Technology *Report*

Issue 54 March 2005

Economic Evaluation of Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention with Stenting

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Cite as: Brown A, Mittmann N, Seung SJ, Cohen E, Oh P, Tang Z, Noorani HZ, Mensinkai S. *Economic evaluation of glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention with stenting* [Technology report no 54]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2005.

CCOHTA is a non-profit organization funded by the federal, provincial and territorial governments.

Legal Deposit - 2005
National Library of Canada
ISBN: 1-894978-63-3 (print)
ISBN: 1-894978-62-5 (online)

PUBLICATIONS MAIL AGREEMENT NO: 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT
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Canadian Coordinating Office for Health Technology Assessment

Economic Evaluation of Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention with Stenting

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March 2005

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This report is a review of existing public literature, studies, materials and other information and documentation (collectively the "source documentation") which are available to CCOHTA. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured or represented in any way by CCOHTA and CCOHTA does not assume responsibility for the quality, propriety, inaccuracies or reasonableness of any statements, information or conclusions contained in the source documentation.

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Authorship

Allan Brown is a health economist at CCOHTA. He was responsible for project coordination. He drafted the executive summary, conclusions, the review of economic literature and economic limitations section. He was responsible for the analysis in the review of economic literature and the sensitivity analysis.

Dr. Nicole Mittmann is a scientist at Sunnybrook and Women's College Health Sciences Centre; assistant professor, department of pharmacology, University of Toronto; and executive director, HOPE Research Centre. She led HOPE team personnel in their work on the economic model development and analysis.

Soo Jin Seung is a research assistant at the HOPE Research Centre. She assisted in model development and drafted sections of the economic evaluation.

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Dr. Paul Oh is the medical director of the Cardiac Rehabilitation Program at the Toronto Rehabilitation Institute and formerly was the director of clinical pharmacology at Sunnybrook and Women's College Health Sciences Centre. He provided expertise and wrote sections on economic model development and economic analysis; and reviewed manuscript drafts.

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Hussein Noorani is a research officer at CCOHTA. He identified included articles and drafted the paragraphs on cardiovascular disease in the background section.

Shaila Mensinkai is an information specialist at CCOHTA. She was responsible for the design and execution of the literature search strategies; for writing the methods section and the associated appendix on literature searching; and for verifying and formatting bibliographic references.

Acknowledgements

The authors thank Doug Coyle for his contribution to the probabilistic sensitivity analysis for the economic evaluation. We also thank Lawrence Title for an early review of the decision analytic model. Special thanks to Nancy Risebrough, the senior research associate at the HOPE Research Centre, who provided key input to the project during the planning phase.

Conflicts of Interest

Eric Cohen reported that Eli Lilly supported an investigator-initiated trial at his institution. He has had speaking engagements and provided ad hoc consultation for Eli Lilly, Schering and Merck. Schering co-sponsors an interventional cardiology meeting of which he is co-chair. Paul Oh reported that he received a research grant from Eli Lilly in 1998 for an evaluation of abciximab.

The other authors and reviewers reported no conflicts.

REPORT *IN BRIEF*

March 2005

Economic Evaluation of Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention with Stenting

Technology Name

Glycoprotein IIb/IIIa inhibitor drugs (abciximab and eptifibatide)

Disease or Condition

Blood clots (thrombi) and atherosclerotic plaque can block the coronary artery supplying blood to the heart. Blockage may result in heart pain (angina) or acute coronary syndrome, including unstable angina and myocardial infarction. Percutaneous coronary interventions (PCI) are medical procedures during which a catheter (a slender tube) is threaded through the skin into a coronary artery to relieve the blockage. Antiplatelet therapy and "scaffold-like" coronary stents embedded in the artery wall at the time of the PCI help prevent immediate clotting and later renarrowing of the artery due to scar tissue formation. However, procedural complications related to thrombus formation can still occur after a PCI with stenting.

Technology Description

Glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor drugs block receptors on the platelet membrane to prevent activation and clumping, which are key factors in thrombus formation and other complications after PCIs.

The Issue

Using GP IIb/IIIa inhibitors as adjunct therapy in PCI with stenting can reduce post-procedural re-narrowing and complications, but the costs may be significantly increased. An economic evaluation is needed to assess the cost-effectiveness.

Assessment Objectives

- To review the economic evidence on the use of GP IIb/IIIa inhibitors as adjunct therapy in PCI with stenting.
- To perform economic evaluations from a Canadian provincial health insurance payer perspective on the cost-effectiveness of abciximab and eptifibatide.

Methods

Full economic evaluations that compared PCI alone to PCI with abciximab or eptifibatide were identified in a literature search. Five studies met the inclusion criteria for the review. Decision analytic modelling was done to estimate the short-term and long-term cost-effectiveness of the two drugs.

Conclusions

- Compared to stenting alone, eptifibatide plus stenting reduced costs to a provincial payer by an average of $59 per procedure in patients requiring elective and urgent PCI. Overall death and serious cardiac outcomes were improved in the short term (one year) and over a lifetime (average of 0.12 adjusted life-years) in all patients.
- Compared to stenting alone, abciximab plus stenting increased costs to a provincial payer by an average of $1,171 per procedure in patients requiring elective and urgent PCI. Overall death and serious cardiac outcomes were improved in the short term (one year) and over a lifetime (average of 0.07 adjusted life-years) in all patients.
- The use of these drugs in patients with diabetes compared with non-diabetic patients may reduce overall costs and improve health outcomes (average 0.22 adjusted life-years observed for both drugs).

This summary is based on a comprehensive health technology assessment available from CCOHTA's web site (www.ccohta.ca): Brown A, Mittmann N, Seung SJ, Cohen E, Tang Z, Noorani HZ, Mensinkai S. *Economic evaluation of glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention with stenting.*

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EXECUTIVE SUMMARY

The Issue

The introduction of stents during percutaneous coronary interventions (PCI) has become widely adopted in Canada. Restenosis, which is a common consequence of a PCI, occurs when there is re-narrowing of a blood vessel that has been opened via a vascular procedure. Coronary stents reduce, but do not eliminate, the occurrence of restenosis. Stenting alone, however, does not reduce the incidence of procedural complications, particularly those that are related to immediate or delayed intravascular thrombus formation. The inhibition of GP IIb/IIIa receptors has been shown to reduce platelet aggregation after a PCI. Abciximab and eptifibatide are GP IIb/IIIa inhibitors that are indicated for adjunct therapy in PCI in Canada. There is, however, limited information on the economic value of GP IIb/IIIa inhibitors for patients who are undergoing elective or urgent PCI with stent implantation.

Objectives

Using a systematic review of economic evaluations and a primary economic evaluation, we examined the cost-effectiveness of the GP IIb/IIIa inhibitors abciximab and eptifibatide as adjuncts to elective and urgent PCI with stenting relative to routine PCI and usual care (with stenting but without the additional drug therapy), from a provincial health insurance payer perspective.

Review of Economic Evaluations

Methods: Using a literature search, we identified full economic evaluations comparing PCI plus one or more of abciximab or eptifibatide with routine PCI alone. Information on the study characteristics and results was summarized. The quality of included studies was assessed using a *British Medical Journal* checklist.

Results: Five studies met the inclusion criteria. Their results suggest that abciximab and eptifibatide fall in the range of what is generally considered to be cost-effective. Only one Canadian economic evaluation, however, scored highly in terms of quality and it only evaluated abciximab.

Primary Economic Evaluation

Methods: The study population was patients undergoing elective or urgent PCI with stenting, excluding those in whom PCI was performed for the immediate treatment of acute myocardial infarction (primary PCI). The interventions were PCI with stenting plus the glycoprotein IIb/IIIa inhibitors abciximab or eptifibatide plus usual care. Usual care consisted of background therapy that included heparin and ASA and possibly other antiplatelet therapy such as clopidogrel. The comparator was PCI with stenting plus usual care.

The perspective was that of an Ontario health insurance payer. Decision analytic models were constructed for each drug, because the patient populations of the clinical studies were different for abciximab and eptifibatide. Short-term models were constructed based on data from relevant clinical trials. Long-term models were developed using the Markov technique. DATA by

TreeAge software was used for the decision analysis. Probabilistic sensitivity analysis was done using Crystal Ball software.

Results: In the overall population, relative to stenting alone, stenting plus eptifibatide were dominant in the short term in terms of costs (reduced on average by $59 per procedure), rates of major adverse cardiac events (MACE) (reduced by 5.6%) and mortality (reduced by 1%). The same trend was found for those with diabetes. Costs were reduced on average by $166, MACE was reduced by 7.1% and mortality was reduced by 2%. In the long-term analysis for the overall population, the use of eptifibatide resulted in lower costs ($59) and increased life-years (0.22 undiscounted years per patient and 0.12 discounted years).

For stenting plus abciximab, costs were higher (on average $1,171 per procedure) and clinical outcomes were better (MACE reduced by 7% and mortality by 1%) relative to stenting alone. Using an incremental cost-effectiveness analysis, we found that abciximab use falls in the range of what is generally considered to be cost-effective (approximately $17,000 per life-year gained for abciximab in the stented patient population).

The results of the economic evaluation were robust to the probabilistic sensitivity analysis. For a value of a life-year of $50,000, the probability that abciximab is more cost-effective than usual care for all patients is 98.6%. For eptifibatide, it is 92.5%.

Conclusions

The review of economic evidence supported the need for an up-to-date economic evaluation of GP IIb/IIIa inhibitors in a Canadian context. The economic evaluation in this study suggests that eptifibatide and abciximab can be considered to be cost-effective adjuncts for the control of complications in patients undergoing elective and urgent PCI. The incremental cost-effectiveness analysis for abciximab in the general study population showed a higher overall cost and better outcomes, with a result that is consistent with what is generally considered to be cost-effective. For eptifibatide in the general study population and for both drugs in those with diabetes, the analysis showed lower costs and better outcomes when compared with usual care. We caution against a direct comparison of eptifibatide and abciximab based on the available data.

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ABBREVIATIONS

ACC	American College of Cardiology
ACS	acute coronary syndrome
ADMIRAL	Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up
APPROACH	Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease
CABG	coronary artery bypass graft
CAD	coronary artery disease
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CBC	complete blood count
CCN	Cardiac Care Network (of Ontario)
CCU	critical care unit
CKMB	creatinine kinase MB isozyme
CPK (MB)	creatinine phosphokinase myocardial band
DM	diabetes mellitus
EPIC	Evaluation of c7E3 for the Prevention of Ischemic Complications
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial
ERASER	Evaluation of ReoPro And Stenting to Eliminate Restenosis
ESPRIT	Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy
Fab	antigen binding fragment
GP	glycoprotein
GPAs	glycoprotein antagonists
HOPE	Health Outcomes and Pharmacoeconomic Research Centre
ICER	incremental cost-effectiveness ratio
ISR	in-stent restenosis
MACE	major adverse cardiac event
MI	myocardial infarction
MRD	most responsible diagnosis
NHS	National Health Service (UK)
OCCI	Ontario Case Costing Initiative
PCI	percutaneous coronary intervention
PRICE	Prairie ReoPro versus Integrilin Cost Evaluation
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality adjusted life years
RCT	randomized clinical trial
STOPAMI	Stent versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction
SWCHSC	Sunnybrook and Women's College Health Sciences Centre
TARGET	Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial
TLR	target lesion revascularization
TVR	target vessel revascularization
µg	microgram
µmol	micromolar

1 INTRODUCTION

1.1 Cardiovascular Disease

At 36%, cardiovascular (CV) diseases (ischemic heart disease and stroke) were the leading cause of death in Canada in 1999.[1] Ischemic heart disease accounted for the greatest proportion of deaths (20%), of which half were attributable to myocardial infarction (MI). CV diseases accounted for 18% of all hospitalizations among men and women in Canada in 2000-2001, a higher percentage than that of any other health problem.[1] The number of elderly people in the Canadian population has been increasing and so has the number of deaths due to stroke and ischemic heart disease. Data showed that, in 1999, the mortality rates for ischemic heart disease increased with age. Demographic trends suggest that CV diseases will continue to be important in terms of mortality and hospitalization rates in Canada.[1]

Ischemic heart disease consists of the narrowing or blockage of coronary arteries, which are the blood vessels that supply blood to the heart. It is almost always due to atherosclerosis and it results in decreased blood and oxygen reaching the cardiac muscle.[2] It occurs in 54% of the deaths due to CV disease.[1] It also affects an individual's quality of life, as it causes chest pain or discomfort (angina pectoris or "angina") and restricts physical activity. Complete occlusion of these blood vessels can lead to a MI.

1.2 Percutaneous Coronary Interventions (PCIs)

Percutaneous coronary interventions (PCIs) involve the insertion of a thin, flexible tube (catheter) through the skin into an artery (in the arm or leg); and the threading of the catheter through the arterial system to the heart, so that its tip is ultimately placed at the site of the blockage in a coronary artery. These medical procedures are used to relieve the narrowing in the coronary arteries. Methods that are used in PCI include balloon angioplasty [sometimes called percutaneous transluminal coronary angioplasty (PTCA)] and coronary stenting.[3] During PTCA, a guide wire is advanced beyond the area of narrowing. A balloon is then advanced over the wire and briefly inflated, opening the artery. In coronary stenting, which has become more widely adopted, a cylindrical wire mesh, which is crimped on top of a balloon, is passed over the guide wire and embedded in the artery wall at the point of narrowing by inflating and then withdrawing the balloon. One or more stents can be placed. Once inserted, they are designed not to move, so that they act as scaffolding to keep the artery dilated. Compared with balloon angioplasty, stenting has been shown to reduce the need for repeat revascularization.[4-10] Brophy *et al.*[11] used a meta-analysis to combine the results of 29 trials comparing stenting to standard PTCA. The pooled populations included stable and unstable angina patients. The authors showed that coronary stenting was associated with reductions in angiographic restenosis rates and the subsequent need for PTCA.[11]

Patients who are eligible to receive PCIs are categorized as elective, urgent or emergent. Patients undergoing elective PCI or scheduled PCI typically have stable angina. An urgent PCI occurs in patients who are experiencing unstable angina, myocardial ischemia (reduced blood flow in the myocardium) and specific electrocardiogram (ECG) manifestations that are

components of an acute coronary syndrome (ACS) diagnosis. Emergent PCIs are done in patients with acute MI conditions. In a preliminary analysis of 212 patients treated at the Sunnybrook campus of Sunnybrook and Women's College Health Sciences Centre (SWCHSC) in Toronto, 25% of patients received elective PCI, 59% received urgent PCI and 12% received emergent PCI (with 4% missing data) (Nancy Cooper, Sunnybrook and Women's College Health Sciences Centre, Toronto: personal communication, fall 2004).

The operational terms "elective," "planned," "urgent" and "emergent" may be based more on scheduling than on patient characteristics, so they should be interpreted cautiously. For example, in many practice settings, particularly when there is a waiting list, "urgent" might be used to describe a patient who is admitted with an ACS and who has stabilized but who requires the procedure within a few days, before discharge from hospital. In other practice settings, particularly those without a waiting list, the same patient might be described as "elective" or "planned."

Restenosis, which is a common consequence of PCI, occurs when there is a re-narrowing of a blood vessel that has been opened via a vascular procedure. One of several angiographic definitions of restenosis refers to a ≥30% increase from the immediate post-PTCA stenosis to the follow-up stenosis or a loss of ≥50% of the gain achieved.[12] In a 1998 consensus statement from the American College of Cardiology (ACC), it was estimated that the angiographic restenosis rate after PTCA and other coronary interventional procedures was 30% to 50%.[13] Despite the fact that coronary stents and antiplatelet therapy are used to lower the occurrence of restenosis, luminal narrowing due to in-stent restenosis (ISR) recurs in many cases when stents are implanted in complex lesions, long lesions and small vessels. In the US, there were an estimated 150,000 cases of ISR in 2001.[14]

The introduction of stents during a PCI has become widely adopted in Canada. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) is an ongoing prospective data collection initiative that began in January 1995. The initiative captures the cohort of patients undergoing cardiac catheterization in Alberta (over three million people). Patients are followed longitudinally for short- and long-term clinical, economic and quality-of-life outcomes. APPROACH reported that the proportion of stent use in Alberta increased from 22.6% of PCI interventions in 1995 to 81.7% in 2001. In Ontario, the Ontario Case Costing Initiative (OCCI) reported that stent use in any PCI procedure was 92.34% in the 2000-2001 fiscal year. At a tertiary hospital level, stents were used in 92.31% of PTCAs at the Sunnybrook campus of SWCHSC in 2002.

1.3 Glycoprotein IIb/IIIa Inhibitors in PCI

Platelet activation and aggregation are factors in thrombus formation after a PCI.[15] The activation of specific platelet membrane receptors (the GP IIb and GP IIIa receptors) has been implicated in this process. Activation of the membrane receptors leads to conformational changes in glycoprotein IIb/IIIa (GP IIb/IIIa), which in turn become receptors for fibrinogen-mediated platelet aggregation.[16] A plug of linked platelets constitutes a thrombus that may obstruct a vessel lumen.[15] The inhibition of GP IIb/IIIa receptors has been shown to reduce

platelet aggregation after a PCI and ultimately to reduce the mortality and morbidity associated with unstable angina and coronary angioplasty.[15]

In this analysis, we examine the clinical outcomes and costs in patients with ACS who are undergoing elective and urgent PCI with stenting. Three GP IIb/IIIa inhibitors are approved for use in Canada: abciximab (ReoPro®), eptifibatide (Integrilin®) and tirofiban (Aggrastat®). All three are indicated for patients with high risk ACS for whom a PCI is planned or anticipated. Only abciximab and eptifibatide are indicated for adjunct therapy initiated at the time of a PCI.[17] In this case, adjunct therapy is defined as GP IIb/IIIa given with a PCI plus stenting. Tirofiban was excluded from this analysis, because it is not approved for adjunct treatment.

Table 1: GP IIb/IIIa inhibitors indicated for patients with high risk ACS for whom PCI is planned or anticipated

Drug	DIN	Strength/ Dosage Form	Cost per Unit	Dose Used
abciximab	02216973	10 mg/5 mL vial	$536.65	bolus 0.25 µg/kg + infusion 0.125 µg/kg/minute (maximum 10 µg/kg/minute) for 12 hours
eptifibatide	02240352 02240351	20 mg/10 mL bolus vial 75 mg/100 mL infusion vial	$38.00 $111.25	bolus 180 µg/kg x 2 + infusion 2 µg/kg/minute for 18 hours (range 18 to 24 hours)

Abciximab is a chimeric human murine monoclonal antibody antigen binding fragment (Fab) that inhibits GP IIb/IIIa binding.[16] Eptifibatide is a parenteral cyclic heptapeptide with a short half-life and high specificity for the GP IIb/IIIa integrin.[18] Abciximab and eptifibatide have shown similar inhibition of platelet aggregation in ex vivo studies.[16]

2 THE ISSUE

The adjunct utilization of GP IIb/IIIa receptor inhibitors can reduce post-procedural ischemic complications in PCI patients.[19,20] GP IIb/IIIa inhibitors, however, are associated with incremental procedural costs based on the cost of the drug and on drug-associated complications such as bleeding. It is unclear whether GP IIb/IIIa inhibitors provide a long-term (>1 year) benefit in the prevention of restenosis.

As limited information is available, there is a need to conduct an economic evaluation on the utilization of GP IIb/IIIa inhibitors in non-acute patients undergoing elective and urgent PCIs.

Additional antiplatelet therapies such as ASA, clopidogrel and heparin may affect clinical outcomes. As these therapies were part of the standard pre- and post-treatments in all the relevant clinical trials, we decided to stay focused on the impact of the GP inhibitors for this study.

3 OBJECTIVE

This report focuses on the cost-effectiveness of the GP IIb/IIIa inhibitors abciximab and eptifibatide as adjuncts to elective and urgent PCI with stenting relative to routine PCI and usual care (with stenting but without the additional drug therapy), from a provincial health insurance payer perspective.

We did a systematic review of economic evaluations and an original economic evaluation in a Canadian context to assess the cost-effectiveness of abciximab and eptifibatide in patients who were undergoing elective or urgent PCIs. A decision analytic modelling approach was taken to estimate the short-term and long-term measures of cost-effectiveness. Abciximab and eptifibatide are modelled separately because of different patient cohorts. A subgroup analysis of diabetic patients was included.

4 ECONOMIC ANALYSIS

4.1 Review of Economic Studies

4.1.1 Methods

A protocol for the study was written a priori and followed throughout the process.

a) Information and data identification and retrieval strategies for economic evidence

For the economic systematic review. MEDLINE®, EMBASE® BIOSIS Previews® and PASCAL were searched on the DIALOG® system without language restrictions. The randomized controlled trial (RCT) filter was not used, as it would have eliminated the economic evaluations based on decision theoretic models. An economic filter was used to limit the search to economic studies. The search results were limited to human studies. Parallel searches were performed and updated on the HEED: Health Economic Evaluations Database, PubMed and the Cochrane Library. It was decided to exclude tirofiban from the analysis, so tirofiban terms were eliminated from subsequent searches (see Appendix 1a for the detailed economic search strategy). Regular alerts were established on BIOSIS Previews®, EMBASE® and MEDLINE® . Recent issues of *Circulation*, *Health Economics*, *The Journal of Health Economics* and *Pharmacoeconomics* were hand-searched.

Grey literature was obtained through searching health technology assessment and related agencies' web sites and databases. We also searched clinical trial registries for completed and ongoing trials. The Internet was searched using Google™ and AlltheWeb™. More information was gathered by manually searching the bibliographies of review articles and contacting experts and agencies.

b) Study selection criteria

A study was eligible for inclusion in the systematic review of economic evaluations if it met each of the criteria in Table 2.

Table 2: Eligibility for inclusion in systematic review of economic evaluations

Criterion	Determinants of Eligibility
Study design	full economic evaluations (comparative analyses of costs and consequences of alternative courses of action), which can be cost benefit studies (consequences measured in dollars), cost effectiveness studies (consequences measured in natural units), cost utility studies (consequences measured in derived units such as quality adjusted life-years) and cost minimization studies (with proof that intervention and comparator are equally effective)
Population	adult patients undergoing elective or urgent PCIs with stenting are primary focus
Intervention	abciximab or eptifibatide administered as an adjunct to PCI
Comparator	routine PCI with stenting without addition of GP IIb/IIIa inhibitor
Primary outcomes	must be presented as incremental measure of implication of moving from comparator to intervention (incremental cost effectiveness ratio or incremental net benefit measure, e.g., incremental cost per quality adjusted life-year, incremental cost per year of life saved, incremental cost per medical event averted)

c) Selection method

Two reviewers (AB and HN) applied the eligibility criteria to the title of each citation, the abstract and the key words (if available). Where disagreements occurred, the paper was retained for the next step in which Reference Manager software was used to check for duplicates and to create a database for management of the study selection process. Retained studies were then retrieved as full-text hard copies.

