

EXECUTIVE SUMMARY

The Issue

Approximately 5.7% of Canadians have cardiovascular disease (CVD).¹ In 2005, 31% of all deaths in Canada were due to CVD.² In 1998, the estimated total cost of CVD in Canada was \$18.5 billion, of which \$1.8 billion was spent on drugs.¹

Clopidogrel, which is used for the prevention of atherothrombotic events, is an expensive drug relative to other treatment options, and the number of reimbursement requests for clopidogrel submitted to Canadian publicly funded drug plans is increasing.

Objectives

The aim of this report is to compare clopidogrel with other antiplatelet agents for the secondary prevention of vascular events in adults with cerebrovascular events [ischemic stroke or transient ischemic attack (TIA)]. This objective will be accomplished by addressing four research questions.

1. What is the comparative clinical effectiveness of clopidogrel (alone or in combination with acetylsalicylic acid [ASA]) versus other antiplatelet regimens (ASA, ticlopidine, dipyridamole, combination of fixed-dose ASA, and extended-release dipyridamole [ERDPP]) for the secondary prevention of vascular events ([myocardial infarction MI], stroke, or vascular death) in adult patients with cerebrovascular events (stroke, TIA)?
 - a) What is the difference in the clinical effectiveness of dual therapy with clopidogrel and ASA based on the ASA dose?
 - b) How is intolerance to ASA defined, including gastrointestinal (GI) and non-GI causes?
 - What are the benefits and harms of using clopidogrel in patients with ASA intolerance?
 - In patients with ASA intolerance manifesting as GI bleeding, is there a difference in the recurrence risk of GI bleeding between monotherapy with clopidogrel versus combination therapy with ASA and a proton pump inhibitor?
 - c) What is the clinical impact (including benefit and harm) of using clopidogrel in patients who have experienced cerebrovascular events with underlying atrial fibrillation in the absence of cardiac disease?
2. What is the optimal duration of treatment with clopidogrel for the secondary prevention of vascular events in adult patients with cerebrovascular events?
 - a. Is the time required for reimbursement approval associated with a delay in initiating clopidogrel therapy?
 - If there is a delay in clopidogrel therapy initiation, what is the impact in terms of clinical benefit and harm?
 - b. Are there patient characteristics that indicate clopidogrel therapy should be continued indefinitely?
 - c. Is there a rebound effect upon withdrawal of clopidogrel therapy?

3. What are the recommendations from North American clinical practice guidelines on the use of clopidogrel for adult patients with cerebrovascular events?
4. What is the comparative cost-effectiveness of clopidogrel (alone or in combination with ASA) versus other antiplatelet regimens (ASA, ticlopidine, dipyridamole, ASA-ERDP) in the secondary prevention of recurrent stroke (fatal or non-fatal), in adult patients who have had a stroke?
Is there a difference in the cost-effectiveness of dual therapy with clopidogrel and ASA based on the ASA dose?

Methods

To address the objectives, a systematic review was conducted to identify studies comparing antiplatelet agents and to identify guidelines on clopidogrel.

A systematic review was conducted of economic evaluations that compared the use of clopidogrel with other antiplatelet therapies for the management of stroke patients.

An economic evaluation was done to determine the cost-effectiveness of clopidogrel, ASA, ASA plus clopidogrel, dipyridamole, ASA-ERDP, or ticlopidine for the management of stroke patients.

