly more attractive costs per QALY when stent costs were reduced by 25 to 50%, something that may in fact already be occurring in the Canadian market. Related, is that all of our analyses and projections are based on an economic evaluation of sirolimus-eluting stents. Paclitaxel-eluting stents are a related innovation and early data suggests relatively comparable costs and benefits. Though the cost per QALY may differ somewhat, the economic considerations will remain the same; is the benefit worth the cost?

Another issue that can not be adequately addressed with our historical patient cohort is how the availability of sirolimus-eluting stents may change the overall referral and decision-making process. With increasing confidence in sirolimus-eluting stents, there is likely to be a channeling of patients previously destined for surgery or medical therapy towards PCI – a phenomenon that our economic evaluation does not take into account. Such a shift has the potential to positively influence both patient outcomes and health system budgets. Future utilization and outcome studies will be needed to determine the broader system impact of sirolimus-eluting stent uptake.

In summary, we offer an alternative presentation of the results of our formal economic evaluation of sirolimus-eluting stents. We have moved the focus away from the

traditional cost per QALY rubric and present the health gains and associated costs in a Canadian context. We present alternative funding strategies, including targeting of high-risk groups, that may maximize the efficiency with which this therapy can be used. Globally, our findings indicate that the "economic case" for funding drug-eluting stents across-the-board is modest at best and that restricted funding scenarios (especially ones focusing on high risk lesions) are perhaps more reasonable.

However, many complex issues remain. When considering the impact of restricted funding scenarios, a clear understanding of the trade-offs is important. Therapies currently being funded, the size of the local budget and, if necessary, what programme resources could be cut or scaled back to fund drug-eluting stents must all be explicitly considered. While decision-makers must consider other characteristics of a new intervention, the central goal of policy-makers should remain to provide the maximum health gains, within the allocated budget.

F. THE IMPACT OF HEALTH-RELATED QUALITY OF LIFE VALUATION ON THE RESULTS OF ECONOMIC EVALUATION

GLOBAL SUBSTUDY OBJECTIVE: To assess the impact on the cost per QALY of applying the UK preference based tariffs and the US preference based tariffs to the EQ-5D estimates used to inform our economic evaluation.

1. Background

Given that many interventions have minimal, if any, impact on life expectancy, the benefit of many treatments may not be quantifiable using a "life years gained" metric. Thus, medical interest has turned towards measuring the impact of therapies on health-related quality of life (HRQOL). While there is general support for the quantification of the concept of "quality of life", there is little consensus about what should be included in a quality of life instrument, how it should be administered and how it should be valued (70).

Broadly speaking, there are two types of instruments used to measure HRQOL; generic health measurement instruments (including utility measurements) and disease specific instruments. Generic HRQOL instruments seek to describe a person's physical, mental and social well-being. These instruments address a variety of health dimensions such as physical function, mental and emotional function, perceived health status, and life satisfaction. For example, the most commonly used generic instrument is the Short-Form 36 (SF-36). It is composed of two components; a mental health score and a physical health score; each of these is made up of 4 domains (71). Generally the two composite scores have been considered separately. While this enables one to consider mental and physical health as two distinct concepts, generic HRQOL instruments cannot be used to inform cost-utility analyses since they do not produce a global measure of HRQOL and are not preference based.

Disease specific instruments address specific symptoms or states related to a specific disease. For example, the Arthritis Impact scale includes several questions on range of motion and joint dexterity, limitations specific to arthritic patients. Disease specific instruments are designed to address changes unique to patient populations with a specific illness or disease. In cardiac populations, the Seattle Angina Questionnaire (SAQ) is often used as a disease specific measure of HRQOL. It is included in the APPROACH 1-year follow-up. Respondents are asked questions specific to the limitations of their CAD such as their ability to climb a flight of stairs, dress themselves or jog.

The choice of generic versus disease-specific instruments is driven by the research question. Generic instruments allow for comparisons across diseases. It is a trade-off between sensitivity of the instrument to changes in health of specific patient populations and generalisability to other patient populations. Disease specific instruments are more sensitive to changes in specific populations but lack generalisability across patient populations.

1.1 Utility Scores

Most HRQOL measures quantify a person's health state according to selected levels of dysfunction. This differs from the concept of "utility" in that a utility score can be seen as the magnitude of the preference for a particular health state taking into account a specific trade-off. According to economic principles, an ideal utility measurement requires patients to trade quality of life against length of life under conditions of uncertainty. Utilities are useful to inform cost-utility analysis which requires the health benefit to be measured in quality-adjusted life years (QALY), which is a function of life expectancy and overall quality of life, measured as a utility. Specifically, QALYs are calculated by multiplying the life years remaining by the utility score. Utility scores range from 0-1 with "0" being the

worst possible imaginable health state and "1" being the best imaginable health state. There are two broad methods for developing utilities; direct and indirect methods.

1.2 Direct Elicitation of Utilities

Direct methods of eliciting utility scores include the standard gamble and time trade-off. A standard gamble (SG) trades off the probability of survival between two scenarios; certain health state "X" which has a reduced HRQOL, and guaranteed full health if one survives an immediate risk of mortality. The goal is to find a point at which the person is indifferent to the two scenarios. A person is presented with a health state and a gamble between full health with probability "p" and an upfront risk of death "1-p" (Figure 8). The person is asked to choose between the gamble scenario and the presented health state. The value of "p" is varied until the person is indifferent between the health state and the gamble. The "p" of indifference is the utility associated with the reduced HRQOL state.

Time trade-off (TTO) involves trading off time between health states. Two scenarios are presented; "t" years in a specific health state and "x" years of full health followed by certain death (Figure 9). The amount of time in the specified health state ("t") is varied until the person is indifferent to the two scenarios. The difference between "t" and "x" is the number of years the person is willing to give up in perfect health. The utility score is the ratio of "x" over "t".

Both approaches have advantages and disadvantages. SG is "risk-neutral" meaning that an individual's risk-aversion is not taken into account. For example, assume that the "p" of indifference is 80%. A patient would be indifferent to any gamble, regardless of the time spent in full health after the uncertainty, with a 20% mortality risk and the specified health state. Intuitively, we would think this is not the case. A person's likelihood to take a gamble is linked to the results of the gamble. While TTO does incorporate the length of

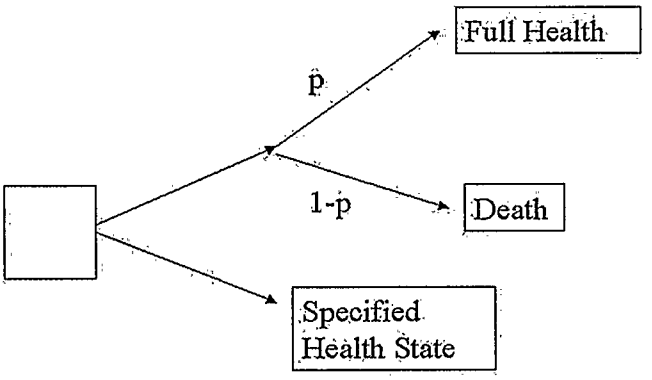


Figure 8. Standard Gamble

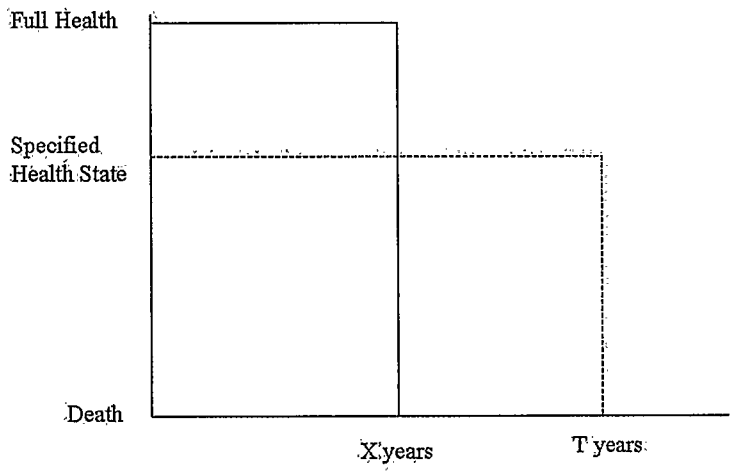


Figure 9. Time Trade-off

time spent in a health state, TTO treats all years of life equivalently. 5 years of life for a 20 year old is valued the same as 5 years of life for an 80 year old. This assumption may be unlikely to hold in the real world. While both methods have flaws and are highly debated in the literature, they have both been used extensively to develop weights to create utility scores from HRQOL measures.

Lastly, visual analogue scales (VAS) have been used to directly elicit utility scores. VAS is presented as a thermometer anchored at "0" representing the worst health state imaginable. The upper value is "100" and patients are asked to mark an "x" on the thermometer representing their health state. The marked value is the patient's utility score. Although patients are not being asked to value their health incorporating trade-offs, VAS can be implemented as a utility score; it ranges from 0-1 and is a statement of preference. VAS is intuitively appealing and easily elicited, however, because it does not incorporate the concept of "trade-off", it is an inferior method of obtaining utility measures.

1.3 Indirect Elicitation of Utilities

There are also indirect utility instruments, also referred to as multi-attribute health status classification systems. For these methods, people rate their quality of life on various dimensions of health. Utility scores are developed for each patient from their responses based on a scoring algorithm. The scoring algorithm has typically been developed using a direct utility measure, such as the time trade-off on a sample of the general population.

There are currently three instruments available with published algorithms for converting HRQOL scores into a utility score, namely, the Quality of Well-Being Scale (QWB), the Health Utilities Index (HUI) and the EuroQOL EQ-5D. For each of these instruments an algorithm, based on social preference weights, was developed to convert the HRQOL score into a utility score ranging from 0 to 1.

Each of the three instruments have been applied in the literature and each instrument has its unique advantages and disadvantages. The QWB was developed in the United States in the early 1970's (72). It includes 3 dimensions of health; mobility, social and physical activity. No measure of mental or emotional health is included, an exclusion that has been widely criticized. The questions are task oriented, such as "I can drive a car, take a bus or ride a train with no help" and are not necessarily appropriate for all patient populations. For example, in patient's everyday lives there may be no need for them drive so a more relevant question may be "can they walk to the grocery store with no help?" As a result of not having a mental health component and the underlying assumptions of the statements, the QWB has not been as widely used in recent work as the other two measures available.

The HUI was developed at McMaster University in the mid 1980s (73). Originally developed for use in the Ontario Child Health Survey, it initially included 6 dimensions of health; sensory ability, happiness, self-care, pain, learning ability and physical ability. In the latest version, HUI Mark III, the dimensions have been modified to specifically include vision, hearing and speech in the sensory ability dimension and self-care was expanded to include dexterity. Notably, this instrument excludes social health. 14 health states were defined and a random sample of parents of school-age children was surveyed to obtain values for each health state. A standard gamble was used and a scoring algorithm was developed using multi-attribute theory.

1.4 EQ-5D

The EQ-5D was developed in the late 1980's by an international group of researchers in Rotterdam (74). The EQ-5D is comprised of a series of five questions that cover five dimensions of health and a visual analogue scale (VAS). The score on the VAS is measured based on where the patient has marked an "X" on a vertical thermometer

anchored at the "best imaginable health" (a score of 100) and "worst imaginable health" (a score of 0). The profile scores incorporate five dimensions of health with three levels of attributes: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Three statements, representing "no problem", "moderate" and "severe", address each of the five dimensions and patients are asked to check a box if the statement describes their health today. For example, one statement is "I have no pain or discomfort", if the patient is not experiencing pain or discomfort today the box corresponding to the statement would be checked.

1.4.1 UK Algorithm for the EQ-5D

The five dimensions are combined into a single score using a validated scoring algorithm. The most widely applied scoring algorithm, published in 1990, was developed in the UK (10). Directly-elicited social preference weights were obtained through a survey of the UK general population. 3,395 respondents were interviewed face-to-face and each respondent valued 15 different health states, including immediate death and perfect health which are used to assess internal validity. Respondents had to value perfect health and immediate death in a logical manner (i.e. perfect health highly valued and immediate death poorly valued) to be included in the sample used for modeling. Using classic time trade-off props, respondents were asked to trade off time in spent in perfect health followed by for time spent in the described health state.

Using generalized least squares regression, weights (or tariffs) for each of the five dimensions were developed. The model has a dummy variable representing each level of health within each dimension, a term indicating any dimension which respondents indicate as "severe" and an intercept term. Of note, no interaction terms are included in this model.