Two reviewers (AB and HN) applied the eligibility criteria to the full-text papers. For inclusion in the review, the study had to satisfy all the selection criteria. Disagreements between the reviewers were resolved by consensus.

Although there were no language restrictions in the search strategy, foreign-language papers were excluded because of cost considerations.

d) Data abstraction strategy

Two reviewers (AB and ZT) used a standard data extraction form to independently extract and document relevant information on author, title, type of program, intervention, comparators, study population and size, study design, time horizon, perspective, data sources for effects, data sources for costs, discounting, health-related quality of life (HRQL), currency, year, base case incremental cost-effectiveness ratio (ICER) results or incremental net benefit, sensitivity analysis and conclusions.

e) Study quality assessment

The quality of each study included in the systematic review was independently assessed by two reviewers (AB and ZT) using a checklist developed for the *British Medical Journal*[21] (Appendix 2).

f) Data analysis methods

A qualitative approach to data synthesis was taken.

4.1.2 Results

a) Study flow

Figure 1 shows a QUOROM flowchart of the management of studies captured in the search.[22] We identified 83 papers for retrieval in full text.

The hand searches and the Internet searches did not yield any papers that were included for review, but some of the material was useful as background information.

b) Identified studies

The five studies included in the review of economic evidence are those by Brown *et al.*,[23] Kreatsoulas *et al.*,[24] Newman *et al.*[25], Zed *et al.*[26] and Palmer *et al.*[27] The Palmer *et al.* study, which was commissioned by the National Institute for Clinical Excellence (NICE), looked at four treatment strategies involving GP IIb/IIIa inhibitors. One of the strategies met our inclusion criteria and is reported here (glycoprotein antagonists as an adjunct to PCI).

c) Study characteristics

Table 3 describes the characteristics of the included studies, which were done in developed countries. Four of the five were of decision theoretic modelling designs and one[23] was an economic evaluation with a clinical trial

Figure 1: Selection of studies for inclusion

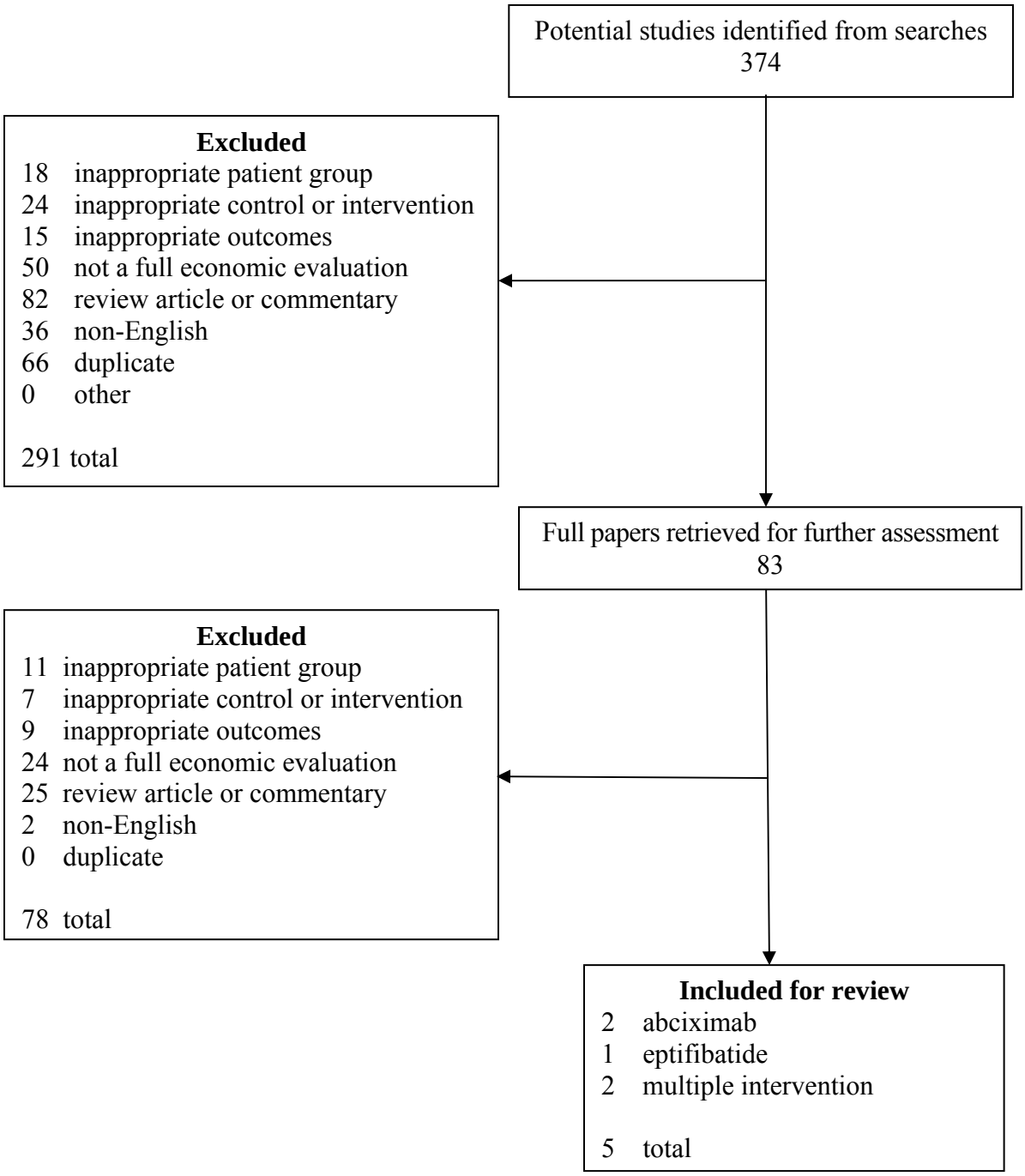


Table 3: Characteristics of economic evaluations included in systematic review

Author	Source	Intervention	Study Design	Geographic Location	Clinical Outcome Source
Brown[23]	journal article	eptifibatide	RCT-based	western Europe	western European PURSUIT trial
Kreatsoulas[24]	abstract	abciximab	decision theoretic	Canada	EPISTENT trial
Newman[25]	abstract	abciximab eptifibatide	decision theoretic	US	various trials
Zed[26]	journal article	abciximab	decision theoretic	Canada	EPILOG trial
Palmer[27]	journal article	abciximab eptifibatide	decision theoretic	UK	meta-regression of 10 trials

d) Cost-effectiveness results

Table 4 summarizes the results of the included studies. The studies were performed from a variety of perspectives and the currency years were all recent.

Table 4: Results of economic evaluations included in systematic review

Author	Study Perspective	Currency	Currency Year	Point Estimate of Cost-effectiveness
Brown[23]	national health care ministry	euros	1999	for eptifibatide, incremental cost per year of life saved: 23,818 euros
Kreatsoulas[24]	provincial ministry of health	C$	1999	ICER for each death averted: $130,271
Newman[25]	not stated	US$	not stated	incremental cost/QALY, short term abciximab: $7,900, eptifibatide: $2,600
Zed[26]	Hospital	C$	1997	abciximab: ICER of $29,700 per event-free patient
Palmer[27]	UK NHS	UK pounds	2000-2001	ICER of £25,811 per QALY

ICER=incremental cost-effectiveness ratio, NHS=National Health Service, QALY=quality adjusted life-year.

e) Quality assessment results

The results of the quality assessment analysis are summarized in Appendix 3. The approach used follows that described by Jefferson *et al.*[28]

The BMJ checklist for quality assessment of economic evaluations includes 35 questions grouped under three headings: study design; data collection; and analysis and interpretation of results. Each question is answered with "yes," "no" or "not clear." The five included studies are all full economic evaluations.

The sum of the "no" and "not clear" answers indicates the extent that issues were not handled.[28] The lower the numerical score, the higher the implied quality. For three studies, the score was relatively low, suggesting a relatively high quality rating (Brown=3, Zed=7 and Palmer=5).

The sum of the "no" and "not clear" answers for three full articles is less than the number of "no" and "not clear" answers for the full economic evaluation by Jefferson *et al.*[28] Many of the articles in the Jefferson *et al.* article, however, were not accepted for publication.

The sum of the "no" and "not clear" answers for two studies suggests a low quality rating: Kreatsoulas=22 and Newman=27.

4.1.3 Discussion

The heterogeneity of study characteristics seen in Tables 3 and 4 is apparent. Two authors look at a similar perspective: national health care ministry and provincial ministry. These are health insurance payers. The study by Zed takes a hospital perspective. This has implications for the costs included in the analyses and therefore, the cost-effectiveness ratios. The Newman study does not state the study perspective.

Other sources of heterogeneity include the variation in geographic location (two are Canadian); the variation in the trials used for clinical outcomes, hence variation in the clinical regimens; the variation in research design, with the Brown study being a "piggy-back" of an economic evaluation onto a clinical trial and the others being decision-theoretic models (i.e., observational and retrospective); and the variation in the consequence considered (including life-years saved, deaths averted, QALY gained and event-free patients).

The results of the review of economic evidence suggest that abciximab and eptifibatide fall in the range of what is generally considered to be cost-effective.[29] In the Palmer study,[27] the strategy of GP IIb/IIIa as an adjunct to PCI was dominated by a strategy of using GP IIb/IIIa as part of initial medical management, i.e., giving patients with ACS an infusion of GP IIb/IIIa inhibitors as soon as they are confirmed as "high risk." There has been one high quality[26] Canadian economic evaluation, which only analyzed abciximab. These results support the need for an up-to-date primary economic evaluation in a Canadian context.

4.2 Primary Economic Evaluation

4.2.1 Methods

a) Data sources

The search strategy for clinical data can be found in Appendices 1b and 1c. A literature search performed for CCOHTA's clinical review of GP IIb/IIIa inhibitors was consulted. The clinical review is released as a separate report entitled "Glycoprotein IIb/IIIa Antagonists: A Meta-Analysis of Clinical Efficacy and Safety in Patients Undergoing Percutaneous Coronary Intervention." The patient group and interventions included in that study are broader than those in the economic study. For the clinical review, published literature without language restrictions was identified by searching electronic databases on the OVID system using the multi-file search feature in August 2001 (see Appendix 1b). Databases searched included MEDLINE®, EMBASE®, BIOSIS Previews®, HealthSTAR and Current Contents®. The three glycoprotein inhibitors that are licensed in Canada (abciximab, eptifibatide and tirofiban) were searched using generic and trade names. Retrieval was limited to human studies. Regular alerts were set up on

the DIALOG® system. Parallel searches were performed and updated on the Cochrane Library and PubMed.

A separate literature search was performed by a library technician for the Macdonald Library at SWCHSC on behalf of the HOPE Research Centre. The HOPE Research Centre search limited results to randomized controlled trials, an adult population and a 10-year timeframe (Appendix 1c).

Clinical studies were included for the economic evaluation according to the following criteria:

- they were randomized controlled trials (RCT)
- they included the GP IIb/IIIa inhibitors abcimiximab and eptifibatide
- GP IIb/IIIa inhibitors were used as primary adjunct therapy in elective and urgent PCI
- >90% of the patient population received stent implantation
- the outcomes evaluated were clinical criteria (MI, repeat revascularization, death)
- clinical outcomes were evaluated at specific points ≥ 30 days after PCI.

Studies were excluded from the analysis if:

- GP IIb/IIIa was not a primary adjunct therapy
- tirofiban was the GP IIb/IIIa being investigated
- <90% of the patient population received stent implantation
- the patient population received PCIs on an emergent basis
- the patient population was non-adult or exclusive (women only, 75+ years)
- acute MI was the primary indication
- the outcomes evaluated were angiographic or non clinical
- the article was not an original RCT (e.g., review, note, meta-analysis, abstract)

Two blinded reviewers examined the studies for inclusion criteria. Six original studies met our inclusion and exclusion criteria: EPISTENT[30] (Evaluation of Platelet IIb/IIIa Inhibition in Stenting Trial); ESPRIT[31] (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy); PRICE[32] (Prairie ReoPro versus Integrilin Cost Evaluation Trial); ERASER[33] (Evaluation of ReoPro And Stenting to Eliminate Restenosis); Tamburino[34] and TARGET[35] (The Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial).

EPISTENT

Seven publications were related to the EPISTENT study. The base study design was a randomized controlled study of abciximab plus stent versus stent only. Abciximab was evaluated at 30 days,[30] six months[36] and one year.[37] Lincoff *et al.* conducted a subgroup analysis in diabetic patients,[38] while Islam *et al.* presented angiographic complications during PCI stenting for the EPISTENT cohort.[39] Cho *et al.* examined gender differences among the EPISTENT diabetic population,[40] while Marso *et al.* evaluated diabetic patients at one year.[41]

ESPRIT

Five publications were related to the ESPRIT study. The base study design was a randomized controlled study of eptifibatide plus stent versus stent only. Eptifibatide was evaluated at 48 hours and 30 days,[31] six months[42] and one year.[43] Diabetic patients at 48 hours, 30 days and one year were described in a separate publication,[44] while Cohen *et al.* evaluated the in-hospital costs for the ESPRIT trial.[45]

PRICE
The PRICE trial was a randomized head-to-head comparator study that examined abciximab and eptifibatide clinical and economic studies in non-urgent balloon or stent PCI patients at 30 days.[32]

ERASER
The ERASER trial was a randomized controlled study that compared abciximab to non-GP therapy in stented patients with outcomes at 30 days being reported.[33]

TAMBURINO
Tamburino *et al.* also compared abciximab to non-GP therapy in stented patients with outcomes at six months evaluated in a randomized controlled study.[34]

TARGET
The TARGET trial[35] was a prospective, multicentre, double-blind, randomized trial in which 4,809 patients undergoing planned stenting were randomized to receive abciximab or tirofiban.

Table 5 provides a summary of these six clinical studies, from baseline characteristics to composite (death, MI, revascularization) outcomes at 30 days, six months and one year for the treatment arms only.

b) Time horizon
Short-term and long-term clinical outcomes were evaluated. The short-term outcomes used were evaluated at 30 days and one year post-PCI procedure, with data based on the clinical trials that met the inclusion criteria. Two analytic decision trees were structured into 30-day and one-year time horizons. Event rates were reported for zero to 30 days and zero to 365 days inclusive. The clinical studies did not report the event rates for 31 to 365 days inclusive. These rates were calculated using the following formula: (day 0 to 365 days) – (day 0 to 30 days) = 31 to 365 days.

For long-term clinical outcomes, data for the estimation of survival beyond the time frame of the clinical trial were calculated. A Markov model was used to calculate survival using different death rates: background mortality up to age 106 years, from Statistics Canada;[46] late mortality associated with peri-procedural MIs after a PCI, based on three-years of follow-up data (pooled)[47] from three landmark studies; and excess mortality after cardiac procedures. [48] The three studies were EPIC,[49] EPILOG[50] and EPISTENT.[30] Results showed that after three years of follow-up, there was a 6.4% mortality rate for the non-GP therapy group as compared to 5.0% for the abciximab group. There was a 1.4% absolute decrease in mortality over a three-year time horizon.[47]

The expected non-vascular mortality for a 60-year old man in Canada is 1.25% over one year.[46] After angioplasty, the additional expected mortality owing to the diagnosis of stable coronary disease is about 2% per year[51] and a peri-procedural MI adds approximately 5% per year.[51] The need for an extra revascularization procedure adds another 0.4% per year.[48]

A discount rate of 5% was applied to the survival estimates for life years accrued beyond the first year.[37]

Table 5: Comparison of treatment arms in clinical trials

	Eptifibatide		Abciximab					
	ESPRIT	**PRICE**	**EPISTENT**	**ERASER 12 hour**	**ERASER 24 hour**	**PRICE**	**Tamburino**	**TARGET**
n	1,040	157	794	79	75	163	54	2,411
Study design	RCT DB	RCT DB	RCT DB	RCT DB	RCT DB	RCT DB	RCT open-label	RCT DB
Mean age	median=62	63	59	median=62	median=58	63	61	62.6
Previous CABG	10%	20%	7.7%	N/A	N/A	22%	N/A	17%
Previous MI	32%	N/A	32.7% (>7 days)	N/A	N/A	N/A	35 (65%)	39%
Previous PCI	23%	37%	N/A	12.7%	12.0%	37%	N/A	30%
Stented	95%	91%	97.3%	100%	100%	91.4%	100%	95%
48-hour composite	6.0%	5.1%	N/A	5.1%	9.3%	4.9%	N/A	N/A
30-day composite	6.8%	6.3%	5.3%	N/A	N/A	5.6%	N/A	6.0%
6-month composite	14.2%	N/A	6.4%	20.3%	22.7%	N/A	11.1%	14.3%
1-year composite	17.5%	N/A	20.1%	N/A	N/A	N/A	N/A	N/A
Included or excluded	included	excluded, because stratified by drug only and not by procedure	included	excluded, because only 48-hour and 6-month data available	excluded, because only 48-hour and 6-month data available	excluded, because stratified by drug only and not by procedure	excluded, because only in-hospital and 6-month data available	excluded, because tirofiban was comparator and only 30-day and 6-month data available

n=number, RCT=randomized controlled trial, DB=double-blind, N/A=not applicable, MI=myocardial infarction, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft.

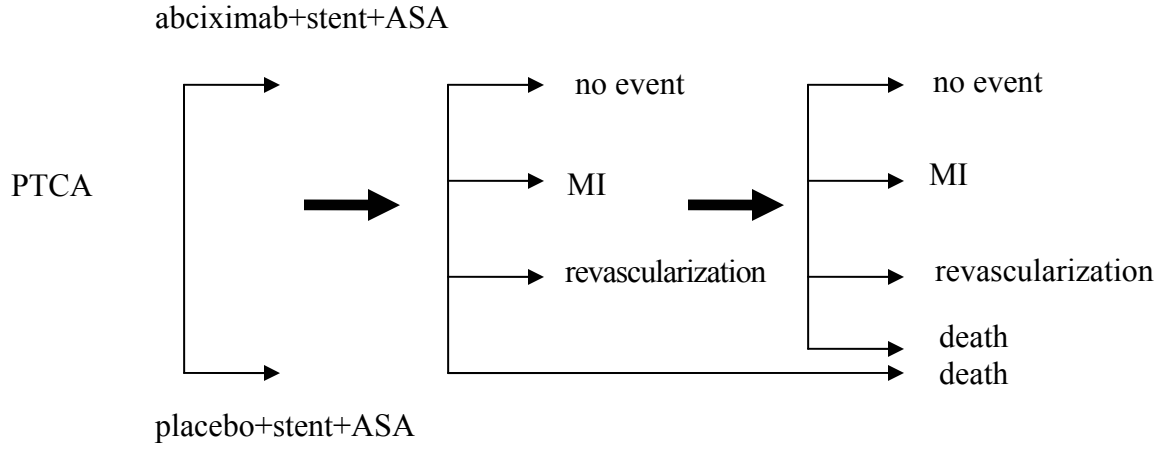
c) Analytical approach

Economic models were constructed using DATA by TreeAge software (V4) and based on clinical data and treatment algorithms. Five short-term and five long-term trees were constructed for this analysis. The ages of the patient populations entering these models were based on the median or mean ages from the clinical trials (62 for ESPRIT and 59 for EPISTENT).

Short-term models

The decision analytic model is shown in Figure 2. The root of the decision tree is the low to moderate risk ACS patients who are undergoing an urgent or elective PCI with stent implantation. The population is stratified into GP+stent and stent-only groups. Two time horizons were constructed in the short-term model: 30 days and one year. For each therapy, there is a probability that a patient will experience no event or a major adverse cardiac event (MACE) within the first 30 days after a procedure. After 30 days post-PCI procedure, an individual may experience no event or a MACE at the one-year point.

Figure 2: Short-term model



PTCA=percutaneous transluminal coronary angioplasty, ASA=acetylsalicylic acid, MI=myocardial infarction.

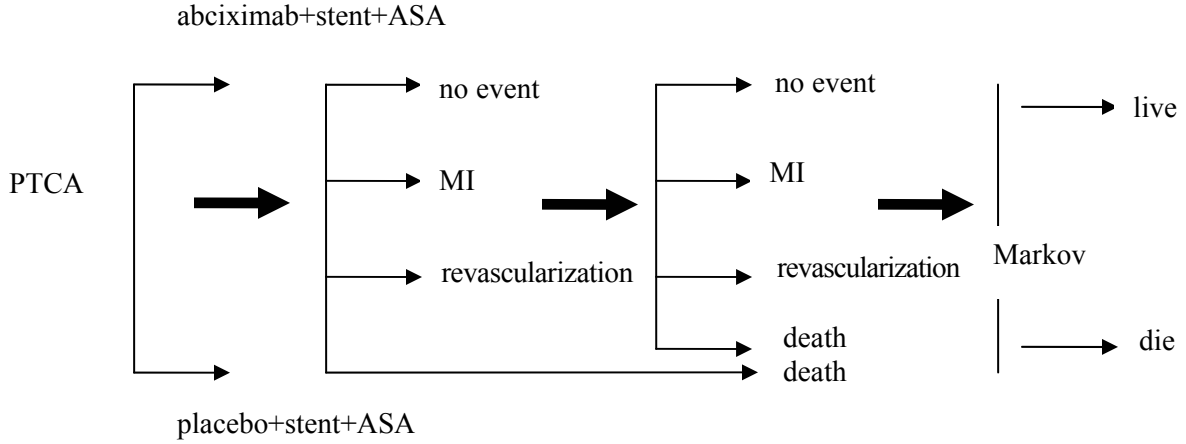
Five short-term decision analytic models were conducted:

- abciximab in the general stent population
- eptifibatide in the general stent population
- abciximab in the diabetic stent subpopulation
- eptifibatide in the diabetic stent subpopulation
- eptifibatide in the non-diabetic stent subpopulation.

Long-term models

Long-term (survival) outcomes in low to moderate risk patients with ACS were obtained by constructing five Markov decision analytic models with a cycle length of one year for a lifetime. "Live" and "die" alternatives were used. The survival model is presented in Figure 3. The probability of events and payoffs were used to populate the short-term and long-term decision analytic models to evaluate the cost-effectiveness of the GP IIb/IIIa inhibitors.

Figure 3: Survival



PTCA=percutaneous transluminal coronary angioplasty, ASA=acetylsalicylic acid, MI=myocardial infarction.

The five long-term decision analytic models are:

- abciximab in the general stent population
- eptifibatide in the general stent population
- abciximab in the diabetic stent subpopulation
- eptifibatide in the diabetic stent subpopulation
- eptifibatide in the non-diabetic stent subpopulation.

d) Health outcomes: identification, measurement and evaluation

Five trials were identified from the literature evaluating GPs as adjunct therapy in PCI patients with stent implantation. All studies included non-emergent patients.

