AN ECONOMIC EVALUATION OF CLOPIDOGREL IN PATIENTS WITH VASCULAR DISEASE

by

Chau Tran, B.Sc.

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Graduate Department of Pharmacology
University of Toronto

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Chau Tran
Graduate Department of Pharmacology
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ABSTRACT

An economic evaluation was undertaken to estimate costs and survival outcomes with clopidogrel, a novel antiplatelet vs comparator drug treatment in patients with ischemic stroke (IS), myocardial infarction (MI) or peripheral arterial disease (PAD).

From a decision analytic model, the use of clopidogrel ($2.47/day) vs ASA ($0.0147/day) as 1st line treatment was associated with a projected gain of 0.29 years on average per patient at a cost of $32,240 per life year (LY) gained for MI, IS and PAD populations. In the PAD population, clopidogrel vs ASA generated 0.94 LYs at $11,401 per LY gained. In 2nd line therapy scenarios, clopidogrel vs ticlopidine ($2.18/day) generated 0.11 LYs at $19,852 per LY gained per stroke patient while clopidogrel vs placebo offered an additional 0.37 LYs at $26,084 per LY gained per MI patient.

This comprehensive economic evaluation assists in quantifying the "value" and defining rational prescribing guidelines of a new therapy.

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LIST OF ABBREVIATIONS

ADP	adenosine diphosphate
ARR	absolute risk reduction
ASA	acetylsalicylic acid
ATC	Antiplatelet Trialists' Collaboration
ATP	adenosine triphosphate
bid	twice a day
C_{max}	maximum concentration
Ca^{2+}	calcium
CABG	coronary artery bypass graft
cAMP	cyclic adenosine monophosphate
CAPRIE	clopidogrel versus ASA in patients at risk of ischaemic events
CATS	Canadian American Ticlopidine Stroke Study
CCU	critical care unit
CEA	cost-effectiveness analysis
CER	costs-effectiveness ratio
CI	confidence interval
CIHI	Canadian Institute for Health Information
CMG	case mix group
CT	computer tomography
CUA	cost-utility analysis
CVD	cardiovascular disease
ECG	electrocardiogram
EDRF	endothelium derived relaxing factor
ER	emergency room
F/U	follow-up
GI	gastrointestinal
GP	glycoprotein
ICD	International Classification of Diseases
IS	ischemic stroke
JPPC	Joint Policy and Planning Committee
LDL	low density lipoprotein
LOS	length of stay
LY	life year
MI	myocardial infarction
MOH	Ministry of Health
NO	nitric oxide

NSAID	non-steroidal anti-inflammatory agent
NVAF	non-valvular atrial fibrillation
OCCP	Ontario Case Costing Project
ODBF	Ontario Drug Benefit Formulary
OHIP	Ontario Health Insurance Plan
QALY	quality adjusted life year
PAD	peripheral arterial disease
PCP	primary care physician
PGH	prostaglandin H
PGD_2	prostaglandin D_2
PGE_2	prostaglandin E_2
PGF_2	prostaglandin F_2
PGG_2	prostaglandin G_2
PGH_2	prostaglandin H_2
PGI_2	prostaglandin I_2
PL	phospholipid
PLA_2	phospholipase A_2
PTCA	percutaneous transluminal coronary angioplasty
RIND	reversible ischemic neurologic deficit
RRR	relative risk reduction
SD	standard deviation
STIMS	Swedish Ticlopidine Multicentre Study
SWCHSC	Sunnybrook & Women's College Health Sciences Centre
TASS	Ticlopidine ASA Stroke Study
TSI	Transition Systems Incorporated
TIA	transient ischemic attack
TXA_2	thromboxane A_2
VSM	vascular smooth muscle
vWF	von Willebrand Factor

1. INTRODUCTION

1.1 CARDIOVASCULAR DISEASE AND EPIDEMIOLOGY

STATEMENT OF THE PROBLEM

Despite advances in pharmacologic and non-pharmacologic therapies, the incidence, prevalence and impact of cardiovascular disease in Canada is still tremendous. Cardiovascular disease (CVD) is the leading cause of death in men and women in Canada and comprises 37% of all fatal events (1). Hospitalizations and procedures related to the management of CVD, i.e., myocardial infarctions (MIs), stroke and peripheral arterial disease (PAD), account for an estimated $7.4 billion in direct costs, the highest amongst all illnesses (1). Disability arising from CVD contributes $15.3 billion to indirect costs (1). These figures suggest that there is still a need for agents with greater therapeutic effectiveness, that will potentially improve clinical outcomes, save resources, as well as improve the quality of life for patients (2).

One of the attempts made to manage CVD is through drug therapy. Over the years, the cost of pharmacological management of CVD has increased related to an increase in drug usage, the aging population and the availability of more costly medications. In 1996, prescription drugs for the treatment of CVD comprised 12.8% of the total 234.6 million prescriptions dispensed in Canada (1) and accounted for the largest proportion (28.5%) of total sales from patented drugs, an estimated $1.6 billion (3). New therapies in general offer enhanced clinical benefits but also carry a further requirement for drug expenditures.

The focus of this thesis is to examine the impact of clopidogrel, a novel anti-platelet, both in terms of therapeutic efficacy and cost. An overview of stroke, MI and PAD will be presented, followed by some background information on pharmacoeconomic analyses.

1.2 ETIOLOGY AND PATHOGENESIS OF VASCULAR DISEASE

The underlying pathogenesis of stroke, MI and PAD are similar, however, for each disorder, it is the clinical manifestation of each disease that varies. Simply, clinical events occur when there is an impairment in blood flow. A stroke is a focal neurologic deficit caused by a disturbance in blood flow to the brain, of any cause and generally of sudden onset (4). There are two major types of stroke: ischemic and hemorrhagic (5). Ischemic stroke accounts for 80% of strokes and is a situation of compromised blood flow as a result of an occlusion. Hemorrhagic stroke accounts for the remaining 20% of strokes and occurs when the vessel wall becomes fatigued, weakened and then ruptures. The outflowing blood seeps into the surrounding areas, becomes coagulated and compresses brain tissue and blood vessels.

Myocardial infarction (MI) is a reduction in blood flow to the heart (ischemia) caused by an occlusive intracoronary thrombus in 90% of the cases (6). The biochemical, functional and morphological responses are dependent on the severity of flow deprivation. With ischemia, loss of contractility occurs, and if ischemia is prolonged, necrosis of the myocardium can occur leading to the two types of MIs, transmural infarction and subendocardial (nontransmural) infarction. A transmural infarction is more common. Ischemia leads to necrosis of the ventricular wall of the heart in the vicinity of a single coronary

artery. In a subendocardial infarct, the area of ischemic necrosis encompasses the inner one third or half of the ventricular wall, extending laterally beyond the perfusion territory of a single coronary artery. Ischemia can also predipose arrhythmias or death.

Peripheral arterial disease (PAD) is described as a condition in which the blood flow to the periphery has become compromised because of reduced systemic blood pressure. It primarily affects the lower limbs and in a third of PAD patients, within 5 to 10 years, surgical intervention is required (i.e., coronary artery bypass grafts (CABGs), percutaneous transluminal coronary angioplasties (PTCAs), or aorta-iliac femoral bypass grafts) (7). If PAD progresses to a severe stage, leg ischemia and necrosis occurs to a level where amputation is necessary.

Stroke, MI or PAD is caused by atherosclerosis that leads to thrombus or embolus formation (5).

1.2.1 ATHEROSCLEROSIS

There are three forms of arteriosclerosis: i) atherosclerosis, ii) arteriolosclerosis and iii) Monckeberg's medial calcific sclerosis. Atherosclerosis is the most important form of arteriosclerosis, or "hardening of the arteries". It is a pathological process in which calcified lipid or fatty deposits from the flowing blood accumulate along the inner vessel wall to become an atheroma or atherosclerotic plaque characterized by intimal thickening and lipid deposition (8). The process of atherosclerosis begins with an alteration in endothelial adhesiveness that permits monocytes to attach to the endothelium (Figure 1). The monocytes infiltrate and accumulate in the subendothelial space. The monocytes are converted into tissue macrophages that express both native low-density lipoprotein (LDL) receptors as well as scavenger receptors. Upon binding to the LDL receptor, LDL functions to remove cholesterol (oxidized lipoprotein) from the blood to liver and extrahepatic tissues (9). The scavenger receptors have a greater affinity for oxidized lipoprotein and are not down-regulated by intracellular levels of cholesterol like LDL receptors. They can become expressed in an uncontrollable fashion, continually binding to and incorporating oxidized lipoprotein. Eventually, they become lipid-laden and transformed into foam cells ("fatty streaks").

In areas where blood flow is disturbed, i.e., bends and bifurcations of the blood vessel, fatty streaks tend to localize. These areas are also associated with an increase in endothelial permeability, reduction of nitric oxide (NO) and prostacyclin release from endothelium, and increased expression of adhesion molecules. NO, also known as endothelium-derived relaxing factor (EDRF), and prostacyclin are vasodilators and inhibitors of platelet aggregation (10). These tend to be vessel constricted areas with increased susceptibility to platelet aggregation. Macrophages accumulate around the fatty streak causing endothelial injury. At the injured site, these cells elaborate oxygen-derived free radicals as well as cytokines and proteases which can also injure and disrupt the overlying endothelium. Platelets may bind to this injured area and release platelet derived growth factor (PDGF) which stimulates vascular smooth muscle (VSM) in the media (2^{nd} layer of the vessel wall) to proliferate and migrate into the area of

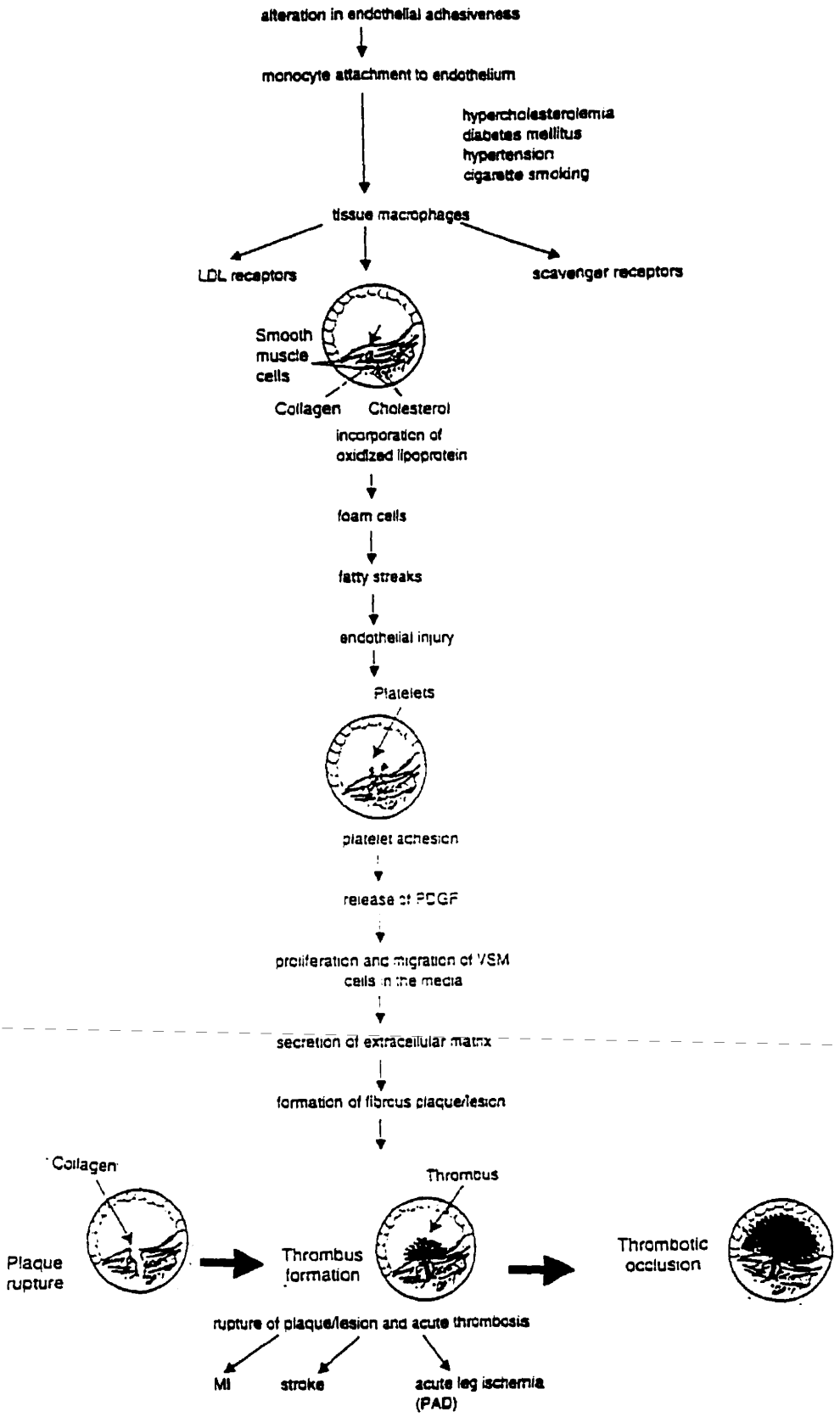


FIGURE 1: Process of atherosclerosis. Adapted from Gonzalez and Kannewurf (1998) (11)

injury. The VSM cells secrete extracellular matrix and form a fibrous plaque or lesion which walls off the underlying macrophage and necrotic debris from the flowing blood.

Over time, monocytes and vascular smooth muscle cells continue to add to the endothelium. The plaque or lesion eventually becomes obstructive causing angina (in coronary artery) or intermittent claudication (in the peripheral artery). Upon rupture of the lesion and subsequent acute thrombosis, a MI, stroke or acute leg ischemia occurs. The rupture of the plaque occurs because of shear stress (the difference in blood flow velocity at the centre of the vessel lumen and its perimeter) exerted on susceptible areas (11). Macrophages infiltrate at the site and release metalloproteinases which gradually dissolve the fibrous plaque or lesion. The necrotic core plaque is exposed to flowing blood which contains thrombogenic tissue factor and macrophages which contribute to a sudden vascular thrombotic occlusion.

The major risk factors for atherosclerosis are poor diet, hyperlipidemia, hypertension, cigarette smoking and diabetes. The minor risk factors for atherosclerosis are obesity, physical inactivity, male gender, increasing age, family history, stress, oral contraceptives, high carbohydrate intake and hyperhomocysteinemia (8).

1.2.2 THROMBUS

A thrombus is a blood clot, an aggregation of platelets and fibrin formed as a result of an atherosclerotic lesion or vessel injury. There are several processes which characterize platelet thrombogenesis, the underlying pathophysiology to which anti-platelet agents are targeted: platelet adhesion, platelet activation, platelet coagulation, platelet contraction and degranulation, activation of the coagulation system, and platelet aggregation (12-14).

With tissue injury or disruption of the endothelium, subendothelial ligands (prothrombic substances) such as type I and III collagen, elastin, and von Willebrand factor (vWF) are exposed (12) (Figure 2). The subendothelial ligands, for example, collagen, stimulates phospholipase A_2 (PLA_2) to convert phospholipids (PL) into arachidonic acid (15). Prostaglandin H (PGH) synthase exhibits catalytic action upon i) cyclooxygenase, which converts arachidonic acid to prostaglandin G_2 (PGG_2) and ii) peroxidase, which converts PGG_2 to prostaglandin H_2 (PGH_2) (10). PGH_2 is then broken down into metabolites that are either vasodilators, (prostaglandin I_2 or prostacyclin (PGI_2) and prostaglandin E_2 (PGE_2)) or vasoconstrictors, (prostaglandin F_2 (PGF_2), prostaglandin D_2 (PGD_2) and thromboxane A_2 (TXA_2)). PGI_2 is the major product formed in endothelial cells whereas TXA_2 is the major product formed in platelets (10). Both autacoids help to modulate cyclic adenosine monophosphate (cAMP) and adenosine triphosphate (ATP) which in turn help to modulate vascular tone and platelet activation. PGI_2 stimulates the conversion of ATP to cAMP. The increase in cAMP and the corresponding decrease in calcium (Ca^{2+}) leads to a decrease in platelet aggregation. However, TXA_2 helps to stimulate platelet aggregation. In the scenario of tissue injury (e.g., atherosclerosis, or laceration), there is a decrease of PGI_2 formation but an increase in TXA_2 formation (leading to vasoconstriction to reduce blood flow to prevent further bleeding) (16). Vascular smooth muscle cells can synthesize PGI_2 provided that they are

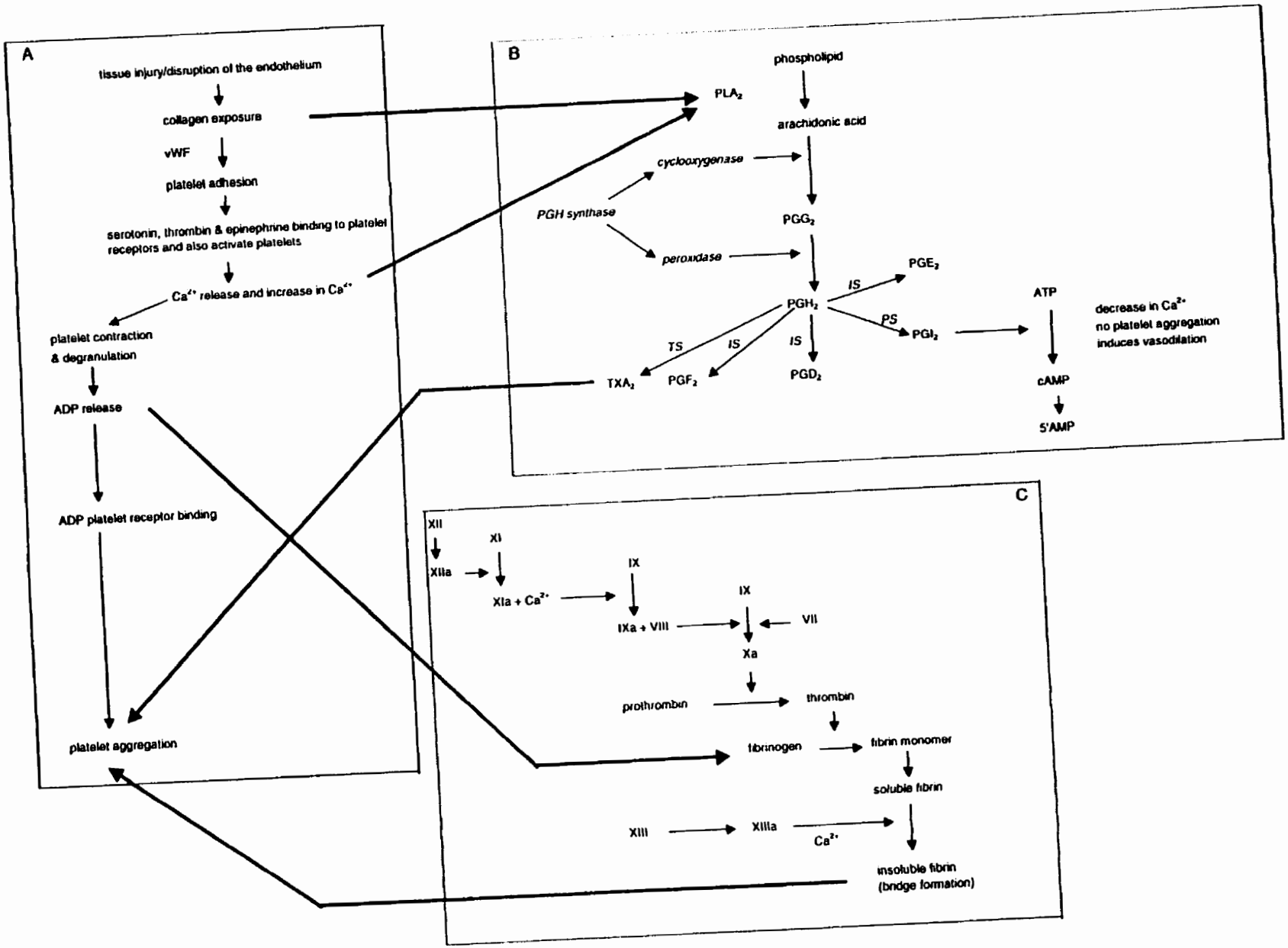


FIGURE 2: Process of thrombus formation via activation of platelets (A), cyclooxygenase pathway (B), and the coagulation cascade (C).

IS - isomerase; *PS* - prostacyclin synthase; *TS* - thromboxane synthase

not also damaged. However, their cyclooxygenase content is less than that of endothelial cells, thus less PGI_2 is produced and formation of TXA_2 is favored leading to platelet aggregation.

The vWF helps to initiate platelet adhesion to the injured site at the vessel wall by binding to platelet membrane glycoprotein (GP) Ib receptors (11). Other subendothelial ligands, such as collagen, bind to their respective platelet receptors and to the vessel wall. Thrombin, serotonin and epinephrine also play a role in platelet adhesion and aggregation upon binding to their platelet receptors (17). Activated platelets then release cytoplasmic Ca^{2+} which initiates two processes of events, platelet contraction or stimulation of the phospholipid pathway and TXA_2 release (12). Platelet contraction then leads to platelet degranulation and the release of adenosine diphosphate (ADP). Free circulating ADP contacts the surface of neighboring platelets, binds to its platelet receptor (high or low affinity purinergic receptor) and initiates further platelet activation. In atherosclerosis, the blood flow is turbulent and this causes ADP and TXA_2 to further initiate platelet activation and aggregation. In this scenario, the intrinsic coagulation cascade is also activated leading to thrombin formation. A thrombus is then formed and stabilized through the formation of fibrin of which ADP has an effect on fibrinogen binding to GPIIb/IIIa platelet receptors ($\alpha_{IIb}\beta_3$ integrin adhesion molecules) on the platelet surface (18). The GPIIb/IIIa receptors are transformed into the GPIIb/IIIa complex, which is the final step in the platelet aggregation pathway. This complex mediates the formation of an insoluble fibrin "bridge" which connects platelets together, to prevent further bleeding.

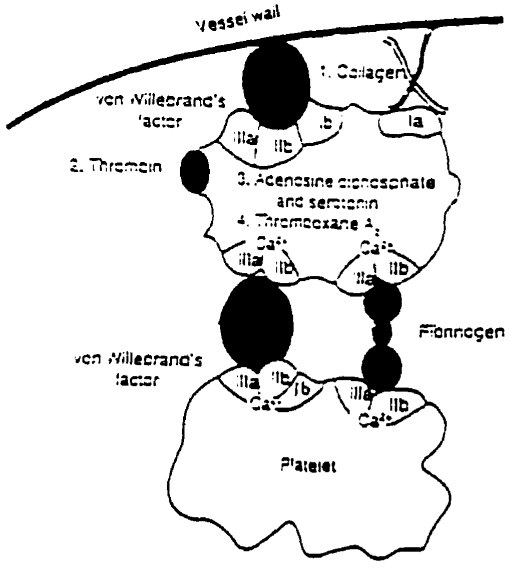


FIGURE 3: Interactions among platelet membrane receptors. Adapted from Fuster et al, 1992 (19)

1.2.3 EMBOLUS

An embolus represents gaseous or particulate matter (e.g., dislodged atherosclerotic plaque or thrombus), that travels. It is carried by the bloodstream until it reaches a narrowed blood vessel where it becomes lodged. The embolus remains in the vessel, clogging the vessel and preventing blood flow

from entering the distal vasculature. The emboli can originate from a variety of locations, such as the heart, lungs, peripheral circulation (PAD), and could reach the cerebral vessels leading to a stroke.

1.3 PHARMACOLOGIC THERAPY

1.3.1 INDICATION FOR ANTI-PLATELET THERAPY

Anitiplatelet therapy is used in the prevention of acute arterial thrombosis in cardiovascular disease (i.e., stroke and MI). It is also prescribed to PAD patients because it has demonstrated effectiveness in decreasing the incidence of cardiovascular events and preventing thrombotic complications after vascular reconstruction (20). There are four classes of antiplatelet agents: I) cyclooxygenase inhibitors (e.g., ASA), ii) agents interfering with ADP-mediated platelet reactions (e.g., ticlopidine, clopidogrel), iii) thrombin inhibitors (e.g., hirudin) and iv) GPIIb/IIIa receptor antagonists (e.g., abciximab) (21). Pharmacological profiles only of clopidogrel, ticlopidine and ASA will be discussed because they are relevant to this thesis.

1.3.2 CLOPIDOGREL

Clopidogrel (Plavix™, SR25990C) is a novel anti-platelet, approved by the Health Protection Branch of Canada in 1999, for the prevention of vascular events in patients who have had a stroke, MI or PAD. It is pharmacologically different from ASA, and more pharmacologically related to its thienopyridine relative, ticlopidine. It irreversibly inhibits platelet aggregation by selectively binding to adenylate cyclase-coupled ADP receptors (low affinity, type 2) on the platelet surface (22). But it has not yet been demonstrated that it directly inhibits fibrinogen binding to membrane glycoprotein (GP IIb/IIIIa) receptors in similarity to ticlopidine.

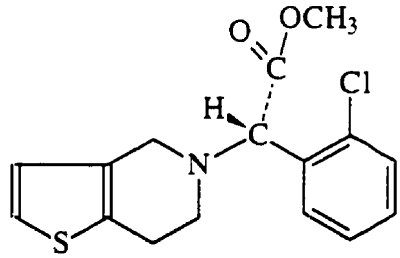


FIGURE 4: Chemical structure of clopidogrel.

Clopidogrel is available in tablet form, 75mg, to be taken orally, once daily. The pharmacokinetic profile of clopidogrel shows rapid absorption that is not affected by food or antacids. It is metabolized to an active metabolite via cytochrome P4501A as demonstrated in rats (23). The structure of the active metabolite has yet to be determined. The pharmacokinetic and pharmacodynamic profiles of the active

metabolite are unavailable and only profiles of the inactive metabolite will be discussed. The CYP2B subfamily of cytochrome P450s has been implicated in the metabolism of clopidogrel into inactive metabolites. SR 26334 is the principal circulating inactive metabolite with an elimination half life of 7.7 hours (24). The time to peak plasma concentration of SR 26334 is 1 hour (25) with the area under the plasma concentration-time curve of 10mg/L·h (24).

Coadministration of ASA with clopidogrel does not modify clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Clopidogrel does not modify the effect of heparin on coagulation nor is a heparin dose adjustment required. As well, there is no effect induced by heparin on clopidogrel anti-platelet action. Coadministration of non-steroidal anti-inflammatory drugs (NSAIDs) causes an increase in gastrointestinal (GI) blood loss as measured by occult fecal blood or GI bleeding events. Clopidogrel administered with atenolol, nifedipine, phenobarbital, cimetidine or estrogen does not produce any changes in clopidogrel pharmacodynamics and vice versa. The pharmacokinetics of digoxin or theophylline are not modified by the coadministration of clopidogrel. At high concentrations in vitro, clopidogrel inhibits CYP2C9 and thus it may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and some NSAIDs.

In animal models (rat and rabbit), clopidogrel does not elicit carcinogenesis, mutagenesis or impairment of fertility. However, as observed in rats, clopidogrel and/or its metabolites are excreted in breast milk.

The pharmacological properties of clopidogrel have translated into better efficacy in treating patients with ischemic vascular diseases. No direct comparisons between clopidogrel and ticlopidine in clinical trials have been performed (26). However, with respect to adverse events, it is more favorable than ticlopidine since neutropenia is not a concern and hematologic monitoring is not required. As well, there is a lower overall adverse event rate associated with clopidogrel usage (20.8%) (27) in comparison to ticlopidine usage (44.1%) (28, 29).

In the CAPRIE study, a large randomized, controlled, trial (n=19,185) in patients with established vascular disease, the use of clopidogrel versus ASA was associated with a 8.7% relative risk reduction in cardiovascular events (ischemic stroke (IS), MI and mortality (vascular death subsequent to being diagnosed with PAD)) over 2 years (27). GI symptoms such as indigestion/nausea/vomiting, GI hemorrhage and abnormal liver function were less common for clopidogrel ($p<0.05$) (27). However, rash and diarrhea were reported more frequently with clopidogrel than with ASA ($p<0.05$) (27). It has been suggested that the combined effect of clopidogrel and ASA (both working by different mechanisms) may be therapeutically advantageous for vascular disease patients, and there is an investigation being conducted (26).

1.3.3. CLOPIDOGREL AND THE CAPRIE STUDY

The CAPRIE study is the only randomized, controlled, clinical trial that has been conducted with clopidogrel. In this trial, clopidogrel, 75 mg daily, was compared to ASA, 325 mg daily. Patients were selected according to the qualifying conditions of IS, MI or PAD. The outcome events recorded were non-fatal events (due to IS, MI, intracranial hemorrhage, and leg amputation), and deaths (due to IS, MI,

hemorrhage, other vascular causes, or non-vascular causes). Other vascular deaths refers to deaths not caused by IS, MI, or hemorrhage and were not clearly non-vascular in nature. The study had 90% power to detect an overall relative-risk reduction (RRR) (in experiencing one of the outcome events) between 12% to 13% in the combined patient populations of IS, MI and PAD for the intent-to-treat analysis. The study was not powered to detect changes within the individual patient groups. In all three patient populations, a total of 9,553 subjects received clopidogrel and 9,546 subjects received ASA. A similar proportion of patients (approximately 21%) in both the clopidogrel and ASA groups discontinued drug therapy. Mean compliance was similar in both treatment groups (approximately 91%). Approximately 14% of patients on clopidogrel and 15% of patients on ASA experienced an outcome event. From the intent-to-treat analysis, the event rate per year was 5.32% and 5.83% for clopidogrel and ASA therapy respectively across all patient populations and this was statistically significant. The absolute risk reduction (ARR) is 0.5% (5.83% minus 5.32%) for clopidogrel versus ASA therapy. In the combined patient populations of IS, MI and PAD, the relative-risk reduction was 8.7% (95% confidence interval (CI) of 0.3% to 16.5%), in favor of clopidogrel treatment, which was found to be statistically significant. This RRR of 8.7% for clopidogrel therapy [(5.83%-5.32%)/5.83] is over and above the reported 25% RRR that ASA produces in such clinical groups as demonstrated in the Antiplatelet Trialists' Collaboration (ATC) Meta-analysis, a statistical compilation of outcomes from antiplatelet therapies (30). Although the CAPRIE trial was not powered to detect changes in the RRR in each of the IS, MI and PAD populations separately, an analysis was still conducted. For the stroke group, the RRR was not significant, i.e., 7.3% (95% CI –5.7% to 18.7%). The MI group did not appear to benefit from clopidogrel therapy, with a RRR of –3.7% (95% CI –22.1% to 12%). However, the PAD group benefited the most from clopidogrel therapy, with a RRR of 23.8% (95% CI 8.9% to 36.2%). A test of heterogeneity for treatment effects was statistically significant suggesting that each of the three clinical groups may not benefit from clopidogrel therapy to the same extent and that such differences in treatment effect are not due to chance alone.

The investigators of the study attempted to offer an explanation for the lack of effect of clopidogrel in the MI group. A subgroup analysis was conducted whereby patients with the qualifying condition of IS or PAD who also had a previous history of a MI were examined. In this scenario, this group had a RRR of 22.7% (95% CI 4.9 to 37.2%). As this group of patients was combined with the MI cohort, the RRR reduced to 7.4% (95% CI –5.2% to 18.6%). This suggests that only patients with an IS or PAD and a previous history of MI benefit from clopidogrel therapy but not patients with MI alone.

Overall, the absolute relative risk reduction suggests that 200 patients need to be treated per year to prevent one event (the number needed to treat equals the inverse of the ARR) (31). Or as stated in the CAPRIE study, according to the sample sizes in each patient population, clopidogrel will prevent 24 events versus aspirin which will prevent 19 events per 1000 patients treated per year. The cost impact of preventing 5 additional events with clopidogrel therapy needs to be elucidated in order to determine the relative worth of introducing this novel anti-platelet for use in the clinical setting amongst other pharmacological agents.

1.3.4 TICLOPIDINE

Ticlopidine is also a thienopyridine derivative, an older relative of clopidogrel. It inhibits the expression, occupation or function of the platelet 2-methylthio-ADP-binding receptor subtype and the ADP-induced exposure of the fibrinogen binding site of the platelet glycoprotein GPIIb/IIIa receptor (32). This produces inhibition of ADP-induced platelet aggregation apparent 24 to 48 hours after the start of multiple dose treatment and maintained for several days after withdrawal (33, 34). Ticlopidine also inhibits platelet aggregation induced by collagen, platelet activation factor, epinephrine, thrombin and arachidonic acid which may be indirect effects of ADP inhibition (35). The exact mechanism of these actions has not yet been fully characterized (36).

