EXECUTIVE SUMMARY

The Issue

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

Clopidogrel is used for the prevention of atherothrombotic events. The daily cost of treatment with clopidogrel is higher than that of some alternatives, 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 and other antiplatelet agents for the secondary prevention of vascular events in adults with acute coronary syndrome (ACS) or peripheral vascular disease (PVD). This objective will be accomplished by addressing the following 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, and a combination of extended-release dipyridamole 200 mg and ASA 25 mg) for the secondary prevention of vascular events (myocardial infarction [MI], stroke, or vascular death) in adult patients with ACS (presenting as unstable angina [UA] or MI) or with PVD?
   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 (PPI)?
c. What is the clinical impact (including benefit and harm) of using long-term clopidogrel in patients who have had previous coronary artery bypass grafting (CABG)?

2. What is the optimal duration of treatment with clopidogrel for the secondary prevention of vascular events in adult patients with ACS or with PVD?
   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. Is treatment duration with clopidogrel different depending on the type of MI (non-ST elevation MI [NSTEMI] versus ST elevation MI [STEMI])?
   c. Are there patient characteristics that indicate clopidogrel therapy should be continued indefinitely?
   d. 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 ACS or with PVD?

4. What is the comparative cost-effectiveness of clopidogrel (alone or in combination with ASA) versus other antiplatelet regimens (ASA, ticlopidine, dipyridamole, and a combination of extended-release dipyridamole 200 mg and ASA 25 mg) in the secondary prevention of vascular events (MI, stroke, or vascular death) in adult patients with ACS (presenting as UA or MI) or adult patients with PVD? 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 of studies comparing clopidogrel with other antiplatelet agents and of North American 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 patients with ACS and patients with PVD. An economic evaluation was done to determine the cost-effectiveness of clopidogrel, ASA, or ASA plus clopidogrel for the management of patients with ACS and patients with PVD. The budgetary impacts of potential changes in clopidogrel and ASA use were assessed based on historical prescribing patterns and market shares of antiplatelet drugs for ACS and PVD indications.

Clinical Effectiveness
Three randomized controlled trials provided information on the benefits and harms of treatment with clopidogrel. One randomized controlled trial (the Clopidogrel in Unstable Angina to Prevent Recurrent Events [CURE] trial) involved patients with ACS; the other two (the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events [CAPRIE] trial and the Clopidogrel for High Atherothrombotic Risk and Ishemic Stabilization, Management, and Avoidance [CHARISMA] trial) involved a mixed population (patients who had experienced a cardiovascular event or who were at high risk of experiencing such an event). The CURE trial showed that there was a reduction in the composite end point of non-fatal MI, non-fatal stroke, or
death from cardiovascular causes; and non-fatal MI with increased major bleeding in the clopidogrel plus ASA group compared with the ASA group (relative risk [RR] [95% confidence interval [CI] 0.82 [0.73, 0.90] for composite end point, 0.71 [0.60, 0.84] for non-fatal MI, and 1.38 [1.13, 1.67] for major bleeding). A post hoc analysis of a subgroup of patients with PVD in the CHARISMA trial showed that there was a reduction in MI favouring clopidogrel plus ASA compared with ASA alone, with an increased risk of minor bleeding (RR [95% CI] 0.63 [0.42 to 0.96] for MI and 1.65 [1.47 to 1.86] for minor bleeding). For a subgroup of patients with ACS in the CAPRIE trial, there were no statistically significant differences in the outcomes between treatments with clopidogrel or ASA. For a subgroup of patients with PVD in the CAPRIE trial, there was a statistically significant reduction in non-fatal MI with clopidogrel compared with ASA. For the other outcomes of vascular death, fatal stroke, non-fatal stroke, and fatal MI, there were no statistically significant differences between the two treatments.

The subgroup analyses were post hoc, and neither the CAPRIE trial nor the CHARISMA trial were designed or powered to determine efficacy in the subgroups. No relevant studies comparing clopidogrel (alone or in combination with ASA) versus ticlopidine, dipyridamole, or extended-release dipyridamole 200 mg plus ASA 25 mg were found.

There is a paucity of evidence on the optimal duration of clopidogrel treatment or patient characteristics that warrant long-term treatment with clopidogrel.

Fourteen guidelines met the inclusion criteria for this report. The combination of clopidogrel and ASA is recommended for patients with ACS. Clopidogrel alone is recommended for patients with ACS and ASA intolerance or allergy, and patients with PVD and ASA intolerance or allergy.

**Economic Review**

In a systematic review, 19 studies were found to be relevant for inclusion in the literature review. Two studies in a Canadian context examined clopidogrel plus ASA therapy for patients with ACS. The studies’ conclusions were similar to those of our primary economic evaluation on patients with ACS.

**Economic Evaluation**

The economic evaluation found that for a population of patients surviving an ACS event, with a mean starting age of 60 years, one year of treatment with clopidogrel plus ASA gave an incremental cost-effectiveness ratio (ICER) of $29,604 per quality-adjusted life-year (QALY) gained relative to ASA. Clopidogrel monotherapy was dominated by ASA (lower expected costs and higher expected QALYs). For a population of patients with a mean age of 60 years at the time of a diagnosis with PVD, treatment with clopidogrel for two years gave an ICER of $8,106 per QALY gained relative to ASA and dominated clopidogrel plus ASA treatment for PVD.
Health Services Impact
For the ACS indication, an increase in the use of the clopidogrel plus ASA 81 mg therapy would lead to an increase in expenditures for each drug plan by up to $144,000 annually. For the PVD indication, an increase in the use of clopidogrel monotherapy would increase expenditures to each drug plan by up to $25,000 annually.

Conclusions
In patients with ACS without ST-segment elevation, therapy with clopidogrel and ASA was more efficacious than ASA alone, with an increased risk of major bleeding. A post hoc analysis of patients with PVD showed that there was a reduction in MI favouring clopidogrel plus ASA compared with ASA alone and an increased risk of minor bleeding.

The economic analysis found that at a willingness-to-pay threshold of $50,000 per QALY, for patients with a mean age of 60 years at the time of the initial event or PVD diagnosis, treatment options that included clopidogrel were the most cost-effective compared with ASA alone for the secondary prevention of vascular events. In patients with ACS, clopidogrel plus ASA was found to be most cost-effective. For patients with PVD, clopidogrel alone was the most cost-effective. As the mean age of patients with PVD increases, clopidogrel plus ASA becomes most cost-effective for patients with PVD as well.

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