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Clopidogrel versus Other Antiplatelet Agents for Secondary Prevention of Vascular Events in Adults with Acute Coronary Syndrome or Peripheral Vascular Disease: Clinical and Cost-Effectiveness Analyses

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Introduction

Cardiovascular disease (CVD) — which includes coronary disease, cerebrovascular disease, and peripheral vascular disease (PVD) — is a cause of illness, disability, and death in Canada, and the associated health care costs are high.[1] The prevalence of CVD in Canada is likely to increase as the population ages and is likely to further burden the health care system.

Atherosclerosis is a common cause of CVD. Artherosclerosis results from the deposition of lipids and platelets, and the accumulation of inflammatory cells, in the arterial wall, causing the formation of atherosclerotic plaques.[2,3] It is believed that antiplatelet therapy prevents the occurrence of ischemic events through the inhibition of platelet thrombus formation and protects distal tissues by maintaining blood flow.[4,5]

Clopidogrel is an antiplatelet agent used for the secondary prevention of atherothrombotic events (myocardial infarction [MI], stroke, and vascular death) in patients with atherosclerosis documented with stroke, MI, or established peripheral arterial disease (PAD).[6] The daily cost of treatment with clopidogrel is higher than that of some alternatives, and the number of reimbursement requests for clopidogrel being submitted to Canadian publicly funded drug plans is increasing. Given limited health care resources, an assessment of the clinical effectiveness and cost-effectiveness of clopidogrel compared with alternatives is needed to inform policy-makers about the sustainability of current reimbursement policies.

Objective

The objective 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 PVD.

This objective will be accomplished by addressing the following research questions:

- 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 (MI, stroke, or vascular death) in adult patients with ACS (presenting as unstable angina [UA] or MI) or with PVD?
  - What is the difference in the clinical effectiveness of dual therapy with clopidogrel and ASA based on the ASA dose?
  - 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)?
    - 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)?
- What is the optimal duration of treatment with clopidogrel for the secondary prevention of vascular events in adult patients with ACS or with PVD?
    - 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?
    - Is treatment duration with clopidogrel different depending on the type of MI (non-ST elevation MI [NSTEMI] versus ST elevation MI [STEMI])?
    - Are there patient characteristics that indicate clopidogrel therapy should be continued indefinitely?
    - Is there a rebound effect upon withdrawal of clopidogrel therapy?
- What are the recommendations from North American clinical practice guidelines on the use of clopidogrel for adult patients with ACS or with PVD?
- 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 undertaken 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 then conducted 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.

Results

Clinical Effectiveness

Three randomized controlled trials[7-9] 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[7]) involved patients with ACS; the other two (the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events [CAPRIE] trial[8] and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA] trial[9]) 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 a reduction in 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 North American clinical practice guidelines met the inclusion criteria for this report.[10-23] The guidelines recommend a combination of clopidogrel and ASA for patients with ACS. They recommend clopidogrel alone for patients with ACS and ASA intolerance or allergy, and patients with PVD and ASA intolerance or allergy.

Economic Review

The literature search found 19 studies to be relevant for inclusion in the economic systematic review. Two studies in a Canadian context[24,25] 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.

Limitations

This review has limitations. Not all trial reports documented data on all the outcomes of interest. This may introduce bias, because it has been shown that statistically significant results are more likely to be reported than statistically non-significant results.[26] For this review, data from the ACS and PVD groups of the CAPRIE trial and the PVD group of the CHARISMA trial were used, which were designed with a mixed population. Therefore, the groups were not randomized in these two RCTs. This needs to be considered when viewing the results of subgroup analyses.

There was variation in the way that the investigators reported data on bleeding, and the definitions also varied. It was not always clear from the reports how measurements were made and assessed.

The economic model has limitations stemming from gaps in available data, including:

- the fact that costs for fatal stroke and MI were obtained from patients with diabetes,

potentially causing the cost for vascular death to be overestimated
- a lack of a RR for clopidogrel for non-vascular death, non-fatal stroke, and non-fatal MI for PVD (requiring assumptions, such as equating RR non-fatal stroke to RR any stroke)
- a lack of Canadian-specific data for the development of transition probabilities
- a lack of Canadian estimates for utility in the first year and subsequent years for a stroke or MI.

The budget impact analyses was based on a claim-based approach[27] rather than a population-based approach. Therefore, budget impact scenarios considering a small percentage of change in the number of claims cannot be interpreted as a per-patient change in utilization. Consequently, the results should be interpreted with caution, particularly for a drug plan such as that in Prince Edward Island, where the number of claims was reported to be low.

Another potential limitation is that the market share of antiplatelet drugs for ACS and PVD was estimated based on a survey of representative Canadian office-based physicians who were asked to record drugs recommended to a patient for a specified diagnosis, which does not necessarily reflect the actual quantity of drugs dispensed (non-compliance). If the non-compliance rates differ across indications, this may lead to biases in the market share estimates. Moreover, each diagnosis was recorded as ICD-9 codes that were used to identify the use of clopidogrel and ASA for ACS, PVD, and other indications. This implies that the accuracy of the market share data provided is subject to the validity of ICD-9 coding.[28]

The budget impact analyses were based on the assumption of the proportional change in the distribution of drug use among antiplatelet therapies, and population dynamics were not considered, such as the effects of an aging population or the potential changes in the total number of antiplatelet users, or both.

The patient selection criteria for the trials were restrictive. As a result, it may not be possible to generalize the results to all patients with ACS or PVD. The settings in the trials are more controlled than those in general practice; thus, the generalizability is limited.

Because the budget impact analyses covers the analyses of nine participating drug plans, the results are generalizable to these drug plans. However, the lack of information from other jurisdictions prevented the authors of this report from providing results at a national level.

None of the trials compared the effect of different antiplatelet agents on quality of life. No studies determined the optimal duration of treatment using clopidogrel for the secondary prevention of vascular events in adult patients with ACS or PVD. Studies to determine if there are certain patient characteristics for which one antiplatelet regimen is preferred compared with another are lacking. More research on patients with ACS or PVD is needed to answer many of the research questions.

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 there was 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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