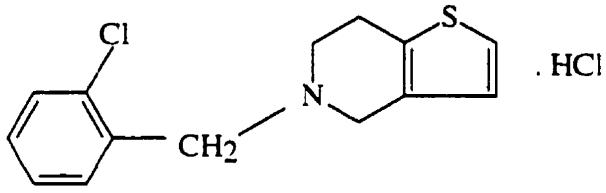


FIGURE 5: Chemical structure of ticlopidine.

Ticlopidine is available in tablet form, administered 250mg twice a day. Examining the pharmacokinetic information, it is metabolised in the liver, principally by N-dealkylation, N-oxidation and oxidation of the thiophene ring (37-39). Approximately 80% to 90% of oral ticlopidine is absorbed (37, 39). Peak plasma concentrations (C_{max}=0.31 to 0.70 mg/L) are attained approximately 2 hours after a single dose administration. With multiple dose administration, C_{max} ranges from 0.89 to 1.42 mg/L and steady state concentration is reached after 5 to 14 days (40, 41). The elimination half life, $t_{1/2\beta}$, after a single dose administration, varies from 7 to 19 hours and with repeated administration, the $t_{1/2\beta}$ can extend to 29 to 98 hours (32). Less than 1% of an oral dose is detected in the urine as the unmodified parent compound. Food intake increases the rate and extent of ticlopidine absorption (39).

Drug interactions have been reported with ticlopidine (36). Ticlopidine potentiates effects of NSAIDs on platelet aggregation. The $t_{1/2}$ of antipyrine is increased by 30% with coadminstration of ticlopidine, hence drugs that are metabolized by CYP450s should be adjusted when starting or stopping ticlopidine treatment. The $t_{1/2}$ of theophylline increases with a corresponding decrease in its total plasma clearance. There is a slight reduction in digoxin plasma levels, however, no change in digoxin efficacy is observed. Chronic coadministration of cimetidine produces a 50% reduction in the clearance of a single dose of ticlopidine. There is a reported 20% decrease in ticlopidine plasma level when administered after antacids. No interaction with phenobarbital has been reported. There is no evidence that ticlopidine induces mutagenicity, carcinogenicity or impairment of fertility as demonstrated in rats.

The primary use of ticlopidine is in the prevention of thrombosis in cerebral vascular and coronary artery disease (20). It is indicated for the reduction of the risk of first or recurrent stroke for patients who

have experienced a complete thromboembolic stroke or a minor stroke (36). It is also administered to patients who are either ASA intolerant or have experienced a secondary event while on ASA treatment. It is also used alone or in combination with ASA after coronary stent procedures in order to prevent platelet activation (thrombus formation) and to allow stent patency (42, 43). In Europe, it is used in the prevention of MI (15).

There have been numerous trials examining the therapeutic efficacy of ticlopidine (44, 45) (46) (47, 48). In particular, there have been three major trials conducted comparing ticlopidine's efficacy against placebo (29, 49) or ASA (28).

The CATS trial, Canadian American Ticlopidine Stroke trial, was a randomised, double-blind, multi-centre study that compared ticlopidine 250mg bid and placebo for up to 3 years in stroke patients (29). This study demonstrated that ticlopidine was significantly more effective than placebo for the prevention of stroke, MI or vascular death (risk reduction 30.2%, p=0.006).

In the STIMS trial, Swedish Ticlopidine Multicentre Study, a double-blind, multicentre study, ticlopidine was also shown to have greater protective efficacy than placebo in patients with intermittent claudication (PAD) (49). There were fewer events (MI or transient ischemic attack, (TIA)), in the ticlopidine group than in the placebo group.

The Ticlopidine Aspirin Stroke Study (TASS) trial was a randomised, double-blind, multicentre investigation comparing ticlopidine 250mg bid, with ASA 650mg bid for the prevention of ischemic events or death in patients who had a TIA, amaurosis fugax, reversible ischemic neurologic deficit (RIND) or a minor stroke (28). Ticlopidine produced significant relative risk reductions of 12% and 21% for death and nonfatal stroke respectively.

From the ATC meta-analysis of anti-platelet regimens, combined trials indicated that ticlopidine produced an additional 10% reduction in MI, stroke or vascular death in comparison to ASA (30). This was found not to be significant, however, it does not imply that ticlopidine therapy is equivalent to ASA therapy. As well, it was found that through an indirect comparison to other antiplatelet regimens, ticlopidine was found to have a 33% reduction in events. However, the major drawback of ticlopidine is the neutropenia monitoring and serious adverse events (e.g., thrombotic thrombocytopenic purpura) which clopidogrel does not have.

1.3.5 ASA

ASA has been the long-standing prescribed treatment for primary and secondary prevention of IS and MI primarily because of its low cost and effectiveness in many types of cardiovascular diseases. It is a salicylate (acetyl salicylic acid) (Figure 6). It acts via the TXA_2 and cyclooxygenase pathway (20). In platelets, the major cyclooxygenase product is TXA_2, a labile inducer of platelet aggregation and a potent vasoconstrictor. ASA blocks production of TXA_2 by covalently acetylating a serine residue near the active site of cyclooxygenase, the enzyme that produces the cyclic endoperoxide precursor of TXA_2 (see Figure 2). The action of ASA is irreversible, considering that platelets are not able to synthesize new proteins and the effect of ASA disappears only upon platelet recycling (after 7-10 days).

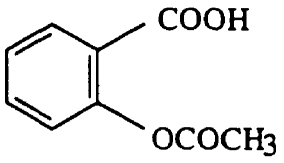


FIGURE 6: Chemical structure of ASA

ASA is rapidly absorbed from the stomach and small intestine with optimal absorption occurring in the pH range of 2.15 to 4.10 (50). The bioavailability of ASA is 70% and the plasma $t_{1/2}$ of ASA is 15 min (51). It takes about 1-2 hours to reach maximum serum concentrations. It is widely distributed in the body tissues and fluids. ASA is hydrolyzed to salicylic acid which is then oxidized, conjugated and renally excreted.

There are numerous drug interactions with ASA (50). ASA in combination with other antipyretic analgesic agents may be associated with nephropathy. Antacids may alkalinize the urine leading to an increase in the renal elimination of ASA. ASA and anticoagulants combined increase the risk of bleeding. Phenytoin metabolism may be inhibited by large doses of ASA. Valproic acid increases platelet aggregation and may cause an increased risk of bleeding if coadministered with ASA. ASA increases the antihyperglycemic response to sulfonylureas. Corticosteroids increase the excretion of ASA. Methotrexate and ASA compete for renal excretion with methotrexate serum levels becoming elevated. Vancomycin and ASA increase the risk of ototoxicity. Vitamin C acidifies the urine and may increase the elimination of ASA. The hepatic metabolism of zidovudine is increased with coadministration of ASA.

ASA crosses the placenta and salicylates are detected in breast milk (50). It may increase the risk of bleeding in the mother, fetus or infant.

ASA has remained the gold standard for treatment of vascular disease. The indications for ASA are numerous namely: MI, unstable angina, bypass grafts, cerebrovascular disease (IS), PAD, atrial fibrillation, primary and secondary prevention of arterial thromboembolism, prevention of thrombus formation after percutaneous transluminal coronary angioplasty (PTCA), and it is used in hip and prosthetic heart valve replacements (20).

In the ATC meta-analysis, it was demonstrated that low doses of ASA (75mg to 300mg per day) are as beneficial as high doses (~1000mg per day) in the treatment of cerebrovascular disease, but there is still no general consensus in the field (30). Higher doses prove to be ineffective because of inhibition of prostacyclin production and carry the risk of increased toxicity (e.g., bleeding). As well, it was shown that patients with peripheral vascular disease should receive ASA therapy long-term. Other high risk groups identified as benefiting from ASA therapy were those having vascular procedures or stable angina (20). In the secondary prevention of arterial thromboembolism, it was demonstrated that no combination of antiplatelet agents was found to be superior to low doses of ASA (75mg to 300mg per day) alone. This finding formed the basis for the recommendation that patients with occlusive vascular event be prescribed long-term therapy with ASA (20). However, intolerance to ASA (because of the side effects or

hypersensitivity) and ASA therapeutic inefficacy (i.e., patient experiences a subsequent stroke or MI), demonstrates the need for a new agent such as clopidogrel.

1.4 IMPORTANCE OF THE PROBLEM

Considering that clopidogrel is a novel anti-platelet, there has yet to be a pharmacoeconomic analysis conducted for this agent in comparison to the other treatment regimens currently used to manage MI, IS and PAD. The major issue is the introduction of this novel anti-platelet agent into provincial formularies and the cost impact that it would have on the health care system. Here, cost is defined as the magnitude of resources consumed (52). The current movement in health care is an attempt to cap expenditures in order to maintain a financially viable health care system (53). Drug therapy is one of the areas that is being targeted to reduce overall spending (54). There are four reasons why pharmaceuticals are being targeted by government regulators: i) absolute expenditures on pharmaceuticals continue to grow, ii) pharmaceuticals are viewed as products rather than services, iii) some pharmaceutical products are perceived to have little value, and iv) there is a concern that new biotechnology will continue to create new pharmaceuticals and push pharmaceutical expenditures to an even higher level (55). It is felt that more effective drugs can be selected that will yield savings in health care by reducing the need for subsequent physician visits or for hospitalizations (56). In 1996, drug spending in Canada accounted for 14.4% of the total health expenditures or more than $10 billion (1).

Pharmacoeconomic analyses are required to be conducted as part of drug formulary submissions in Ontario (57). These act as a preliminary screen to select out the newly introduced and often costly agents in comparison to the older, mature drugs prescribed for the same indication. This analysis is targeted towards formulary decision-makers and clinicians (prescribers) who treat MI, stroke or PAD patients. It has been demonstrated that the criteria with which the majority of physicians select and prescribe a drug are not on the basis of cost and therapeutic effectiveness, but rather on therapeutic effectiveness alone (58). The selection of more cost-effective medications must done *a priori*. Ultimately, this analysis will contribute to the other pharmacoeconomic analyses that help to shape policy making in the area of the adoption of novel pharmacologic agents.

For acceptance of clopidogrel to hospital formularies, three major issues arise: drug safety, drug efficacy and drug cost (59). Drug safety and efficacy are demonstrated through clinical trials but the impact of drug cost can only be demonstrated through specific analyses incorporating medical decision making structured in mathematical models. Results from the pharmacoeconomic analysis will help guide prescribing in a constrained environment where the potential impact of a widely used therapy may be significant. Ultimately, these results will have an impact on the indication for clinical use of clopidogrel.

1.5 STRATEGY USED TO ATTACK THE PROBLEM - REVIEW OF THE METHODS

In the following paragraphs, the methodological approach to conducting pharmacoeconomic analyses will be discussed. The type of pharmacoeconomic analysis has to be established. The perspective from which the analysis will be conducted should next be established as the perspective will determine the type of resource utilization information (i.e., costs and treatment probabilities) required. A model can then be created using the resource utilization information to generate pharmacoeconomic outcomes. The parameters entered into the model can be varied to determine the effect on the outcomes. The pharmacoeconomic outcomes need to be interpreted in the context of other interventions used in vascular disease management to determine the relative value of introducing a novel drug.

1.5.1 Types of Pharmacoeconomic Analyses

In order to demonstrate the impact that the introduction of clopidogrel would have on cost and survival, several types of analyses can be conducted: cost-effectiveness analysis (CEA), cost-consequence analysis (CCA), and cost-utility analysis (CUA) (60, 61). Table 1 provides a summary of the major types of pharmacoeconomic analyses.

TABLE 1: Summary of the major types of pharmacoeconomic analyses.

TYPE OF ANALYSIS	APPLICATION	OUTCOME UNIT	ADVANTAGES	LIMITATIONS
CCA	Used to compare two treatment alternatives that produce the same single effect but to varying degrees	Dollars per event avoided	Identifies the cost expenditure associated with preventing one event from a disease while being on a particular treatment.	-can only represent outcomes in monetary terms
CEA	Same as above	Dollars per natural unit (e.g., life years gained, mm Hg blood pressure)	Can measure health outcomes (effects) in monetary and non-monetary terms	-cannot be used to compare interventions with a different or more than one health outcome -does not consider the patient's quality of life in the health outcome
CUA	Used to compare two treatment alternatives that may individually or both produce more than one single effect to varying degrees	Dollars per quality adjusted life year	Considers both the patient's quality and quantity of life in the health outcome	-assumes that all utilities (or preferences for a particular health state) are common across all individuals -utilities will vary according to the methodology in which they were acquired

CEA is defined as a cost comparison between two treatment alternatives which produce the same single effect, but to different degrees (60). The difference in effect is measured in natural units such as life years (LY) gained (extension of survival) as a result of a particular medical intervention (e.g., surgery, drug therapy, rehabilitation). In the context of pharmacological treatment, the difference in effect can be measured as the difference in therapeutic efficacy between two agents. Therapeutic efficacy can encompass a better adverse event profile, greater number of cures or increased compliance and it is translated into the number of LYs gained. The results are usually represented in the form of an incremental cost-effectiveness ratio (CER), whereby the numerator is the difference in cost between the two regimens and the denominator is the difference in LYs gained (i.e., cost/LY) (Figure 7). The incremental CER represents the additional cost of an alternative treatment relative to its additional effectiveness (62). An average CER is not used as it represents the cost per benefit (i.e., LYs gained) of the new treatment independent of any other comparator treatments. If the difference in effect represents a consequence of drug therapy (e.g., number of event averted), then this is termed a cost-consequence analysis (CCA). Usually, the costs and consequences of drug treatment are displayed separately and not in a ratio (60).

CER	**CER FOR CLOPIDOGREL AND ASA**
$\frac{\text{(Cost Drug A) – (Cost Drug B)}}{\text{(Outcome with Drug A) – (Outcome with Drug B)}}$	$\frac{\text{Lifetime Cost}_{clopidogrel} - \text{Lifetime Cost}_{ASA}}{\text{Survival with clopidogrel - Survival with ASA (i.e., Life Years}_{clopidogrel} - \text{Life Years}_{ASA})}$

FIGURE 7: Equations used to calculate the CER for CEA.

If the outcome unit measured is all quality adjusted life years (QALY), an extra year of life gained in a state of perfect health, then the analysis is referred to as a cost-utility analysis (CUA). This is simply an extension of the CEA whereby more than one effect, not necessarily produced by both treatments, can be considered (60). The lack or presence of the additional effect helps to outline the advantages one drug treatment has over the other. The results are presented in the form of cost/QALY. In CUA, the advantage is that both the quantity and quality of the patient's life can be expressed in the outcome whereby the CEA considers only the patient's quantity of life.

The term utility refers to a number that represents the strength of the individual's preferences for particular outcomes when faced with uncertainty (63). Utilities are measured in patients with particular diseases by a variety of methods such as the standard gamble, time trade off, clinical judgement and ratio scaling (63). It is a method of measuring one's perception of their own current health state on a scale of 0 to 1. It is possible that utilities will differ according to the methodology used to acquire them or

simply due to variation between individuals' preferences. In CUA, this leads to a potential disadvantage in which the utility used may not necessarily account for such variations (64). The QALY was created as a method that could integrate within an individual the health improvements from changes in both the quality and quantity of life, and could also aggregate these improvements across individuals (65, 66). Both utilities and LYs are used by computer programs to compute the QALY in pharmacoeconomic analyses.

There are four outcome scenarios for the CERs which have been transformed into tabular form from the cost-effectiveness plane first conceptualized by Black (1990) (67). In general, the novel drug treatment will be more expensive than the older drug treatment. For example, in Figure 7, the costs associated with Drug A treatment (novel treatment) is more expensive than Drug B (the older drug) treatment, i.e., there is no cost advantage. Hence, there will be an incremental cost associated with Drug A therapy in comparison to Drug B therapy, i.e., cost expenditures associated with the adoption of Drug A treatment. However, the benefits of Drug A, in terms of LYs or QALYs will be greater than the benefits accrued from Drug B usage. In this situation, Drug A is analogous to scenario 1 Table 2 below. If the costs associated with Drug A treatment are less than Drug B treatment and Drug A confers benefits in terms of LYs or QALYs, then the CER will demonstrate a cost savings (negative CER), where Drug B is said to be dominated by Drug A in terms of both therapeutic efficacy and cost. This would be analogous to scenario 2 in Table 2 below. If the therapeutic benefits of the more costly Drug A treatment are less than Drug B treatment, then Drug A is dominated by Drug B therapy or that Drug B is the dominant therapy (60). This would be analogous to scenario 3 in Table 2. Lastly, Drug A could be cheaper but therapeutically ineffective, analogous to scenario 4 in Table 2. However, in either scenario 3 or 4, Drug A does not appear to be an attractive, novel, therapeutic alternative and most likely would not be adopted for use.

TABLE 2: Possible outcomes and interpretation of CERs.

	MORE EXPENSIVE THERAPY	**LESS EXPENSIVE THERAPY**
THERAPEUTICALLY EFFECTIVE	1	2
NOT THERAPEUTICALLY EFFECTIVE	3	4

In order to conduct CEAs or CUAs, treatment costs and probabilities with respect to the outcomes from the treatment are required. Costs are defined as the magnitude of resources consumed (68). There are two types of costs, direct and indirect costs. Direct costs involve the transfer of money whereas indirect costs are unpaid resource commitments (52). Examples of direct costs are drug costs,

surgical fees and physician fees. These are used in all pharmacoeconomic analyses irrespective of the perspective of the analysis. Examples of indirect costs are time off work and home care. These are usually incorporated in pharmacoeconomic analyses conducted from a societal perspective (discussed in the next section) in addition to direct costs. Cost is different from price which is defined as the amount that a patient must pay (out of pocket expenses) for the good or service (68). Cost information can be obtained from the literature, hospital databases or fee schedules.

1.5.2. PERSPECTIVE OF THE ANALYSIS

The perspective of the pharmacoeconomic analysis should be established as it will determine the type of information (i.e., costs and treatment probabilities) necessary for the analysis to be conducted. There are several types of perspectives that a pharmacoeconomic analysis can adopt such as from the perspective of the government, society, or an institution (60). A governmental perspective would be adopted in situations in which the analysis is catered to drug formulary submissions. A formulary represents a list of drugs in which the prescription costs will be covered for particular populations such as the elderly and those receiving social assistance or it can be a list of drugs used in a particular hospital. The type of costing information applicable would be those reimbursed by the government. A societal perspective is one that considers the patient and/or patient's family in the analysis. The concept of lost productivity, and the impact of removing an individual out of society (workforce) because of an illness is assessed. For example, lost wages due to time off of work for the patient or relative can be incorporated into the analysis as a portion of the cost a particular illness burdens upon society. The last type of perspective is an institutional perspective in which pharmacy and therapeutic committees converge to discuss what should be accepted onto the hospital formulary. Thus, the types of costs and treatment probabilities should be related to the hospital and possibly acquired solely from the hospital.

1.5.3 META-ANALYSIS

Probabilities pertaining to the outcome events (e.g., probability of having a stroke, probability of surviving the stroke, adverse event probabilities) associated with a particular drug therapy are compiled from the literature (i.e., randomized controlled clinical trials), expert opinion, or Delphi panels (group of expert opinions) (69). However, randomized controlled trials remain the accepted standard for the collection of safety and efficacy data of pharmaceuticals (60). The probabilities can be combined in a statistical procedure called meta-analysis. A meta-analysis is defined as a statistical analysis of a collection of analytic results from several independent studies on a specific topic for the purpose of integrating the findings (70, 71). It has four specific purposes: 1) to increase statistical power by increasing the sample size; 2) to resolve uncertainty when reports do not agree; 3) to improve estimates of effect size; and 4) to answer questions not posed at the beginning of the study. In the context of this thesis, a meta-analysis is required to extract the overall efficacy of various pharmacological agents used in the treatment of vascular events (i.e., IS, MI or PAD).

1.5.4 DECISION TREE ANALYSIS

Once all of the information has been compiled (i.e., costs and probabilities), it is entered into a decision tree model, a branching structure where each branch represents an event that may take place in the future (72). The decision tree forms the founding basis for decision analysis, a structured methodology which puts uncertainties into perspective and then considers them in the medical decision making process (72). The decision tree is generally created using a computer program (e.g., DATA TreeAge (72)) and the tree structure is dependent upon the type of outcome probabilities acquired.

For simulations over extended periods of time, a Markov model decision tree is usually created because it allows a cohort of patients to move through a number of different health states. It is unlike a conventional decision tree which practically allows for only a limited number of transitions from one health state to another. It is defined as a statistical modelling technique derived from matrix algebra developed according to the Markovian principle (73) which is used to help medical decision making. For each Markov model, it carries the Markovian assumption of all patients in a given health state at a given time have the same prognosis irrespective of how they arrived at that health state and that knowing the present health state of a patient is sufficient to project the entire trajectory of future health states (74). In developing a Markov model, the following sequence should be adopted: I) health states should first be established; ii) health state transitions (transferring from one health state to another) should be defined and iii) probabilities of being in a health state and transferring from one health state to another should be derived (as discussed in section 1.5.3). As an example, in Figure 8, the top row represents the possible health states a person could be in. The person can also make a transition to one of the health states on the bottom row according to defined probabilities acquired in the manner previously discussed. For example, a person can initially be healthy (no previous cardiovascular or cerebrovascular event), but then experiences a stroke and transitions into the stroke health state (as indicated by ➔ and 1 in Figure 8). This person can now have another stroke (2 in Figure 8), a MI (3 in Figure 8), or die (4 in Figure 8). However, this person cannot go back to being in a healthy state. Once the patient reaches the state of death, this is called an absorbing state because the person cannot transition into any other state (72).

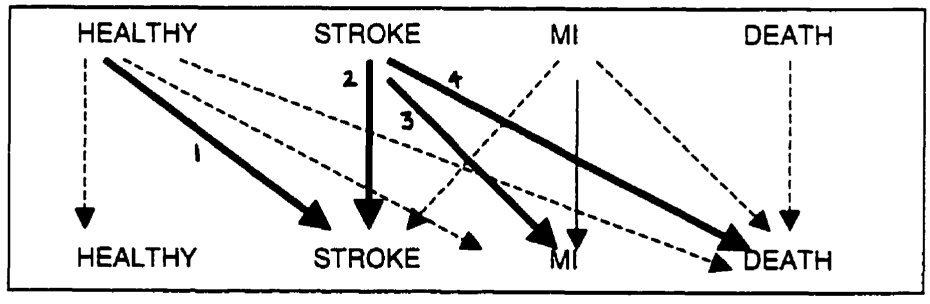


FIGURE 8: Concept of the Markov model

A Markov model has two forms, the Markov chain and the Markov process (74). In a Markov chain, health state transition probabilities (probabilities of transferring from one health state to another) are constant. It is a subset of the Markov process and used more commonly for diseases with a short time horizon. The Markov process allows transition probabilities to vary over time according to preset rules. It is used more commonly in chronic diseases (e.g., arthritis, dementia). In the context of this thesis, it simulates the clinical outcome of the vascular disease patient, i.e., whether they experience an IS, MI or PAD. The computer program executes the necessary mathematical and statistical analyses in order to derive particular pharmacoeconomic results (e.g., cost, LYs) based on the model.

Since there is a time preference associated with costs and benefits (LYs), i.e., a dollar is worth more today than in the future and benefits are preferred to be received immediately as opposed to in the future, both items must be discounted (68). The discount will account for the fact that dollars spent or saved in the future should not weigh as heavily as dollars spent or saved today but rather to reflect their current value when a programme (i.e., IS, MI or PAD disease management) extends over several years (60). The current accepted discount rate is 3% (75). This rate was established to represent the real interest rate on government securities (i.e., interest rate minus inflation rate) (60).

1.5.5 SENSITIVITY ANALYSIS

A thorough examination of the "confidence" of the results of the base case analysis, via sensitivity analyses, is a critical part of the economic evaluation. The probabilities entered into the model are varied in a sensitivity analysis (71). There are three purposes for conducting a sensitivity analysis i) to assess the degree of uncertainty associated with an analytic result, ii) to "debug" and validate the tree, and iii) to determine which probabilities (e.g., probability of death from a MI) or parameters (e.g., cost of a drug) greatly influence the model outcomes (76, 77). Sensitivity analysis can help identify problems with the structure of the model created. As a parameter is varied, the results from this change can be assessed to see if they make logical sense. If the result does not seem logical, then the model must be explored to correct the error. If the result does appear logical, then the change of the parameter is further assessed to see how much of an impact it has on the model. For example, if the outcomes from the sensitivity analysis are still similar to the baseline results, then the model is not sensitive or is "robust" to this probability or parameter. However, if the outcomes differ from the baseline results, then the model is deemed "sensitive" to the probability or parameter varied. Thus, sensitivity analysis is the decision analyst's version of statistical hypothesis testing as it provides "pseudo" confidence intervals or ranges in which the result varies. Throughout this process, the model can be validated by comparing the results from the sensitivity analysis to those reported in the literature.

There are a few approaches one can take in order to vary the parameters: I) one-way sensitivity analysis or ii) multi-way sensitivity analysis (76). In a one-way sensitivity analysis, there is only one variable being varied at a time. The degree to which it is varied is somewhat arbitrary but should be based on some sense of probability sampling and input from the decision maker provided that it is logical and in the context of the analysis being conducted. In a multi-way sensitivity analysis, more than one variable is varied at one time. It is conducted when the results from the one-way analysis indicate that

the model is not sensitive to any variables but may be sensitive to simultaneous changes in multiple variables.

1.5.6 INTERPRETATION OF PHARMACOECONOMIC OUTCOMES

The baseline pharmacoeconomic results need to be interpreted in order to determine the relative value in the adoption of a novel agent in comparison to other currently accepted interventions. Such comparisons will help to identify whether the amount of money spent in order to gain an extra year of life for a novel agent is worthwhile or not. There are two methods of interpretation of the pharmacoeconomic outcomes: i) comparison to benchmark values and ii) comparison to costs of other types of medical interventions used for the same condition (78). There are two needs for this interpretation: i) for the decision analyst to place the economic findings of a particular health treatment in a broader context and ii) for the decision analyst to be informed of the allocation of health care resources between alternative programs (drug regimens) (60).

Using the first method, this would be an extension of the four possible scenarios of the pharmacoeconomic outcomes as explained in Section 1.5.1, Table 2, where actual numerical values (benchmarks) are assigned to further define the boundaries of scenario 1. For example, Laupacis et al (1992) (79) have identified five grades of recommendation for the adoption and appropriate utilization of new technologies on the basis of the cost utility ratio (i.e., cost/QALY) (Table 3).

A	**Compelling evidence for adoption and appropriate utilization** The new technology is as effective as or more effective than the existing one and is less costly.
B	**Strong evidence for adoption and appropriate utilization** The new technology is more effective than the existing one and costs less than $20,000 per QALY gained.
C	**Moderate evidence for adoption and appropriate utilization** The new technology is more effective than the existing one and costs $20,000 to $100,000 per QALY.
D	**Weak evidence for adoption and appropriate utilization** The new technology is more effective than the existing one and costs more than $100,000 per QALY.
E	**Compelling evidence for rejection** The new technology is less effective than or as effective as the existing one and is more costly.

TABLE 3: Grades of recommendation for the adoption and appropriate utilization of new technologies (79).

Here, $20,000/QALY and $100,000/QALY are benchmark values which can be used to help judge whether spending money to adopt a particular intervention in order to gain certain benefits is worthwhile or not.

If the second method of validating the pharmacoeconomic outcomes is used, a sample of medical interventions can be used as comparators. CERs are listed in a league table (Table 4 is a sample illustration of a league table), which is a rank order listing of incremental CERs (80, 81). The interventions listed represent results from published economic evaluations in which the health care or other social program was incrementally compared with an alternative program. The league table can list CERs for interventions related to a particular disease category only or it can include interventions from other diseases or areas such as to gain an appreciation of the allocation of resources in other health care sectors. The league table helps to identify technologies that represent a good investment of dollars spent in order to gain a year of life (those listed at the top of the list). A cut-off CER can then be defined which represents the willingness to pay for a particular intervention and health outcome. If the calculated CER from the CEA is less than this cut-off, then the technology would be adopted. If the CER is greater than the cut-off, then the technology would not be adopted.

INTERVENTION	**CER (cost/LY)**
Beta-blocker treatment for low-risk MI survivors	$17,000US
Percutaneous transluminal coronary angioplasty (PTCA) in patients with mild angina	$24,000US
Lovastatin/low cholesterol diet (vs diet) for men age 60 And cholesterol level of 300 mg/dL	$26,000US
Two vessel coronary artery bypass graft surgery (CABG) (vs medical management)	$28,000US
Heparin/dihyroergotamine (vs stockings) to prevent venous thromboembolism	$42,000US
Coronary care unit for emergency patients with acute chest pain	$250,000US

TABLE 4: Sample illustration of a league table. Adapted from Tengs et al, (1995) (82).

There are some limitations to league tables which should be addressed (78, 81). Firstly, each economic evaluation is conducted via a different methodology. There may be no standardization of the types of evaluations selected from the literature according to the type of methodology used to conduct the CEAs (e.g., type of perspective, type of costs considered, type of utilities). Secondly, economic evaluations can be conducted in different time periods, which amounts to different dollar values. Lastly, the CERs listed represent point estimates where the variation in the CERs are not listed. In spite of these limitations, league tables are helpful in guiding decision making in the adoption of new technologies.

1.6 GENERAL/SPECIFIC OBJECTIVES

The main objective is to determine the therapeutic efficacy and cost-effectiveness of clopidogrel treatment in relation to current therapies in vascular disease (IS, MI, PAD) in conformity to the Ontario Guidelines for Pharmacoeconomic Evaluations (57). The CAPRIE trial was powered only to detect statistical significance for all of the patient groups, IS, MI and PAD, combined. In this analysis, IS, MI and PAD subgroups will also be analyzed separately to determine if they benefit from clopidogrel therapy. Clopidogrel as second line therapy, in situations where ASA failed or was not tolerated, was also considered for particular subgroups I) stroke patients, (second line therapy of clopidogrel versus ticlopidine treatment) and ii) MI patients, (second line therapy of clopidogrel versus placebo).

All costs, complications and health benefits resulting from clopidogrel use compared to ASA and ticlopidine (brand name and generic) will be considered in several analyses with the results being presented in terms of incremental CERs, namely cost/LY gained. These outcomes will be compared with other reported CERs for comparative analysis of the value of the outcomes. Sensitivity analyses will be conducted to determine model sensitive parameters.

1.7 STATEMENT OF RESEARCH HYPOTHESIS

The use of clopidogrel over ASA treatment across all IS, MI and PAD patients combined will be a cost-effective treatment in comparison to other accepted interventions in vascular disease. There will be differences in the therapeutic efficacy and cost effectiveness of clopidogrel treatment in IS, MI and PAD subgroups individually.

1.8 RATIONALE FOR HYPOTHESIS

According to the CAPRIE trial, clopidogrel has demonstrated greater therapeutic efficacy than ASA in the combined population of patients who have experienced an IS, MI and PAD (27). A relative risk reduction for experiencing a secondary event (IS, MI or vascular death) of 8.7% was observed with clopidogrel therapy. For the subgroups, PAD patients alone had the largest relative risk reduction of 23.8% (95% CI of 8.9% to 36.2%) with clopidogrel. Stroke patients had a lower relative risk reduction of 7.3% (95% CI –5.7% to 18.7%), while MI patients actually did not appear to benefit from clopidogrel treatment, a relative risk reduction of –3.7% (95% CI –22.1% to 12.0%).

Despite the wide variety of medications used in the treatment of IS, MI and PAD, it is would be suitable to make comparisons to other commonly used pharmacological agents in this area. ASA would be a relevant comparator to clopidogrel, since it has a lower cost and is first line therapy for IS and MI. The next relevant comparator would be ticlopidine, prescribed as a second line agent in IS. There is not one consistently prescribed medication used in the treatment of PAD. With these comparisons, the advantages of clopidogrel therapy in terms of safety (i.e., a better side effect profile), will be elucidated in terms of benefits seen in the number of LYs gained.

