THE ECONOMICS OF ADJUNCTIVE THERAPIES IN CORONARY ANGIOPLASTY: DRUGS, DEVICES, OR BOTH?

Paul I. Oh, [1] Eric A. Cohen, [2] Nicole Mittmann, [3, 4] Soo Jin Seung [4]

[1]Division of Clinical Pharmacology, Sunnybrook and Women's and Cardiac Rehabilitation and Secondary Prevention Program, Toronto Rehabilitation Institute University of Toronto, Toronto, Ontario, Canada; [2]Schulich Heart Program, Sunnybrook & Women's College Health Sciences Centre, University of Toronto; [3]Division of Clinical Pharmacology and Department of Medicine, Sunnybrook and Women's College Health Sciences Centre; Department of Pharmacology, University of Toronto; Health Outcomes and Pharmacoeconomics (HOPE) Research Centre Toronto, Ontario, Canada; [4]Health Outcomes and Pharmacoeconomics (HOPE) Research Centre Toronto, Ontario, Canada

Corresponding Author: oh.pauldr@torontorehab.on.ca

ABSTRACT

Background
Abciximab reduces the number of ischemic events in patients undergoing angioplasty compared to standard therapy. Coronary stenting reduces the need for repeat procedures. Abciximab or stents individually are considered cost effective interventions. There is a need to quantify the economic value of the combination of abciximab and stenting over stenting alone.

Methods
A decision analytic model was developed incorporating the outcomes from the EPISTENT study. Costs from Canadian sources for hospitalization, procedures and medications were used. Life expectancy was estimated using a Markov model. Total expected costs and outcomes of the abciximab and stent vs. stent alone were compared in an incremental analysis. The perspective of the analysis was a Canadian teaching hospital.

Results
The acquisition cost for abciximab was partially offset by reduced costs for managing clinical events resulting in a net incremental cost of $1,076 per patient over one year ($8,617 combination vs. $7,541 stent alone). This added cost was accompanied by a reduction in large MI or death by an absolute rate of 5.7% at one year (5.3% combination vs. 11.0% stent alone), yielding an incremental cost-effectiveness ratio of $18,877 per death or large MI averted. The long-term survival gain was 0.15 to 0.37 years yielding an attractive incremental cost effectiveness ratio of $2,832 to $7,173 per life year gained.

Conclusions
The combination of abciximab and stenting versus stenting alone provides improved clinical outcomes at a very reasonable cost from the Canadian hospital perspective.

Key Words: abciximab, cost-effectiveness, percutaneous coronary intervention

---

Abciximab (ReoPro™, Lilly and Centocor) is the Fab fragment of a chimeric murine monoclonal antibody that selectively binds to the glycoprotein (GP) IIb/IIIa receptor located on the surface of human platelets.[1] This inhibits platelet aggregation by preventing binding of fibrinogen to the GP IIb/IIIa receptor. Several well conducted studies have demonstrated that abciximab reduces ischemic complications when used in combination with anticoagulant therapy as an adjunct to percutaneous coronary interventions (PCI).[2-4] Abciximab has become a routine therapy for selected individuals undergoing PCI in many institutions across Canada.

The other significant advance in coronary angioplasty over the last decade has been the introduction of coronary stents, which have been shown to reduce the need for repeat revascularization procedures. In 1999 the Cardiac Care Network of Ontario recommended that the use stents in 70% to 75% of angioplasty procedures represented an appropriate rate of utilization.[5] While stenting does reduce the need for emergency coronary bypass surgery, it does not in itself alter the risk of peri-procedural myocardial infarction.

Furthermore, stent deployment is associated with a risk of occlusive stent thrombosis, particularly in the first two weeks following implantation. Although this latter risk has been mitigated by the use of oral anti-platelet agents, combined therapy with a more potent anti-platelet regimen, i.e., a IIb/IIIa inhibitor such as abciximab, has been shown to be the most efficacious method to reduce peri-procedural ischemic complications. Consequently, stents and abciximab may be viewed as complementary rather than competing therapies.