Separate decision analytic models were constructed for the two GP IIb/IIIa drugs, mainly because these non-emergent patients were further divided into non-urgent patients (ESPRIT) and elective or urgent patients (EPISTENT).

ESPRIT

The ESPRIT study[31] was a randomized, double-blind, placebo-controlled, cross-over permitted, parallel group American and Canadian clinical trial. Patients with coronary artery disease who were scheduled to undergo a non-urgent PCI with stent implantation and who would not be routinely treated with a IIb/IIIa inhibitor during the PCI were included in the study. Exclusion criteria for patients were:

- previous treatment with a GP IIb/IIIa inhibitor or a thienopyridine 30 days before randomization
- having a PCI within previous 90 days, a previous stent implant at the target lesion or an anticipated staged PCI 30 days after randomization
- experiencing a MI 24 hours before randomization
- having a history of bleeding diathesis or evidence of abnormal bleeding
- experiencing a stroke or transient ischemic attack 30 days before randomization or having a history of hemorrhagic stroke
- experiencing continued chest pain leading to an urgent referral for a PCI
- having uncontrolled hypertension (systolic blood pressure >200 mm Hg, diastolic blood pressure >110 mm Hg)
- having major surgery within previous six months
- having thrombocytopenia (platelet count $<100x100^9$/L) or serum creatinine >350 μmol/L.

All patients were treated with Aspirin and a thienopyridine (ticlopidine or clopidogrel) before randomization. Patients were randomized to receive either no glycoprotein therapy or eptifibatide immediately before PCI initiation. Any stent type could be used. Eptifibatide was given in a bolus (180 μg/kg) immediately before the PCI. This was followed by an infusion (2.0 μg/kg/minute) that was continued until hospital discharge or after 18 to 24 hours. A second bolus (180 μg/kg) was given 10 minutes after the first. All patients received low dose weight-adjusted unfractionated heparin. This was a low risk population as <20% had ACS within 48 hours of the PCI or an ST-segment elevation within seven days of enrolment.

Bailout eptifibatide open-label was available for emergency conditions (direct treatment of abrupt closure, no reflow, coronary thrombosis or other similar PCI combination). The content of the bailout kits depended on the randomization pattern: two bolus vials of eptifibatide for patients randomized to receive no GP therapy or placebo bailout vials for patients randomized to receive eptifibatide.

The primary end point of the analysis was a composite outcome of death, MI, urgent revascularization and thrombotic bailout within 48 hours of randomization. The secondary outcome was a composite of death, MI and having an urgent target vessel within 30 days of randomization. Urgent target vessel revascularization includes any CABG or a second PCI in the same vessel. Measures of safety included bleeding, transfusion and stroke. Among the 2,064 patients who were randomized, the average weight was 84.4 kg, 27% were female, 23% had undergone a previous PCI, 32% had a previous MI and 26% were from Canadian centres. The baseline characteristics in the eptifibatide (n=1,040) and no GP therapy or stent only (n=1,024) groups were not different. At 48 hours, there was a statistically significant difference in the primary end point (composite of death, MI, urgent revascularization and thrombotic bailout) between eptifibatide (6.6%) and stent only (10.5%) ($p<0.0015$). At 30 days, there was a statistically significant difference of the primary end point (composite of death, MI and urgent revascularization) between eptifibatide (6.8%) and stent only (10.5%) ($p=0.0034$).

Over 88% of the events occurred within the first 48 hours after the PCI. As it was reported that large MI (or enzymatic MI, defined as CK-MB at least three times the upper limit of normal) occurred in 3.3% of the eptifibatide population versus 4.9% for the stent-only group, the large MI percentages for 30 days were calculated to be 2.9% for eptifibatide and 4.3% for placebo.

The administration of eptifibatide in combination with stent implantation significantly and clinically reduced ischemic complications post-procedure. High risk patients were excluded from the study. Appendix 4 summarizes the results at 48 hours, 30 days[31] and one year.[43]

The study outcomes at 48 hours and 30 days were followed by the evaluation of outcomes at one year. These were determined by telephone contact or clinic visit at 12 months.[43] Data were available for 988 out of 1,040 (95%) of the eptifibatide group and 976 of 1,024 (95.3%) in the stent-only group.[43] Baseline demographic and angiographic characteristics were balanced between the groups. Results showed that[43] the composite outcome of death, MI and target vessel revascularization was 17.5% in the eptifibatide group and 22.1% in the stent-only group ($p=0.007$). The difference in death or MI was also statistically significant ($p=0.001$) between the two groups: 12.4% (n=121) for the stent-only cohort and 8.0% (n=79) for the eptifibatide cohort.[43] These outcomes show that the short-term outcomes are sustained until one year.

Labinaz *et al.* also evaluated outcomes at one year.[44] Follow-up was available for 1,039 eptifibatide-treated patients and 1,022 stent-only patients. These results, along with the 30-day clinical outcomes used as model inputs, are summarized in Appendix 5.

EPISTENT

The EPISTENT study[30] was a randomized, double-blind, placebo-controlled, cross-over permitted, parallel-group American and Canadian clinical trial. Patients scheduled to undergo elective or urgent PCI were included. Patients received Aspirin two hours before the PCI and

daily afterwards. Patients were randomized to receive either stent only (n=809), abciximab (bolus=0.5 mg/kg and 0.125 mg/kg/minute infusion for 12 hours) plus stent (n=794) or abciximab plus balloon angioplasty (n=796) up to one hour before PCI initiation. Ticlopidine was given to all patients in the two groups (clopidogrel was not approved at the time of this study). Heparin was weight-adjusted for all patients with dosages dependent on the randomization group. The abciximab cohort received at least 70 U/kg of heparin with additional boluses to achieve and maintain the activated clotting time of >200 seconds, while the stent-only cohort received >100 U/kg with additional boluses to maintain the activated clotting time of >300 seconds.

The primary end point of the analysis was a composite outcome of death, MI and urgent revascularization within 30 days of randomization. Secondary end points were MI and death or large MI. Measures of safety included major and minor bleeding. Only the results for abciximab plus stent and stent-only populations were evaluated for this analysis. An MI in EPISTENT was defined as "new or pathological Q waves or a value of creatine kinase or its MB isoenzyme at least five times the upper laboratory limited in the participating hospital."[30]

Of the 2,399 patients who were evaluated, 1,603 (67%) received a stent. The 796 patients in the balloon angioplasty plus abciximab group were excluded in this analysis. The mean age for all patients was approximately 60 years and 25% were female. The average weight was unspecified, but in Lincoff's analysis of diabetic patients in the EPISTENT trial, 46.1% of 491 diabetic patients versus 33.5% of 1,908 non-diabetic patients weighed >90 kg.[38] Appendix 6 summarizes the results at 30 days[30] and one year.[37]

Death, MI and revascularization were evaluated at 30 days[30] and one year[37] post PCI. Significant benefits were derived from abciximab at 30 days as seen by the reduction of the primary end point of death, MI or urgent revascularization in the abciximab plus stent cohort (n=42) compared to the stent-only cohort (n=87). This was maintained at one year (n=160 versus n=194, p=0.039). The clinical outcomes used as model inputs are summarized in Appendix 7.

ERASER

The ERASER study was a double-blind, placebo-controlled, randomized trial that compared abciximab (0.25 mg/kg for bolus; 0.125 µg/kg/minute infusion) for 12-hour and 24-hour infusions to stent-only patients referred for intracoronary stent implantation in PCI.[33] The total sample size was 225. Clinical outcomes were evaluated at hospital discharge and six months. The results are presented in Appendix 8.

In the ERASER trial, the same dose of abciximab was used as in the EPISTENT study (only the length of infusion varied from 12 hours to 24 hours). A comparison of results at six months follow-up revealed that 20.3% of ERASER 12-hour infused patients experienced the composite outcome (death+MI+TLR) versus 6.4% in EPISTENT (death+MI+urgent repeated revascularization).[36] Also, 97.3% of the abciximab group in EPISTENT[30] received stents, while 100% received stents in ERASER.

Although the ERASER study met all inclusion criteria for the economic evaluation, the clinical outcomes were evaluated at different time points from those in the decision analytic model. Attempts to secure the raw data to extrapolate the six-month data were unsuccessful. Consequently, the study was excluded in this analysis.

PRICE

The PRICE trial was a randomized, double-blind, head to head comparison of abciximab (n=163) and eptifibatide (n=157) in PCI patients.[32] Study eligibility criteria included patients over the age of 21 years, who were undergoing elective, non-urgent coronary balloon angiography or stent implantation. ASA was given >2 hours before PCI. Patients undergoing stent implantation also received clopidogrel. Patients were randomly assigned to receive abciximab (0.25 mg/kg bolus + 0.125 μg/kg/minute infusion) for 12 hours and eptifibatide (180 μg/kg bolus + 2.0 μg/kg/minute continuous infusion for 18 to 24 hours. All patients received weight-adjusted heparin. The primary outcome of interest was the total in-hospital cost for abciximab and eptifibatide. The secondary clinical outcomes included in-hospital and 30 day rates of death, MI, urgent repeat PCI and CABG (Appendix 9).

Results showed that 4.9% individuals in the abciximab group compared to 5.1% of the eptifibatide group had a composite outcome by hospital discharge. At 30 days, 5.6% abciximab patients versus 6.3% eptifibatide patients experienced a composite outcome. At 30 days, 3.1% of abciximab users and 1.9% of eptifibatide users experienced serious bleeding. The results were not statistically significant.

The same doses of abciximab and eptifibatide were used as in EPISTENT and ESPRIT respectively. A comparison of results at 30 days revealed that 6.3% of patients treated with eptifibatide in PRICE experienced the composite outcome versus 6.0% in ESPRIT.[31] In the eptifibatide group in ESPRIT, 95% received stents, while 91.4% received stents in PRICE. For the abciximab treatment groups, 5.6% of PRICE patients experienced the composite outcome versus 6.4% in EPISTENT[36] and 97.3% of EPISTENT[30] patients received stents versus 91% in PRICE.

This study met all the inclusion criteria for the economic evaluation. Unfortunately, the published data were stratified by drug only and not by stent or balloon angioplasty. Consequently, it was impossible to evaluate the drug effect in stent patients.

Tamburino

Tamburino *et al.* compared abciximab to no GP therapy in patients undergoing elective implantation of coronary stents in an open-label, single-centre, randomized study (n=107). The primary variable was a composite of death, MI, urgent revascularization in hospital and at six months. In-hospital and six-month outcomes are listed in Appendix 10.[34]

The same dose of abciximab was used in the Tamburino *et al.* study as in EPISTENT. A comparison of results at six months revealed that 11.1% of patients treated with abciximab experienced the composite outcome versus 6.4% in EPISTENT.[36] In the abciximab group in EPISTENT, 97.3% received stents,[30] while 100% of abciximab patients received stents in the Tamburino *et al.* study.

This study met all inclusion criteria for the economic evaluation. The clinical outcomes, however, were evaluated at different points from those in the decision analytic model and treatments were given open-label. Attempts to secure the raw data and to extrapolate the six-month data were unsuccessful. Consequently, the study was excluded in this analysis.

TARGET

In this prospective, multicentre, double-blind, randomized trial, patients with ACS (n=3,025) were treated with abciximab, resulting in lower rates of MI at 30 days (5.8% versus 8.5%, p=0.004) and at six months (7.2% versus 9.8%, p=0.013). Mortality rates (1.39%) at six months were identical in both treatment groups. In patients without ACS (n=1,784), tirofiban enhanced six-month event-free survival when compared to abciximab (89.7% versus 86.6%, p=0.056).[35] One-year follow-up results were available in a publication of clopidogrel-pretreated TARGET patients.[52] The 30-day primary composite end point of death, MI or urgent TVR was lower among clopidogrel-pretreated patients (6.6% versus 10.4%, p=0.009) as was MI (6.0% versus 9.5%, p=0.012). At one year, clopidogrel pretreatment was associated with a lower mortality rate (1.7% versus 3.6%, p=0.011). The authors concluded that among patients undergoing coronary stent placement with Aspirin and a GP IIb/IIIa inhibitor, clopidogrel pretreatment was associated with a reduction of death and MI irrespective of the type of GP IIb/IIIa inhibitor used.

TARGET met all inclusion criteria for the economic evaluation. Patients, however, were stratified by the type of coronary syndrome (acute or non-acute) and not by stent procedure. Consequently, it was impossible to evaluate the abciximab effect in stent patients.

We considered the possibility of merging the placebo arms for the eptifibatide and abciximab trials to allow a direct comparison. On detailed review, however, of the inclusion and exclusion criteria and pre-treatment details of the relevant clinical trials (Appendices 11 and 12), it was apparent that the differences between the clinical trials were greater than their similarities. These variations included the use of open-label bailout therapy available in emergency conditions for the eptifibatide population, while there was no bailout for the abciximab population. Also, the same heparin-dosing regimen was used for the GP and stent-only treatments arms in the eptifibatide population, while the regimens were differentiated for the two treatments arms in the abciximab population. Based on the exclusion criteria for the eptifibatide trial, the population seemed to be a higher risk group based on the shorter time constraints such as evidence of stroke 30 days before randomization and higher cutoff points such as uncontrolled hypertension (systolic BP >200 mm Hg, diastolic >110 mm Hg) versus history of stroke two years before randomization and uncontrolled hypertension (systolic BP >180 mm Hg, diastolic BP >100 mm Hg) in the abciximab population. As a result, it was decided that the decision analytic models would be constructed for each GP inhibitor separately.

e) Health outcomes: identification, measurement and valuation

Subgroup analysis: diabetic and non-diabetic patients

Diabetic patients form a significant proportion of PCI patients (the trials suggest about 20%). They are considered to be at a higher risk than other PCI patients. This type of subgroup analysis has not been done before. As a result, an analysis was done for diabetic patients. Although stenting can improve intermediate outcomes for patients with diabetes mellitus (DM) compared with balloon angioplasty,[53] diabetic patients continue to be at risk of restenosis after a PCI.[54,55]

Poor glycemic control, vessel size and PTCA are predictors of restenosis in diabetic patients.[56] Diabetic patients have larger platelets and more GP receptors than non-diabetic patients.[57,58] They enter a hypercoagulable state because of increased levels of fibrinogen, factor VII and fibrinopeptide.[59] In general, individuals with type II diabetes are two to four times more likely to develop cardiovascular disease.[60]

Appendices 13a, 13b, 14a and 14b summarize the results of the diabetic and non-diabetic cohorts in ESPRIT and EPISTENT respectively.

ESPRIT

Of 2,061 patients treated in ESPRIT, 466 (22.6%) had diabetes. The beneficial effect of eptifibatide on the composite outcome (death, MI, urgent TVR) in diabetic patients was substantial but statistically nonsignificant at 30 days (5.6% for eptifibatide-treated diabetic patients versus 9.4% for stent-only diabetic patients, p=0.755) and maintained at one year (20.8% versus 28.2%, p=0.639). This trend was observed for the mortality rate and the incidence for MI and TVR. In terms of glycemic control, 24% used insulin, while 65% received an oral hypoglycemic agent.[44] In the non-diabetic cohort (n=1,595), the same beneficial (but not statistically significant) effect of eptifibatide on the composite outcome and each individual component was observed.

EPISTENT

Of 809 stent-only patients in EPISTENT, 173 (21.4%) were diabetic patients, while 162 of the 794 patients treated with abciximab (20.4%) were diabetic patients. Most of the diabetic patients received oral hypoglycemics (82% to 96%) while 24% to 39% used insulin.[38] In the diabetic cohort (n=335), abciximab had a statistical significance (p=0.004) on the death, MI or urgent revascularization composite at 30 days when compared to stent-only treatment; and there was a non-significant trend of lower mortality but significant differences in large MI (p=0.022) and TVR (p=0.035) for the abciximab plus stent cohort at one year.[37] In the non-diabetic cohort (n=1,268), abciximab had a statistical significance (p<0.001) on the death, MI or urgent revascularization composite at 30 days when compared to stent only. At one year, there was a non-significant trend of lower mortality, a significant difference in large MI (p=0.002) and a non-significant trend of higher TVR for the abciximab plus stent cohort (15.6%).[37]

Appendices 15a and 16a summarize the clinical inputs for the two diabetic cohorts, while appendices 15b and 16b summarize the clinical inputs for the two non-diabetic cohorts.

f) Costs: identification, measurement and valuation of resource use

This economic analysis is done from a government payer perspective. As a result, only direct medical costs, such as the cost of drugs, hospitalization, physician visits, nursing, rehabilitation, laboratory and diagnostic procedures, were included. All costs are presented in 2002-2003 Canadian dollars. Indirect costs such as lost productivity, time off work and costs to the patient (e.g., transportation, parking) were not considered in this evaluation because of the perspective.

The costs in the economic analysis came from several sources. Primary cost sources include the Schedule of Benefits,[61] Ontario Drug Benefit Formulary[62] and Ontario Case Costing Initiative (OCCI).[63]

OCCI calculates an aggregate cost per ICD-9-CM hospitalization. This cost consists of two components: direct (nursing time, drugs, inpatient procedures and tests) and indirect or overhead (housekeeping, finance, administration). The cost of nursing is the largest component of the hospitalization cost. Physician costs are separate from the hospitalization cost, as billings are made directly to the Ministry of Health. As a result, the corrected hospitalization cost for 2003 (Appendix 20, column 5) may be higher than what would be expected for a hospitalization cost, because of the inclusion of small indirect, overhead and minor inpatient testing costs. The cost of GP inhibitors and PCI procedural costs were deducted from the hospitalization cost.

GP IIb/IIIa costs

GP IIb/IIIa drug costs were obtained from the PPS Pharma Publication,[64] which listed drug costs per vial. It was assumed that any excess drug in the vial would be wasted. To calculate the total cost for each GP inhibitor, the doses for the bolus and infusion had to be calculated first, using the median weight of patients from the published trials. Appendix 17 summarizes the dosage and cost calculations.

Stent, other drugs and alternative therapy costs in 2003

Appendix 18 summarizes the cost of a bare metal stent used in PCI, the costs of drugs associated with GP IIb/IIIa and alternative therapies.

Hospital costs

Aggregate level costs for hospitalizations relating to MI, revascularization and coronary artery bypass grafting (CABG) were obtained from OCCI. All ICD-9-CM codes were confirmed with an expert interventional cardiologist (Dr. Eric Cohen: Division of Cardiology, Sunnybrook and Women's College Heath Sciences Centre, Toronto: personal communication, spring 2003).

A search of all hospitalizations between April 1, 2000 to March 31, 2001 inclusive was conducted. All patients over the age of 18 years were included in this analysis and divided into eight groups (Appendix 19).

Economic data were obtained from the OCCI, which is an initiative of the Ministry of Health and Long-Term Care. The OCCI was created to continue the work started by the Ontario Case Costing Project (OCCP). The OCCI's primary objectives are the collection of case costing data in support of improved management decision-making and the development of methods for hospital funding. Participating hospitals have implemented a standardized case costing method developed by the OCCI and have participated in a series of milestone audits to ensure the quality of the data. The OCCI collects case cost data for acute inpatient, day surgery and ambulatory care cases. For the 2000-2001 data set, the OCCI collected patient-specific cost records from eight hospitals in Ontario: Arnprior and District Memorial Hospital Corporation, Lakeridge Health Corporation, London Health Sciences Centre, Mount Sinai Hospital, The Ottawa Hospital General Campus, St. Michael's Hospital, Trillium Health Centre and the University Health Network.

OCCI also provided the following data for each of the eight subgroups:

- total number (n) of hospitalizations
- average (+standard deviation) and median OCCI cost with a minimum to maximum range
- number (%) of males and females
- average (+standard deviation) and median age of patient population with range at time of hospitalization
- average (+standard deviation) and median length of hospital stay with range
- number (%) who received stent (ICD-9-CM procedure code 36.06)
- number (%) who received platelet inhibitor (ICD-9-CM procedure code 99.2).

The first column in Appendix 20 lists the four types of hospitalization costs that are used for the models. The corresponding 2000-2001 total average costs (aggregate) are found in column 2. For aggregate costs (column 3 has 2003 inflated costs using the Bank of Canada's inflation rate) of PCI procedures to represent only the hospitalization component, the costs of stent and GP IIb/IIIa (weighted by proportion) were subtracted (column 4).

The cost of revascularization, which was derived as the weighted average of an overall PCI cost (25%) and an overall CABG cost (75%), was calculated to be $10,427. In addition to the procedural cost, the overall cost includes physician billing, drug acquisition costs, cardiac rehabilitation costs and other relevant costs.

The cost of death equalled the cost of MI, as it was assumed that 100% of deaths were due to MI in this patient population. Based on this assumption, the cost of death may be overestimated.

Physician visits, diagnostic procedure and laboratory costs

Physician costs were not incorporated into the OCCI hospitalization cost and were calculated separately (Appendices 21 and 22). Only outpatient diagnostic and laboratory testing costs are outlined in Appendix 22.

Physician visit costs and diagnostic procedure costs were obtained from the Schedule of Benefits[61] for Ontario and were used to represent the rest of Canada. Laboratory costs were obtained from the Laboratory Schedule of Fees[65] for Ontario and were also used to represent the rest of Canada.

The physician billing codes, diagnostic procedure codes and laboratory codes were validated by interventional cardiologists (Dr. Eric Cohen: personal communication, spring 2003. Dr. Lawrence Title, Division of Cardiology, Queen Elizabeth II Health Sciences Center, Halifax: personal communication, spring 2003). Appendix 21 summarizes the physician visit codes per clinical scenario during a hospitalization, Appendix 22 outlines the outpatient diagnostic procedures ordered for patients and Appendix 23 lists the outpatient laboratory tests conducted (each unit has a fixed rate of $0.517).

Determination of resource utilization

Information on resource utilization was based on peer-reviewed literature, treatment algorithms and expert opinion. Exposure to all aspects of the health care system for ACS from PCI to the one-year period was considered. The resource utilization costs for a hospitalization period were not disaggregated, because these data were aggregated in the ICD coding groups. Physician

services (inpatient and outpatient), diagnostic procedures (outpatient) and laboratory costs (outpatient) were costed at a disaggregated level. Appendices 24 to 28 outline the resource utilization data that were incorporated into the decision analytic models. Appendix 29 lists the survival probabilities that were also incorporated into the models.

It was sometimes impossible to obtain the resource utilization data or proportions needed from the published literature, especially for a Canadian population. Population rates for procedures are available for a Canadian context (for example, Cardiac Care Network of Ontario, APPROACH in Alberta, British Columbia). These databases contain broad information on the number of procedures and proportions. There is limited information, however, on the exact clinical management pathway for patients undergoing a PCI.