1.9 REVIEW OF THE PHARMACOECONOMIC LITERATURE

1.9.1 ASA

There are very few economic evaluations of ASA in comparison to other types of antiplatelet therapies for vascular disease. The main reason for this is that ASA still remains the gold standard in vascular disease management because of its efficacy and low cost. There are some pharmacoeconomic studies conducted with ASA alone or in comparison to other treatment regimens (83) (84, 85). As an example, in a study by Gage et al (1995), ASA was compared to warfarin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation (NVAF) (86). Here, the authors constructed a Markov Model to analyze the expected outcomes of three treatment alternatives, warfarin, ASA and no therapy, during a 10 year period for 65 year old patients who had chronic NVAF. Despite the lower costs of ASA, the risk reduction of reinfarction was only 22% versus 68% with warfarin therapy. However, ASA did have a lower rate of major hemorrhage in comparison to warfarin (0.9% and 1.4% respectively). The authors conceded that warfarin therapy would cost $8,000US/QALY in patients with NVAF and one additional risk factor. In 65 year old patients with NVAF only, warfarin therapy would cost $370,000US/QALY. And in 75 year old patients with NVAF alone, it would cost $110,000US/QALY. This study reiterated how costly any other pharmacological treatment is in comparison to ASA. However, the gains are significant in terms of survival and it is the decision maker who decides whether the cost expenditure is acceptable or not.

1.9.2 TICLOPIDINE

There was only one major pharmacoeconomic analysis of ticlopidine performed (87). This was a lifetime analysis with a hypothetical cohort of 100 high risk men and women >65 years of age receiving either ticlopidine (500mg od) or ASA (1300 mg od). The primary source for the data came from the Ticlopidine Aspirin Stroke Study (TASS) (28), a trial involving over 1500 patients randomized to receive ticlopidine or ASA. The advantages of ticlopidine therapy emphasized were the lower rates of gastrointestinal hemorrhage (i.e., 0.5% ticlopidine vs 1.4% ASA), and a lower rate of stroke (i.e., relative risk reduction of 21% with ticlopidine therapy vs 15% with ASA therapy). However, ticlopidine usage incurred costs not only from the difference in drug cost i.e., ticlopidine $2.75US/day in comparison to ASA $0.13US/day, but from neutropenia monitoring and hospitalization. Ticlopidine was demonstrated to prevent an additional two strokes per hundred in comparison to ASA, however, it would cost between $31,200US to $55,500US per QALY gained. Based on clinical and economic data, ticlopidine is currently reimbursed (under drug benefit plans) as a "second-line" therapy in most jurisdictions in Canada. This serves as a useful reference point for this economic analysis of clopidogrel.

2. METHODS

2.1 RESEARCH DESIGN

Several types of analyses were conducted in order to complete a full economic analysis of the impact of introducing clopidogrel into formulary. The rationale for conducting such analyses is such that there are distinct patient groups or scenarios where clopidogrel might be prescribed. The CAPRIE trial had indicated the potential benefits of clopidogrel in IS, MI and PAD populations. It is only these populations that are considered in the analysis.

1. **Analysis A** – Model Based on CAPRIE (27)

This was a CEA quantifying costs and outcomes over two years, the same time period of the CAPRIE trial. The outcome measured was the incremental cost/event per patient. The numerator represented the incremental two year lifetime cost of clopidogrel versus ASA therapy (because clopidogrel is the more expensive therapy). The denominator represented the differential in the event rate for primary outcomes and all outcomes (primary, secondary and tertiary) between clopidogrel and ASA therapy over two years (i.e., clopidogrel has a lower event rate).

2. **Analysis B** - Markov Model

This CEA compared clopidogrel vs. ASA treatment over lifetime to simulate the use of long term clopidogrel therapy. CAPRIE data is entered into the model with a maximum follow-up period of five years from the study itself. Events beyond five years were modeled using data from the literature. This model did not consider adverse events. The outcome measured was cost/LY gained per patient (CER). Refer to Appendix III, Figures 1 and 2 for an illustration of the model used.

3. **Analysis C** - Subgroup Models

Patients qualifying for enrollment in the CAPRIE trial were divided into three subgroups based on their qualifying condition: IS, MI or symptomatic PAD. Classification within the three inclusion criteria subgroups was determined by the patient's most recent ischemic event prior to enrollment in the trial. It should be emphasized that the CAPRIE trial was designed to measure the efficacy of clopidogrel in the combined IS, MI and PAD populations and not the relative benefit of clopidogrel in the three individual inclusion criteria subgroups (27). However, the results of the primary cluster were reported separately for each subgroup in the clinical report. Thus, it was felt worthwhile to present the projected economic figures for these subgroups as well, with the cautions about power limitations and post hoc analysis in mind.

This analysis compared lifetime clopidogrel vs. ASA treatment individually for the MI, IS and PAD populations to determine if there is a more attractive position for clopidogrel as a first line therapy within specific patient populations. This would be of interest to prescribers and payers (i.e., government) who may wish to consider specific therapeutic or disease categories. The outcome measured was cost per LY gained per patient (CER).

4. **Analysis D** - "Second-Line" Stroke

This analysis focused on acute monitoring and tolerability comparing second-line therapy of clopidogrel vs. ticlopidine over a lifetime. The time horizon was chosen such as to simulate the potential use of clopidogrel therapy. The emphasis was on delineating the differences in adverse event profiles between the two agents (e.g., neutropenia, rash and GI events). The outcome measured was cost/LY gained per patient (CER). Refer to Appendix III, Figure 3 for an illustration of the model. The above analyses were performed for both brand name ticlopidine and generic ticlopidine.

5. **Analysis E** - "Second-Line" MI

Clopidogrel was compared to no treatment/placebo because there currently does not exist a single agent consistently used as second-line therapy for the MI patient population. This was a lifetime analysis with outcomes of cost per LY gained per patient (CER). This model did not consider tolerability and adverse events. The outcomes for no treatment/placebo were derived from the ATC Meta-analysis (30).

6. **Sensitivity Analyses**

The following sensitivity analyses were conducted on the above analyses.

a) Varying the Drug Price of Clopidogrel – 50% increase and 50% decrease
b) Varying Costs of Acute and Follow-Up Care – 50% increase and 50% decrease in MI, IS and PAD treatment for clopidogrel, ASA and ticlopidine therapy
c) Varying the Discount Rate – a discount rate of 0% and 5% for both costs and survival
d) Varying Costs of Managing Adverse Events – 50% increase and 50% decrease for both clopidogrel and ticlopidine
e) Varying Adverse Event Rates – 25% increase and 25% decrease in probabilities of experiencing an adverse event individually for clopidogrel and ticlopidine, such as neutropenia, diarrhea and rash. N.B. 50% increase/decrease was not selected as it would have resulted in 100% or 0% probability of such adverse events from occurring.

By varying the price or cost parameters, the effect on cost outcomes can be examined. As indicated earlier, clopidogrel is the more expensive anti-platelet therapy in comparison to ASA and ticlopidine. The effects of reducing or increasing the cost would allow for the type of variation seen in the CERs and also the impact drug price has on the CERs. Varying the costs of acute and follow-up care will demonstrate the impact of treatment costs on the CERs. Increasing or decreasing the amount by which costs and survival are discounted, will lead to different calculations of treatment costs accrued and survival benefits gained affecting the CERs. Since clopidogrel has a more favorable side effect profile than ticlopidine, varying adverse event costs and adverse event rates will identify scenarios which will lead to more or less favorable CERs for clopidogrel therapy.

Decision analytic models were developed for these analyses using the DATA™ (TREEAGE Software, Boston, MA) (72), version 3.0.14. Lifetime costs were rounded to the nearest dollar. LYs were calculated to four decimal places, however, they are shown in this thesis to two decimal places. Hence, simply taking the incremental lifetime cost differential and dividing by the increment in the number of LYs gained will not yield the exact same cost/LY ratio (CER) as given in the tables.

2.2 DATA SOURCES

This pharmacoeconomic evaluation adopted a government payer perspective considering total direct costs, including costs borne by the Ontario Ministry of Health related to medication, hospitals, nursing homes, homecare and outpatient rehabilitation. As well, the government is the relevant audience as vascular disease primarily affects the elderly who receive drug coverage in Ontario (88). A societal analysis was not undertaken because indirect costs are difficult to obtain (little information and difficult to quantify) in the elderly population. Hence, all the cost information and medical care utilization information extracted was in concordance to this perspective.

2.2.1 PROBABILITIES

2.2.1.1 LITERATURE

There were several studies which were relevant to the context of this economic analysis and from which data (probabilities) were extracted regarding MI, IS, PAD and adverse event rates. The relevant comparators for clopidogrel were ASA and ticlopidine. ASA is used in first-line therapy for IS and MI whereas ticlopidine is indicated for IS as second-line therapy. Currently, there is no agent consistently used for second-line treatment of MIs or first-line treatment of PAD.

- CAPRIE (27)
  - clopidogrel
  - clopidogrel vs. ASA
- TASS (46) and CATS (29)
  - ticlopidine
  - ticlopidine vs. ASA
- Antiplatelet Trialists' Collaboration (ATC) Meta-analysis (30)
  - ASA
  - no treatment/placebo

The model was constructed to simulate the actual events that occurred in the CAPRIE trial. Event rates/probabilities for primary, secondary and tertiary cardiovascular events (MI or IS) and mortality (vascular death) were derived from the full CAPRIE database provided by Sanofi Pharma, which indicated only the number of patients experiencing such events and mortality. The CAPRIE database

provided information from 0-36 months after the start of clopidogrel or ASA therapy. The event rate probabilities were calculated for the first six months (i.e., 0-6 months). The event rate probabilities were also calculated for the period after six months (i.e., 7-36 months), however an average event rate was calculated during this time period such as to pool small sample sizes, particularly near the end of the trial (i.e., 36 months) together. These values were used in analyses A-E. Refer to Appendix III, for a complete list of the probabilities derived.

Event rates/probabilities for MI, IS and PAD while on clopidogrel therapy were derived from CAPRIE (27) and for ticlopidine therapy, they were derived from TASS (46), CATS (29) and ATC (30) trials. The types of adverse events considered in Analysis D were neutropenia, diarrhea, rash, and other side effects leading to discontinuation of therapy (Appendix II, Table 11).

Placebo event rates for Analysis E (clopidogrel second-line therapy in MI patients) were simulated using information from the ATC meta-analysis (30). The event rates for MI, IS and PAD observed in the CAPRIE trial with ASA usage were divided by the relative risk reduction in MI, IS and PAD, namely, 34%, 25% and 17% respectively, associated with ASA therapy as calculated in the ATC meta-analysis (30). For example, to estimate the MI event probability with placebo, the equation used was (probability of ASA) / (1 – 0.34) (Appendix III).

In the CAPRIE trial (27), there was an overall RRR of experiencing another IS or MI for IS, MI or PAD patients of 8.7% (95% CI of 0.3% to 16.5%) associated with clopidogrel therapy (27). All the clopidogrel event probabilities (probability of having an IS, MI or vascular death) were adjusted to reflect either the lower end of the RRR (clopidogrel event probabilities were multiplied by 1.09, calculated as such: (8.7% - 0.3%)/100% = 0.08.4; 1/(1-0.084) = 1.09), or the higher end of the RRR range (clopidogrel event probabilities were multiplied by 0.92, calculated as such: (16.5% - 8.7%)/100% = 0.078; 1/(1-0.078)) (Appendix III). This represents the 95% CI for the outcomes (lifetime costs, LYs and cost/LY ratios) associated with clopidogrel therapy for all of the baseline and sensitivity analyses. Note that there are no 95% CIs for the outcomes associated with ASA therapy. As well, this can also be viewed as an alternate form of a one-way sensitivity analysis but expressed in the context of statistical hypothesis testing. These 95% CIs were generated for Analyses A, B, C and E.

In Analysis D, the "Second Line" Stroke model, the 95% CI reported for the RRR in the CAPRIE trial is not applicable to this analysis. Hence, the variation in the lifetime costs, survival and CERs were calculated by a combined 25% decrease/increase in the clopidogrel adverse event rate and a 50% decrease/increase in adverse event costs. This variation was reported for the following sensitivity analyses: i) 50% decrease/increase in clopidogrel drug cost, ii) 50% decrease/increase in acute and follow-up care costs, iii) 0% and 5% discount rate, iv) 25% decrease/increase in ticlopidine adverse event rates. The effect of varying the clopidogrel adverse event costs, adverse event rate, and ticlopidine adverse event rate alone were conducted to determine the effect on the "second-line" stroke model.

2.2.1.2 Sources Used for Patient Management Patterns

The assumptions on patient management and resource use of MI, IS and PAD patients were derived from:

- the medical literature
- analysis of Sunnybrook and Women's College Health Science Centre (SWCHSC) patient data and cost data during the 1997 fiscal year (April 1, 1996 to March 31, 1997)
- Ontario Ministry of Health (MOH).
- expert opinion

2.2.1.3 Patient Management

Patient management for MI and IS patients were divided into four treatment periods:

- Day 1 to Day 14
- Day 15 to the end of 3 months
- Follow-up (after the initial 3 month period)
- Index Follow-Up Period (time from the initial qualifying event)

The acute treatment phases for MI and IS were considered to be from Day 1 to the end of 3 months.

Patient management for PAD patients were divided up into two treatment periods:

- Follow-up for each 3 month period
- Index Follow-up Period

The information and probabilities associated with treatment of MI, IS and PAD patients were derived from patient information at SWCHSC and the patient demographics are described below.

A) Myocardial Infarction (MI) Patients

From SWCHSC, 128 new admission MI patients (66.4% male) were identified according to International Classification of Diseases (ICD-9) code 410. The mean age and standard deviation (SD) of these patients was 67.1$\pm$14.1 years. The mean length of stay (LOS) for MI patients was 7.8$\pm$5.4 days. From this population of 128 patients, there were 113 non-fatal MIs (70.8% males) and 15 fatal MIs (46.7% males). From the total MI patient population, frequencies of procedures were extracted and used in the cost analysis (Appendix II, Tables 1-4). In certain cases where the information was unavailable from this cohort, expert opinion was used (Appendix II, Tables 1-4).

B) Ischemic Stroke (IS) Patients

A total of 100 new admission stroke patients (48.0% male) were identified from the Stroke Registry at SWCHSC. The mean age of these patients was 76.3$\pm$12.2 years. The mean LOS was 19.2$\pm$20.4 days. From this population of 100 patients, there were 78 non-fatal strokes (51.2% males) and 22 fatal strokes (36.4% males). From the total stroke patient population, frequencies of procedures and discharge disposition information were extracted and used in the cost analysis (Appendix II, Tables 5-8). In certain

cases where the information was unavailable from this cohort, expert opinion was used (Appendix II, Tables 5-8).

C) Peripheral Arterial Disease (PAD) Patients

PAD patients were defined as patients who had either a bypass graft (an aorta-iliac-femoral bypass, a vascular shunt bypass defined by ICD-9 procedural codes 39.25, and 39.29 respectively) or an angioplasty (ICD-9 code 39.50). There was a total of 80 bypass graft patients (48.8% male) with a mean age of 62.2±12.1 years. Their mean LOS was 14.1±11.9 days. There was a total of 29 patients (55.2% male) who had an angioplasty. Their mean age was 65.4±10.6 years with a mean LOS of 3.1±3.1 days. From this patient population (n=109), frequencies of treatment procedures were extracted and used in the cost analysis (Appendix II, Tables 9-10). In certain cases where the information was unavailable from this cohort, expert opinion was used (Appendix II, Tables 9-10).

2.2.1.4 Adverse Events

Adverse events were only considered for Analysis D where clopidogrel is compared to ticlopidine as second-line therapy. These adverse events were not considered in analyses A, B, C, or E since major adverse events are similar between clopidogrel and ASA as indicated by the CAPRIE trial (27). The adverse events considered in the model were neutropenia (moderate or severe; if severe, it was further classified as fatal or non-fatal), rash (moderate or severe), diarrhea (moderate or severe), and other adverse events (i.e., elevation in liver function tests and increase in serum cholesterol levels). Adverse event rates used in this analysis were taken from CAPRIE (27), TASS (46) and CATS (29) studies (Appendix II, Table 11). The adverse events were assumed to occur over a three month period (coincident with the time required for neutropenia monitoring while receiving ticlopidine therapy).

2.2.1.5 Concomitant Medication

Inpatient concomitant medication was included in the routine care hospitalization costs incurred by stroke and MI patients for the treatment period of Day 1 to Day 15. Outpatient concomitant medication was determined from a sample analysis of 55 IS, 67 MI and 37 PAD patients and included in the follow-up treatment periods for each of these patient populations (Appendix II, Table 12).

2.2.1.6 Estimation of Life Expectancy for CAPRIE analysis

The estimates of survival used in the analysis was based on the background (age and gender specific) Canadian population mortality from all causes (Canadian Life Tables (89)) plus the cycle specific probability of vascular death from the CAPRIE trial for each patient population of MI, IS and PAD. The male:female ratio (i.e., 0.72:0.28) from the CAPRIE trial (27) was incorporated into the probabilities for the age estimate of survival (Appendix I, Table 1). The estimate of survival for males at each age, from 62 to 100 years, was multiplied by 0.72. The estimate of survival for females at each age, from 62 to 100 years, was multiplied by 0.28. The two values were then summed together to arrive at the age and gender specific mortality.

2.2.1.7 Outcome Measurement

The outcomes measured were as follows:

- life year (LY) gained
- event (stroke, MI, death) averted

A 3% discount rate (75) for life years (survival) accrued after the first year was used (90).

2.2.2 ECONOMIC MEASURES

2.2.2.1 Cost Measurement and Valuation

Total direct costs were considered, including costs borne by the Ontario Ministry of Health, related to medication, hospitals, nursing homes, homecare and outpatient rehabilitation. Hence, cost information was acquired from the following sources:

- Ontario Drug Benefit Formulary
    - drug price
- OHIP (Ontario Health Insurance Plan)
    - physician costs, lab monitoring costs and ambulance costs
- West Park Rehabilitation Hospital
    - rehabilitation costs
- Paramed Health Care Services/Metro Toronto Inter-Community Care Access Centres
    - home care costs
- Sunnybrook & Women's College Health Sciences Centre (SWCHSC) and Transition Systems Incorporated (TSI)
    - hospitalization costs for stroke, MI, GI bleed/ulcer, neutropenia
- Alberta Standard Cost List
    - Cost of amputation associated with PAD
- Joint Policy and Planning Committee
    - Stent costs and utilization

Indirect costs were excluded in this analysis because they were difficult to quantify and less relevant to the population at risk (i.e., elderly) in the context of government payer perspective. A 3% discount rate per annum for all costs accrued beyond the first year was used (75).

The price of clopidogrel was assumed to be $2.47 per day (the cost established by Sanofi Pharma). ASA (325mg per day) was assumed to have a price of $0.0147 per day (91). For calculations of all drug costs, a 10% markup fee was included along with pharmacy dispensing fees calculated as $4.11 ($6.11 dispensing fees minus $2.00 co-payment from the elderly) with 60 day prescriptions. Thus for a period of 6 months, clopidogrel therapy costs $508.18 {[($2.47 + 10%($2.47)) x (365/2)] + 3 x $4.11} while ASA costs $15.27 as used in Analyses A,B,C, and E. For Analysis D, clopidogrel therapy was $2.47 per day

and brand name ticlopidine therapy was considered to be $2.18 per day. A separate analysis was conducted to examine the effect of the introduction of generic ticlopidine at $1.64/day for Analysis D.

2.2.2.2 Cost Of Managing MI, IS and PAD

Overview of Cost Breakdown

The expected cost of managing a MI, IS or PAD is described in this section. The costs were divided into:

- acute costs
    - initial admission
    - initial investigation
    - interventions
    - readmission for interventions
    - in-patient rehabilitation
- follow-up costs
    - out-patient rehabilitation
    - GP/specialist visit
    - follow-up examination
    - complications
    - nursing home
    - home care

The following cost information for MI, IS and PAD treatment was based on cost data derived from SWCHSC cost data, the MOH Schedule of Benefits for physician services (92), MOH Commissioner's Office (93) and from the Ontario Case Costing Project (OCCP) preliminary findings (94).

A) Expected cost of managing a MI

The acute cost of a non-fatal MI was estimated at $9,049.40. The acute cost, defined as the sum of the costs incurred from the point of admission (Day 1 to 14), was calculated from the point of admission (Day 1 to 14) to a three month follow-up period (Day 15 to 3 months) (Appendix II, Table 1-2). The follow-up cost for a non-fatal MI (for costs incurred during the second 6 month block and each 6 month period thereafter) was $1,703.92 (Appendix II, Table 3). The index follow-up cost for a MI (defined as an uncomplicated MI follow-up without surgical intervention) was estimated at $577.81 (Appendix II, Table 4). The fatal MI cost consisted of ambulance costs (80% of fatal stroke patients arrived by ambulance with a cost of $240, thus the expected cost was $192), routine care ($5,289.34), and physician fees ($566.70) with a total cost of $6,048.04. For a 50% decrease or increase in MI treatment costs, refer to Appendix IV, Table 1.

B) Expected cost of managing ischemic stroke (IS)

The acute cost of a non-fatal IS treatment was estimated at $14,190.84. The acute cost was defined as the sum of the costs incurred from the point of admission (Day 1-14) and the three month follow-up

costs (Day 15 to 3 months) (Appendix II, Table 5-6). The follow-up costs for a non-fatal IS at each 6 month period thereafter was $3,807.37 (Appendix II, Table 7). The index follow-up cost (defined as a uncomplicated IS follow-up treatment without surgical intervention) of a non-fatal IS was $525.74 (Appendix II, Table 8). The fatal IS cost consisted of ambulance costs (91% of fatal IS patients arrived by ambulance ($240) resulting in an expected cost of $218.40), routine care ($11,340.16) and physician fees ($555.93) with a total cost of $12,114.49. For a 50% decrease or increase in IS treatment costs, refer to Appendix IV, Table 2.

C) Expected cost of managing PAD

Index follow-up costs for PAD (defined as uncomplicated PAD follow-up treatment without surgical intervention) was estimated at $368.07 (Appendix II, Table 9). Six month follow-up costs for managing an event free PAD patient was $699.81 (Appendix II, Table 10). Amputation and nursing home costs associated with PAD patients were estimated at $17,433.33. The actual cost for an amputation (defined by case mix group code of 185) was $16,396.54 (95). Home care nursing cost per day was $246.87 (96) and it was assumed that the mean LOS for an amputated patient is 42 days and the probability of receiving nursing home care is 0.10, resulting in a total nursing home cost of $1,036.85. For a 50% decrease or increase in PAD treatment costs, refer to Appendix IV, Table 3.

2.2.2.3 Cost Of Adverse Events and Concomitant Medications

A) Adverse Events

The costs associated with adverse event treatment generally were related to physician fees with the exception of severe neutropenia costs, which also considered hospitalization (Appendix II, Table 11). The cost associated with treatment of diarrhea or rash while on clopidogrel or ticlopidine therapy was simply the cost of a general practitioner visit. For a 50% decrease or increase in adverse event costs, refer to Appendix IV, Table 4.

B) Concomitant Medication

Inpatient concomitant medication was included in the routine costs derived for MI, IS and PAD. From a sample of 67 MI, 55 IS, and 37 PAD patients identified at SWCHSC, outpatient concomitant medication for a 6 month period was determined to be $134.25, $151.88, and $184.65 respectively and included in the follow-up treatment costs for each of these patient populations (Appendix II, Table 12).

2.2.2.4 Uncertainty

This analysis is limited by the available information reported in the literature with respect to patient treatment. Hence, expert opinion was given in order to determine certain probabilities (refer to Appendix III, Tables 1-10). There was no published information about the life expectancies of patients after experiencing a MI, IS or being diagnosed with PAD. Hence, certain assumptions based on the literature were made for the vascular death rate experienced by MI, IS or PAD patients. The cost figures

represent the costs from Ontario only and this cost-effectiveness analysis is more representative of the impact of clopidogrel in Ontario formularies.

2.3 DECISION TREE

2.3.1 Time Horizon

For analyses B-E, the time horizon was lifetime (up to 100 years of age), in order to simulate the potential clinical use of clopidogrel. The mean age on entry into the models was 62.5 years, based on the mean age of the population in the CAPRIE study (27). In Analysis A (CAPRIE model), the analysis was conducted for a two year period such as to mimic the mean follow-up period of the CAPRIE study.

2.3.2 How Does It Work?

2.3.2.1 Analyses A-C, E

This model is based on the CAPRIE study and represents the core model that was used in each of Analyses A-C and E. This is a simulation of a cohort of patients over a lifetime from time of index event to death (Appendix III, Figure 1). In Analysis A and B (CAPRIE and Markov Models), it is assumed that a patient will have equal probability (i.e., 1/3; refer to "A" Figure 1, Appendix III) of entering into the model at the index events of stroke, MI or PAD (i.e., the patient has just experienced a stroke or MI or has been diagnosed with PAD). The reason for this is such that in the CAPRIE trial, there were relatively equal number of subjects recruited in each of the IS, MI and PAD populations. The distinguishing features between the Index Stroke, MI or PAD arms (while on clopidogrel, ASA, ticlopidine or no treatment/placebo therapy) are the treatment costs occurred for each population and the probabilities of:

i) experiencing another stroke or MI event
ii) surviving the stroke or MI event
iii) vascular death (not a stroke or MI)

while being in a health state. The model was developed such that a patient would be in a discrete health state at the end of each 6 month cycle, i.e., the patient either has experienced a stroke, MI or died. A 6 month cycle was chosen since the cycle length is dictated by the probabilities available (90) which were derived from more extensive information from the CAPRIE trial (27) and also the frequency with which these clinical events occurred. For diseases with more frequent occurrence of events, a shorter time cycle would have been chosen (90). The health states that were defined for this model were:

i) post index
ii) post index after 6 months
iii) post (2^{nd}) stroke
iv) post (2^{nd}) stroke after 6 months
v) post (2^{nd}) MI
vi) post (2^{nd}) MI after 6 months
vii) post multiple events
viii) dead

As indicated earlier, a patient with IS, MI or PAD experienced a second event within the first 6 months. Subsequent events occurred over the 7-36 month period at a lower frequency but were entered into the model under the health states depicting the period after 6 months (e.g., post (2^{nd}) stroke after 6 months). Multiple events refer to a patient experiencing more than two strokes or two MIs. Refer to Appendix III for a list of the probabilities used in the model. It is assumed that a patient who experienced an event still remains on clopidogrel or comparator therapy.

Once a patient enters the cycle according to the qualifying condition of stroke, MI or PAD, he/she first entered the post index health state as indicated by the number "1" at the post index branch (Appendix III, Figure 1) before entering into any other health state. Transitions from one health state to another via clinical events (i.e MI, IS or death) occurred at mid-point (i.e., at three months) of each cycle. To illustrate how the model works, a patient with stroke will be used as an example (refer to Appendix III, Figure 1). Referring to the *post index* state (period after the stroke), the patient has a chance of living or dying from natural causes. If the patient dies, this is referred to as an absorbing state because the patient cannot transition to any other health state. Since probabilities must sum to one, the probability of living is equal to 1 minus the probability of dying (pDieNatural + pDieVasc) and indicated by the number sign, #. If the patient lives, the patient can experience a stroke or no stroke. The patient can survive or die from the stroke. If the patient survives the stroke, he/she transitions into the *post 2^{nd} stroke* state. If the patient does not have a stroke, he/she has a chance of having a MI or no MI. The patient can survive or die from the MI. If the patient survives the MI, he/she transitions onto the *post MI* state. If the patient has no stroke and no MI, he/she transitions onto the *post index after 6 months* state. The probability of entering into one of the six health states, defined as the net probability, is the product of the path probabilities. For example, the net probability of entering the *post 2^{nd} stroke* state is # multipled by pStroke1 mutliplied by pStrokeLive1. This product then forms the probability that a cohort will begin the *post 2^{nd} stroke* state. Thus, DATA™ redistributes the cohort into the six health states according to the net probabilities calculated at the end of each cycle.

The resource consumption and health status rating are based on events that occur over each cycle and are calculated at the end of each cycle (i.e., at the end of each six month period). See Appendix III, Figure 2 for clarification of how treatment costs are accrued as a patient progresses through one cycle of a particular health state. However, further explanation is required for determining the number of LYs gained in a particular health state. A numerical value is assigned to the number of LYs gained, where 1 represents a full LY gained in a cycle. Since this is a six month cycle, 0.5 represents half a LY gained. Using once again the patient who experienced a stroke as an example, if he/she experiences either a stroke or MI and survives, or has no stroke or MI, then he/she gains half a year of life because he/she has survived the six month period. However, if the patient with a stroke has a fatal stroke or MI, then he/she only gains a quarter year of life (or 0.25 LYs) since the event occurs at the mid-point of the cycle (i.e., 3 months). DATA™ calculates the costs and LYs gained one arm at a time (i.e., all the calculations will be done for clopidogrel therapy followed by ASA therapy).

As previously mentioned, costs and LYs gained in the future (i.e., beyond the first year) were discounted at a 3% rate upon completion of a cycle. The present cost (or LY gained) would be the

product of the future cost (or LY gained) multiplied by the discount factor, $1/(1+r)^n$ where r represents the discount rate (i.e., 3%) and n represents the number of years after the first year (68). As an example, assuming that a patient with a stroke who remains event free for a period of three years, has acute and F/U costs of $10,000 per year, then the total discounted acute and F/U cost would be:

$$\$10,000 \times [1/(1.03)^0] + \$10,000 \times [1/(1.03)^1] + \$10,000 \times [1/(1.03)^2] = \$29,135$$

as opposed to $30,000 if the costs were not discounted (i.e., discount rate of 0%).

As the model is terminated, DATA™ calculates the costs and LYs gained on a per patient basis by taking the total number cycles that were performed in a particular health state and dividing it by the size of the original cohort in that health state. Hence, the total treatment costs accrued or number of LYs gained for a patient on clopidogrel will be the sum of the treatment costs accrued or number of LYs gained in each of the IS, MI and PAD health states. The same applies to a patient on ASA therapy.

In Analysis C, the subgroup models, clopidogrel and aspirin therapies were analyzed individually within the stroke, MI and PAD populations. Hence, rather than having equal probabilities of entering into the index stroke, MI or PAD arms, patients solely entered into the index stroke, MI or PAD arms. As an example, for the stroke subgroup analysis, the probability of entering into the Index Stroke arm was 1 (at "A" in Figure 1, Appendix III), while the rest were zero. This was the only variation, all probabilities used were the same as in Analysis A and B.

In Analysis E, clopidogrel versus no treatment as 2nd line therapy in MI patients, the ASA event probabilities were modified to reflect placebo probabilities as previously described. As well, only MI patients were examined in this analysis. All patients entering the model entered the Index MI arms only for both clopidogrel and no treatment (i.e., probability of 1 at "B" in Figure 1, Appendix III).

2.3.2.2 Analysis D - "Second-Line" Stroke Therapy

In this analysis, clopidogrel is compared to ticlopidine and the patient is assumed either to be intolerant to ASA or to have failed on ASA therapy (i.e., experienced another event) (Appendix III, Figure 3). The initial phase of this Markov model allows a patient already receiving either clopidogrel or ticlopidine therapy to experience an adverse event. Tolerability and acute adverse events were based on a 3 month period based on the TASS (46) and CATS (29) studies. The distinguishing features between the adverse event arms for clopidogrel or ticlopidine therapy are the costs incurred for remedying the adverse event or neutropenia monitoring (in the case of ticlopidine treatment) and the probabilities of experiencing:

i) an adverse event
ii) neutropenia (moderate, severe or fatal)
iii) diarrhea (moderate or severe)
iv) rash (moderate or severe)
v) other adverse event (e.g., elevation in liver function tests and increase in serum cholesterol levels)

In this analysis, upon entering one of the clopidogrel or ticlopidine adverse event arms, the time = 0 months. For the next three months, the patient remains in the adverse event period, receiving treatment to remedy the adverse event. The three month management algorithms and costs were based on Oster et al, (1994) (87) and OHIP (Schedule of Benefits) (92). A list of adverse event probabilities are provided in Appendix III.

If the patient had a moderate adverse event, he/she remains on clopidogrel therapy and will enter the Markov model in such a state. If the patient experiences a severe adverse event, clopidogrel or ticlopidine treatment will be discontinued and the patient enters the Markov model in a no drug treatment (placebo) state. Patients unable to tolerate the active treatment would proceed to no treatment and not ASA since they were already ASA intolerant or failed ASA therapy (i.e., the reason why they were switched to ticlopidine or clopidogrel).

After 3 months, patients would enter into the Markov model (Analysis B) or active treatment or no treatment (i.e., ASA intolerant or ASA failure) as discussed in Section 2.3.2.1. Equal outcomes were assumed for stroke, MI or death for clopidogrel and ticlopidine.

3. RESULTS

The following results are presented on a per patient basis and the CERs reflect incremental CERs. In the tables, the values in the brackets indicate the 95% CI (lower and upper limits) for outcomes associated with clopidogrel therapy only.

