Clopidogrel Compared with Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults Undergoing Percutaneous Coronary Intervention: Clinical and Cost-Effectiveness Analyses

EXECUTIVE SUMMARY

The Issue
Approximately 5.7% of Canadians have cardiovascular disease (CVD). In 2005, 31% of deaths in Canada were due to CVD. In 2006, the estimated total drug cost of CVD in Canada was $5.3 billion (increased by more than 200% from $1.7 billion in 1996).

Clopidogrel, which is used to prevent atherothrombotic events, is a more costly drug than other treatment options, and the number of reimbursement requests for clopidogrel submitted to Canadian publicly funded drug plans is increasing. The generic version of clopidogrel will be available in 2012.

Objectives
The aim of this report is to compare clopidogrel with other antiplatelet agents for the secondary prevention of vascular events in adults undergoing percutaneous coronary intervention (PCI). This objective will be accomplished by addressing four research questions.

1. What is the clinical effectiveness of clopidogrel (alone or in combination with aspirin [ASA]) compared with that of other antiplatelet regimens for the secondary prevention of vascular events (myocardial infarction [MI], stroke, or vascular death) in adult patients undergoing PCI with or without stent (bare metal or drug eluting) insertion?
   a. Is there a 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 and combination therapy with ASA and a proton pump inhibitor (PPI)?
   c. What is the clinical impact (including benefit and harm) of using clopidogrel in patients who are experiencing restenosis, but who are not candidates for re-stenting?
2. What is the optimal duration of treatment with clopidogrel for the secondary prevention of vascular events in adult patients undergoing PCI?
   a. Is the time required for reimbursement approval associated with a delay in starting 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 intracoronary stent inserted?
      • the type of MI?
   c. Are there patient characteristics that indicate clopidogrel therapy should be continued indefinitely?
   d. Is there a rebound effect after withdrawal of clopidogrel therapy?

3. What are the recommendations from North American clinical practice guidelines on the use of clopidogrel for adult patients undergoing PCI?

4. What is the cost-effectiveness of clopidogrel (alone or in combination with ASA) compared with other antiplatelet regimens in the secondary prevention of vascular events (MI, stroke, or vascular death) in adult patients undergoing PCI with or without stent (bare-metal stent or drug-eluting stent) insertion?
   a) 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 clinical studies comparing antiplatelet agents and to identify guidelines on clopidogrel. Where feasible and appropriate, standard random effects meta-analyses and mixed treatment comparison meta-analyses were performed.

The results of a review of economic evaluations were used to inform our economic evaluation of clopidogrel plus ASA, ASA alone, and ticlopidine plus ASA for the prevention of vascular events in adult patients undergoing PCI.

Clinical Effectiveness
Sixteen publications reported findings from 14 randomized controlled trials (RCTs) (total of 11,317 patients). Based on the meta-analyses performed, no clinically important differences between interventions were found in vascular death, urgent target vessel revascularization, non-fatal MI, stroke, or major bleeds. The only difference that was observed occurred in the comparison of ASA plus ticlopidine to ASA alone for the outcome measure of all target vessel revascularizations. A meta-analysis of composite end point data was considered to be inappropriate, but a narrative review of findings from large RCTs suggests that the use of ASA plus clopidogrel reduced the rates of cardiovascular events compared with ASA alone. Moreover, the use of clopidogrel was associated with fewer blood disorders compared with ticlopidine.
One study that enrolled 17,232 patients with PCI was included to address a research question about ASA dose. The study suggested that there is no difference in efficacy or bleeding when higher or lower doses of ASA were used by patients with PCI that was treated with clopidogrel. Clinical studies (RCTs and observational studies) examining the optimal duration of clopidogrel therapy suggest that patients with stent placement benefit from the longer-term use of clopidogrel compared with short-term treatment. Studies indicated that the shorter time required for a reimbursement decision in a Canadian provincial drug reimbursement program for clopidogrel therapy is associated with better patient outcomes. One observational study implied the possibility of a clopidogrel rebound effect. We were unable to identify any study that could help answer research questions 1b, 1c, and 2c. Few studies examine the effectiveness of dipyridamole or ASA extended-release dipyridamole.

According to six evidence-based clinical practice guidelines, patients undergoing PCI are prescribed antiplatelet therapy for the secondary prevention of cardiovascular and cerebrovascular events. The use of ASA, clopidogrel, or ticlopidine is recommended. Clopidogrel is prescribed for patients who are ASA allergic or intolerant. Patients undergoing PCI with drug-eluting stent placement receive clopidogrel for at least 12 months. Those with bare-metal stent placement receive clopidogrel for one month. The use of clopidogrel is recommended over the use of ticlopidine for these patients. The recommendations were supported by various levels of evidence.

**Economic Review**

Of the seven economic evaluations that were relevant for inclusion in the literature review, none evaluated the cost-effectiveness of clopidogrel from the perspective of a Canadian provincial ministry of health.

**Economic Evaluation**

The economic evaluation found that for a population of patients undergoing PCI at age 60, one year of dual antiplatelet therapy with ticlopidine plus ASA, followed by lifetime ASA therapy, dominated clopidogrel plus ASA therapy because of lower costs and better expected health outcomes. When the costs that were associated with the use of ticlopidine plus ASA were added to the sensitivity analysis, this option was shown to be more effective and more costly than clopidogrel plus ASA. In the probabilistic analysis, the incremental cost-effectiveness ratio of ticlopidine plus ASA, compared with ASA alone, was greater than $50,000 per quality-adjusted life-year. The clinical effectiveness of ticlopidine was the most uncertain variable in the model based on the value of information analyses.

**Health Services Impact**

The results of the budget impact analysis indicated that money could be saved in moving away from the use of clopidogrel plus ASA for PCI patients. Given the safety concerns about the use of ticlopidine, the scenarios that were considered were based on small changes in prescribing patterns (5% to 20% of current clopidogrel plus ASA use). If the 5% to 20% reduction in clopidogrel plus ASA use corresponded to an increase in ticlopidine plus ASA use, then the annual net savings to a jurisdiction was predicted to be up to $140,000.
Conclusions

The estimates of relative effectiveness for clopidogrel and ticlopidine with ASA suggest that the optimal therapeutic choice is unclear. Clopidogrel and ticlopidine are at least as effective as ASA for the secondary prevention of vascular events, and could be more effective. Compared with ASA, clopidogrel, and especially ticlopidine, are associated with a higher risk of major bleeds. A review of composite end point data (such as death, MI, stroke, revascularization, and major bleeds) suggests that the use of ASA plus clopidogrel reduced the rates of cardiovascular events compared with ASA alone. The use of clopidogrel was associated with fewer blood disorders compared with ticlopidine in a review of the composite end points data.

Our economic evaluation showed that for patients undergoing PCI at age 60, one year of dual antiplatelet therapy with ticlopidine and ASA, followed by lifetime ASA, may be a more cost-effective treatment (compared with clopidogrel plus ASA, and ASA monotherapy) for the secondary prevention of vascular events. There is hesitancy to prescribe ticlopidine to these patients because of the potentially fatal hematological disorders that are associated with its use. The dominance of this combination is lost when the costs of blood monitoring and occurrence of thrombotic thrombocytopenic purpura are factored into the model. Despite the economic attractiveness of this option, more clinical investigation of this drug is unlikely.

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