Clinical Effectiveness

Seventeen randomized controlled trials comparing clopidogrel, ticlopidine, ASA, dipyridamole, and ASA-ERDP were included. Based on mixed treatment comparison (MTC) meta-analyses, no estimated relative risk (RR) measures and 95% credible intervals (CrI) were found between any pair of interventions that excluded a null difference for vascular death, non-vascular death, fatal stroke, non-fatal stroke, composite end point (death, MI, or stroke), and fatal MI. For non-fatal MI, based on MTC meta-analyses, dipyridamole was associated with an increased risk of non-fatal MI relative to ASA (RR 3.33, 95% CrI 1.05 to 11.86), but RR measures and 95% CrIs between the other pairs of interventions did not exclude a null difference. The MTC meta-analysis showed that dipyridamole was associated with a reduced risk of major bleeds compared with ASA (RR 0.24, 95% CrI 0.08 to 0.54). Clopidogrel plus ASA was found to be associated with more major bleeds relative to clopidogrel alone (RR 2.46, 95% CrI 1.15 to 5.58). Clopidogrel (RR 4.08, 95% CrI 1.25 to 10.97) and clopidogrel plus ASA (RR 8.78, 95% CrI 2.46 to 25.58) were found to be associated with more major bleeds compared with dipyridamole, though these estimates are based on indirect comparisons and are unsupported by head-to-head trial data.

Four studies were included to address questions 1a, 1b, and 1c. One study suggested that a daily ASA dose of less than 100 mg optimizes efficacy and safety in patients receiving dual therapy with clopidogrel and ASA. Two studies on a mixed population comparing ASA plus proton pump inhibitor with ASA alone had divergent results. One study on a mixed population showed that the risk of the composite end point or stroke was less with clopidogrel plus ASA compared with ASA alone, in the stroke or TIA group but the group had not been determined a priori.

Six guidelines were reviewed to address question 3. According to the guidelines, patients who experienced stroke or TIA should be prescribed antiplatelet therapy for the secondary prevention

of recurrent stroke unless there is an indication for anticoagulation. ASA, ASA-ERDP, or clopidogrel may be used depending on the clinical circumstances. Two guidelines mentioned that the long-term use of combination ASA and clopidogrel is not recommended for secondary stroke prevention.

Economic Review

A systematic review resulted in eight studies that were found to be relevant for inclusion in the literature review.

Economic Evaluation

The economic evaluation found that for a population of patients surviving a stroke and with a mean starting age of 60 years at the time of their initial stroke, lifetime treatment using ASA dominated the other treatment options because it had lower expected costs and higher expected quality-adjusted life-years (QALYs). For patients aged 70 years and older, the use of ASA-ERDP was cost-effective relative to ASA, at a willingness-to-pay per QALY of \$50,000. As the mean age at the start of treatment increased clopidogrel started to have positive incremental QALYs relative to ASA. The sequential incremental cost-effectiveness ratio (ICER) results for ASA-ERDP and clopidogrel were \$48,904 and \$1,857,374 at age 70; \$41,004 and \$845,141 at age 75; and \$33,046 and \$214,901 at age 85. For patients not tolerant of ASA, ASA-ERDP may be the most cost-effective alternative. The ICER for ASA-ERDP versus ticlopidine (least expensive cost option after ASA) was \$26,142 per QALY gained.

Health Services Impact

The estimated utilization of ASA is mostly based on its over-the-counter use. Therefore, with an increase in ASA 81 mg monotherapy prescriptions by as much as 30% (with a proportional decrease in other antiplatelet use) the net savings to a drug plan was expected to be \$16,000 to \$800,000 each year, depending on the jurisdiction.

In some provinces clopidogrel is subject to special authorization (SA). If SA cannot be obtained quickly, there is a potential of negative health outcomes. SA can lead to inequities in access.

Conclusions

The estimates of effects with clopidogrel, ticlopidine, and dipyridamole relative to ASA suggest that the therapeutic choice with optimal direct health effects is unclear.

The economic analysis found that for patients who were a mean age of 60 years at the time of their initial stroke, ASA is the most cost-effective treatment option for the secondary prevention of recurrent stroke. For patients in this age group who do not tolerate ASA, ASA-ERDP may be a cost-effective alternative. For patients aged 70 years or more at the time of their initial stroke, ASA-ERDP was found to be the most cost-effective treatment option. These conclusions assume a willingness-to-pay threshold of \$50,000 per QALY, and are subject to the limitations of the analysis.