1.4.2 US Algorithm for the EQ-5D

In 1993, the US Panel on Cost-Effectiveness in Health and Medicine identified the need to develop a scoring algorithm based on health state valuations derived from a representative sample of the US population (38). A team of researchers recently published the results of a preference weighting scoring algorithm for the EQ-5D based on a representative sample of the US population (11). The data collection was adapted from the methodology used in the UK study. The same health states were valued using the same time trade-off technique. 4048 respondents, randomly selected from the general US population with over-sampling of Hispanics and non-Hispanic blacks, formed the final data set.

Probability-weighted least squares regression was applied to develop weights for each of the five dimensions. The model has a dummy variable representing each level of health within each dimension as the UK model. However, the assigned weights to each dummy term differ between the models. Additionally, the US model has several interaction terms. A variable accounts for the number of dimensions at "severe", termed I3. An additional term, D1, accounts for movements away from perfect health in 2 or more dimensions. Lastly, a term, I2-squared, is included which accounts for additional dimensions at "moderate."

Meaningful differences between the valuations of the health states in the UK and US populations have been demonstrated (75). A statistically significant difference (5% significance) was reported in 31 of the 39 health states evaluated. The mean population differences ranged from -0.01 to 0.25 when the UK mean score was subtracted from the US mean score. The authors suggest three possible external influences that may account for the differences seen between the two populations, including differences in interpretation,

cultural differences, or the 10 year time lapse between studies, although these were not formally examined. Whereas differences may exist in the valuations of EQ-5D health states, a more relevant comparison may be for the performance of the different scoring systems derived from those valuations. Important differences between the UK and US are the conceptual basis and functional form of the algorithms, which theoretically lead to differences in outcomes such as QALYs (75). It is not clear, however, if these differences would be important in empirical studies and, in particular, cost-utility analyses.

1.5 Other Considerations

Currently, the HUI and the EQ-5D are the most widely used measures of HRQOL. The EQ-5D has been available through the one-year follow-up APPROACH survey since 1997. Thus, the decision to use the EQ-5D as the measure of HRQOL for our economic evaluation was one of availability. However, it is important to note that, currently, the EQ-5D is the only available instrument to measure HRQOL that is not associated with a "user's fee". The HUI, among others, have a licensing fee associated with their use in any application, academic research or otherwise. Given this fact, it is not surprising that the EQ-5D has been so widely applied.

With a new scoring system now available, the question arises: what are the practical implications of the different scoring technique? Specifically, given that decision models routinely use the EQ-5D to measure HRQOL, what are the consequences of a study finding that different cultural populations value health states differently and result in different scoring algorithms? If the US algorithm results in consistently higher values for health states, we would expect the cost per QALY to artificially decrease since the QALYs gained would be higher simply due to higher utility scores resulting from using the US algorithm. Additionally, if the scoring algorithm chosen affects the outcome of the economic

evaluation this would in turn impact the transportability of the results of economic evaluations across geographic boundaries.

The specific objectives of this HRQOL methodology substudy are:

1) to rescore the EQ-5D raw data using the US scoring algorithm,
2) to describe and compare whether use of the UK and US scoring algorithms result in significant variations in utility scores in this data set
3) to determine whether use of the US- or UK-based EQ-5D scores results in significant differences in the resultant cost-utility ratio in our economic evaluation

2. Methods

2.1 Data Source and Collection

A selected cohort from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart (APPROACH) disease database was used. APPROACH is a prospective, geographically inclusive, registry of all patients undergoing coronary catheterization in Alberta, Canada (41). Patients are followed prospectively gathering clinical, economic and quality of life outcomes. At 1 year post-catheterization consenting APPROACH patients with coronary artery disease are mailed a follow-up survey. Only patients who consent to follow-up at the time of catheterization, have documented coronary artery disease, and have a valid Alberta postal code are mailed a survey. Respondents can complete the survey over the phone or mail back the completed survey.

For the purposes of our original decision model, we selected patients undergoing stented percutaneous coronary intervention (PCI) from 1998-2000 (N=7334). This cohort represented the largest cohort available from APPROACH with at least 1 year of follow-up and stable utilization trends of other therapeutic innovations that affect PCI outcomes.

From this larger group only those with complete EQ-5D data available were included in this study (n=1954; 27%). A comparison of responders and non-responders was completed and the characteristics of the two groups were compared using chi-squared tests.

2.2 Analysis

Each individual's response to the EQ-5D was scored with both the UK and US algorithms, as outlined in Appendix 1. The mean, standard deviation and overall range resulting from each algorithm were compared using paired t-tests. The comparisons were completed overall, and subsequently considering the same subgroups reported in the decision model (i.e., subgroups based on subsequent interventions, age and diabetic status). Additionally, the difference between the utility score produced by each algorithm was calculated for each individual (i.e., US score - UK score). The mean, standard deviation and range of the differences were calculated overall and again, subsequently by subgroup. All statistical analyses were completed using SAS version 8.1.

2.3 Cost-utility Model

As noted, to determine the impact of using the different scoring algorithms on the results of a formal cost utility analysis, we used our previously described decision model which compared the cost per QALY gained for patients with ischemic heart disease treated with PCI and a drug eluting stent compared to a bare metal stent. A Markov process was used to model the cost and clinical outcomes for stented patients post-PCI in 6-month time intervals. Patients progress through the following five Markov health states based on the health state transitions that may occur after an initial PCI: 1) alive with no clinical restenosis (i.e. event free), 2) clinical restenosis as determined by the need for a subsequent coronary artery bypass grafting (CABG) surgery, 3) clinical restenosis as determined by the need for repeat PCI, 4) repeat catheterization with no subsequent revascularization and 5)

death (Figure 3). Utility scores were assigned to each health state based on the mean EQ-5D values observed for APPROACH patients who existed in each health state.

The Markov model was run twice; once with utility scores estimated using the UK algorithm and then subsequently using the US algorithm. We compared the resulting cost utility ratios. As recommended by the CCOHTA guidelines for economic evaluation, Monte-Carlo simulation was used to develop a distribution for the cost-utility ratios (76). Monte-Carlo simulation allows for all variables for which there was uncertainty in the estimates to be varied simultaneously. Given that, in this case, we are specifically interested in the uncertainty in the utility scores, and how variation in these scores impacts the cost-utility ratio, we only sampled values for the utility variable from the normal distribution based on the mean score and variance of each scoring method. Repetition of this process builds a statistical distribution around the incremental cost-utility ratio estimate. Subsequently, the resulting two cost-utility ratios were compared using a t-test. Cost-utility modeling was done in DATA 4.0.

3. Results

3.1 Baseline characteristics of responders

The EQ-5D response profile of the 1954 respondents is shown in Figure 10. Non-responders were more likely to be female (26.0 % of non-responders vs. 23.3% of responders, p-value: 0.02) and over the age of 75 years (13.3% vs. 9.5%, p-value: <0.001). Patient responses for each of the 5 domains were dichotomized, enabling comparison between the number of patients indicating "no problems" and those indicating "some" or "severe" problems. Overall, our patient cohort reported a relatively good HRQOL with just 5.2%, 22.4%, 29.1%, 35%, and 35.2% of patients indicating some or severe problems with

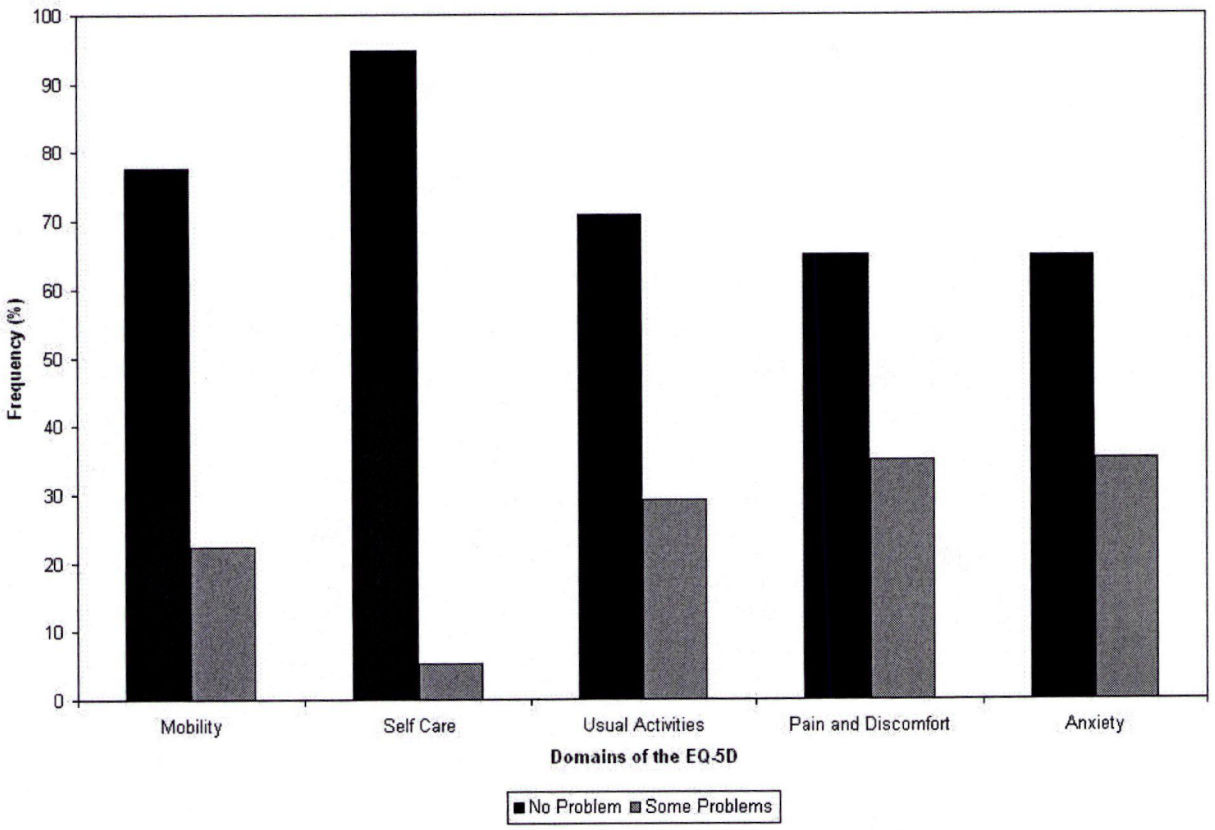


Figure 10. Categorized responses ("No problem" versus "Some" or "Severe" problems) for each of the five dimensions of the EQ-5D (N=1954 patients)

self-care, mobility, completing their usual activities, with pain and discomfort, and with anxiety, respectively.

3.2 Algorithm Differences

The overall mean score was slightly different between the two algorithms; 0.83 (SD: 0.20) using the UK algorithm and 0.87 (SD: 0.15) when the US algorithm is applied (Table 6). All differences in Table 6 were statistically significant (p-values = <0.001). The range of values produced by the UK algorithm includes negative values whereas the lowest value produced by the US algorithm is 0.05. Not surprising given the worst health state (level 3 in all dimensions) using the US algorithm is values at -0.11 whereas the UK algorithm assigns it a value of -0.60. When individual differences (differences within health states) are considered, the mean difference is 0.04, as expected. However, the range of differences is wide. For one particular health state (some problems with mobility and self-care and severe problems with usual activities, pain/discomfort and anxiety and depression {health state 22333}), the difference between the US and UK score is 0.41, a considerable difference given that the scale ranges from 0 to 1.

When patient subgroups based on age are considered, similar patterns emerge (Table 6). Those under 65 years of age reported the highest HRQOL applying both algorithms. Scores decrease with increasing age, with similar findings noted in the two algorithms. Subgroups based on diabetic status produce similar results; patients with diabetes have a lower HRQOL score regardless of which algorithm is applied. However, the decrement in the mean score for those with diabetes is more marked when the UK algorithm is applied. The mean within-individual differences are small across all subgroups considered. However, the range is wide in all cases.