3.1 Analysis A - CAPRIE Model (Two Year)

This was a cost-consequence analysis with a time horizon of two years. The incremental difference in two year cost of clopidogrel therapy versus ASA therapy is $1,777 (i.e., $9,339 minus $7,562) (Table 5). Clopidogrel conferred benefits over ASA as there were fewer first outcome events (stroke and MI) experienced on clopidogrel, a decrement of 0.51% (i.e., 5.83% minus 5.32%) over ASA over a one year period as reported in the CAPRIE study (27). Hence, over a two year period, the decrement would be 1.02% (2x0.51%). Overall, the incremental cost per event avoided is $174,216 per patient.

TABLE 5: Results from Analysis A – Two year CAPRIE Model considering primary events

DRUG	COST (2 years)	EVENT RATE OVER 1 YEAR	Δ COST/EVENT AVOIDED
ASA	$7,562	5.83%	
CLOPIDOGREL	$9,339	5.32%	$174,216/event
	($9,322-$9,363)		($172,549 -$176,569/event)

In another cost-consequence analysis considering all outcome events (1st, 2nd and 3rd outcomes) over a two year period, the incremental difference in two year cost of clopidogrel therapy versus ASA therapy was $1,777 (Table 6). Clopidogrel conferred survival benefits over ASA as there were fewer first outcome events (stroke and MI) experienced on clopidogrel, a decrement of 0.66% over ASA for a one year period (as calculated from the CAPRIE study). Hence, for a two year period, the differential in event rate between clopidogrel and ASA would be 1.32% (2x0.66%). Overall, the incremental cost per event avoided was $134,621 per patient.

TABLE 6: Results from Analysis A – Two year CAPRIE Model considering all outcome events

DRUG	COST (2 years)	EVENT RATE OVER 1 YEAR	Δ COST/EVENT AVOIDED
ASA	$7,562	6.54%	
CLOPIDOGREL	$9,339	5.88%	$134,621/event
	($9,322-$9,363)		($133,333-$136,439/event)

3.2 Analysis B – Markov Model

The incremental difference in lifetime cost of first-line clopidogrel therapy versus ASA therapy was $9,501 (Table 7). The incremental difference is caused by the higher drug price for clopidogrel ($2.47/day) versus ASA therapy ($0.0147/day) and also the survival benefits associated with clopidogrel. This translate into patients remaining longer on clopidodgrel therapy, thus, drug and treatment costs are incurred. Clopidogrel conferred survival benefits with a gain of 0.2947 LYs over ASA therapy. The CER illustrates an overall "moderate" cost-attractiveness for clopidogrel treatment over ASA treatment.

TABLE 7: Markov Model Lifetime Analysis

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
ASA	$40,663	9.08 LY	
CLOPIDOGREL	$50,164	9.37 LY	$32,240/LY
	($49,084 - $51,310)	(9.31 – 9.61 LY)	($20,081/LY - $153,109/LY)

3.3 Analysis C - Subgroup Models For First Line Therapy

3.3.1 Analysis C1 - Stroke Subgroup

This analysis considered patients entering the model only after experiencing a stroke. The incremental difference in lifetime cost of first-line clopidogrel therapy versus ASA therapy in patients who experience a stroke is $9,169 (Table 8). Clopidogrel confers survival benefits with a gain of 0.1023 LYs which do not offset the incremental difference in lifetime cost. Hence, the CER illustrates that clopidogrel treatment was not economically attractive compared with ASA treatment.

TABLE 8: Stroke subgroup analysis

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
ASA	$71,550	9.00 LY	
CLOPIDOGREL	$80,719	9.10 LY	$89,629/LY
	($78,875 – $82,921)	(8.84 – 9.40 LY)	($28,492/LY – dominated by ASA therapy)

3.3.2 Analysis C2 - MI Subgroup

This analysis considered patients entering the model only after experiencing a MI. The incremental difference in lifetime cost of clopidogrel therapy versus ASA therapy is $8,580 (Table 9). Clopidogrel does not confer any survival benefits over ASA with a decrement of 0.1614 LYs. Hence, clopidogrel

therapy is dominated by ASA therapy as first-line treatment in MI patients. ASA is more effective and less costly than clopidogrel.

TABLE 9: MI subgroup analysis

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
ASA	$34,615	9.36 LY	
CLOPIDOGREL	$43,195	9.20 LY	Dominated by ASA
	($42,133 - $44,137)	(8.94 – 9.43 LY)	($133,175/LY – dominated by ASA)

3.3.3 Analysis C3 - PAD Subgroup

This analysis considered patients entering the model only after being diagnosed with PAD. The incremental difference in lifetime cost of clopidogrel therapy versus ASA therapy is $10,752 (Table 10). Clopidogrel confers survival benefits over ASA with a gain of 0.9431 LYs which offset the incremental difference in lifetime cost. This results in a CER illustrating an overall cost-attractiveness for first line clopidogrel versus ASA treatment in patients with PAD.

TABLE 10: PAD Subgroup Analysis

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
ASA	$15,825	8.87 LY	
CLOPIDOGREL	$26,577	9.81 LY	$11,401/LY
	($26,243 - $26,873)	(9.61 – 9.99 LY)	($9,863 - $14,038/LY)

3.4 Analysis D – Second Line Stroke Therapy

3.4.1. Analysis D1 - Clopidogrel vs Brand Name Ticlopidine

The incremental difference in lifetime cost of second-line clopidogrel therapy versus ticlopidine therapy is $2,125 (Table 11). This incremental difference in lifetime cost is smaller than previously reported incremental differences (in Analyses B-C where clopidogrel was compared to ASA), because there is less of a drug price difference between clopidogrel and ticlopidine (i.e., $2.47/day and $2.18/day respectively) versus clopidogrel and ASA ($2.47/day and $0.0147/day respectively). Clopidogrel confers survival benefits with a gain of 0.1071 LYs. The CER illustrates a moderate cost-attractiveness of clopidogrel therapy in stroke patients because of a balance between the smaller incremental in lifetime costs and survival benefits.

TABLE 11: "Second-Line" Stroke Analysis for Lifetime Treatment Period. The values in the brackets represent the variation in clopidogrel treatment outcomes.

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
TICLOPIDINE	$77,599	9.25 LY	
$2.18/day			
CLOPIDOGREL	$79,724	9.36 LY	$19,852/LY
	($79,813-$79,752)	(9.36-9.37 LY)	($19,546-$20,046/LY)

3.4.2. Analysis D2 - Clopidogrel vs Generic Ticlopidine

There is no difference in the lifetime cost of clopidogrel in this analysis versus the analysis conducted with brand name ticlopidine (Table 11). The lifetime cost differential of ticlopidine treatment in this analysis versus the analysis conducted with brand name ticlopidine is $1,594. This difference is due to the change in drug price of ticlopidine (from $2.18/day to $1.64/day). The incremental difference in lifetime cost of second-line clopidogrel therapy versus ticlopidine therapy is $3,719. Clopidogrel confers survival benefits with a gain of 0.1071 LYs. The CER illustrates a moderate cost-attractiveness of clopidogrel therapy in stroke patients. The difference in cost/LY for this analysis versus the analysis conducted with brand name ticlopidine is $14,873.

TABLE 12: "Second-Line" Stroke Analysis with Generic Ticlopidine at $1.64. Values in non-italicized brackets represent the variation in clopidogrel treatment outcomes. Values in the italicized brackets represent the results from the same analysis conducted with brand name ticlopidine at $2.18/day.

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
TICLOPIDINE	$76,005	9.25 LY	
$1.64/day	*($77,599)*		
CLOPIDOGREL	$79,724	9.36 LY	$34,725/LY
	($79,813-$79,752)	(9.36-9.37 LY)	($33,606-$34,877/LY)
	($79,724)		*($19,852/LY)*

3.5 Analysis E – Second Line MI Therapy

The incremental difference in lifetime cost of clopidogrel therapy versus no therapy is $9,570 (Table 13). This incremental difference is present because of I) the difference in drug price, clopidogrel at $2.47/day versus no treatment at $0/day and ii) the gain in survival benefits which maintain patients on clopidogrel therapy who incur further treatment costs. Clopidogrel confers survival benefits over no

treatment with a gain of 0.3669 LYs. The CER illustrates cost-attractiveness of second-line clopidogrel treatment in MI patients.

TABLE 13: Clopidogrel as "second-line" therapy in MI

DRUG	COST (lifetime)	ESTIMATED SURVIVAL	Δ COST/LY
NO TREATMENT	$33,625	8.83 LY	
CLOPIDOGREL	$43,195	9.20 LY	$26,084/LY
	($42,133 - $44,136)	(8.94 – 9.43 LY)	($17,524 - $78,853/LY)

4.0 SENSITIVITY ANALYSIS

All sensitivity analyses were conducted on Analysis B (Markov Model), Analysis C (1st Line Therapy in Subgroups IS, MI and PAD), Analysis D (2nd Line Stroke Therapy) and Analysis E (2nd Line MI Therapy). Please note that the results presented below are on a per patient basis. **For a more detailed description of the change in the lifetime costs, LYs gained and CERs (cost/LY gained), refer to Appendix IV.**

4.1. Overall IS, MI and PAD Populations

For a more detailed description of the change in the lifetime costs, LYs and CERs, refer to Appendix IV, Table 5.

4.1.1 Varying the Drug Cost of Clopidogrel

With a 50% decrease in clopidogrel drug cost, the lifetime cost of clopidogrel therapy decreases to $45,535. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $4,872 ($45,535 minus $40,663) versus $9,501 ($50,164 minus $40,663) in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is lower, at $16,536/LY which is more favourable than the baseline result of $32,240/LY (Figure 9).

With a 50% increase in clopidogrel drug cost, the lifetime cost of clopidogrel therapy increases to $54,830. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $14,167 versus $9,501 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $48,079/LY, in comparison to the baseline result.

4.1.2 Varying Acute and Follow-Up Treatment Costs

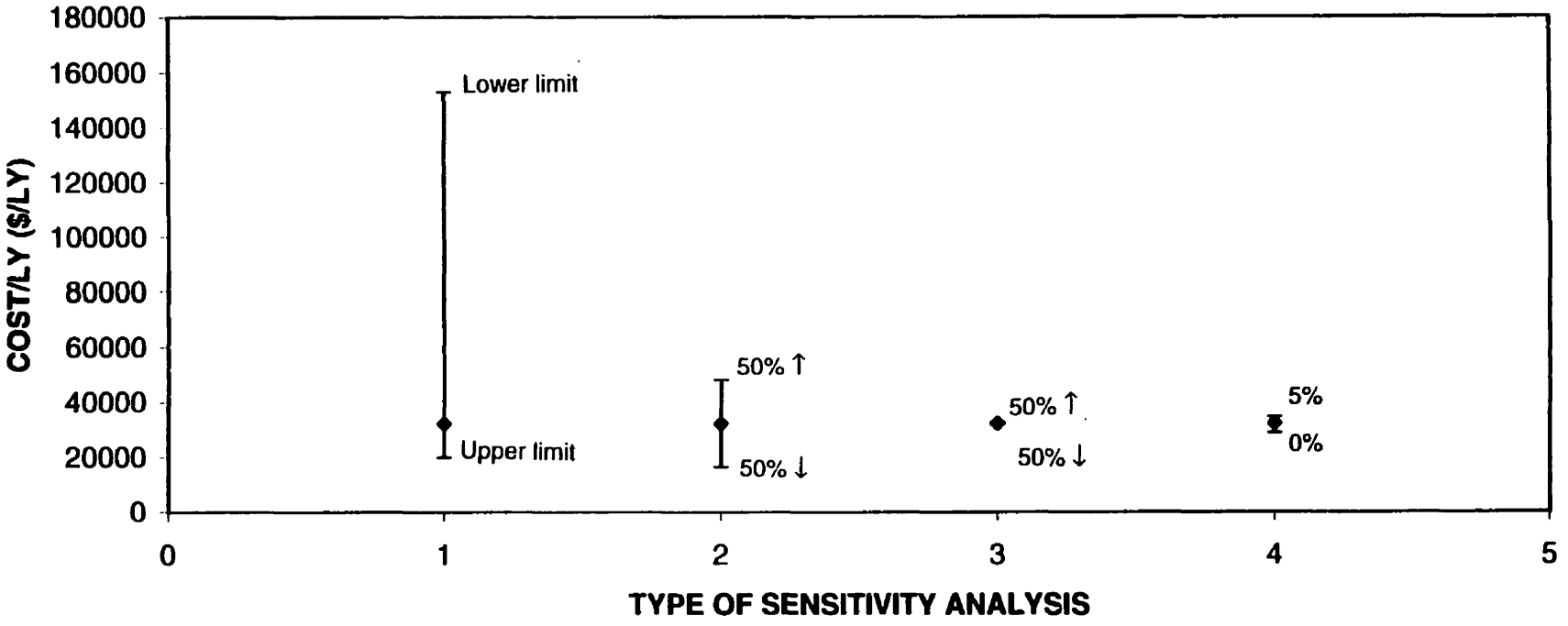
With a 50% decrease in acute and F/U treatment costs, the lifetime costs of clopidogrel and ASA therapy both decrease to $29,845 and $20,470 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $9,375 versus $9,501 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $31,815 representing a small decrement from the baseline result of $32,240/LY (Figure 9).

With a 50% increase in acute and F/U treatment costs, the lifetime costs of clopidogrel and ASA therapy both increase to $70,483 and $60,856 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $9,627 versus $9,501 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $32,672 representing a small increment from the baseline result.

4.1.3 Varying the Discount Rate

With a 0% discount rate, the lifetime costs of clopidogrel and ASA therapy both increase to $62,441 and $50,542 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy

FIGURE 9: SENSITIVITY ANALYSIS FOR OVERALL IS, MI AND PAD POPULATIONS



◆baseline cost/LY

1 Lower and upper limit of the 95% CI for the relative risk reduction (0.3% and 16.5%) for events and death with clopidogrel therapy

2 50% decrease/increase in clopidogrel drug cost

3 50% decrease/increase in acute/FU treatment costs

4 0% and 5% discount rate

is $11,899 versus $9,501 in the baseline analysis. There is an increase in the number of LYs gained with clopidogrel therapy, with an incremental difference of 0.42 LYs versus 0.29 LYs in the baseline analysis. The incremental cost/LY is lower, at $28,720/LY, in comparison to the baseline result of $32,240/LY (Figure 9).

With a 5% discount rate, the lifetime costs of clopidogrel and ASA therapy both decrease to $44,156 and $35,820 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $8,336 versus $9,501 in the baseline analysis. There is a decrease in the number of LYs gained with clopidogrel therapy, with an incremental difference of 0.24 LYs versus 0.29 LYs in the baseline analysis. The incremental cost/LY is higher, at $34,667/LY, in comparison to the baseline result.

4.2 Subgroup Analyses

4.2.1 Stroke Subgroup

For a more detailed description of the change in the lifetime costs, LYs and CERs, refer to Appendix IV, Table 6.

4.2.1.1 Varying the Drug Cost of Clopidogrel

With a 50% decrease in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $76,223. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $4,673 versus $9,169 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is lower, at $45,681, in comparison to the baseline result of $89,629/LY (Figure 10).

With a 50% increase in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $85,252. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $13,702 versus $9,169 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $133,932, in comparison to the baseline result.

4.2.1.2 Varying Acute and Follow-Up Treatment Costs

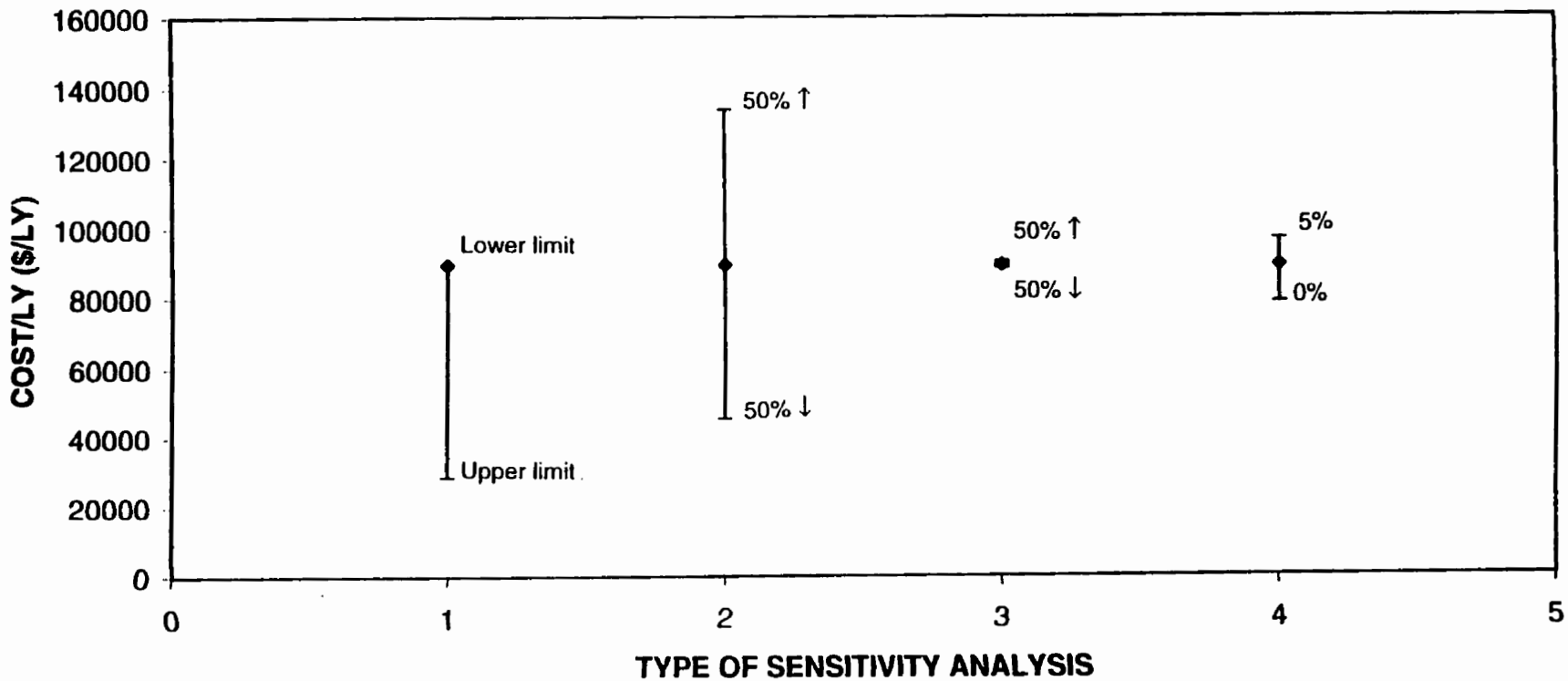
With a 50% decrease in acute and F/U treatment costs, the lifetime costs of clopidogrel and ASA therapy both decrease to $44,986 and $35,912 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $9,074 versus $9,169 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $88,693 representing a small decrement from the baseline result of $89,629/LY (Figure 10).

With a 50% increase in acute and F/U treatment costs, the lifetime costs of clopidogrel and ASA therapy both increase to $116,452 and $107,187 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $9,267 versus $9,169 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $90,562 representing a small increment from the baseline result.

4.2.1.3 Varying the Discount Rate

With a 0% discount rate, the lifetime costs of clopidogrel and ASA therapy both increase to $100,516 and $89,041 respectively. The incremental difference in lifetime cost of clopidogrel versus

FIGURE 10: SENSITIVITY ANALYSIS OF STROKE SUBGROUP



◆baseline cost/LY

1 Lower and upper limit for the 95% CI for the relative risk reduction (0.3% and 16.5%) for events and death with clopidogrel therapy

* N.B. lower limit of 95% CI for the relative risk reduction resulted in aspirin being the dominant therapy

2 50% decrease/increase in clopidogrel drug cost

3 50% decrease/increase in acute/FU treatment costs

4 0% and 5% discount rate

ASA therapy is $11,475 versus $9,169 in the baseline analysis. There is an increase in the incremental number of LYs gained, 0.15 LYs versus 0.10 LYs in the baseline analysis. The incremental cost/LY is lower, at $79,084/LY, in comparison to the baseline result of $89,629/LY (Figure 10).

With a 5% discount rate, the lifetime costs of clopidogrel and ASA therapy both decrease to $71,004 and $62,954 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $8,050 versus $9,169 in the baseline analysis. There is a decrease in the number of LYs gained with clopidogrel therapy, an increment of 0.08 LYs versus 0.10 LYs in the baseline analysis. The incremental cost/LY is higher, at $97,197/LY, in comparison to the baseline result.

4.2.2 MI Subgroup

For a more detailed description of the change in the lifetime costs, LYs and CERs, from all the sensitivity analyses, refer to Appendix IV, Table 7. For all the sensitivity analyses conducted, ASA still remained the dominant therapy with the exception of altering the event and death probabilities to reflect the upper 95% CI in the relative risk reduction. In this scenario, the lifetime cost of clopidogrel therapy is $44,137. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $9,522 versus $8,580 in the baseline analysis. There is an increase in the number of LYs gained with clopidogrel, an increment of 0.13 LYs in comparison to no gain in LYs as in the baseline analysis. The incremental cost/LY is $133,175/LY as opposed to being dominated by ASA therapy.

4.2.3 PAD Subgroup

For a more detailed description of the change in the lifetime costs, LYs and CERs, from all the sensitivity analyses, refer to Appendix IV, Table 8.

4.2.3.1 Varying the Drug Cost of Clopidogrel

With a 50% decrease in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $21,732. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $5,907 versus $10,752 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is lower, at $6,263, in comparison to the baseline result of $11,401/LY (Figure 11).

With a 50% increase in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $31,462. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $15,637 versus $10,752 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $16,580, in comparison to the baseline result.

4.2.3.2 Varying Acute and Follow Up Treatment Costs

With a 50% decrease in acute and F/U treatment costs, the lifetime costs of clopidogrel and ASA therapy both decrease to $18,275 and $8,048 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $10,227 versus $10,752 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $10,884 representing a small decrement from the baseline result of $11,401/LY (Figure 11).

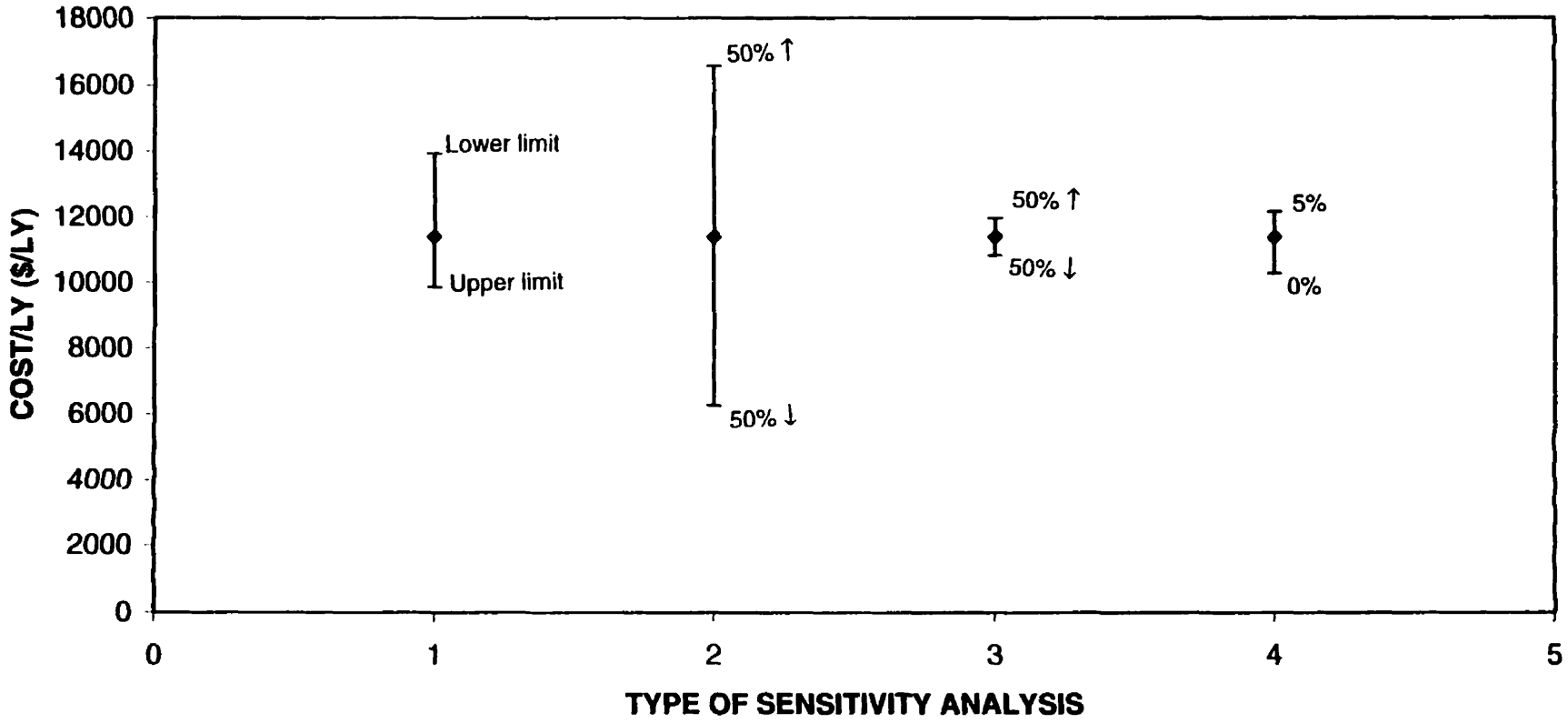
With a 50% increase in acute and F/U treatment costs, the lifetime costs of clopidogrel and ASA therapy both increase to $34,880 and $23,602 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $11,278 versus $10,752 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $11,958 representing a small increment from the baseline result.

4.2.3.3 Varying the Discount Rate

With a 0% discount rate, the lifetime costs of clopidogrel and ASA therapy both increase to $33,246 and $19,569 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $13,677 versus $10,752 in the baseline analysis. There is an increase in the number of LYs gained with clopidogrel therapy, with an increment of 1.33 LYs versus 0.94 LYs in the baseline analysis. The incremental cost/LY is lower, at $10,291/LY, in comparison to the baseline result of $11,401/LY (Figure 11).

With a 5% discount rate, the lifetime costs of clopidogrel and ASA therapy both decrease to $23,338 and $13,990 respectively. The incremental difference in lifetime cost of clopidogrel versus ASA therapy is $9,348 versus $10,752 in the baseline analysis. There is a decrease in the number of LYs gained, with an increment of 0.77 LYs versus 0.94 LYs. The incremental cost/LY is higher, at $12,165/LY, in comparison to the baseline result.

FIGURE 11: SENSITIVITY ANALYSIS FOR PAD SUBGROUP



◆baseline cost/LY

1 Lower and upper limit for the 95% CI for the relative risk reduction (0.3% and 16.5%) for events and death with clopidogrel therapy

2 50% decrease/increase in clopidogrel drug cost

3 50% decrease/increase in acute/FU treatment costs

4 0% and 5% discount rate

4.3 Clopidogrel versus Brand Name Ticlopidine

For a more detailed description of the change in the lifetime costs, LYs and CERs from the sensitivity analyses, refer to I) Appendix IV, Table 9 for variations in the drug cost of clopidogrel, acute and follow-up treatment costs, discount rate and ticlopidine adverse event rates (illustrated with the lower and upper limits in variation of outcomes) and II) Appendix IV, Table 10 for variations in the adverse event costs, adverse event rates for clopidogrel and adverse event rates for ticlopidine alone with no variation in outcomes.

4.3.1 Varying the Drug Cost of Clopidogrel

With a 50% decrease in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $75,640. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $1,959, which is lower in comparison to the baseline difference of $2,033. There is no change in the number of LYs gained. The incremental cost/LY is -$18,291 indicating that clopidogrel is a dominant therapy (i.e., clopidogrel is less expensive and generates a greater number of LYs gained) (Figure 12).

With a 50% increase in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $83,842. The incremental difference lifetime cost of clopidogrel therapy versus ticlopidine therapy is $6,243 versus $2,033 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $58,291/LY, in comparison to the baseline result of $19,852/LY.

4.3.2 Varying the Acute and Follow-Up Treatment Costs

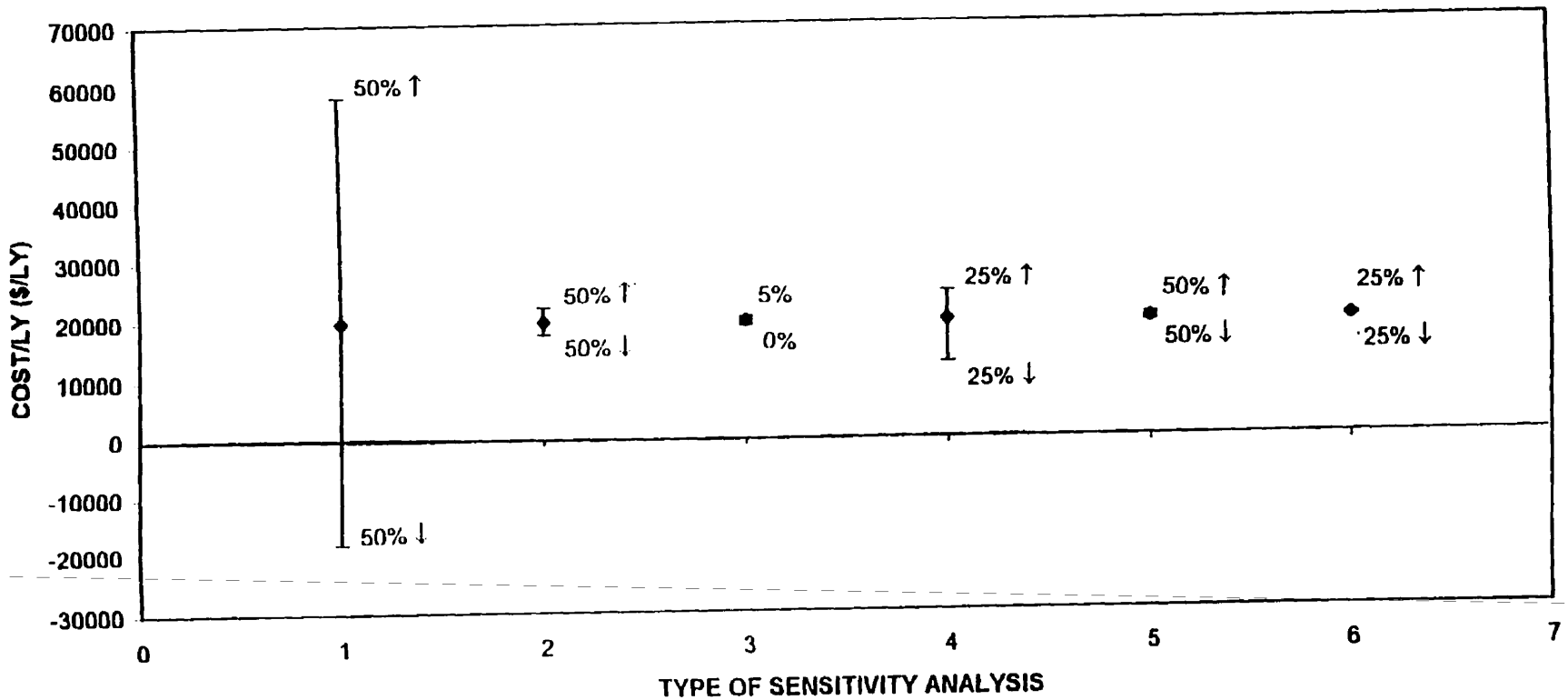
With a 50% decrease in acute and F/U treatment costs, the lifetime costs of clopidogrel and ticlopidine therapy both decrease to $44,087 and $42,207 respectively. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $1,880 versus $2,033 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is lower, at $17,554, in comparison to the baseline result of $19,852/LY (Figure 12).

With a 50% increase in acute and F/U treatment costs, the lifetime costs of clopidogrel and ticlopidine therapy both increase to $115,361 and $112,991 respectively. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $2,370 versus $2,033 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $22,129, in comparison to the baseline result.

4.3.3 Varying the Discount Rates

With a 0% discount rate, the lifetime costs of clopidogrel and ticlopidine therapy both increase to $99,129 and $96,386 respectively. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $2,743 versus $2,033 in the baseline analysis. There is an increase in the number of LYs gained, an increment of 0.14 LYs versus 0.11 LYs in the baseline analysis. The incremental cost/LY is lower, at $19,075/LY, in comparison to the baseline result of $19,852/LY (Figure 12).