As the costs used in this analysis were based in Ontario, the authors of this report decided to use expert opinion based in Ontario. Dr. Eric Cohen is the director of the cardiac catheterization laboratory at SWCHSC in Toronto. He has been an interventional cardiologist there since 1992. He is also an associate professor in the faculty of medicine at the University of Toronto and is chair of the CCN (Cardiac Care Network) of Ontario catheterization and angioplasty working group. He served as chair of the CCN expert panel on coronary stenting and abciximab in 1997-1998. Since 1995, he has been on the executive of the Canadian Association of Interventional Cardiologists (CAIC, which is a subgroup of the Canadian Cardiovascular Society). An interim version of this report, which included the resource utilization components, was reviewed by Dr. Lawrence Title, who is an interventional cardiologist and researcher with the Queen Elizabeth II Health Sciences Centre in Halifax and Dr. Stephen Fremes, who is a cardiac surgeon with the Schulich Heart Centre at SWCHSC in Toronto.

To determine the physician cost of a PTCA (Appendix 21), Dr. Eric Cohen (Dr. Eric Cohen: personal communication, spring 2003) was asked to provide his expert opinion regarding the percentage breakdown for the number of vessels requiring angioplasty (Appendix 24).

The physician cost of a CABG was also weighted by the number of vessels (Appendix 21), so Dr. Stephen Fremes (Dr. Stephen Fremes, Division of Cardiology, Sunnybrook and Women's Health Sciences Centre, Toronto: personal communication, spring 2003) was asked to provide his expert opinion regarding the percentage breakdown for the number of vessels requiring CABG (Appendix 25).

Appendices 26 to 28 outline the algorithms relating to the inpatient and outpatient costs for the original PCI and any subsequent complications ("scenarios") that were applied to the decision analytic models when treatment (abciximab or eptifibatide) was given. The relevant clinical inputs (Appendices 5, 7, 15a, 15b, 16a, 16b) were also included in the decision analytic models, but are excluded in Appendices 26 to 28. These algorithms are similar for the stent-only treatment arm with the exclusion of the cost of the GP IIb/IIIa.

In addition, proportions and survival probabilities were required to complete the decision analytic models (Appendices 29 and 30). Two interventional cardiologists (Dr. Eric Cohen: personal communication, spring 2003. Dr. Lawrence Title: personal communication, spring 2003) provided their expert opinion for most of the proportions incorporated into the models.

Background mortality up to age 106 years was used for the long-term survival models, but survival probabilities relating to vascular death and vascular death post-event were also incorporated (Appendix 30).

g) Incremental analysis

An incremental analysis should be conducted when there is no dominance associated with one of the treatments. This incremental analysis will consider costs and outcomes. The primary outcome of interest will be "event avoided" and will compare an individual GP IIb/IIIa to stent-only treatment by using the calculation:

$$\text{incremental ratio} = \frac{\text{cost of IIb/IIIa} - \text{cost of stent only}}{\text{outcome of IIb/IIIa} - \text{outcome of stent only}}$$

Short-term analysis

For the short-term analysis, the outcome is major adverse cardiac event (MACE) avoided. The cost per MACE avoided for abciximab and eptifibatide compared to the stent only in patients receiving stent implantation is found in Appendices 31, 32, 36 and 37. We will also consider the cost per death avoided.

Long-term analysis

For the long-term analysis, the outcome is life years gained. The cost per life years gained for abciximab and eptifibatide compared to stent-only patients is found in Appendices 31, 32, 36 and 37.

h) Sub-group analysis on diabetic and non-diabetic patients

An analysis for diabetic and non-diabetic patients was conducted using the clinical inputs outlined in Appendices 13 to 16. The economic model was designed using DATA by TreeAge software (V4).

Four primary short-term decision trees were conducted: diabetic patients and abciximab; non-diabetic patients and abciximab; diabetic patients and eptifibatide; and non-diabetic patients and eptifibatide.

Four primary long-term decision trees were conducted: diabetic patients and abciximab; non-diabetic patients and abciximab; diabetic patients and eptifibatide; and non-diabetic patients and eptifibatide.

i) Key assumptions

- EPISTENT evaluated elective and urgent patients. ESPRIT evaluated elective patients. All patients were considered to be non-emergent.
- Patients in the trials generally had single-vessel disease. For example, in the EPISTENT population, <10% of >1 vessels required intervention. As a result, one PCI was used for resource utilization.
- All deaths reported in the clinical trials were assumed to be cardiac (MI) deaths.
- In EPISTENT, approximately 50% of composite outcomes occurred within six months of a PCI.[36,37] As a result, it was assumed that all post-hospital events (death, MI, CABG, revascularization) occurred at six months.

- The costs of secondary clinical events were identical to the costs of primary clinical events (for example, repeat PCI was costed equally as original PCI).
- The cost of death was assumed to be the same as the cost of MI.
- The study did not distinguish between the cost of a large MI and a small MI in terms of aggregate OCCI hospitalization costs.
- Bleeding rates and rates for large MIs for the diabetic population were the same used for the stented population.
- The decision tree was structured into 30-day and one-year time horizons. Event rates were reported from zero to 30 days and day zero to 365 days. The clinical studies did not report the event rates for 31 days to 365 days. These rates were calculated using the following equation: (31 to 364 days) = (0 days to 365 days) − (0 days to 30 days).
- In terms of resource utilization, individuals with an MI or CABG received one extra cardiology outpatient visit and two extra general practitioner visits.

For outpatient resource utilization in general, it was assumed that there would not be any incremental difference after the first year.

4.2.2 Results

Appendices 31 to 36 present the results (average expected cost, MACE and death rate) for abciximab and eptifibatide at two time points (short term or 30 days and long term or survival) in the stented population. Appendices 33 and 36 present the incremental analyses conducted for abciximab, which was not required for eptifibatide because of its dominance in cost and outcome (life-years).

a) Short-term analysis

At one year, eptifibatide was cheaper and had better clinical outcomes than the stent by itself, while abciximab was more expensive than the stent but led to better clinical outcomes.

Eptifibatide

Eptifibatide was considered to be the dominant treatment in terms of costs and outcomes. Eptifibatide had a lower cost (−$59) and lower rates of MACE (−5.6%) and mortality (−1%) when compared to the stent by itself (Appendix 31). Given the dominance, no incremental analysis was calculated.

Abciximab

Abciximab was more expensive than the stent by itself (+$1,171). Abciximab, however, led to fewer clinical events (−7%) and a lower mortality rate (−1%) when compared to the stent (Appendix 32). Therefore, an incremental ratio was calculated (Appendix 33).

b) Long-term analysis

In terms of survival, both GP IIb/IIIa inhibitors showed an increase in life-years gained (discounted and undiscounted) (Appendices 34, 35).

Eptifibatide
Eptifibatide had a lower cost (−$59) and led to a greater increase in unadjusted life-years (+0.22) and adjusted life-years (+0.12) when compared to the stent (Appendix 34). Given the dominance in cost and outcomes, no incremental analysis was calculated.

Abciximab
Abciximab was more expensive than the stent (+$1,171), but it led to more unadjusted life-years (+0.12) and adjusted life-years (+0.07) when compared to the stent (Appendix 35). An incremental ratio was calculated (Appendix 36).

c) Subgroup analysis of diabetic population
In the diabetic population, Appendices 37 to 42 show the results (average expected cost, MACE and death rate) for abciximab and eptifibatide at two time points (short term or 30 days and long term or survival).

Short-term analysis of diabetic patients
Eptifibatide: Eptifibatide was considered to be the dominant treatment in terms of costs. Eptifibatide had a lower cost (−$166) and led to lower rates of MACE (−7.1%) and mortality (−2%) when compared to the stent (Appendix 37). Given the dominance, no incremental analysis was calculated.

Abciximab: Abciximab was more expensive than the stent by itself (+$81), but it led to lower rates of MACE (−18.5%) and a lower mortality rate (−3%) when compared to the stent (Appendix 38). Therefore, an incremental ratio was calculated (Appendix 39).

Long-term analysis of diabetic patients
In terms of survival, both GP IIb/IIIa inhibitors showed an increase in unadjusted and adjusted life-years gained (Appendix 40, 41).

Eptifibatide: Eptifibatide had a lower cost (−$166) and led to a greater increase in unadjusted life-years (+0.31) and adjusted life-years (+0.22) when compared with the stent (Appendix 40). Given the dominance in cost and outcomes, no incremental analysis was calculated.

Abciximab: Abciximab was more expensive than the stent by itself (+$1,171), but led to more unadjusted life-years (+0.35) and adjusted life-years (+0.22) when compared with the stent (Appendix 41). An incremental ratio was calculated (Appendix 42).

d) Non-diabetic population
In the non-diabetic population, Appendices 43 and 44 show the results (average expected cost, MACE and death rate) for abciximab and eptifibatide at two time points (short term or 30 days and long term or survival).

Short-term analysis of non-diabetic patients
Eptifibatide: Eptifibatide was considered to be the dominant treatment in terms of costs. Eptifibatide had a lower cost (−$140) and lower rates of MACE (−6.4%) and mortality (−1%) when compared with the stent by itself (Appendix 43). Given the dominance, no incremental analysis was calculated.

Abciximab: There were no 30-day clinical outcome data available for the abciximab non-diabetic population.

Long-term analysis of non-diabetic patients

Eptifibatide: Eptifibatide had a lower cost (−$140) and led to a greater increase in unadjusted life-years (+0.15) and adjusted life-years (+0.07) when compared with the stent by itself (Appendix 44). Given the dominance in cost and outcomes, no incremental analysis was calculated.

Abciximab: Although there were one-year clinical data available, the "31 to 364 day" calculations could not be performed, because of the absence of 30-day clinical outcome data for the non-diabetic population.

e) Summary of results

The costs per node of each decision analytic model for each population are listed in Appendices 44b (overall), 44c (diabetic patients) and Appendix 44d (non-diabetic patients). Based on the weighted average of the four outcomes (no event, MI, revascularization and death) in the overall population, eptifibatide was the inexpensive choice compared to the stent by itself (savings of $59) while abciximab was more costly than placebo (loss of $1,171). In the diabetic population, both GP IIb/IIIa inhibitors were the less expensive choice over the stent by itself.

f) Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was done using Crystal Ball™ software. Probabilistic analysis, through Monte Carlo simulation, has been considered to be an appropriate form of analysis to address uncertainty with model inputs in the evaluation of health care interventions.[66] In a Monte Carlo simulation, different estimates of outcomes such as costs and life expectancies are obtained by re-running a decision model using different values for each data input.[67] Values for each data input are randomly selected from specified probability distributions. Based on several such replications, a set of outcomes can be obtained. No rule is used to determine the appropriate number of replications, as this is a function of the level of uncertainty for the outcomes of interest. The greater the number of replications conducted, the more precise the estimate of the outcomes. For this analysis, we adopted a simulation with 5,000 replications.

For the economic analysis of GP IIb/IIIa inhibitors, it is necessary to specify probability distributions for four sets of parameters: baseline short-term probabilities of clinical outcomes (MI, no event, revascularization, bleeding and death), the relative risk of short-term events specific to treatments, long-term annual mortality specific to disease history and costs (Appendix 45).

For transition probabilities, uncertainty is characterized by a beta distribution. Baseline short-term probabilities data were obtained by combining data from the stent-only arms of the clinical trials of abciximab and eptifibatide. For long-term mortality data, distributions were based on the available raw data. For relative risks, uncertainty was characterized by log normal distributions. For cost data, it was assumed that uncertainty could be characterized by a normal distribution. Given that data were based on clinical expert opinion, we followed previous studies by assuming a standard deviation equivalent to 50% of the mean and assumed a sample size of four (thus, the standard error is 25% of the mean).[68] Drug costs were assumed to be fixed.

The cost-effectiveness of treatment options are presented in terms of the incremental cost per life-year gained (ICER), which is the ratio of the mean incremental costs and incremental benefits.[69] The analysis was focused on individual comparison between treatment and no treatment. Cost-effectiveness is expressed as the expected value of net monetary benefit, which is a function of the maximum willingness to pay for a unit of outcome (λ).[70] For example, for a given level of λ, if the net benefit of a treatment is positive, the treatment is considered to be cost-effective.

In this analysis, the calculation of the net monetary benefit (NMB) of abciximab and eptifibatide was based on the assumption of a threshold value of a life-year of $50,000 with further analysis assuming a range from $20,000 to $100,000.[29]

Uncertainty about the cost-effectiveness of abciximab and eptifibatide was assessed through credible intervals and cost-effectiveness acceptability curves. Credible intervals are similar to confidence intervals and present the lower and upper limits of a 95% interval for outcomes. Cost-effectiveness acceptability curves report the probability that treatment is cost-effective as a function of willingness to pay given the available data.[71]

Appendix 46 reports the expected value of incremental costs and benefits and cost-effectiveness parameters for the comparison of abciximab and standard treatment without GP IIb/IIIa inhibitors as adjuncts and the comparison of eptifibatide and standard treatment without GP IIb/IIIa inhibitors for all patients. Appendix 47 reports the same for diabetic patients.

Abciximab is more costly but more effective than standard treatment. The ICER for the comparison with standard treatment was $6,000 for all patients and $2,000 for diabetics. For all patients, eptifibatide is less costly and more effective than standard treatment. For diabetic patients, eptifibatide is more costly and more effective with an ICER of $300.

The uncertainty about the incremental costs and effects of both therapies and about which therapy is most cost-effective cannot be addressed in this analysis, as the GP IIb/IIIa therapies were analyzed separately, because of the different study patient populations. There is limited uncertainty, however, over the cost-effectiveness of treatment (GP IIb/IIIa+stent+usual care) compared to standard treatment (stent+usual care).

The cost-effectiveness acceptability curves for all patients and diabetic patients show that for values of a life-year >$20,000, the probability that standard treatment is more cost-effective when compared to abciximab or eptifibatide is <20% (Appendices 48 and 49). For a value of a life-year of $50,000, the probability that abciximab is more cost-effective than standard treatment for all patients is 98.6%. For eptifibatide, the figure is 92.5%

.

4.2.3 Discussion

The costs associated with the use of GP IIb/IIIa inhibitors have been calculated in several studies. For abciximab, one cost analysis that was conducted from the European societal perspective presented six-month direct medical costs for stent only (EUR 8207), abciximab+stent (EUR 8971) and abciximab+angioplasty (EUR 8085).[72] Another analysis was for overall costs based on EPISTENT (US population only). The abciximab+stent patients had higher hospital costs (US $5,096) than the stent-only patients (US $4,723). These costs were less than those for

the angioplasty+stent patients (US $6,013) in the initial period.[37] Results showed an incremental value of $6,213 per added life-year gained for the stent+abciximab group compared with the stent-only group. The initial costs from both studies[37,72] confirm the results of our analysis, which found that abciximab was more expensive than the stent by itself.

Cohen *et al.,* found that the estimated in-hospital costs in ESPRIT[45] (excluding drug costs) were $185 lower per patient for the eptifibatide group compared with the stent-only group ($10,412). Abciximab, which has a higher acquisition cost than eptifibatide, has been associated with a higher cost than eptifibatide during hospitalization (US$8,268 versus US$7,207) and at six months in lower risk patients.[32]

In a review article, Hillegass *et al.*[73] examined the clinical results from many trials investigating patients with PCI and non-ST-segment ACS. They reported ICERs of between US$2,800 to US$14,000.

Our adjusted incremental value of $16,729 per life-year gained for abciximab in the stented population ranks comparably with the accepted benchmarks of other therapeutics.[74] Incremental analyses were not conducted for eptifibatide in the total stented population and for both drugs in the diabetic populations, as they were dominant in cost and outcome.

The results of our study were based on trials that excluded the "emergent" patients (those at the highest risk undergoing immediate PCI for primary treatment of acute ST-segment elevation MI). The population included was low or moderate risk when measured against the full spectrum of risk. Consequently, our results may not be representative of those for high risk patients. The results, however, apply to most patients undergoing PCI, as ST-segment elevation MI is an infrequent indication for PCI in most practice settings.

Restenosis rates are high in cases with complex lesions, especially small vessels and long lesions.[75] The trials evaluated in our analysis excluded patients with lesions that were considered to be unsuitable for stenting. Based on the stents available when the trials were performed, this would have had the effect of excluding some patients with long lesions or small vessels and limiting the generalizability to this subgroup of patients.[76-79]

Our study focused on direct medical costs only. The decision to exclude indirect costs was based on the perspective of the analysis and the fact that employment status was not significantly affected by a different revascularization.[80]

The effect of GP IIb/IIIa inhibitors on the length of hospital stay has been investigated.[81] Results from a database of 72 US hospitals with patients undergoing PCI revealed that abciximab patients stayed in hospital 0.83 fewer days than eptifibatide patients ($p<0.001$). Closer examination, however, showed that eptifibatide patients were significantly older than those in the abciximab group and the eptifibatide-treated patients received angioplasty more than stents compared with abciximab patients.

Clinical data specific to diabetic patients were available for abciximab and eptifibatide. Approximately 20% of the two populations were diabetic patients, but only the ESPRIT study collected 30-day and one-year outcome data for non-diabetic patients. A comparison of results to one year between the diabetic and non-diabetic populations treated with eptifibatide revealed that death and MI outcomes were similar, whereas revascularization was required in 16% of diabetic patients versus 10% in non-diabetic patients.

This study does not directly compare abciximab and eptifibatide. In principle, one could combine the control arms in ESPRIT for eptifibatide and EPISTENT for abciximab, to obtain the base rates of MI, death, revascularization and bleeding for the stent-alone option. A decision model could then be run with three arms: pooled stent-alone, eptifibatide and abciximab. This approach requires that patient groups in the trials be comparable. Dr. Eric Cohen was on the steering committee for both trials. Although the two trials excluded emergent patients, EPISTENT included elective (scheduled) and urgent (recent or ongoing chest pain) percutaneous coronary revascularization patients, while ESPRIT included only elective patients without ongoing refractory symptoms. Appendix 11 outlines the differences between the two trials. As the patient populations were different and separate analyses were required, the overall results were not compared between abciximab and eptifibatide.

Dr. Cohen explained that ESPRIT was begun after EPISTENT, which had already shown the apparent benefit of abciximab in stented patients. EPISTENT included a full spectrum of risk, although the highest risk (acute MI and cardiogenic shock) was excluded. It was thought that it was unethical to do ESPRIT given the findings of EPISTENT. Because of cost issues, however, most centres were limiting their use of abciximab to higher than average risk patients. As a result, it would be ethical to enrol average and below average risk patients into ESPRIT. Therefore, the overall risk profile in ESPRIT is lower than that of EPISTENT, because the highest risk patients were kept out of the trial (this is apparent in the baseline characteristics for both trials). In Dr. Cohen's practice and at other centres, abciximab is used for higher risk patients and eptifibatide for average and lower risk patients. The authors interpret "higher risk" to mean primarily acute MI and diabetic patients (EC, unpublished observations, 2003).

Although patients with acute MI were excluded from our study, many studies have found GP IIb/IIIa inhibitors plus stents to be effective in this indication. In the Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial[82] and Stent versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction (STOPAMI) trial,[83] the outcomes of abciximab with or without stenting in patients with acute MI of <48 hour duration were evaluated. Results showed that abciximab+stenting was more effective than stenting alone.

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study[84] was a randomized non-blind multicentre trial of 2,082 patients with acute MI who underwent PTCA alone (n=518), PTCA plus abciximab (n=528), stenting alone (n=512) or stenting plus abciximab (n=524). At six months, the primary end point (composite of death, reinfarction, disabling stroke and ischemia-driven revascularization of the target vessel) had occurred in 20.0% of patients after PTCA, 16.5% after PTCA plus abciximab, 11.5% after stenting and 10.2% after stenting plus abciximab ($p<0.001$).[84]

Limitations of economic evaluation

- The economic model excludes the long-term costs associated with the management of patients. Including these costs would lead to a less favourable ICER for treatment. Most resource use estimates for the model come from expert opinion. Ideally, an economic evaluation should be done prospectively with complete capture of actual resource utilization and clinical outcomes in the practice setting over a long period of follow-up. This is sometimes impossible.
- Models are typically populated with outcomes that are based on controlled clinical trial study designs. These data cannot necessarily be extrapolated to real practice.
- This study did not try to directly compare abciximab and eptifibatide, as the study patient populations and some study design characteristics were found to be different (Appendix 11). There have been no head-to-head clinical trials of abciximab and eptifibatide.
- Costs used in this analysis were based on Ontario costs and may vary in other provinces. Some costs used in this analysis were based on those of the SWCHSC and may vary in other hospitals.
- The authors were unable to determine the effect of differential hospital days on the overall economic analysis, because the hospital cost obtained was based on an aggregate hospital cost and was not calculated on a disaggregated level.
- Serious morbidity is limited to cardiac event rates. Stroke incidence, for example, was documented inconsistently in the relevant clinical trials. The rates for stroke were low and would not have had a cost impact on the analysis (Appendices 50a, 50b, 50c). Brown[85] examined 450 reports of death related to treatment with GP IIb/IIIa inhibitors that were submitted to the FDA between November 1, 1997 and December 31, 2000 (Appendix 51). These were reviewed and a standard rating system for assessing causation was applied to each event. All the deaths deemed to be definitely or probably related to GP IIb/IIIa inhibitor treatment were associated with excessive bleeding. These findings suggest that patients treated in normal clinical practice may be at greater risk than those treated in clinical trials. Thus, judicious use of these agents is appropriate. A prospective follow-up to monitor adverse events in this patient population is encouraged.

5 CONCLUSIONS

This review of economic evidence supports the need for an up-to-date economic evaluation of GP IIb/IIIa inhibitors in a Canadian context. The economic evaluation in this study suggests that eptifibatide and abciximab can be considered to be cost-effective adjuncts for the control of complications in patients undergoing elective and urgent PCI. The incremental cost-effectiveness analysis for abciximab in the general study population showed a higher overall cost and better outcomes, with a result consistent with what is generally considered to be cost-effective. For eptifibatide in the general study population and for both drugs in the diabetic subgroup, the analysis showed lower costs and better outcomes versus usual care. We caution against a direct comparison of eptifibatide and abciximab based on the available data.

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APPENDIX 1a: Literature Search: Economic Systematic Review

Legend:	
!	Explode the search term.
?	Truncation symbol, one character.
*	Truncation symbol, any number of characters.
()	Proximity operator. Words must be adjacent.
N	Terms are near each other, in any order
#N	Terms are near each other, specified number of words.
Next	Proximity operator. Words must be adjacent.
ti	Search in record title.
ab	Search in record abstract.
de	Descriptor i.e subject heading
ME	Medical subject heading.
MeSH	Medical subject heading.
RN	Registry number

Databases

DIALOG®

MEDLINE®
(1966-2003/Jan W3)
EMBASE®
(1974-2003/Jan W3)
BIOSIS Previews®
(1969-2003/Jan W3)
PASCAL
(1973-2003/Jan W3)

DIALOG® Alerts:
MEDLINE®
EMBASE®
BIOSIS Previews®

Search and updates on PubMed and
the Cochrane Library (CD-ROM, 2003, 2004)

Web sites of HTA and related agencies, trial registers and other databases were searched for grey literature.