Coronary stents and glycoprotein IIb/IIIa inhibitors are both associated with significant acquisition costs. Prior economic evaluations of stents and abciximab individually have suggested that these are cost effective interventions. A US analysis based on the EPIC study found that the costs associated with abciximab use would be largely offset by the savings in medical care for avoided cardiac events.[6] Coronary stenting was projected to have a reasonable incremental CE ratio of <$20,000 per life year gained over balloon angioplasty.[7] The question currently relevant to many institutions relates to the cost-effectiveness of using combined abciximab and stenting over stenting alone – in other words the economic justification for choosing drugs, devices, or both?

METHODS

This economic analysis incorporated clinical information and cost data in a decision analytic model examining the relative costs and outcomes (clinical events and life expectancy) to address the following question:

Is the use of abciximab in combination with stenting (versus stenting alone) "cost-effective" from the perspective of a Canadian health care system providing interventional cardiac services?

The development of this economic model required inputs from a number of sources, which were then validated through the testing of uncertainty. The steps used are outlined below.

Clinical Data

Data on outcomes for the analysis was drawn from the EPISTENT study, a randomized, prospective, double-blind, multi-centre study that evaluated the effect of abciximab, stents alone or in combination in 2399 patients undergoing PCI in 63 hospitals in the US and Canada.[8,9] The methods are described in the original publication.[8,9]

The primary outcome was a composite of death, myocardial infarction (MI) or urgent repeat revascularization (surgery or PTCA) at 30 days, with a pre-specified secondary outcome of death, MI or target vessel revascularization at six months and one year. There were three arms in that study:

(i) stenting only;

(ii) bolus and infusion of abciximab with balloon angioplasty only (0.25 mg/kg bodyweight up to 60 minute before intervention followed by an infusion of 0.125 mcg/kg per minute up to a maximum of 10 mcg per minute for 12 hours post PCI);

(iii) stenting plus abciximab (combination).

This analysis focused on comparing stenting to abciximab plus stenting. Peri-procedural myocardial infarction was defined as CK-MB (creatinine kinase myocardial band) at least three times upper normal, while large myocardial infarction was defined as CK-MB or CK at least five times upper normal during the index admission, or a new Q wave MI at any time. In

our analysis, we focused on death or large MI because there is greater certainty as to the adverse prognostic impact of large peri-procedural MI.[10]

At one year follow-up, 8 (1%) of 794 patients in the stent plus abciximab group had died, compared with 19 (2.4%) of 809 in the stent only group (hazard ratio 0.43 [95% CI 0.19-0.97], p=0.037). The combined endpoint of death or large MI at one year occurred in 42 (5.3%) and 89 (11.0%) respectively (0.46 [0.32-0.67], p<0.001). Major bleeding rates at 30 days were similar (2.2% vs. 1.5%). The outcome probabilities are summarized in Table 1.

TABLE 1: EPISTENT Results for 30 days and One Year

	Abciximab + Stent (N=794)	Placebo + Stent (N=809)	Sources
30 Days			
Primary composite endpoint (death, MI, urgent revascularization)	5.3% (N=42)	10.8% (N=87)	EPISTENT study [9]
Death, MI	3.0% (N=24)	7.8% (N=63)	EPISTENT study[9]
Any revascularization	6.4% (N=51)	12.7% (N=103)	Text-EPISTENT study[9]
Death	2/784	5/803	EPISTENT study[9]; Zwart-van Rijkom, 2001 [27] EPISTENT study[9]; Islam, 2002 [28]
MI	14/784	26/803	EPISTENT study[9]; Islam, 2002 [28]
Urgent revascularization	9/784	15/803	EPISTENT study[9]; Islam, 2002 [28]
Major Bleeding	1.5% (N=12)	2.2% (N=18)	EPISTENT study[9]
One Year			
Primary composite endpoint (death, MI, urgent revascularization)	20.1% (N=160)	24.0% (N=194)	Topol, 1999[8]
Death and MI (any)	6.8% (N=54)	13.1% (N=106)	Topol, 1999[8]
Target vessel revascularization	15.2% (N=121)	15.6% (N=126)	Topol, 1999[8]
Death	1.0% (N=8)	2.4% (N=19)	Topol, 1999[8]
MI (any)	5.9% (N=47)	11.3% (N=91)	Topol, 1999[8]

Estimation of Survival

Survival beyond the time frame of the clinical trial was estimated using three distinct methodologies.