FIGURE 12: SENSITIVITY ANALYSIS FOR CLOPIDOGREL VS TICLOPIDINE



◆ baseline cost/LY
1 50% decrease/increase in clopidogrel drug cost
2 50% decrease/increase in acute/FU treatment costs
3 0% and 5% discount rate
4 25% decrease/increase in ticlopidine adverse event rate
5 50% decrease/increase in adverse event costs
6 25% decrease/increase in clopidogrel adverse event rate

With a 5% discount rate, the lifetime costs of clopidogrel and ticlopidine therapy both decrease to $70,193 and $68,363 respectively. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $1,830 versus $2,033 in the baseline analysis. There is a decrease in the number of LYs gained, with an increment of 0.09 LYs versus 0.11 LYs in the baseline analysis. The incremental cost/LY is higher, at $20,356/LY, in comparison to the baseline result.

4.3.4 Varying Ticlopidine Adverse Event Rates

Decreasing all the ticlopidine adverse event rates by 25% produced an increase in the lifetime cost of ticlopidine therapy to $78,017. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $1,707 versus $2,125 from the baseline analysis. There is a decrease in the number of LYs gained, with an increment of 0.06 LYs versus 0.11 LYs in the baseline analysis. The incremental cost/LY increases somewhat to $27,166/LY, in comparison to the baseline result of $19,852/LY (Figure 12).

Increasing all the ticlopidine adverse event rates by 25% produced a decrease in the lifetime cost of ticlopidine therapy to $75,417. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $4,308 versus $2,125 from the baseline analysis. There is an increase in the number of LYs gained, with an increment of 0.18 LYs versus 0.11 LYs. The incremental cost/LY increases to $23,671/LY, in comparison to the baseline result.

4.3.5 Varying the Adverse Event Costs

For a 50% decrease in adverse event costs, the lifetime costs of ticlopidine treatment decreased in comparison to the baseline analysis. $77,528. The incremental difference in lifetime cost of clopidogrel therapy versus brand name ticlopidine therapy is $2,192 versus $2,125 in the baseline analysis. There were no changes in terms of LYs saved. The incremental cost/LY is $20,475, a small increase, in comparison to the baseline result of $19,852/LY (Figure 12).

For a 50% increase in adverse event costs in the analysis comparing clopidogrel with brand name ticlopidine, the lifetime cost of ticlopidine and clopidogrel treatment increased to $77,669 and $79,728 respectively. The incremental difference in lifetime cost of clopidogrel therapy versus brand name ticlopidine therapy is $2,059 versus $2,125 in the baseline analysis. There were no changes in terms of LYs saved. The incremental cost/LY is $19,229/LY, a small decrease in comparison to the baseline result.

4.3.6 Varying Clopidogrel Adverse Event Rates

Decreasing all the clopidogrel adverse event rates by 25% produced an increase in the lifetime cost of clopidogrel therapy to $79,816. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $2,217 versus $2,125 from the baseline analysis. There is a small increase in the number of LYs gained, an increment of 0.1133 LYs versus 0.1071 LYs in the baseline analysis. The incremental cost/LY is $19,568/LY, a small decrease in comparison to the baseline result of $19,852/LY (Figure 13).

A 25% increase in clopidogrel adverse event rates produced an increase in the lifetime cost of clopidogrel therapy to $79,747. The incremental difference in lifetime cost of clopidogrel versus ticlopidine therapy is $2,148 versus $2,125 over the base case analysis. There is no change in the survival benefits. The incremental cost/LY is $19,998/LY, a small increase in comparison to the baseline result.

4.4 Clopidogrel versus Generic Ticlopidine

For a more detailed description of the change in the lifetime costs, LYs and CERs from the sensitivity analyses, refer to I) Appendix IV, Table 11 for variations in clopidogrel drug cost, acute and follow-up treatment costs, discount rate and ticlopidine adverse event rate (illustrated with the lower and upper limits in variation of outcomes) and II) Appendix IV, Table 12 for variations in the adverse event costs, clopidogrel adverse event rates, and ticlopidine adverse event rates alone with no variation in outcomes.

4.4.1 Varying the Drug Cost of Clopidogrel

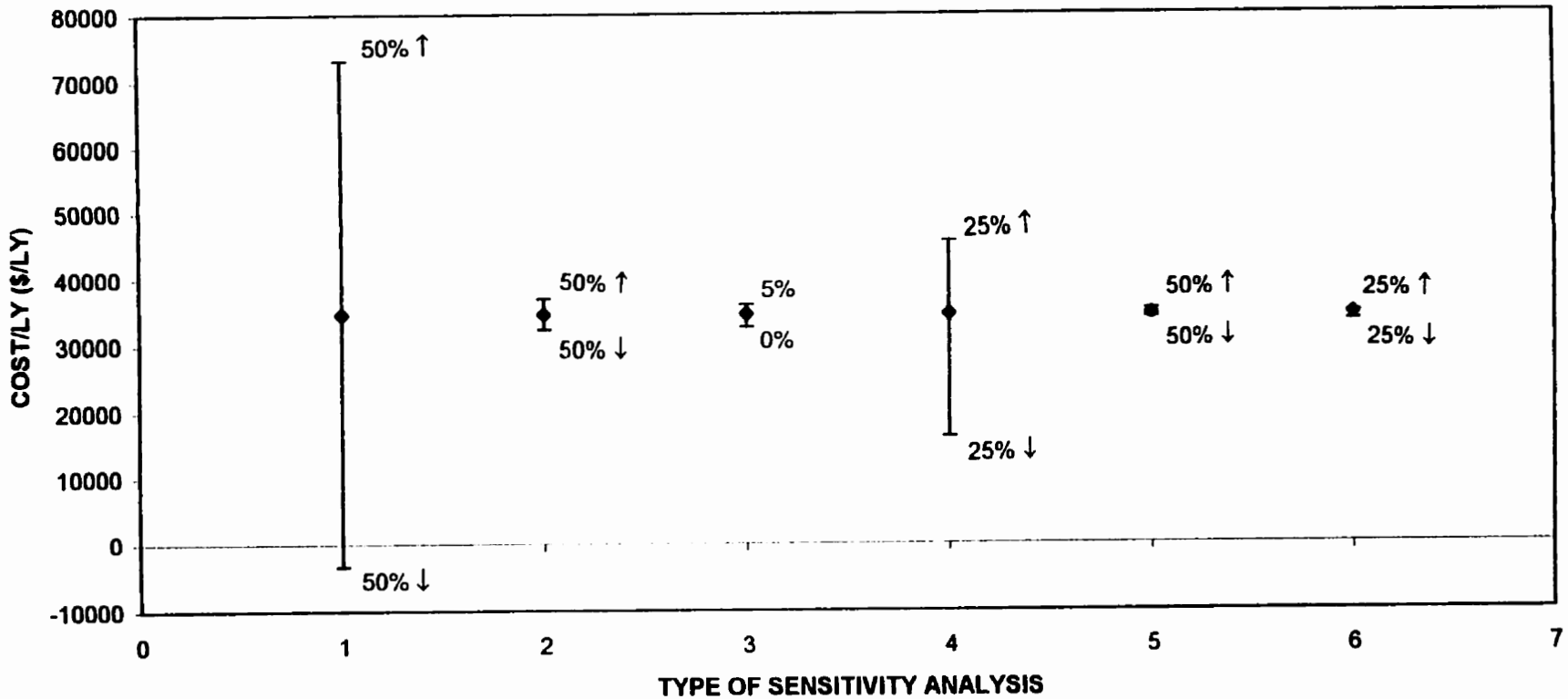
With a 50% decrease in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $75,640. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is -$365 (cost savings) versus $3,719 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is -$3,408/LY representing dominance by clopidogrel therapy (i.e less expensive and generates a greater number of LYs) (Figure 13).

With a 50% increase in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $83,842. The incremental difference lifetime cost of clopidogrel therapy versus generic ticlopidine therapy is $7,837 versus $3,719 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $73,175/LY, in comparison to the baseline result of $34,725/LY.

4.4.2 Varying Acute and Follow-Up Treatment Costs

With a 50% decrease in acute and F/U treatment costs, the lifetime cost of clopidogrel and generic ticlopidine therapy both decrease to $44,087 and $40,614 respectively. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $3,473 versus $3,719 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is lower, at $32,428/LY, in comparison to the baseline result of $34,725/LY (Figure 13).

FIGURE 13: SENSITIVITY ANALYSIS FOR CLOPIDOGREL VS GENERIC TICLOPIDINE



◆ baseline cost/LY
1 50% decrease/increase in clopidogrel drug cost
2 50% decrease/increase in acute/FU treatment costs
3 0% and 5% discount rate
4 25% decrease/increase in ticlopidine adverse event rate
5 50% decrease/increase in adverse event costs
6 25% decrease/increase in clopidogrel adverse event rate

With a 50% increase in acute and F/U treatment costs, the lifetime cost of clopidogrel and generic ticlopidine therapy both increase to $115,361 and $111,397 respectively. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $3,964 versus $3,719 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $37,012/LY, in comparison to the baseline result.

4.4.3 Varying the Discount Rate

With a 0% discount rate, the lifetime costs of clopidogrel and generic ticlopidine therapy both increase to $99,129 and $94,429 respectively. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $4,700 versus $3,719 in the baseline analysis. The incremental difference in the number of LYs gained is 0.14 LYs versus 0.11 LYs gained in the baseline analysis. The incremental cost/LY is lower, at $32,675/LY, in comparison to the baseline result of $34,725/LY (Figure 13).

With a 5% discount rate, the lifetime costs of clopidogrel and generic ticlopidine therapy both decrease to $70,193 and $66,948 respectively. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $3,245 versus $3,719 in the baseline analysis. The incremental difference in the number of LYs gained is 0.09 LYs versus 0.11 LYs gained in the baseline analysis. The incremental cost/LY is higher, at $36,084/LY, in comparison to the baseline result.

4.4.4 Varying Ticlopidine Adverse Event Rates

Decreasing all the ticlopidine adverse event rates by 25% produced an increase in the lifetime cost associated with generic ticlopidine therapy to $76,375 versus $76,005 in the baseline analysis. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $3,349 versus $3,719 from the baseline analysis. There is a decrease in the number of LYs gained, an increment of 0.06 LYs versus 0.11 LYs gained in the baseline analysis. The incremental cost/LY is greater, at $53,288/LY, in comparison to the baseline result of $34,725/LY (Figure 13).

Increasing all the ticlopidine adverse event rates by 25% produced a decrease in the lifetime cost associated with generic ticlopidine therapy to $76,962 versus $76,005 in the baseline analysis. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $4,308 versus $3,719 from the baseline analysis. There is an increase in the number of LYs gained, an increment of 0.18 LYs versus 0.11 LYs in the baseline analysis. The incremental cost/LY is lower, at $23,671/LY, in comparison to the baseline result .

4.4.5 Varying the Adverse Event Costs

For a 50% decrease in adverse event costs for clopidogrel versus generic ticlopidine, the lifetime cost of ticlopidine and clopidogrel treatment both decreased in comparison to the baseline analysis. The lifetime costs of both clopidogrel and generic ticlopidine decreased minimally to $79,721 and $75,935 respectively. The incremental difference in lifetime cost of clopidogrel therapy versus generic ticlopidine therapy is $3,786 versus $3,719 in the baseline analysis. There is no change in the survival benefits.

The incremental cost/LY is slightly higher, at $35,350/LY, in comparison to the baseline result of $34,725/LY (Figure 13).

For a 50% increase in adverse event costs in the analysis comparing clopidogrel with generic name ticlopidine, the lifetime cost of ticlopidine and clopidogrel treatment increased. The lifetime cost of both clopidogrel and generic ticlopidine increased minimally to $79,728 and $76,076. The incremental difference in lifetime cost of clopidogrel therapy versus generic ticlopidine therapy is $3,652 versus $3,719 in the baseline analysis. There is no change in the survival benefits. The incremental cost/LY is slightly less, at $34,099/LY, in comparison to the baseline result.

4.4.6 Varying the Clopidogrel Adverse Event Rates

Decreasing all the clopidogrel adverse event rates by 25% produced an increase in the lifetime cost of clopidogrel therapy to $79,816 versus $79,724 in the baseline analysis. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $3,810 versus $3,719 from the baseline analysis. There is a slight increase in the number of LYs gained, an increment of 0.1133 LYs versus 0.1071 LYs in the baseline analysis. The incremental cost/LY is slightly lower, at $33,627/LY, in comparison to the baseline result of $34,725/LY (Figure 13).

For clopidogrel versus generic ticlopidine, increasing all clopidogrel adverse event rates by 25% produced an increase in lifetime cost of clopidogrel therapy to $79,747 versus $79,724 in the baseline analysis. The incremental difference in lifetime cost of clopidogrel versus generic ticlopidine therapy is $3,742 versus $3,719 from the baseline analysis. There is no change in the survival benefits. The incremental cost/LY is slightly higher, at $34,939/LY, in comparison to the baseline result.

4.5 Second Line MI Therapy

For a more detailed description of the change in lifetime costs, LYs and CERs from the sensitivity analyses, refer to Appendix IV, Table 13.

4.5.1 Varying Clopidogrel Drug Cost

With a 50% decrease in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $38,652. The incremental difference in lifetime cost of clopidogrel versus placebo therapy is $5,027 versus $9,570 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is lower, at $13,701/LY, in comparison to the baseline result of $26,084/LY (Figure 14).

With a 50% increase in clopidogrel drug cost, the lifetime cost of clopidogrel therapy is $47,776. The incremental difference in lifetime cost of clopidogrel versus placebo therapy is $14,151 versus $9,570 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is higher, at $38,567/LY, in comparison to the baseline result.

4.5.2 Varying Clopidogrel Acute and Follow-Up Care Costs

With a 50% decrease in acute and F/U treatment costs, the lifetime cost of clopidogrel and placebo therapy both decrease to $26,273 and $16,812 respectively. The incremental difference in lifetime cost

of clopidogrel versus placebo therapy is $9,461 versus $9,570 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $25,784/LY, a small decrease from the baseline result of $26,084/LY (Figure 14).

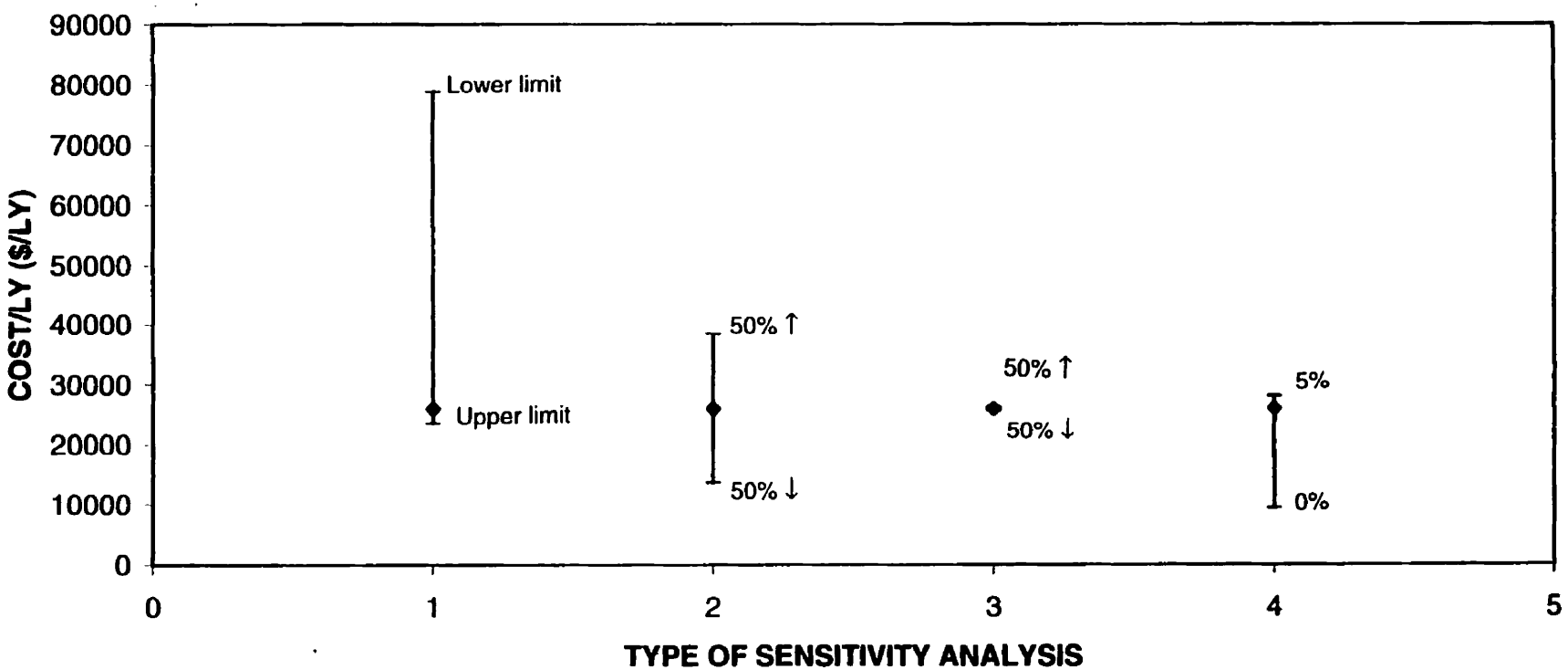
With a 50% increase in acute and F/U treatment costs, the lifetime cost of clopidogrel and placebo therapy both increase to $60,118 and $50,437 respectively. The increment in lifetime cost of clopidogrel versus placebo therapy is $9,681 versus $9,570 in the baseline analysis. There is no change in the number of LYs gained. The incremental cost/LY is $26,383/LY, a small increase from the baseline result.

4.5.3 Varying the Discount Rate

With a 0% discount rate, the lifetime cost of clopidogrel and placebo therapy both increase to $53,561 and $41,412 respectively. The incremental difference in lifetime cost of clopidogrel versus placebo therapy is $12,149 versus $9,570 in the baseline analysis. There is an increase in the number of LYs gained with clopidogrel therapy, with an incremental difference of 0.53 LYs versus 0.37 LYs in the baseline analysis. The incremental cost/LY is much lower, at $23,155/LY, in comparison to the baseline result of $26,084/LY (Figure 14).

With a 5% discount rate, the lifetime cost of clopidogrel and placebo therapy both decrease to $38,125 and $29,791 respectively. The incremental difference in lifetime cost of clopidogrel versus placebo therapy is $8,334 versus $9,570 in the baseline analysis. There is a decrease in the number of LYs gained with clopidogrel therapy, with an incremental difference of 0.30 LYs versus 0.37 LYs in the baseline analysis. The incremental cost/LY is higher, at $28,127/LY, in comparison to the baseline result.

FIGURE 14: SENSITIVITY ANALYSIS FOR SECOND LINE MI THERAPY



◆baseline cost/LY
1 Lower and upper limit for the 95% CI for the relative risk reduction (0.3% and 16.5%) for events and death with clopidogrel therapy
2 50% decrease/increase in clopidogrel drug cost
3 50% decrease/increase in acute/FU treatment costs
4 0% and 5% discount rate

5.0 DISCUSSION

The results of the CAPRIE study showed that clopidogrel offers a significant reduction in fatal and nonfatal cardiovascular events over ASA in a mixed and overlapping population of patients with a history of IS, MI, and PAD. This economic evaluation of clopidogrel has defined four attractive scenarios, in terms of cost and survival, for clopidogrel usage: 1st line therapy for all patients with MI, IS or PAD, 1st line therapy in PAD, 2nd line therapy in stroke and 2nd line therapy in MI. These results are not only in accordance with the findings of the CAPRIE trial (27) but have identified additional specific subgroups who could potentially benefit from clopidogrel therapy.

For lifetime treatment with clopidogrel, there is an overall "moderate" cost-attractiveness for clopidogrel over ASA as first-line therapy in all groups (IS, MI and PAD). The cost/LY ratio per patient appeared reasonable over this long period of time. However, clopidogrel therapy does not appear to be as attractive over a shorter period of time as was demonstrated with the two year analyses, the actual study duration under which clopidogrel was investigated. A total of $174,216 must be spent in order to prevent a primary event with clopidogrel. The analysis considering all events, primary, secondary, and tertiary, portrays the more inclusive scenario of the cost per event avoided, but the ratio still remains high at $134,621/event avoided per patient.

In the interpretation of the results for the subgroup analysis, it is important to re-emphasize that the CAPRIE study was not powered to detect changes amongst each of the stroke, MI and PAD subgroups. Hence, the results illustrated here are for the purpose of demonstrating the potential usage of clopidogrel under alternative circumstances.

As 1st line therapy, clopidogrel demonstrates its greatest efficacy in the PAD patient population. Currently, there is not a single consistently prescribed anti-platelet agent used in patients with PAD to prevent subsequent coronary events and stroke. Patients with PAD in the CAPRIE trial benefited the most (i.e., relative risk reduction of 23.8%). Hence, clopidogrel is a reasonable alternative because it has greater efficacy than ASA, can be used in ASA intolerant patients or in patients that have experienced an atherosclerotic event while taking ASA (59).

So, why did the outcomes appear unfavorable for the stroke and MI subgroups? Addressing the stroke subgroup first, the primary reason is that the probability of a primary event and survival from the event while on clopidogrel is not all that much more favorable in comparison to ASA. It is the primary event rate that determines the ultimate outcome in terms of cost and LYs. Referring to the nature of the Markov model, it can be seen that a primary event further propels the cohort towards the endpoint of death. Hence, with an event rate similar to that of ASA, the accumulation of costs associated with clopidogrel treatment (which is much more costly than ASA) also increases as the cohort progresses through the Markov model. For example, considering the IS population in the CAPRIE dataset, more patients died due to natural causes while on clopidogrel therapy (Table 14). As well, despite preventing stroke events, the mortality following each stroke was greater with clopidogrel therapy than with ASA therapy. Thus, there was only a small overall gain in LYs that resulted in a high incremental CER.

TABLE 14: Comparison of event probabilities for clopidogrel and ASA therapy, in the stroke population at the post index health state, to explain the unattractive CERs in the IS and MI subgroups.

STAGE IN THE MARKOV MODEL	CLOPIDOGREL PROBABILITY	ASA PROBABILITY	CLOPID MINUS ASA DIFFERENCES	INTERPRETATION OF DIFFERENCES
LIVE	0.99443	0.99499	-0.00056	Less patients live on clopidogrel
DEAD	0.00557	0.005	0.00057	More patients die from natural causes while on clopidogrel
STROKE	0.03701	0.04148	-0.00447	Less patients have strokes with clopidogrel
NO STROKE	0.96299	0.95852	0.00447	More patients are stroke-free with clopidogrel
LIVE	0.94958	0.95455	-0.00497	Less patients survive strokes with clopidogrel
DEAD	0.05042	0.04545	0.00497	More patients die from strokes with clopidogrel
POST 2ND STROKE	1	1	0	
MI	0.00258	0.00393	-0.00135	Less patients have MIs with clopidogrel
NO MI	0.99742	0.99607	0.00135	More patients do not have MIs with clopidogrel
LIVE	0.75	0.75	0	no difference
DEAD	0.25	0.25	0	no difference
POST MI	1	1	0	
POST INDEX	1	1	0	

For the MI subgroup, first line therapy does not appear to be appropriate as ASA therapy was dominant in terms of cost (less expensive) and LYs gained (greater survival). The results reported in the CAPRIE trial indicated that there was no statistical difference between clopidogrel and ASA therapy in the MI subgroup with a RRR of -3.7%, with 95% CI ranging from –22.1% to 12.0% (i.e., there was a higher risk of experiencing an event for the MI subgroup receiving clopidogrel therapy, but this was not found to be signficant) (27). The CAPRIE investigators attempted to offer an explanation for this apparent unfavorable result claiming that the any patient with an IS or PAD and a previous history of a MI would benefit from clopidogrel therapy. It should be noted that the ATC meta-analysis (the statistical compilation of outcomes from anti-platelet therapies investigated in randomized controlled trials) demonstrated the effect of anti-platelet therapies to be consistent and homogeneous (20% to 25% odds ratio reduction compared with no therapy) across these patient groups when enough studies are considered (30). This meta-analysis included over 142 trials involving more than 70,000 subjects to arrive at such conclusions. Thus, the benefits of clopidogrel in the PAD group may be over-represented while the outcomes in the MI subgroup may be significantly underestimated in the CAPRIE study and this

economic analysis. Furthermore, it is possible that the usage of absolute values (i.e., event probabilities) derived from the CAPRIE study created an "artificial" difference in the results generated from the model, as the study was not powered to detect changes in the RRR for the individual IS, MI and PAD subgroups.

Clopidogrel as second-line therapy for the treatment of IS appears to be a reasonable alternative to ticlopidine. In comparison to both brand name and generic ticlopidine, lifetime costs and survival benefits associated with clopidogrel resulted in reasonable cost/LY ratios. The survival benefits of clopidogrel can be attributed to the better side effect profile and greater tolerance in comparison to ticlopidine. The incremental difference in lifetime cost between clopidogrel and ticlopidine treatment reflects the effect of I) the difference in drug cost and ii) lower clopidogrel adverse event rates which lead to patients cycling through the Markov model for a longer period of time. Thus, costs associated with IS or MI treatments including drug treatment are accrued.

For the MI patient population, second line treatment with clopidogrel is a plausible suggestion considering that there is not one medication consistently prescribed in this scenario. Clopidogrel generated greater benefits in terms of survival with reasonable cost/LY ratios. This analysis identified a possible niche for clopidogrel that was not explored in the CAPRIE trial (27). In addition to this finding from this analysis, it was also suggested that this patient population would benefit from clopidogrel usage in four manners (59). Firstly, clopidogrel could be used in ASA intolerant patients. Secondly, patients who are taking ASA but experience a second event can be switched to clopidogrel treatment. (The next two suggestions for clopidogrel usage was not investigated in this analysis.) Thirdly, patients who are at high risk of subsequent events because of other comorbidities (e.g., diabetes), would benefit more from clopidogrel. Lastly, coronary stent patients who might otherwise be treated with ticlopidine could be treated with clopidogrel.

The sensitivity analyses identified the main drivers of the models and determinants of the CER namely i) the drug price of clopidogrel, ii) the event and/or death rate probabilities for clopidogrel and iii) ticlopidine adverse event rates. Changing the drug price of clopidogrel generated CERs that varied from being cost attractive to cost unattractive. Variations in clopidogrel event probabilities ranged to the extent of which aspirin became the dominant therapy (e.g., stroke subgroup analysis). Varying ticlopidine adverse event rates produced a greater spread in the range of CERs in comparison to the other sensitivity analyses conducted that did not have as such a prominent effect on the CERs.

The changes in the incremental difference in lifetime costs and survival benefits determined the outcome in terms of cost/LY. In all analyses, a large proportion of the incremental difference in lifetime costs between clopidogrel and comparator treatment were solely due to the drug cost of clopidogrel itself. With a 50% decrease in the cost of clopidogrel ($1.24/day), this produced a corresponding decrease in the lifetime cost of clopidogrel. The incremental difference in lifetime cost between clopidogrel and ASA therapy was smaller in comparison to baseline with no changes in the incremental difference in the number of LYs gained. Hence, this resulted in lower cost/LY ratios. With a 50% increase ($3.71/day) in the drug cost, this produced a corresponding increase in the lifetime cost of clopidogrel. The incremental difference in lifetime cost also increased in comparison to baseline but there were no changes in the incremental difference in the number of LYs gained. This translated into a larger cost/LY ratio. This was

determined from the sensitivity analysis of the cost of clopidogrel (50% decrease and increase) which affected the incremental difference in lifetime cost associated with clopidogrel treatment, but did not change the number of LYs gained.

Variations in the relative risk reductions (and to a lesser extent, the discount rate) produced changes in survival (LY gained). In particular, upon further scrutiny of the CAPRIE data, the vascular death event rates and the probability of survival after experiencing a stroke or a MI dictated the cost outcome for clopidogrel. This can be understood in terms of an example using a stroke patient. If the patient experiences a stroke and has a low chance of survival after the event (i.e., low relative risk reduction or a high discount rate), then fewer costs (treatment and drug costs) are incurred over a lifetime. Hence, the incremental difference in lifetime cost and survival are lower in comparison to the baseline analysis resulting in higher cost/LY ratios. Using a 5% discount rate in the stroke subgroup population as an example, (Table 15), the lifetime cost of clopidogrel and ASA therapy are both lower in comparison to the baseline results. The incremental difference in lifetime cost between the two therapies with the 5% discount is lower, at $8,050 ($71,004 - $62,954), versus $8,629 ($80,719 - $71,550) in the baseline analysis. The incremental difference in the number of LYs gained between clopidogrel and ASA with the 5% discount is 0.09 LYs gained (8.05 LYs – 7.96 LYs) versus 0.10 LYs gained (9.10 LYs – 9.0 LYs) in the baseline analysis. The combination of the decrease in lifetime costs and LYs gained results in a higher incremental cost/LY ratio of $97,222/LY in comparison to the baseline result of $89,629/LY.

TABLE 15: Sensitivity analysis conducted for the stroke subgroup population at a 5% discount rate. Values in the brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in brackets represent the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
DISCOUNT RATE 5%	ASA	$62,954 *($71,550)*	7.96 LY *(9.00 LY)*	
	CLOPIDOGREL	$71,004 ($69,553-$72,749) *($80,719)*	8.05 LY (7.83-8.29 LY) *(9.10 LY)*	$97,222/LY ($30,278/LY-dominated) *($89,629/LY)*

However, if the patient has an increased chance of survival after the stroke event (i.e., high relative risk reduction or low discount rate), the patient cycles through the model for a longer period of time. Greater lifetime costs (treatment and drug costs) are incurred which makes clopidogrel appear unfavorable in terms of costs. Hence, the incremental difference in lifetime cost and survival increments are higher in comparison to the baseline analysis resulting in lower cost/LY ratios.

These observations suggest that economic models are not sensitive to treatment costs alone per se but when combined with the event probabilities, these two parameters determine the benefits in terms of costs and survival associated with any drug usage.

The analysis comparing clopidogrel to ticlopidine treatment was sensitive to changes in ticlopidine adverse event rates for neutropenia, diarrhea, rash and other adverse events. With an increase in

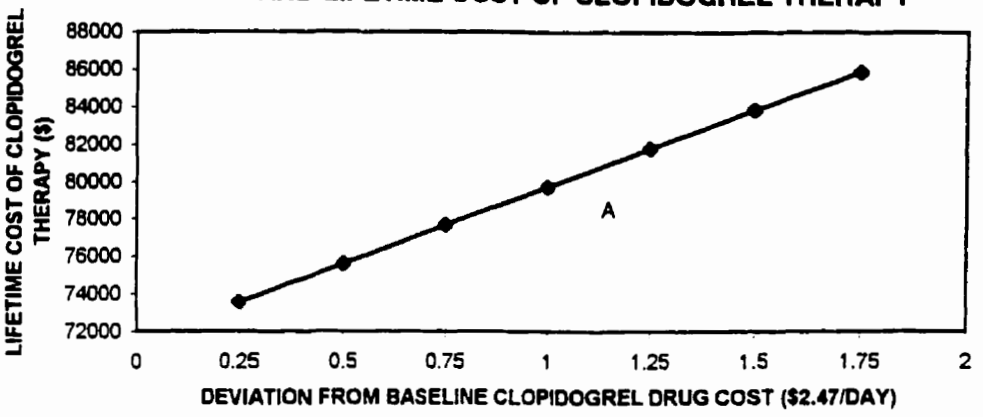
ticlopidine adverse event rates, there was a larger difference in the probability of experiencing an adverse event between ticlopidine and clopidogrel in which clopidogrel appears more favorable. Hence, more patients on ticlopidine therapy would be experiencing adverse events, some of which were fatal, which would decrease survival. This resulted in a greater incremental difference in the number of LYs gained between clopidogrel and ticlopidine (a larger denominator). The cost/LY ratio decreased in comparison to baseline. The effect of this alteration is pronouced because the drug cost of ticlopidine is less than that of clopidogrel, however the higher adverse event rates (and thus adverse event costs) compensate for the difference in drug cost between the two medications. The exact opposite occurred with a decrease in the adverse event rate.

The variation in adverse event rates deserves special mention. The type of relationship between changes in the sensitivity analysis parameters and costs has so far been linear e.g., a decrease in clopidogrel drug cost produces a lower cost/LY ratio (Figure 15). However, this was not the case for the results observed with variations in either clopidogrel or ticlopidine adverse event rates. The relationship demonstrated was not linear but U-shaped (Figure 16). The variation in lifetime costs and survival are not typical in the sense of representing lower and upper limits that should encompass the baseline result. For example, with a 25% decrease in clopidogrel adverse event rates, there was a slight increase in the lifetime cost of clopidogrel treatment (as opposed to a decrease) because there was an increase in the continuation of therapy and thus survival with ongoing medical management. However, there was a slight increase in survival (number of LYs gained) as expected. With a 25% decrease in clopidogrel adverse event rates, there was still an increase in lifetime cost of clopidogrel therapy because of the increase in adverse event costs. There was a decrease in survival (number of LYs gained) as expected. This relationship reiterates how adverse events have an impact on survival (LYs gained) and costs, both of which have been identified as having an impact on the CER.