For eg: NICE, AHRQ; University of York NHS Centre for Reviews and Dissemination – CRD database; LILACS; National Research Register; CMA Infobase;

One Search on DIALOG® System

1. platelet glycoprotein gpiib-iiia complex/de
   [MEDLINE]
2. glycoprotein iib/de OR glycoprotein iiia/de
   [EMBASE]
3. abiciximab/de or eptifibatide/de or tirofiban/ de
   [BIOSIS, EMBASE]
4. abciximab/ti,ab or reopro/ti,ab or eptifibatide/ti,ab or integrilin/ti,ab or
5. intigrilin/ti,ab or integrilin/ti,ab
6. (gp? or glycoprotein?)()(iib or 2b))/ti,ab
7. gpiib/ti,ab or gp2b/ti,ab or glycoproteiniib/ti,ab or glycoprotein2b/ti,ab
8. RN=143653-53-6 or RN=144494-65-5 or RN=188627-80-7
9. s1:s8
10. angina pectoris!/de or exp myocardial ischemia!/ or angina, unstable/ or coronary disease!/ or myocardial infarction!/de or coronary restenosis/de
    [MEDLINE]
11. angina pectoris!/ or heart infarction!/de or heart muscle ischemia/de or restenosis/de or coronary artery disease!/de
    [EMBASE]
12. myocardial ischemia!/de or heart attack/de or heart failure/de
13. angina pectoris!/de or myocardial infarction/de or stable angina/de or stable angina pectoris/de or unstable angina/de or unstable angina pectoris/de or coronary disease!/de or restenosis/de
    [BIOSIS]
14. unstable()angina/ti,ab or stable()angina/ti,ab or heart()infarction?/ti,ab or coronary()disease?/ti,ab or coronary()syndrome?/ti,ab or restenosis/ti,ab
15. angioplasty, transluminal, percutaneous coronary!/de or catheter, ablation/de or angioplasty, balloon!/de

16. stents/de and coronary/ti,ab [MEDLINE]
17. percutaneous transluminal angioplasty/de or transluminal coronary angioplasty/de or coronary stent/de or artery catheterization/de or heart muscle revascularization/de or coronary artery recanalization/de [EMBASE]
18. percutaneous transluminal coronary angioplasty/ or coronary stenting/ or coronary stent/ [BIOSIS Previews]
19. pci/ti,ab or percutaneous()coronary() intervention?/ti,ab
20. balloon()angioplast?/ti,ab
21. PTCA/ti,ab
22. ((coronary or heart or balloon or percutaneous) (2N) (angioplast? or stent? or intervention? or revascularization? or recanalization?))/ti,ab
23. ((atherectomy, coronary!/de or coronary(1n)atherectom?) and (directional or rotational or extraction?))/ti,ab
24. catheter()ablation?/ti,ab
25. s10:s24
26. economics!/ or quality of life/de or quality-adjusted life years/de or costs-and-cost analysis!/de or or health economics/ or budgets/ or economics, medical/ or economics, pharmaceutical/ or economics, hospital/ [MEDLINE]
27. cost-effectiveness analysis/de or cost minimization analysis/de or cost-benefit analysis/de or cost utility analysis/de or economic- evaluation/de or health care cost/de or quality adjusted life year/de [EMBASE]
28. economics/de or economic factors/de or economic impact/de or economic value/de or cost/de or cost analysis/de or cost effectiveness/de or cost savings/de or costs/de or quality of life/de or health care cost/de or pharmacoeconomics/de [BIOSIS]
29. economic?/ti,ab or cost?/ti,ab or price?/ti,ab or pricing/ti,ab or expenditure?/ti,ab or budget?/ti,ab or QOL/ti,ab or qaly/ti,ab or quality()adjusted life()year?/ti,ab or cost(2N)effect?/ti,ab or cost (2N) benefit?/ti,ab or cost(2N) utilit?/ti,ab or pharmacoeconomic?/ti,ab
30. willingness(2N) pay/ti,ab or value (3N) life/ti,ab
31. s26:s30
32. s9 and s25 and s31
33. human? or people or person?
34. s32 and s33
35. RD s34

Total Hits 504 unique records
MEDLINE 159 records
EMBASE 276 records
BIOSIS Previews 64 records
PASCAL 5 records

Search performed on January 27, 2003. Regular alerts set up using same subject headings (except in EMBASE alerts).

The Cochrane Library (CD-ROM)

The numerical drug qualifiers were not used for the Cochrane search as they are ignored by the software used by the Cochrane Library.

1 Platelet Glycoprotein GPIIB-IIIA Complex single term (MeSH)
2 (abciximab or integrilin or integrelin or tirofiban or aggrastat or glycoprotein*)
3 (gpiib or glycoproteiniib* or gp2b* or glycoprotein2b*)
4 (glycoprotein next iib*) or (gp next iib*)
5 (#1 or #2 or #3 or #4)
6 MYOCARDIAL ISCHEMIA explode tree 1 (MeSH)
7 ANGINA UNSTABLE explode tree 1 (MeSH)
8 CORONARY DISEASE explode tree 1 (MeSH)
9 (myocardi* next infarct*)
10 (heart next attack*)
11 ((coronary next disease*) or (coronary next syndrome*))
12 (unstable next angina)
13 (#6 or #7 or #8 or #9 or #10 or #11 or #11 or #12)
14 (#5 and #13)
15 ATHERECTOMY CORONARY single term (MeSH)
16 CATHETER ABLATION single term (MeSH)
17 ANGIOPLASTY TRANSLUMINAL PERCUTANEOUS CORONARY single term (MeSH)

18 MYOCARDIAL REVASCULARIZATION explode tree 2 (MeSH)
19 STENTS single term (MeSH) and coronary
20 (((percutaneous next coronary next intervention*) or (percutaneous next transluminal next coronary next angioplasty) or ptca or pci or (balloon next angioplast*))
21 (#15 or #16 or #17 or #18 or #19 or #20)
22 # 13 and #21
23 #5 and #22

HEED:Health Economic Evaluations Database, 2003, 2004

Same keywords as the original DIALOG® search
78 records

PubMed

PubMed updates were performed periodically to retrieve pre-Medline and additional references.

APPENDIX 1b: Literature Search: Clinical Systematic Review

Legend:

exp	Explode the search term. Retrieve the search .
?	Truncation symbol, one character.
$	Truncation symbol, any number of characters.
adj	Proximity operator. Words must be adjacent. Terms are near each other, in any order
adj#	Terms are near each other,specified number of words.
tw	Textwords
/	Descriptor i.e subject heading
ME	Medical subject heading.
MeSH	Medical subject heading.
rn	Registry number
mp	Search in major headings including title, keywords, subject headings, abstract, heading word, registry number

Databases

Ovid Technologies, Inc:
MEDLINE®
EMBASE®
BIOSIS Previews®
Current Contents®
HealthSTAR®

DIALOG® Alerts:

MEDLINE®
EMBASE®
BIOSIS Previews®

Search and updates on PubMed and the Cochrane Library (CD-ROM, 2001-2004, Issue 1)

Web sites of HTA and related agencies, trial registers and other databases were searched for grey literature.

For e.g.: NICE, AHRQ; University of York NHS Centre for Reviews and Dissemination – CRD database; LILACS; National Research Register; CMA Infobase;

Multiple-file Search on OVID Technologies

1. exp platelet glycoprotein gpiib-iiia complex/ [MEDLINE]
2. exp glycoprotein iib/ OR glycoprotein iiia/ [EMBASE]
3. abiciximab/ or eptifibatide/ or tirofiban/ [BIOSIS, EMBASE]
4. (abciximab or reopro).mp.
5. (eptifibatide or integrilin or intigrilin).mp.
6. (gpiib$ or gp2b$ or glycoproteiniib$ or glycoprotein2b$).mp.
7. 143653-53-6.rn. or 144494-65-5.rn. or 188627-80-7.rn.
8. (tirofiban or abciximab or eptifibatide or reopro or aggrastat or integrelin or integrilin).tw,mp.
9. ((gp or glycoprotein) adj iib).mp.
10. or/1-9
11. exp myocardial ischemia/ or angina, unstable/ or exp coronary disease/ or myocardial infarction/ [MEDLINE]
12. unstable angina pectoris/ or exp heart infarction/ or exp heart muscle ischemia/ or restenosis/ or exp coronary artery disease/ [EMBASE]
13. exp myocardial ischemia/ or heart attack/ or heart failure/
14. coronary atherosclerosis/ or coronary restenosis/ or unstable angina/ or unstable angina pectoris/ [BIOSIS]
15. unstable angina.mp, tw.or restenosis.mp or heart adj3 attack$.mp,tw or coronary disease$.mp,tw. or myocardial infarct$
16. or/11-15
17. exp angioplasty, transluminal, percutaneous coronary/
18. exp stents/ and coronary.mp. [MEDLINE]
19. percutaneous transluminal angioplasty/ or coronary stent/ [EMBASE]

20. percutaneous transluminal coronary angioplasty/ or coronary stenting/ or coronary stent/ [BIOSIS]
21. ((pci or percutaneous adj coronary adj intervention$).mp, tw.
22. ((balloon adj angioplast$).mp, tw.
23. PTCA.mp.
24. percutaneous transluminal coronary angioplast$.mp,tw.
25. exp atherectomy, coronary/ [MEDLINE]
26. (coronary adj atherectomy).mp,tw.
27. (directional or rotational or extraction).mp, tw.
28. ((24 or 25) and 26)
29. (transluminal adj extraction atherectomy).mp.
30. (transluminal adj extraction adj catheter$).mp.
31. or/19-23, 27-30
32. 16 and 31
33. 32 and 10
34. exp meta analysis/ or exp clinical trial/ or placebo/ major clinical study/ or exp controlled study/ or crossover procedure/ or exp comparative study/ or exp evidence based medicine/ [EMBASE]
35. meta-analysis/ or clinical trial/ or placebo/ or randomized clinical trial/ or randomized controlled trial/ or comparative study/ or evidence-based medicine/ [BIOSIS]
36. exp clinical trials/ or meta analysis/ or comparative study/ or evidence based medicine/ or cross-over studies/ or meta-analysis.pt. or controlled clinical trial.pt.or randomized controlled trial.pt. or exp epidemiologic research design/ [MEDLINE]
37. (meta analysis or metaanal$ or meta analy$).mp.tw.
38. crossover$.mp,tw. or cross-over$.mp,tw.
39. controlled clinical trial$.tw,mp.
40. (research adj2(integrati$ or overview)).tw,mp.
41. (quantitative adj2 (review$ or overview$ or synthes?s)).tw,mp.
42. ((methodologic or systematic or collaborative) adj2 (review$ or overview$)).tw,mp.
43. (multicent$ adj stud$).tw,mp.
44. (multicent$ adj trial$).tw,mp.
45. comparative adj stud$.tw,mp.
46. ((singl$ or doubl$ or treble$ or tripl$) adj5 (blind$ or mask$ or dumm$)
47. (placebo$ or prospectiv$ or random$ or rct$).mp,tw.
48. or/34-47
49. 33 and 48
50. human$ or people or person$.tw.mp
51. 49 and 50
52. remove duplicates from 51

Total hits 781 records
MEDLINE 126 records
EMBASE 644 records
BIOSIS Previews 6 records
HealthSTAR 3 records
Current Contents 2 records

Search performed 14 November 2001..

DIALOG® Alerts

Bi-weekly alerts were set up for MEDLINE® EMBASE®, BIOSIS Previews® on the DIALOG® system.

1. Platelet glycoprotein gpiib-iiia complex/de or glycoprotein iib/ or glycoprotein iiia/ [MEDLINE, EMBASE]
2. abiciximab/de or eptifibatide/de or tirofiban/ de [BIOSIS, EMBASE]
3. RN=143653-53-6 OR RN=144494-65-5 OR RN=188627-80-7
4. abciximab/ti,ab or reopro/ti,ab or aggrastat/ti,ab or integrelin/ti,ab or integrilin/ti,ab
5. gpiib?/ti,ab or gp2b? or glycoproteiniib? or glycoprotein2b?
6. tirofiban/ti,ab or aggrastat/ti,ab or eptifibatide/ti,ab
7. gp(1n)iib? or glycoprotein(1n)iib? or gp(1n)2b? or glycoprotein(1n)2b?
8. S1:S7 *(adds sets together)*
9. angina, unstable/de or coronary disease!/de or myocardial infarction!/de

[MEDLINE]
10. myocardial ischemia!/de or heart attack/de or heart failure/de or coronary restenosis/de or unstable angina/de or unstable angina pectoris/de [BIOSIS]
11. coronary()restenosis/ti,ab or unstable()angina/ti,ab
12. S9:S11 *(adds sets together)*
13. angioplasty, transluminal, percutaneous coronary/de [MEDLINE]
14. percutaneous transluminal coronary angioplasty/de or coronary stenting/de or coronary stent/de or percutaneous transluminal angioplasty/de [BIOSIS]
15. pci/ti,ab or coronary()intervention? or coronary()angioplast?
16. atherectomy, coronary!/de
17. transluminal()extraction()atherectom?/ti,ab
18. transluminal()extraction()catheter?/ti,ab
19. stents!/de and coronary
20. s13:s19 *(adds sets together*)
21. meta-analysis/de or clinical trial!/de or placebo/de or randomized clinical trial/de or comparative study/de or randomized controlled trial/de or evidence-based medicine/de [BIOSIS]
22. clinical trials!/de or evidence based medicine/de or epidemiologic research design!/de or dt=meta-analysis or dt=controlled clinical trial or dt=randomized controlled trial [MEDLINE]
23. meta(1n)analy? or metaanaly? or meta()analy?
24. crossover? or cross-over?
25. ((singl? or doub? or trebl? or tripl?)(5n)(blind? or mask? or dumm?))
26. placebo? or prospectiv? or random? or rct?
27. s21:s26 *(adds sets together)*
28. human? or people? or person?
29. s8 and s12 and s20 and s27 and s28

The Cochrane Library (CD-ROM)

The numerical drug qualifiers were not used for the Cochrane search as they are ignored by the software used by the Cochrane Library. Clinical trial filter excluded from the search.

1. Platelet Glycoprotein GPIIB-IIIA Complex:ME
2. (abciximab or integrilin or integrelin or tirofiban or aggrastat or glycoprotein*)
3. (gpiib or glycoproteiniib*)
4. (glycoprotein next iib*) or (gp next iib*)
5. (#1 or #2 or #3 or #4)
6. MYOCARDIAL ISCHEMIA explode tree 1 (MeSH)
7. ANGINA UNSTABLE explode tree 1 (MeSH)
8. (myocardi* next infarct*)
9. (heart next attack*)
10. ((coronary next disease*) or (coronary next syndrome*))
11. (unstable next angina)
12. (#6 or #7 or #8 or #9 or #10 or #11 or #11)
13. (#5 and #12)
14. ATHERECTOMY CORONARY single term (MeSH)
15. CATHETER ABLATION single term (MeSH)
16. ANGIOPLASTY TRANSLUMINAL PERCUTANEOUS CORONARY single term (MeSH)
17. MYOCARDIAL REVASCULARIZATION explode tree 2 (MeSH)
18. STENTS single term (MeSH) and coronary
19. (((percutaneous next coronary next intervention*) or (percutaneous next transluminal next coronary next angioplasty) or ptca or pci or (balloon next angioplast*))
20. (#15 or #16 or #17 or #18 or #19)
21. # 13 and #20

PubMed

PubMed updates were performed periodically using same MeSH headings and keywords as MEDLINE® to retrieve pre-Medline and additional references

APPENDIX 1c: HOPE Research Centre Search Strategy

Limits:	English only, humans only
Publication type:	randomized controlled trials
Publication years:	1993 to 2004
Age group:	adults
Text words:	abciximab (ReoPro®) eptifibatide (Integrilin®) tirofiban (Aggrastat®) glycoprotein IIb/IIIa inhibitors percutaneous coronary intervention (PCI) stenting
Databases:	BIOSIS Previews Current Contents EMBASE MEDLINE University of York Center for Reviews and Dissemination

APPENDIX 2: BMJ Checklist for Quality Assessment

Item		Yes	No
Study design			
1	Research question is stated		
2	Economic importance of research question is stated		
3	Viewpoint(s) of analysis is clearly stated and justified		
4	Rationale for choosing alternative programs or interventions compared is stated		
5	Alternatives being compared are clearly described		
6	Form of economic evaluation used is stated		
7	Choice of economic evaluation is justified in relation to questions addressed		
Data collection			
8	Source(s) of effectiveness estimates used is stated		
9	Details of design and results of effectiveness study are given (if based on one study)		
10	Details of method of synthesis or meta-analysis of estimates are given (if based on overview of effectiveness studies)		
11	Primary outcome measure(s) for economic evaluation is stated		
12	Methods to value health states and other benefits are stated		
13	Details of subjects from whom evaluations were obtained are given		
14	Productivity changes (if included) are reported separately		
15	Relevance of productivity changes to study question is discussed		
16	Quantities of resources are reported separately from unit costs		
17	Methods for estimation of quantities and unit costs are described		
18	Currency and price data are recorded		
19	Details of price adjustments for inflation or currency conversion are given		
20	Details of any model used are given		
21	Choice of model used and key parameters on which it is based are justified		
Analysis and interpretation of results			
22	Time horizon of costs and benefits is stated		
23	Discount rate(s) is stated		
24	Choice of rate(s) is justified		
25	Explanation is given if costs or benefits are not discounted		
26	Statistical tests and confidence intervals are given for stochastic data		
27	Approach to sensitivity analysis is given		
28	Choice of variables for sensitivity analysis is justified		
29	Ranges over which variables are varied are stated		
30	Relevant alternatives are compared		
31	Incremental analysis is reported		
32	Major outcomes are presented in disaggregated and aggregated forms		
33	Answer to study question is given		
34	Conclusions follow from data reported		
35	Conclusions are accompanied by appropriate caveats		

APPENDIX 3: Quality Assessment Results

	Zed	Newman	Kreatsoulas	Brown	Palmer
Study design					
Research question is stated	Y	N	Y	Y	Y
Economic importance of research question is stated	Y	N	Y	Y	Y
Viewpoint of analysis is stated and justified	Y	N	Y	Y	Y
Rationale for choosing alternative programs or interventions compared is stated	N	N	N*	N*	Y
Alternatives being compared are described	N	N	N*	N*	Y
Form of economic evaluation used is stated	Y	Y	N	Y	N
Choice of form of economic evaluation is justified in relation to questions addressed	N	N	N	Y	N
Data collection					
Source of effectiveness estimates is stated	Y	Y	Y	Y	Y
Details of design and results of effectiveness study are given (if based on one study)	N/A	N/A	N	Y	N/A
Details of method of synthesis or meta-analysis of estimates are given (if based on overview of effectiveness studies)	N/C	N	N/A	N/A	N#
Primary outcome measure for economic evaluation is stated	Y	Y	Y	Y	Y
Methods to value health states and other benefits are stated	Y	Y	N	Y	Y
Details of subjects from whom valuations were obtained are given	Y	N	N	Y	Y
Productivity changes (if included) are reported separately	N/A	N	N/A	N/A	N/A
Relevance of productivity changes to study question is discussed	N/A	N	N/A	N/A	N/A
Quantities of resources are reported separately from unit costs	N	N	N	Y	N
Methods for estimation of quantities and unit costs are described	Y	N	N	Y	Y
Currency and price data are recorded	Y	N	Y	Y	Y
Details of price adjustments for inflation or currency conversion are given	Y	N	N	Y	Y
Details of any model used are given	Y	N	N/A	Y	Y
Choice of model used and key parameters on which it is based are justified	Y	N	N/A	Y	Y
Analysis and interpretation of results					
Time horizon of costs and benefits is stated	Y	N	N	Y	Y
Discount rate is stated	N/A	N	N	Y	Y
Choice of rate is justified	N/A	N	N	Y	Y
Explanation is given if costs or benefits are not discounted	Y	N	N	N/A	N/A

	Zed	Newman	Kreatsoulas	Brown	Palmer
Details of statistical test and confidence intervals are given for stochastic data	N	N	N	Y	Y
Approach to sensitivity analysis is given	Y	N	N	N	N
Choice of variables for sensitivity analysis is justified	Y	N	N	Y	Y
Ranges over which variables are varied are stated	Y	N	N	Y	Y
Relevant alternatives are compared	N[$]	N	N	Y	Y
Incremental analysis is reported	Y	Y	Y	Y	Y
Major outcomes are presented in disaggregated and aggregated forms	Y	Y	N	Y	Y
Answer to study question is given	Y	N	N	Y	Y
Conclusions follow from data reported	Y	Y	Y	Y	Y
Conclusions are accompanied by appropriate caveats	Y	N/C	N/C	Y	Y
Sum of N and N/C	7	27	22	3	5

Y=yes, authors dealt with issue, N=no, they did not, N/C=not clear, N/A=issue was not applicable to the particular submission, *economic evaluation was done in parallel with an RCT (trial protocol and clinical results published in another article), [$]author cannot find similar economic evaluations to compare with this study, #method of data synthesis is stated in accompanying systematic review.

Brown *et al.*[23] was a cost-effectiveness analysis alongside an RCT. Five of seven answers in the study design group were scored "yes" for this study. The research question and economic importance of the research question and the viewpoint of the analysis were stated. Similar to Bakhai *et al*., the comparator was not described in detail and the reason for the choice of comparator was not stated. The details of the RCT were published in another article. This study met all the criteria for data collection. The details of the design, results and source of effectiveness in the RCT were given. The method and source of primary outcome and valuation of effectiveness were addressed in the study. The study also satisfied the criteria in the costing and modeling section. Twelve of 13 answers in the analysis and interpretation group were scored "yes." The study considered the adjustments for timing of costs and benefits. The discounting and sensitivity analysis was also analyzed for uncertainty, but the name of the approach for sensitivity analysis was not stated.

Zed *et al.*[26] was a cost-effectiveness analysis using a decision analytic model. Four of seven items in the study design were scored "yes" for this study. The research question, the economic importance of the research question and the viewpoint of the analysis were stated. The comparators of the three RCTs included in the model were stated. The rationale for choosing the comparator and details of the comparator, however, were not addressed. This study met nine of the 11 criteria in the data collection section. There was a failure to report the quantities of resources separately from their unit costs and to describe the method of synthesis. Ten of 12 answers in the analysis and interpretation of results group were scored "yes." The study considered the adjustments for the timing of costs and benefits. The discounting and sensitivity analysis were also analyzed for the uncertainty, but the confidence intervals were not provided for stochastic data. The study did not compare the result of study to other studies with similar end points, because no similar Canadian economic evaluations were found.