Table 6. Comparison of EQ-5D index results using the UK and US scoring algorithms, overall and by subgroup

		UK Algorithm		US Algorithm		Within Individual Difference (US-UK)	
	N	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Overall	1954	0.83 (0.20)	-0.31-1.0	0.87 (0.15)	0.05-1.0	0.04 (0.06)	-0.02-0.41
Age Subgroup							
Under 65 yrs.	1218	0.84 (0.20)	-0.31-1.0	0.88 (0.15)	0.05-1.0	0.03 (0.06)	-0.02-0.41
65-75 yrs.	551	0.83 (0.20)	-0.18-1.0	0.87 (0.14)	0.20-1.0	0.03 (0.06)	-0.02-0.38
Over 75 yrs.	185	0.77 (0.22)	-0.02-1.0	0.82 (0.16)	0.31-1.0	0.05 (0.07)	-0.02-0.32
Diabetic Status Subgroup							
No Diabetes	1666	0.84 (0.19)	-0.31-1.0	0.88 (0.14)	-0.31-1.0	0.03 (0.06)	-0.02-0.41
Diabetes	288	0.76 (0.24)	-0.18-1.0	0.82 (0.17)	0.20-1.0	0.05 (0.08)	-0.02-0.38
Procedure Subgroup							
Event free	1536	0.85 (0.19)	-0.24-1.0	0.88 (0.14)	0.17-1.0	0.03 (0.06)	-0.02-0.41
Repeat Catheterization	223	0.77 (0.23)	-0.18-1.0	0.82 (0.16)	0.20-1.0	0.05 (0.07)	-0.02-0.38
Repeat PCI	141	0.77 (0.23)	-0.31-1.0	0.82 (0.16)	0.05-1.0	0.05 (0.07)	-0.02-0.37
CABG	54	0.78 (0.27)	-0.07-1.0	0.83 (0.19)	0.26-1.0	0.05 (0.09)	-0.02-0.34

Patients could undergo one of three possible second procedures after their initial catheterization (repeat catheterization, CABG or PCI). For those patients who underwent such procedures, we recalculated utility scores for each subgroup and noted that HRQOL scores for patients undergoing any type of second procedure are very similar, while those that do not undergo a second procedure after index catheterization report higher mean scores for both scoring algorithms.

3.3 Cost-Utility Ratios

Table 7 reports the cost-utility ratios for the analysis overall and for specific patient subgroups, comparing the US and UK algorithms. Overall, the US algorithm produces slightly lower cost-utility ratios with the observed difference approaching statistical significance; using second order Monte Carlo Simulation, and varying the utility estimates from the UK and US scoring algorithms resulted in a cost per QALY gained of $58,635 per QALY (95% CI: $58,360 – $58,909), and $58,229 (95% CI: $58,095 - $58,364), respectively (p=0.07). In both absolute and relative terms, however, the difference of $406 noted in the cost-utility values produced by the two algorithms is very small. Table 7 presents similar comparisons across age and diabetes subgroups, with again, only modest cost-utility differences between algorithms.

Table 7. Cost-utility ratios resulting from the UK and US scoring algorithm, overall and by subgroup

		UK Algorithm		US Algorithm	
	Incremental Cost ($)	Incremental Effectiveness (QALY)	Incremental Cost-utility Ratio ($/QALY)	Incremental Effectiveness (QALY)	Incremental Cost-utility Ratio ($/QALY)
Overall	**2,500**	**0.043**	**58,721**	**0.043**	**58,290**
Age Subgroup					
Under 65 yrs.	2,600	0.036	72,464	0.035	73,975
65-75 yrs.	2,400	0.050	47,441	0.051	46,392
Over 75 yrs.	2,600	0.065	40,129	0.069	37,932
Diabetic Status Subgroup					
No Diabetes	2,500	0.040	63,383	0.040	63,013
Diabetes	2,400	0.055	44,135	0.056	43,682

4. Discussion

As would be expected, the US algorithm consistently values health states higher than the UK algorithm, and in some cases, the two scoring algorithms produce quite notable differences within individuals. The effect of scoring algorithms on the mean score, however, is less pronounced. In the context of our economic evaluation, meanwhile, the effect of the choice of scoring algorithm on resulting cost-utility ratios is relatively small, and unlikely to change the bottom-line interpretation of our economic evaluation's results in a policy setting application. This is encouraging for the transferability of economic evaluations across cultural settings.

Based on the results of Johnson et al, we hypothesized that the US algorithm would produce higher cost-utility ratios than the UK algorithm; the differences between health states are smaller using the US algorithm, so the decrement associated with reduced health states is less than when the UK algorithm is applied (75). Somewhat counter-intuitively, however, the US algorithm resulted in a lower cost-utility ratio due to the higher utility in the "event-free" group when using the US algorithm, resulting in the cohort accumulating more QALYs in the US scoring algorithm approach.

The results of our study are similar to those of Johnson et al. who showed that US population scores are consistently higher than those of the UK population (75). Two hypotheses were proposed by Johnson et al to explain the differences seen; specifically cultural differences between the US and UK, or time lapses (the UK study was completed in the early 1990s whereas the US study was completed in 2002)

Additionally, Luo et al have demonstrated a lack of agreement between the utility scores resulting from the UK and US scoring algorithms (77). In our data, large differences were seen within individuals, particularly for those in worse health states. This likely

results from the fact that when developing the scoring algorithms, different transformations were applied to states valued worse than death. The US study yielded higher values for worse health states. Thus, the possible range of values when applying the US algorithm is narrower than the range resulting from the UK algorithm. The ranges in our dataset reflect this. Given that our respondents indicated a relatively high level of HRQOL, the use of the US scoring algorithm made very little difference to the overall mean score. In a different clinical population in poorer health, the difference between the two algorithms may be much greater.

The differences seen between the two scoring algorithms are similar in magnitude to those seen when different measures of indirect utilities are compared. A direct comparison of the HUI-2, HUI-3, SF-6D and EQ-5D in rheumatoid arthritis patients reported mean utility scores of 0.71, 0.53, 0.63, and 0.66 respectively, thus, a maximum difference of 0.18 between instruments (78). Similarly, for patients enrolled in a multi-centre randomized control trial undergoing PCI, the difference in the mean utility scores was 0.04 when comparing the HUI-3 and SF-6D, 0.63 to 0.67 respectively (79).

Several authors have suggested values to represent a "clinically meaningful difference." The threshold for the HUI-2 and HUI-3 is a difference of 0.03 (80;81). For the EQ-5D, applying the UK weights, a difference of 0.03 has been suggested (10). However, a threshold of 0.07 was recently suggested for the US scoring algorithm (77). Thus, the difference between the overall means (0.04) in our study is at the margin of being clinically meaningful. However, Luo et al acknowledge that the suggested threshold of 0.07 may be an overestimate since their definition of a "minor improvement" may equate to a significant increase in health.

It is interesting to note that our study suggests that differences in utility scores of the magnitude seen between the US and UK scoring algorithms (or 'functions') had relatively little impact on the results of a cost-utility study. Thus, while the differences may be meaningful in absolute terms, when only the differences between health states are considered across an entire treated population, as in a cost-utility study, the choice of algorithm is unlikely to result in different policy decisions.

Our study has several limitations. First, our results are from a selected population, those undergoing stented PCI in Alberta Canada from 1998-2000. While this may limit the generalisability of our findings, it should be noted that most cost-utility studies have a narrow population since most technologies apply to a specific target group. Additionally, our sample is geographically inclusive and population-based limiting sampling bias. However, not all patients are followed up and our respondent sample may not be fully representative as demographic differences are noted between responders and non-responders.

The QALY accumulation in our model is driven by a large extent by the death rate as death is a frequent outcome in a cardiac patient population. In patient populations where death occurs less frequently the difference between the two algorithms may be more pronounced since the HRQOL differences contribute more to the QALY calculation than the time spent in a given state.

As it seemed unlikely that a HRQOL decrement associated with a procedure would persist long-term, our model only considered a HRQOL decrement for one year. Interestingly, when we perform a sensitivity analysis sustaining the HRQOL decrement associated with a second procedure over the patient's lifetime, the difference between the two algorithms is more pronounced; $8,878 per QALY when the UK algorithm is applied

compared to $11,260 per QALY when the US algorithm is applied. In clinical situations where the HRQOL differences between patient groups remain over longer periods of time, the choice of scoring algorithm may have a greater impact on the resulting cost-utility ratio.

Lastly, it is difficult to comment comprehensively on the on cross-cultural differences when we are assessing a different culture (Canadians) than that used to develop both algorithms (UK and US). Based on the current literature, we are unable to gauge how a Canadian derived scoring algorithm may differ and impact the findings of economic evaluation.

In conclusion, the US algorithm consistently assigns higher values to EQ-5D health states than the UK algorithm, but despite this, the incremental cost-utility ratios did not change in a clinically meaningful fashion when the different algorithms were applied to a cardiac disease cohort in an economic evaluation. Given that differences may be more pronounced in different clinical populations or for different technologies, we can not confidently assert that the choice of algorithms is always of negligible importance. More data and research is required to fully understand the impact of the new scoring algorithm on the outcomes for economic evaluations. However, as the US algorithm is based on the preferences of the general adult US population, it is more appropriate than the UK algorithm for use in US-based studies. In studies where either scoring algorithm might be used (e.g., studies of populations where local preferences for EQ-5D health states have not been determined), researchers should for the time being consider completing sensitivity analyses applying the both scoring algorithms to their data.

G. THE IMPACT OF DIFFERENT METHODS OF COSTING CARE ON THE RESULTS OF ECONOMIC EVALUATION

GLOBAL SUBSTUDY OBJECTIVE: To assess the impact of three different methodological approaches to measuring health care costs on the cost per QALY.

1. Background

There are many reasons to measure costs of health care. Firstly, costs have an administrative role. In order to operate within a certain budget, costs must be tracked. Costs also have a role in research. In economic evaluations, in particular, costs are an essential data input. As such, it is important for detailed costing data to be available to complete such studies to inform decision-makers.

Generally speaking, there are two types of costs; direct and indirect. Although this terminology is inconsistent, herein direct costs are those costs incurred directly by the Health care system (e.g. staff hours, recovery beds, operating room overhead) and indirect costs are those not incurred by the system (e.g. lost labour cost, travel time) (33). Given that we had no information on indirect costs and there is no reason to suspect they may differ between the two treatment strategies, this work only considers direct costs, including hospitalisation costs and non-hospitalisation costs such as home care, drug costs, physician visits and ambulatory care costs.

Currently, there are two general approaches to measuring the direct cost of health care that are in current use within Canada; microcosting and classification groupers. In Alberta, three sources of hospitalisation costing data are available; microcosting, "Refinement Grouper Number" (RGN)-derived estimates from Alberta Health and Wellness (AHW) and "Case-Mix Grouper" (CMG)-derived estimates developed by the Canadian Institute for Health Information (CIHI). The RGN is the Albertan equivalent to the "Refined-

Diagnosis-Related Grouper" (RDRG) whereas the CMG is the Canadian equivalent to the "Diagnosis-Related Grouper" (DRG) system (82;83).

Our previously published economic evaluation comparing the cost per QALY of sirolimus-eluting stents to that of bare metal stents used the RGN-derived estimates to estimate costs, overall, and subsequently by age and diabetes subgroup (84). The calculated means were then used to run our decision model.

Currently, the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) guidelines for health technology assessment provide no guidance regarding which method of costing to apply in an economic evaluation (76). The guidelines clearly outline that all relevant costs should be included. There is, however, no mention of which of the different costing methods should be used to construct the relevant costs. Additional publications from CCOHTA state that the choice of method should strike the appropriate balance between the needs of the analysis and the precision of the estimates available (85). Both Oostenbrink et al and Gold et al. provide similar guidance stating that the choice between microcosting and classification groupers should be carefully considered and the choice should be driven be the needs of the analysis (38;86). There is a smattering of other studies examining different methods of costing (87;88) showing differences between more detailed costing approaches and grouping-based approaches. However, none of these explicitly compare the sources of data available in Canada. This work provides a uniquely Canadian perspective to the broader question of how different costing strategies affect the outcomes of economic evaluations.

The objectives of this substudy are to:

1) use the three available costing methodologies; microcosting, Alberta Health and Wellness RGN, and Canadian Institute for Health Information CMG, to develop costing estimates for the selected APPROACH cohort
2) compare the costs produced within subject and across subjects using the three different costing methodologies, and
3) to determine whether the use of the different costing methods results in significant differences in the resulting incremental cost-utility ratio in our economic evaluation

2. Methods

2.1 Overview of the Costing methods

2.1.1 Microcosting

Microcosting is a technique where a detailed list of the cost for each component of a patient's care is captured and valuated separately for each facet of a patient's hospitalisation. Microcosting is the ideal method of capturing costs and generally considered the "gold standard" for costing inpatient stays. It combines allocation and assignment of all direct and indirect costs associated with an in-patient encounter from the time a patient is admitted to the hospital to the time they are discharged. Thus, the nursing hours, the electricity required to light the recovery room, the catheter implanted, the operator's time, the share of the capital cost of the hospital, the food costs, etc. are captured and detailed. It is, however, labour intensive for both the analysts and the staff reporting costs. As a result of the intensity of this costing method, microcosting is not implemented in the majority of hospitals in across Canada. In our case, complete

microcosting is available for one hospital in Calgary. In the hospitals outside of the urban centres (Calgary and Edmonton) microcosting systems are not widely implemented.