The parameters that the models were not sensitive to were i) acute and follow-up treatment costs, ii) discount rate, iii) adverse event costs and iv) clopidogrel adverse event rates. A decrease in the acute and follow-up treatment costs produced corresponding decreases in the lifetime costs. The incremental difference in lifetime cost between clopidogrel and comparator therapy decreased slightly with no change in the number of LYs gained (with the exception of 25% decrease in clopidogrel adverse event rates which did produce a slight change in the number of LYs gained without a major variation in the CER). This resulted in slightly lower or higher cost/LY ratios in comparison to the baseline analysis. The alterations in the discount rate affected the probabilities and cost minimally as well. The exact opposite scenario occurred with an increase in the acute and follow-up treatment costs. With a larger discount rate, despite the concurrent decrease in cost, less survival benefits are incurred and thus, the cost/LY ratios cannot be offset (i.e., large numerator of cost with a small denominator of survival) and vice versa for a smaller discount rate. Changes in the adverse event costs produced minor alterations in the lifetime cost of clopidogrel or ticlopidine therapy. With a decrease in adverse event costs, the lifetime cost of clopidogrel and ticlopidine therapy also decrease. However, the incremental difference in the lifetime cost increased (i.e., larger numerator) in comparison to baseline analysis with no changes in the number of LYs gained. Hence, this resulted in a higher cost/LY ratio in comparison to baseline. The exact

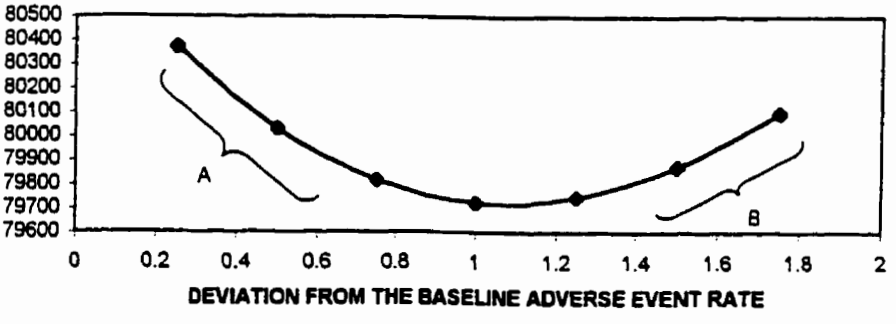
opposite scenario occurred for an increase in adverse event costs. As previously described with ticlopidine adverse event rates, changing clopidogrel adverse event rates produces the same effect but not to the same extent. The reason for this is the drug cost of clopidogrel is greater than that of ticlopidine. Even with a decreased adverse event rate (and thus decreased adverse event costs), this does not outweigh the impact that the drug cost has on the outcomes (cost/LY ratio).

FIGURE 15: RELATIONSHIP BETWEEN CLOPIDOGREL DRUG COST AND LIFETIME COST OF CLOPIDOGREL THERAPY



LEGEND
A - linear relationship between clopidogrel drug cost and lifetime cost of clopidogrel therapy (i.e. an increase in drug cost leads to a corresponding increase in lifetime cost of clopidogrel therapy)

FIGURE 16: RELATIONSHIP BETWEEN CLOPIDOGREL ADVERSE EVENT RATE AND LIFETIME COST OF CLOPIDOGREL THERAPY



LEGEND
A - higher lifetime cost because of an increase in survival (decreased probability of having an adverse event)
B - higher lifetime cost because of an increased probability of having an adverse event (increase in treatment costs for the adverse events)

An indirect consequence of conducting the sensitivity analyses was a validation of the Markov model. The survival estimates in each of the individual populations appear to be in concordance with those life expectancies derived from the literature. For example, with a 0% discount rate, the estimate of survival in the stroke subgroup was 11.11 LYs with ASA therapy. In a study by Oster et al, 1994 (87), the reported life expectancy with ASA therapy was 10.71 years, illustrating that reasonable parameters and a sound model were created.

The pharmacoeconomic outcomes have been presented and can be subjected to two methods of interpretation: i) comparison to benchmark values outlined by Laupacis et al (1992) (79) and ii) comparison to other types of currently accepted medical interventions used for the same condition (78). The first method is not applicable to this thesis since this analysis did not involve cost-utility measures. Using the second method of validating the cost of clopidogrel treatment, a sample of medical interventions can be used as comparators. To make comparisons with other first line drug treatments such as HMG-CoA reductase inhibitors, it was estimated that fluvastatin therapy would produce a cost/LY of $21,600 to $63,900CDN depending upon age and the risk factors present (97). In order to appreciate the cost effectiveness ratio of clopidogrel 2nd line therapy in MI patients this study, Mark et al, (1995) reported that the use of t-PA versus streptokinase for acute MI would cost approximately $49,017/LY (98). In another analysis comparing the cost of thrombolytic therapy versus no thrombolytic therapy in acute MI, the cost/LY derived was $21,657/LY (99). If comparisons are made against medical interventions used in these disease states, clopidogrel treatment still appears to be a reasonable alternative. For example, a two vessel coronary artery bypass graft surgery versus medical management in MI patients has a reported cost of $42,000/LY (82). Overall, from the above mentioned CERs, there are four scenarios of clopidogrel therapy in the CEA which would suggest appropriate spending of health care dollars, i) clopidogrel as first line therapy for the combined IS, MI and PAD populations ($32,240/LY gained), ii) clopidogrel as first line therapy in PAD ($11,401/LY gained), iii) clopidogrel as second line therapy in stroke ($19,852/LY gained) and iv) clopidogrel as second line therapy in MI ($26,084/LY gained).

LIMITATIONS

Some limitations of this analysis should be pointed out. The life expectancy and mortality used in the model were estimates derived from the combination of CAPRIE data with Canadian life expectancy data. It would have been more preferable to have directly measured these parameters from the CAPRIE population itself, however this was not possible. Detailed data from the trial was available up to a period of five years, but events beyond this period had to be modeled from the literature and Canadian mortality statistics. For certain probabilities relating to treatment, an estimate was made via expert opinion. Hence, these probabilities were not available from the literature nor were they measured. A few sample sizes relating to cost measures derived for IS, MI, PAD patients and for outpatient drug costs were small. These sample sizes were dependent upon the availability of patient charts and cost information.

For the MI, IS and PAD inclusion criteria subgroup models, the limited statistical power arising from the reduced sample sizes has already been indicated. Hence, these results may not be representative of

the actual results. In the models considering clopidogrel as second line therapy, there were no clinical trials directly comparing the two drugs. Thus, the data inputs were based on the CAPRIE outcomes and results from the literature. Hence, as with virtually all models, the use of clinical trial literature leads to estimates of cost-efficacy (whether the drug can work as demonstrated under ideal conditions) (60) rather than cost-effectiveness (whether the drug does work in the real world environment).

The manner in which the sensitivity analysis was conducted could be considered arbitrary in the following contexts: identification of which variables to vary and which to remain fixed, the selection of the degree to which the variables should be varied, and the determination of the amount of change around a variable such as to consider it a robust finding (100). For example, a 50% decrease or increase in clopidogrel drug cost was chosen. However, it was demonstrated that there was a positive linear relationship between drug cost and outcome (cost/LY ratio), such that the percentage decrease or increase would have less relevance.

FUTURE STUDIES

A potential niche for clopidogrel is to be used in addition to ASA in stroke prevention. Considering that both drugs act via different mechanisms, ADP receptor inhibition and inhibition of cyclooxygenase pathway, respectively, clopidogrel could be combined with ASA to produce additional therapeutic benefits. Combined ticlopidine and ASA therapy is already being used with promising results to date (42, 101, 102). In rabbit models, it has been demonstrated that the anti-aggregating and anti-thrombotic activity of clopidogrel is potentiated by ASA (103). A large clinical trial (OASIS II Trial) is currently underway to address the potential benefit of this combined therapy in humans (26, 104). A recent meta-analysis showed that the use of ASA in the first 48 hours may convey some immediate benefit in preventing stroke recurrence (105). Thus, it was suggested that these patients could start off initially with ASA but then have clopidogrel added later to yield even greater benefits (59). Of course, there is the concern that the combined anti-platelet effect could have negative effects as well such as increased risk of GI bleeding. Only future studies will be able to elucidate the potential benefits of such a therapy in terms of therapeutic efficacy and cost.

6.0 CONCLUSION

The economic burdens of cardiovascular disease demonstrate the great need to reduce its incidence and reduce its long-term disability and mortality. Undoubtedly, any new drug released on the market will have claims of greater therapeutic efficacy, but the tradeoff is the cost. Irrespective of any new anti-platelet regimen that becomes available, ASA will still remain the gold standard because of its effectiveness and low daily acquisition cost. Despite this, clopidogrel has demonstrated to be effective both in terms of cost and survival for the treatment of vascular disease. Clopidogrel was associated with a projected survival advantage over ASA at a moderately attractive incremental cost per LY gained for the overall cohort of MI, IS and PAD patient populations as defined in the CAPRIE study. Even more favourable results were obtained for the PAD inclusion group subpopulation. Considering patients with postulated ASA intolerance or failure, clopidogrel was also an attractive and cost-effective intervention for the MI and IS subgroups. Overall, from an economic standpoint, adoption of clopidogrel treatment can be recommended under these identified scenarios. However, novel pharmacological management is still welcomed as the search for the ideal antiplatelet agent, one that is potent, reduces atherosclerotic plaque formation, safe to use and inexpensive, continues.

7.0. REFERENCES

1. **Health Canada.** (Laboratory Centre for Disease Control). Heart Disease and Stroke in Canada. June 1997
2. **Drummond M, Davies L.** Economic evaluation of drugs in peripheral vascular disease and stroke. *Journal of Cardiovascular Pharmacology.* 1994;23 Suppl 3:S4-7
3. **Buske L.** Spending on drugs surpasses $10 billion. *Canadian Medical Association Journal.* 1998;158(3):456
4. **Futrell N, Millikan CH.** Stroke is an emergency. *Disease-A-Month.* 1996;42(4):199-264
5. **Hademenos GJ, Massoud TF.** Biophysical Mechanisms of Stroke. *Stroke.* 1997;28:2067-2077
6. **Schoen FJ.** The Heart. In: Cotran RS, Kumar V, Robbins SL, Schoen FJ, eds. *Robbins Pathologic Basis of Disease.* Vol. 5th Ed. United States: WB Saunders; 1994:517-541
7. **Hirsch J.** (McMaster University). Guidelines for Antithrombotic Therapy. Summary of the American College of Chest Physicians. 1996 1996. Report No.: 2nd Edition
8. **Schoen FJ.** Blood Vessels. In: Cotran RS, Kumar V, Robbins SL, Schoen FJ, eds. *Robbins Pathologic Basis of Disease.* Vol. 5th ed. United States: WB Saunders; 1994:467-488
9. **Forster C.** Hyperlipoproteinemias and antihyperlipidemic drugs. In: Kalant H, Roschlau WHE, eds. *The Principles of Medical Pharmacology.* 6th ed. Toronto: Oxford University Press; 1998:486-499
10. **McNamara DB, Champion HC, Kadowitz PJ.** Pharmacologic management of peripheral vascular disease. *Surgical Clinics of North America.* 1998;78(3):447-464
11. **Gonzalez ER, Kannewurf BS.** Atherosclerosis: a unifying disorder with diverse manifestations. *American Journal of Health System Pharmacy.* 1998;55(suppl 1):S4-S7
12. **Ito MK, Smith AR, Lee ML.** Ticlopidine: a new platelet aggregation inhibitor. *Clinical Pharmacy.* 1992;11(7):603-17
13. **Harker L, Fuster V.** Pharmacology of platelet inhibitors. *Journal of American College of Cardiology.* 1986;8(6):21B-32B
14. **Robert S, Miller AJ, Fagan SC.** Ticlopidine: a new antiplatelet agent for cerebrovascular disease. *Pharmacotherapy.* 1991;11(4):317-325
15. **Roschlau WHE.** Drugs Affecting Hemostasis. In: Kalant H, Roschlau WHE, eds. *Principles of Medical Pharmacology.* Vol. 6th ed. New York: Oxford University Press; 1998: 526-540.
16. **McNamara DB, Akers DL, Kerstein MD.** Pharmacologic option in treatment of peripheral vascular disease. In: Kerstein MD, White JV, eds. *Alternatives to Open Vascular Surgery.* Philadelphia: JB Lippincott; 1995:65
17. **Sharis PJ, Cannon CP, Loscalzo J.** The antiplatelet effects of ticlopidine and clopidogrel. *Annals of Internal Medicine.* 1998;129:394-405
18. **Harker LA.** Therapeutic inhibition of platelet function in stroke. *Cerebrovascular Diseases.* 1998;8(suppl 5):8-18

19. **Fuster V, Badimon L, Badimon JJ.** The pathogenesis of coronary artery disease and the acute coronary syndromes. *New England Journal of Medicine.* 1992;326:310-318
20. **Majerus PW, Broze GJ, Miletich JP, Tollefsen DM.** Anticoagulant, thrombolytic, and antiplatelet drugs. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. *Goodman and Gillman's The Pharmacological Basis of Therapeutics.* Vol. 9th Ed. Toronto: McGraw-Hill; 1996:1341-1359
21. **Schror K.** Antiplatelet drugs. A comparative review. *Drugs.* 1995;50(1):7-28
22. **Coukell AJ, Markham A.** Clopidogrel. *Drugs.* 1997;54(4):745-750
23. **Savi P, Combalbert J, Gaich C, et al.** The antiaggregating activity of clopidogrel is due to a metabolic activation by the hepatic cytochrome P450-1A. *Thrombosis & Haemostasis.* 1994;72(2):313-7
24. **Herbert JM, Frehel D, Vallee E.** Clopidogrel, a novel antiplatelet and anti-thrombotic agent. *Cariovascular Drug Review.* 1993;11(2):180-198
25. **Guillin MC, Bonnet G, Sissmann J.** Pharmacodynamics and pharmacokinetics of the novel anti-platelet agent, clopidogrel, in the young and the elderly with and without symptomatic atherosclerosis (abstract). *European Heart Journal.* 1996;17 (suppl):161
26. **Natarajan MK.** Beyond ASA: Newer antiplatelet therapies. *Canadian Journal of Diagnosis.* 1998;15(7):73-81
27. **CAPRIE Steering Committee.** A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet.* 1996;348(9038):1329-39
28. **Hass WK, Easton JD, Adams HP, Jr., et al.** A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *New England Journal of Medicine.* 1989:321(8):501-7
29. **Gent M, Blakely JA, Easton JD, et al.** The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet.* 1989;1(8649):1215-20
30. **Antiplatelet Trialists Collaboration.** Collaborative overview of randomised trials of antiplatelet therapy - I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *British Medical Journal.* 1994;308:81-106
31. **Misson J, Clark W, Kendall MJ.** Clopidogrel: secondary prevention of vascular ischaemic events. *Journal of Clinical Pharmacy and Therapeutics.* 1998;23:91-95
32. **Noble S, Goa KL.** Ticlopidine. A review of its pharmacology, clinical efficacy and tolerability in the prevention of cerebral ischaemia and stroke. *Drugs & Aging.* 1996;8(3):214-32
33. **Knudsen JB, Kjoller E, Skagen K, Gormsen J.** The effect of ticlopidine on platelet functions in acute myocardial infarction. A double blind controlled trial. *Thrombosis & Haemostasis.* 1985;53(3):332-6
34. **Thebault JJ, Blatrix CE, Blanchard JF, Panak EA.** Effects of ticlopidine, a new platelet aggregation inhibitor in man. *Clinical Pharmacology and Therapeutics.* 1975;18:485-490

35. **McTavish D, Faulds D, Goa KL.** Ticlopidine: an updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs.* 1990;40:238-259

36. **Roche.** Ticlid Product Monograph. In: Gillis MC, Welbanks L, Bergeron D, et al., eds. *Compendium of Pharmaceuticals and Specialties.* Vol. 33. Ottawa: Canadian Pharmacists Association; 1998:1676-1678

37. **Bruno JJ, Maloney BA.** Ticlopidine. In: Scriabine A, ed. *New Drugs Annual.* New York: Raven Press; 1983:295-316

38. **Roche.** Ticlopidine Product Monograph. 1995

39. **Panak E, Maffrand JP, Picard-Fraire C.** Ticlopidine: a promise for the prevention and treatment of thrombosis and its complications. *Haemostatis.* 1983;13(Suppl 1):1-54

40. **Knudsen JB, Bastain W, Sefton CM, Allen JG, Dickinson JP.** Pharmacokinetics of ticlopidine during chronic oral administration to healthy volunteers and its effects on antipyrine pharmacokinetics. *Xenobiotica.* 1992;22:579-589

41. **Shah J, Teitelbaum P, Molony B, Gabuzda T, Massey I.** Single and multiple dose pharmacokinetics of ticlopidine in young and elderly subjects. *British Journal of Clinical Pharmacology.* 1991;32:761-764

42. **Schomig A, Neumann FJ, Walter H, et al.** Coronary stent placement in patients with acute myocardial infarction: comparison of clinical and angiographic outcome after randomization to antiplatelet or anticoagulant therapy. *Journal of the American College of Cardiology.* 1997;29(1):28-34

43. **Neumann FJ, Gawaz M, Dickfeld T, et al.** Antiplatelet effect of ticlopidine after coronary stenting. *Journal of the American College of Cardiology.* 1997;29(7):1515-9

44. **Harbison JW.** Ticlopidine versus aspirin for the prevention of recurrent stroke. Analysis of patients with minor stroke from the Ticlopidine Aspirin Stroke Study. *Stroke.* 1992;23(12):1723-7

45. **Grotta JC, Norris JW, Kamm B, Subgroup TBaAD.** Prevention of stroke with ticlopidine: Who benefits the most? *Neurology.* 1992;42:111-115

46. **Bellavance A.** Efficacy of ticlopidine and aspirin for prevention of reversible cerebrovascular ischemic events. The Ticlopidine Aspirin Stroke Study. *Stroke.* 1993;24(10):1452-7

47. **Weisberg LA.** The efficacy and safety of ticlopidine and aspirin in non-whites: analysis of a patient subgroup from the Ticlopidine Aspirin Stroke Study. *Neurology.* 1993;43(1):27-31

48. **TASS Group.** Ticlopidine versus aspirin for stroke prevention: on-treatment results from the Ticlopidine Aspirin Stroke Study. *Journal of Stroke and Cerebrovascular Disease.* 1993;3:168-176

49. **Janzon L, Bergqvist D, Boberg J, et al.** Prevention of myocardial infarction and stroke in patients with intermittent claudication; effects of ticlopidine. Results from STIMS, the Swedish Ticlopidine Multicenter Study. *Journal of Internal Medicine.* 1990;227:301-308

50. **Canadian Pharmacists Association.** ASA Product Monograph. In: Gillis MC, Welbanks L, Bergeron D, et al., eds. *Compendium of Pharmaecuticals and Specialties.* Vol. 33. Ottawa: Canadian Pharmacists Association; 1998:142-144

51. **Kadar D.** Anti-inflammatory Analgesics. In: Kalant H, Roschlau WHE, eds. *Principles of Medical Pharmacology*. Vol. 6th ed. New York: Oxford University Press; 1998: 410-427.
52. **Jacobs P.** The economics of health and medical care. In: Jacobs P, ed. *The Economics of Health and Medical Care*. 3rd ed. Aspen: Gaithersburg; 1991:47-48
53. **Tully P, Saint-Pierre E.** Downsizing Canada's hospitals, 1986/87 to 1994/1995. *Health Reports*. 1997;8(4):33-39
54. **Detsky AS.** Guidelines for economic analysis of pharmaceutical products: A draft document for Ontario and Canada. *Pharmacoeconomics*. 1993;3(5):354-361
55. **Dickson M, Bootman JL.** Pharmacoeconomics: An international perspective. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. 2nd ed. Cincinnati: Harvey Whitney Books; 1996:20-42
56. **Tu JV, Naylor CD.** Choosing among drugs of different price for similar indications. *Canadian Journal of Cardiology*. 1998;14(3):349-351
57. **Ministry of Health of Ontario.** Ontario Guidelines for Economic Analysis of Pharmaceutical Products. . 1996:1-15
58. **Shulkin DJ.** The rising cost of pharmaceuticals: a physician's perspective. *American Journal of Hospital Pharmacy*. 1993;50(suppl 4):S8-10
59. **Ferguson JJ, Gonzalez ER, Kannel WB, Olin JW.** Roundtable discussion: Clinical safety efficacy of clopidogrel-implication of the clopidogrel versus aspirin in patient at risk of ischemic event. *Clinical Therapeutics*. 1998;20(Suppl B):B42-B53
60. **Drummond MF, O'Brien B, Stoddart GL, Torrance GW.** *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed Toronto: Oxford Medical Publications; 1997
61. **Bootman JL, Townsend RJ, McGhan WF.** Introduction to Pharmacoeconomics. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. 2nd ed. Cincinnati: Harvey Whitney Books Company; 1996:4-18
62. **Chrischilles EA.** Cost-effectiveness Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. 2nd ed. Cincinnati: Harvey Whitney Books; 1996:76-101
63. **Torrance GW, Feeny D.** Utilities and quality-adjusted life years. *International Journal of Technology Assessment in Health Care*. 1989;5:559-575
64. **Coons SJ, Kaplan RM.** Cost-Utility Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. 2nd ed. Cincinnati: Harvey Whitney; 1996:102-126
65. **Torrance GW, Thomas WH, Sackett DLA.** A utility maximization model for evaluation of health care programs. *Health Services Research*. 1972;7:118-133
66. **Weinstein M, Stasson WB.** Foundations of cost-effectiveness analysis for health and medical practices. *New England Journal of Medicine*. 1977;296:716-721
67. **Black WC.** The CE plane: A graphic representation of cost-effectiveness. *Medical Decision Making*. 1990;10:212-214

68. **Larson LN.** Cost Determination and Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. Second ed. Cincinnati: Harvey Whitney Books; 1996:45-59
69. **Barr JT, Schumacher GE.** Decision analysis and pharmacoeconomic evaluations. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. 2nd ed. Cincinnati: Harvey Whitney; 1996:150-177
70. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Controlled Clinical Trials*. 1986;7:177-188
71. **Dawson-Saunders B, Trapp RG.** *Basic and Clinical Biostatistics*. 2nd ed Toronto: Prentice Hall; 1994
72. DATA program. TreeAge; Williamstown, MA. 1997
73. **Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS.** Primer on Medical Decision Analysis: Part 5 - Working with Markov Processes. *Medical Decision Making*. 1997;17:152-159
74. **Beck JR, Pauker SG.** The Markov Process in medical prognosis. *Medical Decision Making*. 1983;3(4):419-457
75. **Gold MR, Siegel JE, Russell LB, Weinstein MC.** *Cost-effectiveness in Health and Medicine* Toronto: Oxford University Press; 1996
76. **Krahn MD, Naglie G, Naimark D, Redelmeier DA, Detsky AS.** Primer on Medical Decision Analysis: Part 4 - Analyzing the model and interpreting the results. *Medical Decision Making*. 1997;17:142-151
77. **McGhan WF, Kitz DS.** Cost-benefit Analysis. In: Bootman JL, Townsend RJ, McGhan WF, eds. *Principles of Pharmacoeconomics*. 2nd Edition ed. Cincinnati: Harvey Whitney Books; 1996:60-75
78. **Drummond M, Torrance G, Ma J.** Cost-effectiveness league tables: more harm than good? *Social Science Medicine*. 1993;37(1):33-40
79. **Laupacis A, Feeny D, Detsky AS, Tugwell PX.** How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Canadian Medical Association Journal*. 1992;146(4):473-481
80. **Maynard A.** Developing the health care market. *Economic Journal*. 1991;101:1277-1286
81. **Holloway RG.** Cost-effectiveness analysis: what neurologists should know. *The Neurologist*. 1996;2:365-373
82. **Tengs TO, Adams ME, Pliskin JS, et al.** Five-hundred life-saving interventions and their cost-effectiveness. *Risk Analysis*. 1995;15(3):369-390
83. **Schadlich PK, Brecht JG.** Cost-effectiveness analysis of prevention of reinfarction using low-dose acetylsalicylic acid; model calculation [Article in German]. *Soziale Praventivmed*. 1997;42(2):114-120
84. **Eckman MH, Falk RH, Pauker SG.** Cost-effectiveness of therapies for patients with non-valvular artrial fibrillation. *Archives of Internal Medicine*. 1998;158(15):1669-1677
85. **Kurz X, Annemans L, Dresse A.** An acetylsalicylic acid-dipiridamole combination (Asantine) in the prevention of the recurrence of cerebrovascular accidents (a cost-effectiveness analysis) [Article in French]. *Revue Medicale de Liege*. 1998;53(5):265-269

86. **Gage BF, Cardinalli AB, Albers GW, Owens DK.** Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation . *Journal of the American Medical Association.* 1995;274(23):1839-45

87. **Oster G, Huse DM, Lacey MJ, Epstein AM.** Cost-effectiveness of ticlopidine in preventing stroke in high-risk patients. *Stroke.* 1994;25(6):1149-56

88. **Grootendorst PV, O'Brien BJ, Anderson GM.** On becoming 65 in Ontario: Effects of drug plan eligibility on use of prescription medicines. *Medical Care.* 1997;35(4):386-398

89. **Statistics Canada.** Life Tables, Canada and Provinces, 1990-1992. 1995. Report No.: 84-537

90. **Sonnenberg FA, Beck R.** Markov Models in medical decision making: A practical guide. *Medical Decision Making.* 1993;13:322-338

91. **Ministry of Health of Ontario.** Drug Benefit Formulary: comparative drug index. 1997

92. **Ministry of Health of Ontario.** Schedule of Benefits: Physician Services under the Health Insurance Act. 1992 October 1, 1992

93. **Ambulance Commissioner's Office and the Ministry of Health of Ontario.** Ambulance costs and utilization. 1997

94. **Cohen E.** (Sunnybrook Health Science Centre and the Ontario Ministry of Health). Ontario Case Costing Program. December 1997

95. **Jacobs P, Hall EM, Bachynsky J.** (University of Alberta, Health Economics Research Center). An Alberta standard cost list for health economics evaluations. 1996 March 1996

96. **Ministry of Health of Ontario.** Hospital Statistics 1991/1992. 1991/1992

97. **Martens LL, Guibert R.** Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clinical Therapeutics.* 1994;16(6):1052-1062

98. **Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL.** Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *New England Journal of Medicine.* 1995;332:1418-28

99. **Castillo PA, Palmer CS, Halpern MT, Hatziandreu EJ, Gersh BJ.** Cost-effectiveness of thrombolytic therapy for acute myocardial infarction. *Annals of Pharmacotherapy.* 1997;31(5):596-603

100. **Canadian Coordinating Office for Health Technology Assessment.** Guidelines for economic evaluation of pharmaceuticals: Canada. October 1997

101. **Lablanche JM, McFadden EP, Bonnet JL, et al.** Combined antiplatelet therapy with ticlopidine and aspirin. A simplified approach to intracoronary stent management. *European Heart Journal.* 1996;17(9):1373-80

102. **Hall P, Nakamura S, Maiello L, et al.** A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation.* 1996;93(2):215-22

103. **Hebert JM, Dol F, Bernat A, Falotico R, Lale A, Savi P.** The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. *Thrombosis and Haemostasis.* 1998;80:512-518

104. **Hankey GJ.** One year after CAPRIE, IST and ESPS 2. Any changes in concepts? *Cerebrovascular Diseases.* 1998;8(suppl 5):1-7

105. **CAST Collaborative Group.** CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke. *Lancet.* 1997;349:1641-1649

106. **Cardiac Funding Working Group and Joint Policy and Planning Committee.** (Ministry of Health). Stent costs and utilization. 1996

107. **Cardiac Catherization Lab.** (Sunnybrook Health Science Centre). Probability of stent procedure. 1996

108. **Canadian Institute for Health Information.** Costs according to case mix groups (CMG). 1994

109. **Kuntz KM, Lee TH.** Cost-effectiveness of accepted measures for intervention in coronary heart disease. *Coronary Artery Disease.* 1995;6(6):472-478

110. **Oldridge N, Guyatt G, Jones N, et al.** Effects on quality of life with comprehensive rehabilitation after acute myocardial infarction. *American Journal of Cardiology.* 1991;67:1084-1089

111. **Mark DB, Naylor CD, Hlatky MA, et al.** Use of medical resources and quality of life after acute myocardial infarction in Canada and the United States. *New England Journal of Medicine.* 1994;331:1130-1135

112. **Greenland P, Chu J.** Cardiac Rehabilitation Services. *Annals of Internal Medicine.* 1988;109:671-673

113. **Greenland P, Chu JS.** Efficacy of cardiac rehabilitation services. With emphasis on patients after myocardial infarction. *Annals of Internal Medicine.* 1988;109:650-663

114. **Paramed Health Care Services of Ontario.** Professional fees. Home Care Services - Ontario Ministry of Health; 1997

115. **Metro Toronto Inter-community Care Access Centre Committee.** Patient utilization of home care services. : Home Care Services - Ontario Ministry of Health; 1997

116. **Oh PIT.** Expert opinion. 1997

117. **Kannel WB, Sorlie P, McNamara PM.** Prognosis after initial myocardial infarction: The Framingham Study. *The American Journal of Cardiology.* 1979;44:53-59

118. **Gottlieb SO, Gottlieb SH, Achuff SC, Baumgardner R, Mellits ED, Weisfeldt G.** Silent ischaemia on Holter monitoring predicts mortality in high risk post-infarction patients. *Journal of the American Medical Society.* 1988;259:1030-1035

119. **Topol EJ, Burek BS, O'Neill WW, Kewman DG, Kander NH, Shea MJ.** A randomised controlled trial of hospital discharge three days after myocardial infarction in the era of reperfusion. *New England Journal of Medicine.* 1988;318:1083-1088

120. **Moss AJ, Benhorin J.** Prognosis and management after a first myocardial infarction. *New England Journal of Medicine.* 1990;322(11):743-753

121. **Northover BJ.** Impact on survival of a decade of a change in the management of patients who have sustained a myocardial infarction. *Cardiology.* 1993;83:82-92

122. **West Park Hospital.** Inpatient rehabilitation for cerebral vascular accidents. 1997

APPENDIX I – OUTCOME MEASURES

TABLE 1: List of probabilities derived for the life expectancy of MI, IS and PAD patients

AGE (YEARS)	STATS CAN TOTAL pDIENATURAL	STATS CAN CAPRIE WEIGHTED (0.72) PDIENATURAL MALES	STATS CAN CAPRIE WEIGHTED (0.28) pDIENATURAL FEMALES	CANADA STATS CAN (qx) pDIENATURAL MALES	CANADA STATS CAN (qx) pDIENATURAL FEMALES
51	0.0044056	0.0035712	0.0008344	0.00496	0.00298
52	0.0048856	0.0039672	0.0009184	0.00551	0.00328
53	0.0054144	0.0044064	0.001008	0.00612	0.0036
54	0.0059876	0.0048816	0.001106	0.00678	0.00395
55	0.006624	0.0054144	0.0012096	0.00752	0.00432
56	0.0073392	0.006012	0.0013272	0.00835	0.00474
57	0.0081448	0.0066888	0.001456	0.00929	0.0052
58	0.009038	0.0074448	0.0015932	0.01034	0.00569
59	0.0100216	0.00828	0.0017416	0.0115	0.00622
60	0.0110812	0.00918	0.0019012	0.01275	0.00679
61	0.0122368	0.0101592	0.0020776	0.01411	0.00742
62	0.0134896	0.0112104	0.0022792	0.01557	0.00814
63	0.0147996	0.0123048	0.0024948	0.01709	0.00891
64	0.0161712	0.0134496	0.0027216	0.01868	0.00972
65	0.0176588	0.014688	0.0029708	0.0204	0.01061
66	0.0193096	0.016056	0.0032536	0.0223	0.01162
67	0.0211696	0.0175968	0.0035728	0.02444	0.01276
68	0.0232016	0.0192816	0.00392	0.02678	0.014
69	0.0253556	0.0210744	0.0042812	0.02927	0.01529
70	0.02772	0.0230328	0.0046872	0.03199	0.01674
71	0.030372	0.0252144	0.0051576	0.03502	0.01842
72	0.0333888	0.0276768	0.005712	0.03844	0.0204
73	0.0367088	0.0303696	0.0063392	0.04218	0.02264
74	0.0402836	0.033264	0.0070196	0.0462	0.02507
75	0.0441988	0.0364176	0.0077812	0.05058	0.02779
76	0.0485516	0.0399024	0.0086492	0.05542	0.03089
77	0.053422	0.043776	0.009646	0.0608	0.03445
78	0.0587732	0.048024	0.0107492	0.0667	0.03839
79	0.064538	0.052596	0.011942	0.07305	0.04265
80	0.0707932	0.0575352	0.013258	0.07991	0.04735
81	0.0776124	0.0628704	0.014742	0.08732	0.05265
82	0.0850668	0.0686448	0.016422	0.09534	0.05865
83	0.0931152	0.0748368	0.0182784	0.10394	0.06528
84	0.1017064	0.0814176	0.0202888	0.11308	0.07246
85	0.1109144	0.0884304	0.022484	0.12282	0.0803
86	0.12081	0.095904	0.024906	0.1332	0.08895
87	0.13147	0.1038816	0.0275884	0.14428	0.09853
88	0.1428432	0.1123344	0.0305088	0.15602	0.10896
89	0.15489	0.121248	0.033642	0.1684	0.12015
90	0.1676712	0.130644	0.0370272	0.18145	0.13224
91	0.1812708	0.1405728	0.040698	0.19524	0.14535
92	0.1957612	0.1510704	0.0446908	0.20982	0.15961
93	0.2110912	0.162108	0.0489832	0.22515	0.17494
94	0.2272168	0.173664	0.0535528	0.2412	0.19126
95	0.2442076	0.1857744	0.0584332	0.25802	0.20869
96	0.2621432	0.1984824	0.0636608	0.27567	0.22736
97	0.2810944	0.2118168	0.0692776	0.29419	0.24742
98	0.3010088	0.225756	0.0752528	0.31355	0.26876
99	0.3218452	0.2402784	0.0815668	0.33372	0.29131
100	0.3436732	0.25542	0.0882532	0.35475	0.31519

APPENDIX II – COST MEASUREMENT AND VALUATION

The following tables provide reference sources for the costs derived in this analysis. Fee codes refers to codes derived from the Schedule of Benefits for Physician Services in Ontario (92).