In Palmer *et al.*,[27] the NICE cost-effectiveness model was a cost-utility analysis using decision analytic modelling. Five of seven answers in the study design group were scored "yes." The study stated the research question, the economic importance of the research question and the viewpoint of the analysis. The comparator was described and the rationale for its choice was stated. It was stated that QALYs were the outcome measure in this study, but the form of economic evaluation was not stated. The reason for choosing this form of economic evaluation was not addressed. Nine of 11 answers in the data collection group were scored "yes." The source of the effectiveness measures and costs used were stated. The benefit measurement and valuation were addressed in detail. The details of the method of meta-analysis of estimates were not given, but the data synthesis was done in an accompanying clinical systematic review. Regarding the cost, the quantities of resources were not reported separately from the unit costs. The unit costs came from other trials conducted in the UK. The date of the currency and price was stated. Details of the models used were addressed. Twelve of 13 answers in the analysis and interpretation of results group were scored "yes." The study considered the adjustments for the timing of costs and benefits. Many factors were considered in the sensitivity analysis, but the approach to sensitivity analysis was not given in the study. Relevant alternatives were compared.

Kreatsoulas *et al.*[24] was an abstract for a cost-effectiveness analysis alongside an RCT.
Four of seven answers in the study design group were scored "yes." The abstract satisfied the three criteria regarding the study question. Details about alternatives were excluded, but the clinical effectiveness of this economic evaluation came from EPISTENT. The form of economic evaluation used was not stated. The ICER was reported in the study, but the method of analysis is described as a cost-benefit analysis. Regarding the data collection, the abstract met three of nine criteria. It stated the source of effectiveness estimates used, the primary outcome measures for the economic evaluation and the currency date. Details of the study, details for benefit measurement and valuation and costing, however, were not provided in the abstract. Two of 11 answers in the group were scored "yes." The abstract only reported the ICER and the conclusion. Sensitivity analysis was done in the study, but the approach and details were not provided. This abstract did not state the adjustments for timing of costs and benefits, the discounting or confidence intervals for stochastic data. It did not compare the results to those of other studies or provide an assessment of the cost-effectiveness of abciximab with PCI use.

Newman *et al.*[25] was an abstract for a cost-effectiveness analysis using a decision analytic model. One of seven answers in the study design section was scored "yes." The form of economic evaluation used was stated, but the reason for the choice was not. The research question, economic importance of the research question and viewpoint were not stated. There was no description of comparators or choice of comparators. Regarding the data collection, the abstract met three of 13 criteria. It stated the source of effectiveness estimates used, the primary outcome measure for the economic evaluation, and addressed the methods to value health states and other benefits. Other details on the data collection were not stated. Three of 11 answers in the group were scored "yes." The abstract provided the disaggregated and aggregated forms of major outcomes and the result of the incremental analysis. The study, however, did not state the adjustments for the timing of costs and benefits. Methods for describing uncertainty, like sensitivity analysis and confidence intervals for stochastic data were not addressed. The study did not compare its results to other studies with similar end points, so it was difficult to determine if the conclusions were appropriate or not. The research question was not stated.

APPENDIX 4: ESPRIT Results for 48 Hours, 30 Days and One Year

	Eptifibatide (n=1,040)	**Stent only (n=1,024)**	**Significance**	**Sources**
30 days				
Death, MI, urgent revascularization (composite)	6.8% (n=71)	10.5% (n=106)	p=0.0030	figure 4, ESPRIT investigators[31]
Death, MI	6.4% (n=66)	10.2% (n=103)	p=0.0014	figure 4, ESPRIT investigators[31]
Death	0.4% (n=4)	0.6% (n=6)	N/A	table 2, O'Shea[42]
MI	6.2% (n=64)	9.7% (n=99)	N/A	table 2, O'Shea[42]
Large MI	2.9% (n=30)	4.3% (n=44)	N/A	calculated based on 48-hour findings
Target vessel revascularization	1.9% (n=20)	2.3% (n=24)	N/A	table 2, O'Shea[42]
1 year[43]				
Death, MI, TVR (composite)	17.5% (173/988)	22.1% (216/976)	p=0.007	figure 2B, text[43]
Death, MI	8.0% (79/988)	12.4% (121/976)	p=0.001	figure 2A, text[43]
Death	1.4% (14/988)	2% (20/976)	p=0.28	text (page 620)[43]
1 year[44]				
Death, MI, TVR (composite)	17.1% (178/1,039)	21.6% (221/1,022)	N/A	table 3
Death, MI	8.0% (83/1,039)	12.2% (125/1,022)	N/A	table 3
Death	1.3% (14/1,039)	2.0% (20/1,022)	N/A	table 3
MI	69/1,039	105/1,022	N/A	calculation (death, MI-death)
TVR	11.3% (117/1,039)	12.6% (129/1,022)	N/A	table 3

MI=myocardial infarction, TVR=target vessel revascularization, N/A=not applicable.

APPENDIX 5: ESPRIT Clinical Inputs

Eptifibatide	**PCI to 30 Days**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year**
Death	4/1,040	10/1,036	14/1,039
MI	64/1,040	5/1,036	69/1,039
Large MI	30/1,040	N/A	N/A
Revascularization (urgent at 30 days, target vessel at 1 year)	20/1,040	97/1,036	117/1,039
Major bleeding	13/1,040	N/A	N/A
Stent only	**PCI to 30 Days (n=1,024)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=1,022)**
Death	6/1,024	14/1,018	20/1,022
MI	99/1,024	6/1,018	105/1,022
Large MI	44/1,024	N/A	N/A
Revascularization (urgent at 30 days, target vessel at 1 year)	24/1,024	105/1,018	129/1,022
Major bleeding	4/1,024	N/A	N/A

MI=myocardial infarction, N/A=not applicable.

APPENDIX 6: EPISTENT Results for 30 Days and 1 Year

	Abciximab+Stent (n=794)	**Stent-only (n=809)**	**Significance**	**Sources**
30 days				
Death, MI, urgent revascularization (composite)	5.3% (n=42)	10.8% (n=87)	p<0.001	figure 2, EPISTENT[30]
Death	0.3% (n=2)	0.6% (n=5)	N/A	figure 3, EPISTENT[30]
MI	4.5% (n=36)	9.6 (n=78)	N/A	figure 3, EPISTENT[30]
Q-wave MI	0.9% (n=7)	1.4% (n=11)	N/A	figure 3, EPISTENT[30]
Urgent revascularization	1.3% (n=10)	2.1% (n=17)	N/A	figure 3, EPISTENT 1998[30]
Major bleeding	1.5% (n=12)	2.2% (n=18)	N/A	table 3, EPISTENT[30]
1 year				
Death, MI, any TVR (composite)	20.1% (n=160)	24.0% (n=194)	p=0.039	table 1, Topol[37]
Death	1.0% (n=8)	2.4% (n=19)	p=0.037	table 1, Topol[37]
MI (any)	5.9% (n=47)	11.3% (n=91)	p<0.001	table 1, Topol[37]
TVR (all)	15.2% (n=121)	15.6% (n=126)	p=0.805	table 1, Topol[37]

APPENDIX 7: EPISTENT Clinical Inputs

Abciximab	**PCI to 30 Days (n=794)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=794)**
Death	2/794	6/792	8/794
MI (any)	36/794	11/792	47/794
Q-wave MI	7/794	N/A	N/A
Revascularization (urgent at 30 days, target vessel at 1 year)	10/794	111/792	121/794
Major bleeding	12/794	N/A	N/A
Stent only	**PCI to 30 Days (n=809)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=809)**
Death	5/809	14/804	19/809
MI	78/809	13/804	91/809
Q-wave MI	11/809	N/A	N/A
Revascularization (urgent at 30 days, target vessel at 1 year)	17/809	109/804	126/809
Major bleeding	18/809	N/A	N/A

APPENDIX 8: ERASER Results for In-hospital and Six Months

	Abciximab (12 hours)+Stent (n=79)	**Abciximab (24 hours)+Stent (n=75)**	**Stent Only (n=71)**	**Sources**
In-hospital (48 hours)				
Composite (death, MI, TLR)	5.1% or 4/79	9.3% or 7/75	11.3% or 8/71	table 4, ERASER[33]
Death	0% or 0/79	0% or 0/75	0% or 0/71	table 4, ERASER[33]
MI (any)	5.1% or 4/79	9.3% or 7/75	11.3% or 8/71	table 4, ERASER[33]
TLR	0% or 0/71	0% or 0/71	1.4% or 1/71	table 4, ERASER[33]
Major bleed (TIMI)	3.8% or 3/79	1.3% or 1/75	1.4% or 1/71	table 4, ERASER[33]
6 months				
Composite (death, MI, TLR)	20.3% or 16/79	22.7% or 17/75	25.4% or 18/71	table 4, ERASER[33]
Death	0% or 0/79	0% or 0/75	2.8% or 2/71	table 4, ERASER[33]
MI (any)	7.6% or 6/79	9.3% or 7/75	12.7% or 9/71	table 4, ERASER[33]
TLR	13.9% or 11/71	13.3% or 10/71	15.5% or 11/71	table 4, ERASER[33]

APPENDIX 9: PRICE Results for In-hospital and 30 Days

	Abciximab (n=163)	**Eptifibatide (n=157)**	**p Value**
In-hospital			
Composite (death, non-fatal MI, urgent TVR)	4.9% (n=8)	5.1% (n=8)	0.84
Death	0.6% (n=1)	0% (n=0)	0.99
Non-fatal MI	3.7% (n=6)	4.4% (n=7)	0.96
Urgent repeat PCI	0.6% (n=1)	0% (n=0)	0.99
Serious bleeding	3.1% (n=5)	1.9% (n=3)	0.72
30 days			
Composite (death, non-fatal MI, urgent TVR)	5.6% (n=9)	10 (6.3%)	0.95
Death	0.6% (n=1)	0.6% (n=1)	0.99
Non-fatal MI	4.3% (n=7)	5.1% (n=8)	0.96
Urgent repeat PCI or CABG	1.2% (n=2)	1.3% (n=2)	0.99

APPENDIX 10: Tamburino Results for Major In-hospital and Six-month Follow-up Adverse Cardiac Events

	Abciximab+ Stent (n=54)	**Stent Only (n=53)**	**Significance**
Composite (death, MI, revascularization)	3.7% or 2/54	11.3% or 6/53	p=0.13
Death	0% or 0/54	1.8% or 1/53	N/A
MI (Q-wave and non Q-wave)	3.7% or 2/54	7.5% or 4/53	N/A
Acute stent thrombosis	0% or 0/54	1.8% or 1/53	N/A
Urgent revascularization	0% or 0/54	0% or 0/53	N/A
Composite (death, MI, revascularization)	11.1% or 6/54	24.5% or 13/52	N/A
Death	0% or 0/54	0% or 0/52	N/A
MI (Q-wave and non Q-wave)	0% or 0/54	3.8% or 2/52	N/A
Acute stent thrombosis	11.1% or 6/54	20.7% or 11/52	p=0.17
Target lesion revascularization	11.1% or 6/54	21.1% or 11/52	p=0.06

Source: Tamburino[34]

APPENDIX 11: Inclusion and Exclusion Criteria of ESPRIT and EPISTENT (plus pretreatment details)

ESPRIT[31]	EPISTENT [30]
Included if patients with coronary artery disease scheduled to undergo PCI with stent implantation in a native coronary artery and would not routinely be treated with GP IIb/IIIa inhibitor	Included if patients scheduled to undergo elective or urgent percutaneous coronary revascularization, if target lesions had caused stenosis of >60% amenable to balloon angioplasty or stenting and if target vessel was not an unprotected left main stem stenosis
Excluded if MI 24 hours before randomization; history of bleeding diathesis; evidence of abnormal bleeding, stroke or transient ischemic attack 30 days before randomization; history of hemorrhagic stroke; continuing chest pain leading to urgent referral for PCI; PCI within previous 90 days; previous stent implant at target lesion; major surgery within previous 6 months; uncontrolled hypertension (systolic BP >200 mm Hg, diastolic >110 mm Hg); thrombocytopenia (platelet count $<100x100^9$/L); serum creatinine >350 μmol/L; already treated with GP IIb/IIIa inhibitor or a thienopyridine 30 days before randomization; or anticipated staged PCI 30 days after randomization	Excluded if history of bleeding diathesis, intracranial neoplasm, history of stroke 2 years prior, uncontrolled hypertension (systolic BP >180 mm Hg, diastolic >100 mm Hg), no recent surgery, no PCI 3 months prior, on concurrent warfarin therapy and if INR >1.5 at baseline
All pretreated with Aspirin and a thienopyridine (ticlopidine or clopidogrel) with a loading dose on day of randomization.	All pretreated with 325 mg Aspirin orally >2 hours before intervention and daily thereafter; ticlopidine 250 mg bid started at discretion of investigator before start of study agent, if possible
Randomization done in catherization laboratory after coronary angiography confirmed plan to proceed to PCI	Randomization done after call received on telephone hotline
Heparin dosing not controlled by unblinded coordinator; for both groups, heparin bolus dose was 60 U/kg (maximum 6,000 U) followed by weight-adjusted regimen to target activated clotting time between 200 seconds to 300 seconds; after PCI, further heparin discouraged	In stent-only cohort, heparin bolus dose was 100 U/kg (maximum 10,000 U) with additional boluses to maintain activated clotting time of >300 seconds; in abciximab cohort, heparin bolus dose was 70 U/kg (maximum 7,000 U) with additional boluses to maintain activated clotting time of >200 seconds, recommendation that heparin be stopped immediately after PCI and vascular sheaths be removed when activated clotting time was <175 seconds (after about 4 hours)
Vascular access sheaths removed (with femoral arteriotomy closure device or external compression for hemostasis) within 3 to 4 hours of PCI	Potential bleeding complications avoided via early removal of sheaths, avoidance of routine placement of femoral venous sheath and compression of femoral access site for >30 minutes to achieve hemostasis
Any stent type with regulatory agency approval could be implanted	First choice was Palmaz-Schatz stent, but different designs could be used if this was unavailable
Eptifibatide given as 2 boluses (second given 10 minutes after first) followed by infusion for 18 to 24 hours or hospital discharge	Abciximab bolus given up to 60 minutes before intervention, followed by infusion every minute for 12 hours
Open-label bailout therapy available for emergency conditions [direct treatment of abrupt disclosure, no reflow, coronary thrombosis or other similar PCI combination; content of bailout kits depended on randomization pattern (two bonus vials of eptifibatide for patients randomized to receive no GP therapy or placebo bailout vials for patients randomized to receive eptifibatide)]	No bailout therapy

APPENDIX 12: Comparison of Stent-only Arms in ESPRIT and EPISTENT

	ESPRIT	**EPISTENT**
N	1,024 (50%)	809 (34%)
Mean age	median=62	59
Previous CABG	10%	11.1%
Previous MI	31%	38.6% (>7 days)
Previous PCI	24%	N/A
Stented	97%	96%
48-hour composite	9.3%	N/A
30-day composite	10.5%	10.08%
6-month composite	18.3%	12.1%
1-year composite	22.1%	24.0%

APPENDIX 13a: ESPRIT Results for Events in Diabetic Cohort

Diabetic Cohort (n=466)	**Eptifibatide+Stent (n=232)**	**Stent Only n=234)**	**Sources**
30 days			
Death, MI, urgent TVR	5.6% (n=13)	9.4% (n=22)	table 3, Labinaz[44]
Death, MI	5.6% (n=13)	9.0% (n=21)	table 3, Labinaz[44]
Death	0.4% (n=1)	0.9% (n=2)	table 3, Labinaz[44]
MI	n=13−1=12	n=21−2=19	calculation
TVR	n=13−13=0	n=22−21=1	calculation
1 year (94.4% clinical result availability, 98.3% mortality availability)			
Death, MI, TVR	20.8% (n=47)	28.2% (n=64)	table 3, Labinaz[44]
Death, MI	7.8% (n=18)	13.4% (n=31)	table 3, Labinaz[44]
Death	1.3% (n=3)	3.5% (n=8)	table 3, Labinaz[44]
MI	n=18−3=15	n=31−8=23	calculation
TVR	16.1% (n=36)	18.1% (n=40)	table 3, Labinaz[44]

APPENDIX 13b: ESPRIT Results for Events in Non-diabetic Cohort

Non-diabetic Cohort (n=1,585)	Eptifibatide+Stent (n=807)	Stent Only (n=788)	Sources
30 days			
Death, MI, urgent TVR	7.2% (n=58)	10.7% (n=84)	table 3, Labinaz[44]
Death, MI	6.6% (n=53)	10.4% (n=82)	table 3, Labinaz[44]
Death	0.4% (n=3)	0.5% (n=4)	table 3, Labinaz[44]
MI	n=53−3=50	n=82−4=78	calculation
TVR	n=58−53=5	n=84−82=2	calculation
1 year (95.6% clinical result availability, 98.5% mortality availability)			
Death, MI, TVR	16.6% (n=131)	20.2% (n=157)	table 3, Labinaz[44]
Death, MI	8.1% (n=65)	12.0% (n=94)	table 3, Labinaz[44]
Death	1.4% (n=11)	1.5% (n=12)	table 3, Labinaz[44]
MI	n=65−11=54	n=94−12=82	calculation
TVR	10.4% (n=81)	11.6% (n=89)	table 3, Labinaz[44]

APPENDIX 14a: EPISTENT Results for Events in Diabetic Cohort

Diabetic Cohort (n=335)	Abciximab+Stent (n=162)	Stent Only (n=173)	Sources
30 days (various sources)			
Composite (death, MI, urgent revascularization)	5.6% or 9/162	12.1% or 21/173	figure 5, EPISTENT[30]
Death, MI, urgent repeat revascularization	6.9% or 11/162	10.8% or 19/173	text, Lincoff AHJ[38]
Death, MI, TVR	6% or 10/162	13% or 22/173	interpolation of figure 1, Marso[41]
Death, MI	5% or 8/162	12% or 21/173	interpolation of figure 1, Marso[41]
Death	assumption 0.6% (n=1) (6 months: 0.6% or n=1)	assumption 1.7% (n=3) (6 months: 1.7% or n=3)	reference for 6 months data: Marso[41]
MI	assumption 4.4% (n=7) (6 months: 6.2% or n=10)	assumption 10.4% (n=18) (6 months: 11% or n=19)	reference for 6 months data: Marso[41]
TVR	1% or 2/162	4% or 7/173	interpolation of figure 1, Marso[41]
6 months			
Repeat TVR	8.1%	16.6%	figure 3, Lincoff[38]
1 year			
Death, MI, TVR	N/A	N/A	
Death, MI (large)	4.9% (n=8)	14.0% (n=24)	table 2, Topol[37]
Death	1.2% (n=2)	4.1% (n=7)	table 2, Topol[37]
MI (large)	4.3% (n=7)	11.1% (n=19)	table 2, Topol[37]
TVR	13.7% (n=22)	22.4% (n=39)	table 2, Topol[37]

APPENDIX 14b: EPISTENT Results for Events at 30 Days and One Year in Non-diabetic Cohort (n=1,268)

	Abciximab+Stent (n=632)	**Stent Only (n=636)**	**Sources**
30 days (various sources)			
Composite (death, MI, urgent revascularization)	5.2% or 33/632	10.5% or 67/636	figure 5, EPISTENT[30]
Death, MI, urgent repeat revascularization	N/A	N/A	N/A
Death, MI, TVR	N/A	N/A	N/A
Death, MI	N/A	N/A	N/A
Death	N/A	N/A	N/A
MI	N/A	N/A	N/A
TVR	N/A	N/A	N/A
6 months			
Repeat TVR	9.0%	8.8%	figure 3, Lincoff[38]
1 year			
Death, MI, TVR	N/A	N/A	N/A
Death, MI (large)	5.4% or 34/632	10.3% or 65/635	table 2, Topol[37]
Death	1.0% or 6/632	1.9% or 12/635	table 2, Topol[37]
MI (large)	4.4% or 28/632	8.7% or 55/635	table 2, Topol[37]
TVR	15.6% or 99/632	13.7% or 87/635	table 2, Topol[37]

MI=myocardial infarction, TVR=target vessel revascularization, N/A=not applicable.

APPENDIX 15a: ESPRIT Diabetic Clinical Inputs

Eptifibatide	**PCI to 30 Days (n=232)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=232)**
Death	1/232	2/231	3/232
MI	12/232	3/231	15/232
Revascularization (urgent at 30 days, target vessel at 1 year)	0/232	36/231	36/232
Stent Only	**PCI to 30 Days (n=234)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=234)**
Death	2/234	6/232	8/234
MI	19/234	4/232	23/234
Revascularization (urgent at 30 days, target vessel at 1 year)	1/234	39/232	40/234

MI=myocardial infarction.

APPENDIX 15b: ESPRIT Non-diabetic Clinical Inputs

Eptifibatide	**PCI to 30 Days (n=807)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=807)**
Death	3/807	8/804	11/807
MI	50/807	4/804	54/807
Revascularization (urgent at 30 days, target vessel at 1 year)	5/807	76/804	81/807
Stent Only	**PCI to 30 Days (n=788)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=788)**
Death	4/788	8/784	12/788
MI	78/788	4/784	82/788
Revascularization (urgent at 30 days, target vessel at 1 year)	2/788	87/784	89/788

MI=myocardial infarction.

APPENDIX 16a: EPISTENT Diabetic Clinical Inputs

Abciximab	**PCI to 30 Days (n=162)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=162)**
Death	1/162	1/161	2/162
MI (any)	7/162	0/161	7/162
Revascularization (urgent at 30 days, target vessel at 1 year)	2/162	20/161	22/162
Stent Only	**PCI to 30 Days (n=173)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=173)**
Death	3/173	4/170	7/173
MI	18/173	1/170	19/173
Revascularization (urgent at 30 days, target vessel at 1 year)	7/173	32/170	39/173

MI=myocardial infarction.

APPENDIX 16b: EPISTENT Non-diabetic Clinical Inputs

Abciximab	**PCI to 30 Days (n=632)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=632)**
Death	N/A	N/A	6/632
MI (any)	N/A	N/A	28/632
Revascularization (urgent at 30 days, target vessel at 1 year)	N/A	N/A	99/632
Stent Only	**PCI to 30 Days (n=636)**	**PCI: 31 to 364 Days (mathematical deduction)**	**PCI to 1 Year (n=635)**
Death	N/A	N/A	12/635
MI	N/A	N/A	55/635
Revascularization (urgent at 30 days, target vessel at 1 year)	N/A	N/A	87/635

N/A=not applicable, MI=myocardial infarction.

