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**Antiplatelet Agents in the Secondary Prevention of Vascular Events in Adults Undergoing
Percutaneous Coronary Intervention: Cost-Effectiveness, Budget Impact and Research Priorities**

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ANTIPLATELET AGENTS IN THE SECONDARY PREVENTION OF VASCULAR
EVENTS IN ADULTS UNDERGOING PERCUTANEOUS CORONARY
INTERVENTION:

COST-EFFECTIVENESS, BUDGET IMPACT AND RESEARCH PRIORITIES

ERIN LEIGH RUSSELL

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies (FGPS) in partial
fulfilment of the requirements for the MSc degree in Epidemiology

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ABSTRACT

This thesis was undertaken to investigate the cost-effectiveness of various antiplatelet regimens used in the secondary prevention of vascular events in adults undergoing percutaneous coronary intervention (PCI). Analyses include the first economic evaluation to evaluate three antiplatelet regimens (clopidogrel + ASA, ticlopidine + ASA, and ASA alone) for the PCI indication from the perspective of the Canadian provincial/territorial healthcare payer, budget impact analyses investigating potential consequences of changing prescribing patterns, and a value of information analysis indicating future research priorities. Results demonstrate that, for a population of patients undergoing PCI at age 60, one year of antiplatelet therapy with ticlopidine + ASA, followed by lifetime ASA therapy, dominates clopidogrel + ASA therapy due to lower costs and better health outcomes (ICER = \$523.44 vs. ASA alone). The clinical effectiveness of ticlopidine is proven to be the most uncertain variable in the model, and further clinical research is recommended.

ACRONYMS AND ABBRVIATIONS

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
ASA	acetyl salicylic acid
BIA	budget impact analysis
BMS	bare metal stent
CAD	coronary artery disease
CDTI	Canadian Disease Therapeutic Index
CEA	cost-effectiveness analysis
CEAc	cost-effectiveness acceptability curve
CIHI	Canadian Institute for Health Information
CLARITY	CLopidogrel as Adjunctive Reperfusion TherapY
CLASSICS	CLopidogrel ASpirin Stent International Cooperative Study
CREDO	Clopidogrel for the Reduction of Events During Observation
CUA	cost-utility analysis
CURE	Clopidogrel in Unstable angina to prevent Recurring Events
DES	drug-eluting stents
DSA	deterministic sensitivity analysis
EVPI	estimated value of perfect information
EVPPi	estimated value of partial perfect information
FDA	Food and Drug Administration
HRQL	health-related quality of life
HUI	health utility index
ICER	incremental cost-effectiveness ratio
INB	incremental net benefit
LOE	languages other than English
LYG	life-years gained
MI	myocardial infarction
MTC	mixed treatment comparison

NICE	National Institute for Clinical Excellence
NMB	net monetary benefit
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QOL	quality of life
RR	relative risk
TTO	time trade-off
TTP	thrombotic thrombocytopenic purpura
UK	United Kingdom
WTP	willingness-to-pay

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1. Introduction

1.1 Background

Percutaneous revascularization techniques were first described by Grüntzig et al. in the late 1970s.¹ Initially synonymous with percutaneous transluminal coronary angioplasty (PTCA), the term percutaneous coronary intervention (PCI) now includes several techniques used to relieve coronary narrowing; including the insertion of bare-metal or drug-eluting stents (BMS and DES, respectively).² Following the intervention, patients are at risk of thrombus formation at the site of the reopened artery. For this reason, aspirin, heparin, and antiplatelet agents are given before and after PCI, in order to prevent complications.³

Ticlopidine was the first thienopyridine approved for use in patients undergoing PCI.⁴ The first clinical trial to evaluate ticlopidine in this indication was published in 1996.⁵ This publication showed no significant difference in the incidence of stent thrombosis at one month post-PCI between patients receiving ticlopidine + 5 days of aspirin versus those receiving aspirin only.⁵ Subsequent trials compared dual antiplatelet therapy with ticlopidine + aspirin to aspirin + anticoagulation and found that ticlopidine + ASA then, dual antiplatelet therapy has been adopted as the standard of care following PCI.

Clopidogrel is a second generation thienopyridine. It has been suggested that it has a superior side effect profile to ticlopidine.^{4,7} The CLASSICS safety study, published in 2000, found that the composite end point of major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of the study drug for noncardiac

adverse events occurred in 9.1% of patients in the ticlopidine + ASA group, versus 4.6% of patients in the clopidogrel + ASA group, at one month follow up.⁸ As a result, clopidogrel has become the antiplatelet of choice for use, in combination with ASA, in the PCI setting.

Antiplatelet hyporesponsiveness, or 'resistance', is a newly-described phenomenon.^{7,9} It has been estimated that ten to fifteen percent of the population is resistant to aspirin, and 29% is resistant to clopidogrel, with approximately 9% of people being resistant to both.⁷ In March 2010, the US FDA added a boxed warning to clopidogrel indicating that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form¹⁰. There also exists a *P2Y12* hyperfunction allele, which converts more clopidogrel to its active metabolite and may be associated with increased bleeding.

Prasugrel is a third generation thienopyridine approved by the Food and Drug Administration (FDA) in the summer of 2009 for the treatment of patients with acute coronary syndrome (ACS) undergoing PCI.¹¹ At the time of writing, it has not been approved for this indication in Canada. Prasugrel is metabolized by the CYP liver enzymes, as is clopidogrel, but the literature suggests that the active metabolite of this new antiplatelet agent is generated more efficiently, resulting in more rapid, potent, and consistent platelet inhibition than with clopidogrel.⁹ In the US, prasugrel was introduced at a price 18% higher than clopidogrel¹².

The economic evaluation of antiplatelet therapies in adult patients undergoing PCI is of interest due to the significant variation in cost between the three therapeutic options currently available (ASA is approximately \$50/yr, ticlopidine \$500/yr., and clopidogrel over \$1000/yr.), and the expected market approval of the more-expensive prasugrel. Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend 75 mg of clopidogrel for a minimum of one month following BMS placement, three months for sirolimus-coated stents and at least six months for tacrolimus-coated stents.¹³ Despite these recommendations, there remains significant inter-patient variation with regards to antiplatelet therapy in adults undergoing PCI and it has been reported that almost 1 in 7 patients discontinue thienopyridine therapy within one month of receiving a DES.¹⁴ Garavalia et al. asked health care providers to identify barriers to clopidogrel continuance and found that the the most common response was cost.¹⁴

In Canada, most patients requiring treatment for the secondary prevention of vascular events are likely to have their treatment costs covered by the public healthcare jurisdictions. However, most Canadians must also realize that these healthcare jurisdictions have limited capacity to fund the ever-increasing costs of prescription medications. In order to maximize the efficiency of our healthcare system, it is important that an economic evaluation be conducted from the perspective of the provincial healthcare system to determine the most clinically- and cost-effective treatment option for the secondary prevention of vascular events in adults undergoing percutaneous coronary intervention.

Economic evaluation is a widely accepted tool for the appraisal of health care programs.¹⁵

“The main purpose of an economic evaluation is to “identify, measure, value and compare the costs and consequences of alternatives being considered” to inform “value for money judgements about an intervention or program.”¹⁵ Economic evaluation deals with the costs and benefits of a given intervention.¹⁶ Of particular importance is the opportunity cost, and the aim of economic evaluation in health care is to ensure that the benefits of the programs implemented are greater than the opportunity costs of such programs.¹⁵

Conducting an economic evaluation requires an understanding of the natural history of disease that the intervention is designed to treat. A Markov model is a commonly used approach in economic modelling.¹⁷ This type of model is structured around exclusive disease states.¹⁷ All major health states that could arise should be considered. Disease prognosis is then modelled as a set of possible transitions between health states over discrete time periods, referred to as cycles.¹⁷ Baseline probabilities of the occurrence of these states (or events) can be obtained from published epidemiological sources. Clinical trial data provide relative risk estimates for each health state in order to value the outcomes resulting from different treatment options.

Each health state included in an economic evaluation must have a specific cost associated with it. The costs considered in an economic evaluation depend, at least in part, on the perspective of the analysis. For example, an evaluation conducted from a societal point

of view may include travel costs accrued by the patient or caregiver, whereas these costs are not considered if the evaluation is being conducted from the perspective of the Ministry of Health.

While the identification of costs is similar across most economic evaluations, there are several different strategies for how to measure the benefits of a given health intervention, relative to another.¹⁸ For example, a cost-effectiveness analysis measures health benefits in natural units, commonly life years gained.¹⁶ A cost utility analysis measures the relative effect of the intervention on both the quality and the quantity of life gained, using quality-adjusted life years (QALYs).¹⁶ QALYs are generally calculated by multiplying the quality-adjustment weight, or utility value, for each health state by the time in that state.¹⁸ Conducting a cost-utility analysis requires both cost and utility estimates for each health state.

Each of the estimates used to populate an economic model is associated with a certain degree of uncertainty, as is the model itself. “Uncertainty occurs when the true value of a parameter is unknown, thus reflecting the fact that knowledge or measurement is imperfect.”¹⁵ The Guidelines for the Economic Evaluation of Health Technologies: Canada recommends that a deterministic sensitivity analysis (DSA) should be performed for all model inputs and encourages the use of a probabilistic sensitivity analysis (PSA) in economic evaluation.¹⁵ A DSA involves substituting different values for one or more model inputs.¹⁵ A PSA uses the probability distributions for all model parameters in a Monte Carlo simulation, for a large number of iterations.¹⁵ The expected values obtained

from a PSA take into account uncertainty surrounding all of the parameters in the model.¹⁵ Decision uncertainty can be represented using cost-effectiveness acceptability curves (CEACs).¹⁹ A CEAC shows the probability that a given intervention is more cost-effective than its comparators, across different willingness-to-pay (WTP) thresholds.¹⁸

It is recognized that many health care decisions are made based on imperfect, or uncertain, information. A value of information analysis attempts to quantify this uncertainty, using the probability that a decision made based on current information will be wrong and the consequences of making a wrong decision.¹⁷ The expected value of perfect information (EVPI) places an upper bound on the value of conducting further research, while the expected value of perfect information for parameters (EVPPI) indicates what type of additional evidence holds the greatest value to the decision-maker.¹⁷

1.2 Objectives

The purpose of this study is to review the current economic literature regarding the use of antiplatelet agents in the secondary prevention of vascular events in adults undergoing percutaneous coronary intervention and to assess the cost-effectiveness of various treatment regimens. Further analyses will identify both future research priorities and the potential budgetary impacts of changes in antiplatelet prescribing practice.

2. Review of Economic Studies

2.1 Objective

A review of existing economic evaluations was undertaken in order to obtain previous estimates of cost-effectiveness, to look for relevant Canadian analyses, and to locate any relevant data for the primary economic evaluation.

2.2 Methods

The following bibliographic databases were searched on January 6th, 2010, through the Ovid interface: MEDLINE, EMBASE, and BIOSIS. Parallel searches were run in the Health Economic Evaluations Database (HEED) and Centre for Reviews and Dissemination (CRD). The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were PCI and six antiplatelet medications (aspirin, Aggrenox, clopidogrel, dipyridamole, prasugrel, ticlopidine), and the search logic also included all indirect comparisons between these drugs (see **Appendix 1** for the detailed search strategy). Methodological filters were applied to limit the retrieval to economic studies. The search was not restricted by date, but was restricted to English language articles only. The exclusion of languages other than English (LOE) from the review is not expected to have biased the results. This assumption is supported by a systematic review of published studies.²⁰

A limited grey literature search was performed in order to identify literature not commercially published. This was done by searching the websites of economic agencies, organizations, and specialized databases (see **Appendix 2** for a list of these websites). It is assumed that full economic evaluations satisfying the search criteria would not be published elsewhere.

An economic evaluation was included for review if it satisfied all of the following criteria:

- Population: Adult patients undergoing percutaneous coronary intervention
- Intervention: Any of: ASA, ticlopidine, clopidogrel, dipyridamole, extended-release dipyridamole-ASA combination, prasugrel
- Comparator: Any of: ASA, ticlopidine, clopidogrel, dipyridamole, extended-release dipyridamole-ASA combination, prasugrel
- Outcomes: An indicator of the trade-off between incremental costs and incremental consequences (cost per QALY, cost per life year gained, cost per event avoided, etc.)
- Study design: A full economic evaluation (study providing a summary measure of the trade-off between costs and consequences)
- Selection was limited to English language articles and abstracts were not included
- Publication time frame: Search was not limited by date

The selection criteria were applied to the title and abstract (if available) of the literature obtained in the first phase of the literature search to identify its relevance to the review objective. For articles rated as confirmed or undecided, full-text hard copies were obtained. In the second phase of the literature search, the selection criteria were applied to the full-text articles. If a study satisfied all the inclusion criteria, it was included for review.

The methods and results of the economic evaluations included in the review were abstracted using the data extraction sheet found in **Appendix 3**. Characteristics of interest were the author, year of publication, title, reporting of industry sponsorship, study perspective, interventions and comparators, study design, country of origin, and data sources used to populate the model. The perspective and design of the study, as well as the data used to populate the economic model, provides a framework in which to interpret the results. The data used to populate the various models were also of interest for the design of the economic model carried out herein. The estimate of cost-effectiveness, the currency and year used to value this cost-effectiveness and the authors' conclusions were also abstracted.

As the studies varied in terms of design, data collection, and analysis, no effort was made to meta-analyze the results quantitatively. Instead, each study was summarized, and a qualitative comparison was undertaken in order to describe the current economic evidence regarding antiplatelet agents in the secondary prevention of vascular events in adults undergoing PCI and to assess the applicability of the findings to a Canadian

setting. Data extracted from included economic studies were checked by a second reviewer.

A checklist developed for the *British Medical Journal (BMJ)* was applied in order to assess the quality of the included economic evaluations.²¹ This checklist is appropriate for full economic evaluations; that is, evaluations that present the costs and consequences of health interventions and a summary measure of the trade-off between the two.

2.3 Results

The economic literature search identified 335 potentially relevant articles. Of these, 42 were obtained as full-text hard copies (**Figure 1, Appendix 4**). After applying the inclusion criteria, eight articles were included for review.

Figure 1: Selected reports

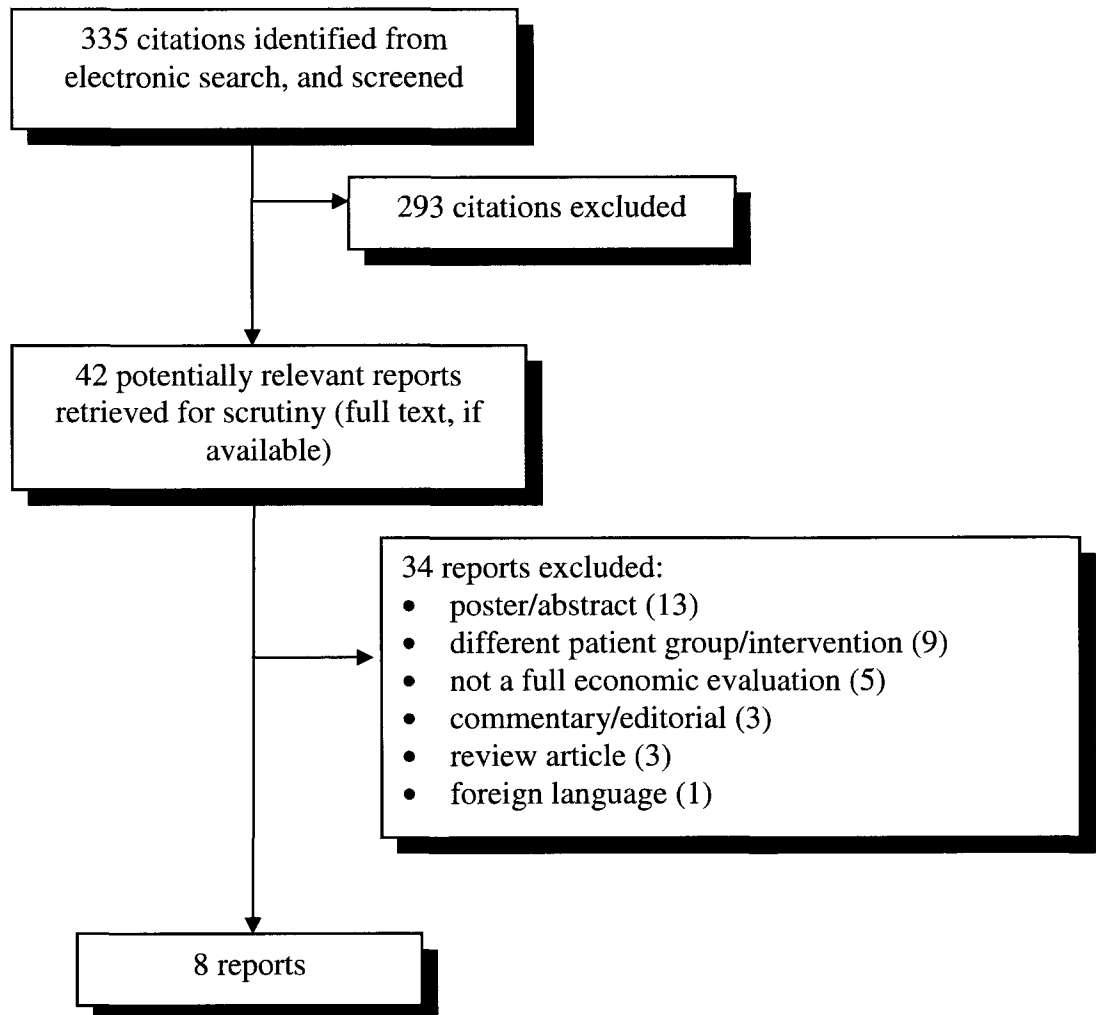


Table 1 summarizes the characteristics of the included studies. Four of the eight studies were published in 2005. The more current studies were those by Berg²² (2008), Heeg²³ (2007), and Mahoney^{24,25} (2006 & 2010). Three studies claimed to be from the American societal perspective (2000-2001 US dollars)^{24,26,27}, one from the perspective of the US healthcare system (2005 US dollars)²⁵, two from the Swedish societal perspective (2004 Euros/2004 Swedish crowns)^{28,29}, and one from the Dutch healthcare perspective (2004

Euros). A further study considered costs and outcomes from the Swedish (societal), German (payer) and French (payer) perspectives (2006 Euros)²². The majority of the studies were industry sponsored.

Table 1: Characteristics of economic evaluations included in the review

Author	Location	Industry sponsorship	Study perspective	Clinical data source	Study design
Beinhart 2005 ²⁶	US	Yes (Sanofi-Synthelabo and Bristol-Myers Squibb)	Societal	CREDO	Cost-effectiveness analysis
Berg 2008 ²²	Sweden, Germany, France	Yes (Sanofi-Aventis and Bristol-Myers Squibb)	Sweden: societal, France and Germany: payer	PCI-CURE CREDO PCI-CLARITY	Cost-utility analysis
Cowper 2005 ²⁷	US	Eric Peterson (4 th author) holds a grant from BMS, Sanofi for a separate study	Societal	CREDO	Cost-effectiveness analysis
Heeg 2007 ²³	The Netherlands	Yes (Sanofi-Aventis)	Healthcare provider	PCI-CURE CREDO	Cost-effectiveness analysis Cost-utility analysis
Lindgren 2005 ²⁸	Sweden	Yes (funded in part by Sanofi-Synthelabo)	Societal	PCI-CURE	Cost-effectiveness analysis
Mahoney 2006 ²⁴	US	Yes (Sanofi-Synthelabo and Bristol-Myers Squibb)	Societal	PCI-CURE	Cost-effectiveness Analysis
Mahoney 2010 ²⁵	US	Yes (Eli Lilly & Co, Inc.)	US healthcare system	TRITON-TIMI 38	Cost-effectiveness Analysis, cost-utility analysis
Ringborg 2005 ²⁹	Sweden	Yes (Sanofi-Aventis)	Societal	CREDO	Cost-effectiveness analysis, Cost-utility analysis

Clinical effectiveness data for the economic evaluations included in this review came from four trials: PCI-CURE³⁰, CREDO³¹, PCI-CLARITY³², and TRITON-TIMI³³. The first three trials³⁰⁻³² used a combination of clopidogrel + ASA as the intervention and

placebo + ASA as the comparator. All patients in those trials received clopidogrel in the weeks immediately following PCI. The TRITON-TIMI trial compared prasugrel + ASA with clopidogrel + ASA. Specific details of the intervention and comparator regimens used in the trials are outlined in **Appendix 5**.

Appendix 6 describes the data sources and methods of the economic evaluations included in this review. Baseline event rates were taken from various sources. The Framingham Heart Study and Saskatchewan Health database were used in three of the American studies to estimate life expectancy.²⁴⁻²⁶ The fourth American study obtained baseline rates of MI, death, and repeat revascularization from the Duke Information System for Cardiovascular Care (DISCC).²⁷ Baseline data for the Swedish studies were taken from various databases: Berg et al.²² obtained baseline event rates during the first month from the Swedish Hospital Discharge and Cause of Death registers and used regression methods to model forecasts beyond that time; Lindgren et al.²⁸ used the Swedish national registry (RIKS-HIA) as a principal data source; and Ringborg et al. used data from the Centre for Epidemiology at the Swedish National Board of Health and Welfare. Effectiveness data were taken primarily from PCI-CURE³⁰ and CREDO.³¹ The 2008 analysis by Berg²² also considered data from PCI-CLARITY.³² Data from TRITON-TIMI³³ were used in the 2010 economic evaluation by Mahoney.²⁵

Costs

In six of eight studies, the stated perspective was societal^{22,28,29}. However, non-healthcare costs were included in only three of these studies^{22,28,29}, two of which included them only

in the sensitivity analysis^{28,29}. The other three economic evaluations^{24,26,27} can truly be referred to as being conducted from the health-care perspective.

The study by Heeg et al.²³ was carried out from the perspective of the Dutch healthcare provider. Healthcare costs associated with each specific health state were obtained from published sources. Data on non-healthcare costs (travel, informal care, productivity losses) were not available and therefore not included. The authors suggested that any cost savings here would likely be minor, given the age of the patients, and would favour clopidogrel therapy. Given concerns that their cost data were somewhat dated, the authors performed sensitivity analyses using broad ranges surrounding unit costs.

The economic evaluations by Beinart²⁶ and Mahoney²⁴⁻²⁶ were trial based, basing their cost data on resource use in the CREDO, PCI-CURE, and TRITON-TIMI trials, respectively. The trials captured direct medical care costs for hospitalization and drug costs, but not direct costs associated with outpatient visits and testing or indirect costs attributable to lost productivity. In the studies comparing clopidogrel +ASA to ASA alone, costs were estimated for each diagnoses-related group (DRG) based on three different costing methods: Average Medicare reimbursement rates, average private payer rates (MEDSTAT), and a blended estimate of the two fee schedules. In the prasugrel + ASA versus clopidogrel + ASA analysis, costs were assigned on the basis of DRG-specific Medicare reimbursement rates, plus separate incremental costs were assigned to reflect the occurrence of procedure-related complications that do not result in changes to the DRG assignment. The Cowper study²⁷ used unit costs based on Medicare

reimbursement rates for DRG categories. Again, non-healthcare costs were excluded from the analysis due to lack of available data.

The Berg study²² took on multiple perspectives: The Swedish analysis was done from the societal perspective (using direct and indirect costs), the German and French analyses from the payer perspective (using direct costs only). The other two studies from the Swedish perspective, those by Ringborg²⁹ and Lindgren²⁸, included cost of added life years in the sensitivity analysis only, in order to facilitate comparison with other studies.

Utilities

Utility values, where reported^{22,23,25,28,29}, were based on the literature. The Swedish studies, by Berg²² and Ringborg²⁹, used utility values from a 2001 study by Burstrom et al.³⁴, designed to investigate the feasibility of obtaining mean quality of life (QoL) weights by mapping survey data to the EQ-5D. Burstrom et al.³⁴ described and valued health-related quality of life in the general Swedish population. Their data were obtained from the 1996-1997 Survey of Living Conditions (ULF), a cross-sectional study based on personal interviews with a sample of 11,698 people aged 16-84. Survey responses were mapped to the EQ-5D self-classifier and the United Kingdom (UK) time trade-off (TTO) index, a social tariff that generates a single index value, was used to obtain mean QoL weights from the modified EQ-5D dimensions. The utility reductions reported by Burstrom, after controlling for age and sex, were -0.1156 for ischemic heart disease and -0.2743 for stroke³⁴.

The Ringborg study²⁹ questioned the applicability of these estimates to post-PCI patients, and used LYG as the main measure of effectiveness with QALYs used only in secondary analysis. The Berg study²² used an additional utility reduction of 0.03 for revascularization. This value was obtained from a cross-sectional survey of hospitalized patients at coronary-care units in Sweden, published only in abstract form.³⁵

The Heeg study²³ also included a cost utility analysis. Whereas the Swedish studies applied utility reductions to age-stratified utility values, Heeg et al. reported a single utility value per event. The 0.91 post-MI utility value had been previously reported by Tsevat et al.³⁶. Two references were provided for the 0.66 utility value applied to the post-stroke state; one by Hallan,³⁷ which reported median utility values of 0.91 for minor stroke and 0.61 for major stroke, and a second by Lee³⁸ which reported utility values of 0.75 for minor stroke and 0.30 for major stroke.

Utility values after multiple events were assumed to be equal to the product of the utilities after single events [ie. $0.91(\text{post-MI}) * 0.66(\text{post-stroke}) = 0.60 \text{ post-MI+stroke}$].

In their sensitivity analysis, Lindgren et al.²⁸ applied a utility reduction for the post-MI state, assuming that patients who suffer a MI have their utility reduced by 0.1 each year. This value was taken from a previous study by Johannesson³⁹.

None of the studies were able to apply a utility loss for bleeding, due to lack of data. The Berg study²² was the only one to address this issue. They explained that, given the short-term nature of bleeding events, the impact on the overall results would likely be minimal.

Modelling frameworks

Five of the eight studies used decision modelling techniques in their economic evaluations^{22,23,27-29}. The studies by Beinart²⁶ and Mahoney^{24,25} were trial-based and do not have modelling frameworks. The study by Cowper et al.²⁷ used a decision tree model. All other studies used Markov modelling^{22,23,28,29}; although Berg et al.²² used a combination decision tree Markov model. Among the Markov models, the most commonly reported model states include: post-PCI (free of events), stroke, MI, and death^{22,23,29}. Lindgren et al.²⁸ did not include stroke in their model. Ringborg et al. noted that stroke was the most costly of model events. The models reported cycle lengths of 6 months²³ or one year.^{28,29} It was difficult to decipher the cycle length used in the Berg model²². The time horizon in all of the studies was the lifetime of the patient. The longest treatment duration reported was “up to 15 months” – this in the evaluation conducted by Mahoney²⁵ and based on the TRITON-TIMI trial³³.

Analysis methods

A discount rate of 3% was applied on costs and effects beyond the first year in seven out of eight studies; the study by Heeg et al.²³ used a rate of 4% per year. Deterministic sensitivity analyses were included in all of the economic evaluations included in the review. Subgroup analyses, based on patient risk levels, were performed by Cowper²⁷

and Lindgren²⁸. Heeg²³ and Berg²² presented probabilistic multivariate sensitivity analyses and four of the studies (Lindgren²⁸, Ringborg²⁹, Berg²², Heeg²³) included cost effectiveness acceptability curves.