1. A Markov model was used to calculate survival based on the following death rate assumptions:
   - i) Background mortality[12] for those patients without a repeat procedure or a complication;
   - ii) Late mortality associated with peri-procedural MIs following a PCI based on three year follow up data from the EPIC study[11] and;
   - iii) Excess mortality following cardiac procedures.[7]

For example, the expected non-vascular mortality for a 60-year-old man in Canada is 1.25% over one year.[12] Following angioplasty the additional expected mortality owing to the diagnosis of stable coronary disease is about 2% per year[11] and a peri-procedural MI adds approximately 5% per year.[11] The need for an extra revascularization procedure adds another 0.4% per year.[7] EPIC patients were considered high risk patients.

2. Life expectancy estimates were also derived from extrapolations of one year EPISTENT results to a lifetime time frame using the Duke cardiac registry. This analysis focused on differences in survival only and did not consider the potential long-term impact of other events such as peri-procedural MIs. Compared with the stent only group, the combination arm had an expected incremental life expectancy of one year per survivor (expected duration of life for a survivor) or 0.15 years per patient treated (discounted at 3%).[8] The extrapolation from the Duke cardiac registry yielded more conservative estimates for survival gain with combination therapy and these were used in the base case analysis.

3. A third analysis used mortality data from a published analysis pooled survival data in three randomized trials (EPIC, EPILOG and EPISTENT) that evaluated abciximab. After three years of follow-up, there was a 6.4% mortality rate for the placebo group as compared to 5.0% for the abciximab group, an absolute decrease of 1.4% over a three year time horizon.[13]

Economic Data and Analysis

A decision analytic model was developed using DATA 4.0 software (TreeAge, Williamstown, MA) to simulate the clinical outcomes and resource consumption of patients being managed using stenting or combination therapy.

The simulated pathways included the baseline and follow-up hospitalizations using the primary endpoints as described in the EPISTENT trial. Costs for angioplasty, other procedures and hospitalizations were obtained from the Ontario Case Costing Initiative (OCCI), a clinical and financial database of 13 teaching and community hospitals in the province of Ontario (Table 2). OCCI methodology is described elsewhere (www.occi.org).

The cost of a stent was incorporated into the overall hospital cost from the OCCI. Physician, non-medical and indirect costs were excluded from the analysis. All costs shown are in 1998 Canadian dollars based on Ontario hospital costs. Costs are not discounted given the one year time horizon (Table 2).

TABLE 2: Cost Data

Item	Description	Average Total Cost Estimate	Source
PTCA	Uncomplicated PTCA	$3,592	OCCI
PTCA + CABG	PTCA complicated by acute CABG	$15,152	OCCI
PTCA + MI	PTCA complicated by acute MI	$7,772	OCCI
PTCA + bleeding	PTCA complicated by acute major bleed	$6,867	OCCI
Death	PTCA complicated by death	$5,219	OCCI
CABG	CABG in follow up period	$17,995	OCCI
MI	MI in follow up period	$5,219	OCCI
Abciximab	3 vials @ $536.67	$1,610	Eli Lilly Canada

Time Horizons

The cost-effectiveness analyses were conducted over two time horizons: one year and over a lifetime. The first analysis provided a measure of incremental cost per clinical event avoided over the clinical trial period. In order to gauge the relative value of abciximab plus stenting compared with other accepted cardiac interventions, we also estimated the incremental cost per projected gain in survival. A discount rate of 3% was applied to the survival estimates for life years accrued beyond the first year.