APPENDIX 17: Dosage and Cost (2003) Calculations for Eptifibatide and Abciximab

Cost of eptifibatide

1. Based on ESPRIT clinical trials, dosages were bolus 180 μg/kg x 2 + infusion 2 μg/kg/min for 18 hours (range 18 hours to 24 hours)
2. Based on ESPRIT clinical trials, median weight of patients given eptifibatide=84 kg

3a. Dose calculation for bolus=180 μg/kg x 84 kg x 2=30,240 μg=30.24 mg

3b. As one 20 mg/10 mL bolus vial=$38.00, need to use two bolus vials=$76.00

4a. Dose calculation for infusion=2 μg/kg/min x 84 kg x (18 hours x 60 minutes/hour)=181,440 μg=181.44 mg

4b. Cost calculation: one 75 mg/100 mL infusion vial=$111.25, need to use three infusion vials=$333.75

5. Total cost for eptifibatide treatment ($76.00+$333.75=$409.75)

Cost of abciximab

1. Based on EPISTENT clinical trials, dosages were bolus 0.25 μg/kg + infusion 0.125 μg/kg/minute (maximum 10 μg/kg/minute) for 12 hours
2. EPISTENT clinical trials did not report average weight (just BMI and % over 90 kg, which was 33.5% in non-diabetic patients), so median weight of patients who got eptifibatide in ESPRIT trial was used (=84 kg)

3a. Dose calculation for bolus=0.25 mg/kg x 84 kg=21 mg

3b. Dose calculation for infusion=0.125 μg/kg x 84 kg x (12 hours x 60 minutes/hour) =7,560 μg=7.560 mg

4. Total dose of abciximab=28.56 mg

5. As one 10 mg/5 mL vial=$536.65, need to use three vials of abciximab=$1,609.95

APPENDIX 18: Drug and Device Costs

Item	Cost	Dose	Cost per Year	Source
Bare metal stent	$780 per stent	N/A	Dependent on number of stents used.	(Dr. Eric Cohen: personal communication, spring 2003)
			Mean number of stents per stent case was 1.58 in single and multivessel cases.	Cardiac Care Network of Ontario Statistical Report[86]
ASA	$5.37 per month	81 mg	$64.44	ODB[62]
Clopidogrel	$67.24 per month	75 mg	$806.88	ODB[62]
Brachytherapy	$3,000	N/A	N/A	"The special catheter costs $2,500 plus time of physicist to provide RT in the catherization laboratory (<$500). $3,000 is the estimate to be used." (Nancy Cooper, Angioplasty Program Nurse Room, Sunnybrook and Women's College Health Sciences Centre, Toronto: personal communication, spring 2003)
Cardiac rehabilitation outpatient regimen	$1,580	N/A	N/A	The Ontario Cardiac Rehabilitation Pilot Project Report and Recommendations[87]

N/A=not applicable.

APPENDIX 19: Description of OCCI Subpopulations

Group	Description	ICD Codes
1: all PCI patients	any of three ICD-9-CM procedure codes that need to be intersected with any of five ICD-9-CM "most responsible diagnosis" codes to establish average total OCCI cost	36.01 or 36.02 or 36.05 (procedure codes or P.codes) and any of 411.1 or 411.81 or 411.89 or 413.9 or 414.01 (most responsible diagnosis codes or MRD)
2: PCI without complications	subpopulation with any of same three procedure codes that need to be intersected with any of five "most responsible diagnosis" codes to establish average total OCCI cost, but 43 diagnosis codes (first five codes listed are procedure codes) are to be excluded from any of remaining procedure and diagnosis fields, including primary procedure and diagnosis	36.01 or 36.02 or 36.05 (P.codes) and any of 411.1 or 411.81 or 411.89 or 413.9 or 414.01 (MRD) excluding any of the following 36.10 or 36.11 or 36.12 or 36.13 or 36.14 (P.codes for exclusion) or 410.00 or 410.01 or 410.02 or 410.10 or 410.11 or 410.12 or 410.20 or 410.21 or 410.22 or 410.30 or 410.31 or 410.32 or 410.40 or 410.41 or 410.42 or 410.50 or 410.51 or 410.52 or 410.60 or 410.61 or 410.62 or 410.70 or 410.71 or 410.72 or 410.80 or 410.81 or 410.82 or 410.90 or 410.91 or 410.92 or 432.9 or 459.0 or 578 or 578.9 or 998.11 + E879.0 or 998.12 + E879.0 or 998.11 + E947.8 or 998.12 + E947.8 (exclusion codes)
3: PCI with CABG complications only	patients with any of same three procedure codes and with CABG complications only	(36.01 or 36.02 or 36.05) AND (36.10 or 36.11or 36.12 or 36.13 or 36.14) (P.codes) and any of 411.1 or 411.81 or 411.89 or 413.9 or 414.01 (MRD) excluding any of the following 410.00 or 410.01 or 410.02 or 410.10 or 410.11 or 410.12 or 410.20 or 410.21 or 410.22 or 410.30 or 410.31 or 410.32 or 410.40 or 410.41 or 410.42 or 410.50 or 410.51 or 410.52 or 410.60 or 410.61 or 410.62 or 410.70 or 410.71 or 410.72 or 410.80 or 410.81 or 410.82 or 410.90 or 410.91 or 410.92 or 432.9 or 459.0 or 578 or 578.9 or 998.11 + E879.0 or 998.12 + E879.0 or 998.11 + E947.8 or 998.12 + E947.8 (exclusion codes)
4: PCI with MI as additional MRD	patients with any of same three procedure codes and with MI as additional MRD	36.01 or 36.02 or 36.05 (P.codes) and any of 411.1 or 411.81 or 411.89 or 413.9 or 414.01 or 410.00 or 410.01 or 410.02 or 410.10 or 410.11 or 410.12 or 410.20 or 410.21 or 410.22 or 410.30 or 410.31 or 410.32 or 410.40 or 410.41 or 410.42 or 410.50 or 410.51 or 410.52 or 410.60 or 410.61 or 410.62 or 410.70 or 410.71 or 410.72 or 410.80 or 410.81 or 410.82 or 410.90 or 410.91 or 410.92 (MRD) excluding any of the following 36.10 or 36.11 or 36.12 or 36.13 or 36.14 (P.codes for exclusion) or 432.9 or 459.0 or 578 or 578.9 or 998.11 + E879.0 or 998.12 + E879.0 or 998.11 + E947.8 or 998.12 + E947.8 (exclusion codes)
5: PCI with MI as only MRD	patients with any of same three procedure codes and with MI as a MRD	36.01 or 36.02 or 36.05 (P.codes) and any of 410.00 or 410.01 or 410.02 or 410.10 or 410.11 or 410.12 or 410.20 or 410.21 or 410.22 or 410.30 or 410.31 or 410.32 or 410.40 or 410.41 or 410.42 or 410.50 or 410.51 or 410.52 or 410.60 or 410.61 or 410.62 or 410.70 or 410.71 or 410.72 or 410.80 or 410.81 or 410.82 or 410.90 or 410.91 or 410.92 (MRD] excluding any of the following 36.10 or 36.11 or 36.12 or 36.13 or 36.14 (P.codes for exclusion) or 432.9 or 459.0 or 578 or 578.9 or 998.11 + E879.0 or 998.12 + E879.0 or 998.11 + E947.8 or 998.12 + E947.8 (exclusion codes)

Group	Description	ICD Codes
6: PCI with hemorrhage complication	patients with any of same three procedure codes and hemorrhage complication	36.01 or 36.02 or 36.05 (P.codes) and any of 411.1 or 411.81 or 411.89 (MRD) as well as any subsequent diagnosis 413.9 or 414.01 or 432.9 or 459.0 or 578 or 578.9 or 998.11 + E879.0 or 998.12 + E879.0 or 998.11 + E947.8 or 998.12 + E947.8 excluding any of the following 36.10 or 36.11 or 36.12 or 36.13 or 36.14 (P.codes for exclusion) or 410.00 or 410.01 or 410.02 or 410.10 or 410.11 or 410.12 or 410.20 or 410.21 or 410.22 or 410.30 or 410.31 or 410.32 or 410.40 or 410.41 or 410.42 or 410.50 or 410.51 or 410.52 or 410.60 or 410.61 or 410.62 or 410.70 or 410.71 or 410.72 or 410.80 or 410.81 or 410.82 or 410.90 or 410.91 or 410.92 (exclusion codes)
7: MI as MRD without CABG complication	groups 7 and 8 consist of no procedure codes, just any of "most responsible diagnosis" codes and any of the exclusion diagnosis codes (group 7 only)	410.00 or 410.01 or 410.02 or 410.10 or 410.11 or 410.12 or 410.20 or 410.21 or 410.22 or 410.30 or 410.31 or 410.32 or 410.40 or 410.41 or 410.42 or 410.50 or 410.51 or 410.52 or 410.60 or 410.61 or 410.62 or 410.70 or 410.71 or 410.72 or 410.80 or 410.81 or 410.82 or 410.90 or 410.91 or 410.92 (MRD) excluding any of the following 36.10 or 36.11 or 36.12 or 36.13 or 36.14 (P.codes for exclusion)
8: CABG as MRD	no procedure codes, just any of "most responsible diagnosis" codes	36.10 or 36.11 or 36.12 or 36.13 or 36.14 (MRD)

MRD=most responsible diagnosis, CABG=coronary artery bypass graft, ICD=international classification of diseases, MI=myocardial infarction, PCI=percutaneous coronary intervention

APPENDIX 20: Corrected Total Average Costs for Hospitalizations Included in Decision Analytic Models

Type of Hospitalization	2000-2001 Total Average Cost	Inflated 2003 Cost*	Deduction Components	Corrected 2003 Cost
group 2=original PCI	$4,903	$5,208	stent=90.9% x $780=$709 drug=19.21% x $1,007.85=$193.61	$4,305.39
(group 6) – (group 2)=bleed	$5,626 – $4,903 =$723	$5,976	$5,976 stent=94.12% x $780=$734.136 drug=17.8% x $1,007.85=$179.40	$5,062.46− $4,305.39 =$757.07
group 7=MI	$7,863	$8,353	N/A	$8,353
group 8=CABG	$13,822	$14,683	N/A	$14,683

N/A=not applicable

*The Bank of Canada provides an on-line inflation calculator (http://www.bankofcanada.ca/en/inflation_calc.htm) that uses monthly consumer price index (CPI) data from 1914 to present to show changes in cost of fixed "basket" of consumer purchases. Results generated by the inflation calculator are based on most recent month for which CPI data are available (approximately two months before current month).

APPENDIX 21: Physician Codes and Costs (2003) for Inpatient Services

Description	Code	Page	Costs
First PCI (elective or urgent) and no complications			
Non-emergency hospital inpatient cardiology service consultation	C605	A12	$112.35
Transluminal coronary angioplasty; one or more sites on one major vessel	Z434	J6	$427.10
Each additional major vessel	G262	J6	$192.30
Coronary angioplasty stent	G298	J6	$71.45
First PCI+repeat PCI			
Non-emergency hospital in-patient cardiology service consultation	C605	A12	$112.35
Angiogram and selective coronary catheterization	G297 Z442	J6 J6	$107.50 $160.53
First PCI+extended hospitalization (3 days in CCU)			
Critical care provided by physician in charge first day	G400	J15	$207.00
Second to 10th day (inclusive) per diem	G401	J15	$89.70
First PCI+CABG complication (clopidogrel is stopped and Aspirin therapy initiated)			
Non-emergency hospital in-patient cardiology service consultation	C605	A12	$112.35
ACBx1 Coronary artery repair (1 vessel) 18 units* of surgical assistant 20 units of anesthetist Pump bypass 28 units of anesthetist Special care unit premium (ICU)	 R742 E650 C101	 Q3 Q3 Q3 Q1 Q1 xlvii	 $878.00 $183.60 $235.40 $359.30 $329.66 $8.50x2 =$2,002.86
ACBx2 Coronary artery repair (2 vessels) 18 units of surgical assistant 20 units of anesthetist Pump bypass 28 units of anesthetist Special care unit premium (ICU)	 R743 E650 C101	 Q2 Q2 Q2 Q1 Q1 xlvii	 $1,178.85 $183.60 $235.40 $359.30 $329.66 $8.50x2 =$2,303.81
Each additional bypass	E654	Q3	$184.00

*Time units are calculated by allowing for each 15 minutes or part thereof.

APPENDIX 22: Physician Visits and Diagnostic Procedure Codes and Costs (2003) for Outpatient Services

Description		Code	Page	Costs
First PCI (no complications, repeat PCI, extended hospitalization)				
Outpatient cardiology medical visit (assessment)		C603	A11	$57.10
Stress testing (maximal stress ECG)		G315 G319	J8	$91.45
Myocardial perfusion scintigraphy (6) • stress • rest • wall motion • wall motion repeat • SPECT (nuclear) • SPECT (nuclear)	Page B3 J807/J607 $220.95 (H)+$44.10 (P1)+$22.55 (P2) = $287.60 J808/J608 $81.35 (H)+$23.75 (P1)+$11.80 (P2) = $116.90 J813/J613 $137.25 (H)+$77.35 (P1)+$39.35 (P2) = $253.95 J814/J614 $48.90 (H)+$39.35 (P1)+$20.30 (P2) = $108.55 J809/J609 $44.15 (H)+$26.20 (P1)+$13.15 (P2) = $83.50 J866/J666 $44.15 (H)+$26.20 (P1)+$13.15 (P2) = $83.50 Total = $934.00			
Family practitioner outpatient visit (general assessment)		A003	A1	$54.10
Clopidogrel for 4 weeks		N/A	N/A	$67.24
Clopidogrel for 1 year		N/A	N/A	$806.88
First PCI+CABG complications (clopidogrel is stopped and Aspirin therapy initiated)				
Cardiovascular and thoracic surgery (specific assessment)		A093	A12	$40.40
Stress testing x 2		G315 G319	J8	$182.90
Family practitioner outpatient visit (general assessment)		A003	A1	$53.55

APPENDIX 23: Laboratory Tests Costs During Outpatient Care (2003)

Laboratory Test	Units	Total Cost (1 unit = $0.517)
Complete blood count	16	$8.272
Triglycerides	5	$2.585
Cholesterol, total	5	$2.585
Glucose, random	5	$2.585

APPENDIX 24: Percentage Breakdown of Number of Vessels Requiring Angioplasty (based on expert opinion)

Number of Vessels	Proportion of Individuals (%)
1	100
2	25
3	5
4	0
5	0

APPENDIX 25: Percentage Breakdown of Number of Vessels Requiring CABG (based on expert opinion)

Number of Vessels	Proportion of Individuals (%)
1	100
2	20
3	50
4	20
5	5

APPENDIX 26: Cost Algorithms for Clinical Scenarios after Original PCI and No 30-day Event of Treatment Arm

Scenario	**Algorithm for Costs**		
• no 30-day event • no 1-year event	glycoprotein(±) bleed rate rehabilitation	NoEvent30day	NoEvent1year
• no 30-day event • 1-year MI	glycoprotein(±) bleed rate rehabilitation	NoEvent30day	MI1year MIPhysicianCCU 2(GPvisit) Outptvisitphysician Clopidogrel 1year
• no 30-day event • 1-year revascularization ("revascularization" is a weighted average of repeat PTCA and CABG)	glycoprotein(±) bleed rate rehabilitation	NoEvent30day	InptCardConsult PhysicianSelectCoronary Brachytherapy PTCArepeat 2b3adrug Stent Laboutpt Diagoutpt PTCAphysician Angioplastyphysician Vesselphysician 2(Outptvisitphysician) Stresstest Perfusiontest 2(GPvisit) Clopidogrel 1year
			InptCardConsult CABG CABGphysician OutptvisitCTsurgeon 2(Stresstest) Aspirin 2(GPvisit) Clopidogrel 1year
• no 30-day event • death at 1 year	same as	no 30-day event 1 year MI	

APPENDIX 27: Cost Algorithms for Clinical Scenarios after Original PCI and MI at 30 Days of Treatment Arm

<table>
<tr><th>Scenario</th><th colspan="3">Algorithm for Costs</th></tr>
<tr><td>• 30-day MI
• no 1-year event</td><td>glycoprotein(±)
bleed rate
rehabilitation</td><td>MI1year
MIPhysicianCCU
2(GPvisit)
Outptvisitphysician
Clopidogrel 1year</td><td>NoEvent1year</td></tr>
<tr><td>• 30-day MI
• 1-year MI</td><td>glycoprotein(±)
bleed rate
rehabilitation</td><td>MI1year
MIPhysicianCCU
2(GPvisit)
Outptvisitphysician
Clopidogrel 1year</td><td>MI1year
MIPhysicianCCU
GPvisit
Outptvisitphysician
Clopidogrel 1year</td></tr>
<tr><td rowspan="2">• 30-day MI
• 1-year revascularization

(“revascularization” is a weighted average of repeat PTCA and CABG)</td><td rowspan="2">glycoprotein(±)
bleed rate
rehabilitation</td><td rowspan="2">MI1year
MIPhysicianCCU
2(GPvisit)
Outptvisitphysician
Clopidogrel 1year</td><td>InptCardConsult
PhysicianSelectCoronary
Brachytherapy
PTCArepeat
2b3adrug
Stent
Laboutpt
Diagoutpt
PTCAphysician
Angioplastyphysician
Vesselphysician
2(Outptvisitphysician)
Stresstest
Perfusiontest
2(GPvisit)
Clopidogrel 1year</td></tr>
<tr><td>InptCardConsult
CABG
CABGphysician
OutptvisitCTsurgeon
2(Stresstest)
Aspirin
2(GPvisit)
Clopidogrel 1year</td></tr>
<tr><td>• 30-day MI
• death at 1 year</td><td colspan="3">same as 30-day MI
1-year MI</td></tr>
</table>

APPENDIX 28: Cost Algorithms for Clinical Scenarios after Original PCI and Revascularization at 30 Days of Treatment Arm

Scenario	Algorithm for Costs		
• 30-day revascularization • no 1-year event ("revascularization" is a weighted average of repeat PTCA and CABG)	glycoprotein(±) bleed rate rehabilitation	InptCardConsult PhysicianSelectCoronary Brachytherapy PTCArepeat 2b3adrug Stent Laboutpt Diagoutpt PTCAphysician Angioplastyphysician Vesselphysician 2(Outptvisitphysician) Stresstest Perfusiontest 2(GPvisit) Clopidogrel 1year	NoEvent1year
		InptCardConsult CABG CABGphysician OutptvisitCTsurgeon 2(Stresstest) Aspirin 2(GPvisit) Clopidogrel 1year	
1) 30-day revascularization 2) 1-year MI	glycoprotein(±) bleed rate rehabilitation	InptCardConsult PhysicianSelectCoronary Brachytherapy PTCArepeat 2b3adrug Stent Laboutpt Diagoutpt PTCAphysician Angioplastyphysician Vesselphysician 2(Outptvisitphysician) Stresstest Perfusiontest 2(GPvisit) Clopidogrel 1year	MI1year MIPhysicianCCU 2(GPvisit) Outptvisitphysician Clopidogrel 1year
		InptCardConsult CABG CABGphysician OutptvisitCTsurgeon 2(Stresstest) Aspirin 2(GPvisit) Clopidogrel 1year	

• 30-day revascularization • 1-year revascularization	glycoprotein(±) bleed rate rehabilitation	InptCardConsult PhysicianSelectCoronary Brachytherapy PTCArepeat 2b3adrug Stent Laboutpt Diagoutpt PTCAphysician Angioplastyphysician Vesselphysician 2(Outptvisitphysician) Stresstest Perfusiontest 2(GPvisit) Clopidogrel 1year	InptCardConsult PhysicianSelectCoronary Brachytherapy PTCArepeat 2b3adrug Stent Laboutpt Diagoutpt PTCAphysician Angioplastyphysician Vesselphysician Outptvisitphysician Stresstest Perfusiontest GPvisit
		InptCardConsult CABG CABGphysician OutptvisitCTsurgeon 2(Stresstest) Aspirin 2(GPvisit) Clopidogrel 1year	InptCardConsult CABG CABGphysician OutptvisitCTsurgeon Stresstest(2) Aspirin GPvisit(2) Clopidogrel 1year
• 30-day revascularization • death at 1 year	same as	30-day revascularization 1-year MI	

APPENDIX 29: Proportion Breakdown of Variables

Variable	Proportion	Source
Brachytherapy treatment	3.19%	"In 2002, 38 brachytherapy treatments were given out of a total of approximately 1,190 PCI procedures at SWCHSC." (Nancy Cooper: personal communication, spring 2003)
Cardiac rehabilitation outpatient regimen	20%	Cardiac Care Network Statistical Report[88]
Coronary artery disease (CAD) in diabetic patients	2-fold increase	Haffner[60]
Myocardial perfusion scintigraphy	60%	expert opinion
Clopidogrel 4 weeks	All original PCI	expert opinion
Clopidogrel 1 year	All secondary procedures at 30-days and 1 year (MI, repeat PCI, CABG)	expert opinion
Revascularization (CABG)	25%	expert opinion
Revascularization (PTCA)	75%	expert opinion
Stress testing (maximal stress ECG)	25%	expert opinion

APPENDIX 30: Survival Probabilities

Variable	Value (%)	Source
Probability of a vascular death	2	Topol[51]
Probability of a vascular death after an MI	2	Topol[51]
Annual cardiac mortality post revascularization procedure	0.4	Cohen[48]

APPENDIX 31: Eptifibatide Short-term Model

Treatment	Average Expected Cost	MACE	Death Rate
Eptifibatide+stent	$2,838	0.192	0.01
Stent only	$2,897	0.228	0.02
Difference (eptifibatide minus placebo)	−$59	−0.056	−0.01

APPENDIX 32: Abciximab Short-term Model

Treatment	Average Expected Cost	MACE	Death Rate
Abciximab+stent	$4,512	0.222	0.01
Stent only	$3,341	0.292	0.02
Difference (abciximab minus stent-only)	$1,171	−0.070	−0.01

APPENDIX 33: Abciximab Incremental Analyses

Incremental analysis for cost per MACE avoided

$$= \frac{\text{cost of abciximab+stent} - \text{cost of stent only}}{\text{outcome of abciximab+stent} - \text{outcome of stent only}}$$
$$= (\$4{,}512 - \$3{,}341) / (0.222 - 0.292)$$
$$= \$16{,}729 \text{ per MACE avoided}$$

Incremental analysis for cost per death avoided

$$= \frac{\text{cost of abciximab+stent} - \text{cost of stent only}}{\text{outcome of abciximab+stent} - \text{outcome of stent only}}$$
$$= (\$4{,}512 - \$3{,}341) / (0.01 - 0.02)$$
$$= \$117{,}100 \text{ per death avoided}$$

APPENDIX 34: Eptifibatide Long-term (Survival) Model

Treatment	Unadjusted Life-Years	Adjusted Life-Years (5%)
Eptifibatide+stent	15.33	10.19
Stent only	15.11	10.07
Difference (eptifibatide minus stent only)	0.22	0.12

APPENDIX 35: Abciximab Long-term (Survival) Model

Treatment	Unadjusted Life-Years	Adjusted Life-Years (5%)
Abciximab+stent	16.95	10.84
Stent only	16.83	10.77
Difference (abciximab minus stent only)	0.12	0.07