Validity

Quality assessment for the included economic evaluations was conducted. (**Appendix 7**) Based on the 35-point BMJ checklist²¹, every study was deemed of sufficient quality for the majority of checklist items (range of number of items for which the studies were sufficient quality = 32 to 35). The checklist item which was least likely to be deemed of sufficient quality was related to the “Quantities of resources reported separately from unit costs” (87% failure). Other areas where the quality of reporting could have been improved include stating the economic importance of the research question and clarifying the true intervention, comparator, and the durations of treatment. More detailed individual reviews of the economic evaluations can be found in **Appendix 8**.

Results and conclusions

Results and conclusions of economic evaluations included in the review are presented in additional detail in **Appendix 9**. Briefly, cost per life-year gained was the primary outcome in six of the eight studies. Only the study by Berg²² reported costs per QALY-gained as the primary outcome measure. Heeg²³ and Ringborg²⁹ reported costs per QALY as a secondary outcome. All of the clopidogrel + ASA vs. ASA studies concluded that pre-treatment and long-term treatment with clopidogrel + ASA is cost-effective for patients undergoing PCI, when compared to short-term treatment with clopidogrel + ASA

+ placebo. Only one²³ found this strategy to be dominant (cost-saving and more effective). None of the studies included in the review could comment as to the relative cost-effectiveness of clopidogrel + ASA versus ticlopidine + ASA. The most recent Mahoney evaluation²⁵ concluded that prasugrel compared with clopidogrel is highly cost-effective and, under many circumstances, cost-saving.

2.4 Conclusions

This review identified eight full-length economic evaluations of antiplatelet agents in the secondary prevention of vascular events in adult patients undergoing percutaneous coronary intervention. All but one of the economic evaluations included in the review compared clopidogrel + ASA versus ASA monotherapy. The most recently published analysis compared prasugrel + ASA to clopidogrel + ASA. Ticlopidine + ASA was not included as a comparator in any of the economic evaluations included in the review. Furthermore, there were no comparisons evaluating clopidogrel versus a true (inactive) placebo.

Fifty percent of the identified studies were American, fifty percent European, and none of the studies were Canadian. This discovery confirms the need for an economic evaluation conducted from the Canadian perspective; ideally one evaluating all available treatment options.

The quality of studies included in this review was assessed using BMJ Guidelines. These guidelines assess whether specific components of an economic evaluation are reported,

not whether the reporting is done clearly or accurately. As such, what is reported as 'high quality' is in fact 'comprehensive reporting'. The studies included in the review were primarily industry-funded, which may lead to bias, but this is not addressed in the BMJ checklist.

3. Economic Evaluation

3.1 Objective

The review of previously reported economic evaluations highlighted a number of potential limitations of existing studies that assessed the cost-effectiveness of antiplatelet agents in the secondary prevention of vascular events for percutaneous coronary intervention patients. As none of the studies compared all of the interventions of interest in a Canadian setting, a primary economic evaluation from the Canadian perspective was undertaken.

3.2 Methods

The research question was answered using a cost-utility analysis to facilitate reimbursement decisions. Outcomes were measured in terms of quality-adjusted life years (QALYs) in order to incorporate meaningful differences in both life expectancy and health-related quality of life (HRQL). The target population for this economic evaluation was adult patients who have undergone PCI. The perspective was that of a provincial ministry of health. Only the direct medical costs relevant to a provincial health care provider were considered. Direct costs accruing to the patient (i.e. travel costs) and indirect costs accruing to society (i.e. lost production) were not included. The interventions being compared were twelve months of treatment with: (1) clopidogrel plus ASA, (2) ticlopidine plus ASA, or (3) ASA alone, followed by lifetime treatment with ASA. Prasugrel (a new thienopyridine, produced by Eli Lilly, that had not yet been

approved for use in Canada at the time of writing) + ASA was considered in the sensitivity analysis.

3.2.1 Modelling

A model for cost-utility analysis was constructed using Microsoft® Office Excel version 2003. A hypothetical cohort of patients with mean age of 60 years undergoing PCI was followed to the age of 100 years. This corresponds to a time horizon of 40 years – effectively a lifetime horizon.

Short-term events

All patients entered the model in the post-PCI state. In the first year following the procedure, patients could have:

- (i) had no further events for one year (and remained in the post-PCI state);
- (ii) had an MI within the following year (and entered the MI year 1 state);
- (iii) had a stroke within the following year (and entered the stroke year 1 state);
- (iv) died (and entered the death state).

Long-term events

A Markov model was constructed to model the disease process after the initial 12 months.

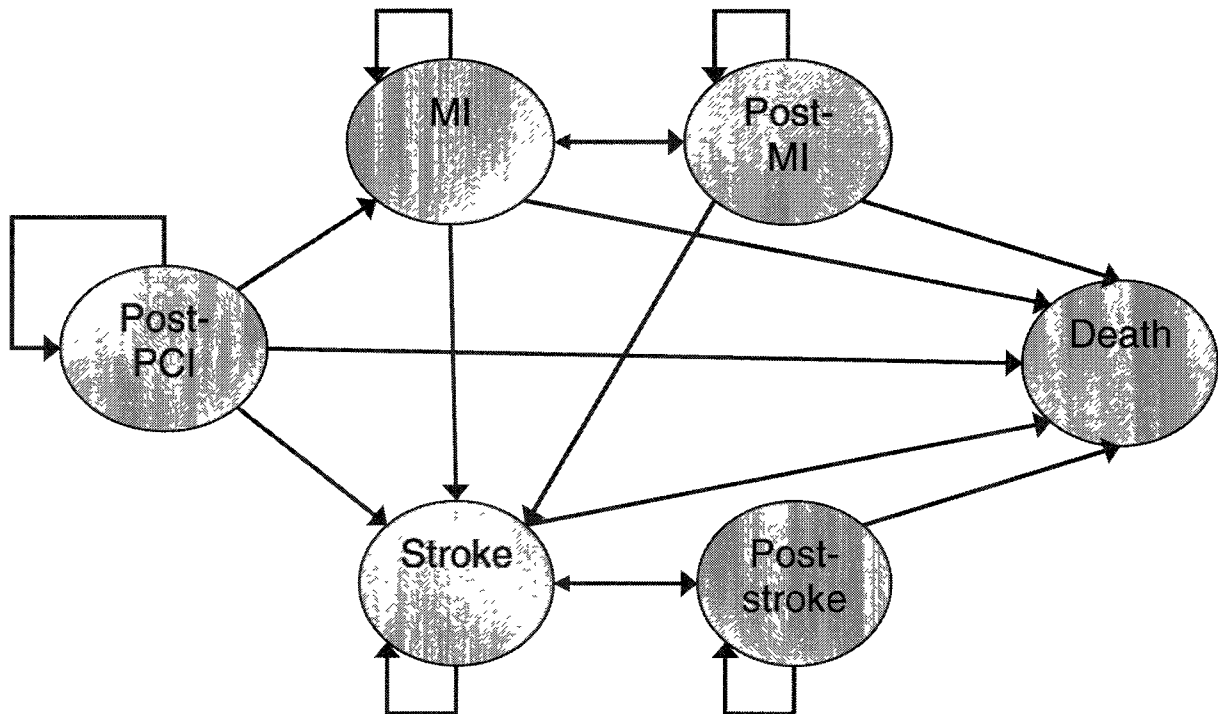
Each cycle, from years 2-40, patients could have:

- (i) had no further events (and remained in the post-PCI state);
- (ii) had an MI (and entered the MI state);

- (iii) recovered from an MI without having another cardiovascular incident (and entered the post-MI state);
- (iv) remained in the post MI state;
- (v) had a stroke (and entered the stroke state);
- (vi) recovered from a stroke without having another cardiovascular incident (and entered the post-stroke state);
- (vii) remained in the post stroke state
- (viii) died (and entered the death state).

As shown in the influence diagram in **Figure 2**, patients could move from MI or post-MI to the stroke state, but not the reverse. This was a necessary simplification of the model which has little impact on the estimated incremental costs and outcomes. Costs associated with stroke and post-stroke are greater than those for MI and post-MI (**Table 7**). Since there were no cost, utility, or probability data for a post-stroke, post-MI health state, this was the most conservative option available.

Figure 2: Influence diagram



Probabilities of Outcomes within First 12 months

Baseline probabilities

Baseline probabilities (i.e. probabilities of events for ASA monotherapy) for the first 12 months were taken from the ASA arms of the largest trial for which outcome data were available. The probabilities of MI and death within the first 12 months came from the PCI-CURE trial³⁰. This trial did not capture cerebrovascular events so the rate of stroke was taken from the CREDO trial³¹ (the second largest trial). The first-year outcome rates used in the analysis can be found in **Table 2**. In the first year, patients could also have experienced a major bleed and/or required target vessel revascularization. These events were not sub-states in the model: Although they do not affect disease progression, there were specific costs associated with each.

Outcome	No. of events	Trial (sample size)	Rate
MI (non-fatal)	47	PCI-CURE (1345)	0.035
Stroke (non-fatal)	12	CREDO (1063)	0.011
Death	31	PCI-CURE (1345)	0.023
Revascularization	38	PCI-CURE (1345)	0.028
Major bleed	33	PCI-CURE (1345)	0.025

Effectiveness

The probabilities of outcomes for ticlopidine + ASA and clopidogrel + ASA were obtained by weighting the probabilities for ASA by relative effect. The effectiveness inputs used in this primary economic evaluation are summarized in **Table 3**. These estimates were derived from mixed treatment comparison (MTC) meta-analyses of clinical trials evaluating antiplatelets in patients undergoing PCI. The MTC approach enables comparison between treatments enclosed in a network of studies⁴⁰.

Outcome	MTC relative risk (credible interval)		
	clopidogrel + ASA	ticlopidine + ASA	ASA
MI (non-fatal)	0.36 (0.06, 1.34)	0.28 (0.06, 1.41)	1.00
Stroke (non-fatal)	0.75 (0.06, 8.72)	0.75 (0.06, 8.72)	1.00
Death	0.91 (0.21, 3.66)	0.27 (0.02, 3.14)	1.00
Revascularization	0.72 (0.29, 1.42)	0.44 (0.14, 0.93)	1.00
Major bleed	1.42 (0.69, 3.82)	1.96 (0.58, 4.62)	1.00

The data used to calculate the treatment effectiveness model inputs can be found in **Appendix 10**. Briefly, a literature search conducted by CADTH researchers found 16 reports describing 14 RCTs addressing the comparative clinical effectiveness of antiplatelet regimens in adult patients undergoing PCI.⁴¹ Data extraction was conducted in order to capture and compare reported trial outcomes. Three RCTs^{30,42,43} reported the outcome of vascular death (with >3 months follow-up), nine RCTs^{5,6,30,31,43-47} reported

target vessel revascularization (TVR), three RCTs^{31,45,47} reported stroke data, five RCTs^{6,30,42,44,48} provided data regarding the observed frequency of non-fatal MI, and eight RCTs^{6,30,31,43-45,47,48} provided data regarding the observed frequency of major bleeds.

Both MTC and direct relative risk estimates were calculated for each of the six outcomes above. Standard random effects meta-analyses of RRs using head-to-head trials were computed using Review Manager 5.0 software (Cochrane Collaboration). The comparison of the effects of the interventions used to populate the economic model would have ideally been based on the evaluation of head to head trials, but there was no trial data evaluating the relative risk of vascular death or stroke with ticlopidine + ASA versus ASA alone. Song et al.⁴⁹ and Vandermeer et al.⁵⁰ have found that similar conclusions are derived from indirect comparisons and syntheses of direct comparisons so long as appropriate consideration to assumptions is practiced.⁵¹

The MTC analysis was computed using WinBUGS software⁵², an interactive Windows version of the BUGS program for Bayesian analysis of complex statistical models using Markov chain Monte Carlo techniques. The measures of effect were estimated according to the WinBUGS routine developed by the Evidence Synthesis Group from the Universities of Bristol and Leicester (the code is available from their website⁵³ and is provided in **Appendix 11**).⁴¹ Prior distributions for the overall effects and study-specific effect estimates were assigned vague normal prior distributions centered at 0 with large variances so that the collected data would drive the calculation of pooled estimates.⁴¹ Model diagnostics were assessed to ensure model convergence.⁴¹ Three chains, each

using 50,000 or more iterations, with a burn-in of 50,000 or more iterations, were fit to evaluate convergence. Pair-wise odds ratios (ORs) were estimated and converted to risk ratios (RRs) using $RR=OR/[(1-p_0)+(p_0*OR)]$.⁴¹

The initial MTC analysis, presented in **Table 3**, conducted as part of a CADTH health technology assessment⁴¹, included three treatment options (clopidogrel + ASA, ticlopidine + ASA, and ASA). The WinBUGS analysis was re-computed as part of this thesis in order to confirm original estimates and include data from the recent Triton-TIMI trial to allow for the consideration of prasugrel. (**Appendix 12**).

Transition probabilities post 12 months

Long term transition probabilities required for the model were related to the probability of further strokes, MIs, and death. The probability of these events was a function of previous history of events, age, and age at PCI, and was not influenced by treatment administered in the initial months following PCI. Treatment influenced progression only through the impact on event rates during the first year – i.e. treatment in the first 12 months had no impact on the transition between states post 12 months.

Transition probabilities beyond 12 months were derived from the Ringborg study²⁹. The authors had extracted data from the Swedish national inpatient register for a sample of patients who had undergone PCI.²⁹ The demographic characteristics of the register population were similar to those of the CREDO³¹ trial in terms of age, sex, and stroke/MI

history, and thus these risks were assumed to be generalizable to the Canadian population.

Yearly risks of MI, stroke, and mortality were estimated using parametric Weibull survival regression where the baseline hazard is expressed as:

$$H_0(t) = \lambda \gamma t^{\gamma-1},$$

where γ is the shape parameter and the scale parameter $(\lambda) = \exp(\beta_0)$.

Age at PCI (covariate z) was controlled for in these regressions using the following:

$$H(t_1) = \lambda * t_1^p * \exp(b*z)$$

$$H(t_0) = \lambda * t_0^p * \exp(b*z)$$

Transition probabilities in the first year following an event were estimated using logistic regression. Transition probabilities for following years were estimated through exponential survival regression. In both cases, current age was included as a risk factor in the regressions. The parameter estimates used in the calculation of transition probabilities were taken from the literature,²⁹ and are reproduced in **Tables 4-6**. Sample calculations can be found in **Appendix 13**.

Table 4: Parameter estimates of the Weibull survivor functions for calculation of transition probabilities²⁹

	age at PCI (years)	constant	p
post-PCI MI years 2 onwards	0.033	-8.829	2.337
post-PCI stroke years 2 onwards	0.073	-11.226	2.321
post-PCI mortality years 2 onwards	0.072	-10.392	2.185

Table 5: Parameter estimates of the logistic regressions for calculation of transition probabilities²⁹

	current age (years)	constant
Post-PCI post-MI mortality, year 1	0.060	-6.427
Post-PCI post-stroke mortality, year 1	0.057	-5.899

Table 6: Parameter estimates of the exponential survivor functions for calculation of transition probabilities²⁹

	current age (years)	constant
Post-PCI post-MI mortality, years 2 onwards	0.043	-6.050
Post-PCI post-stroke mortality, years 2 onwards	0.073	-8.103

3.2.2 Costs

The costs of drug therapy, the costs to the health care system of being in a particular health state, and the cost of adverse effects of target vessel revascularization and bleeding were incorporated in the model. A cost estimate of being in each health state was needed for the Markov model, and was sought from published literature sources. All costs are presented in 2009 Canadian dollars (**Table 7**). Costs from other years were adjusted using the Canadian Consumer Price Index inflation calculator available from the Bank of Canada⁵⁴.

Treatment costs

The annual drug costs of therapy include a \$7.00 dispensing fee incurred four times a year and an 8% mark-up.^{55,56} Drug prices were obtained from the Ontario Drug Benefit Formulary Comparative Drug Index.⁵⁷ Drug dosages and frequencies were based on a review of clinical trials and practice guidelines and consultation with clinical experts. Treatment costs were applied for the first year only. Beyond the first year, the cost of aspirin was applied to all living patients in the model.

Health state costs

The typical follow-up strategy post-PCI was assumed to be two cardiology consultations at a cost of \$132.50 per session⁵⁸. The health state costs relating to MI, post-MI, stroke, and post-stroke came from a population cohort study for the Province of Ontario for the years 1995-2005^{59,60}. The costs associated with the non-diabetes study cohort, consisting of all patients without diabetes over the age of 34 years in the province of Ontario, were used for this analysis. Costs were recorded for the index year of the comparison and the 4 years following the event⁵⁹. The post-MI and post-stroke costs used in this study are weighted averages for years 2-5.

Costs of adverse effects

The cost of bleeding complications came from a Canadian study investigating the cost-effectiveness of self-managed anticoagulation therapy.⁶¹ The cost of revascularization came from a large prospective “real world” cohort study based on all stent procedures in the province of Ontario between December 1, 2003, and March 31, 2005.⁶² Costs involved in blood cell monitoring for patients treated with ticlopidine are considered as sensitivity analyses, along with increased risks associated with thrombotic thrombocytopenic purpura (TTP) and neutropenia.

The costs in **Table 7** were applied to the probabilities developed in the model to derive a series of discounted costs by age for patients on the lifetime ASA treatment comparator and for the interventions.

Table 7: Annual Costs (2009 \$C)	
Annual health state costs (\pm SE)	
Post PCI**	\$265 \pm 33.80 ⁵⁸
Non-fatal stroke initial year	\$20,860.22 \pm 178.90 ⁵⁹
Non-fatal stroke subsequent years	\$4,343.69 \pm 109.90 ⁵⁹
Non-fatal MI initial year	\$10,843.76 \pm 159.21 ⁵⁹
Non-fatal MI subsequent years	\$3,117.54 \pm 225.90 ⁵⁹
Major bleed	\$6,691.39 \pm 851.84 ⁶¹
Revascularization	\$9,451.00 \pm 1205.48 ⁶²
Death	\$0
Annual drug therapy costs*	
ASA (325 mg/day)	\$51.06 ⁵⁷
Clopidogrel plus ASA (300 mg loading dose, 75 mg + 325 mg/day)	\$1,105.42 ⁵⁷
Ticlopidine plus ASA (2 \times 250 mg + 325 mg/day)	\$509.84 ⁵⁷

*Includes an 8% mark-up and a \$7.00 dispensing fee incurred four times per year for each drug.

**Assumed the cost of 2 visits with a cardiologist.

SE = standard error

3.2.3 Valuing outcomes

Utility values were required for each of the health states in the model (post-PCI, MI, post-MI, stroke, post-stroke, and death). Death was considered by convention to have a utility value of zero. Sullivan's National Catalog of Preference-Based Scores for Chronic Conditions in the United States^{63,64} was consulted in order to obtain utility values for the other health states. Sullivan's Catalog⁶⁴ contains preference-based scores for chronic and associated sociodemographic conditions obtained through the Medical Expenditure Panel Survey (MEPS). The MEPS is a nationally representative survey of the US civilian, noninstitutionalized population.⁶⁵ As part of the MEPS, a total of 38,678 respondents completed the EuroQol-5D (EQ-5D) self-administered questionnaire (SAQ). The EQ-5D measures five dimensions of health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each attribute has three possible levels (no problem, some problems, and major problems), resulting in 243 (3⁵) unique health states.

A multiattribute value function (MAVF) was then used to map preferences for these health states. The preference values for the EQ-5D fall on the scale of -0.11 to 1.0 (perfect health). A utility value of 0 is assigned to the health state “dead”. Negative scores reflect health states that society values as being worse than dead.

The utility value for coronary heart disease (0.725) was taken as the baseline utility value for patients entering into the model post-PCI. The utility values used to populate the economic model are listed in **Table 8**.

Table 8: Utility values (+/- SE)	
Coronary heart disease	0.725 ± 0.0002 ⁶⁴
MI	0.704 ± 0.0010 ⁶⁴
Post-MI	0.725 ± 0.0002 ⁶⁴
Stroke	0.655 ± 0.0009 ⁶⁴
Post-stroke	0.694 ± 0.0002 ⁶⁴

SE = standard error

Discount rate

The discount rate for costs and outcomes for the base case scenario was 5%, with sensitivity analyses at 3% and 0%, as suggested in the CADTH guidelines for economic evaluations¹⁵.

3.2.4 Variability and uncertainty

Subgroup analyses were conducted evaluating the cost-effectiveness of the three different antiplatelet treatment regimens in patients of different ages (65, 75, and 85 years of age at the time of PCI) and genders (male).

One-way sensitivity analyses were undertaken to assess the robustness of the results to changing assumptions in the model regarding costs (of ticlopidine and clopidogrel), discount rate, disutility (associated with a major bleed), excluding certain relative risks (stroke and death), approval of prasugrel, and treatment duration.

A probabilistic sensitivity analysis (PSA) was conducted on the base case scenario using Monte Carlo simulation (MCS).¹⁵ Since the relationship between input parameters and outcomes can be non-linear, the expected values of outcomes obtained from MCS can differ from a deterministic analysis.⁶⁶ The probabilistic sensitivity analysis provides a truer reflection of cost-effectiveness as it takes into account uncertainty in model parameters, however the use of PSA as part of the reference case has not been widely accepted.¹⁹

For the MCS, standard probability distributions were specified for: the health state costs (gamma, or normal), the health state utility values (normal), the probabilities for first year health outcomes with lifetime ASA treatment (beta), parameter estimates of the Weibull survivor functions, logistic regressions, and exponential survivor functions for calculation of transition probabilities (normal), and the relative risks of events with ticlopidine + ASA and clopidogrel + ASA, relative to ASA alone (lognormal). Details on the distributions chosen and the reasons for each choice are outlined in **Table 9**.

Table 9: Probability distributions used in MCS	
Normal Distribution	According to the <i>central limit theorem</i> , the sampling distribution of the mean will be normally distributed, provided the data informing the estimation is of sufficient sample size. ¹⁷ This was assumed to be the case for certain estimates of health state costs, utility values, and the regression coefficients from the Weibull, exponential and logistic regressions used in the calculation of transition probabilities.
Beta Distribution	The beta distribution is constrained on the interval of 0-1, which makes it appropriate for probability parameters, and is the reason it was applied to the probability estimates for first year health outcomes with lifetime ASA treatment. ¹⁷
Lognormal Distribution	Confidence limits for relative risk parameters are calculated on the log scale and so the lognormal distribution was applied to the relative risk estimates of events with ticlopidine + ASA and clopidogrel + ASA, relative to ASA alone. ¹⁷
Gamma Distribution	The gamma distribution is constrained on the interval 0 to positive infinity, as are the costs associated with the different health states in the economic model. ¹⁷ For costs with extremely low coefficient of variation, normal distributions were used.

Estimates of costs and QALYs associated with each treatment option were obtained by re-running the model with 5,000 replications, using values randomly selected from the probability distributions around the stochastic variables.

Cost-effectiveness acceptability curves (CEACs) were derived for the base case, and several additional scenarios. In a CEAC, the probability that a therapy is the optimal treatment (i.e. the net monetary benefit of a therapy is positive in all comparisons) is depicted for each potential value of the threshold value for a QALY (λ). CEACs are primarily illustrative in nature and they must be interpreted with care: “A CEAC simply presents the probability that an intervention is cost-effective, compared with the alternative, for a range of values of λ .”⁶⁷ A CEAC should not be used to make conclusions about anything other than the degree of uncertainty associated with the decision model.

3.3 Results

The base-case analysis assumed treatment duration for the interventions of one year post-PCI, followed by ASA treatment for the remaining years. It also assumed a mean starting age of 60 years for patients, and a discount rate for costs and outcomes of 5%. The base case analysis was conducted by a deterministic analysis using point estimates for each parameter, and an estimate of the cost-effectiveness of treatment is presented in terms of the incremental cost per QALY gained, which is the ratio of the mean incremental costs and mean incremental QALYs⁶⁸. In **Tables 10 to 30**, treatment options are listed in order of increasing cost, with dominated therapies coming last.

Table 10 shows the outcomes for the base case in natural units (life years) and costs before discounting. The lifetime ASA treatment option had the lowest undiscounted costs (\$41,980.51) and ticlopidine + ASA had the highest undiscounted life years (16.5316).

Table 10: Base case costs and life years (undiscounted)		
Treatment option	Cost (\$)	Life Years
ASA	\$41,980.51	16.2531
Clopidogrel + ASA	\$42,164.32	16.2994
Ticlopidine + ASA	\$42,182.70	16.5316

Table 11 shows the outcomes for the base case in terms of costs and QALYs after applying a discount rate of 5%. This table also shows the base case incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) results. Incremental cost, incremental QALYs, and NMB are all calculated relative to ASA. NMB is calculated for

each treatment option relative to ASA at a \$50,000 threshold value for a QALY gained.

That is, $\$50,000 \times (QALY_i - QALY_{ASA}) - (Cost_i - Cost_{ASA})$.

Table 11: Base Case ICER and NMB Results (Deterministic)						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0718	Reference case	Reference case		Reference case
Ticlopidine + ASA	\$22,111.82	8.2116	\$73.19	0.1398	\$523.44	\$6917.88
Clopidogrel + ASA	\$22,368.82	8.0991	\$330.19	0.0273	Dominated by ticlopidine+ASA	\$1037.09

The results of the base case analysis indicate that by prescribing ticlopidine in addition to aspirin therapy, on average patients would gain 0.14 quality-adjusted life years at an incremental cost per QALY gained of \$523.44. Clopidogrel + ASA is the most expensive of the three treatment options and, while it provides better health outcomes than aspirin monotherapy, it is dominated by the less costly and more effective ticlopidine + ASA treatment option.

3.3.1 Results of variability analysis

Variability in Age

The base case analysis assumed a mean starting age of 60 years for patients. **Table 12** presents the results of the subgroup analysis of patients undergoing PCI at the age of 65. Compared to the base case, patients five years more advanced in age are less costly to treat, but the health benefits gained are also less. The incremental cost of ticlopidine +

ASA versus ASA is higher in this patient population, while the incremental QALYs of ticlopidine + ASA versus ASA are less, leading to a higher ICER.

Table 12: Subgroup results - PCI at 65 years						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$20,674.93	7.3193	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$20,788.90	7.4464	\$113.97	0.1271	\$896.67	\$6,241.43
Clopidogrel + ASA	\$21,059.19	7.3453	\$384.27	0.0260	Dominated by ticlopidine + ASA	\$915.61

Table 13 presents the results of the subgroup analysis of patients undergoing PCI at the age of 75. At this age, the QALYs to be expected with treatment vary from 5.91 with ASA to 6.01 with ticlopidine + ASA. The additional 1/10 of a QALY comes at a cost of \$189.45.

Table 13: Subgroup results - PCI at 75 years						
Treatment Option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$17,583.71	5.9101	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$17,773.16	6.0147	\$189.45	0.1045	\$1812.07	\$5,038.07
Clopidogrel + ASA	\$18,075.40	5.9347	\$491.69	0.0246	Dominated by ticlopidine + ASA	\$736.16

Table 14 evaluates the cost effectiveness of the three antiplatelet treatment options in a hypothetical cohort of 85 year old patients undergoing PCI.