Incremental Analysis

The incremental analysis determined the cost per composite event avoided. The composite events were considered death and large MI. The cost per composite event avoided was difficult to interpret in the absence of similar benchmarks for cost-effectiveness in other cardiovascular interventions. For comparability, the cost per life years gained was also calculated.

Sensitivity Analyses

Uncertainty in the cost effectiveness estimates was tested by varying the relative risk reductions, bleeding rates and survival estimates in a number of one-way sensitivity analyses for combination therapy compared with stenting alone. A Monte Carlo analysis wherein all event probabilities were varied simultaneously through a simulation of 10,000 individual patient trials was also conducted. Ninety-five percent confidence intervals on cost and incremental cost effectiveness ratios were generated.

RESULTS

The expected cost over a one year period was $8,617 for the abciximab plus stent arm, compared with $7,541 for the stent only group, yielding an incremental cost of $1,076. One-third of the additional cost of abciximab was offset by reductions in expenditures on hospitalizations for ischemic events and interventional procedures over the one year time frame. The one year endpoint of death or large MI occurred in 42 patients (5.3%) in the combination group and 89 patients (11.0%) in the stent only group.

The incremental cost per death or large MI avoided was therefore $18,874 for the combination compared with stent alone (crude 95% CI based on bounds of hazard ratio $14,559-$30,657). Expected gains in survival were incorporated into the decision analytic model. The survival based on the Markov model that incorporated higher death rates following coronary events or procedures in this population was 11.57 years for the abciximab plus stent group and 11.19 years for the stent only group, a difference of 0.38 years. Results from the Duke database suggested that the expected survival gain with combination therapy would be smaller at 0.15 years (based on the extrapolation of the difference in survival only).[9]

Assuming that there would be no difference in follow up costs beyond the initial one year and thus applying the cost differential of $1,076 to the conservative estimate of survival gain of 0.15 years, the incremental cost effectiveness ratio for the use of combination therapy over stenting alone was $7,173 per life years gained. Using the survival difference from the Markov model the cost effectiveness ratio was smaller at $2,832 per life year gained.

The third analysis calculated survival with an absolute mortality difference of 1.4%. The stent plus glycoprotein group had a survival time of 11.77 years compared to the stent only group survival time of 11.53 years. The effectiveness ratio was $4,483 per life year saved.

Sensitivity Analyses

For the analyses described above, the models were re-calculated using variations in outcome and bleeding rates through the 95% confidence intervals of the composite endpoints for the abciximab arms in each of the trials. The baseline cost-effectiveness ratio of $7,173 per life year gained had variability from $4,615 up to $45,167, with changes in the 30 day outcomes and mortality post-MI having the most effect.

The Monte Carlo sensitivity analysis involved simultaneous variation of all event probabilities in 10,000 individual simulations of the cost model. This yielded a 95% confidence interval around expected incremental cost for combination therapy versus stent alone: $601 to $1,536 (base case $1,076).

Using these bounds for costs showed that the estimates for incremental cost effectiveness ratios based on the Duke mortality estimates varied over a relatively small range of $4,007 to $10,240.

DISCUSSION

Platelet inhibition by antagonism of the glycoprotein IIb/IIIa receptor has been shown to offer important clinical improvements in many patients undergoing coronary angioplasty.[2-4,14,15] The economic analysis presented in this paper suggests that the use of abciximab is also justifiable on economic grounds, specifically the estimate of $7,173 per life year gained is attractive and reasonably robust.[14]

A critical issue for this analysis involves the selection of relevant outcomes. Examination of 30 day clinical events alone does not provide an adequate gauge of the value of the therapy. The pooled results of the EPIC, EPILOC and EPISTENT cohorts demonstrate that abciximab treated patients may experience a long-term survival benefit.[13]

Therefore, the difference in life expectancy is an appropriate outcome measure. Furthermore, it is important to translate the intermediate events into an estimate of survival in order to gauge the relative value of abciximab against other therapies. A comparison of the economic outcomes of our models to other commonly employed cardiac interventions indicated that the use of abciximab is quite attractive.