2.2.2 Diagnosis-related groupers

In 1967, the first diagnosis-related groupers (DRG) were developed (82). DRGs were first used on a wide-scale basis within the United States in response to the need for the Centre for Medicare and Medicaid Services (Medicare) to establish a fixed reimbursement rate for an in-patient stay. The system classifies patients based on similar clinical attributes and utilization patterns. Initially developed at Yale, the classification system was based on the organizational scheme applied in the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9). Twenty-three "Major Diagnostic Categories" were developed. Each category captured cases of similar clinical, utilization and length of stay characteristics. The categories were then further subdivided based on secondary diagnoses, sex, age and discharge status creating DRGs. The system was widely criticized for being unable to capture severity of illness and being too static to keep up with the changes in technology and treatment.

In 1983, the DRG system was adopted by Medicare as a prospective payment system (82). Medicare assumed responsibility for annual updates and undertook modifications to ensure DRGs accurately captured the population included in Medicare's mandate, specifically the elderly and disabled. The major addition initiated was the development of the "Refined-DRG" (RDRG) which applies a complication and comorbidity (CC) overlay to the DRG. Four complexity levels were defined: non-CC, moderate-CC, major-CC and catastrophic-CC. Thus, the principal diagnoses groups similar cases, as in the original DRG system, and the secondary diagnoses are used to subsequently classify cases into RDRG.

In 1987, the DRG system was more broadly adopted as a prospective payment system (82). However, the generalisability of the modifications made by Medicare to the broader population was questioned thus, 3M Health Information Systems (3M) was contracted to develop a more comprehensive system of classification applicable to a wider range of health issues. 3M developed a similar system to the RDRG adding a complexity and comorbidity classification system as well and additional DRGs to capture a wider range of cases and health interventions. As a result, cases are classified based on three characteristics: 1) the principal diagnosis or procedure which determines the DRG classification, 2) the severity of illness based on secondary diagnoses and 3) the risk of mortality of given subgroups based on secondary diagnoses, age, sex and the presence of non-operative procedures.

In Alberta, a system based on RDRGs was used to group cases into groups comprised of similar cases (83). The groupers are developed using a two step process. First, based on the principal diagnosis or procedure code, cases are grouped together. Subsequently, cases are further grouped, within principal diagnosis group, based on secondary diagnoses and procedural codes. The two-step grouping process classifies cases into "Refinement Group Numbers" (RGN).

A cost is developed by AHW for each RGN using the microcosted data submitted from sites in the Calgary Health Region and the Capital Health Region. An average cost for each RGN is calculated separately for each hospital by dividing the total cost of all the cases within a specific RGN by the total number of submitted cases within that RGN. A Hospital Specific Relative Value is then calculated by dividing the hospital-specific average cost for each RGN by the average cost of all the cases submitted from the hospital. A weighted average of this value, across hospitals, is then divided by the total number of cases within

each RGN across the province. This calculation results in a province-wide relative value for each RGN. Lastly, for each hospital a case-mix index which adjusts for differing severity of case mixes across hospitals is calculated and the relative value is adjusted to account for this variation. For each RGN, the adjusted relative values are divided by the total number of cases in each RGN and then multiplied by the province-wide average cost per case. This results in a province-specific cost per RGN.

As of April 2000, AHW switched to the Case-Mix Grouper (CMG) methodology used at the national level. Currently, the same methodology described above is used to develop an Alberta-specific cost per CMG.

2.2.3 Case-Mix Groupers

Annually, in addition to being submitted to AHW, all admission/discharge abstracts are submitted to the CIHI, the national institution responsible for compiling and reporting health information. Each province, except Quebec, is required to submit all admission/discharge abstracts. From these, CIHI develops CMGs.

Introduced into Canada in 1983, CMGs are the Canadian equivalent of the DRG system that applied ICD-9-CM (82). Essentially the same groupers are employed in the CMGs as the DRGs although some adaptations had to be made to accommodate the use of ICD-9 and the Canadian Classification of Procedures (CCP) used many Canadian provinces. Cases are classified into CMGs based on the most responsible diagnosis as opposed to the principal diagnosis used in the DRG methodology (82). Thus, CMGs attempt to capture the diagnosis responsible for the greatest proportion of the hospitalisation instead of the admitting diagnosis.

From the micro-costing data reported from the two health regions in Alberta, selected hospitals in Ontario and British Columbia, an overall cost for an "average patient" is

created using similar methods as applied to develop the Alberta RGNs. A relative index weight (RIW) is developed for each CMG which is a weight representing the severity of the cases included in a specific CMG compared to the "average patient." An average cost is calculated from all cases submitted. The average cost is assigned to a RIW of 1.0. To calculate CMG specific costs, the RIW is multiplied by the average cost. The CMGs, the assigned RIW for each CMG and average cost associated with a RIW of 1.0 varies annually.

2.2 Patient Cohort

A selected cohort from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart (APPROACH) disease database was used. APPROACH is a prospective, geographically inclusive, registry of all patients undergoing coronary catheterization in Alberta, Canada (41). Patients are followed prospectively gathering clinical, economic and quality of life outcomes. Since microcosting was only available in the Calgary Health Region, we limited our analysis to Calgary Health Region residents, based on their resident postal code using the Health Region boundaries prior to April 2002.

For the purposes of our original decision model, we selected patients undergoing stented PCI from 1995-1997. We requested all hospitalisations and outpatient procedures from April 1, 1995 to March 31, 2001 from the Calgary Health Region. A similar request was made to AHW but expanded to include all drug claims, physician visits, home care and ambulatory costs; costs not captured in the microcosting system available in the Calgary Health Region. Patients were matched based on Personal Health Number, Hospital Chart Number, last name, sex and birthdate. All patients had a minimum of four years of follow-up cost data. Only patients with an index hospitalisation matching to the APPROACH database in both the microcosting and AHW data were included in this analysis (N=636).

Patients were matched within +/- 7 days of the APPROACH admission date. The data from AHW contains both RGN and CMG for each hospitalisation. Thus, from the data received from AHW we were able to calculate both RGN- and CMG-derived costs. All costs were inflated to 2001 Canadian dollars using the Consumer Price Index (43).

2.3 Implementation of the three costing methods

2.3.1 Microcosting

Total hospital costs were calculated including all direct costs available in the database. A total cost was calculated for each admission abstract. RGNs and CMGs were obtained for each admission allowing for an analysis directly comparing the microcosting estimates with RGN-derived and CMG-derived costs. An overall total inpatient cost was also calculated for the entire 4-year period of follow-up.

2.3.2 RGN-Derived Costs

Total costs were calculated from the *Health Costing in Alberta 1999 Annual Report* which contains a detailed list of RGN-specific costs (83). These costs are calculated using the above described methodology of weighting. Both hospitalisation and total inpatient costs were calculated.

2.3.3 CMG-Derived Costs

CMG specific costs were calculated using the RIW associated with each CMG. The average annual cost per admission was taken from the *2000/01 Cost List* published by the Institute for Health Economics since CIHI does not release the average cost of an admission where the RIW=1.0 (89). Thus, a cost for each hospitalisation was calculated by multiplying the CMG-specific RIW by the average Canadian cost per case ($3,103 per case).

2.4 Analysis

All costs are presented in 2001 Canadian dollars. First, a descriptive comparison of the costing estimates derived by the three methods was completed. The total inpatient costs were described using the mean, standard deviation, median, interquartile range and range. Additionally, the total costs were compared (including non-hospital costs that do not vary across the three methods). Scatterplots were used to visually compare the two grouping-based approaches to microcosting. The intra-class correlation coefficient was calculated for each grouping-based method compared to microcosting. The intra-class correlation coefficient is similar to the kappa statistic but allows for correlation between two measurements in relation to a specific target (90). It has been suggested that the Landis and Koch cut points suggested for kappa can be applied to the intra-class correlation coefficient; less than 0.4 for weak agreement, 0.4-0.6 for moderate agreement, 0.6-0.8 for good agreement and greater than 0.8 as excellent agreement (91).

A comparison of the microcosting estimates and RGN- and CMG-specific costs was completed. To enable this, we selected ten of the most common cardiac RGNs and five of the most common CMGs. CMGs are broader groupers than RGNs and as such there were only five commonly seen in the cohort. Basic descriptive statistics were calculated and boxplots were used to visually assess the scatter of microcosting estimates observed within a RGN or CMG. All analyses were completed using SAS, Version 8.1.

2.5 Cost-Utility Model

As noted, to determine the impact of using the different costing methods on the results of a formal cost utility analysis, we used our previously published decision model (Section D) which compared the cost per QALY gained for patients with ischemic heart disease treated with PCI and a drug-eluting stent compared to a bare metal stent. A Markov

process was used to model the cost and clinical outcomes for stented patients post-PCI in 6-month time intervals. Patients progress through the following five Markov health states based on the health state transitions that may occur after an initial PCI: 1) alive with no clinical restenosis (i.e. event free), 2) clinical restenosis as determined by the need for a subsequent coronary artery bypass grafting (CABG) surgery, 3) clinical restenosis as determined by the need for repeat PCI, 4) repeat catheterization with no subsequent revascularization and 5) death (Figure 3). During the first year, costs are assigned to each procedure. In subsequent years, costs are calculated based on age and diabetes subgroup.

The Markov model was run three times; once with costs calculated from microcosting, once with costs calculated using RGN-derived estimates and finally using the CMG-derived estimates. We compared the resulting cost utility ratios. As recommended by the CCOHTA guidelines for economic evaluation, Monte-Carlo simulation was used to develop a distribution for the cost-utility ratios (76). Monte-Carlo simulation allows for all variables for which there was uncertainty in the estimates to be varied simultaneously. Given that, in this case, we are specifically interested in the uncertainty in the costing estimates, and how variation in costs impacts the cost-utility ratio, we only sampled values for the costing variables from the log-normal distribution based on the mean and variance of the log-transformed costs of each costing method. Repetition of this process builds a statistical distribution around the incremental cost-utility ratio estimate. Subsequently, the resulting three sets (one dataset resulting from each simulation) of cost-utility ratios were compared using an ANOVA F-test. Cost-utility modeling was done in DATA 4.0.

3. Results

3.1 Patient-level Comparisons

Microcosting and CMG-derived methods result in very similar mean estimates for the 4-year accrued health care costs (Table 8). However, when the RGN-derived costs are used, the mean value is approximately $6,000 less than the other two methods ($16,684 when microcosting used, $16,232 when CMG-derived estimates are calculated, compared to $10,474 with RGN-derived estimates). Microcosting results in the widest range of total inpatient costs and has the largest variability (range: $521-$172,784, SD: $18,031). The RGN scatter indicates consistent underestimation of costs compared with the microcosting estimates with the scatter being concentrated in the lower left corner and the points generally falling above the line of agreement (Figure 11). The intra-class correlation coefficient is 0.73 (95% CI: 0.69-0.77) indicating "good" agreement. In general, the CMG-derived estimates seem to more closely estimate microcosts (Figure 12). The CMG-derived estimates scatter around the line of agreement with little rotation above or below the line. The agreement between the methods is "excellent" with an intra-class correlation coefficient of 0.86 (95% CI: 0.84-0.88).

Table 8. 4-year accumulated health care costs (N=636)

Unit of analysis: Patient

Method	Mean (SD) ($)	Median (IQR) ($)	Range ($)
Total Inpatient Costs*			
Microcost	16684 (18031)	10786 (7317-18752)	521-172784
RGN-derived	10474 (9803)	6932 (5016-12230)	3514-70137
CMG-derived	16232 (14305)	12088 (7326-19171)	1455-134800
Total Non-hospital Costs**	3939 (2535)	3380 (2324-4866)	0-17550
Total 4 yr. Costs			
Microcost	20623 (19181)	14504 (10420-23170)	2469-176539
RGN-derived	14414 (11228)	10375 (7689-16786)	4203-80343
CMG-derived	20172 (15838)	15454 (10591-23735)	2836-142521

* Includes all hospitalisation costs, including index stay

**Includes physician claims, drug costs, homecare costs and ambulatory care costs

3.2 Hospitalisation-level Comparisons

Table 9 compares microcosting estimates within the ten most common cardiac RGNs. The RGN estimate is lower than the microcost estimate in the majority of RGNs selected. The scatter within each RGN is visually displayed in Figure 13. The median microcosted value is shown with the horizontal bar, the box is drawn by the 25^{th} and 75^{th} percentile (Interquartile range) and the brackets represent the 5^{th} and 95^{th} percentile values. All the RGNs, with the exception of "1240", have extreme outlying microcosting values (indicated by the dots) meaning that in each RGN there are microcosted cases with extremely high costs. In Table 10, which compares the microcost estimate within the five most common cardiac CMGs, we see no observable pattern. For some CMGs the microcost estimate is higher and for others it is lower. The scatter is displayed visually in Figure 14. Again, extreme outlying values are seen in all CMGs.