Table 14: Subgroup results - PCI at 85 years						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$14,488.29	4.7132	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$14,747.42	4.7996	\$259.13	0.0864	\$2,998.55	\$4,061.87
Clopidogrel + ASA	\$15,082.07	4.7374	\$593.78	0.0242	Dominated by ticlopidine + ASA	\$616.74

Patient QALYs and lifetime costs are lower among older patient groups, regardless of treatment option. Compared to aspirin monotherapy, incremental costs for ticlopidine + ASA and clopidogrel + ASA are higher among older patient subgroups, while incremental QALYs are lower. Thus, the net monetary benefits of ticlopidine and clopidogrel, compared to ASA, tend to decrease with increasing patient age at PCI. Clopidogrel + ASA therapy remains dominated by ticlopidine + ASA therapy in all age subgroups.

Variability in Gender

The ideal gender sub-analysis would have included separate baseline probabilities, relative risks with treatment, and utility values for male and female patients. However, the majority of the literature used to populate the economic model did not differentiate between the sexes. As such, the only values for which separate estimates for males and females were available were the utility values.⁶⁵ As shown in **Table 15**, when the male coefficient is applied to the utility values in the model, ticlopidine becomes slightly less

attractive (ICER of \$526.12, as compared to \$523.44 in the base case analysis), but it still dominates clopidogrel + ASA.

Table 15: Subgroup results - males

Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0302	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,111.92	8.1693	\$73.19	0.1391	\$526.12	\$6,882.24
Clopidogrel +ASA	\$22,368.82	8.0575	\$330.19	0.0272	Dominated by ticlopidine + ASA	\$1,030.40

3.3.2 Results of uncertainty analysis

Costs associated with ticlopidine treatment

Ticlopidine hydrochloride tablets may cause life-threatening adverse reactions, including neutropenia and thrombotic thrombocytopenic purpura (TTP).

The CLASSIC Study⁶⁹ reported one case of neutropenia among 340 patients randomized to treatment with 250 mg BID ticlopidine and 325 mg aspirin for 28 days following PCI. While, no cost was applied for neutropenia in the base case analysis because “In most, but not all cases, the neutropenia resolves with cessation of drug administration”⁷⁰, the average cost of treating neutropenia has also been estimated at \$7,365.⁷¹ In order to detect neutropenia, “it is recommended that blood counts be checked every 2 weeks for at least the first three months of therapy”⁷⁰. For the sensitivity analyses surrounding ticlopidine treatment, costs of blood cell monitoring, and of treating neutropenia were considered.

The cost of a biweekly limited physician consult and complete blood count (CBC) for the first three months of treatment with ticlopidine was included, as was a 1/340 risk of complication and a cost of \$7,365 to treat^{69,71}.

The onset of TTP is difficult to predict, despite close monitoring of platelet counts.⁷² The risk of disease is less than 1 in 1000, and the mortality rate is between 24-50%.^{72,73} The analysis presented in **Table 16** includes a conservative 1/1000 risk of developing TTP, with 100% fatality.

When the increased costs associated with potential adverse events related to ticlopidine are included in the analysis, ticlopidine + ASA no longer dominates clopidogrel + ASA. However, clopidogrel + ASA is subject to extended dominance by ticlopidine + ASA. An intervention is subject to extended dominance when it cannot be cost-effective regardless of a decision-maker's willingness to pay for health benefits.

Table 16: Sensitivity analysis - including cost of blood testing, neutropenia, and increased risk of death (1/1000) with ticlopidine

Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0719	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,513.93	8.2041	\$475.30	0.1323	\$3593.20	\$6,138.56
Clopidogrel + ASA	\$22,368.82	8.0991	\$330.19	0.0273	Extended dominance by ticlopidine + ASA	\$1,037.09

Table 17 presents findings from an analysis that used a more realistic risk of TTP (1/2000) and a 33.33% death rate, for a 1/6000 mortality rate. The same costs of blood cell monitoring and treatment of neutropenia were applied as in **Table 16**.

Table 17: Sensitivity analysis - including cost of blood testing and increased risk of death (1/6000) with ticlopidine

Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0719	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,530.77	8.2104	\$492.13	0.1386	\$3,551.74	\$6,435.93
Clopidogrel + ASA	\$22,368.82	8.0991	\$330.19	0.0273	Extended dominance by ticlopidine + ASA	\$1037.09

Discount Rate

A 5% discount rate was applied in the base case, as is standard practice for Canadian economic evaluations¹⁵. In other countries, lower discount rates are often used. **Table 18** shows the results of the analysis, using a 3% discount rate. When the discount rate was decreased, the cost of ticlopidine + ASA relative to the other treatment options increased. This is at least partially due to the fact that patients on ticlopidine + ASA have better health outcomes. With a 5% discount rate, as in the base case, costs incurred 10 years in the future are only worth 75% of their current value, and those 40 years away are only valued at 15% of current value.

Table 18: Sensitivity analysis - 3% discount rate						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$27,941.51	9.2015	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$28,045.98	9.3612	\$104.47	0.1596	\$654.41	\$7877.36
Clopidogrel +ASA	\$28,222.28	9.2316	\$280.76	0.0301	Dominated by ticlopidine + ASA	\$1222.73

When future costs are valued at current value (as in **Table 19**), ticlopidine + ASA becomes the most costly treatment option. Because the discount rate is applied to both costs and outcomes, a decreased discount rate also produces better health outcomes, due to the increased value placed on future QALYs. The difference in outcomes (between ASA and clopidogrel + ASA or between ASA and ticlopidine + ASA) increases along with the incremental costs when smaller discount rates are applied to the analysis. With a 0% discount rate, clopidogrel + ASA is less costly than ticlopidine + ASA.

Table 19: Sensitivity analysis - 0% discount rate						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$41,980.51	11.6332	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$42,182.70	11.8343	\$202.19	0.2010	\$1005.66	\$9,850.58
Clopidogrel +ASA	\$42,164.32	11.6681	\$183.81	0.03485	Extended dominance by ticlopidine + ASA	\$1,558.77

Disutility of major bleeds

Table 20 presents the results of the sensitivity analysis on the disutility of major bleeds. In the base case, major bleeds were analyzed in terms of costs, but not utilities, due to data limitations. The sensitivity analysis adds the extreme assumption of a utility value of 0 for a major bleed. The risk of major bleeds is highest with ticlopidine + ASA so this treatment group is most affected by the zero utility for major bleeds assumption. However, the increase in the ICER from the base case is small: from \$523.44 to \$596.26.

Table 20: Sensitivity analysis including disutility of a major bleed						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0540	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,111.82	8.1768	\$73.19	0.1227	\$596.26	\$6064.05
Clopidogrel + ASA	\$22,368.82	8.0739	\$330.19	0.0199	Dominated by ticlopidine + ASA	\$663.54

Relative Risks

Table 21 presents the results of the sensitivity analysis assuming no difference in the relative risk of stroke outcome. Both ticlopidine + ASA and clopidogrel + ASA had a relative risk reduction of 25% over aspirin monotherapy. The removal of this advantage makes them both less attractive than in the base case analysis.

Table 21: Sensitivity analysis - excluding RR of stroke						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038 63	8 0718	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,239 85	8 2094	\$201 21	0 1377	\$1,461 71	\$6,681 49
Clopidogrel +ASA	\$22,496 85	8 0967	\$458 21	0 0252	Dominated by ticlopidine + ASA	\$800 71

Table 22 presents the results of the sensitivity analysis assuming no difference in the relative risk of death. Both ticlopidine + ASA and clopidogrel + ASA had relative risk reductions over aspirin monotherapy. The removal of this clinical advantage reduces the QALYs gained with dual antiplatelet therapy (ticlopidine + ASA or clopidogrel + ASA). Costs are decreased as a function of decreased life years. As a result, ticlopidine + ASA dominates both alternate treatment options.

Table 22: Sensitivity analysis - excluding RR of death						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
Ticlopidine + ASA	\$21,771 74	8 0847	-\$266 89	0 0129	Reference case	\$911 26
ASA	\$22,038 63	8 0718	Reference case	Reference case	Dominated by ticlopidine + ASA	Reference case
Clopidogrel +ASA	\$22,326 90	8 0835	\$288 26	0 0117	Dominated by ticlopidine + ASA	\$296 55

Cost of clopidogrel

Table 23 presents the results of the sensitivity analysis assuming a loss of patent for clopidogrel and subsequent price drop of 50%. Should a loss of patent for clopidogrel actually produce a price reduction of 50%, clopidogrel + ASA would be the least costly antiplatelet regimen considered in this analysis, and would dominate treatment with aspirin alone. The ICER of ticlopidine + ASA, compared to half-priced clopidogrel + ASA, was \$2,209.80.

Table 23: Sensitivity analysis – 50% price reduction for clopidogrel						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
Clopidogrel + ASA	\$21,863.27	8.0991	-\$175.36	0.0273	Reference case	\$1,542.64
Ticlopidine + ASA	\$22,111.82	8.2116	\$73.19	0.1398	\$2,209.80	\$6,917.88
ASA	\$22,038.63	8.0718	Reference case	Reference case	Dominated by clopidogrel + ASA	Reference case

Table 24 includes clopidogrel at the predicted generic price point and excludes the ticlopidine + ASA treatment option.

Table 24: Sensitivity analysis – 50% price reduction for clopidogrel						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
Clopidogrel + ASA	\$21,863.27	8.0991	-\$175.36	0.0273	Reference case	\$1,542.64
ASA	\$22,038.63	8.0718	Reference case	Reference case	Dominated by clopidogrel + ASA	Reference case

Introduction of prasugrel

Table 25 presents the results of the sensitivity analysis including a fourth treatment arm: prasugrel + ASA. The cost of prasugrel was estimated to be 18% higher than the cost of clopidogrel since upon FDA approval, prasugrel was priced 18% more than clopidogrel in the US. The MTC meta-analysis was re-run, including the data from Triton-TIMI, in order to produce relative risks for the prasugrel + ASA treatment arm. The results of this analysis show that, should prasugrel be introduced at a cost of 118% the cost of clopidogrel, it would be dominated by ticlopidine + ASA.

Table 25: Sensitivity analysis – introduction of prasugrel						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0718	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,113.47	8.2116	\$74.83	0.1398	\$535.18	\$6,916.23
Clopidogrel +ASA	\$22,368.82	8.0991	\$330.19	0.0273	Dominated by ticlopidine + ASA	\$1,037.10
Prasugrel +ASA	\$22,624.43	8.1072	\$585.80	0.0354	Dominated by ticlopidine + ASA	\$1,184.47

Because ticlopidine does not occupy significant space in the antiplatelet market the sensitivity analysis surrounding the introduction of prasugrel is presented in **Table 26** without the ticlopidine + ASA treatment option. The ICER of clopidogrel + ASA compared to ASA alone is \$12,074.67, while the ICER of prasugrel + ASA compared to clopidogrel + ASA is \$31,714.50.

Table 26: Sensitivity analysis – introduction of prasugrel, exclusion of ticlopidine						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0718	Reference case	Reference case	Reference case	Reference case
Clopidogrel +ASA	\$22,368.82	8.0991	\$330.19	0.0273	\$12,074.67	\$1,037.10
Prasugrel +ASA	\$22,624.43	8.1072	\$585.80	0.0354	\$31,714.50	\$1,184.47

A sensitivity analysis was conducted to evaluate one possible future scenario whereby clopidogrel is available in a generic version (50% of current cost), prasugrel is available (at 118% the current cost of clopidogrel), and ticlopidine is no longer available. The results are presented in **Table 27**. In this scenario, generic clopidogrel + ASA would be the dominant treatment strategy.

Table 27: Sensitivity analysis – introduction of prasugrel, generic clopidogrel						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
Clopidogrel + ASA	\$21,863.27	8.0991	-\$175.36	0.0273	Reference case	\$1,542.64
ASA	\$22,038.63	8.0718	Reference case	Reference case	Dominated by clopidogrel + ASA	Reference case
Prasugrel +ASA	\$22,624.43	8.1072	\$585.80	0.0354	Extended dominance by clopidogrel + ASA	\$1,184.47

Treatment Duration

A sensitivity analysis was conducted to analyse the relative cost-effectiveness of different treatment duration of the various interventions (three months, six months, and 2 years). The ASA comparator treatment was assumed to be lifetime, as in the base case and other analyses. Treatment with the interventions was assumed to be followed by ASA

treatment until the end of life. In all three duration scenarios, ASA had the lowest cost of the treatment options and ticlopidine had the highest number of QALYs gained.

Table 28: Sensitivity analysis - three month treatment duration						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0718	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,056.93	8.1067	\$18.30	0.0350	\$523.44	\$1,729.47
Clopidogrel + ASA	\$22,121.18	8.0786	\$82.55	0.0068	Dominated by ticlopidine + ASA	\$259.27

Table 29: Sensitivity analysis - six month treatment duration						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0718	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,075.23	8.1417	\$36.59	0.0699	\$523.44	\$3,458.94
Clopidogrel + ASA	\$22,203.73	8.0855	\$165.09	0.0137	Dominated by ticlopidine + ASA	\$518.55

Table 30: Sensitivity analysis - two year treatment duration						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$22,038.63	8.0718	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$22,691.17	8.2294	\$652.54	0.1576	\$4140.68	\$7,227.06
Clopidogrel + ASA	\$23,736.78	8.1017	\$1698.15	0.0299	Dominated by ticlopidine + ASA	-\$204.52

Tables 28-30 show that both the cost of treatment and the QALYs gained increase with increasing treatment duration. In order to predict the optimal treatment duration, it is

useful to compare the relative costs and effects of different durations of the same treatment, as in **Tables 31** and **32**. When analysing the various treatment durations of ticlopidine, the sequential ICER is highest when comparing 24 months versus 12 months of ticlopidine + ASA.

Table 31: Various treatment durations of ticlopidine + ASA			
	Costs	QALYs	Sequential ICERs
ASA	\$22,038.63	8.0718	Reference case
3 months of ticlopidine + ASA	\$22,056.93	8.1067	\$523.44
6 months of ticlopidine + ASA	\$22,075.23	8.1417	\$522.86
12 months of ticlopidine + ASA	\$22,111.82	8.2116	\$523.46
24 months of ticlopidine + ASA	\$22,691.17	8.2294	\$32,547.75

The various treatment durations of clopidogrel are presented in **Table 32**. Because clopidogrel is a more costly treatment option than ticlopidine, the incremental costs of increasing treatment duration are much higher, while the increment QALY values observed with longer treatment duration of clopidogrel + ASA are not as high as those observed with ticlopidine + ASA. The results of **Table 32** demonstrate that it is unlikely that continuation of clopidogrel treatment after 12 months is cost-effective.

Table 32: Various treatment durations of clopidogrel + ASA			
	Costs	QALYs	Sequential ICERs
ASA	\$22,038.63	8.0718	Reference case
3 months of clopidogrel + ASA	\$22,121.18	8.0786	\$12,139.71
6 months of clopidogrel + ASA	\$22,203.73	8.0855	\$11,963.77
12 months of clopidogrel + ASA	\$22,368.82	8.0991	\$12,138.97
24 months of clopidogrel + ASA	\$23,736.78	8.1017	\$526,138.46

3.3.3 Results of the probabilistic analysis

Table 33 compares the outcomes of the deterministic base case analysis with the probabilistic analysis. Treatment options are listed in order of increasing costs for the deterministic analysis. Clopidogrel + ASA and ticlopidine + ASA were more costly and less effective in the probabilistic analysis than in the deterministic analysis because of the uncertainty surrounding the effectiveness data used to populate the model. The distribution of possible effectiveness estimates is skewed. The median RR, as reported by the meta-analysis (and used in the deterministic model) overestimates the relative effectiveness, as compared to the mean. The probabilistic model involves sampling from the whole distribution of the RR and is therefore more reflective of the mean value.

Table 33: Base case outcomes - deterministic versus probabilistic results						
Treatment option	Deterministic results			Probabilistic results		
	Life years	QALYs	Costs	Life years	QALYs	Costs
ASA	11.2309	8.0718	\$22,038.63	10.6030	7.6207	\$21,551.60
Ticlopidine + ASA	11.4235	8.2116	\$22,111.82	10.7240	7.7062	\$26,040.85
Clopidogrel+ASA	11.2671	8.0991	\$22,368.82	10.5812	7.6034	\$24,293.95

Figure 3 shows the incremental net benefit (INB) of ticlopidine + ASA vs. ASA alone. For the purpose of this illustration, only the first 500 replications are graphed. Due to uncertainty around the effectiveness estimates, there are some outlying point in which ticlopidine + ASA is either significantly more expensive or more effective than ASA alone.

Figure 3: Incremental net benefit of ticlopidine + ASA vs. ASA

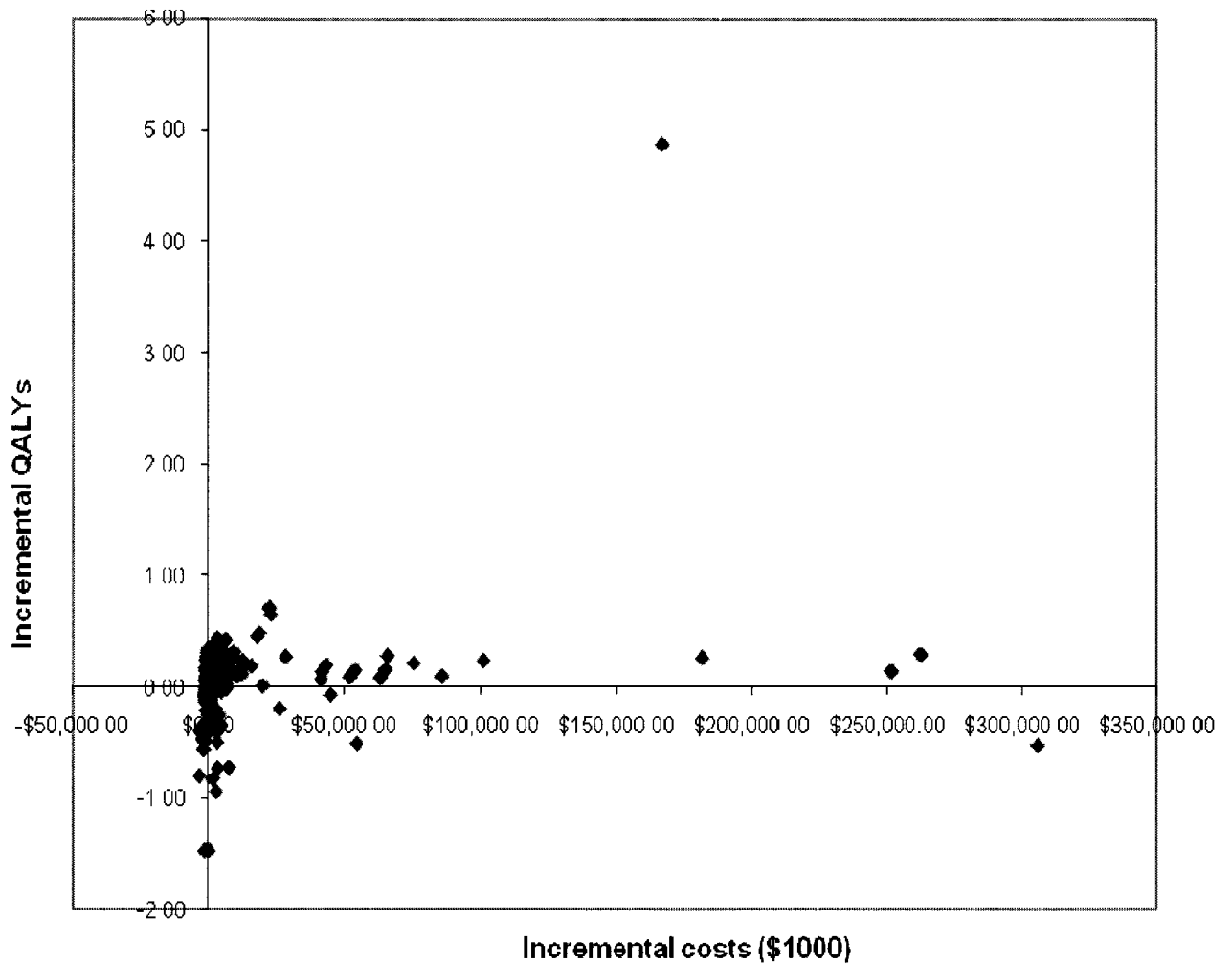


Table 34 shows the ICER and NMB results for the probabilistic analysis. The pattern of positive incremental costs and negative incremental QALYs gives the result that ASA dominates treatment with clopidogrel +ASA. Ticlopidine + ASA demonstrates more favourable effects than ASA alone, but at a cost of \$52,544.03 per QALY. Both dual antiplatelet treatment options have negative NMBs relative to ASA.

Table 34: Base case ICER and NMB results for the probabilistic analysis						
Treatment option	Cost	QALYs	Incremental cost vs ASA	Incremental QALYs vs ASA	ICER (sequential)	NMB (relative to ASA)
ASA	\$21,551.60	7 6207	Reference case	Reference case	Reference case	Reference case
Ticlopidine + ASA	\$26,040.85	7 7062	\$4,489 25	0.0864	\$52,544.03	-\$218 27
Clopidogrel + ASA	\$24,293.95	7 6034	\$2,742 36	-0 0174	Dominated by ASA	-\$3,611.27

Cost-effectiveness acceptability (CEAc) curves

The CEAc curves below present the probability that each treatment option is optimal for threshold values between \$20,000 and \$100,000. (Based on previous funding decisions, it is unlikely a treatment option will be accepted based on economic arguments with an ICER greater than \$100,000). **Figure 4** assumes the availability of three treatment options: ticlopidine + ASA, clopidogrel + ASA, and ASA (as in the base case economic analysis). Ticlopidine + ASA is associated with the highest probability (63.62%-68.78%) of being the optimal treatment at all threshold values between \$20,000 and \$100,000.

Figure 4: CEAc comparing ticlopidine + ASA, clopidogrel + ASA, and ASA

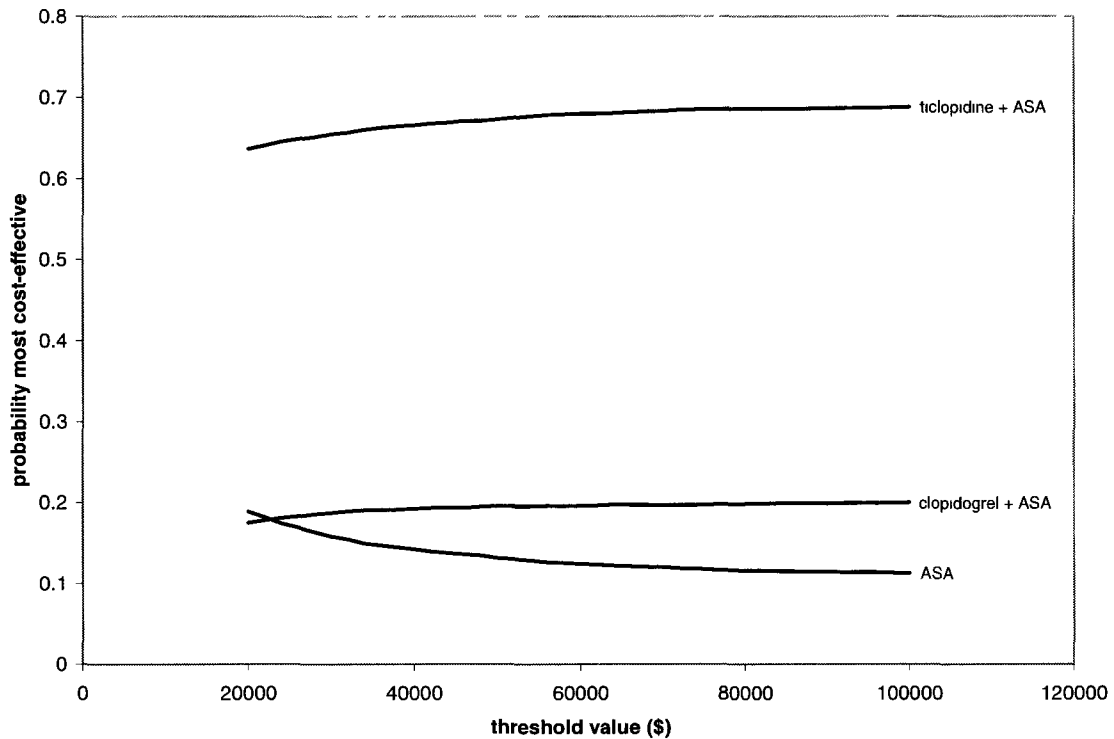


Figure 5 looks more closely at the two treatment options most commonly used for the secondary prevention of vascular events in adults undergoing PCI: clopidogrel + ASA, and ASA. At lower threshold values, ASA has a higher probability of being cost-effective. At a threshold value of \$50,000, both have equal probability of being most cost-effective, and at higher threshold values, it is clopidogrel + ASA that has the highest probability of being most cost-effective.

Figure 5: CEAc comparing clopidogrel + ASA vs. ASA

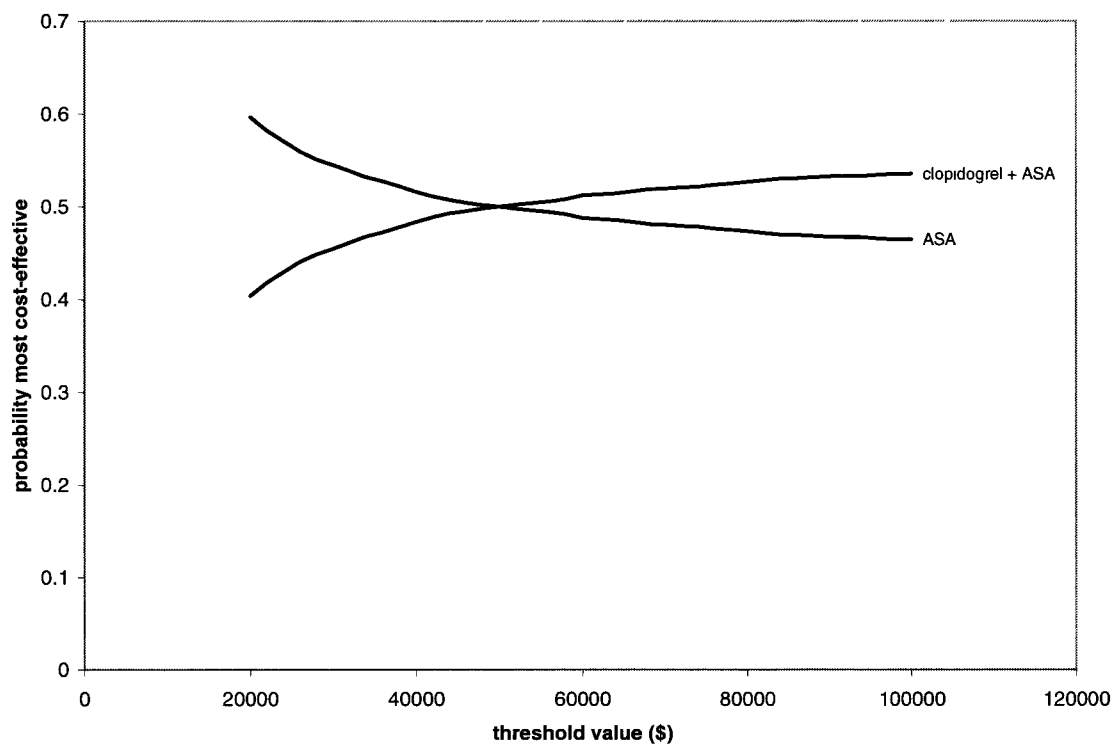


Figure 6 includes prasugrel + ASA, in addition to ticlopidine + ASA, clopidogrel + ASA, and ASA. As in the base case, ticlopidine + ASA is associated with the highest probability (60.2%-65.9%) of being the optimal treatment at all threshold values between \$20,000 and \$100,000.