For instance, the use of recombinant tissue plasminogen activator (rtPA) over streptokinase for the treatment of acute myocardial infarction in the GUSTO study was associated with an incremental cost effectiveness ratio of $32,678 US per life year gained[6] format reference.

In another economic analysis, the use of coronary stenting compared with conventional balloon angioplasty had an estimated incremental cost-effectiveness ratio of $23,000 US per quality-adjusted life year gained.[7] Our estimates may be conservative because they do not incorporate physician costs. Since abciximab reduces ischemic complications, and with contemporary dosing of co-administered drugs, particularly heparin, does not significantly increase bleeding, the inclusion of physician fees would probably have diminished the incremental net cost associated with abciximab due to the decrease in complications.

Our sensitivity analyses indicated that the base case results were stable or "robust." In nearly all the "worst case" scenarios for abciximab in the three populations, the incremental cost effectiveness ratios were still under $20,000 per life year gained, making it an intervention with "strong evidence for adoption" according to published guidelines regarding the attractiveness of medical therapies.[14]

Our results agree with other published economic evaluations. Lucore and colleagues examined the costs and outcomes of stenting with and without abciximab in a cohort of community patients undergoing PCI between 1995 and 1997.[16] Costs were derived from the hospital financial database. Totals costs for the stent population with and without abciximab were $12,027 and $10,493 (US$-1995-1997) respectively. The costs calculated were based on a high risk population in whom stenting plus abciximab was more common.

Other analyses have also suggested that abciximab is favourable in economic terms. As part of the US EPIC study, economic data, including physician fees, were collected prospectively.[6] During the six-month follow-up, abciximab decreased the repeat hospitalization rate by 23% (p=0.004) and repeat revascularization by 22% (p=0.04), producing a mean $1,270 savings per patient. With a cost of $1,407 US for the abciximab bolus and infusion, the net cost over six months was $293 US per patient. In the subgroup of patients with unstable angina, abciximab was considered a dominant strategy leading to improved clinical outcomes and a cost savings of $763 US per patient treated.[15]

In our analysis from the Canadian health care system perspective, the cost of abciximab was only partially offset by the costs associated with reductions in clinical events and hospitalizations, since these events have a much lower "price tag" than in the US. For example, based on the OCCI data, we estimated that the average total hospital cost of coronary bypass surgery in the follow-up period was $17,995 CDN and of an angioplasty was $3,592 CDN. In the US analysis, these figures were much higher at $26,747 US and $8,877 US respectively.[11]

An Australian economic analysis, based on EPIC study results, indicated that the use of abciximab was associated with a cost per additional life-year gained of $5,547 (Australian), which is similar to our findings.[17]

Two other glycoproteins inhibitors, eptifibatide and tirofiban, are available in Canada, although tirofiban is not indicated for use during PCI unless it has already been initiated for treatment of acute coronary syndrome. The ESPRIT study, comparing eptifibatide to placebo in patients receiving stents, showed improved outcomes associated with the drug therapy.

In that study, the primary composite clinical end points of death, MI and urgent revascularization were significantly different (p=0.003) at 30 days in the eptifibatide group (6.8%) when compared to the placebo group (10.5%).[18] Consequently, eptifibatide may show comparable economic value; particularly as its acquisition cost is less than abciximab.

An interesting and related question involves the incremental cost-effectiveness of using abciximab in place of eptifibatide, rather than in place of placebo. There is limited data directly comparing clinical outcomes with abciximab and eptifibatide.

The PRICE trial examined the 30 day clinical and economic outcomes for abciximab and eptifibatide in a mixed population of elective balloon angioplasty and stent implantation. In that study, composite clinical end points of death, non-fatal MI and urgent revascularization occurred in 4.9% of abciximab and 5.1% of eptifibatide patients (p=0.84) by hospital discharge.[19] At 30 days, results showed that 5.6% of abciximab patients compared to 6.3% of eptifibatide patients had a composite endpoint (p =0.95).