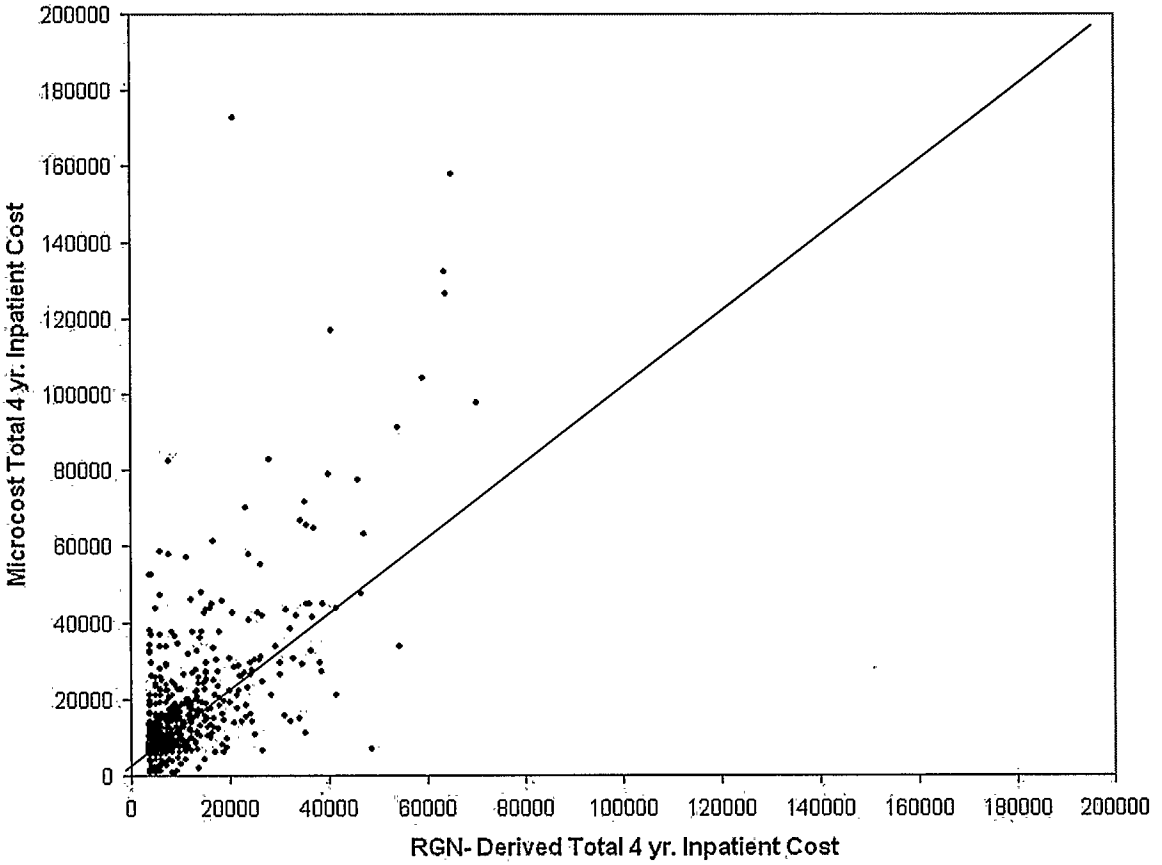


Figure 11. Scatterplot of microcosts versus RGN-derived costs

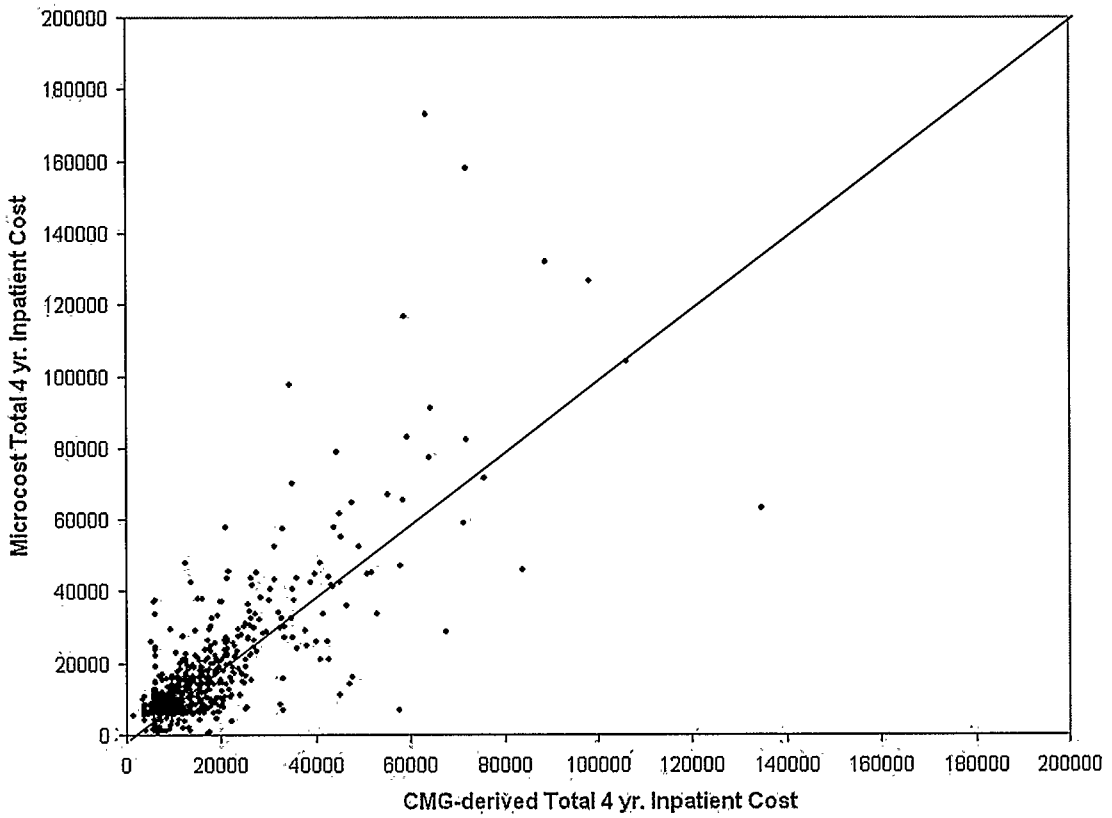


Figure 12. Scatterplot of microcosts versus CMG-derived costs

Table 9. Hospitalisation costs for the ten most common cardiac RGNs

Unit of analysis: Hospitalisation

RGN	N	RGN Cost ($)	Microcost ($) Mean (SD)	Microcost ($) Median (IQR)	Range
1120 – Percutaneous cardiovascular procedures with no complications	41	4181	6503 (2942)	6468 (5832-7880)	726 - 13767
1121- Percutaneous cardiovascular procedures with class C complications	319	5802	7908 (4112	7246 (5878-9336)	720 - 31670
1122 -Percutaneous cardiovascular procedures with class B complications	282	7489	9128 (4336)	8271 (6331-11203)	443-28538
1123 - Percutaneous cardiovascular procedures with class A complications	9	14474	14925 (6040)	16624 (10324-18065)	6550-25396
1161 – Perm Card Pace Impl W/O AMI, Hrt Fail/Shk-class B complications	52	14528	10843 (6666)	10162 (6616-12290)	2396-39818
1240 – Circulatory Disorders except AMI with no complications	19	2943	3302 (2010)	3169 (1640-5059)	171-6681
1241 - Circulatory Disorders except AMI with class C complications	57	4205	4187 (2326)	3627 (2978-5527)	667-14251
1320 - Atherosclerosis with no complications	50	2314	3418 (2313)	2873 (2047-4071)	560-13916
1321 – Atherosclerosis with class C complications	24	2996	3346 (2055)	2673 (1865-4699)	939-9862
1430 – Chest pain with no complications	32	1385	3191 (3823)	1956 (1348-3663)	347-18353

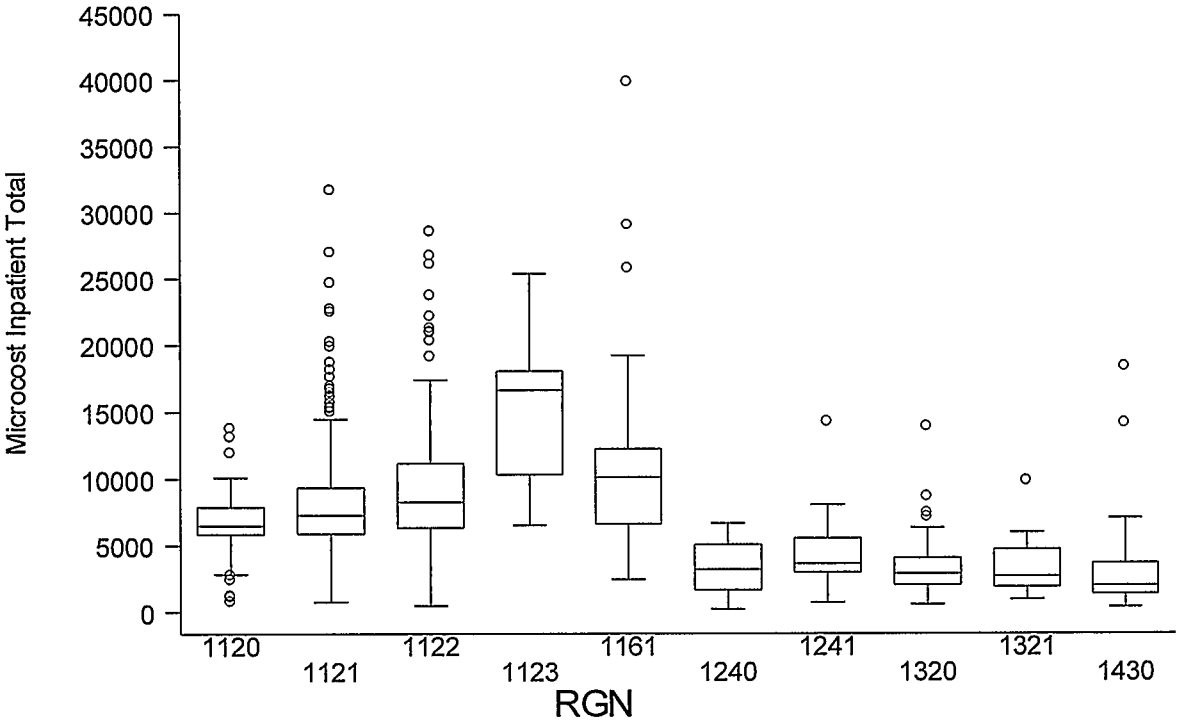


Figure 13 . Distribution of microcosts for specific RGNs

Table 10. Hospitalisation costs for the five most common cardiac CMGs

Unit of Analysis: Hospitalisation

CMG	N	CMG Cost ($)	Microcost ($) Mean (SD)	Microcost ($) Median (IQR)	Range
188 – Percutaneous Transluminal Coronary Angioplasty Angioplasty With Complicating Cardiac Conditions	138	9617	9273 (4836)	9600 (5876 – 11860)	577 - 25433
189 - Percutaneous Transluminal Coronary Angioplasty Angioplasty Without Complicating Cardiac Conditions	275	5960	8353 (6166)	6790 (5726 – 9912)	443 – 43244
208 – AMI without Cardiac Catheterization Without Specified Cardiac Conditions	47	10892	6791 (3612)	6415 (5533 – 7622)	657 – 20885
222 – Heart Failure	108	6257	8970 (5566)	7776 (5801 – 11474)	369 – 40449
229 – Atherosclerosis (May not Require Hospitalisation)	90	10277	5202 (3617)	5609 (2047 – 7479)	867 – 19113