Figure 6: CEAc comparing ticlopidine + ASA, prasugrel + ASA, clopidogrel + ASA, and ASA

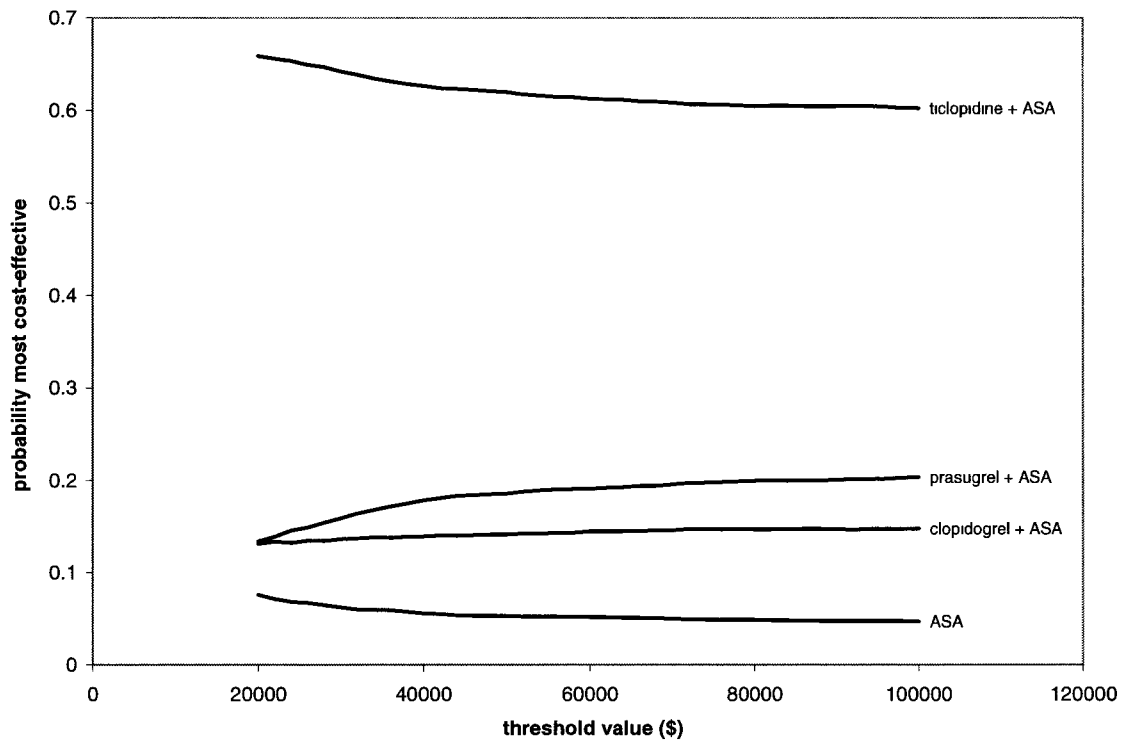
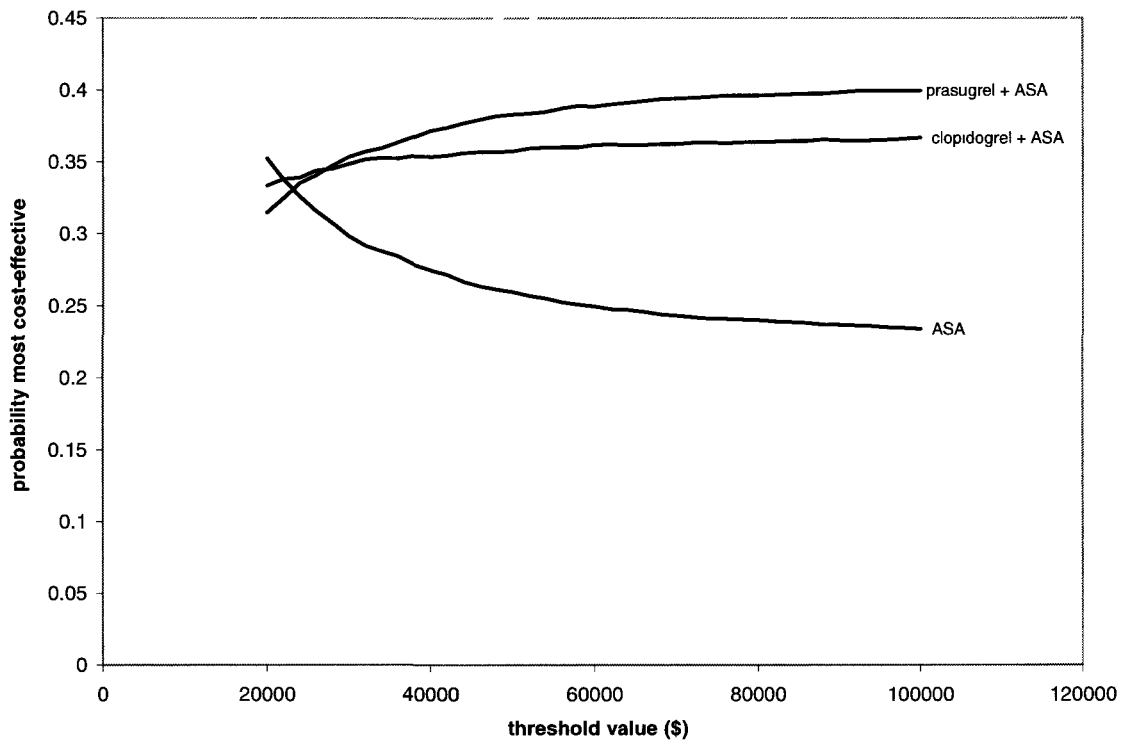


Figure 7 also includes prasugrel + ASA, clopidogrel + ASA, and ASA, but not ticlopidine + ASA. At lower threshold values, ASA has a higher probability of being cost-effective, at a threshold value of \$22,000, ASA and clopidogrel + ASA have equal probability of being most cost-effective, and at threshold values greater than \$28,000, it is prasugrel + ASA that this the highest probability of being most cost-effective.

Figure 7: CEAc comparing prasugrel + ASA, clopidogrel + ASA, and ASA



3.4 Conclusions

This economic evaluation is the first to evaluate multiple treatment options in the secondary prevention of vascular events in adults undergoing PCI. Furthermore, it is the first economic evaluation of antiplatelet agents conducted, for this indication, from a Canadian perspective. Only direct medical costs relevant to a provincial health care provider were considered in this analysis, in order to make it relevant to decision-makers.

A number of sensitivity analyses were conducted to account for patient variability and model/parameter uncertainty. In many of these analyses, ticlopidine + ASA was the dominant treatment option. Only when a 50% price reduction was applied to the cost of

clopidogrel did treatment with clopidogrel + ASA dominate ASA monotherapy. A probabilistic sensitivity analysis (PSA) was conducted in order to incorporate decision uncertainty into the model. Results of the PSA favour ASA monotherapy rather than ticlopidine as found in the deterministic analysis. CEA curves were presented comparing various treatment options. Ticlopidine + ASA was found to have the highest probability of being cost-effective when compared to clopidogrel + ASA, ASA, and prasugrel + ASA.

4.0 Value of Information Analysis

4.1 Objective

A value of information analysis was performed in order to identify which parameters were contributing most to the uncertainty of the study results. Decision uncertainty can be characterized using a Bayesian approach⁷⁴. Decision-makers may choose to maximize expected health by reimbursing the treatment option with the highest expected net benefits, or to reduce the level of decision uncertainty by acquiring additional evidence⁷⁴. Often, these choices are mutually exclusive, as once approval is granted, manufacturers have little incentive to provide additional evidence. As such, estimates of decision uncertainty can be interpreted as the potential value of information forgone.

4.2 Methods

4.2.1 Expected Value of Perfect Information (EVPI)

The expected value of perfect information (EVPI) is the difference between the expected net benefit with perfect and current information.¹⁷ Given the level of uncertainty demonstrated in the probabilistic analysis of this report, further research in this area would be of obvious value for decision-makers. Each of the parameter estimates used to populate the model are known, with uncertainty, to fall within a range of plausible values.⁷⁴ In the probabilistic sensitivity analysis, each parameter was varied simultaneously according to its assigned distribution and model outputs were recorded.

In order to calculate the population EVPI, the per patient estimate was multiplied by the number of decisions expected to be made on the basis of this additional information.

4.2.2 Expected Value of Perfect Information for Parameters (EVPPI)

The methodology below comes from a 2008 methods paper by Coyle and Oakley⁷⁵:

Notation

Standard notation relating to treatment options, costs, effects, cost effectiveness and parameters:

- T : the set of alternative treatment options
- t_j : an individual treatment option
- E_{t_1} : the expected value of health benefits (QALYs) from treatment t_1
- C_{t_1} : the expected value of costs
- X : the set of k data parameters (X_1, \dots, X_k) used to estimate the cost and effects of the alternative treatment options
- X_p : a sub group of parameters within X
- X_i : an individual parameter
- X_i^c and X_p^c denote the complement sets of input parameters (all members of X other than X_i or X_p)

The net monetary benefit (NMB) for t_1 is defined as:

$$NB_{t_1} = \lambda * E_{t_1} - C_{t_1}$$

where λ = the maximum willingness to pay for a unit of health benefit

The incremental net benefit (INB) when comparing two treatment options (t_1 and t_2) is defined as:

$$INB_{t_1 t_2} = \lambda * (E_{t_1} - E_{t_2}) - (C_{t_1} - C_{t_2})$$

The treatment with the greatest net benefit (NB) can be considered the optimal treatment (noted as t^*). The expected value of perfect partial information (EVPPI) for an individual parameter X_1 is defined as:

$$EVPPI_{X_1} = E_{X_1} \left[\max_t E_{X|X_1} (NB_t | X_1) \right] - NB_{t^*}$$

EVPPI for a sub-group of parameters X_p is defined as:

$$EVPPI_{X_p} = E_{X_p} \left[\max_t E_{X|X_p} (NB_t | X_p) \right] - NB_{t^*}$$

If INB is multi-linear (or almost multi linear) in X_1^c (or X_p^c), EVPPI for X_1 (or X_p) can be estimated as follows: One random value $X_p^{(j)}$ will be generated from the joint distribution of X_p .⁷⁵ The net benefit for each treatment option t will be calculated using parameter values $X_p = X_p^{(j)}$ and $X_p^c = E(X_p^c | X_p = X_p^{(j)})$.⁷⁵ This will give the value of $E(NB_t | X_p = X_p^{(j)})$.⁷⁵ The maximum of the net benefits will be obtained using $\max_t E(NB_t | X_p = X_p^{(j)})$.⁷⁵ These steps will be repeated 5000 times.

EVPPI will be estimated by:

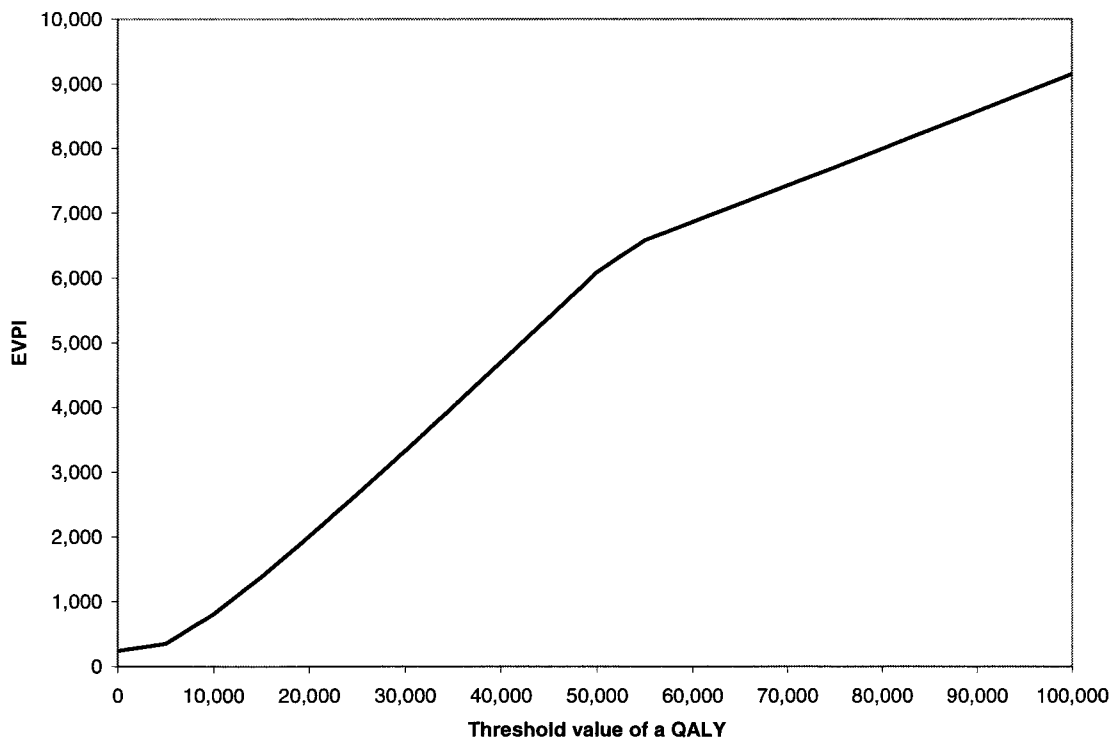
$$\sum_{j=1}^J \max_t E(NB_t | X_p = X_p^{(j)}) / J - NB_{t^*}$$
⁷⁵

4.3 Results

4.3.1 Expected Value of Perfect Information (EVPI)

Assuming a \$50,000 threshold value of a QALY, the expected value of perfect information (EVPI) for the overall model is \$6,091 per patient. **Figure 8** shows the per patient EVPI with respect to the threshold value of a QALY used for decision-making purposes.

Figure 8: Expected value of perfect information, per patient



Using cardiac revascularization rates reported by the Canadian Institute for Health Information (CIHI) and reproduced in **Table 35**, it was determined that there were over 40,000 PCIs performed in Canada in 2007-2008 (age-standardized incidence of 162 per

100,000), thus it would be worth over \$250 million per year to reduce all uncertainty in the model. This information could be applied to reimbursement decisions until the patent on clopidogrel expires (expected in 2012), corresponding to a \$502 million value of perfect information.

Table 35: Rates of cardiac revascularization procedures, Canada			
Year	Age-Standardized rate per 100,000 population		
	CABG	PCI	Cardiac Revascularization
1998-1999	91	96	187
1999-2000	93	108	201
2000-2001	93	122	214
2001-2002	93	135	228
2002-2003	91	142	232
2003-2004	90	156	246
2004-2005	86	168	253
2005-2006	84	177	259
2006-2007	77	175	251
2007-2008	75	162	235

Source Health Indicators 2009⁷⁶ Figure 1, page 23

Calculated by dividing the total number of discharges for PCI patients age 20 years and older by the total mid-year population age 20 years and older and multiplying this by 100,000

4.3.2 Expected Value of Perfect Information for Parameters (EVPPI)

The expected value of perfect partial information (EVPPI) was greater for clinical trial data than for baseline transition probabilities, costs, or utilities, suggesting that most of the uncertainty in the model was related to the relative effectiveness of the different antiplatelet therapies (**Table 36**). A closer evaluation of the relative risk parameters found that further research into the event risks associated with ticlopidine, specifically the risk of death, would bring the greatest value to the analysis (\$1,873/patient).

Table 36: EVPI/EVPPI			
	Per person (\$)	Per population/year (\$)	Per population, until 2012 (\$)
All	6,091	251,000,000	502,000,000
Costs	0	0	0
Utilities	0	0	0
Clinical probabilities	4	164,964	329,928
First year	0	0	0
Years 2+	3	123,723	246,446
Study data	4,812	198,000,000	396,000,000
clopidogrel	7	288,687	577,374
MI	0	0	0
Stroke	0	0	0
Death	7	288,687	577,374
Revascularization	0	0	0
Major bleed	0	0	0
ticlopidine	3,610	149,000,000	298,000,000
MI	0	0	0
Stroke	232	9,600,000	19,100,000
Death	1,911	79,000,000	158,000,000
Revascularization	0	0	0
Major bleed	0	0	0

4.4 Conclusions

The results of this analysis indicate that, assuming a \$50,000 threshold value of a QALY, the value of perfect information is \$6,091 per patient, or \$251M per year for the population. The greatest need for future research, as identified by the EVPPI analysis, is surrounding the clinical effectiveness of ticlopidine.

5.0 Budget Impact Analysis

5.1 Objective

The budget impact analyses (BIA) were conducted in order to estimate expenditures for each participating jurisdiction for antiplatelet drugs for patients undergoing percutaneous coronary intervention, assuming alternative prescribing patterns (or scenarios). As part of these analyses, trends in PCI procedure rates, and antiplatelet drug utilization patterns were investigated. The BIA should be viewed as complementary to the economic evaluation; its purpose is to predict how hypothetical changes in prescribing patterns might affect total spending on a given condition⁷⁷ (in this case, patients undergoing PCI).

5.2 Methods

The baseline scenario assumed that the number of future claims for each treatment remained constant at its average level of the past five to six fiscal years (2002/03-2007/08). Following the results from the economic analyses, which showed ticlopidine + ASA to be a cost-effective treatment strategy, alternative scenarios, based on a reduction in the number of recommendations for clopidogrel +ASA, with a subsequent increase in ticlopidine + ASA and/or ASA monotherapy, were considered. Finally, the introduction of prasugrel to the Canadian market was considered. The perspective of the analyses was that of the jurisdictional drug plan. Only net expenditures to the drug plan (drug cost + mark-up + dispensing fees – beneficiary co-payment) were considered.

Antiplatelet drug utilization for PCI

Antiplatelet drug utilization for PCI was estimated using data from the Canadian Disease and Therapeutic Index (CDTI). The CDTI is based on a sample of 652 physicians in office-based medical practice and covers 15 specialty groups. Physicians are asked to record the drug therapy recommended to each patient, by diagnosis. Since PCI is a procedure associated with the diagnosis of ACS, when calculating the estimated number of recommendations for antiplatelet drugs, it was assumed that 2/3 of ACS patients would undergo a PCI during their index admission. It further assumed that neither clopidogrel nor ticlopidine would be given as monotherapy. The average number of recommendations for ASA, as captured by the CTDI survey data from 2002 to 2008, was 348,391. The average numbers of recommendations for clopidogrel and ticlopidine were subtracted from this in order to determine the average number of recommendations for ASA monotherapy. This number divided by the total number of recommendations for ASA (as monotherapy or in combination) provided the estimate that 46% of ASA prescribed would be prescribed as monotherapy.

Average expenditure per claim

Participating jurisdictions provided estimates for the total expenditure and number of claims for each antiplatelet drug class (for any indication) for the past five to six fiscal years. Average expenditures per drug claimed had been calculated previously by dividing total drug expenditures for the last five to six fiscal years by the total number of claims for the same period for each jurisdiction (regardless of indication).⁷⁸

Baseline prescriptions (and expenditures)

The proportion of each drug used for PCI indication over total use of each antiplatelet drug class was estimated using IMS data. Estimated drug expenditures were obtained by multiplying the number of prescriptions for each therapy (for indication of PCI) by the average expenditures per claim. The estimated total expenditures for PCI indication for each drug plan were estimated by adding the estimated expenditures of each individual therapeutic option.

Budget impact analysis

Baseline cost estimates were compared with alternative scenarios in which the number of claims for clopidogrel + ASA was reduced by 5%, 10% and 20% and the number of claims taken away from clopidogrel + ASA was added to ASA monotherapy and ticlopidine according to one of the following:

Scenario 1: all additional claims are assumed to be for ticlopidine + ASA.

Scenario 2: according to the current usage patterns.

Scenario 3: all additional claims are assumed to be for ASA monotherapy.

Total expenditure under each of the alternative scenarios was calculated by multiplying the average cost per claim under the baseline scenario by the total projected number of claims for each therapeutic option. The budgetary impact was calculated by subtracting the total expenditures estimated under an alternative scenario from those under the base case scenario. Sensitivity analyses were performed to evaluate the effect of changing

ASA coverage patterns (i.e. over the counter (OTC) versus prescription) in addition to the altering prescribing patterns.

Finally, a scenario in which prasugrel is introduced to the market at a cost of 18% more than the current cost of clopidogrel was considered. In this sensitivity analysis, 5%, 10%, 20%, 30%, 40%, and 50% of the claims for clopidogrel + ASA were shifted to prasugrel + ASA.

5.3 Results

Nine drug plans provided utilization data for antiplatelet drug classes for the past five to six fiscal years. **Appendix 14** summarizes the total number of prescriptions and expenditures reported from these jurisdictions. Using information in **Appendix 14**, the average number of claims for each drug therapy over the past fiscal years was calculated and was considered as the base-case utilization. Each drug can be indicated for diagnoses other than PCI. The proportion of each drug class used for PCI among total use of the drug class was estimated using IMS data for fiscal years 2002/03 to 2007/08. The results are presented in **Table 37**. These results were used to estimate the proportion of ASA prescribed for PCI as monotherapy (46%).

Antiplatelet drug utilization for PCI

Table 37 and **Figure 9** show the estimated number of antiplatelet drug recommendations for PCI. Currently, the market is split between ASA alone and Clopidogrel + ASA, with ASA alone accounting for just over half of the antiplatelet drug recommendations made

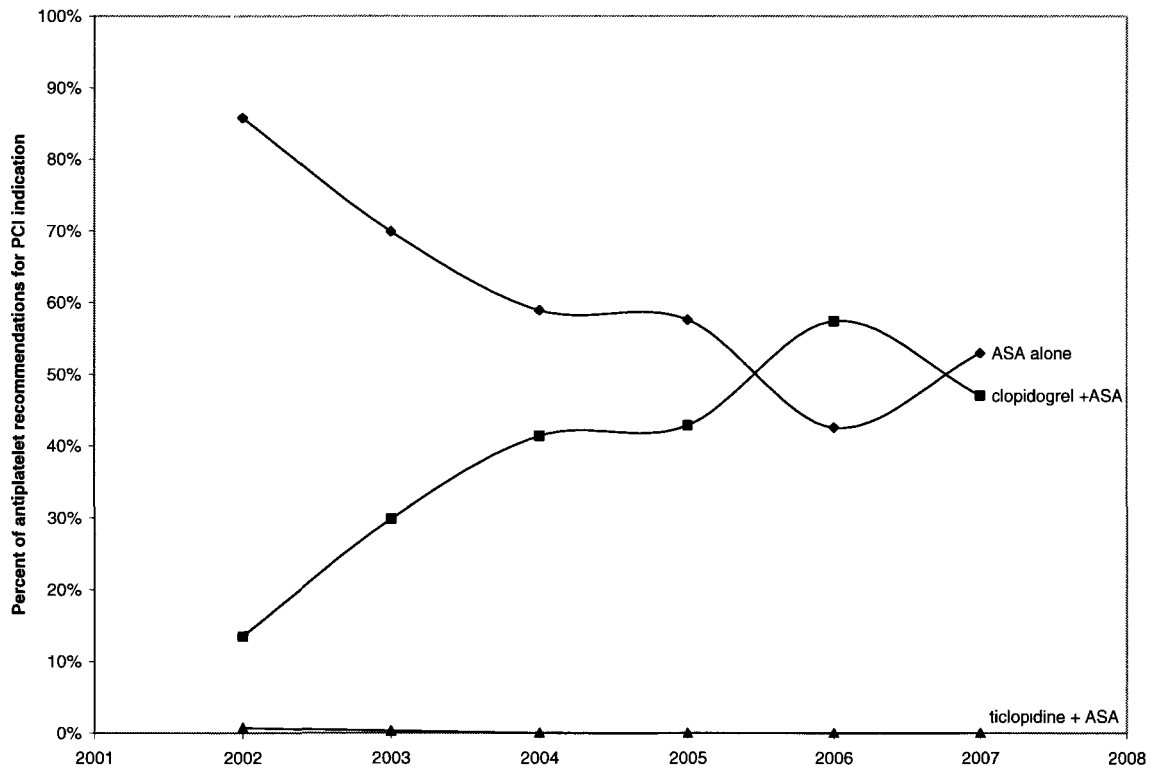
by Canadian office-based physicians for PCI. The last time ticlopidine was reported to be a recommended therapy for ACS was in 2003/2004 when it made up 0.31% of the market share for the antiplatelet drugs for PCI indication.

Table 37: Estimated number (%) of antiplatelet drug recommendations made by Canadian office-based physicians for PCI indication [2002/03 - 2007/08]

Drug class	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08
ASA alone	401,410 (85.79%)	239,690 (69.86%)	207,373 (58.90%)	170,080 (57.60%)	127,763 (42.58%)	173,570 (52.97%)
Clopidogrel + ASA*	63,127 (13.49%)	102,347 (29.83%)	146,487 (41.40%)	127,690 (42.88%)	172,270 (57.42%)	154,120 (47.03%)
Ticlopidine + ASA	3,360 (0.72%)	1,060 (0.31%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	467,897	343,097	353,860	297,770	300,033	327,690

Source: IMS Health Inc., Canadian Diseases & Therapeutic Index (CDTI)

Figure 9: Estimated percent market share of different antiplatelet drugs for the indication of PCI, by year



Average expenditure per claim

Average costs per claim are presented in **Table 38**. It should be noted that these costs are not specific to the indication of PCI. Significant variation was observed between jurisdictions. The average expenditure per clopidogrel claim ranged from \$64.38 (with Veterans Affairs) to \$144.07 (in Alberta). Average expenditures for ASA ranged from \$0.46 (in Manitoba) to \$22.54 (in BC), and ticlopidine expenditures from \$31.47 (with the NIHB) to \$67.02 (in New Brunswick).