Although clinical outcomes were not statistically significant, eptifibatide use was associated with lower in-hospital and 30-day costs compared with abciximab in patients undergoing elective PCI. Limitations of this study include the small sample size (N=320), and the limited power to detect differences in clinical events.

There are a number of limitations to this evaluation. Models are criticized because they are theoretical and based in part on assumptions about patient management and outcomes. Data are often derived from a variety of sources and costs that reflect assumptions rather than true utilization. There are a number of ways to address the uncertainty resulting from decision analytic modeling including sensitivity analysis, sub analysis, population criteria and prospective economic evaluation.

Sensitivity analysis is used to explore the impact of the model inputs. Our sensitivity analysis results showed similar cost-effectiveness ratios when bleeding rates and survival were varied. Examination of different study populations (i.e., diabetes, gender) can also provide confirmation of the clinical outcomes.[23, 24]

Models are typically populated with outcomes based on controlled clinical trial study designs. This data cannot necessarily be extrapolated to real world practice. This concern might be addressed by the application of stringent inclusion and exclusion criteria, mirroring those of the clinical trials, in the selection of patients who will be treated with abciximab. Ideally, an economic evaluation should be done prospectively with complete capture of actual resource utilization and clinical outcomes in our own practice setting over a long period of follow up. No Canadian data was available and we therefore used modeling techniques while testing of uncertainty in the models.

Some authors have questioned the importance of small peri-procedural myocardial infarctions; however, the long-term EPIC data[11] as well as several other observational studies,[25, 26] demonstrate a relationship between even modest cardiac enzyme rise and survival. We did explore alternate scenarios (i.e., lower MI rates and less or even no impact on survival of peri-procedural MI) in the sensitivity analyses, and the results did not differ appreciably from the conclusions in the base case.

The decision analytic results presented here are further validated by Topol and colleagues, who published an economic evaluation based on one-year outcomes in EPISTENT.[9] The incremental cost-effectiveness ratio for abciximab plus stent vs. placebo plus stent of $6,213 US per life year gained was of similar scale to our results ($7,153/CDN life year gained). European investigators presented similar costs for stented (EUR 7,844) and non-stented (EUR 7,904) patients.[27]

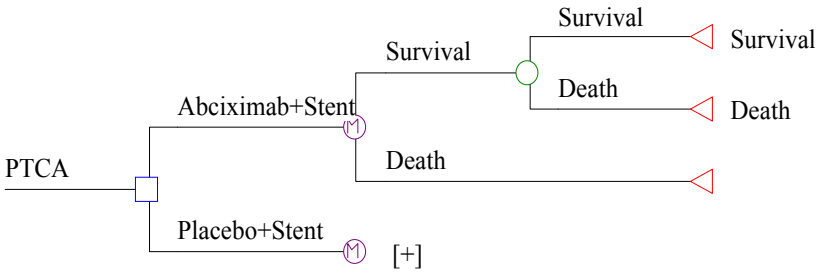
CONCLUSIONS

In a broad range of patients undergoing coronary angioplasty, the use of abciximab is associated with reductions in ischemic events and the need for repeat interventions is at a very reasonable cost from the Canadian perspective.

The incremental cost effectiveness ratios for the combination of abciximab plus stenting versus stenting alone compare favourably with other accepted cardiac interventions; and thus there is justification for adoption of this intervention into clinical practice.

Figure 1 Decision analytic model for a one-year time horizon

Figure 2 Decision analytic model for survival



Funding sources

This investigator initiated project was supported by a research grant from Eli Lilly Canada Inc. Authors had independent control of the analysis. Dr. Cohen has received speaker's honoraria and ad hoc consulting fees <$10,000 (in the past 3 years) from Eli Lilly Canada. Drs. Oh and Mittmann have received consulting grants. The institution receives research and educational support from Eli Lilly Canada.