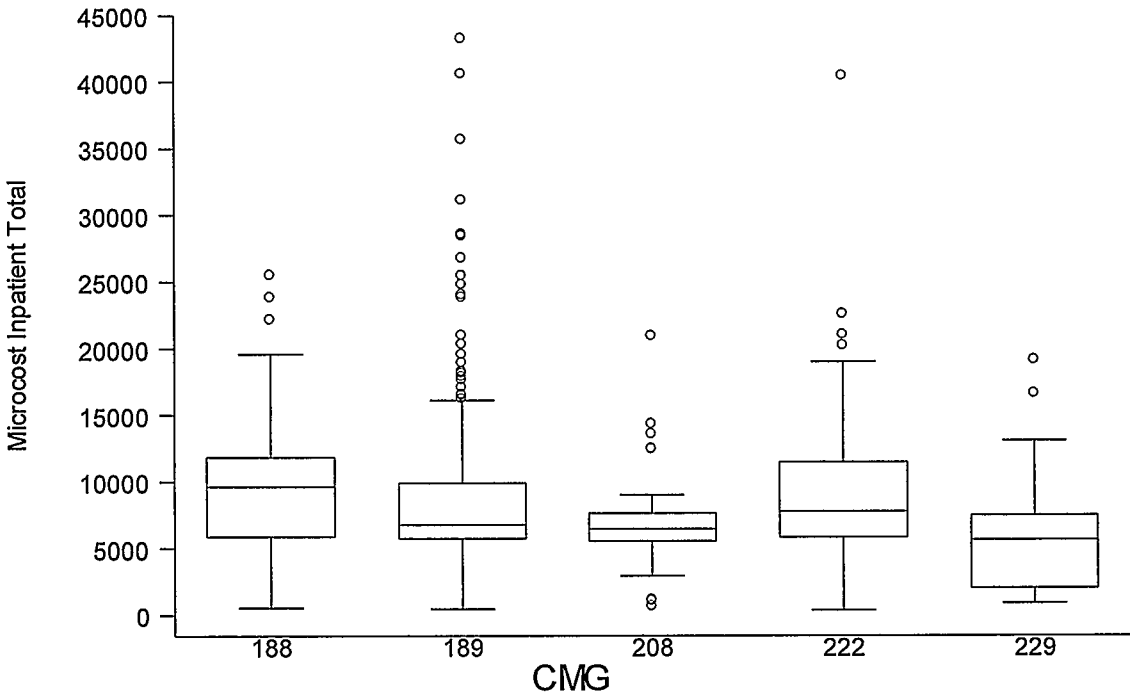


Figure 14. Distribution of microcosts for specific CMGs

3.3 Cost-utility Analysis

All three costing methods have face validity when the input values for our economic evaluation are calculated; those under 65 years of age cost less then those over 75 years of age, patients with no diabetes cost less than those with diabetes (Table 11). Overall, microcosting estimates are higher than the other two methods.

Interestingly, the resulting incremental cost-utility ratios vary across the methods (Table 12). The same pattern emerges with those over 75 and those with diabetes having the most attractive costs per QALY. Using second order Monte Carlo Simulation, varying the costing estimates resulted in a cost per QALY gained of $41,764 (95% CI: $41,182 – $42,346) when microcosting estimates are used, $42,538 per QALY (95% CI: $42,167 - $42,907) when the RGN-derived estimates are used, and $36,566 per QALY (95% CI: $36,172 - $36960) when CMG-derived estimates are used (p-value=0.001). In both absolute and relative terms, the difference in the cost-utility values produced by the three methods is modest but notable.

Table 11. Costing estimates used for the economic evaluation, considering the three different costing methods

	Overall (N=636)	Age group			Diabetic Status	
		< 65 (n = 371)	65-75 (n = 201)	>75 (n = 64)	No Diabetes (n = 535)	Diabetes (n = 101)
Microcosted	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Index Hospitalisation Cost	8385 (8044-8726)	8014 (7633-8395)	8617 (8006-9228)	9808 (8087-11529)	8258 (7905-8591)	9113 (7962-10263)
Year 1						
Event-free	5618 (4926-6310)	4369 (3498-5239)	6743 (5640-7847)	8997 (6136-11858)	5218 (4544-5892)	7888 (5307-10469
CABG	41025 (31046-51004)					
Repeat PCI	13110 (11135-15085)					
Repeat Cath without Revasc.	11215 (9631-12799)					
Year 2	5446 (4942-5950)	4760 (4150-5370)	6573 (5505-7641)	5883 (4813-6953)	5086 (4600-5573)	7353 (5520-9187)
Year 3	2080 (1709-2451)	1736 (1265-2207)	2730 (1969-3490)	2031 (1400-2664)	1891 (1516-2267)	3077 (1852-4303)
Year 4	2216 (1686-2748)	1950 (1252-2648)	2760 (1719-3800)	2060 (1086-3035)	2231 (1630-2832)	2141 (1098-3185)
RGN-Derived						
Index Hospitalisation Cost	5472 (5254-5690)	5230 (5024-5436)	5562 (5167-5957)	6988 (6419-7558)	5360 (5162-5557)	6068 (5176-6960)
Year 1						
Event-free	5952 (5383-6520)	4674 (4034-5314)	7314 (6219-8410)	8778 (6643-10913)	5555 (4990-6120)	8206 (6217-10195)
CABG	29986 (20549-39424)					
Repeat PCI	14673 (12159-17187)					
Repeat Cath without Revasc.	12796 (11014-14578)					
Year 2	5172 (4757-5587)	4381 (3895-4867)	6440 (5547-7333)	5773 (4849-6697)	4887 (4477-5296)	6682 (5235-8129)
Year 3	1129 (956-1302)	771 (555-986)	1672 (1322-2022)	1504 (1182-1825)	1071 (884-1257)	1440 (979-1901)
Year 4	828 (719-937)	559 (426-692)	1175 (968-1382)	1297 (959-1636)	809 (688-930)	928 (680-1176)
CMG-Derived						
Index Hospitalisation Cost	6794 (6518-7071)	6513 (6203-6822)	6988 (6419-7558)	7819 (6739-8900)	6801 (6496-7105)	6762 (6089-7436)
Year 1						
Event-free	7647 (6988-8307)	6132 (5460-6804)	9568 (8074-11061)	10084 (8209-11959)	7184 (6545-7823)	10281 (7822-12741)
CABG	41734 (30636-52832)					
Repeat PCI	18300 (15262-21339)					
Repeat Cath without Revasc.	14165 (12194-16135)					
Year 2	5409 (4994-5825)	4556 (4113-4999)	6729 (5781-7677)	6214 (5159-7269)	5017 (4620-5414)	7490 (5978-9002)
Year 3	2120 (1740-2500)	1483 (1103-1864)	3034 (2229-3838)	2945 (1249-4641)	1879 (1532-2226)	3398 (1872-4924)
Year 4	1879 (1513-2245)	1521 (1112-1931)	2532 (1687-3377)	1904 (1162-2645)	1830 (1438-2222)	2140 (1129-3151)

Table 12. Incremental cost-utility ratios resulting from use of costing estimates derived from the three different costing methods, overall and by subgroup

	Incremental Effectiveness (QALY)	**Microcosted**		**RGN-Derived**		**CMG-Derived**	
		Incremental Cost ($)	Incremental Cost-Utility Ratio ($/QALY)	Incremental Cost ($)	Incremental Cost-Utility Ratio ($/QALY)	Incremental Cost ($)	Incremental Cost-Utility Ratio ($/QALY)
Overall	**0.04**	**1,960**	**45,671**	**1,950**	**45,328**	**1,640**	**38,216**
Age Subgroup							
Under 65	0.04	1,850	52,279	1,850	52,245	1,520	42,935
65-75	0.05	2,020	40,551	2,000	40,087	1,700	34,149
Over 75	0.07	2,360	36,209	2,200	35,220	2,100	32,167
Diabetes Status							
No Diabetes	0.04	1,980	49,432	1,980	49,404	1,670	41,863
Diabetes	0.06	1,870	33,792	1,800	32,454	1,480	26,695

4. Discussion

Within subject, the three costing methods produce quite different estimates. Microcosting generally produced the highest costing estimates and, as expected, the widest range of values. In general, CMG-derived estimates were closer to microcost estimates whereas RGN-derived estimates tended to underestimate costs compared with the microcosting estimates. Within CMG and RGN, there is a wide range of microcosts noted within almost all CMGs and RGNS including some extreme outlying values. However, when focusing on the overall means and medians, the difference is less notable between methods.

When examined in the context of an economic evaluation, the different methods resulted in significantly different cost-utility ratios. As such, the adoption of the results of an economic evaluation into a policy setting may vary with the different costing methods. When various "thresholds" are considered (such as those proposed by Laupacis et al. and Gold et al.), the resulting incremental cost-utility ratios would not change whether or not the technology was adopted in this example (38;39). However, the CMG-derived cost-utility ratio was 16% lower than the cost-utility ratio resulting from microcosting estimates, a relative difference large enough to move the cost per QALY across the proposed threshold in a different situation. In the various subgroups considered, the difference between the methods is even more notable with a 21% difference between the CMG-derived and the microcosting cost-utility ratios noted in the diabetes subgroup. This difference deserves even more consideration when we return to the notion of opportunity cost. Changes in the cost-utility ratios, such as we observe across the costing methods, may affect the adoption of new technologies.

Our results are similar to those reported by Heery et al. whose work compared the specific DRG costs to microcosting (88). Using the Irish DRG system and available microcosting at one hospital, a comparison of the mean microcosted value per DRG and the cost resulting from applying the average case cost to the RIW for each DRG was completed for those DRGs representing acute myocardial infarction (AMI), heart failure and HIV. Significant differences resulted from the two different costing methods within DRG. The largest reported difference was seen in the DRG representing "Percutaneous cardiac procedures for AMI" with the microcosted mean cost being 66% higher than the RIW cost. Heery et al. draw similar conclusions stating that the different methods result in different decisions, particularly when budgeting at the national level. However, this work is limited to one hospital in the Irish system and specific DRGs. Our work includes a broader population in a different country. In addition, we compare two grouping based methods (RGNs and CMGs) to microcosts both within subject and across patient subgroups and specifically, we consider how these different methods impact the outcome of an economic evaluation; a novel contribution to help guide future economic work.

Our model is mainly driven by avoided costs due to avoided second procedures. The difference seen between cost-utility ratios resulting from the three methods is particularly due to the difference in the cost for a repeat PCI. The incremental difference between the cost for those that remain event-free and those that undergo a repeat PCI is approximately $7,500 when microcosting is used, $8,700 when RGN-derived estimates are applied and $10,600 when CMG-derived estimates are used. The larger incremental difference seen with CMG-derived costs is the main driver of the lower cost per QALY. Interestingly, Chumney et al, completed a similar study, comparing DRG costs to a microcosted database, with an economic evaluation of HIV/AIDS therapies (92). Their

work found no significant difference in the resulting cost-effectiveness ratio when using the different costing methods and concluded that in heterogenous conditions such as HIV/AIDS the costing method has little effect on the outcome of a decision model.

Our study has several limitations. Our sample was 636 patients, a selected subset of our original sample. In a situation where the outcome is highly left-skewed, such as costs, this is a small sample size. Additionally, our sample is comprised of patients from one urban centre which may limit the generalisability of the results.

Costs of care are fundamental to performing an economic evaluation. Without a clear understanding of the different sources of costs and the potential bias in the resulting estimates from each method, the limitations of our economic evaluations are not explicitly acknowledged. With different sources of costing data available within Canada, it is important to understand how the different sources affect the outcomes of economic evaluations. Our work provides guidance to those embarking on economic evaluations by explicitly examining the three different approaches to costing, outlining some of the sources of potential bias and the impact on the resulting cost-utility ratios. When microcosts are available, they should be used. However, in many situations, researchers are limited to using grouper-based costs simply due to a lack of availability of microcosts. In these cases, it is important that researchers be aware that their resulting costs may not reflect the true costs to the system. In our particular economic evaluation, the cost per QALY resulting from RGN-derived estimates better approximated the cost per QALY when using microcosted estimates. The CMG-derived cost per QALY was notably different.

H. GLOBAL CONCLUSIONS

1. Relevance of Economic Evaluations

Given the scarcity of resources, both human and monetary, in the publicly-funded health care system, we must explicitly examine the use of available resources and consider whether or not we are using them efficiently. Within the limited funding envelope available, the goal of health care is to achieve maximum health benefits whilst incurring minimal opportunity cost. As such, we need a tool that incorporates both costs and potential benefit to allow us to quantify the returns we get for the resources we invest. Economic evaluations, particularly cost-utility analysis, are a powerful tool used to explicitly weigh the costs and benefits for a given intervention. They allow us to calculate how much we would have to spend in order to receive the expected benefit, one QALY. This provides a standardized measure of benefit that allows for comparison across health interventions for different patient groups and with different expected benefits. The resulting cost per QALY can then be applied in the policy-making realm to help decision-makers use the available resources most efficiently.

In our case, with the development of drug-eluting stents, it is important to weigh the cost of using the new stents in place of the current standard of care against the potential benefit. We completed a formal cost-utility analysis comparing the cost per QALY of drug-eluting stents, specifically sirolimus-eluting stents, to that of bare metal stents.