Table 38: Average expenditure per claim (over five fiscal years starting 2003/04)									
	SK	NS	BC	VA[^]	PEI	NIHB	NB	AB	MB
Clopidogrel	\$72.14	\$114.74	\$88.05	\$64.38	\$73.14	\$71.80	\$121.49	\$144.07	\$93.03
ASA 325mg	\$6.32	\$8.44	\$22.54	\$8.57	\$2.78	\$4.86	\$6.25	---	\$0.46
Ticlopidine	\$34.35	\$63.72	\$55.38	\$52.38	\$36.75	\$31.47	\$67.02	\$64.32	\$58.52

Calculated as the sum of expenditures over four (or five) fiscal years divided by the sum of claims over the same fiscal years

[^] Utilization for ASA 81 mg and 350 mg was reported together

^{^^} Any dosage (25mg, 50mg or 75mg)

Base-line prescriptions (and expenditures)

The costs in **Table 38** were applied to the estimated number of claims for antiplatelet drugs for PCI patients in order to provide the base-line jurisdictional expenditures in **Table 39**. Calculations suggest a total of 137,670 prescriptions for PCI, related to formulary patients in specific jurisdictions, per year. It should be noted that many of the patients undergoing PCI may not be covered by a jurisdictional plan. CIHI data⁷⁶ indicate that over 40,000 PCIs are performed in Canada annually. Prescriptions are generally filled for 3 months at a time, with many patients taking antiplatelet therapy for years after PCI. Given all of this, the BIA estimate of 137,670 prescriptions claimed

through participating jurisdictional drug plans is consistent with the population impact assessment estimate of 40,000 PCIs nationally, per year. Baseline total expenditure for antiplatelet therapies for PCI ranges from \$43,642 (PEI) to \$1.8 million (BC). (Table 39)

Table 39: Base-line prescriptions (and expenditures) for antiplatelets for PCI indication							
	ASA 325 mg Rx alone	ASA 325 mg OTC alone	ASA 325 mg Rx + clopidogrel	ASA 325 mg OTC + clopidogrel	ASA 325 mg Rx + ticlopidine	ASA 325 mg OTC + ticlopidine	Total
MB	466 (\$214)	8,797 (\$0)	541 (\$50,546)	10,215 (\$950,282)	3 (\$171)	55 (\$3,205)	20,076 (\$1,004,418)
AB	0 (\$0)	7,681 (\$0)	0 (\$0)	8,872 (\$1,278,145)	0 (\$0)	95 (\$6,141)	16,648 (\$1,284,285)
BC	1,541 (\$34,743)	15,617 (\$0)	1,780 (\$196,903)	18,040 (\$1,588,448)	19 (\$1,475)	192 (\$10,620)	37,190 (\$1,832,188)
NB	1,295 (\$8,094)	1,987 (\$0)	1,496 (\$191,085)	2,296 (\$278,912)	16 (\$1,161)	24 (\$1,629)	7,114 (\$480,881)
PEI	128 (\$356)	380 (\$0)	146 (\$11,103)	433 (\$31,677)	3 (\$135)	10 (\$371)	1,101 (\$43,642)
SK	1,748 (\$11,045)	4,646 (\$0)	2,027 (\$159,055)	5,389 (\$388,729)	13 (\$545)	36 (\$1,225)	1,3859 (\$560,599)
VA	4,307 (\$36,898)	4,914 (\$0)	5,016 (\$365,912)	5,723 (\$368,430)	12 (\$761)	14 (\$747)	19,986 (\$772,748)
NIH B	5,078 (\$24,655)	1,152 (\$0)	5,861 (\$449,253)	1,330 (\$95,476)	67 (\$2,451)	15 (\$482)	13,503 (\$572,317)
NS	2,682 (\$22,621)	1,098 (\$0)	3,072 (\$378,367)	1,258 (\$144,355)	59 (\$4,252)	24 (\$1,538)	8,193 (\$551,133)
Total	17,245 (\$138,626)	46,272 (\$0)	19,939 (\$1,802,224)	53,556 (\$5,124,454)	192 (\$10,951)	465 (\$25,958)	137,670 (\$7,102,211)

Budget impact analysis

Three scenarios, each involving a 5-20% reduction in clopidogrel +ASA use, were considered in the base case BIA. **Table 40** presents only the ten percent reduction, the complete results can be found in **Appendix 15**.

Under **Scenario 1**, a 5-20% reduction in clopidogrel + ASA use, and a corresponding increase in ticlopidine + ASA, was assumed. This resulted in annual net savings of up to

\$140,000 for an individual drug plan, or \$575,000 nationally. Under **Scenario 2**, the same 5-20% reduction in clopidogrel + ASA use was assumed, this time with a corresponding increase in ASA monotherapy and ticlopidine + ASA (according to current utilization patterns). This resulted in annual net savings of up to \$346,000 for an individual drug plan, or \$1.3 million nationally. Since ticlopidine + ASA use is currently minimal, the results of **Scenario 3**, an increase was in ASA monotherapy, were very similar to scenario 2, increase in ASA monotherapy and ticlopidine +ASA, according to current utilization patterns.

Table 40: Projected budget impact of a ten percent reduction in clopidogrel + ASA utilization and corresponding increase in other antiplatelet therapies for PCI

Jurisdiction	Base-case	Scenario 1	Savings	Scenario 2	Savings	Scenario 3	Savings
MB	\$1,004,418	\$967,304	\$37,114	\$904,749	\$99,669	\$904,360	\$100,058
AB	\$1,284,285	\$1,213,536	\$70,749	\$1,157,171	\$127,114	\$1,156,471	\$127,814
BC	\$1,832,188	\$1,767,427	\$64,761	\$1,658,998	\$173,190	\$1,657,667	\$174,522
NB	\$480,881	\$460,229	\$20,652	\$435,123	\$45,758	\$434,816	\$46,065
PEI	\$43,642	\$41,534	\$2,109	\$39,460	\$4,182	\$39,405	\$4,237
SK	\$560,599	\$532,577	\$28,022	\$507,296	\$53,303	\$507,102	\$53,497
VA	\$772,748	\$759,864	\$12,884	\$703,774	\$68,974	\$703,611	\$69,137
NIHB	\$572,317	\$543,320	\$28,996	\$520,986	\$51,330	\$520,690	\$51,627
NS	\$551,133	\$529,042	\$22,091	\$502,045	\$49,088	\$501,452	\$49,681

Scenario 1: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims

Scenario 2: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims and ASA monotherapy claims in the same proportion as in base-case

Scenario 3: The total numbers of clopidogrel + ASA claims reduced was added to the base-case number of ASA monotherapy claims

Sensitivity analyses

The outcomes of the three scenarios considered in the primary BIA are dependent on whether aspirin usage is primarily over-the-counter (no cost to the jurisdictional health plan) or by prescription. The primary analysis assumed no change in the ratio of OTC/Rx

aspirin usage. Sensitivity analyses considered the extreme cases (ASA covered 100% by the health plans (**Table 41**) and ASA entirely patient purchased (**Table 42**)). As in the base case, **Tables 41 and 42** present only the ten percent reduction, the complete results can be found in **Appendix 15**.

If all ASA were to be entirely at the expense of the health plan, many jurisdictions would find that their total antiplatelet budget for the indication of PCI would increase, despite the hypothesized trend away from clopidogrel +ASA.

Jurisdiction	Base-case	Scenario 1	Savings	Scenario 2	Savings	Scenario 3	Savings
MB	\$1,004,418	\$976,070	\$28,348	\$913,516	\$90,902	\$913,127	\$91,291
BC	\$1,832,188	\$2,530,441	(\$698,253)	\$2,422,012	(\$589,824)	\$2,420,681	(\$588,492)
NB	\$480,881	\$487,152	(\$6,271)	\$462,046	\$18,834	\$461,739	\$19,142
PEI	\$43,642	\$43,821	(\$179)	\$41,747	\$1,895	\$41,692	\$1,950
SK	\$560,599	\$596,211	(\$35,612)	\$570,929	(\$10,330)	\$570,735	(\$10,136)
VA	\$772,748	\$851,105	(\$78,357)	\$795,014	(\$22,266)	\$794,851	(\$22,103)
NIHB	\$572,317	\$555,445	\$16,872	\$533,111	\$39,206	\$532,815	\$39,502
NS	\$551,133	\$549,124	\$2,009	\$522,127	\$29,006	\$521,533	\$29,600

Alberta is omitted from this analysis because ASA is not available by prescription in that jurisdiction.

Numbers in parentheses indicate negative savings, or added costs.

Scenario 1: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims

Scenario 2: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims and ASA monotherapy claims in the same proportion as in base-case

Scenario 3: The total numbers of clopidogrel + ASA claims reduced was added to the base-case number of ASA monotherapy claims

Should ASA be entirely patient funded - that is, not available at the expense of the drug plan - the forementioned scenarios could result in savings of over \$400,000 for individual jurisdictions, and \$1.6 million at the national level.

Table 42: Sensitivity analysis - ASA funded by patient

Jurisdiction	Base-case	Scenario 1	Savings	Scenario 2	Savings	Scenario 3	Savings
MB	\$1,004,418	\$966,840	\$37,578	\$904,285	\$100,133	\$903,896	\$100,522
AB	\$1,284,285	\$1,213,536	\$70,749	\$1,157,171	\$127,114	\$1,156,471	\$127,814
BC	\$1,832,188	\$1,692,123	\$140,065	\$1,583,694	\$248,494	\$1,582,363	\$249,826
NB	\$480,881	\$442,686	\$38,195	\$417,581	\$63,300	\$417,273	\$63,607
PEI	\$43,642	\$40,761	\$2,881	\$38,688	\$4,954	\$38,633	\$5,010
SK	\$560,599	\$508,638	\$51,961	\$483,356	\$77,243	\$483,162	\$77,437
VA	\$772,748	\$679,889	\$92,859	\$623,798	\$148,950	\$623,635	\$149,113
NIHB	\$572,317	\$489,882	\$82,435	\$467,548	\$104,769	\$467,251	\$105,066
NS	\$551,133	\$480,012	\$71,121	\$453,015	\$98,118	\$452,422	\$98,711

Scenario 1: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims

Scenario 2: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims and ASA monotherapy claims in the same proportion as in base-case

Scenario 3: The total numbers of clopidogrel + ASA claims reduced was added to the base-case number of ASA monotherapy claims

In the final sensitivity analysis (**Table 43**), patients were assumed to switch from clopidogrel + ASA to prasugrel + ASA. Larger switches (of up to 50%) were considered in this analysis, as physicians tend to embrace new treatments more readily than they do old ones. Prasugrel was valued at a cost 18% higher than the jurisdiction’s price for clopidogrel, thus there is a cost increase, rather than a cost savings, observed in this analysis. Should prasugrel be approved for use in Canada at a cost 18% higher than clopidogrel, and 50% of patients switch from clopidogrel + ASA to prasugrel + ASA, it could cost some of the individual jurisdictions (Alberta and BC) upwards of an additional \$100,000 per year.

Table 43: Sensitivity analysis - switch from clopidogrel + ASA to prasugrel + ASA

	Base-case	5%	10%	20%	30%	40%	50%
MB	\$1,004,418	\$1,013,423	\$1,022,428	\$1,040,439	\$1,058,449	\$1,076,460	\$1,094,470
Cost increase		\$9,005	\$18,010	\$36,021	\$54,031	\$72,042	\$90,052
AB	\$1,284,285	\$1,295,789	\$1,307,292	\$1,330,299	\$1,353,305	\$1,376,312	\$1,399,318
Cost increase		\$11,504	\$23,007	\$46,014	\$69,020	\$92,027	\$115,033
BC	\$1,832,188	\$1,847,895	\$1,863,602	\$1,895,016	\$1,926,430	\$1,957,844	\$1,989,258
Cost increase		\$15,707	\$31,414	\$62,828	\$94,242	\$125,656	\$157,070
NB	\$480,881	\$485,027	\$489,173	\$497,464	\$505,756	\$514,047	\$522,339
Cost increase		\$4,146	\$8,292	\$16,583	\$24,875	\$33,166	\$41,458
PEI	\$43,642	\$44,024	\$44,405	\$45,168	\$45,930	\$46,693	\$47,456
Cost increase		\$382	\$763	\$1,526	\$2,288	\$3,051	\$3,814
SK	\$560,599	\$565,414	\$570,229	\$579,858	\$589,488	\$599,117	\$608,747
Cost increase		\$4,815	\$9,630	\$19,259	\$28,889	\$38,518	\$48,148
VA	\$772,748	\$778,970	\$785,193	\$797,637	\$810,082	\$822,527	\$834,972
Cost increase		\$6,222	\$12,445	\$24,889	\$37,334	\$49,779	\$62,224
NIHB	\$572,317	\$576,963	\$581,610	\$590,903	\$600,196	\$609,489	\$618,781
Cost increase		\$4,646	\$9,293	\$18,586	\$27,879	\$37,172	\$46,464
NS	\$551,133	\$555,604	\$560,076	\$569,018	\$577,961	\$586,903	\$595,846
Cost increase		\$4,471	\$8,943	\$17,885	\$26,828	\$35,770	\$44,713
Total	\$7,102,211	\$7,163,109	\$7,224,007	\$7,345,802	\$7,467,597	\$7,589,392	\$7,711,187
Cost increase		\$60,898	\$121,796	\$243,591	\$365,386	\$487,181	\$608,976

5.4 Conclusions

The results of the budget impact analysis indicate that there is money to be saved by the jurisdictional drug plans should prescribers move away from clopidogrel + ASA for PCI patients, particularly if ASA is patient-funded. Given the concerns surrounding ticlopidine, the scenarios in the BIA considered only small changes in prescribing

patterns (5-20% of current clopidogrel +ASA use). The sensitivity analysis surrounding the introduction of prasugrel indicates the added costs that the jurisdictional drug plans might expect should prasugrel be introduced at a cost 18% greater than clopidogrel, as in the US.

6. Discussion

The economic review found no Canadian studies evaluating the cost-effectiveness of clopidogrel in adults undergoing PCI. Most of the studies included in the review compared long term use of clopidogrel + ASA to a combination of short-term clopidogrel + ASA + placebo. The most recently-published economic evaluation included in the review compared clopidogrel + ASA versus prasugrel + ASA. There were no comparisons evaluating clopidogrel versus older treatment alternatives or clopidogrel versus a no treatment alternative.

Treatment with ticlopidine + ASA was found to dominate clopidogrel + ASA treatment in a number of scenarios considered in the economic evaluation. When the costs of blood cell monitoring, treating neutropenia cases, and risk of death due to TTP were included in the sensitivity analysis, ticlopidine + ASA was no longer dominant over clopidogrel +ASA, but clopidogrel + ASA was subject to extended dominance. When considering a 50% price reduction for clopidogrel, as may occur in the coming years with the loss of patent protection for Plavix, treatment with clopidogrel + ASA dominated ASA monotherapy – although ticlopidine is likely to be more cost-effective with an ICER of \$2,209.80 compared to clopidogrel + ASA. In the probabilistic analysis, treatment with clopidogrel + ASA was dominated by ASA, while ticlopidine +ASA had an ICER of \$52,544.03 compared with ASA monotherapy.

The value of information analysis indicated that, assuming a \$50,000 threshold value of a QALY, the value of perfect information is \$6,091/patient, or \$251M/year for the population. This high value of future research is indicative of a high degree of uncertainty. The cost-effectiveness acceptability curves presented in this thesis indicate that there is only a 64-69% probability that ticlopidine + ASA is the most cost-effective treatment of the three considered in the base case. The majority of the value of additional information could be obtained with further investment into a clinical trial comparing ticlopidine + ASA and clopidogrel + ASA, focussing on a primary outcome of mortality.

The results of the budget impact analyses indicate that there is money to be saved in moving away from clopidogrel + ASA, towards either ticlopidine + ASA or ASA monotherapy. Just how much stands to be gained depends on the percentage of patients who make the switch, which alternate treatment option they switch to, and whether ASA is paid for by the drug plan or the patient. Switching patients from clopidogrel + ASA to prasugrel + ASA could greatly increase the amount of money spent by the jurisdictional drug plans on antiplatelet agents in the secondary prevention of vascular events in patients undergoing PCI.

6.1 Strengths and Limitations

The economic review conducted as part of this analysis provides a thorough and unbiased synthesis of the available economic evidence regarding antiplatelet agents in the secondary prevention of vascular events in adults undergoing percutaneous coronary intervention. The review is limited primarily by the lack of available evidence. For

example, there was no previously published economic evaluation conducted from the Canadian perspective.

The studies included in the review were found to be well reported using the BMJ Guidelines. The BMJ Guidelines look to see whether specific components of the economic evaluation are reported or described. They do not, for the most part, evaluate whether this is done clearly or accurately. For example, all seven economic evaluations scored a “yes” for “Viewpoint(s) of analysis clearly stated and justified”, despite the fact that three of the eight analyses were not actually conducted from the viewpoint stated. Furthermore, the Guidelines do not question whether or not a given study was funded by industry, which the majority of studies included in this review were. Industry sponsorship does not imply reporting bias, but the potential for biases is there.

The relationship between source funding and economic results has been evaluated by Bell⁷⁹ and Miners⁸⁰. Miners et al. compared incremental cost effectiveness ratios (ICERs) from 27 appraisals submitted to the National Institute for Clinical Excellence (NICE) in the UK⁸⁰. For each appraisal, ICERs were provided by the manufacturers of the relevant healthcare technologies and by contracted university-based assessment groups⁸⁰. In seventy-eight percent (21/27) of the pairwise comparisons, the manufacturer-submitted ICER was lower than the ICER submitted by the assessment group⁸⁰. On a larger, global scale, Bell et al. conducted a systematic literature search for all original English language cost-utility analyses published between 1976 and 2001. Their search resulted in 494 studies; 240 of which were non-industry sponsored, 88 that

were industry-sponsored, and 166 that did not specify a funding source. The authors found that those studies funded by industry had a greater likelihood of reporting ICERs under the three thresholds investigated (20,000 USD per QALY, 50,000 USD per QALY, and 100,000 USD per QALY) than those funded by non-industry.

The economic model used in this thesis is based on a previously published model by Ringborg et al.²⁹ The six discrete health states used in this model were: post-PCI, MI, post-MI, stroke, post-stroke, and death. In order to optimise the usefulness and ease of interpretation of this analysis, the intervention and comparator regimens being compared were clearly stated. Furthermore, every effort was made to report quantities of resources separately from unit costs.

The clinical effectiveness data came from MTC meta-analysis. Not all trial reports documented data on all the outcomes of interest. This may introduce bias, as statistically significant results are more likely to be reported than non-significant results.⁸¹ There was variation in the way that the investigators reported data on bleeding outcomes and revascularization. The definitions varied and it was difficult to group the data. For major bleeds, events reported as major hemorrhages, life-threatening bleeds, and bleeding episodes that required transfusion were included. Revascularization included both emergency bypass surgery and/or repeat PTCA.

The results of the deterministic analysis indicate that ticlopidine + ASA is more cost-effective than clopidogrel + ASA in the secondary prevention of vascular events in

patients undergoing PCI. However, ticlopidine is reported to carry the risk of potentially serious blood dyscrasias, and for this reason it is not a common treatment option for this indication. Clopidogrel has been the preferred antiplatelet treatment option for this indication since its market entry and current guidelines recommend dual antiplatelet therapy with clopidogrel + ASA following PCI. It may be unrealistic to expect physicians to practice in discordance with the guidelines, however, sensitivity analyses in this thesis took into account additional costs of blood cell monitoring, risks and costs of neutropenia, and risk of death due to TTP, and still found ticlopidine and ASA to be a viable treatment option.

In the probabilistic analysis, clopidogrel + ASA was dominated by ASA monotherapy, while ticlopidine + ASA had an ICER of \$52,544, compared to ASA alone. The difference between the deterministic and probabilistic results is due to the uncertainty surrounding the efficacy estimates for these treatment regimens, as compared to ASA. The median values used in the calculation of relative risk estimates for the deterministic analysis overestimate the relative effectiveness of treatment, as compared to the mean values used in the probabilistic analysis. This uncertainty was further demonstrated by cost-effectiveness acceptability curves and a value of information analysis. At this point in time, given the level of uncertainty, the safest recommendation may be to forgo dual antiplatelet therapy until the incremental benefits of adding a second antiplatelet (be it clopidogrel, ticlopidine, or prasugrel) are better understood.

While the cost-effectiveness acceptability curves presented in this thesis demonstrate that ticlopidine + ASA has the highest probability of being the optimal treatment at all threshold values between \$20,000 and \$100,000, the clinical effectiveness of ticlopidine was one of the most uncertain variables in the model, with an EVPPI of almost \$300 million for the Canadian population over the next two years. Further clinical research would provide a more robust estimate of the clinical efficacy of ticlopidine + ASA in patients undergoing PCI, but some may consider this unethical, given the suggested health risks with this therapeutic strategy.

Study considerations regarding budget impact analyses are that, first, analyses reported here were based on average historical drug utilization and do not reflect actual changes or trends in prescribing patterns, nor do they reflect changing population dynamics (i.e. potential changes in the number of PCIs performed). Second, the proportion of prescriptions which were for the indication of PCI was estimated based on IMS market share data, which is based on a survey of representative Canadian office-based physicians. Because drugs that are recorded in IMS Health data were recommended by a physician, they may not reflect the actual quantity that is dispensed (for example, patients may not take the drugs). (Source: IMS Health Inc., Canadian Disease and Therapeutic Index [CDTI]. This information may not be reproduced in any way without written consent from IMS Health Incorporated). If compliance patterns differ between PCI patients and patients taking antiplatelets for other indications, or if there is significant variation in compliance between PCI patients (i.e. patient more likely to fill one

prescription over another), the estimated market shares for PCI over total indications may be biased.

7. Conclusions

This thesis provides a thorough evaluation of the economic considerations involved in the use of antiplatelet agents in the secondary prevention of vascular events in adults undergoing PCI. The results are limited by the availability of clinical data, but suggest that ticlopidine + ASA deserves the consideration of physicians treating patients for this indication. The CLASSICS safety study of 2000 prompted physicians to abandon ticlopidine, in favour of clopidogrel, as ticlopidine was shown to cause greater incidence of bleeding complications and blood dyscrasias. However, the relative risks of death, MI, and revascularization calculated by MTC meta-analysis are lower for patients on ticlopidine + ASA than those taking clopidogrel + ASA. Upon Health Canada's approval of prasugrel, jurisdictional drug spending on antiplatelet agents is likely to increase. A change in clinical prescribing patterns can only occur with the support of physicians, who may be leery of economic-based arguments. For this reason, it is strongly suggested that the three generations of antiplatelet agents (ticlopidine, clopidogrel, and prasugrel) be evaluated in a head-to-head-to-head manner in order to provide physicians with a more conclusive answer as to which is the optimal antiplatelet agent to be used, in combination with aspirin, for adult patients undergoing PCI.

8. References

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APPENDICES

APPENDIX 1: SEARCH STRATEGY

exp Angioplasty/
Angioplasty, Balloon
Angioplasty, Balloon, Laser-Assisted
Angioplasty, Transluminal, Percutaneous Coronary
Angioplasty, Laser
Angioplasty, Balloon, Laser-Assisted
Atherectomy
Atherectomy, Coronary

(percutaneous coronary intervention* or pci or ptca).ti,ab.

(angioplasty or angioplasties or endoluminal repair or endoluminal repairs).ti,ab

(stent or stents or stenting or restenosis).ti,ab

(atherectomy or atherectomies).ti,ab

brachytherapy.ti,ab

antiplatelet

platelet aggregation inhibitor

thrombus inhibitor

Aspirin

Clopidogrel

Prasugrel – subject heading in Embase

150322-43-3.rn

(CS 747 or CS-747 or Effient or LY 640315 or LY-640315 or LY640315).ti,ab,rn

Ticlopidine

Dipyridamole

Aggrenox

APPENDIX 2: GREY LITERATURE SEARCH

Institute of Health Economics (IHE)

<http://www.ihe.ca>

EURONHEED (European Network of Health Economic Evaluation Databases)

<http://infodoc.inserm.fr/euronheed/Publication.nsf>

Health Economics Research Unit (HERU), University of Aberdeen

<http://www.abdn.ac.uk/heru/>

Health Economics Research Group (HERG), Brunel University, UK

<http://www.brunel.ac.uk/about/acad/herg>

TRIP database (Turning Research Into Practice)

<http://www.tripdatabase.com/>

Centre for Reviews and Dissemination (CRD), University of York

<http://www.york.ac.uk/inst/crd/crddatabases.htm>

APPENDIX 3: ECONOMIC DATA EXTRACTION SHEET

Part 1 – Characteristics of Included Economic Studies

Author/Year of publication

Title

Industry sponsorship

Study perspective

Interventions and comparators

Study design (including Markov or one episode of disease; sensitivity analysis or not and type of analysis; costs and/or consequences discounted or not and rate used; time horizon)

Location/Country of origin

Outcomes and source

Part 2 – Results of included Economic Studies

Author/Year of publication

Currency and year

Estimate of cost effectiveness or relative cost

Conclusions

APPENDIX 4: FULL TEXT ECONOMIC ARTICLES OBTAINED FOR REVIEW AS POTENTIALLY RELEVANT

Author/Year	Included/Excluded	Reason for exclusion
Angiolillo 2006 ⁸²	Excluded	Commentary
Annemans 2003	Excluded	Abstract
Antioch 2002 ⁸³	Excluded	Not a complete economic evaluation
Beinart 2003 ⁸⁴	Excluded	Abstract
Beinart 2005 ²⁶	Included	
Berg 2007 ⁸⁵	Excluded	Abstract
Berg 2008 ²²	Included	
Bennett 2009 ⁸⁶	Excluded	Different patient group
Berglund 2002	Excluded	Not a complete economic evaluation
Blanco 1998 ⁸⁷	Excluded	Abstract
Calver 2000 ⁸⁸	Excluded	Not a complete economic evaluation
Cheng 2007 ⁸⁹	Excluded	Different patient group
Cowper 2005 ²⁷	Included	
Cowper 2005 ⁹⁰	Excluded	Commentary
Eriksson 2005 ⁹¹	Excluded	Commentary
Fidan 2007 ⁹²	Excluded	Different patient group
Filion 2009 ⁹³	Excluded	Different intervention
Frey 1997 ⁹⁴	Excluded	Abstract
Gonzalez 2000 ⁹⁵	Excluded	Not a complete economic evaluation
Hashiguchi 2004 ⁹⁶	Excluded	Not a complete economic evaluation
Heeg 2007 ²³	Included	
Heeg 2007 ⁹⁷	Excluded	Different patient group
Ho 2004 ⁹⁸	Excluded	Different patient group
Kabir ⁹⁹ 2006 (Circulation)	Excluded	Abstract
Latour-Perez 2008 ¹⁰⁰	Excluded	Different treatment
Lindgren 2005 ²⁸	Included	
Lyseng-Williamson 2006 ¹⁰¹	Excluded	Review
Mahoney 2006 ²⁴	Included	
Mahoney 1999 ¹⁰²	Excluded	Abstract
Mahoney 2003 ¹⁰³	Excluded	Abstract
Mahoney 2010 ²⁵	Included	
McCullough 1999 ¹⁰²	Excluded	Abstract
Mehta 2003 ¹⁰⁴	Excluded	Abstract
Neyt 2009 ¹⁰⁵	Excluded	Different treatment
Omeish 2007 ¹⁰⁶	Excluded	Review
Ringborg 2005 ²⁹	Included	
Valentin 2001 ¹⁰⁷	Excluded	Foreign language
Weintraub 2004 ¹⁰⁸	Excluded	Abstract
Weintraub 2004 ¹⁰⁹	Excluded	Review
Weintraub 2005 ¹¹⁰ (Eur Heart J)	Excluded	Abstract
Zhang 2006 ¹¹¹ (Circulation - May)	Excluded	Abstract
Zhang 2006 ¹¹² (Int J Cardiol)	Excluded	Different patient population