TABLE 1: Non-fatal MI costs from day 1 to day 14

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	PHYSICIAN FEES ($)	TOTAL UNIT COST ($) (B)	EXPECTED COST ($), (A*B)	FEE CODES	DESCRIPTION OF FEE CODES
PRIOR TO HOSPITALISATION								
Ambulance	0.97	SHSC data	240		240	232.80		MOH Commissioner's Office quote (93)
INITIAL HOSPITALISATION								
Routine care includes	1		4,464 29	75 8	4,464 29	5030.99	H055	ER physician
nursing (for acute and alternative level of care days)				105 4	566 70		C605	Cardiologist
lab procedures				85 5	5,030.99		C098	Cardiologist 5 days on ward in CCU
concomitant medications				300				CCU
				566.7				
Angiography (increment to routine	0 094	SHSC data	725 00	100 90	907 09	85.27	G297	procedure
care)				48 94				Ontario Case Costing Program (OCCP) (94)
				32 25			X160	diagnostic radiology; prof & tech
				182 09				
Emergency PTCA (increment to	0 21	SHSC data	1766 86	68 35	1,766 86	526.35	Z509	angiogram
routine care)				448 90	749 09		Z448	procedure
				231 84	2,515.95		Z448	anesthetist (20 units + 1 hour = 21 *$11.04)
				749.09				
Emergency CABG (increment to	0 063	SHSC data	12863 7	68 35	12,863 74	844.15	Z509	angiogram
routine care)				400 80	535 39		Z434	procedure
				66 24	13,399.13		Z434	anesthetist (5 units + 1 hour = 6*$11.04)
				535.39				
Emergency stent (increment to	0 21*0 7	JPPC(106)	2,750 00		2,750 00	404.25		JPPC;(106)
routine care)*								SWCHSC Cardiac Catheterization Lab(107)
TOTAL COST						7,125.81		

*NOTE: On average, 1.5 stents per patient are performed with the cost for a stent at $1,500 with an additional cost of $500 per patient (i.e. $2000x1.5 = $2,750) (108).

TABLE 2: Follow-up cost of a non-fatal MI from day 15 to the end of 3 months

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	FEE CODES	DESCRIPTION OF FEE CODES	PHYSICIAN FEES ($)	FEE CODES	DESCRIPTION OF FEE CODES	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Outpatient Rehabilitation*	0.12	assumption (109) (110-113)	1,000.00					SWCHSC data	1,000.00	**120.00**
Home care#	0.055	SWCHSC data	1,944.00					MOH(114, 115)	1,944.00	**106.94**
Specialist visit	2	expert opinion(116)				105.40	A605	cardiologist consultation	105.40	**159.00**
						53.60	A603	cardiologist general assessment	53.60	
						159.00			**159.00**	
PCP visit	2	expert opinion(116)				51.40	A005	PCP consultation	51.40	**99.60**
						48.20	A003	PCP gen assessment	48.20	
						99.60			**99.60**	
ECG	1	expert opinion(116)	22.80	G653	level 2, recording	31.40	G653	level 2, prof. comp	54.20	**87.60**
			15.60	G653	level 2, scanning	8.0	G661	event record, tech. comp	23.60	
			4	G661	event record, tech. comp	3.90	G311	interpretation of ECG strip	7.90	
			1.90	G311	interpretation of ECG strip					
			44.30			**43.30**			**87.60**	
Exercise tolerance test	1	expert opinion(116)	20.10	G175		54.50	G175		107.40	**107.40**
			32.80	G175						
			52.90							
COMPLICATIONS										
Angina	0.125	see refs (117-119)	3,678.78		CMG 215(108)				3,678.78	**459.85**
Angina F/U	0.125	see refs (117-119)	69.30				A675	repeat consultation	69.30	**8.66**
Chronic heart failure	0.035	assumption(117-120)	5,610.00		CMG 199(108)				5,610.00	**196.35**
Chronic heart failure F/U	0.035	assumption(117-120)	69.30				A675	repeat consultation	69.30	**2.43**
Arrhythmia	0.155	see (119-121)	3,172.52		CMG 212, 213, 214(108)				3,172.52	**491.74**
Arrythmia F/U	0.155	see refs (119-121)	69.30				A675	repeat consultation	69.30	**10.74**
Concomitant Medication	1	SHSC data	73.29		ODBF (91)				73.29	**73.29**
TOTAL FOLLOW-UP COST										**1,923.59**

*NOTE: 11 sessions of 3hrs of rehabilitation with a professional fee of $30/hr (expert opinion (116))

#NOTE: Assumption for home care visit: one nurse visit per week at $19.50/vist with 15hrs of homemaker services at $9.50/hr for a maximum of 3 months(114, 115)

TABLE 3: Follow-up cost of a non-fatal MI for the second 6 month period and each 6 month period thereafter

COST ITEM	PROBABILITY (A)	REFEREENCE SOURCE	UNIT COST ($)	FEE CODES	DESCRIPTION OF FEE CODES	PHYSICIAN FEES ($)	FEE CODES	DESCRIPTION OF FEE CODES	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Specialist visit	2	expert opinion(116)				105 40	A605	cardiologist consultation	105.40	159.00
						53 60	A603	cardiologist general assessment	53.60	
						159.00			159.00	
PCP visit	2	expert opinion(116)				51 40	A005	PCP consultation	51.40	99.60
						48 20	A003	PCP general assessment	48.20	
						99.60			99.60	
ECG	1	expert opinion(116)	22 80	G653	level 2, recording	31 40	G653	level 2, prof Comp	54.20	87.60
			15 60	G653	level 2, scanning	8 00	G661	event record, tech. Comp	23 60	
			4 00	G661	event record, tech comp	3 90	G311	interpretation of ECG strip	7.90	
			1 90	G311	interpretation of ECG strip					
			44.30			43.30			87.60	
Exercise tolerance test	0.5	expert opinion(116)	20 10	G175		54 50	G175		107.40	53.70
			32 80	G175						
			52.90							
COMPLICATIONS										
Angina	0 125	see refs (117-119)	3678 78						3678.78	459.85
Angina F/U	0.125	see refs (117-119)	69 3						69.3	8.66
Chronic heart failure	0.035	assumption(117-120)	9999 11						9999.11	349.97
Chronic heart failure F/U	0.035	assumption(117-120)	69 3						69.30	2.43
Arrhythmia	0.155	see (119-121)	3172 52						3172.52	491.74
Arrythmia F/U	0 155	see (119-121)	69 3						69.30	10.74
Concomitant Medication	1		134 25		ODBF (91)				134.25	134.25
F/U COSTS FOR SECOND 6 MONTHS										1703.92

TABLE 4: Index follow-up cost of a non-fatal MI

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	FEE CODES	DESCRIPTION OF FEE CODES	PHYSICIAN FEES ($)	FEE CODES	DESCRIPTION OF FEE CODES	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Specialist visit	2	expert opinion(116)				105.4	A605	cardiologist consultation	105.40	159.00
						53.6	A603	cardiologist general assessment	53.60	
						159			159.00	
PCP visit	2	expert opinion(116)				51.4	A005	PCP consultation	51.40	99.60
						48.2	A003	PCP general assessment	48.20	
						99.6			99.60	
ECG	1	expert opinion(116)	22.80	G653	level 2, recording	31.4	G653	level 2, prof. comp	54.20	87.60
			15.6	G653	level 2, scanning	8	G661	event record, tech. comp	23.60	
			4.00	G661	event record, tech. comp	3.9	G311	interpretation of ECG strip	7.90	
			1.90	G311	interpretation of ECG strip					
			44.30			43.3			87.60	
Exercise tolerance test	0.5	expert opinion(116)	20.10	G175		54.5			107.40	53.70
			32.80	G175						
			52.90							
COMPLICATIONS										
Angina F/U	0.25	see refs (117-119)				69.3			69.30	17.33
Chronic heart failure F/U	0.07	assumption(29-32)				69.3			69.30	4.85
Arrythmia F/U	0.31	see refs (119-121)				69.3			69.30	21.48
Concomitant Medication	1	SWCHSC data	134.25		ODBF(91)				134.25	134.25
INDEX FOLLOW UP COST OF MI										577.81

TABLE 5: Non-fatal ischemic stroke costs from day 1 to day 14

COST ITEM	PROBABILITY (A)	DESCRIPTION OF PROBABILITY	UNIT COST ($)	PHYSICIAN FEES ($)	FEE CODES	DESCRIPTION OF FEE CODES	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
PRIOR TO HOSPITALISATION								
Ambulance	0.92	SWCHSC data	240.00				240.00	220.80
INITIAL HOSPITALISATION								
Routine care including CT scan,	1	assumption	8,582.94	105.40	A185	neurologist consultation	555.93	9,138.87
(routine care includes				105.40	A135	internal medicine	8582.94	
CCU				75.80	H055	ER physician	**9,138.87**	
special investigations and tests				10.5*17.10	C132	internal medicine on ward * x days		
physician charges				10.5*8.55	C182	neurologist on ward * x days		
inpatient medications				555.93				
Physiotherapy								
occupational therapy								
nursing (for acute and alternative level of care)								
PROCEDURES INCREMENT TO ROUTINE CARE								
Carotid arteriography	0.05	Expert opinion (116)		48.94	X160	direct puncture, unilateral	317.89	15.89
(carotid angiogram)				32.25				
				80.60	J031	carotid angiogram		
				55.20		anesthetist at 5 units		
				100.90	G297	procedural fee		
				317.89				
Carotid endarterectomy	0.05	Expert opinion (116)	6,857.00	703.50	R792	surgeon	909.60	388.33
				95.70	R792	assistant at 10 units	6857	
				110.40	R792	anesthetist	**7,766.60**	
				909.60				
TOTAL COST								**9,763.89**

TABLE 6: Follow-up costs for a non-fatal ischemic stroke from day 15 to the end of 3 months

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	FEE CODES	DESCRIPTION OF FEE CODES	PHYSICIAN FEES ($)	FEES COST	DESCRIPTION OF FEES COST	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Outpatient rehabilitation	0.026	SWCHSC data	250.00					SWCHSC data	250.00	6.50
Nursing home	0.27	SWCHSC data	11,232.59					Ontario Hospital Statistics(96)	11,232.59	3,032.80
Home nursing care~	0.128	SWCHSC data	1,944.00					MOH(114, 115)	1,944.00	248.83
Inpatient rehabilitation#	0.10*48.3	SWCHSC data	141.66					SWCHSC data		684.22
Specialist visit	2	expert opinion (116)				105.4	A185	neurologist	105.40	105.40
(at month 1 and 3)										
PCP visit	3	expert opinion (116)				51.4	A005	PCP consultation	147.80	147.80
(at month 1, 2 and 3)						96.4	A003	PCP general assessment *2		
						147.8				
Duplex ultrasound	0.5	expert opinion (116)	57.95	J190/J490	Doppler scan - extracranial				127.35	63.68
			34.70	J193/J493	Doppler scan - peripheral					
			34.70	J207/J507	Assessment of flow direction					
			127.35							
blood tests	2	expert opinion (116)		L396	CBC	28.49			28.49	56.98
					platelets					
					lytes					
					urea					
					creatinine					
					glucose					
					INR(PT)					
					PTT					
					urinalysis					
Concomitant Medication	1	SWCHSC data	80.74		ODBF(91)				80.74	80.74
TOTAL FOLLOW-UP COST										4,426.95

*NOTE: Nursing home costs annually is $44,930.34, hence for a 3 month period, nursing home costs are estimated at ($44,930.34/4) $11,232.59
NOTE: Assumption for home care visit: one nurse visit per week at $19.50/vist with 15hrs of homemaker services at $9.50/hr for a maximum of 3 months (114, 115)
#NOTE: For stroke patients receiving in-patient rehabilitation services at West Park Hospital, the mean LOS was 48.3 days (122).

TABLE 7: Follow-up costs of a non-fatal ischemic stroke patient for each 6 month period thereafter the initial event

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	FEE CODES	DESCRIPTION OF FEE CODES	PHYSICIAN FEES ($)	FEES COST	DESCRIPTION OF FEES COST	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Nursing home	0.27	SWCHSC data	11,232.59					Ontario Hospital Statistics(96)	11,232.59	3032.80
Home nursing care	0.128	SWCHSC data	1,944.00					MOH(114, 115)MOH	1,944.00	248.83
Specialist visit	2	expert opinion (116)				105.40	A185	neurologist	105.40	105.40
PCP visit	3	expert opinion (116)				51.40	A005	PCP consultation	147.80	147.80
						96.40	A003	PCP general assessment *2		
						147.80				
Duplex ultrasound	0.5	expert opinion (116)	57.95	J190/J490	Doppler scan - extracranial					63.68
			34.7	J193/J493	Doppler scan - peripheral					
			34.7	J207/J507	Assessment of flow direction					
			127.35							
blood tests	2	expert opinion (116)		1396	CBC	28.49	A003	0.5 of general assessment	28.49	56.98
					platelets					
					lytes					
					urea					
					creatinine					
					glucose					
					INR(PT)					
					PTT					
					urinalysis					
Concomitant Medication	1	SWCHSC data	151.88		ODBF(91)				151.88	151.88
TOTAL F/U FOR EACH 6 MONTH PERIOD										3,807.37

TABLE 8: Index follow-Up costs of a non-fatal ischemic stroke

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	FEE CODES	DESCRIPTION OF FEE CODES	PHYSICIAN FEES ($)	FEES COST	DESCRIPTION OF FEES COST	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Specialist visit	2	expert opinion (116)				105.40	A185	neurologist	105.40	105.40
PCP visit	3	expert opinion (116)				51.40	A005	PCP consultation	147.80	147.80
						96.40	A003	PCP general assessment *2		
						147.80				
Duplex ultrasound	0.5	expert opinion (116)	57.95	J190/J490	Doppler scan - extracranial					63.68
			34.70	J193/J493	Doppler scan - peripheral					
			34.70	J207/J507	Assessment of flow direction					
			127.35							
blood tests	2	expert opinion (116)		1396	CBC	28.49	A003	0.5 of general assessment	28.49	56.98
					platelets					
					lytes					
					urea					
					creatinine					
					glucose					
					INR(PT)					
					PTT					
					urinalysis					
Concomitant Medication	1	SWCHSC data	151.88		ODBF(91)				151.88	151.88
TOTAL INDEX F/U COST										525.74

TABLE 9: Index follow-up costs of managing an event free PAD patient

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	PHYSICIAN FEES ($)	FEE CODES	DESCRIPTION OF FEE CODES	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Specialist visit	0	expert opinion (116)	0	55.9	A095	vascular surgeon consultation	55.90	0
PCP visit	2	expert opinion (116)	0	48.2	A003	PCP, general assessment	48.20	96.40
ECG	0.5	expert opinion (116)	0	43.3	G653	level 2, professional comp	43.30	21.65
					G661	event record, tech. Comp		
					G311	interpretation of ECG strip		
Blood tests	0.5	expert opinion (116)	38.08			other products, CBC, PT	38.08	19.04
Duplex ultrasound	0.5	expert opinion (116)	0	92.65			92.65	46.33
Concomitant Medication	1	SWCHSC data	184.65			ODBF(91)	184.65	184.65
TOTAL COST OF F/U PER 6 MONTH PERIOD								368.07

TABLE 10: Follow-up costs of managing an event free PAD patient

COST ITEM	PROBABILITY (A)	REFERENCE SOURCE	UNIT COST ($)	PHYSICIAN FEES ($)	FEE CODES	DESCRIPTION OF FEE CODES	TOTAL UNIT COST ($), (B)	EXPECTED COST ($), (A*B)
Specialist visit	0	expert opinion (116)		55 9	A095	vascular surgeon consultation	55.90	0
PCP visit	2	expert opinion (116)		48 2	A003	PCP, general assessment	48 20	96 40
ECG	0 5	expert opinion (116)		43 3	G653	level 2, prof. comp	43 30	21.65
					G661	event record, tech. comp		
					G311	interpretation of ECG strip		
Blood tests	0 5	expert opinion (116)				other products, CBC, PT	38 08	19 04
Duplex ultrasound	0 5	expert opinion (116)		92 65			92 65	46.325
COMPLICATIONS PER 6 MONTHS								
Angioplasty	0 0044	SWCHSC data	2,113 52	400 80	Z434	coronary angioplasty	2,580.74	11.355256
				66 42	Z434	anesthetist (5 units + 1 hour)		
				467.22				
By-pass operation	0 023	SWCHSC data	11,048 7 0	609 20	R937	ilio-femoral bypass graft	11,779 67	270.93
				121 77	R862	anesthetist		
				730.97				
Amputation	(39/3233)/4	CAPRIE data	16,396 5 4			CIHI (108)	49.45	49.45
Concomitant Medication	1	SWCHSC data	184 65			ODBF(91)	184 65	184 65
TOTAL COST OF F/U PER 6 MONTH PERIOD								699.81

TABLE 11: Adverse event rates expressed as probabilities and the corresponding cost associated with each event

ADVERSE EVENT	PROBABILITY CLOPIDOGREL	PROBABILITY TICLOPIDINE	TREATMENT COST	DESCRIPTION OF COST	REFERENCE SOURCE
Neutropenia	0.0104	0.0238			
severe	0.5	0.75	$3,790		SWCHSC data
moderate	0.5	0.25	$70.28		Schedule of benefits(92)
fatal	0.26	0.26	$3,790	neutropenia hospitalization	SWCHSC data
			$62.04	blood monitoring	Schedule of benefits(92)
			$228.15	drug cost for 3 months	ODBF(91)
			$4,080.19		Oster (46)
Diarrhea	0.046	0.2068			
severe	0.091	0.304	$24.80 + drug cost	GP visit	Schedule of benefits(92)
moderate	0.909	0.696	$24.80	GP visit + drug cost	Schedule of benefits(92) ODBF(91)
Rash	0.060	0.1160			
severe	0.009	0.293	$24.80 + drug cost	GP visit	Schedule of benefits(92)
moderate	0.991	0.707	$24.80	GP visit + drug cost	Schedule of benefits(92) ODBF(91)
any adverse event	0.208	0.441			

TABLE 12: Probabilities (SWCHSC data) and costs (91) for outpatient concomitant medications for MI, IS and PAD patients

DRUG DISTRIBUTION	STROKE PATIENTS		MI PATIENTS		PAD PATIENTS	
	PROBABILITY	COST PER 6 MONTHS ($)	PROBABILITY	COST PER 6 MONTHS ($)	PROBABILITY	COST PER 6 MONTHS ($)
ACE inhibitors	0.056	17.29	0.095	17.70	0.096	17.87
Analgesic	0.073	3.25	0.004	0.50	0.090	7.99
anemia therapy	0	0	0	0	0.026	0.45
antacid/antiulcer/GI drug	0.113	15.07	0.033	2.99	0.12	36.15
anti-arrythmic	0	0	0	0	0.006	2.69
anti-biotic	0.006	0.52	0	0	0.045	27.52
anti-coagulant	0.050	19.26	0.008	0.48	0.32	2.23
anti-diabetic	0.039	2.04	0.025	0.87	0.045	1.70
anti-fungal	0.011	1.51	0	0	0.006	1.48
anti-neoplastic	0	0	0.008	23.27	0	0
anti-platelet	0.220	16.30	0.251	9.02	0.122	21.89
anti-psychotic	0.090	10.96	0.021	3.75	0.051	4.2
Asthma	0.006	2.75	0.120	3.15	0.032	14.20
b-blocker	0.057	5.91	0.210	17.89	0.071	9.45
Ca^{2+} channel blocker	0.057	11.02	0.058	14.22	0.045	17.73
cholesterol red	0.068	29.56	0.165	26.46	0.019	5.26
coronary vasodilator	0.006	0.10	0.012	2.93	0	0
corticosteroid	0	0	0.004	0.06	0.019	1.85
dig glycoside	0.034	1.38	0.004	0.12	0.026	0.75
Diuretic	0.051	1.30	0.021	0.39	0.051	0.95
Estrogen	0.010	0.60	0.012	0.51	0.006	0.13
glaucoma therapy	0.017	11.70	0	0	0	0
hormone therapy	0.028	0.57	0.021	0.62	0.064	2.59
peripheral vasodilator	0.006	0.78	0.037	9.32	0.026	7.23
Vitamin	0	0	0	0	0.006	0.33
TOTAL	1	151.88	1	134.25	1	184.65

APPENDIX III – DECISION TREE

1.0 LIST OF PROBABILITIES USED IN THE MARKOV MODEL

Abbreviations

pDieVasc - probability of vascular death
pMI - probability of having a MI
pMILive - probability of having a MI and surviving the MI
pStroke - probability of having an IS
pStrokeLive - probability of having a stroke and surviving the stroke

Variation in the Relative Risk Reduction (95% CI)

To reflect the lower limit of the relative risk reduction (i.e., 0.3%), clopidogrel probabilities number 1-21 of pDieVasc, pMI, pMILive, pStroke and pStrokeLive were multiplied by 1.09, with a maximum probability of 1 (i.e., probabilities can range only between 0 and 1).

To reflect the upper limit of the relative risk reduction (i.e 16.5%), clopidogrel probabilities number 1-21 of pDieVasc, pMI, pMILive, pStroke and pStrokeLive were multiplied by 0.92.

In Analysis E, second line therapy of clopidogrel versus placebo, to derive the probability of having a MI at various stages while on placebo, ASA probabilities number 29-35, were divided by (1-0.34). To derive the probability of having an IS at various stages while on placebo, ASA probabilities number 29-35, were divided by (1-0.25). To derive the probability of vascular death in PAD patients at various stages while on placebo, ASA probabilities number 29-35, were divided by (1-0.17).

pDieVasc1 = 0.00557
pDieVasc10 = 0.1429
pDieVasc11 = 0.0130
pDieVasc12 = 0.1411
pDieVasc13 = 0.0115
pDieVasc14 = 0.2
pDieVasc15 = 0
pDieVasc16 = 0.
pDieVasc17 = 0.1728
pDieVasc18 = 0.0127
pDieVasc19 = 0.3088
pDieVasc2 = 0.00543
pDieVasc20 = 0.01587
pDieVasc21 = 0.04
pDieVasc22 = 0.0050
pDieVasc23 = 0.0055
pDieVasc24 = 0.0799
pDieVasc25 = 0.00175
pDieVasc26 = 0.2941
pDieVasc27 = 0.0169
pDieVasc28 = 0.1095
pDieVasc29 = 0.0111
pDieVasc3 = 0.0698
pDieVasc30 = 0.0032
pDieVasc31 = 0.1951
pDieVasc32 = 0.02

pDieVasc33 = 0.1436
pDieVasc34 = 0.0109
pDieVasc35 = 0.1429
pDieVasc36 = 0.00526
pDieVasc37 = 0.00724
pDieVasc38 = 0.1341
pDieVasc39 = 0.
pDieVasc4 = 0.0122
pDieVasc40 = 0.2593
pDieVasc41 = 0.0351
pDieVasc42 = 0.1219
pDieVasc5 = 0.25
pDieVasc6 = 0
pDieVasc7 = 0.04065
pDieVasc8 = 0.00954
pDieVasc9 = 0.00565
pMI1 = 0.00258
pMI10 = 0.
pMI11 = 0.0132
pMI12 = 0.0652
pMI13 = 0.0277
pMI14 = 0.0938
pMI15 = 0.0041
pMI16 = 0.00563
pMI17 = 0
pMI18 = 0.
pMI19 = 0.0652
pMI2 = 0.0036
pMI20 = 0.0162
pMI21 = 0.
pMI22 = 0.00393
pMI23 = 0.00394
pMI24 = 0.
pMI25 = 0.00369
pMI26 = 0.0606
pMI27 = 0.0339
pMI28 = 1
pMI29 = 0.0261
pMI3 = 0
pMI30 = 0.00934
pMI31 = 0.0322
pMI32 = 0.0204
pMI33 = 0.0805
pMI34 = 0.0258
pMI35 = 0.05714
pMI36 = 0.0104
pMI37 = 0.00786
pMI38 = 0.01493
pMI39 = 0.
pMI4 = 0
pMI40 = 0.12
pMI41 = 0.00909
pMI42 = 0.03125
pMI5 = 0.1935
pMI6 = 0.02083
pMI7 = 0.
pMI8 = 0.02520
pMI9 = 0.00864
pMILive1 = 0.75
pMILive10 = 1.0

pMILive11 = 0.8824
pMILive12 = 0.8824
pMILive13 = 0.8824
pMILive14 = 1.0
pMILive15 = 0.7692
pMILive16 = 0.7273
pMILive17 = 1
pMILive18 = 1
pMILive19 = 1
pMILive2 = 0.75
pMILive20 = 1
pMILive21 = 1
pMILive22 = 0.75
pMILive23 = 0.7179
pMILive24 = 0.6667
pMILive25 = 0.6667
pMILive26 = 0.6667
pMILive27 = 0.6667
pMILive28 = 0.
pMILive29 = 0.8765
pMILive3 = 1
pMILive30 = 0.8709
pMILive31 = 0.7619
pMILive32 = 0.7619
pMILive33 = 0.7619
pMILive34 = 0.7619
pMILive35 = 1
pMILive36 = 0.7575
pMILive37 = 0.7467
pMILive38 = 0.7273
pMILive39 = 1
pMILive4 = 1
pMILive40 = 0.7273
pMILive41 = 0.7273
pMILive42 = 0
pMILive5 = 0.7143
pMILive6 = 0.7143
pMILive7 = 1.0
pMILive8 = 0.8718
pMILive9 = 0.8824
pStroke1 = 0.0370
pStroke10 = 0.0556
pStroke11 = 0.
pStroke12 = 0.0143
pStroke13 = 0.0156
pStroke14 = 0.
pStroke15 = 0.00558
pStroke16 = 0.0064
pStroke17 = 0.0746
pStroke18 = 0.0256
pStroke19 = 0.0213
pStroke2 = 0.0190
pStroke20 = 0.
pStroke21 = 0.
pStroke22 = 0.0415
pStroke23 = 0.0204
pStroke24 = 0.0836
pStroke25 = 0.0491
pStroke26 = 0.0833
pStroke27 = 0.

pStroke28 = 0.0379
pStroke29 = 0.00544
pStroke3 = 0.0751
pStroke30 = 0.0024
pStroke31 = 0.0606
pStroke32 = 0.
pStroke33 = 0.
pStroke34 = 0.00368
pStroke35 = 0.0278
pStroke36 = 0.00747
pStroke37 = 0.006
pStroke38 = 0.0563
pStroke39 = 0.0374
pStroke4 = 0.0412
pStroke40 = 0.0625
pStroke41 = 0.
pStroke42 = 0.1111
pStroke5 = 0.0606
pStroke6 = 0.0204
pStroke7 = 0.05932
pStroke8 = 0.00578
pStroke9 = 0.00243
pStrokeLive1 = 0.9496
pStrokeLive10 = 1.0
pStrokeLive11 = 1.0
pStrokeLive12 = 1.0
pStrokeLive13 = 1.0
pStrokeLive14 = 1.0
pStrokeLive15 = 0.8333
pStrokeLive16 = .873
pStrokeLive17 = 0.875
pStrokeLive18 = 0.875
pStrokeLive19 = 0.875
pStrokeLive2 = 0.9436
pStrokeLive20 = 1
pStrokeLive21 = 1
pStrokeLive22 = 0.9545
pStrokeLive23 = 0.9515
pStrokeLive24 = 0.8246
pStrokeLive25 = 0.8246
pStrokeLive26 = 0.8246
pStrokeLive27 = 1
pStrokeLive28 = 1
pStrokeLive29 = 0.8235
pStrokeLive3 = 0.9556
pStrokeLive30 = 0.7917
pStrokeLive31 = 1
pStrokeLive32 = 1.0
pStrokeLive33 = 1.0
pStrokeLive34 = 1.0
pStrokeLive35 = 1
pStrokeLive36 = 0.9167
pStrokeLive37 = 0.931
pStrokeLive38 = 1
pStrokeLive39 = 1
pStrokeLive4 = 0.9556
pStrokeLive40 = 1
pStrokeLive41 = 1
pStrokeLive42 = 1
pStrokeLive5 = 0.9556

pStrokeLive6 = 0.9556
pStrokeLive7 = 1
pStrokeLive8 = 0.8889
pStrokeLive9 = 0.875

2.0 LIST OF PROBABILITIES USED IN ANALYSIS D, CLOPIDOGREL VERSUS TICLOPIDINE AS SECOND LINE THERAPY

In conducting the sensitivity analysis, the following changes were made to the probabilities and costs that appear below:

a) For a 25% decrease or increase in adverse event rates, the following probabilities were multiplied by 0.75 or 1.25 respectively:

- pAdverseEvent
- pDiarrhea
- pFatalNeutropenia
- pNeutropenia
- pRash
- pSevereDiarrhea
- pSevereNeutropenia
- pSevereRash

b) For a 50% decrease or increase in the drug price of clopidogrel, cClopidogrel was multiplied by 0.5 or 1.5 respectively

c) For a 50% decrease or increase in the adverse event costs, the following costs were multiplied by 0.5 or 1.5 respectively
- cBloodMonitoring
- cGP (cost of physician visit)
- cModerateNeutropenia
- cSevere Neutropenia

CLOPIDOGREL ARM

cBloodMonitoring = 0
cClopidogrel = 2.47
cDispensing = 4.11
cDrug3months = cClopidogrel*1.1*90 + 3*cDispensing
cGP = 24.8
cModerateNeutropenia = 70.28
cSevereNeutropenia = 3790
duAE = .05/12
duHosp = .5/12
pAdverseEventC = .208
pDiarrheaC = .221
pFatalNeutropenia = .26
pNeutropeniaC = .005
pRashC = .288
pSevereDiarrheaC = .091
pSevereNeutropeniaC = .5
pSevereRashC = .009

AT THE TICLID ARM

cBloodMonitoring = 62.04
cDispensing = 4.11
cDrug3months = cTiclopidine*1.1*90 + cDispensing*3
cGP = 24.80
cModerateNeutropenia = 70.28
cSevereNeutropenia = 3790
cTiclopidine = 2.18
duAE = .05/12
duHosp = .5/12
pAdverseEventT = .441
pDiarrheaT = .469
pFatalNeutropenia = .26
pNeutropeniaT = .054
pRashT = .263
pSevereDiarrheaT = .304
pSevereNeutropeniaT = .75
pSevereRashT = .293

FIGURE 1: The core Markov model comparing clopidogrel versus ASA. The Post Index Branch has been expanded to indicate the full descriptive nature of the tree at this health state and also for the other health states (Post Index after 6 months, Post 2nd Stroke, etc.) for both the clopidogrel and ASA arms. Note: 1) >6 months refers to the period of 7-36 months following the stroke or MI event; 2) Multiple events refers to the 3rd stroke or 2nd MI (in the case of the stroke patient) experienced during the time period of 0-36 months after the 2nd stroke or 1st MI. **A** and **B** indicate where the probabilities change when conducting Analyses C (subgroups) and E (2nd line therapy in MI).