APPENDIX 36: Abciximab Incremental Analyses

Incremental analysis for cost per unadjusted life-year gained

$$= \frac{\text{cost of abciximab+stent} - \text{cost of stent only}}{\text{outcome of abciximab+stent} - \text{outcome of stent only}}$$
$$= (\$4{,}512 - \$3{,}341) / (16.95 - 16.83)$$
$$= \$9{,}758 \text{ per unadjusted life-year gained}$$

Incremental analysis for cost per adjusted life-year gained

$$= \frac{\text{cost of abciximab+stent} - \text{cost of stent only}}{\text{outcome of abciximab+stent} - \text{outcome of stent only}}$$
$$= (\$4{,}512 - \$3{,}341) / (10.84 - 10.77)$$
$$= \$16{,}729 \text{ per adjusted life-year gained}$$

APPENDIX 37: Eptifibatide Short-term Model for Diabetic Patients

Treatment	Average Expected Cost	MACE	Death Rate
Eptifibatide+stent	$3,262	0.233	0.01
Stent only	$3,428	0.303	0.03
Difference (eptifibatide minus stent only)	−$166	−0.071	−0.02

APPENDIX 38: Abciximab Short-term Model for Diabetic Patients

Treatment	Average Expected Cost	MACE	Death Rate
Abciximab+stent	$4,161	0.191	0.01
Stent only	$4,080	0.376	0.04
Difference (abciximab minus stent only)	$81	−0.185	−0.03

APPENDIX 39: Diabetic Abciximab Incremental Analyses

Incremental analysis for cost per MACE avoided

$$= \frac{\text{cost of abciximab+stent – cost of stent only}}{\text{outcome of abciximab+stent – outcome of stent only}}$$
= ($4,161– $4,080) / (0.191– 0.376)
= $438 per MACE avoided

Incremental analysis for cost per death avoided

$$= \frac{\text{cost of abciximab+stent - cost of stent only}}{\text{outcome of abciximab+stent – outcome of stent only}}$$
= ($4,161– $4,080) / (0.01– 0.04)
= $2,700 per death avoided

APPENDIX 40: Eptifibatide Long-term (Survival) Model

Treatment	Unadjusted Life-Years	Adjusted Life-Years (5%)
Eptifibatide+stent	9.71	7.45
Stent only	9.40	7.23
Difference (eptifibatide minus stent only)	0.31	0.22

APPENDIX 41: Abciximab Long-term (Survival) Model for Diabetic Patients

Treatment	Unadjusted Life-Years	Adjusted Life-Years (5%)
Abciximab+stent	10.82	8.01
Stent only	10.48	7.79
Difference (abciximab minus stent only)	0.35	0.22

APPENDIX 42: Diabetic Abciximab Incremental Analyses

Incremental analysis for cost per unadjusted life-year gained in diabetics

$$= \frac{\text{cost of abciximab+stent} - \text{cost of stent only}}{\text{outcome of abciximab+stent} - \text{outcome of stent only}}$$
$$= (\$4{,}161 - \$4{,}080) \,/\, (10.82 - 10.48)$$
$$= \$231 \text{ per unadjusted life-year gained}$$

Incremental analysis for cost per adjusted life-year gained in diabetics

$$= \frac{\text{cost of abciximab+stent} - \text{cost of stent only}}{\text{outcome of abciximab+stent} - \text{outcome of stent only}}$$
$$= (\$4{,}161 - \$4{,}080) \,/\, (8.01 - 7.79)$$
$$= \$368 \text{ per adjusted life-year gained}$$

APPENDIX 43: Eptifibatide Short-term Model for Non-diabetic Patients

Treatment	Average Expected Cost	MACE	Death Rate
Eptifibatide+stent	$2,718	0.181	0.01
Stent only	$2,858	0.244	0.02
Difference (eptifibatide minus stent only)	–$140	–0.064	–0.01

APPENDIX 44a: Eptifibatide Long-term (survival) Model in Non-diabetic Patients

Treatment	Unadjusted Life-Years	Adjusted Life-Years (5%)
Eptifibatide+stent	15.33	10.19
Stent only	15.18	10.12
Difference (eptifibatide minus stent only)	0.15	0.07

APPENDIX 44b: Summary of Costs at Each End Node in Overall Population (short term)

	Eptifibatide	Stent Only	Abciximab	Stent Only
No event	$2,070	$1,770	$3,953	$2,244
MI	$11,332	$11,032	$13,215	$11,506
Revascularization	$12,588	$11,981	$15,370	$12,455
Death	$843	$427	$2,046	$441
Weighted average	$2,838	$2,897	$4,512	$3,341

MI=myocardial infarction.

APPENDIX 44c: Summary of Costs at Each End Node in Diabetic Population (short term)

	Eptifibatide	Stent Only	Abciximab	Stent Only
No event	$2,791	$2,651	$3,630	$2,744
MI	$12,053	$11,913	$12,891	$12,005
Revascularization	$13,309	$12,861	$15,047	$12,954
Death	$843	$427	$2,046	$441
Weighted average	$3,262	$3,428	$4,161	$4,080

MI=myocardial infarction.

APPENDIX 44d: Summary of Costs at Each End Node in Non-diabetic Population (short term)

	Eptifibatide	Stent	Abciximab	Stent Only
No event	$2,084	$1,923	N/A	N/A
MI	$11,346	$11,184	N/A	N/A
Revascularization	$12,602	$12,133	N/A	N/A
Death	$843	$427	N/A	N/A
Weighted average	$2,718	$2,858	N/A	N/A

MI=myocardial infarction, N/A=not applicable.

APPENDIX 45: Probability Distributions for Sensitivity Analysis

Variable	Base Value	Probability Distribution
Costs		
Bleeding episode	$757.07	normal (757.07, 189.27)
Rehabilitation	$15,000	normal (15000, 3750)
No event	$108.20	normal (108.20, 27.05)
MI	$9,369.92	normal (9369.92, 2342.48)
Revascularization	$10,318.40	normal (10318.40, 2579.60)
Base Probabilities		
MI 30 days: all patients	0.096	beta (177, 1656)
Revascularization 30 days: all patients	0.022	beta (41, 1792)
Death 30 days: all patients	0.006	beta (11, 1822)
MI 1 year: all patients	0.010	beta (19, 1803)
Revascularization 1 year: all patients	0.117	beta (214, 1608)
Death 1 year: all patients	0.015	beta (28, 1794)
MI 30 days: diabetic patients	0.090	beta (37, 370)
Revascularization 30 days: diabetic patients	0.019	beta (8, 399)
Death 30 days: diabetic patients	0.011	beta (5, 402)
MI 1 year: diabetic patients	0.012	beta (5, 397)
Revascularization 1 year: diabetic patients	0.176	beta (71, 331)
Death 1 year: diabetic patients	0.024	beta (10, 392)
Bleeding	0.012	beta (22, 1811)
Annual mortality: MI	0.02	beta (3.76, 184.24)
Annual mortality: revascularization	0.02	beta (65, 3209)
Annual mortality: vascular	0.004	beta (7, 1743)
Relative Risks: Abciximab		
MI 30 days: all patients	0.47	log normal (0.47, 1.22)
Revascularization 30 days: all patients	0.60	log normal (0.60, 1.48)
Death 30 days: all patients	0.41	log normal (0.41, 2.31)
MI 1 year: all patients	0.86	log normal (0.86, 1.50)
Revascularization 1 year: all patients	1.03	log normal (1.03, 1.13)
Death 1 year: all patients	0.44	log normal (0.44, 1.62)
MI 30 days: diabetics	0.42	log normal (0.42, 1.54)
Revascularization 30 days: diabetic patients	0.31	log normal (0.31, 2.21)
Death 30 days: diabetic patients	0.36	log normal (0.36, 3.36)
MI 1 year: diabetic patients	0.35	log normal (0.35, 5.51)
Revascularization 1 year: diabetic patients	0.66	log normal (0.66, 1.30)
Death 1 year: diabetic patients	0.26	log normal (0.26, 3.04)
Relative Risks: Eptifibatide		
MI 30 days: all patients	0.64	log normal (0.64, 1.17)
Revascularization 30 days: all patients	0.82	log normal (0.82, 1.35)
Death 30 days: all patients	0.66	log normal (0.66, 1.90)
MI 1 year: all patients	0.82	log normal (0.82, 1.83)
Revascularization 1 year: all patients	0.91	log normal (0.91, 1.14)
Death 1 year: all patients	0.70	log normal (0.70, 1.51)

MI 30 days: diabetic patients	0.64	log normal (0.64, 1.43)
Revascularization 30 days: diabetic patients	0.34	log normal (0.34, 5.51)
Death 30 days: diabetic patients	0.50	log normal (0.50, 3.39)
MI 1 year: diabetic patients	0.75	log normal (0.75, 2.13)
Revascularization 1 year: diabetic patients	0.93	log normal (0.93, 1.24)
Death 1 year: diabetic patients	0.33	log normal (0.33, 2.25)

MI=myocardial infarction

APPENDIX 46: Incremental Results of Probabilistic Analysis for All Patients

	Eptifibatide versus Standard Treatment	**Abciximab versus Standard Treatment**
Incremental life-years gained	0.11 (−0.05, 0.22)	0.19 (0.05, 0.30)
Incremental costs	−$30 (−480, 420)	$1,200 (680, 1,730)
ICER	dominant	$6,200
NMB (life-year=$50,000)	$5,600 (−2,600, 11,500)	$8,400 (1,000, 13,800)

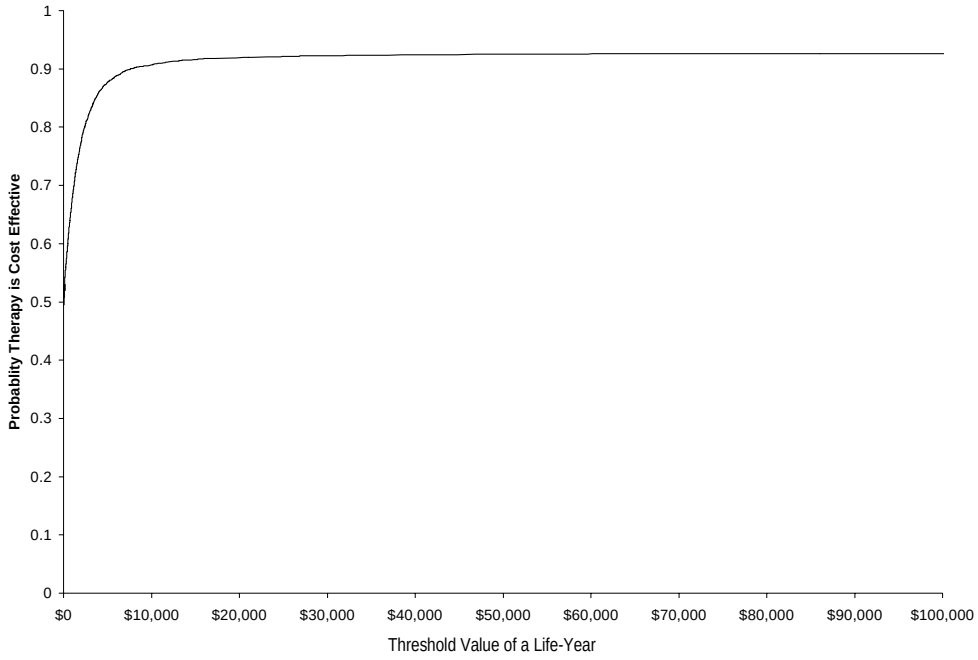
Figures in parenthesis are 95% credible intervals. ICER=incremental cost-effectiveness ratio, NMB=net monetary benefit.

APPENDIX 47: Incremental Results of Probabilistic Analysis for Diabetic Patients

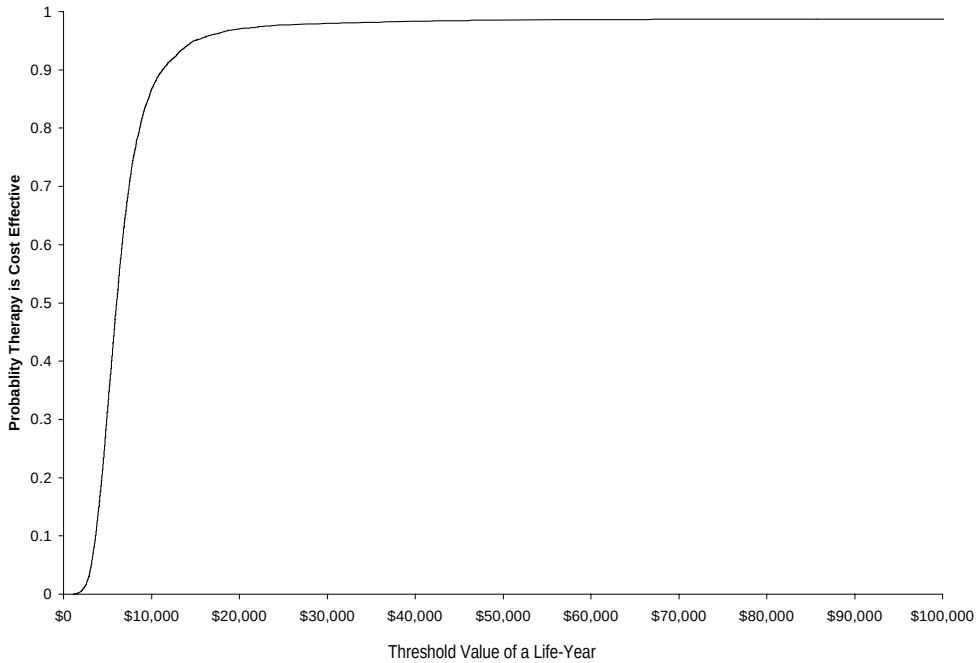
	Eptifibatide versus Standard Treatment	**Abciximab versus Standard Treatment**
Incremental life-years gained	0.15 (−0.40, 0.40)	0.24 (−0.36, 0.49)
Incremental costs	$40 (−1,060, 1,550)	$550 (−540, 1,860)
ICER	$300	$2,300
NMB (life-year=$50,000)	$7,500 (−21,100, 20,600)	$ 11,200 (−19,400, 24,600)

Figures in parenthesis are 95% credible intervals. ICER=incremental cost-effectiveness ratio, NMB=net monetary benefit.

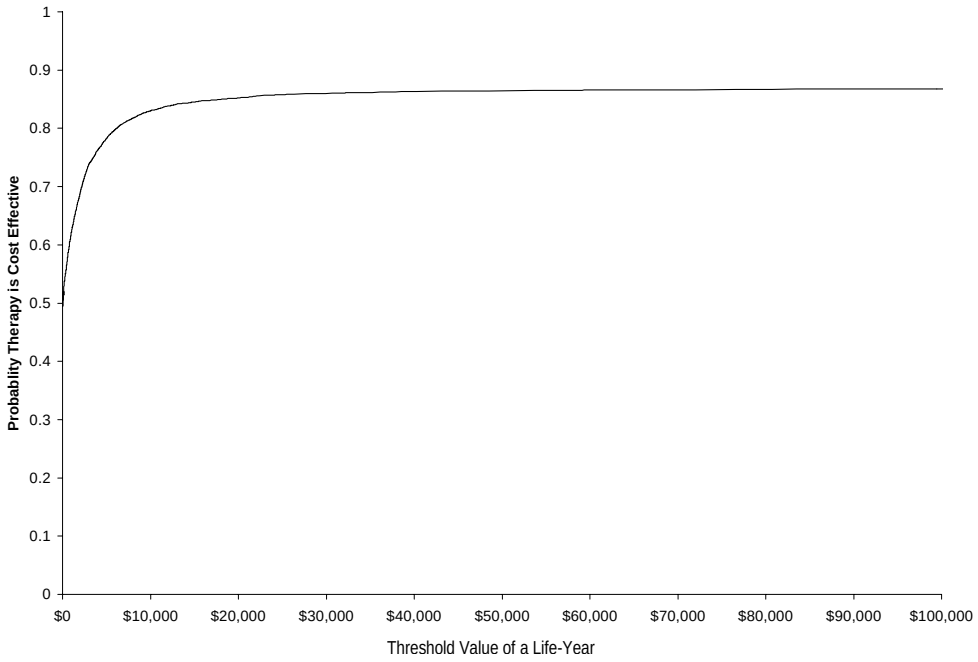
APPENDIX 48a: Cost-effectiveness Acceptability for All Patients: Eptifibatide



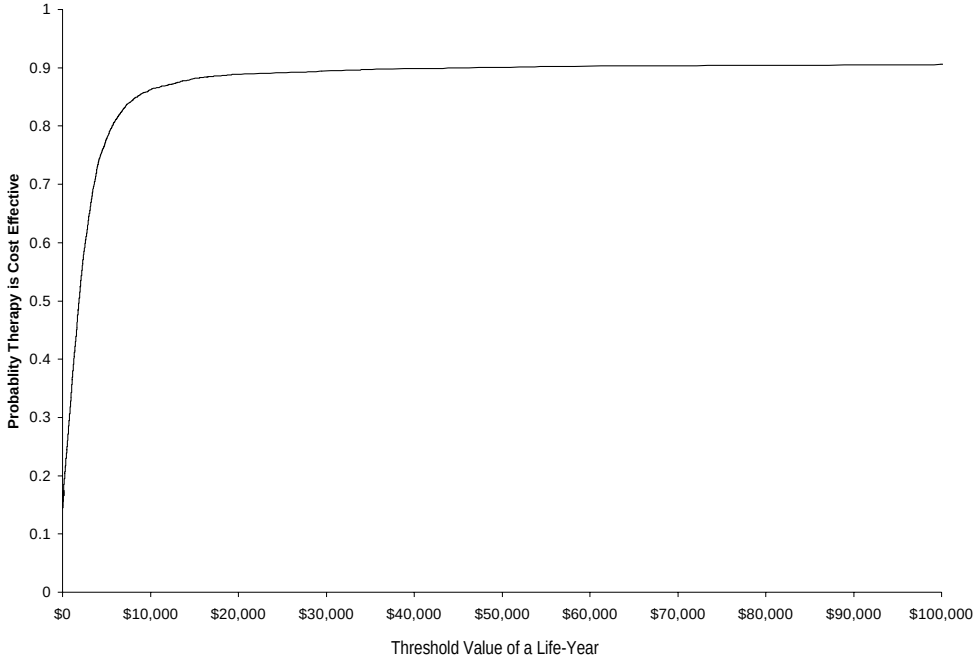
APPENDIX 48b: Incremental Results of Probabilistic Analysis for Diabetic Patients: Abciximab



APPENDIX 49a: Cost-effectiveness Acceptability for Diabetic Patients: Eptifibatide



APPENDIX 49b: Cost-effectiveness Acceptability for Diabetic Patients: Abciximab



APPENDIX 50a: Stroke and Bleed Complications in ESPRIT

	30 Days		1 Year	
	Eptifibatide	**Stent Only**	**Eptifibatide**	**Stent Only**
n	1,040	1,024	988	976
Non-hemorrhagic stroke	0.1% (n=1)	0%	N/A	N/A
Intracranial bleeding	0.2% (n=2)	0.1% (n=1)	N/A	N/A
RBC transfusions (including CABG-related transfusions)	1% (n=15)	1% (n=10)	N/A	N/A

n=number, RBC=red blood cell, CABG=coronary artery bypass graft, N/A=not applicable.

APPENDIX 50b: Stroke and Bleed Complications in EPISTENT

	30 Days		1 Year	
	Abciximab	**Stent Only**	**Abciximab**	**Stent Only**
n	794	809	794	809
Non-hemorrhagic stroke	0.4%	0.1%	N/A	N/A
Intracranial bleeding	0%	0%	N/A	N/A
Transfusions (including CABG-related transfusions of RBC and platelets)	2.8%	2.2%	N/A	N/A

n=number, RBC=red blood cell, CABG=coronary artery bypass graft, N/A=not applicable.

APPENDIX 50c: Angiographic Complications in EPISTENT at Six Months

	Abciximab	**Stent Only**
n	784	803
Major or minor coronary dissection	12.0% (n=94)	16.6% (n=133)
Distal embolization	1.3% (n=10)	1.2% (n=10)
Thrombus postintervention	1.4% (n=11)	1.5% (n=15)
Side branch occlusion	2.4% (n=19)	4.5% (n=36)
Other vessel occlusion	0.1% (n=1)	0.6% (n=5)
Residual stenosis >50%	0.8% (n=8)	1.5% (n=12)
Transient coronary occlusion	1.4% (n=11_	2.4% (n=19)
Final thrombolysis in myocardial infarction flow <3	2.5% (n=19)	4.6% (n=36)
Referred for CABG	0.6% (n=5)	0.5% (n=4)
Localized perforation	0.3% (n=2)	0.2% (n=2)

N=number, RBC=red blood cell, CABG=coronary artery bypass graft, N/A=not applicable.

APPENDIX 51: Food and Drug Administration Reporting of Adverse Events Associated with Glycoprotein Inhibitor Treatment

Deaths associated with platelet glycoprotein IIb/IIIa inhibitor treatment. Heart. 2003 May;89(5):535-7. Brown DL.

BACKGROUND: The glycoprotein (GP) IIb/IIIa inhibitors are potent antagonists of platelet aggregation that are approved to prevent thrombotic complications of percutaneous coronary intervention and for medical treatment of patients with acute coronary ischaemic syndromes. From safety data obtained from clinical trials, these agents appear to be associated with a definite but well tolerated increase in non-fatal bleeding complications. However, the bleeding risk of patients enrolled in clinical trials may not be representative of the population actually being treated with these agents. OBJECTIVE: To conduct a review of the adverse events related to GP IIb/IIIa inhibitors reported to the Food and Drug Administration (FDA). METHODS: 450 reports of death related to treatment with GP IIb/IIIa inhibitors were submitted to the FDA between 1 November 1997 and 31 December 2000. These were reviewed and a standard rating system for assessing causation was applied to each event. RESULTS: Of the 450 deaths, 44% were considered to be definitely or probably related to the use of GP IIb/IIIa inhibitors. The mean age of patients who died was 69 years and 47% of deaths occurred in women. All of the deaths deemed to be definitely or probably related to GP IIb/IIIa inhibitor treatment were associated with excessive bleeding. The central nervous system was the most common site of fatal bleeding. CONCLUSIONS: Treatment with GP IIb/IIIa inhibitors may result in fatal bleeding complications in some patients. These findings suggest that patients treated in normal clinical practice may be at greater risk than those treated in clinical trials. Judicious use of these agents is therefore appropriate.

	Eptifibatide	**Tirofiban**	**Abciximab**	**Total**
Death (n)	103	143	207	450
Female %	38	51	45	47
Mean age	70	71	67	69
Hemorrhage %	85	72	82	80
MI %	16	24	17	19
Thrombocytopenia %	6	18	14	13