APPENDIX 5: CHARACTERISTICS OF TRIALS ON WHICH ECONOMIC EVALUATIONS INCLUDED IN THE REVIEW ARE BASED

Trial	n	Patient population	Primary Outcome	Intervention	Comparator
PCI CURE ³⁰ Clopidogrel in Unstable angina to prevent Recurrent Events	2,658	Patients with non-ST-elevation acute coronary syndrome undergoing PCI	Composite of cardiovascular death, myocardial infarction, or urgent target vessel revascularization within 30 days of PCI	Loading dose 300mg clopidogrel	Loading dose placebo
				Pre-treatment with aspirin and clopidogrel 75 mg daily for a median of 10 days before PCI	Pre treatment with aspirin and placebo 75 mg daily for a median of 10 days before PCI
				All patients treated with open label thienopyridine (either clopidogrel or ticlopidine) in combination with aspirin for 2-4 weeks	
				Aspirin and clopidogrel 75 mg daily until the end of follow up (3 12 months after randomization)	Aspirin and placebo daily until the end of follow-up (3 12 months after randomization)
CREDO ³¹ Clopidogrel for the Reduction of Events During Observation	2,116	Patients with coronary artery disease undergoing planned or probable PCI	At 1 year Composite of death, MI, and stroke (intent-to-treat population) At 28 days Composite of death, MI, or urgent target vessel revascularization (per protocol population)	Loading dose (300 mg clopidogrel + 325 mg ASA) 3-24 hours before PCI	Loading dose (placebo + 325 mg ASA) 3 24 hours before PCI
				All patients treated with clopidogrel (75 mg/d) + ASA (325 mg/d) for days 1-28	
				Clopidogrel 75 mg daily until the end of the study period (day 29- 1 year) Aspirin at the discretion of the investigator	Placebo daily until the end of the study period (day 29 1 year) Aspirin at the discretion of the investigator
PCI-CLARITY ³² Clopidogrel as Adjunctive Reperfusion Therapy	1,863	Patients with recent ST-segment elevation MI undergoing PCI	Composite of cardiovascular death, recurrent MI, or stroke from PCI to 30 days after randomization	Loading dose (300mg clopidogrel)	Loading dose placebo
				Pre-treatment with clopidogrel 75 mg/day for 2-8 days prior to angiography	Pre-treatment with placebo for 2 8 days prior to angiography
				Open label clopidogrel was recommended for patients who underwent coronary artery stenting	
TRITON TIMI 38 ³³ Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction	13,608	Patients with moderate-to-high-risk ACS with scheduled PCI	Efficacy endpoint Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke Safety endpoint Major bleeding	Loading dose prasugrel (60 mg) administered between randomization and 1 hour after leaving the catheterization laboratory	Loading dose clopidogrel (300 mg) administered between randomization and 1 hour after leaving the catheterization laboratory
				Maintenance doses of prasugrel (10 mg) daily Use of aspirin was required Daily dose of 75 162 mg was recommended	Maintenance doses of clopidogrel (75 mg) daily Use of aspirin was required Daily dose of 75-162 mg was recommended
				Follow up for 6-15 months	

APPENDIX 6: DATA SOURCES AND METHODS OF ECONOMIC EVALUATIONS INCLUDED IN THE REVIEW

Author	Cost/Utility Data Source(s)	Baseline Event Rate Data Source(s)	Effectiveness Data Source(s)	Form of Analysis	Time Horizon
Beinhart 2005 ²⁶	Health care costs were calculated by applying unit costs to resource utilization reported over the course of the CREDO trial. ³¹ Costs estimated for each DRG were based on average Medicare reimbursement rates, average MEDSTAT reimbursement rates, and a blended cost estimate of the two fee schedules.	Framingham and Saskatchewan databases	In-trial (CREDO ³¹) estimates of event rates (death, MI, and stroke)	Trial-based	First year costs, lifetime effectiveness
Berg 2008 ²²	In Sweden , direct and indirect costs during the first year following MI or stroke were taken from a retrospective study, ¹¹³ second year costs were derived from a Swedish modelling study. ¹¹⁴ In Germany , the direct cost of MI came from a resource utilization study, ¹¹⁵ and the direct cost of stroke from a population-based registry study. ¹¹⁶ In France , the direct cost of MI was taken from a modelling study, ¹¹⁷ and the direct cost of stroke from a prospective study. ¹¹⁸ Utilities were taken from a cross-sectional study in Sweden. ³⁴	Baseline event rates during the first month taken from Swedish Hospital Discharge and Cause of Death Registers, after 30 days, risks calculated using logistic regression analysis, after 13 months, risks modelled using Weibull regression, risks in untreated population taken from observations from 1995-2001 (prior to trial results from CURE), bleeding risks in the untreated population were calculated as a weighted mean from the placebo arms of the three clinical trials (PCI-CURE, ³⁰ CREDO, ³¹ and PCI-CLARITY ³²)	The relative risk of the combined end-point of MI, CV death, and major bleeding from pretreatment and long-term treatment with clopidogrel was based on a meta-analysis of PCI-CURE, ³⁰ CREDO, ³¹ and PCI-CLARITY ³²	Combined decision tree Markov model	Lifetime
Cowper 2005 ²⁷	Hospitalization costs were based on average Medicare reimbursement, incremental cost of bleeds taken from the literature, ¹¹⁹ Physician fees taken from Medicare fee schedules, cost of clopidogrel based on average wholesale price + monthly dispensing fee, costs adjusted to 2000 USD using the average annual Producer Price Index for general medical and surgical hospitals.	Baseline rates of MI, death, revascularization after PCI (given 1 month of clopidogrel) obtained from DISCC through annual mail and telephone follow-up of patients, supplemented by searches of Duke claims data and the National Death Index, rates of major bleeding based on CREDO ³¹ trial.	Relative risks of prolonged clopidogrel on rates of MI, major bleeding, repeat revascularization, and death during the 1- to 12-month follow up period based on CREDO ³¹ per-protocol data	Decision model	Lifetime

Author	Cost/Utility Data Source(s)	Baseline Event Rate Data Source(s)	Effectiveness Data Source(s)	Form of Analysis	Time Horizon
Heeg 2007 ²³	Costs taken from published sources (de Boer, ¹²⁰ Niessen, ¹²¹ and Serruys ¹²²). Costs were converted to 2004 values using appropriate price indices and rounded to units of €250, drug costs derived from Dutch Pharmacopoeia Utility values from published sources ^{36-38,123,124}	Several sources were consulted to estimate epidemiological parameters (CBS, ¹²⁵ Hollander, ¹²⁶ and Koek ¹²⁷)	First year event probabilities (MI, death from MI, stroke, death from stroke, cardiovascular death, and other death) taken from PCI-CURE ³⁰ and CREDO. ³¹ Weibull survival modelling provided individual event probabilities during first and second six months	Markov model	Lifetime (50 yrs)
Lindgren 2005 ²⁸	First year costs taken from a retrospective study, ¹¹³ costs during subsequent years assumed the same as those in a model developed by Johannesson. ³⁹ Utility reduction taken from previous economic evaluation. ³⁹	RIKS-HIA	Outcomes taken from Swedish national registry RIKS-HIA	Markov model	Lifetime
Mahoney 2006 ²⁴	Hospitalizations for all PCI-CURE ³⁰ patients were assigned a DRG on the basis of information reported on the case report forms, costs associated with each DRG were estimated using 3 approaches: average Medicare reimbursement rates, average private payer rates (MEDSTAT), and a blended estimate of the two fee schedules.	Saskatchewan Health database used to estimate life expectancy after a non-fatal stroke or MI, piecewise parametric regression used to estimate the hazard of death over time according to the pattern of events, Framingham Heart Study used in sensitivity analysis.	Outcomes from PCI-CURE ³⁰	Trial-based	First year costs, lifetime effectiveness
Mahoney 2010 ²⁵	The primary economic endpoint was total in-trial costs: Data to characterize resource use were collected for patients enrolled in TRITON-TIMI in one of 8 prespecified countries (US, Australia, Canada, Germany, Italy, Spain, UK, and France) and multiplied by price weights derived from comparable populations of US patients. Utility values were derived from published sources.	Saskatchewan Health database used to estimate life expectancy after a non-fatal stroke or MI; piecewise parametric regression used to estimate the hazard of death over time according to the pattern of events.	Outcomes from TRITON-TIMI 38	Trial-based	Net costs over a median of 14.7 months, lifetime effectiveness
Ringborg 2005 ²⁹	First year costs derived from a retrospective study, ¹¹³ costs during subsequent years assumed the same as those in a model developed by Johannesson. ³⁹ Utility values from published source. ³⁴	Epidemiological data provided by the Centre for Epidemiology at the Swedish National Board of Health and Welfare	Event rates based on those seen in the CREDO trial. ³¹	Markov model	Lifetime

DISCC = Duke Information System for Cardiovascular Care, DRG = Diagnosis-related group, RIKS-HIA = Register of Information and Knowledge about Swedish Heart Intensive care Admissions, RR = relative risk

APPENDIX 7: QUALITY OF REPORTING IN THE ECONOMIC EVALUATIONS INCLUDED IN THE REVIEW

First author	Beinart et al.	Berg et al.	Cowper et al.	Heeg et al.	Lindgren et al.	Mahoney 2006	Mahoney 2010	Ringborg et al.
Study design								
1 Research question is stated	y	y	y	y	y	y	y	y
2 Economic importance of research question is stated	y	y	y	y	n/c	n/c	y	y
3 Viewpoint(s) of analysis clearly stated and justified	y	y	y	y	y	y	y	n/c
4 Rationale for choosing alternative programs or interventions compared stated	y	y	y	y	y	y	y	y
5 Alternatives being compared clearly described	y	y	y	y	y	y	y	y
6 Form of economic evaluation used stated	y	y	y	y	y	y	y	y
7 Choice of economic evaluation justified in relation to questions addressed	y	y	y	y	y	y	y	y
Data collection								
8 Source(s) of effectiveness estimates used stated	y	y	y	y	y	y	y	y
9 Details of design and results of effectiveness study given (if based on 1 study)	y	n/a	n/c	y	y	y	y	y
10 Details of method of synthesis or meta-analysis of estimates given (if based on overview of effectiveness studies)	n/a	y	n/a	n/a	n/a	n/a	n/a	n/a
11 Primary outcome measure(s) for economic evaluation stated	y	y	y	y	y	y	y	y
12 Methods to value health states and other benefits stated	n/a	y	n/a	y	n/a	n/a	y	y
13 Details of subjects from whom valuations obtained given	n/a	y	n/a	y	n/a	n/a	y	y
14 Productivity changes (if included) reported separately	n/a	y	n/a	n/a	y	n/a	n/a	y
15 Relevance of productivity changes to study question discussed	y	y	n/a	n/a	y	n/a	n/a	n/c
16 Quantities of resources reported separately from unit costs	y	n	n	n	n	n/c	n/c	n
17 Methods for estimation of quantities and unit costs described	y	y	y	y	y	y	y	y

First author	Beinart et al.	Berg et al.	Cowper et al.	Heeg et al.	Lindgren et al.	Mahoney 2006	Mahoney 2010	Ringborg et al.
18 Currency and price data recorded	y	y	y	y	y	y	y	y
19 Details of price adjustments for inflation or currency conversion given	n/a	y	y	y	y	n/a	n/a	y
20 Details of model used given	y	y	y	y	y	y	y	y
21 Choice of model used and key parameters on which it is based justified	y	y	y	y	y	y	y	y
Analysis and interpretation of results								
22 Time horizon of costs and benefits stated	y	y	y	y	y	y	y	y
23 Discount rate(s) stated	y	y	y	y	y	y	y	y
24 Choice of rate(s) justified	y	y	y	y	y	y	y	y
25 Explanation given if costs or benefits not discounted	n/a	n/a	n/a	n/a	n/a	y	n/a	n/a
26 Statistical test and confidence intervals given for stochastic data	y	y	n	y	y	y	y	y
27 Approach to sensitivity analysis given	y	y	y	y	y	Y	y	y
28 Choice of variables for sensitivity analysis justified	y	y	y	y	y	Y	y	y
29 Ranges over which variables varied stated	y	y	y	y	y	Y	y	y
30 Relevant alternatives compared	y	y	y	y	y	Y	y	y
31 Incremental analysis reported	y	y	y	y	y	Y	y	y
32 Major outcomes presented in disaggregated and aggregated forms	y	y	y	y	y	Y	y	y
33 Answer to study question given	y	y	y	y	y	Y	y	y
34 Conclusions follow from data reported	y	y	y	y	y	Y	y	y
35 Conclusions accompanied by appropriate caveats	y	y	y	y	y	Y	y	y
Sum of “no” and “not clears”	0	1	3	1	2	2	1	3

y = yes, n = no, n/c = not clear, n/a = not applicable

APPENDIX 8: DETAILED REVIEWS OF ECONOMIC STUDIES

Review of Cowper (2005). Economic effects of prolonged clopidogrel therapy after percutaneous coronary intervention²⁷

Overview

The Cowper study²⁷ examined, from the American societal perspective, the cost-effectiveness of extending clopidogrel therapy from one month to one year after PCI.

Summary of effectiveness data

The patient population under investigation were those undergoing PCI at Duke Medical Center between January 1, 1999, and December 31, 2005 who were treated with no more than one month of clopidogrel after the procedure (n=4,037). The effect of prolonged clopidogrel therapy on rates of MI, revascularization, major bleeding, and death was based on data from the CREDO trial. The death rate among Duke patients was three times as high as in CREDO (4.2% vs. 1.4%) suggesting that patients treated in the community have a less favourable risk profile than those enrolled in RCTs.

Summary of resource utilization and cost data

The quantities of resources used were not reported separately from unit costs.

Variable	Amount (year 2000 U.S. dollars)
Hospitalization cost	
CABG	\$26,918
PCI (no MI/MI)	\$9,035/\$11,309
MI (no death/death)	\$5,580/\$6,440
Death (no other event)	\$4,465
Bleed (no other event)	\$4,127
Incremental cost of death	\$2,011
Incremental cost of major bleed	\$3,592
Physician fees	
CABG admission (+/- MI, death)	\$3,637-\$4,427
MI admission (no death/death)	\$502/\$798
PCI admission (+/- MI, death)	\$1,471-\$2,058
Major bleed admission (no death/death)	\$480/\$815
Death only	\$463
Incremental fee for bleed admission	\$123
Clopidogrel cost	\$3.22/day + \$2.50/month dispensing fee

Summary of modelling framework

The authors developed a decision model to compare the outcomes and costs of one year of peri-procedural clopidogrel treatment, compared to one month. The model included 4 major clinical outcomes: myocardial infarction (MI), revascularization (CABG vs. PCI), major bleeding and death. Rare events and those of minimal economic consequences, such as stroke and minor bleeds, were not included, as their effect on the results was deemed negligible.

Summary of cost-effectiveness data

Cowper et al. reported the cost of extending clopidogrel therapy after PCI from one month to one year was \$34,336 per MI avoided, or \$15,696 per life year saved. In the high-risk subgroup, defined as patients having diabetes, multivessel intervention, or MI within 24 h preceding their procedure, the incremental cost per MI avoided with the longer duration of clopidogrel treatment was \$21,893, or \$10,333 per life year saved

Summary of sensitivity analysis

The cost-effectiveness of long-term clopidogrel therapy is contingent on the relative risk of MI with clopidogrel. The relative risk of MI with clopidogrel used in the model was 0.56 (95% CI: 0.3, 1.0). In the sensitivity analysis, an absolute increase of 10% in RR of MI with clopidogrel was found not to change the cost-effectiveness substantially. A RR of 0.85, would fall within the 95% confidence interval, and would produce an ICER greater than \$50,000.

Comments

This study was not funded by industry.

The data on which the study was based were collected prior to the introduction of drug-eluting stents (DES). With the advent of the DES, clopidogrel therapy is now typically recommended for three to six months after PCI.

The absence of stroke in the model is a major limitation of this study.

Review of Beinhart (2005). Long-term cost-effectiveness of early and sustained dual oral antiplatelet therapy with clopidogrel given for up to one year after percutaneous coronary intervention²⁶

Overview

Like the Cowper study²⁷, the objective of the Beinhart study²⁶ was to evaluate the long-term cost effectiveness of clopidogrel in patients receiving PCI from an American societal perspective. This was a trial-based analysis of the CREDO trial.

Summary of effectiveness data

After one year, patients in the clopidogrel arm (300 mg 3-24 hrs pre-PCI and 75 mg daily for 1-year post-PCI) had an 8.5% event (cardiovascular death, nonfatal MI, or stroke) rate, compared to 11.5% in the placebo group. This corresponds to a relative risk reduction (RRR) of 26.9% (95% CI 3.9%, 44.4%). The authors reported a trend toward major bleeding in the clopidogrel group that did not reach statistical significance.

Summary of resource utilization and cost data

Direct medical care costs for hospitalization and drug costs were included, but not direct costs associated with outpatient visits and testing or indirect costs attributable to lost productivity, as these costs were not captured in the CREDO trial. Health care costs were calculated by applying unit costs to resource utilization reported over the course of the trial, making this the only study to clearly report the quantities of resources separately from unit costs. Costs were estimated for each diagnoses-related group (DRG) based on three different costing methods: Average Medicare reimbursement rates, average private payer rates (MEDSTAT), and a blended estimate of the two fee schedules. One year costs were found to be higher for the clopidogrel arm using all three costing methods.

	Clopidogrel	Placebo	Δ	95% CI of Δ
Initial hospitalization				
Medicare	\$13,886	\$14,094	-\$208	-\$736, \$359
MEDSTAT	\$16,834	\$17,002	-\$168	-\$749, \$422
Blend	\$15,614	\$15,744	-\$130	-\$706, \$461
Follow-up hospitalization costs				
Medicare	\$5,205	\$5,235	-\$29	-\$971, \$887
MEDSTAT	\$5,658	\$5,717	-\$58	-\$1,159, \$978
Blend	\$5,459	\$5,464	-\$5	-\$999, \$977
Clopidogrel and ASA costs (1 yr)	\$902	\$102	\$800	\$774, \$825
1-yr total cost				
Medicare	\$19,994	\$19,431	\$563	-\$483, \$1,642
MEDSTAT	\$23,394	\$22,821	\$573	-\$633, \$1,765
Blend	\$21,974	\$21,310	\$664	-\$461, \$1,784

Summary of cost-effectiveness data

Despite higher 1-year costs in the clopidogrel arm, the authors concluded that the loading strategy, followed by one year of clopidogrel therapy is a cost-effective option for patients undergoing PCI. The incremental cost-effectiveness ratios (ICERs) ranged from \$2,929-\$4,353/LYG, depending on the costing method and source of life expectancy

estimates used. Based on a \$50,000/LYG threshold, the probability that clopidogrel was cost effective was greater than 95%.

Comments

This is an American economic analysis of a trial with both American and Canadian patients. US costs were applied to patients in both health systems, without accounting for potential variation in resource use. A cost-accounting approach would have allowed for variability of costs within a DRG. The analysis also assumes that there would be no differences in non-fatal events between the two arms of the trial after clopidogrel is stopped (ie. at the end of the trial). The study was funded by a grant from Sanofi-Synthelabo and Bristol-Myers Squibb.

Review of Lindgren (2005). The long-term cost effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden²⁸

Overview

The purpose of the Lindgren paper was to estimate, from the perspective of Swedish society, the long-term cost-effectiveness of adding clopidogrel to aspirin.

Summary of effectiveness data

Long-term treatment with clopidogrel plus aspirin was reported to have a relative risk of non-fatal MI or cardiovascular death of 0.72, compared with aspirin alone.¹⁰⁴ After the first year of treatment, patients in both arms were assumed to have the same risk of events. The model predicted that patients receiving combination therapy would have an extra 0.04 life-years compared to those in the aspirin only arm.

Summary of resource utilization and cost data

Costs during the first year following MI were taken from a study by Zethareus et al. Costs for subsequent years were assumed to be the same as those in the model developed by Johanneson. Costs related to increased survival of patients outside the healthcare sector were included in the sensitivity analysis.

Summary of modelling framework

The Markov model constructed for this purpose consisted of 4 states: after PCI (the starting state for all patients), first year after MI, second/subsequent year after MI, and death. The model was run using a lifetime perspective using data from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) for patients who fulfilled the inclusion criteria of the PCI-CURE study.

Summary of cost-effectiveness data

The model predicted an increase in both survival and costs when adding clopidogrel to aspirin therapy for patients undergoing PCI. The resulting cost-effectiveness ratio was less appealing than Lindgren's 2004 analysis of the entire CURE trial population¹²⁸, but still well below the levels of what is generally considered to be acceptable.

Comments

This study was funded in part by a grant from Sanofi-Synthelabo.

The authors recognized their failure to perform a cost utility analysis as a study limitation, and indicated a need for further research regarding the relationship between cardiovascular events and reduction in quality of life.

This was the only study not to include stroke as a potential outcome in their model. The primary endpoint of the PCI-CURE study was a composite of cardiovascular death, myocardial infarction, or urgent target-vessel revascularization within 30 days of PCI which may explain the exclusion of stroke, but other studies based on PCI-CURE were still able to include 'stroke' in their modelling frameworks.

Review of Ringborg (2005). The cost-effectiveness of dual oral antiplatelet therapy following percutaneous coronary intervention: A Swedish analysis of the CREDO trial²⁹

Overview

The Ringborg study evaluated the long-term cost effectiveness of clopidogrel + ASA for 12-months post-PCI, including a pre-procedural loading dose, versus 28-day clopidogrel therapy and long-term ASA.

Summary of effectiveness data

The risks of stroke, MI, and mortality during the year following PCI were taken from the results of the CREDO trial. After the first 12 months, risks were assumed to be equal between the treatment group and the control group.

Summary of resource utilization and cost data

Like in the Lindgren study, costs during the first year following MI were taken from a study by Zethareus¹¹³ and costs for subsequent years from a model developed by Johanneson. The cost of gastrointestinal bleeding was taken from the University Hospital of Lund. The authors acknowledged that analyses from the societal perspective should include costs in added life years. However, these costs were only included in the sensitivity analysis, not the base case analysis, in order to facilitate comparison with other studies.

Summary of utility data

The authors would have wanted the model states representing MI and stroke to have been associated with a utility reduction equivalent to that experienced by post-PCI patients succumbing to these events. However, due to the fact that there were no good utility estimates for the initial post-PCI state available, utility was not considered in the primary analysis. The values below were applied in the secondary analysis.

Age	Utility
60-69 years	0.77
70-79 years	0.71
80-84 years	0.60

Event	Utility Reduction
MI/ischaemic heart disease	reduction of 0.12
stroke	reduction of 0.27

Summary of modelling framework

The authors recognized that any benefit of long-term treatment with clopidogrel achieved during the 12-month treatment period will have an effect beyond it. Given this, the authors constructed a Markov model with the lifetime of the patient as its time horizon and carried out the analysis from a societal perspective.

Summary of cost-effectiveness data

It is difficult to distinguish the effect of 12-month post-PCI clopidogrel treatment from the effect of the pre-procedural dose, but the combination is a cost-effective strategy (ICER €7,492/LYG, €8,184/QALY), particularly when indirect costs (not including the cost of added life-years) are included (ICER = €3,022/LYG, €3,301/QALY).

Comments

Utility values were included in the sensitivity analysis, but not in the base case analysis. The reason for this was that no good utility estimates for the initial post-PCI state were available, and so the authors relied on utility reductions for stroke and MI (without PCI) reported by Burstom et al. The cost/QALY ratios were only marginally higher than the cost/LYG ratios. This study was funded by a grant from Sanofi-Aventis.

Review of Mahoney (2006). Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation²⁴

Overview

The 2006 study by Mahoney et al. was a trial-based economic evaluation of clopidogrel use for up to one year, carried out from a US societal perspective. Patient-level outcomes and resource use came from the PCI-CURE trial.

Summary of effectiveness data

From the PCI-CURE trial, the primary impact of clopidogrel was on the rate of MI (absolute risk reduction of 1.5% before PCI, and an additional 1.9% post-PCI).³⁰ This was the primary driver for the estimated 0.0885 life years gained with clopidogrel + ASA vs. ASA alone.

Summary of resource utilization and cost data

Costs of outpatient treatment, cardiac rehabilitation, other institutional care, and lost productivity were not captured in the CURE trial, and thus were excluded from the analysis. As in the study by Beinhart et al., costs were estimated for each diagnoses-related group (DRG) based on three different costing methods: Average Medicare reimbursement rates, average private payer rates (MEDSTAT), and a blended estimate of the two fee schedules.

	MEDSTAT cost (\$)	Medicare cost (\$)	Initial hospitalization		Subsequent hospitalizations	
			Clopidogrel	Placebo	Clopidogrel	Placebo
Unstable angina	4295	3542	256	229	147	149
Unstable angina with angiography	11 947	8010	82	62	187	173
MI—expired	15 441	7651	0	0	4	2
MI—simple	12 132	6337	141	125	0	2
MI—complex	15 198	8643	7	13	24	28
Other cardiovascular	23 109	10 897	19	21	4	6
PCI	14 209	10 342	793	876	486	475
CABG surgery	36 080	29 127	9	7	47	53
PCI + CABG	46 660	38 850	6	11	3	3
Stroke	11 776	6493	0	1	12	8
Chest pain	3914	3447	0	0	41	68
Nonfatal cardiac arrest	12 380	5627	0	0	0	1
Heart failure	8142	5449	0	0	21	23
Other CT surgery	52 148	29 034	0	0	2	6

No incremental differences in costs were assumed after the end of the trial period (12 months). Cost estimates were higher in the clopidogrel arm, using all three costing methods (\$253 greater with Medicare/MEDSTAT, \$341 greater with MEDSTAT, and \$423 greater with Medicare).

Summary of cost-effectiveness data

Results from the primary analysis demonstrate that pre-treatment with clopidogrel plus aspirin followed by long-term therapy for up to 1 year in patients undergoing PCI is cost-effective. The authors compare its cost-effectiveness to other commonly accepted treatments in the US such as thrombolytic therapy in the elderly or statin therapy for patients with coronary heart disease. A separate cost effectiveness analysis was carried out, based on a subset of patients who underwent PCI during initial hospital stay. The purpose of the subset analysis was to evaluate the generalizability of the study results to US patients for whom guidelines recommend early invasive strategy. The results in this group were more favourable due to the reduction in rehospitalisation costs for the clopidogrel arm and a (non-significant) reduction in the rate of cardiovascular death.

Comments

The time horizon was the lifetime of the patient, under the assumption that there were no incremental cost differences between the two treatment groups beyond the end of the trial.

The Mahoney study draws strength from the use of patient level data, but is limited in the multinational nature of the PCI-CURE study (differences in treatment practices and resource use between countries are probable).

The PCI-CURE study compared clopidogrel + ASA vs. ASA-alone, but the Mahoney publication reports the analysis in terms of clopidogrel vs. placebo.

Review of Heeg (2007). Long-term clopidogrel therapy in patients receiving percutaneous coronary intervention²³

Overview

The Heeg study was the first and only analysis of clopidogrel use in PCI patients performed from the Dutch healthcare perspective.