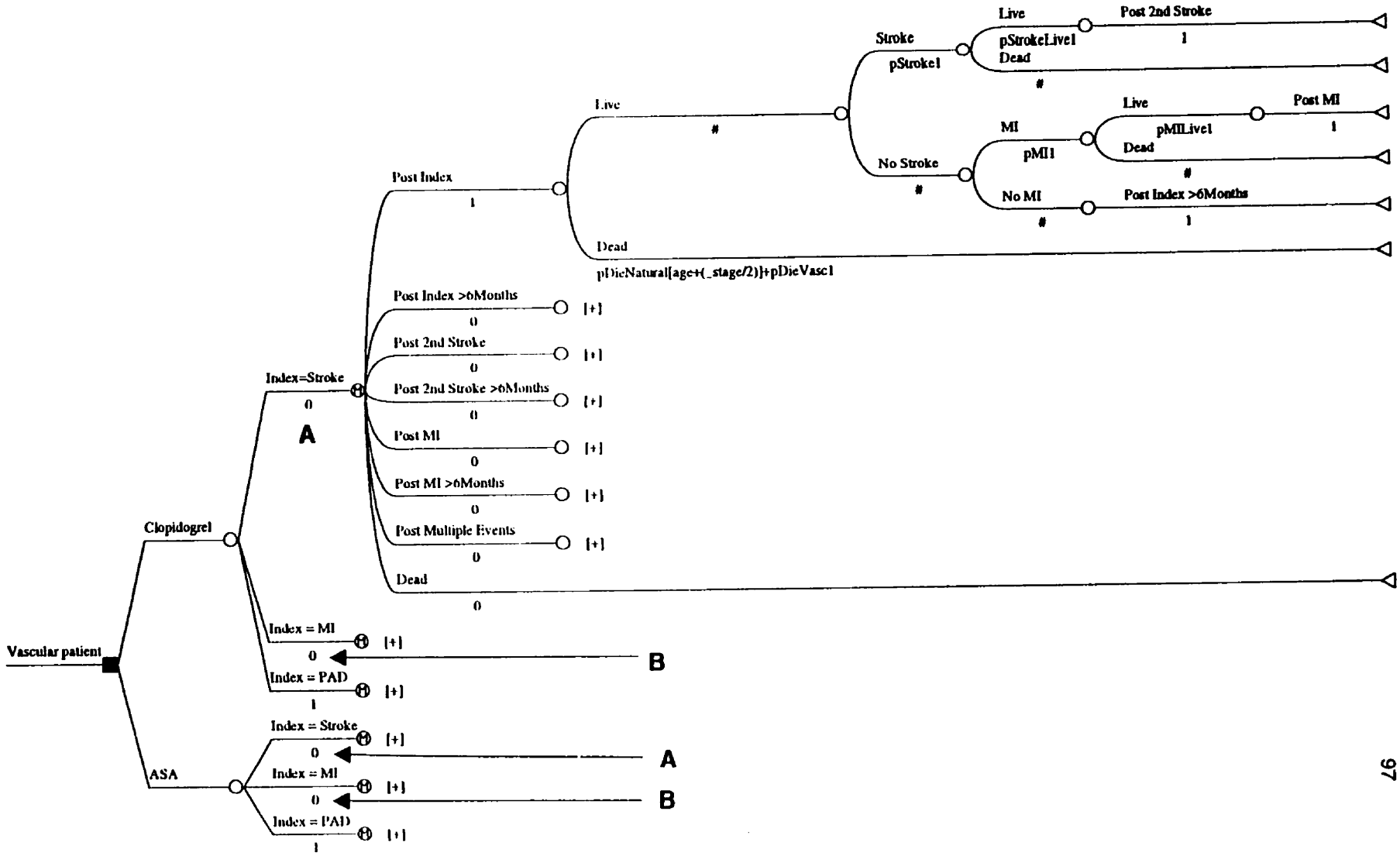


FIGURE 2: Explanation of the Markov Model Using a Stroke Patient Profile (I.e patient entered Index Stroke arm)

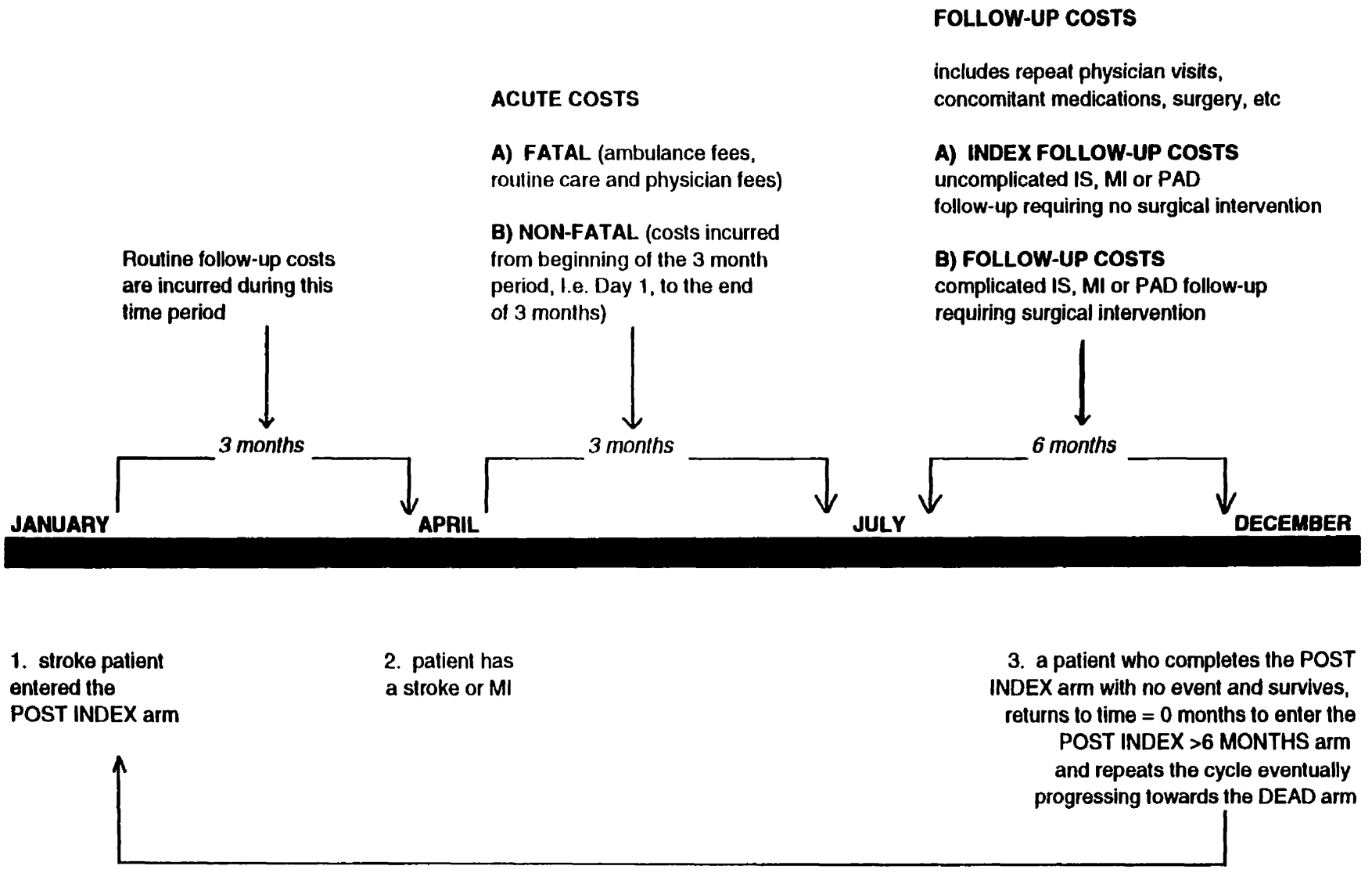
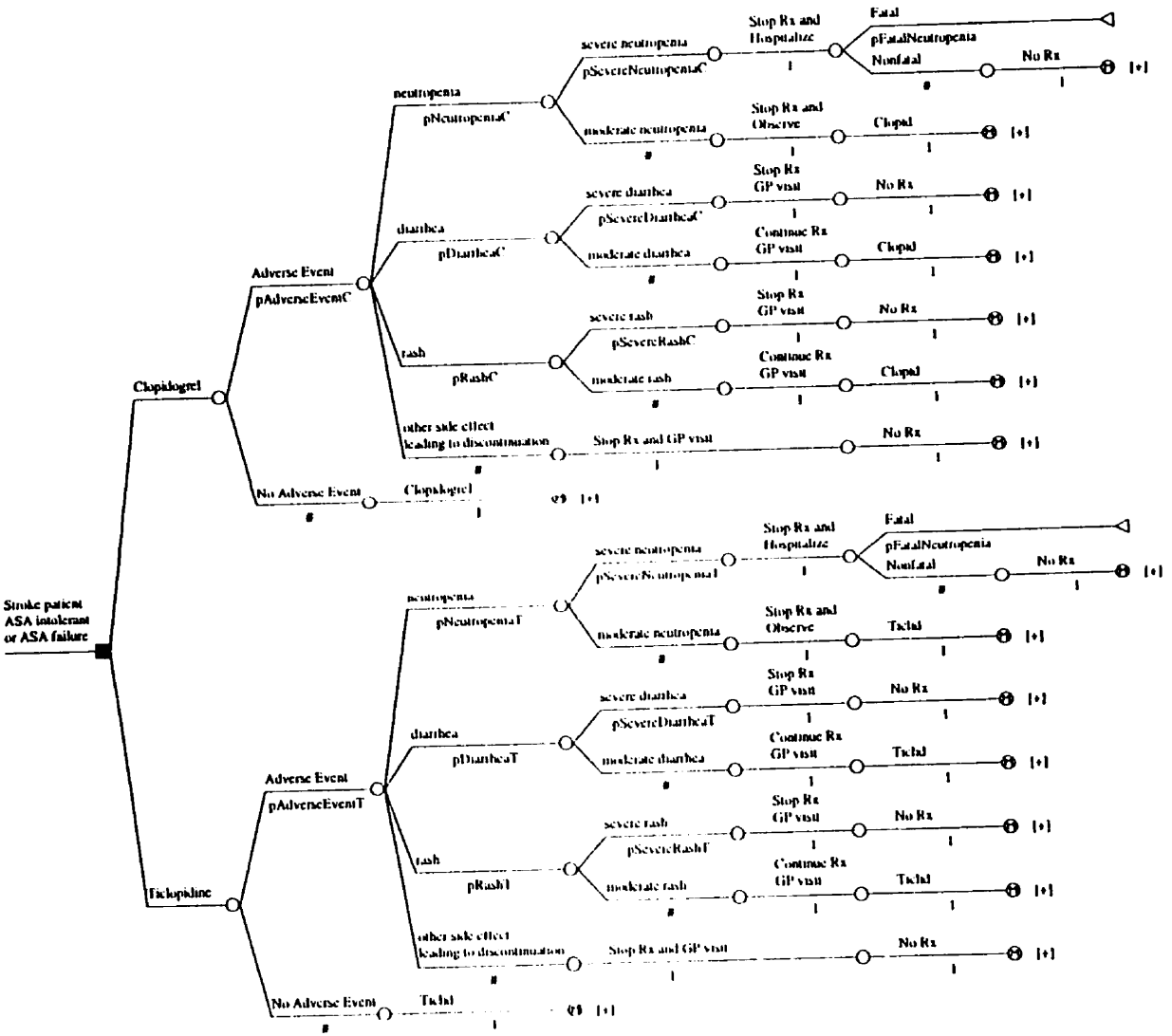


FIGURE 3: Adverse event model (Analysis D) comparing second line treatment between clopidogrel and ticlopidine.



APPENDIX IV – SENSITIVITY ANALYSIS

TABLE 1: Variation in MI treatment costs

TREATMENT PERIOD	EXPECTED COST ($)	50% INCREASE IN COST ($)	50% DECREASE IN COST ($)
Acute care	9049.40	13574.10	4524.70
Follow-up	1703.92	2555.88	851.96
Index follow-up	577.81	866.72	288.91
Fatal	6048.04	9072.06	3024.02

TABLE 2: Variation in IS treatment costs

TREATMENT PERIOD	EXPECTED COST ($)	50% INCREASE IN COST ($)	50% DECREASE IN COST ($)
Acute care	14190.84	21286.26	7095.42
Follow-up	3807.37	5711.06	1903.69
Index follow-up	525.74	788.61	262.87
Fatal	12114.49	18171.74	6057.25

TABLE 3: Variation in PAD treatment costs

TREATMENT PERIOD	EXPECTED COST ($)	50% INCREASE IN COST ($)	50% DECREASE IN COST ($)
Follow-up	699.81	1049.72	349.91
Index follow-up	368.07	552.11	184.04

TABLE 4: Variation in adverse event treatment costs

TREATMENT COSTS	EXPECTED COST ($)	50% INCREASE IN COST ($)	50% DECREASE IN COST ($)
General practitioner visit	24.80	37.20	12.40
Neutropenia blood monitoring	62.04	93.06	31.02
Moderate neutropenia	70.28	105.42	35.14
Severe neutropenia requiring hospitalization	3790.00	5685.00	1895.00

TABLE 5: Sensitivity analyses conducted for overall IS, MI and PAD populations in the lifetime Markov Model analysis. The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in the brackets represent the baseline values; if no brackets are indicated, then there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	ASA	$40,663	9.08 LY	
	CLOPIDOGREL ($1.24/DAY)	$45,535 ($44,574-$46,565) *($50,164)*	9.37 LY (9.13-9.61 LY)	$16,536/LY ($11,131-$71,115/LY) *($32,240/LY)*
50% INCREASE IN CLOPIDOGREL DRUG COST	ASA	$40,663	9.08 LY	
	CLOPIDOGREL ($3.71/DAY)	$54,830 ($53,630-$56,093) *($50,164)*	9.37 LY (9.13-9.61 LY)	$48,070/LY ($29,100-$235,807/LY) *($32,240/LY)*
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$20,470 *($40,663)*	9.08 LY	
	CLOPIDOGREL	$29,845 ($29,183-$30,538) *($50,164)*	9.37 LY (9.13-9.61 LY)	$31,815/LY ($18,986-$158,436/LY) *($32,240/LY)*
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$60,856 *($40,663)*	9.08 LY	
	CLOPIDOGREL	$70,483 ($68,985-$72,083) *($50,164)*	9.37 LY (9.13-9.61 LY)	$32,672/LY ($21,172-$147,818/LY) *($32,240/LY)*
0% DISCOUNT RATE	ASA	$50,542 *($40,663)*	11.22 LY *(9.08 LY)*	
	CLOPIDOGREL	$62,441 ($60,848-$64,124) *($50,164)*	11.64 LY (11.30-11.98 LY) *(9.37 LY)*	$28,720/LY ($18,100-$141,345/LY) *($32,240/LY)*
5% DISCOUNT RATE	ASA	$35,820 *($40,663)*	8.02 LY *(9.08 LY)*	
	CLOPIDOGREL	$44,156 ($43,304-$45,062) *($50,164)*	8.26 LY (8.07-8.45 LY) *(9.37 LY)*	$34,667/LY ($21,454-$161,476/LY) *($32,240/LY)*

TABLE 6: Sensitivity analyses conducted for stroke subgroup population. The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in brackets represent the baseline values; if no italicized brackets are indicated, there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	ASA	$71,550	9.00 LY	
	CLOPIDOGREL ($1.24/DAY)	$76,223 ($74,510-$78,278) *($80,719)*	9.10 LY (8.84-9.40 LY)	$45,681/LY ($16,862/LY-dominated) *($89,629/LY)*
50% INCREASE IN CLOPIDOGREL DRUG COST	ASA	$71,550	9.00 LY	
	CLOPIDOGREL ($3.71/DAY)	$85,252 ($83,276-$87,601) *($80,719)*	9.10 LY (8.84-9.40 LY)	$133,932/LY ($40,226/LY-dominated) *($89,629/LY)*
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$35,912 *($71,550)*	9.00 LY	
	CLOPIDOGREL	$44,986 ($43,930-$46,238) *($80,719)*	9.10 LY (8.84-9.40 LY)	$88,693/LY ($25,876/LY-dominated) *($89,629/LY)*
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$107,187 ($71,550)	9.00 LY	
	CLOPIDOGREL	$116,452 ($113,820-$119,603) ($80,719)	9.10 LY (8.84-9.40 LY)	$90,562/LY ($31,117/LY-dominated) *($89,629/LY)*
DISCOUNT RATE 0%	ASA	$89,041 *($71,550)*	11.11 LY	
	CLOPIDOGREL	$100,516 ($97,790-$103,739) *($80,719)*	11.25 LY (10.88-11.67 LY)	$79,084/LY ($25,848/LY-dominated) *($89,629/LY)*
DISCOUNT RATE 5%	ASA	$62,954 *($71,550)*	7.96 LY *(9.00 LY)*	
	CLOPIDOGREL	$71,004 ($69,553-$72,749) *($80,719)*	8.05 LY (7.83-8.29 LY) *(9.10 LY)*	$97,197/LY ($30,278/LY-dominated) *($89,629/LY)*

TABLE 7: Sensitivity analyses conducted for MI subgroup population. The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in the brackets represent the baseline values; if no italicized brackets are indicated, then there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	ASA	$34,615	9.36 LY	
	CLOPIDOGREL ($1.24/DAY)	$38,652 ($37,718-$39,478) *($43,195)*	9.20 LY (8.94-9.43 LY)	ASA dominant ($68,034/LY-dominated)
50% INCREASE IN CLOPIDOGREL DRUG COST	ASA	$34,615	9.36 LY	
	CLOPIDOGREL ($3.71/DAY)	$47,776 ($46,584-$48,833) *($43,195)*	9.20 LY (8.94-9.43 LY)	ASA dominant ($198,889/LY-dominated)
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$17,450 *($34,615)*	9.36 LY	
	CLOPIDOGREL	$26,273 ($25,610-$26,862) *($43,195)*	8.94 LY (8.94-9.43 LY) *(9.20 LY)*	ASA dominant ($131,653/LY–dominated)
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$51,779 *($34,615)*	9.36 LY	
	CLOPIDOGREL	$60,118 ($58,656-$61,411) *($43,195)*	9.15 LY (8.94-9.43 LY) *(9.20 LY)*	ASA dominant ($134,740/LY-dominated) *(ASA dominant)*
DISCOUNT RATE 0%	ASA	$43,015 *($34,615)*	11.63 LY *(9.36 LY)*	
	CLOPIDOGREL	$53,561 ($52,029-$54,923) *($43,195)*	11.40 LY (11.04-11.73 LY) *(9.20 LY)*	ASA dominant ($121,957/LY-dominated)
DISCOUNT RATE 5%	ASA	$30,515 *($34,615)*	8.25 LY *(9.36 LY)*	
	CLOPIDOGREL	$38,125 ($37,275-$38,878) *($43,195)*	8.12 LY (7.91-8.31 LY) *(9.20 LY)*	ASA dominant ($142,590/LY-dominated)

TABLE 8: Sensitivity analyses conducted for PAD subgroup population. The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in the brackets represent the baseline values; if no italicized brackets are indicated, then there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	ASA	$15,825	8.87 LY	
	CLOPIDOGREL ($1.24/DAY)	$21,732 ($21,494-$21,940) *($26,577)*	9.81 LY (9.61-9.99 LY)	$6,263/LY ($5,458-7,582/LY) *($11,401/LY)*
50% INCREASE IN CLOPIDOGREL DRUG COST	ASA	$15,825	8.87 LY	
	CLOPIDOGREL ($3.71/DAY)	$31,462 ($31,030-$31,846) *($26,577)*	9.81 LY (9.61-9.99 LY)	$16,580/LY ($14,302-$20,337/LY) *($11,401/LY)*
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$8,048 *($15,825)*	8.87 LY	
	CLOPIDOGREL	$18,275 ($18,008-$18,513) *($26,577)*	9.81 LY (9.61-9.99 LY)	$10,844/LY ($9,342-$13,322/LY) *($11,401/LY)*
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	ASA	$23,602 *($15,825)*	8.87 LY	
	CLOPIDOGREL	$34,880 ($34,478-$35,233) *($26,577)*	9.81 LY (9.61-9.99 LY)	$11,958/LY ($10,383-$14,545/LY) *($11,401/LY)*
DISCOUNT RATE 0%	ASA	$19,569 *($15,825)*	10.93 LY *(8.87 LY)*	
	CLOPIDOGREL	$33,246 ($32,726-$33,709) *($26,577)*	12.26 LY (11.98-12.51 LY) *(9.81 LY)*	$10,291/LY ($8,992-$12,566/LY) *($11,401/LY)*
DISCOUNT RATE 5%	ASA	$13,990 *($15,825)*	7.85 LY *(8.87 LY)*	
	CLOPIDOGREL	$23,338 ($23,085-$23,561) *($26,577)*	8.62 LY (8.46-8.76 LY) *(9.81 LY)*	$12,165/LY ($10,513-$14,892/LY) *($11,401/LY)*

TABLE 9: Sensitivity analyses conducted for clopidogrel versus brand name ticlopidine ($2.18/day) (2nd Line stroke therapy) subgroup population. The non-italicized values in brackets indicate the variation in clopidogrel treatment outcomes. Italicized values in the brackets represent baseline values; if no brackets are indicated, there is no change from the baseline values. RRR – relative risk reduction.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	TICLOPIDINE	$77,599	9.25 LY	
	CLOPIDOGREL ($1.24/DAY)	$75,640 ($75,675-$75,637) *($79,724)*	9.36 LY (9.36-9.37 LY)	-$18,291/LY (cost savings) (-$16,973 to -$18,268/LY) *($19,852/LY)*
50% INCREASE IN CLOPIDOGREL DRUG COST	TICLOPIDINE	$77,599	9.25 LY	
	CLOPIDOGREL ($3.71/DAY)	$83,842 ($83,952-$83,868) *($79,724)*	9.36 LY (9.36-9.37 LY)	$58,291/LY ($56,065-$58,353/LY) *($19,852/LY)*
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	TICLOPIDINE	$42,207 *($77,599)*	9.25 LY	
	CLOPIDOGREL	$44,087 ($44,166-$44,119) *($79,724)*	9.36 LY (9.36-9.37 LY)	$17,554/LY ($17,290-$17,802/LY) *($19,852/LY)*
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	TICLOPIDINE	$112,991 *($77,599)*	9.25 LY	
	CLOPIDOGREL	$115,361 ($115,461-$115,385) *($79,724)*	9.36 LY (9.36-9.37 LY)	$22,129/LY ($21,801-$22,291/LY) *($19,852/LY)*
0% DISCOUNT RATE	TICLOPIDINE	$96,386 *($77,599)*	11.34 LY *(9.25 LY)*	
	CLOPIDOGREL	$99,129 ($99,248-$99,164) *($79,724)*	11.48 LY (11.48-11.49 LY) *(9.36 LY)*	$19,075/LY ($18,763-$19,204/LY) *($19,852/LY)*
5% DISCOUNT RATE	TICLOPIDINE	$68,363 *($77,599)*	8.23 LY *(9.25 LY)*	
	CLOPIDOGREL	$70,193 ($70,269-$70,218) *($79,724)*	8.32 LY (8.32-8.32 LY) *(9.36 LY)*	$20,356/LY ($20,049-$20,592/LY) *($19,852/LY)*
25% DECREASE IN TICLOPIDINE ADVERSE EVENT RATES	TICLOPIDINE	$78,017 *($76,005)*	9.30 LY *(9.25 LY)*	
	CLOPIDOGREL	$79,724 ($79,813-$79,752) *($79,724)*	9.36 LY (9.37-9.36 LY)	$27,166/LY ($26,003-$27,455/LY) *($19,852/LY)*
25% INCREASE IN TICLOPIDINE ADVERSE EVENT RATES	TICLOPIDINE	$75,417 *($77,599)*	9.18 LY *(9.25 LY)*	
	CLOPIDOGREL	$79,724 ($79,813-$79,752) *($79,724)*	9.36 LY (9.37-9.36 LY)	$23,671/LY ($15,150-$15,303/LY) *($19,852/LY)*

TABLE 10: Sensitivity Analyses performed on Clopidogrel versus Brand Name Ticlopidine ($2.18/day). The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in the brackets represent the baseline values; if no italicized brackets are indicated, there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	COST/LY AND COST/QALY
50% DECREASE IN ADVERSE EVENT COSTS	TICLOPIDINE	$77,528 *($77,599)*	9.25 LY	
	CLOPIDOGREL	$79,721 *($79,724)*	9.36 LY	$20,475/LY *($19,852/LY)*
50% INCREASE IN ADVERSE EVENT COSTS	TICLOPIDINE	$77,669 *($77,599)*	9.25 LY	
	CLOPIDOGREL	$79,728 *($79,724)*	9.36 LY	$19,229/LY *($19,852/LY)*
25% DECREASE IN CLOPIDOGREL ADVERSE EVENT RATES	TICLOPIDINE	$77,599 *($77,599)*	9.25 LY	
	CLOPIDOGREL	$79,816 *($79,724)*	9.37 LY *(9.36 LY)*	$19,566/LY *($19,852/LY)*
25% INCREASE IN CLOPIDOGREL ADVERSE EVENT RATES	TICLOPIDINE	$77,599 *($77,599)*	9.25 LY	
	CLOPIDOGREL	$79,747 *($79,724)*	9.36 LY	$19,998/LY *($19,852/LY)*

TABLE 11: Sensitivity analyses conducted for clopidogrel versus generic ticlopidine ($1.64/day) (2nd line stroke therapy). The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. Italicized values in the brackets represent the baseline values; if no italicized brackets are indicated, there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	TICLOPIDINE	$76,005	9.25 LY	
	CLOPIDOGREL ($1.24/DAY)	$75,640 ($75,675-$75,637) *($79,724)*	9.36 LY (9.37-9.36 LY)	-$3,408/LY (cost savings) (-$2,913 to $3,436/LY) *($34,725/LY)*
50% INCREASE IN CLOPIDOGREL DRUG COST	TICLOPIDINE	$76,005	9.25 LY	
	CLOPIDOGREL ($3.71/DAY)	$83,842 ($83,952-$83,868) *($79,724)*	9.36 LY (9.37-9.36 LY)	$73,175/LY ($70,125-$73,183./LY) *($34,725/LY)*
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	TICLOPIDINE	$40,614 *($76,005)*	9.25 LY	
	CLOPIDOGREL	$44,087 ($44,166-$44,119) *($79,724)*	9.36 LY (9.37-9.36 LY)	$32,428/LY ($31,351-$32,632./LY) *($34,725/LY)*
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	TICLOPIDINE	$111,397 *($76,005)*	9.25 LY	
	CLOPIDOGREL	$115,361 ($115,461-$115,385) *($79,724)*	9.36 LY (9.37-9.36 LY)	$37,012/LY ($35,861-$37,121/LY) *($34,725/LY)*
DISCOUNT RATE 0%	TICLOPIDINE	$94,429 *($76,005)*	11.34 LY *(9.25 LY)*	
	CLOPIDOGREL	$99,129 ($99,248-$99,164) *($79,724)*	11.48 LY (11.49-11.48 LY) *(9.36 LY)*	$32,675/LY ($31,593-$32,727 LY) *($34,725/LY)*
DISCOUNT RATE 5%	TICLOPIDINE	$66,948 *($76,005)*	8.23 LY *(9.25 LY)*	
	CLOPIDOGREL	$70,193 ($70,269-$70,218) *($79,724)*	8.32 LY (8.32-8.32 LY) *(9.36 LY)*	$36,084/LY ($34,936-$36,301/LY) *($34,725/LY)*
25% DECREASE IN TICLOPIDINE ADVERSE EVENT RATES	TICLOPIDINE	$76,375 *($76,005)*	9.30 LY *(9.25 LY)*	
	CLOPIDOGREL	$79,724 ($79,813-$79,752) *($79,724)*	9.36 LY (9.37-9.36 LY)	$53,288/LY ($49,768-$53,432/LY) *($34,725/LY)*
25% INCREASE IN TICLOPIDINE ADVERSE EVENT RATES	TICLOPIDINE	$75,417 *($77,599)*	9.18 LY *(9.25 LY)*	
	CLOPIDOGREL	$79,724 ($79,813-$79,752) *($79,724)*	9.36 LY (9.37-9.36 LY)	$23,671/LY ($23,360-$23,778/LY) *($34,725/LY)*

TABLE 12: Sensitivity Analyses performed on Clopidogrel versus Generic Ticlopidine ($1.64/day). The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in the brackets represent the baseline values; if no italicized brackets are indicated, there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	COST/LY AND COST/QALY
50% DECREASE IN ADVERSE EVENT COSTS	TICLOPIDINE	$75,935 *($76,005)*	9.25 LY	
	CLOPIDOGREL	$79,721 *($79,724)*	9.36 LY	$35,350/LY *($34,725/LY)*
50% INCREASE IN ADVERSE EVENT COSTS	TICLOPIDINE	$76,076 *($76,005)*	9.25 LY	
	CLOPIDOGREL	$79,728 *($79,724)*	9.36 LY	$34,099/LY *($34,725/LY)*
25% DECREASE IN CLOPIDOGREL ADVERSE EVENT RATES	TICLOPIDINE	$76,005 *($76,005)*	9.25 LY	
	CLOPIDOGREL	$79,816 *($79,724)*	9.37 LY *(9.36 LY)*	$33,627/LY *($34,725/LY)*
25% INCREASE IN CLOPIDOGREL ADVERSE EVENT RATES	TICLOPIDINE	$76,005 *($76,005)*	9.25 LY	
	CLOPIDOGREL	$79,747 *($79,724)*	9.36 LY	$34,939/LY *($34,725/LY)*

TABLE 13: Sensitivity analyses conducted for 2nd line MI (clopidogrel versus no treatment/placebo) population. The non-italicized values in brackets indicate the 95% CI for clopidogrel therapy outcomes. The italicized values in the brackets represent the baseline values. If no italicized brackets are indicated, then there is no change from the baseline values.

ANALYSIS	DRUG	LIFETIME COST	ESTIMATE SURVIVAL	Δ COST/LY
50% DECREASE IN CLOPIDOGREL DRUG COST	PLACEBO	$33,625	8.83 LY	
	CLOPIDOGREL ($1.24/DAY)	$38,652 ($37,718-$39,478) *($43,195)*	9.20 LY (8.93-9.43 LY)	$13,701/LY ($9,758-$37,935/LY) *($26,084/LY)*
50% INCREASE IN CLOPIDOGREL DRUG COST	PLACEBO	$33,625	8.83 LY	
	CLOPIDOGREL ($3.71/DAY)	$47,776 ($46,584-$48,833) *($43,195)*	9.20 LY (8.93-9.43 LY)	$38,567/LY ($25,353-$120,104/LY) *($26,084/LY)*
50% DECREASE IN ACUTE AND FOLLOW-UP CARE COSTS	PLACEBO	$16,812 *($33,625)*	8.83 LY	
	CLOPIDOGREL	$26,273 ($25,610-$26,862) *($43,195)*	9.20 LY (8.93-9.43 LY)	$25,784/LY ($16,753-$81,553/LY) *($26,084/LY)*
50% INCREASE IN ACUTE AND FOLLOW-UP CARE COSTS	PLACEBO	$50,437 *($33,625)*	8.83 LY	
	CLOPIDOGREL	$60,118 ($26,862-$58,656) *($43,195)*	9.20 LY (8.93-9.43 LY)	$26,383/LY ($16,753-$76,173/LY) *($26,084/LY)*
DISCOUNT RATE 0%	PLACEBO	$41,412 *($32,066)*	9.86 LY *(8.10 LY)*	
	CLOPIDOGREL	$53,561 ($52,029-$54,923) *($43,195)*	11.40 LY (11.04-11.73 LY) *(9.20 LY)*	$23,155/LY ($15,830-$67,129/LY) *($26,084/LY)*
DISCOUNT RATE 5%	PLACEBO	$29,791 *($32,066)*	7.82 LY *(8.10 LY)*	
	CLOPIDOGREL	$38,125 ($37,275-$38,878) *($43,195)*	8.12 LY (7.91-8.31 LY) *(9.20 LY)*	$28,127/LY ($18,743-$88,150/LY) *($26,084/LY)*