2. Limitations of Economic Evaluations

While providing valuable information, the traditional cost per QALY has various limitations. The results of an economic evaluation are affected by the input values required to complete the analysis. For example, as our work has shown, the choice of method used to estimate costs does affect the resulting cost per QALY. The choice of comparison

therapy is crucial to the applicability of the model and lastly, all modeling approaches are simulations of what would have happened if the new technology was applied. The generalisability of the results to the "real world" should be critically assessed.

In addition, the cost per QALY alone does not answer the question of whether or not a technology should be funded. Several authors have proposed cost per QALY "thresholds" for whether or not a new technology should be adopted (38-40). However, simply adopting a new technology if the cost per QALY is below a certain amount is a prescription for potentially uncontrolled spending growth in health care (62). When we return to the motion of opportunity cost, we must explicitly examine the trade-offs of funding a particular technology at the cost of funding another.

When considering adopting a new strategy, in the Canadian system, restrictive funding strategies are possible; allowing select groups to receive treatment whilst withholding it from other groups. When adopting restrictive criteria, it is important to consider the impact of such strategies on equity. However, it is important to note that depending on the definition of equity adopted, restricted funding strategies need not violate the principle of equity. There is a growing literature attempting to identify other characteristics that should be considered. These include 1) whether an intervention is immediately life saving and less so the expected gain in life expectancy, 2) the impact on quality of life, 3) the number of people eligible for treatment, 4) the age of the potentially treatable patients (younger versus older), 5) whether the treatment was for people with good or poor underlying baseline health, 6) the likelihood of the treatment being successful, and 7) its impact on equality of access to therapy (67;68). All these issues should be weighed when considering the case for adopting a new treatment. An organized approach to weighing the costs and benefits of treatments is necessary to aid decision-makers.

Providing guidance to those responsible for the implementation of new strategies helps make decisions more transparent and evidence-based.

3. Translation of Findings

Recognizing the complexity of these issues, this thesis attempted to do much more than the traditional economic evaluation. Both methodological and presentation issues were tackled. Understanding that the cost per QALY rubric is often uninformative to decision-makers, we re-packaged our results in concrete terms; we projected the potential benefit, and cost, associated with various funding scenarios for the Alberta population. We completed a detailed budget impact analysis and presented a thorough discussion of the issues facing decision-makers including equity, opportunity cost, and the current setting in which decisions for funding new technology are made.

Globally, our findings indicate that the "economic case" for funding drug-eluting stents across-the-board is modest at best and that restricted funding scenarios (especially ones focusing on high risk lesions) are perhaps more reasonable. When considering the impact of restricted funding scenarios, a clear understanding of the trade-offs is important. Therapies currently being funded, the size of the local budget and, if necessary, what programme resources could be cut or scaled back to fund drug-eluting stents must all be explicitly considered. While decision-makers must consider other characteristics of a new intervention, the central goal of policy-makers should remain to provide maximize health gains, within the allocated budget.

4. Methodological Exploration

Economic evaluations are the sum of their parts. The input values required to perform an economic evaluation can introduce bias into the model. In the case of cost-utility analysis, the model is dependent on the utility scores and the costs. The CCOHTA

guidelines, and other published guidelines, offer little guidance concerning measurement of both costs and benefits. Thus, we completed two sub-studies in which we examined the impact of using different methods to estimate health-related quality of life and costs on the resulting cost-utility ratio. We explored two different scoring algorithms for the EQ-5D and three different methods available to measure costs.

Within our dataset, we found quite notable differences between subjects when we compared the different scoring approaches for the EQ-5D. However, when compared across various subgroups the differences in the means were modest and negligible when input into the cost-utility analysis. In different clinical populations and contexts, however, the impact of the different methods may vary.

When different costing methods were compared a similar pattern was observed. Within subjects the differences between the methods were notable. However, when we considered differences across subjects, the differences in the means were less notable. In the context of our economic evaluation, unlike the HRQOL substudy, we found a significant difference between the cost-utility ratios resulting from the three methods.

Ideally, other researchers should complete similar analyses. Our additional analyses provided insight into the impact of different methodological choices on the outcome of an economic evaluation. However, due to the timeliness often required when completing a cost-utility analysis and the lack of available data, the completion of such analyses is not always feasible. Our work will provide guidance to those undertaking similar work and allow other researchers to understand the possible impact on the outcome of their analyses.

5. Reiteration of Significance

The work presented here goes beyond a traditional economic evaluation. We attempted to present the results of our study in an accessible, easy-to-understand fashion for

decision-makers to better use our results. Additionally, we explored how different methodological choices, for measuring both costs and health-related quality of life, can impact the results of a decision model. This work not only informs decision-makers concerning the cost per QALY of sirolimus-eluting stents but also provides guidance to other researchers undertaking similar work.

K. REFERENCE LIST

(1) Heart and Stroke Foundation of Canada. The Growing Burden of Heart Disease and Stroke in Canada 2003. 2003. Ottawa, Heart and Stroke Foundation of Canada.

(2) Faris PD, Grant FC, Galbraith PD, Gong Y, Ghali WA, For the CCORT Investigators. Diagnostic Cardiac Catheterization and Revascularization Rates for Coronary Heart Disease. Can J Cardiol 20[4], 390-397. 2004.

(3) Cutlip DE, Chauhan MS, Baim DS, Ho KKL, Popma JJ, Carrozza JP et al. Clinical Restenosis After Coronary Stenting: Perspectives From Multicenter Clinical Trials. J Am Coll Cardiol 40[12], 2082-2089. 2002.

(4) Weaver WD, Reisman MA, Griffin JJ, et al. Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): A Randomized trial. Lancet 355, 2199-2203. 2000.

(5) Morice MC, Serruys PW SJ, Fajadet J, Ban Hayashi E, Perin M, Colombo A et al. A Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization. N Engl J Med 346[23], 1773-1780. 6-6-2002.

(6) Moses JW, Leon MB, Popma J, Fitzgerald PJ, Holmes DR, O'Shaughnessy C et al. Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery. N Engl J Med 349[14], 1315-1323. 10-2-2003.

(7) Schampaert E, et al, for the C-SIRIUS Investigators. The Canadian Study of Sirolimus-eluting Stent in the Treatment of Patients with Long De Novo Lesions in Small Native Coronary Arteries (C-SIRIUS). JACC 43[6], 1110-1115. 2004.

(8) Schofer J, et al, for the E-SIRIUS Investigators. Sirolimus-eluting Stents for Treatment of Pateints with Long Atherosclerotic Lesions in Small Coronary Arteries: Double-blind Randomised Controlled Trial (E-SIRIUS). The Lancet 362, 1093-1099. 2003.

(9) Coding Guidelines for Drug-Eluting Stents. 10-10-2003.

(10) Dolan P. Modelling Valuations for the EuroQol Health States. Med Care 35, 1095-1108. 1997.

(11) Shaw JW, Johnson JA, Coons SJ. US Valuations of the EQ-5D Health States: Development and Testing of the D1 Valuation Model. Medical Care 43[3], 203-220. 2005.

(12) Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion:operative technique. Ann Thorac Surg 5, 334-339. 1968.

(13) The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven Year survival in the Veteran's Administration randomized trial of coronary bypass surgery for stable angina. N Engl J Med 311, 1333-1339. 1984.

(14) Varnauskas E, for the European Coronary Study Group. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 319, 332-337. 1998.

(15) Alderman EL, Bourassa MG, Cohen LS, et al. Ten year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation 82, 1629-1646. 1990.

(16) Detre KM, Peduzzi P, Murphy M, et al. Effect of bypass surgery on survival of patients in low- and high-risk subgroups delineated by the use of simple clinical variables: Veterans Administration cooperative study of surgery for coronary arterial occlusive disease. Circulation 63, 1329-1338. 1981.

(17) Passamani E, Davis KB, Gillespie MJ, Killip T, CASS principal Investigators. A randomized trail of coronary artery bypass surgery: survival in patients with low ejection fraction. N Engl J Med 312, 1665-1671. 1985.

(18) Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary arery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 301, 61-8. 1979.

(19) The Bypass Angioplasty Revascularisation Investigation Investigators (BARI). Comparison of Coronary Bypass Surgery with Angioplasty in Patients with Mutlivessel Disease. N Engl J Med 335, 217-225. 1996.

(20) Protocol for the Bypass Angioplasty Revascularization Investigation. Circulation 84:Suppl V, V1-V27. 1991.

(21) Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. Lancet 346, 1184-1189. 1995.

(22) Fallen EL, et al. Management of the postmyocardial infarction patient: a consensus report--revision of 1991 CCS guidelines. Can J Cardiol 11[6], 477-486. 1995.

(23) McGrath PD, Malenka DJ, Wennberg DE, et al, For the Northern New England Cardiovascular Disease Study Group. Changing Outcomes in Percutaneous Coronary Interventions: A Study of 34,752 Procedures in Nothern New England, 1990-1997. J Am Coll Cardiol 34, 674-680. 1999.

(24) Serruys PW, De-Jaegere P, Kiemeneji F, et al., For the BENESTENT Study Group. A comparison of Balloon-expandable Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease. N Engl J Med 331, 489-495. 1994.

(25) Fischman DL, Leon MB, Baim DS, et al, Stent Restenosis Study Investigators. A Randomized Compariosn of Coronary Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease. N Engl J Med 331, 496-501. 1994.

(26) Suwaidi JA, Holmes DR, Salam AM, Lennon R, Berger PB. Impact of Coronary Artery Stents on Mortality and Nonfatal Myocardial Infarction: Meta-analysis of

Randomized Trials Comparing a Strategy of Routine Stenting with that of Balloon Angioplasty. Am Heart J 147, 815-822. 2004.

(27) Babapulle MN, Eisenberg, MJ. Coated Stents for the Prevention of Restenosis: Part II. Circulation 106, 2859-2866. 2002.

(28) Marks AR. Sirolimua for the Prevention of In-Stent Restenosis in a Coronary Artery. N Engl J Med 349[14], 1307-1309. 2003.

(29) Marx SO, Jayaraman T, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of profileration in vascular smooth muscle cells. Circ Res 76, 412-417. 1995.

(30) Gallo R, Padurean A, Chesebro JH, et al. Inhibition of initimal thickening after balloon in porcine coronary arteries by targeting regulators of cell cycle. Circulation 99, 2164-2170. 1998.

(31) Lovdahl C, Thyberg J, Hultgardh-Nilsson A. The Synthetic Metalloproteinase Inhibitor Batimastat Suppresses Injury-induced Phosphorylation of MAP Kniase ERK1/ERK2 and Phenotype Modification of Arterial Smooth Muscle Cell in Vitro. J Vasc Res 37, 345-354. 2000.

(32) Health Canada. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2003/cypher_hpc-cps_e.html , -Accessed Sept. 2003. 2006.

(33) Donaldson C, Shackley P. Economic Evaluation in Oxford Textbook of Public Health (3 ed). Chap 26. 1997. Oxford, Oxford University Press.

(34) Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 2 ed. 1997. Oxford, UK, Oxford University Press.

(35) O'Brien B. Economic Evaluation of Pharmaceuticals: Frankenstein's Monster or Vampire of Trials? Med Care 34[12], DS99-DS108. 1996.

(36) Detsky AS, et al. Primer on Medical Decision Analysis. Med Decis Making 17, 123-159. 1997.

(37) Weinstein MC. Clinical Decision Analysis. 1980. Toronto, Saunders.

(38) Gold M. Panel on cost-effectiveness in health and medicine. Med Care 34[Suppl 12], DS197-DS199. 1996.

(39) Laupacis A, Feeny D, Detsky AS, Tugwell PX. Tentative Guidelines for Using Clinical and Economic Evaluations Revisited. Can Med Assoc J 148[6], 927-929. 1993.

(40) National Institute for Clinical Excellence. NICE Clinical Guidelines. 2003.

(41) Ghali WA, Knudtson ML, on behalf of the APPROACH Investigators. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease. Can J Cardiol 16[10], 1225-1230. 2000.

(42) Statistics Canada. Statistics Canada Catalogue no. 91-213. 2002.

(43) Statistics Canada. Latest release from consumer price index. Daily Statistics Canada , 1-4. 11-19-2003.

(44) Egger M, Davey Smith G, Altman DG, Chalmers I. Systematic Reviews in Health Care: Meta-analysis in context. 2001. London, BMJ Publishing Group.

(45) Ghali WA, Quan H, Shrive FM, Hirsch GM, for the Canadian Cardiovascular Outcomes Research Team (CCORT). Outcomes after coronary artery bypass graft surgery in Canada: 1992/93 to 2000/01. Can J Cardiol 19[7], 774-781. 2003.

(46) Goodney PP, O'Connor GT, Wennberg DE, Birkmeyer JD. Do Hospitals with low mortality rates in coronary artery bypass also perform well in valve replacement? Ann Thorac Surg 76, 1131-1137. 2003.