Summary of effectiveness data

In the PCI-CURE population, 0.03 life-years were gained with clopidogrel therapy and the number needed to treat to avoid one event was estimated at 29. In the CREDO population there was an incremental savings of 0.10 life-years per patient treated with clopidogrel.

Summary of resource utilization and cost data

The analysis included direct healthcare costs only. In the PCI-CURE population, €1119 was saved, over 50 years, with long-term clopidogrel therapy, as compared to short-term. In the first year, long-term clopidogrel is associated with a savings of €179. In the CREDO population, clopidogrel was not found to be cost saving in the first year (€275 in additional costs), but once long-term consequences are taken into account, the treatment becomes cost-saving.

Summary of utility data

Utility values for MI and stroke were taken from the literature (Hiatt, Tsevat, Mark, Lee, and Hallan) and utility values after multiple events were expressed as the product of the corresponding single event utilities.

Event	Utility value
MI	0.91
stroke	0.66
MI + stroke	0.60

Summary of modelling framework

Heeg et al. used a Markov model adapted from an earlier study of clopidogrel versus aspirin in high-risk acute coronary syndrome patients in Denmark¹²⁹. The model was run separately for patients with ACS (PCI-CURE population) and patients undergoing elective PCI (CREDO population). The authors adopted a lifetime perspective to estimate the costs and effects of clopidogrel therapy, given that the drug is used to treat a chronic disease state. All patients entered the model 'free of events' and over time, they progressed to MI, stroke, or death.

Summary of cost-effectiveness data

The authors concluded, as a result of their analysis, that the loading dose of clopidogrel prior to PCI, followed by 9-12 months of long-term therapy is dominant when compared to short-term (4 weeks) clopidogrel (both added to aspirin therapy).

Comments

This article was supported by a grant from Sanofi-Aventis, but the authors maintained control of all analysis and the content of the manuscript. One potential limitation of this study is the fact that the PCI-CURE and CREDO trials took place prior to the introduction of the drug-eluting stent (DES), and therefore, may underestimate the current benefits of long-term clopidogrel.

Review of Berg (2008). Cost-effectiveness of clopidogrel treatment in percutaneous coronary intervention: a European model based on meta-analysis of the PCI-CURE, CREDO, and PCI-CLARITY trials²²

Overview

The Berg study²² assessed the cost-effectiveness of clopidogrel following PCI in Sweden, Germany, and France. The Swedish analysis was carried out from the societal perspective, the others from the payer perspective. The authors had previously shown the use clopidogrel to be cost effective in pre-treatment and long-term treatment of patients with non-ST-segment elevation ACS undergoing PCI²⁸ and patients undergoing elective PCI²⁹. It was the objective of this study to conduct a comprehensive cost-effectiveness analysis of clopidogrel pre-treatment and treatment for up to one year in patients undergoing PCI by building on a meta-analysis of all relevant trials: PCI-Clopidogrel in Unstable angina to prevent Recurrent Events (CURE), CREDO, and PCI-CLopidogrel as Adjunctive TherapY (CLARITY).

Summary of effectiveness data

A meta-analysis of the effect of clopidogrel treatment on MI and CV death was conducted using both fixed-effects and random-effects modelling techniques. The results, at both 30 days and end of follow-up, were shown to be homogeneous using a chi-squared test for heterogeneity. The pooled effects suggest a stable treatment effect over time with a RR of 0.711 at 30 days and 0.745 at the end of follow-up.

Summary of resource utilization and cost data

Costs and utilities, and their assumed distributions, were described in tabular form. Cost data was taken from different sources in the literature (ref IDs pending: Zethraeus, Levy, Rossnagel, Johannesson), but quantities of resources were not reported separately from costs.

Summary of utility data

Utility values reported by age and disease from Burstrom et al.³⁴

Age	Utility
50-59 years	0.82
60-69 years	0.76
70-79 years	0.71
80-84 years	0.61

Event	Utility Reduction
MI/ischaeamic heart disease	reduction of 0.1156 (applied during first year only)
stroke	reduction of 0.2743 (applied for lifetime)

Referenced a 2007 economic evaluation of atorvastatin vs. simvastatin by Lindgren et al.³⁵ for utility reductions for revascularization (reduction of 0.03).

Summary of cost-effectiveness data

Using a combined decision tree and Markov model, simulations were run until patients reached 100 years, with costs and effects discounted at 3% annually. The incremental cost effectiveness ratios (ICERs) were all found to be well below the €50,000/QALY and 3x GDP thresholds.

Comments

The authors noted difficulty matching patient populations from different sources. The three trials analyzed had different patient populations, different endpoints, and different treatment strategies. Where PCI-CURE and CREDO mainly included non-STEMI patients and compared clopidogrel to aspirin, the PCI-CLARITY trial focused on patients with STEMI, and used placebo as comparison. The authors use the homogeneity of their pooled efficacy results at day 30 to justify their analysis.

The use of Swedish register data from 1995-2003 represents another limitation of this study. There is much a wider spectrum of patients undergoing PCI today than in the previous decade. If we assume that there has been an increase in low risk patients undergoing PCI, this study could have overestimated the risk reduction associated with clopidogrel use.

The study was funded by an unrestricted grant from Sanofi-Aventis and Bristol-Myers Squibb.

Review of Mahoney (2010). Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: Results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with pasugrel thrombolysis in myocardial infarction TRITON-TIMI 38 ²⁵

Overview

Most recently, the 2010 Mahoney study²² evaluated the cost-effectiveness of prasugrel versus clopidogrel from the perspective of the US healthcare system.

Summary of effectiveness data

Effectiveness data for the economic evaluation came from the TRITON-TIMI 38 trial, which compared prasugrel (60 mg loading dose, 10 mg maintenance dose) with clopidogrel (300 mg loading dose, 75 mg maintenance dose) for 6 to 15 months.

Summary of resource utilization and cost data

Resource utilization data from all eight countries with patients enrolled in the trial (US, Australia, Canada, Germany, Italy, Spain, UK, and France) were multiplied by price weights derived from comparable populations of US patients in order to estimate in-trial costs. Costs were reported in 2005 US dollars.

	Prasugrel (\$)	Clopidogrel (\$)	ΔP-C (\$)	95% CI
Total index hospitalization costs	19,740	19,752	-12	(-174,-156)
Total rehospitalisation costs	4,465	4,982	-517	(-1040,-25)
Total hospitalization costs	24,205	24,734	-530	(-1066, -9)
Study drug costs	1,862	1,554	308	(269, 347)
Total costs	26,067	26,288	-221	(-759, 299)

Summary of utility data

Age- and sex-specific utility values were derived from the Beaver Dam Health Outcomes Study.

Event	Multiplicative Utility Adjustment
In-trial MI	0.88 (for the first year of follow-up)
In-trial stroke	0.52 (for the patient’s remaining lifetime)

Event	Utility Reduction
Major bleed	reduction of 0.015

Summary of cost-effectiveness data

Treatment with prasugrel, as opposed to clopidogrel, was found to be economically dominant with a decrease in costs of \$221 and an increase in life expectancy of 0.102 years. Prasugrel remained the dominant treatment strategy in 79.7% of bootstrap replicates.

Comments

This is the first prospectively-designed economic evaluation of prasugrel and clopidogrel in patients with planned PCI.

The TRITON-TIMI trial indicated that the primary clinical benefit of prasugrel is in the reduction of nonfatal MIs, while the primary economic benefit was in reduced rehospitalisation for repeat PCI without MI. The threshold for hospitalization in other countries participating in the trial may differ from that in the United States, in which case the economic benefit of prasugrel over clopidogrel may be exaggerated.

The study was funded by a research grant from Eli Lilly & Co., Inc.

APPENDIX 9: RESULTS OF ECONOMIC EVALUATIONS INCLUDED IN THE REVIEW

Author	Currency, Year	Estimate of Cost-Effectiveness	Conclusions
Beinhart 2005 ²⁶	US dollars, 2001	<i>For clopidogrel loading dose + 28 day clopidogrel+ASA + 11 months clopidogrel (w discretionary ASA) vs. ASA loading dose + 28 day clopidogrel+ASA + 11 months placebo (w discretionary ASA)</i> \$2,929 to \$4,353 per LYG	Loading strategy followed by one year of anti-platelet therapy with clopidogrel is cost-effective for patients undergoing PCI.
Berg 2008 ²²	Euros, 2006	<i>For pre-treatment and long-term clopidogrel + ASA vs. pre-treatment and long-term ASA:</i> In Sweden, €6282 per QALY gained (direct costs) In Germany, €7871 per QALY gained In France, €5226 per QALY gained	The cost-effectiveness ratios for combined pre-treatment and long-term treatment with clopidogrel fall within commonly accepted standards for cost-effectiveness
Cowper 2005 ²⁷	US dollars, 2000	<i>For clopidogrel loading dose + 28 day clopidogrel+ASA + 11 months clopidogrel (w discretionary ASA) vs. ASA loading dose + 28 day clopidogrel+ASA + 11 months placebo (w discretionary ASA):</i> \$34,336 per MI avoided \$15,696 per LYG	Continuous clopidogrel therapy after PCI beyond one month and out to at least one year is economically attractive, relative to currently accepted treatments. Value of prolonged therapy varies with patient characteristics and is greatest for patients at high risk of MI.
Heeg 2007 ²³	Euros, 2004	<i>For clopidogrel loading dose and pre-treatment + 2-4 wks thienopyridine+ASA + clopidogrel+ASA until the end of follow-up vs. Placebo loading dose and ASA pretreatment + 2-4 wks thienopyridine+ASA + ASA+placebo until the end of follow-up (PCI-CURE³⁰),</i> Incremental cost savings €11190, 0.03 LYG, 0.07 QALYs gained. Clopidogrel dominant <i>For clopidogrel loading dose + 28 day clopidogrel+ASA + 11 months clopidogrel (w discretionary ASA) vs. ASA loading dose + 28 day clopidogrel+ASA + 11 months placebo (w discretionary ASA) (CREDO³¹),</i> incremental cost savings €497, 0.10 LYG, 0.14 QALYs gained. Clopidogrel dominant.	Loading dose of clopidogrel before PCI, followed by long-term therapy (9-12 months) is dominant (cost saving and more effective).
Lindgren 2005 ²⁸	Euros, 2004	<i>For clopidogrel loading dose and pre-treatment + 2-4 wks thienopyridine+ASA + clopidogrel+ASA until the end of follow-up vs. Placebo loading dose and ASA pretreatment + 2-4 wks thienopyridine+ASA + ASA+placebo until the end of follow-up</i> €10,993 per LYG (direct costs only) €8127 per LYG (direct and indirect costs)	Treatment with clopidogrel plus aspirin appears cost-effective for patients with unstable CAD undergoing PCI in Sweden.
Mahoney 2006 ²⁴	US dollars, 2001	<i>For clopidogrel loading dose and pre-treatment + 2-4 wks thienopyridine+ASA + clopidogrel+ASA until the end of follow-up vs. Placebo loading dose and ASA pretreatment + 2-4 wks thienopyridine+ASA + ASA+placebo until the end of follow-up</i> \$2856 to \$4775 per LYG	Early and sustained clopidogrel therapy for up to 1 year in patients with ACS who undergo PCI is a highly cost-effective compared with a strategy of no pretreatment and short-term therapy for only 4 weeks after PCI treatment.

Author	Currency, Year	Estimate of Cost-Effectiveness	Conclusions
Mahoney 2010 ²⁵	US dollars, 2005	<i>Treatment with prasugrel (60 mg loading dose + 10 mg daily maintenance dose) vs. clopidogrel (300 mg loading dose + 75 mg daily maintenance dose) for a median of 14.7 months</i> Treatment with prasugrel dominates – decreases cost by \$221 and increases life expectancy by 0.102 years	For patients undergoing PCI in the ACS setting, treatment with prasugrel compared with clopidogrel is highly cost effective.
Ringborg 2005 ²⁹	Swedish crowns, 2004	<i>For clopidogrel loading dose + 28 day clopidogrel+ASA + 11 months clopidogrel (w discretionary ASA) vs. ASA loading dose + 28 day clopidogrel+ASA + 11 months placebo (w discretionary ASA)</i> €3,022 per LYG (total costs) €7,492 per LYG (direct costs) €3,301 per QALY gained	Antiplatelet treatment with clopidogrel and ASA for 12 months following PCI appears to be cost-effective compared to 28 days of treatment with clopidogrel and long-term ASA following PCI.

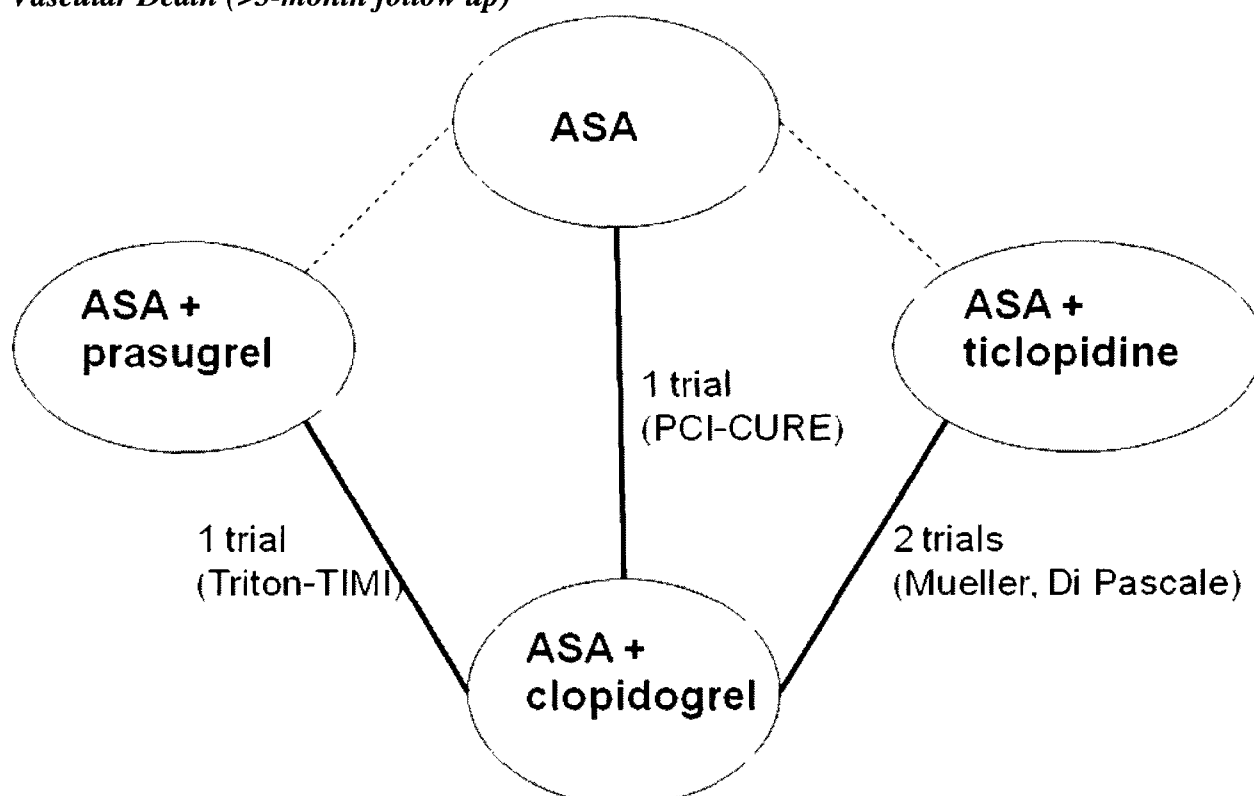
ASA = acetylsalicylic acid, LYG = life years gained, PCI = percutaneous coronary intervention, QALY = quality-adjusted life year

APPENDIX 10: MTC META-ANALYSIS

Below are network diagrams and data tables summarizing the trial information used in mixed treatment comparisons analyses comparing ASA, clopidogrel + ASA and ticlopidine + ASA for the outcomes of interest. Within each figure, solid black lines are used to denote comparisons supported by evidence from head-head trials, and dashed lines denote comparisons without supporting trials. Within each table, the columns t[,1], and t[,2] denote the treatments that correspond to the numbers of clinical events and sample sizes provided in the columns r[,1], r[,2] and n[,1], n[,2], respectively. The column na[] denotes the number of arms in each trial included for analysis. For each outcome, for all analyses, the following numbering of treatments was used:

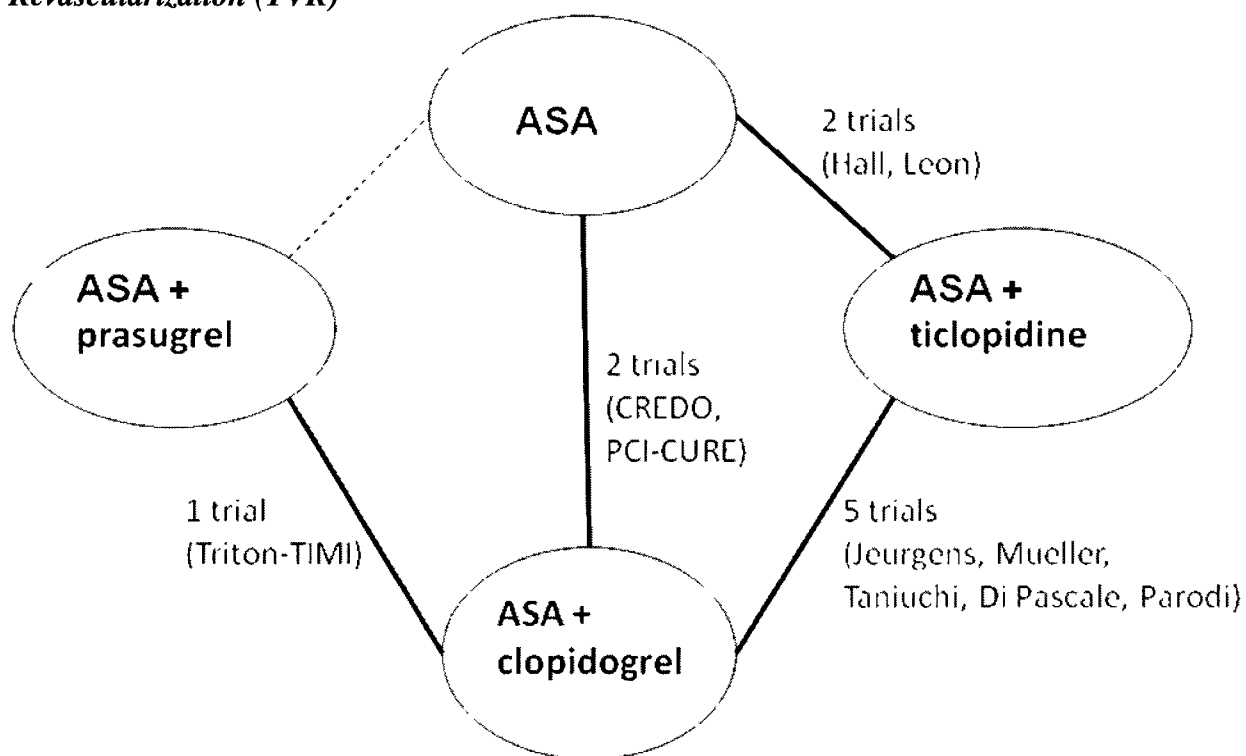
- 1 = ASA or ASA + placebo (A or A+P),
- 2 = ASA + clopidogrel (C+A),
- 3 = ASA + ticlopidine (T+A),
- 4 = ASA + prasugrel (P+A)

Vascular Death (>3-month follow up)



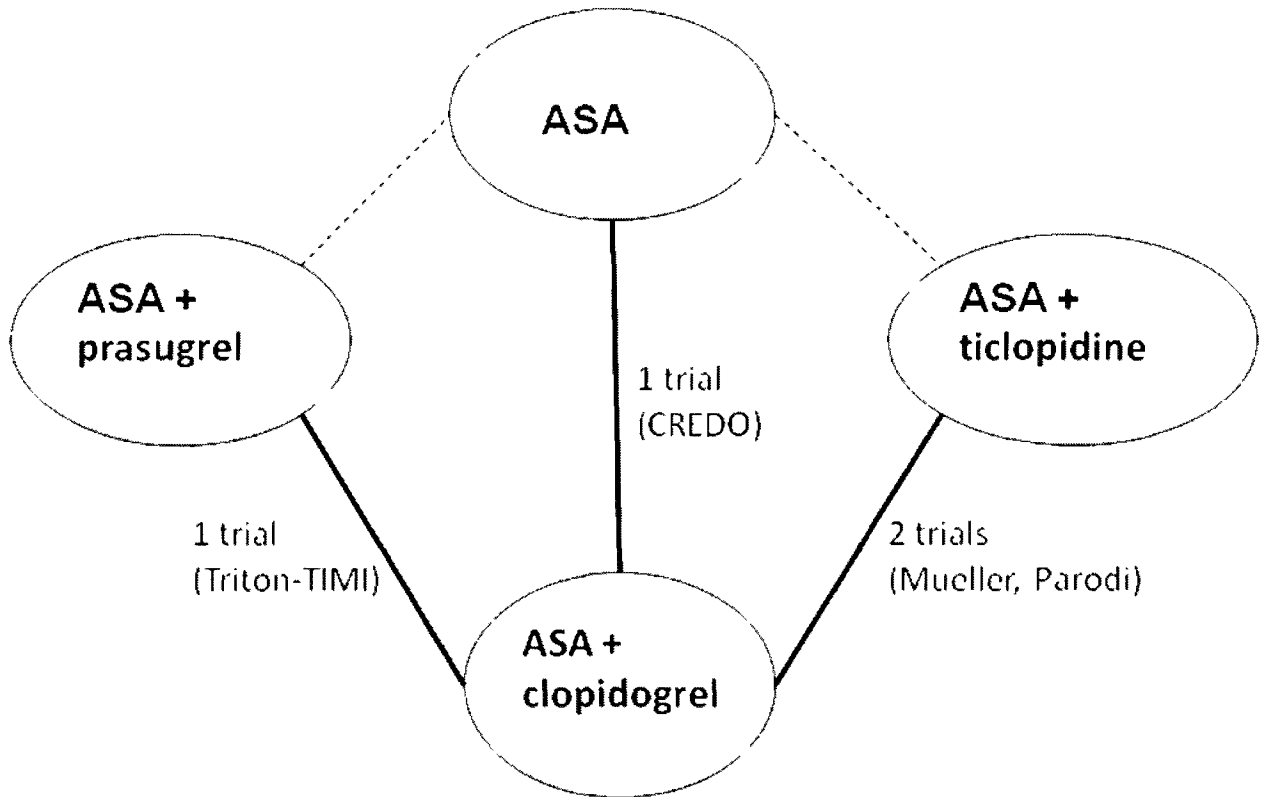
Study	Comparators	r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	T[,2]	na[]
PCI-CURE ³⁰	A or A+P, C+A	31	1345	32	1313	1	2	2
Mueller ⁴²	C+A, T+A	26	355	8	345	2	3	2
Di Pasquale ⁴³	C+A, T+A	0	214	0	214	2	3	2
TRITON-TIMI 38 ³³	C+A, P+A	150	6795	133	6813	2	4	2

Revascularization (TVR)



Study	Comparators	r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	T[,2]	na[]
CREDO ³¹	A or A+P, C+A	144	1063	139	1053	1	2	2
PCI-CURE ³⁰	A or A+P, C+A	38	1345	25	1313	1	2	2
Jeurgens ⁴⁴	C+A, T+A	3	154	1	153	2	3	2
Müller ⁴⁵	C+A, T+A	6	355	2	345	2	3	2
Taniuchi ⁴⁶	C+A, T+A	12	494	12	522	2	3	2
Di Pasquale ⁴³	C+A, T+A	48	214	44	214	2	3	2
Parodi ⁴⁷	C+A, T+A	0	66	0	67	2	3	2
Hall ⁵	A, A+T	2	103	1	123	1	3	2
Leon ⁶	A, A+T	19	557	3	546	1	3	2
TRITON-TIMI-38 ³³	C+A, P+A	233	6795	156	6813	2	4	2

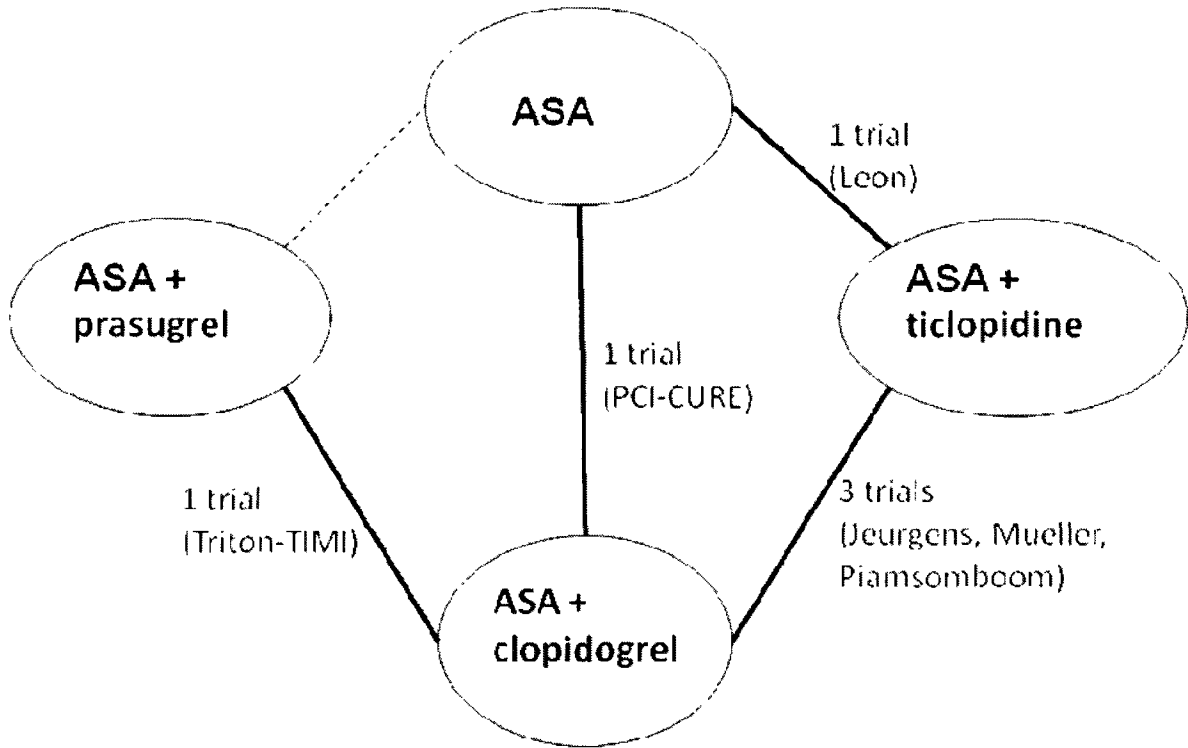
Stroke



Study	Comparators	r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	T[,2]	na[]
CREDO ³¹	A or A+P, C+A	12	1063	9	1053	1	2	2
Müller ⁴⁵	C+A, T+A	0	355	0	345	2	3	2
Parodi ^{1,47}	C+A, T+A	0	66	0	67	2	3	2
TRITON-TIMI-38 ³³	C+A, P+A	60	6795	61	6813	2	4	2