REFERENCES

1. Lefkovits, J, Plow EF, and Topol EJ, Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Engl J Med 1995;332(23):1553-9.
2. Topol, EJ, et al., Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. The EPIC Investigators. Lancet 1994;343(8902):881-6.
3. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. N Engl J Med 1994;330(14):956-61.
4. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. N Engl J Med, 1997; 336(24):1689-96.
5. Canadian Cardiac Network, CCN-Expert Panel on Coronary Stenting (www.ccn.on.ca). 1999.
6. Mark, DB, et al., Economic assessment of platelet glycoprotein IIb/IIIa inhibition for prevention of ischemic complications of high-risk coronary angioplasty. EPIC Investigators. Circulation, 1996;94(4):629-35.
7. Cohen, DJ, et al., Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease. Use of a decision-analytic model. Circulation, 1994;89(4):1859-74.
8. Topol, E, et al., Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. Lancet, 1999;354:2019-2024.
9. The EPISTENT Investigators, Randomised placebo-controlled and balloon-angioplast-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Lancet, 1998;352:87-92.
10. Califf, RM, et al., Myonecrosis after revascularization procedures. J Am Coll Cardiol, 1998;31(2): 241-51.
11. Topol, EJ, et al., Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. JAMA, 1997;278(6):479-84.
12. Statistics Canada, Life tables. 1995.
13. Topol, E, et al., Multi-year follow-up of abciximab therapy in three randomized, placebo controlled trials of percutaneous coronary revascularization. American Journal of Medicine, 2002;113:1-6.
14. Laupacis, A., et al., How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J, 1992;146(4):473-81.
15. Lincoff, AM, et al., Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. EPIC Investigators. Evaluation of 7E3 in Preventing Ischemic Complications. J Am Coll Cardiol, 1997;30(1):149-56.
16. Lucore, C, et al., Impact of abciximab and coronary stenting on outcomes and costs of

percutaneous coronary interventions in a community hospital. Coronary Artery Disease, 2001;12:135-142.
17. Aristides, M, et al., Effectiveness and cost effectiveness of single bolus treatment with abciximab (Reo Pro) in preventing restenosis following percutaneous transluminal coronary angioplasty in high risk patients. Heart, 1998;79(1):12-7.
18. ESPRIT Investigators, Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet, 2000;356(9247):2037-44.
19. The PRICE Investigators, Comparative 30-day economic and clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor use during elective percutaneous coronary intervention: Prairie ReoPro versus Integrilin Cost Evaluation (PRICE) Trial. American Heart Journal, 2001;141(3):402-409.
20. Juergens, C, et al., A mutlicenter study of the tolerability of tirofiban versus placebo in patients undergoing planned intracoronary stent placement. Clinical Therapeutics, 2002;24(8):1332-1344.
21. Topol, E, et al., Comparison of two platlet glycoprotein IIb/IIIA inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. NEJM, 2001;344(25):1888-1894.
22. Moliterno, DJ, et al., Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. Lancet, 2002;360(9330):355-60.
23. Cho, L, et al., Optimizing percutaneous coronary revascularization in diabetic women: analysis from the EPISTENT trial. Journal of Women's Health and Gender Based Medicine, 2000;9(7):741-746.
24. Marso, SP, et al., Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of platelet IIb/IIIa inhibitor for stenting trial) diabetic substudy. Circulation, 1999;100(25):2477-84.
25. Kong, TQ, et al., Prognostic implication of creatine kinase elevation following elective coronary artery interventions. JAMA, 1997;277(6):461-6.
26. Abdelmeguid, AE, et al., Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. Circulation, 1996;94(7):1528-36.
27. Zwart-van Rijkom, J, et al., Costs and effects of combining stenting and abciximab (RePro) in daily practice. International Journal of Cardiology, 2001;77:299-303.
28. Islam, M, et al., Effect of abciximab on angiographic complications during percutaneous coronary stenting in the evaluation of platelet IIb/IIIa inhibition in stenting trial (EPISTENT). American Journal of Cardiology, 2002;90:916-921.