(47) Jamal SM, Shrive FM, Ghali WA, Knudtson ML, Eisenberg MJ, for the Canadian Cardiovascular Outcomes Research Team (CCORT). In-hospital outcomes after percutaneous coronary intervention in Canada: 1992/93 to 2000/01. Can J Cardiol 19[7], 782-789. 2003.

(48) Ellis SG, et al, for the Multivessel Angioplasty Prognosis Study Group. Coronary Morphologic and Clinical Determinants of Procedural Outcome with Angioplasty for Multivessel Coronary Disease: Implications for Patient Selection. Circulation 82[4], 1193-1201. 1990.

(49) World Bank. World development indicators 2000. 2001. Washington DC, World Bank.

(50) Malenka DJ, Wennberg DE et al, For the Northern New England Cardiovascular Disease Study Group. Gender-related Changes in Practice and Outcomes of Percutaneous Coronary Interventions in Northern New England From 1994 to 1999. J Am Coll Cardiol 40[12], 2092-2101. 2002.

(51) Greenberg D, Bakhai A, Cohen DJ. Can we afford to eliminate restenosis? Can we afford not to? JACC 43[4], 513-518. 2004.

(52) Harvard Center for Risk Analysis. The CEA registry: Standardizing the methods and practices of cost-effectiveness analysis. 2003. Boston, Harvard Center for Risk Analysis.

(53) Pilskin JS, Stason WB, Weinstein MC, et al. Coronary artery bypass graft surgery: clinical decision making and cost-effectiveness analysis. Med Decis Making 1, 10-28. 1981.

(54) Weinstein MC, Stason WB. Cost-effectiveness of coronary-artery bypass surgery. Circulation 66[Suppl III], III56-III66. 1982.

(55) Owens DK, Saunders GD, Harris RA, et al. Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. Ann Intern Med 126, 1-12. 1997.

(56) CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 287[15], 2542-2551. 2002.

(57) Giedd KN, Bergmann SR. Myocardial Perfusion Imaging Following Percutaneous Coronary Intervention: The importance of Restenosis, Disease Progression, and Directed Reintervention. JACC 43[3], 328-336. 4-2-2004.

(58) Hill R, Bagust A, Bakhai A, et al. Coronary Artery Stents: A Rapid Systematic Review and Economic Evaluation. Health Technol Assess 2004, 1-242. 2006.

(59) Smith SC, et al., American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty)the Society for Cardiac Angiography and Interventions. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)-executive summary: a report of the American College of Cardiology/American Heart Association task force on

practice guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty) endorsed by the Society for Cardiac Angiography and Interventions. Circulation 103[24], 3019-3041. 2001.

(60) Donaldson C, Currie G, Mitton C. Cost effectiveness analysis in health care: contradiction. BMJ 325, 891-894. 2002.

(61) Birch S, Gafni A. The "NICE" Approach to Technology Assessment: An Economics Perspective. Health Care Manag.Sci 7, 35-41. 2004.

(62) Gafni, Birch S. Guidelines for the Adoption of New Technologies:A Prescription for Uncontrolled Growth in Expenditures and How to Avoid the Problem. Can Med Assoc J 148[6], 913-917. 1993.

(63) Mushlin AI, Hall WJ, Swanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. Circulation 97, 2129-2135. 1998.

(64) O'Brien BJ, et al, For the CIDS Investigators. Cost-Effectiveness of the Implantable Cardioverter-Defibrillator: Results from the Canadian Implantable Defibrillator Study (CIDS). Circulation 103, 1416-1421. 2001.

(65) Culyer AJ. Equity - some Theory and its Policy Implications. Journal of Med Ethics 27, 275-283. 2001.

(66) Culyer AJ, Wagstaff A. Equity and equality in health and health care. J Health Econ 12, 431-457. 1993.

(67) Dolan P, Cookson R. A Qualitative Study of the Extent to Which Health Gain Matters when Choosing Between Groups of Patients. Health Policy 51, 19-30. 2000.

(68) Schwappach DLB. Resource Allocation, Social Values and the QALY: A Review of the Debate and Empirical Evidence. Health Expectations 5, 210-222. 2002.

(69) Mitton C, Donaldson C. Tools of the trade: a comparative analysis of approaches to priority setting in healthcare. Health Serv Manage Res 16[2], 96-105. 2003.

(70) Guyatt GH, Feeny DH, Patrick DL. Measuring Health-related Quality of LIfe. Ann Intern Med 118[8], 622-629. 1993.

(71) Jenkinson C, Layte R, Wright L, Coulter A. Manual and interpretation guide for the UK SF-36. 1996. Oxford, Oxford: Health Services Research Unit.

(72) Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. Pharmacoeconomics. 17[1], 13-35.

(73) Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI) System for Assessing Health Related Quality of Life in Clinical Studies. Ann Intern Med 33, 375-384. 2001.

(74) EuroQol Group. EuroQol: A New Facility for teh Measurement of Health-related Quality of LIfe. Health Policy 16, 199-208. 1990.

(75) Johnson JA, Luo N, Shaw JW, Kind P, Coons SJ. Valuations of EQ-5D Health States: Are the United States and United Kingdom Different? Medical Care 43[3], 221-228. 2005.

(76) Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluations of pharmaceuticals: Canada. [2 ed.]. 1997. Ottawa, Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

(77) Luo N, Johnson JA, Shaw JW, Coons SJ. Comparative Performance of the D1 (US) and N3 (UK) Scoring Functions for the EQ-5D. UNDER REVIEW. 2006.

(78) Marra CA, Esdaile JM, Guh D, Kopec JA, Brazier JE, Koehler BE et al. A Comparison of Four Indirect Methods of Assessing Utility Values in Rheumatoid Arthritis. Medical Care 42[11], 1125-1131. 2004.

(79) Hatoum HT, Brazier JE, Akhras KS. Comparison of the HUI3 with the SF-36 Preference Based SF-6D in a Clinical Trial Setting. Value In Health 7[5], 602-609. 2004.

(80) Feeny DH, Furlong WJ, Torrance GW, Goldsmith CH, Zhu Z, DePauw S et al. Multiattribute and Singe-attribute Utility functions for the Health Utilities Index Mark 3 System. Medical Care 40[2], 113-128. 2001.

(81) Torrance GW, Feeny DH, Furlong WJ, Barr R, Zhang Y, Wang Q. Multiattribute Utility Function for a Comprehensive Health Status Classification System: Health Utilities Index Mark 2. Medical Care 34[7], 702-722. 1999.

(82) Canadian Institute for Health Information. Acute Care Grouping Methodologies: From Diagnosis Related Groups to Case Mix Groupers Redevelopment. 2004. Ottawa.

(83) Health Resourcing Branch AHW. Health Costing in Alberta: 1999 Annual Report. 1999.

(84) Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA, for the APPROACH Investigators. Economic Evaluation of Sirolimus-eluting Stents. CMAJ 172, 345-351. 2005.

(85) Canadian Coordinating Office for Health Technology Assessment. A Guidance Document for the Costing Process. 1996.

(86) Oostenbrink JB, Koopmanschap MA, Rutten FFH. Standardisation of Costs: The Dutch Manual for Costing in Economic Evaluations. Pharmacoeconomics 20[7], 443-454. 2002.

(87) Cohen DJ, Breall JA, Ho KK, et al. Economics of Elective Coronary Revascularization: Comparison of costs and charges for conventional Angioplasty, directional atherectomy, stenting and bypass surgery. J Am Coll Cardiol 22, 1052-1059. 1993.

(88) Heerey A, McGowan B, Ryan M, Barry M. Microcosting versus DRGs in the provision of costs estimates for use in pharmacoeconomic evaluation. Expert Review Pharmacoeconomics Outcomes Research 2[1], 29-33. 2002.

(89) The Institute of Health Economics. Provincial and National cost per Weighted Case for Inpatient Services for Fiscal Year 2000/1. www.ihe.ca, accessed Jan 17, 2006. 2006.

(90) Shrout PE, Fleiss JL. Intraclass Correlations: Uses in Assessing Rater Reliability. Psychological Bulletin 86[2], 420-428. 1979.

(91) Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics 33, 159-174. 1977.

(92) Chumney EC, Biddle AK, Simpson KN, Weinberger M, Magruder KM, Zelman WN. The effect of cost construction based on either DRG or ICD-9 codes or risk stratification on the resulting cost-effectiveness ratio. Pharmacoeconomics. 22[18], 1209-1216. 2004.

L. APPENDIX

Comparison of the UK- and US-based Scoring Algorithms

Both scoring algorithms begin by assigning a score of 1 to each patient. The below coefficients are for indicator variables which are equal to 1 if the patient's response is the level indicated. The values are subtracted from the score.

UK Scoring Algorithm		**US Scoring Algorithm**	
Term	Co-efficient	Term	Co-efficient
Mobility-2	0.069	Mobility-2	0.146
Mobility-3	0.314	Mobility-3	0.558
Self Care-2	0.104	Self Care-2	0.175
Self Care-3	0.214	Self Care-3	0.471
Usual Activities-2	0.036	Usual Activities-2	0.140
Usual Activites-3	0.094	Usual Activites-3	0.374
Pain/Discomfort-2	0.123	Pain/Discomfort-2	0.173
Pain/Discomfort-3	0.386	Pain/Discomfort-3	0.537
Anxiety-2	0.071	Anxiety-2	0.156
Anxiety-3	0.236	Anxiety-3	0.450
Constant-2*	0.081	D1†	-0.140
Constant-3**	0.269	I2-Squared††	0.011
		I3•	-0.122
		I3-Squared••	-0.015

* Indicates one or more items at level 2 or 3

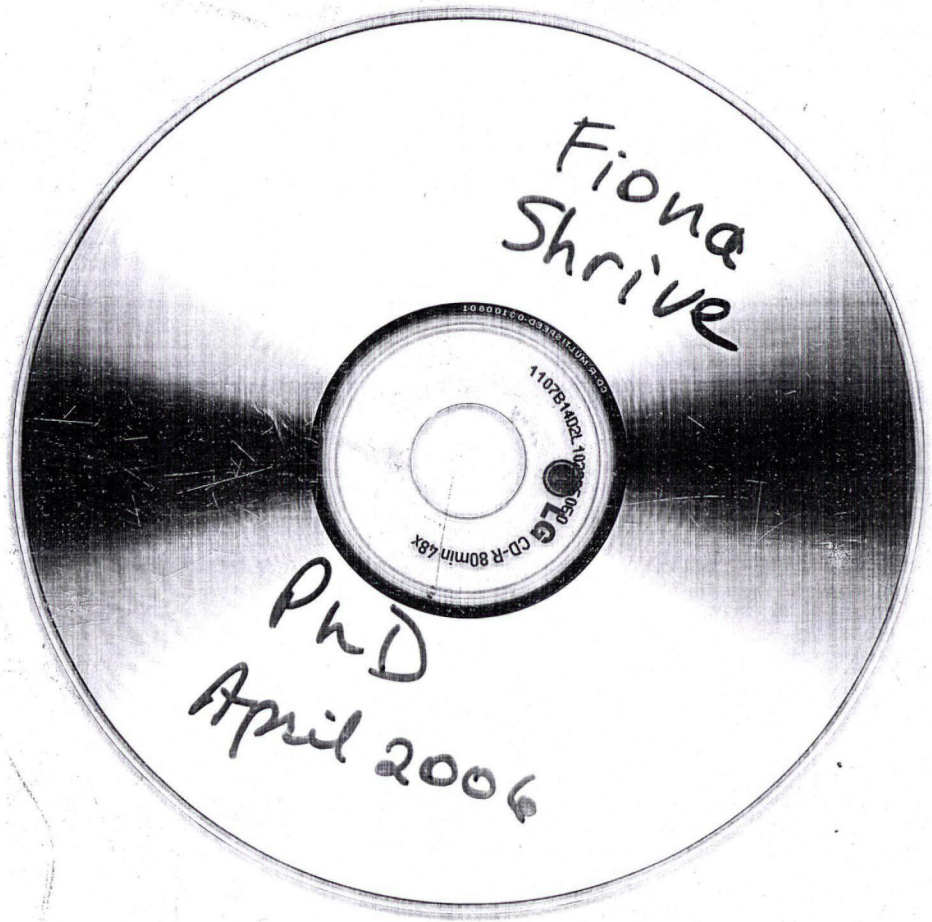
** Indicates one or more items at level 3

†Indicates the number of movements away from perfect health

††Indicates the number of items at level 2 beyond the first – Squared

•Indicates the number of items at level 3 beyond the first

•• Indicates the number of items at level 3 beyond the first - Squared


Fiona
Shrive
PhD
April 2006
CD-R 80min 48x