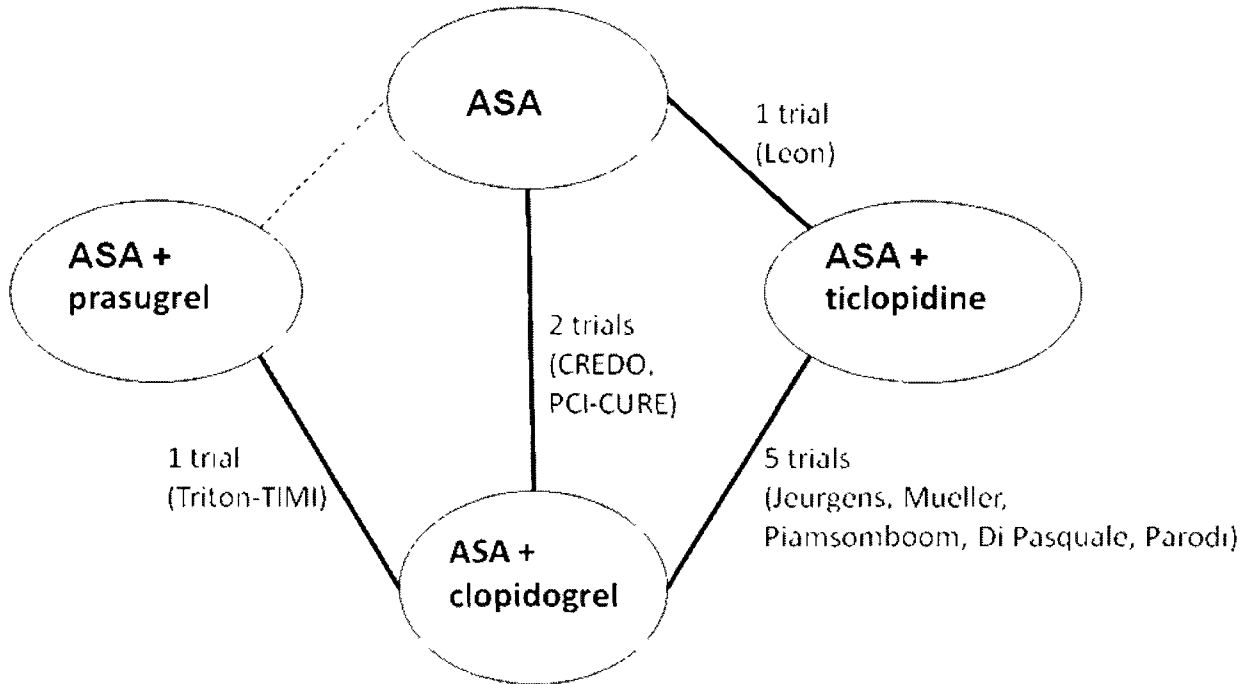
*NOTE: 0.5 was added to zero cells for this analysis to achieve convergence

Non-fatal MI



Study	Comparators	r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	t[,2]	na[]
PCI-CURE ³⁰	A or A+P, C+A	47	1345	20	1313	1	2	2
Jeurgens ⁴⁴	C+A, T+A	2	154	2	153	2	3	2
Mueller ⁴²	C+A, T+A	17	355	12	345	2	3	2
Piamsomboom ⁴⁸	C+A, T+A	0	37	1	31	2	3	2
Leon ⁶	A, A+T	15	557	3	546	1	3	2
TRITON-TIMI-38 ³³	C+A, P+A	620	6795	475	6813	2	4	2

Major bleeds



Study	Comparators	r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	t[,2]	na[]
CREDO ³¹	A or A+P, C+A	71	1063	93	1053	1	2	2
PCI-CURE ³⁰	A or A+P, C+A	33	1345	36	1313	1	2	2
Di Pasquale ⁴³	C+A, T+A	2	214	2	214	2	3	2
Piamsomboom ⁴⁸	C+A, T+A	2	37	1	31	2	3	2
Jeurgens ⁴⁴	C+A, T+A	1	154	0	153	2	3	2
Müller ⁴⁵	C+A, T+A	2	355	3	345	2	3	2
Parodi ⁴⁷	C+A, T+A	2	66	1	67	2	3	2
Leon ⁶	A, A+T	10	557	30	546	1	3	2
TRITON-TIMI-38 ³³	C+A, P+A	111	6795	146	6813	2	4	2

APPENDIX 11: MTC MODEL CODE, WINBUGS

```

model{
for(i in 1:NS){
  w[i,1] <-0
  delta[i,t[i,1]]<-0
  mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
  for (k in 1:na[i]) {
    r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]) # binomial likelihood
    logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]] }
# model
  for (k in 2:na[i]) {
    delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]]) # trial-specific LOR distributions
    md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of LOR distributions
    taud[i,t[i,k]] <- tau *2*(k-1)/k #precision of LOR distributions
    w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]]) #adjustment, multi-arm RCTs
    sw[i,k] <-sum(w[i,1:k-1])/(k-1) } # cumulative adjustment for multi-arm trials
  }

d[1]<-0
for (k in 2:NT){d[k] ~ dnorm(0,.001) } # vague priors for basic parameters
sd~dunif(0,2) # vague prior for random effects standard deviation
tau<-1/pow(sd,2)

p0~dbeta(alpha,beta)

# Absolute log odds(success) on Treatment A, based on a seperate model on the
# 19 trials Treatment A arms.
mA ~ dnorm(0,0.01)
# Absolute pr(success) Treatments based on T[1] and the
# MEAN Relative treatment effects
for (k in 1:NT) { logit(T[k])<- mA +d[k] }

# ranking

for (k in 1:NT) { rk[k]<-NT+1 - rank(T[],k)
  best[k]<-equals(rk[k],NT)}

# pairwise ORs
for (c in 1:(NT-1))
  { for (k in (c+1):NT)
    { lor[c,k] <- d[k] - d[c]
      log(or[c,k]) <- lor[c,k]
      rr1[c,k] <- or[c,k]/((1-p0)+(or[c,k]*p0))
    }
  }
}
}

```

**APPENDIX 12: RELATIVE RISKS FOR RELEVANT OUTCOMES
(MTC META-ANALYSIS RESULTS)**

Outcome	MTC Relative Risk (credible interval)			
	clopidogrel + ASA	ticlopidine + ASA	prasugrel + ASA	ASA
MI (non-fatal)	0.36 (0.06, 1.34)	0.28 (0.06, 1.41)	0.28 (0.02, 2.38)	1.00
Stroke (non-fatal)	0.75 (0.06, 8.66)	0.75 (0.06, 8.66)	0.76 (0.02, 19.88)	1.00
Death	0.91 (0.21, 3.66)	0.27 (0.02, 3.18)	0.87 (0.07, 8.33)	1.00
Revascularization	0.72 (0.28, 1.42)	0.44 (0.13, 0.93)	0.50 (0.08, 1.90)	1.00
Major bleed	1.42 (0.69, 3.82)	1.97 (0.58, 4.61)	1.84 (0.43, 9.35)	1.00

APPENDIX 13: WORKED EXAMPLES OF TRANSITION PROBABILITIES CALCULATIONS

Worked example of Weibull calculation:

Where $\lambda = 0.000146425$

$$\gamma = 2.337$$

age at PCI = 60

$$p = 1 - \text{EXP}(\lambda * t_0^\gamma * \text{EXP}(0.033 * \text{age at PCI}) - \lambda * t_1^\gamma * \text{EXP}(0.033 * \text{age at PCI}))$$

$$p = 1 - \text{EXP}(0.000146425 * 0^{2.337} * \text{EXP}(0.033 * 60) - 0.000146425 * 1^{2.337} * \text{EXP}(0.033 * 60))$$

$$p = 1 - \text{EXP}(0.000146425 * 0 - 0.000146425 * 7.242743)$$

$$p = 1 - \text{EXP}(-0.000146425 * 7.242743)$$

$$p = 1 - \text{EXP}(-0.00106)$$

$$p = 1 - 0.99894$$

$$p = 0.00106$$

Worked example of regression calculation:

Where $\text{OR} = \text{EXP}(-6.427 + 0.060 * \text{Current age})$

Current age = 61

$$p = \text{OR} / (1 + \text{OR})$$

$$p = \text{EXP}(-6.427 + 0.060 * 61) / (1 + \text{EXP}(-6.427 + 0.060 * 61))$$

$$p = \text{EXP}(-2.767) / (1 + \text{EXP}(-2.767))$$

$$p = 0.062850273 / 1 + 0.062850273$$

$$p = 0.059133704$$

APPENDIX 14: ANTIPLATELET PRESCRIPTIONS AND EXPENDITURES BY JURISDICTIONS, ALL INDICATIONS

Table A1: Antiplatelet prescriptions and expenditures for Veterans Affairs

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	46,300	57,899	69,126	75,557	79,183	\$3,430,003	\$4,024,773	\$4,465,335	\$4,582,874	\$4,618,534
ASA	47,754	58,767	68,926	77,247	84,821	\$449,593	\$532,527	\$597,683	\$641,434	\$670,122
Ticlopidine	1,172	810	498	296	198	\$66,825	\$41,712	\$25,521	\$13,700	\$8,034
Total	95,226	117,476	138,550	153,100	164,202	\$3,946,421	\$4,599,012	\$5,088,539	\$5,238,008	\$5,296,690

ASA: 81mg or 325mg

Source: Drug utilization data provided by the Veterans Affairs Canada, Health Canada, Ottawa, ON.

Table A2: Antiplatelet prescriptions and expenditures for Manitoba

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	50,896	58,510	67,369	71,283	80,536	\$5,006,963	\$5,802,083	\$6,328,636	\$6,517,905	\$6,912,282
ASA	10,420	9,311	7,546	4,934	4,274	\$5,629	\$4,024	\$3,242	\$2,276	\$1,603
Ticlopidine	2,054	1,400	1,192	945	821	\$125,642	\$87,286	\$66,939	\$50,895	\$44,469
Total	63,370	69,221	76,107	77,162	85,631	\$5,138,234	\$5,893,393	\$6,398,817	\$6,571,076	\$6,958,354

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa, ON, Canada

Table A3: Antiplatelet prescriptions and expenditures for New Brunswick

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	17,196	20,799	23,789	26,288	27,762	\$1,981,981	\$2,503,040	\$2,927,490	\$3,231,303	\$3,429,029
ASA	23,979	21,907	20,207	18,259	17,114	\$152,431	\$135,482	\$124,279	\$112,790	\$109,240

Ticlopidine	1,332	1,034	827	682	590	\$87,152	\$70,096	\$56,117	\$44,906	\$40,987
Total	42,507	43,740	44,823	45,229	45,466	\$2,221,564	\$2,708,618	\$3,107,886	\$3,388,999	\$3,579,256

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa, ON, Canada

Table A4: Antiplatelet prescriptions and expenditures for NIHB

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	27628	37584	45386	52743	56332	\$2,099,163	\$2,696,954	\$3,340,207	\$3,769,127	\$3,866,768
ASA	75613	116618	160836	205043	252665	\$546,967	\$821,176	\$1,062,916	\$1,364,242	\$1,812,795
Ticlopidine	2529	2151	1742	1388	1396	\$89,135	\$69,761	\$55,980	\$41,141	\$33,722
Total	105,770	156,353	207,964	259,174	310,393	\$2,735,265	\$3,587,891	\$4,459,103	\$5,174,510	\$5,713,285

Source: Drug utilization data provided by the Non-Insured Health Benefits (NIHB) Program, Health Canada, Ottawa, ON.

Table A5: Antiplatelet prescriptions and expenditures for Prince Edward Island

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	n/a	2,806	3,382	3,667	4,304	n/a	\$198,511	\$245,499	\$269,199	\$322,402
ASA	n/a	2,556	2,294	1,790	1,396	n/a	\$1,866	\$3,862	\$7,787	\$8,822
Ticlopidine	n/a	380	334	273	215	n/a	\$13,713	\$12,660	\$10,098	\$7,697
Total	n/a	5,742	6,010	5,730	5,915	n/a	\$214,090	\$262,021	\$287,084	\$338,921

n/a: Not reported

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa, ON, Canada

Table A6: Antiplatelet prescriptions and expenditures for Alberta

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	36,390	47,521	56,541	63,099	67,486	\$4,898,748	\$6,637,463	\$8,227,679	\$9,253,791	\$10,029,851
ASA	---	---	---	---	---	---	---	---	---	---

Ticlopidine	3,042	2,495	2,000	1,685	1,394	\$197,782	\$162,043	\$126,721	\$106,972	\$89,323
Total	39,432	50,016	58,541	64,784	68,880	\$5,096,530	\$6,799,506	\$8,354,400	\$9,360,763	\$10,119,174

--- Not covered

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa, ON, Canada

Table A7: Antiplatelet prescriptions and expenditures for Saskatchewan

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	29,284	39,667	47,074	50,715	59,813	\$1,954,573	\$2,703,989	\$3,253,898	\$3,561,547	\$4,869,543
ASA	36,120	32,462	27,627	22,619	18,141	\$219,773	\$198,039	\$170,441	\$148,263	\$128,980
Ticlopidine	1,742	1,351	915	726	721	\$57,316	\$46,559	\$31,972	\$25,146	\$26,405
Total	67,146	73,480	75,616	74,060	78,675	\$2,231,662	\$2,948,587	\$3,456,311	\$3,734,956	\$5,024,928

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa, ON, Canada

Table A8: Antiplatelet prescriptions and expenditures for Nova Scotia

	Number of prescriptions					Total expenditures				
	2003/04	2004/05	2005/06	2006/07	2007/08	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	21,804	24,839	26,969	28,506	30,157	\$2,234,429	\$2,754,792	\$3,125,072	\$3,393,893	\$3,669,443
ASA	55,317	48,174	41,635	35,270	29,732	\$433,419	\$393,378	\$356,195	\$312,822	\$276,784
Ticlopidine	2,911	2,122	1,762	1,362	1,079	\$172,440	\$138,643	\$117,526	\$88,788	\$71,144
Total	80,032	75,135	70,366	65,138	60,968	\$2,840,288	\$3,286,813	\$3,598,793	\$3,795,503	\$4,017,371

Source: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa, ON, Canada

Table A9: Antiplatelet prescriptions and expenditures for British Columbia

	Number of prescriptions						Total expenditures					
	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08	2002/03	2003/04	2004/05	2005/06	2006/07	2007/08
Clopidogrel	58479	71924	97846	122522	145581	167656	\$7,460,89	\$7,544,56	\$9,675,621	\$11,119,87	\$12,050,65	\$12,925,92

1							1	5		8	4	3
ASA	34136	29165	27069	24705	23459	16377	\$521,452	\$533,027	\$547,424	\$566,467	\$547,537	\$528,017
Ticlopidine	8573	6137	5322	4401	3903	3668	\$618,430	\$395,209	\$315,159	\$242,451	\$193,507	\$151,197
Total	101,188	107,226	130,237	151,628	172,943	187,701	\$8,600,773	\$8,472,801	\$10,538,204	\$11,928,796	\$12,791,698	\$13,605,137

Source: Drug utilization data provided by the BC PharmaCare Program, Victoria, BC.

APPENDIX 15: BUDGET IMPACT ANALYSIS – COMPLETE RESULTS

Table A-10: Budget impact analysis										
Projected budget impact of a reduction in clopidogrel+ASA utilization and corresponding percentage increase in other antiplatelet therapies for PCI indication										
	Base-case	Scenario 1			Scenario 2			Scenario 3		
		5%	10%	20%	5%	10%	20%	5%	10%	20%
MB	\$1,004,418	\$985,861	\$967,304	\$930,189	\$954,584	\$904,749	\$805,081	\$954,389	\$904,360	\$804,302
		(\$18,557)	(\$37,114)	(\$74,229)	(\$49,834)	(\$99,669)	(\$199,337)	(\$50,029)	(\$100,058)	(\$200,116)
AB	\$1,284,285	\$1,248,911	\$1,213,536	\$1,142,787	\$1,220,728	\$1,157,171	\$1,030,058	\$1,220,378	\$1,156,471	\$1,028,656
		(\$35,375)	(\$70,749)	(\$141,498)	(\$63,557)	(\$127,114)	(\$254,228)	(\$63,907)	(\$127,814)	(\$255,629)
BC	\$1,832,188	\$1,799,808	\$1,767,427	\$1,702,666	\$1,745,593	\$1,658,998	\$1,485,808	\$1,744,928	\$1,657,667	\$1,483,145
		(\$32,381)	(\$64,761)	(\$129,522)	(\$86,595)	(\$173,190)	(\$346,380)	(\$87,261)	(\$174,522)	(\$349,043)
NB	\$480,881	\$470,555	\$460,229	\$439,576	\$458,002	\$435,123	\$389,366	\$457,849	\$434,816	\$388,751
		(\$10,326)	(\$20,652)	(\$41,304)	(\$22,879)	(\$45,758)	(\$91,515)	(\$23,032)	(\$46,065)	(\$92,129)
PEI	\$43,642	\$42,588	\$41,534	\$39,425	\$41,551	\$39,460	\$35,278	\$41,524	\$39,405	\$35,168
		(\$1,054)	(\$2,109)	(\$4,217)	(\$2,091)	(\$4,182)	(\$8,364)	(\$2,119)	(\$4,237)	(\$8,475)
SK	\$560,599	\$546,588	\$532,577	\$504,556	\$533,947	\$507,296	\$453,992	\$533,850	\$507,102	\$453,604
		(\$14,011)	(\$28,022)	(\$56,043)	(\$26,652)	(\$53,303)	(\$106,607)	(\$26,749)	(\$53,497)	(\$106,995)
VA	\$772,748	\$766,306	\$759,864	\$746,980	\$738,26	\$703,774	\$634,799	\$738,179	\$703,611	\$634,474
		(\$6,442)	(\$12,884)	(\$25,768)	(\$34,487)	(\$68,974)	(\$137,949)	(\$34,569)	(\$69,137)	(\$138,274)
NIHB	\$572,317	\$557,819	\$543,320	\$514,324	\$546,652	\$520,986	\$469,656	\$546,503	\$520,690	\$469,062
		(\$14,498)	(\$28,996)	(\$57,993)	(\$25,665)	(\$51,330)	(\$102,661)	(\$25,814)	(\$51,627)	(\$103,255)
NS	\$551,133	\$540,088	\$529,042	\$506,952	\$526,589	\$502,045	\$452,957	\$526,292	\$501,452	\$451,771
		(\$11,045)	(\$22,091)	(\$44,181)	(\$24,544)	(\$49,088)	(\$98,176)	(\$24,840)	(\$49,681)	(\$99,362)
Total	\$7,102,211	\$6,958,523	\$6,814,834	\$6,527,456	\$6,765,908	\$6,429,603	\$5,756,995	\$6,763,892	\$6,425,573	\$5,748,934
		(\$143,689)	(\$287,378)	(\$574,756)	(\$336,304)	(\$672,608)	(\$1,345,217)	(\$338,319)	(\$676,639)	(\$1,353,278)

Numbers in parentheses are net savings compared with the base-case scenario (in Canadian dollars).

Scenario 1: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims

Scenario 2: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims and ASA monotherapy claims in the same proportion as in base-case

Scenario 3: The total numbers of clopidogrel + ASA claims reduced was added to the base-case number of ASA monotherapy claims

Table A-11: Sensitivity Analysis, ASA covered 100%

Projected budget impact of a reduction in clopidogrel+ASA utilization and corresponding percentage increase in other antiplatelet therapies for PCI indication

	Base-case	Scenario 1			Scenario 2			Scenario 3		
		5%	10%	20%	5%	10%	20%	5%	10%	20%
MB	\$1,004,418	\$994,627	\$976,070	\$938,956	\$963,350	\$913,516	\$813,848	\$963,156	\$913,127	\$813,069
		(\$9,790)	(\$28,348)	(\$65,462)	(\$41,068)	(\$90,902)	(\$190,570)	(\$41,262)	(\$91,291)	(\$191,349)
BC	\$1,832,188	\$2,562,822	\$2,530,441	\$2,465,680	\$2,508,607	\$2,422,012	\$2,248,822	\$2,507,941	\$2,420,681	\$2,246,159
		(-\$730,633)	(-\$698,253)	(-\$633,491)	(-\$676,419)	(-\$589,824)	(-\$416,634)	(-\$675,753)	(-\$588,492)	(-\$413,971)
NB	\$480,881	\$497,478	\$487,152	\$466,500	\$484,925	\$462,046	\$416,289	\$484,772	\$461,739	\$415,675
		(-\$16,597)	(-\$6,271)	(\$14,381)	(-\$4,044)	(\$18,834)	(\$64,592)	(-\$3,891)	(\$19,142)	(\$65,206)
PEI	\$43,642	\$44,875	\$43,821	\$41,712	\$43,838	\$41,747	\$37,565	\$43,811	\$41,692	\$37,455
		(\$1,233)	(-\$179)	(\$1,930)	(-\$196)	(\$1,895)	(\$6,077)	(-\$168)	(\$1,950)	(\$6,188)
SK	\$560,599	\$610,222	\$596,211	\$568,189	\$597,581	\$570,929	\$517,626	\$597,484	\$570,735	\$517,238
		(-\$49,622)	(-\$35,612)	(-\$7,590)	(-\$36,982)	(-\$10,330)	(\$42,974)	(-\$36,885)	(-\$10,136)	(\$43,362)
VA	\$772,748	\$857,547	\$851,105	\$838,221	\$829,501	\$795,014	\$726,040	\$829,420	\$794,851	\$725,714
		(-\$84,798)	(-\$78,357)	(-\$65,473)	(-\$56,753)	(-\$22,266)	(\$46,709)	(-\$56,672)	(-\$22,103)	(\$47,034)
NIHB	\$572,317	\$569,944	\$555,445	\$526,449	\$558,777	\$533,111	\$481,781	\$558,628	\$532,815	\$481,187
		(\$2,373)	(\$16,872)	(\$45,868)	(\$13,540)	(\$39,206)	(\$90,536)	(\$13,689)	(\$39,502)	(\$91,130)
NS	\$551,133	\$560,169	\$549,124	\$527,033	\$546,670	\$522,127	\$473,039	\$546,374	\$521,533	\$471,852
		(-\$9,036)	(\$2,009)	(\$24,100)	(\$4,463)	(\$29,006)	(\$78,094)	(\$4,759)	(\$29,600)	(\$79,281)
Total (w/o AB)	\$7,102,211	\$6,697,683	\$6,589,368	\$6,372,739	\$6,533,250	\$6,260,503	\$5,715,008	\$6,531,585	\$6,257,173	\$5,708,348
		(-\$879,756)	(-\$771,442)	(-\$554,813)	(-\$715,323)	(-\$442,576)	\$102,918	(-\$713,658)	(-\$439,246)	\$109,578

Numbers in parentheses are net savings compared with the base-case scenario (in Canadian dollars).

Scenario 1: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims

Scenario 2: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims and ASA monotherapy claims in the same proportion as in base-case

Scenario 3: The total numbers of clopidogrel + ASA claims reduced was added to the base-case number of ASA monotherapy claims

Table A-12: Sensitivity Analysis, ASA covered 0%**Projected budget impact of a reduction in clopidogrel+ASA utilization and corresponding percentage increase in other antiplatelet therapies for PCI indication**

	Base-case	Scenario 1			Scenario 2			Scenario 3		
		5%	10%	20%	5%	10%	20%	5%	10%	20%
MB	\$1,004,418	\$985,397 (\$19,021)	\$966,840 (\$37,578)	\$929,725 (\$74,693)	\$954,120 (\$50,298)	\$904,285 (\$100,133)	\$804,617 (\$199,801)	\$953,925 (\$50,493)	\$903,896 (\$100,522)	\$803,838 (\$200,580)
AB	\$1,284,285	\$1,248,911 (\$35,375)	\$1,213,536 (\$70,749)	\$1,142,787 (\$141,498)	\$1,220,728 (\$63,557)	\$1,157,171 (\$127,114)	\$1,030,058 (\$254,228)	\$1,220,378 (\$63,907)	\$1,156,471 (\$127,814)	\$1,028,656 (\$255,629)
BC	\$1,832,188	\$1,724,504 (\$107,685)	\$1,692,123 (\$140,065)	\$1,627,362 (\$204,826)	\$1,670,290 (\$161,899)	\$1,583,694 (\$248,494)	\$1,410,504 (\$421,684)	\$1,669,624 (\$162,565)	\$1,582,363 (\$249,826)	\$1,407,841 (\$424,347)
NB	\$480,881	\$453,012 (\$27,869)	\$442,686 (\$38,195)	\$422,034 (\$58,847)	\$440,459 (\$40,421)	\$417,581 (\$63,300)	\$371,823 (\$109,058)	\$440,306 (\$40,575)	\$417,273 (\$63,607)	\$371,209 (\$109,672)
PEI	\$43,642	\$41,816 (\$1,827)	\$40,761 (\$2,881)	\$38,653 (\$4,989)	\$40,779 (\$2,863)	\$38,688 (\$4,954)	\$34,506 (\$9,137)	\$40,751 (\$2,891)	\$38,633 (\$5,010)	\$34,395 (\$9,247)
SK	\$560,599	\$522,649 (\$37,951)	\$508,638 (\$51,961)	\$480,616 (\$79,983)	\$510,008 (\$50,591)	\$483,356 (\$77,243)	\$430,053 (\$130,547)	\$509,911 (\$50,688)	\$483,162 (\$77,437)	\$429,665 (\$130,935)
VA	\$772,748	\$686,331 (\$86,417)	\$679,889 (\$92,859)	\$667,005 (\$105,743)	\$658,285 (\$114,463)	\$623,798 (\$148,950)	\$554,824 (\$217,924)	\$658,204 (\$114,544)	\$623,635 (\$149,113)	\$554,498 (\$218,250)
NIHB	\$572,317	\$504,380 (\$67,937)	\$489,882 (\$82,435)	\$460,885 (\$111,432)	\$493,213 (\$79,104)	\$467,548 (\$104,769)	\$416,217 (\$156,100)	\$493,065 (\$79,252)	\$467,251 (\$105,066)	\$415,624 (\$156,693)
NS	\$551,133	\$491,057 (\$60,076)	\$480,012 (\$71,121)	\$457,921 (\$93,212)	\$477,559 (\$73,574)	\$453,015 (\$98,118)	\$403,927 (\$147,206)	\$477,262 (\$73,871)	\$452,422 (\$98,711)	\$402,741 (\$148,392)
Total	\$7,102,211	\$5,409,145 (\$1,693,066)	\$5,300,831 (\$1801,380)	\$5,084,202 (\$2,018,009)	\$5,244,712 (\$1,857,499)	\$4,971,965 (\$2,130,246)	\$4,426,471 (\$2,675,740)	\$5,243,047 (\$1,859,164)	\$4,968,635 (\$2,133,576)	\$4,419,811 (\$2,682,400)

Numbers in parentheses are net savings compared with the base-case scenario (in Canadian dollars).

Scenario 1: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims

Scenario 2: The total number of clopidogrel + ASA claims reduced was added to the base-case number of ticlopidine + ASA claims and ASA monotherapy claims in the same proportion as in base-case

Scenario 3: The total numbers of clopidogrel + ASA claims reduced was added to the base-case number of ASA monotherapy claims