Objective

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.

- 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?
  - Is there a 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 and combination therapy with ASA and a proton pump inhibitor (PPI)?

- 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?

What is the optimal duration of treatment with clopidogrel for the secondary prevention of vascular events in adult patients undergoing PCI?

- 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?
- Is treatment duration with clopidogrel different depending on:
  - the type of intracoronary stent inserted?
  - the type of MI?
- Are there patient characteristics that indicate clopidogrel therapy should be continued indefinitely?
- Is there a rebound effect after withdrawal of clopidogrel therapy?

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

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?

- Is there a difference in the cost-effectiveness of dual therapy with clopidogrel and ASA based on the ASA dose?

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**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 the 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\(^3\)\(^-\)\(^8\) reported findings from 14 randomized controlled trials (RCTs) with a 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\(^9\) 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 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. The authors were unable to identify any study that could help answer the third (plus fourth and fifth), sixth, and thirteenth research question. 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.

**Limitations**

This review has limitations. Not all trial reports documented data on all of the outcomes of interest. This may introduce bias, because statistically significant results are more likely to be reported than non-statistically significant results. Not all RCTs could be included in the analyses for all outcomes, resulting in reduced power. A
handful of clinical trials were used in quantitative data analysis, and the event rates that were reported for some clinical outcomes (such as stroke, major bleeds, and some adverse events) were low. The related computational issues may limit the analyses, and the results are interpreted with caution.

There was variation in the way investigators reported data on bleeding outcomes and revascularization. The definitions also varied, and it was difficult to group the data.

Because of the inadequate evidence found from RCTs to answer some of the research questions, observational studies with large sample sizes and longer follow-ups were considered. Many of these observational studies were retrospective, and non-random allocation of treatment and potential confounding by indication led to concerns about the reliability of results.

Although our review suggests that ticlopidine is more cost-effective than clopidogrel in the secondary prevention of cardiovascular and cerebrovascular events, many clinical trials have reported undesirable effects in using ticlopidine. In our review, the data did not conclusively show an unfavourable effect that was associated with ticlopidine, and a more extensive review of observational studies may be needed for the assessment of adverse events related to this drug.

The patient selection criteria for the included trials were restrictive. As a result, it may not be possible to generalize the results to all patients undergoing PCI who receive antiplatelet therapy. The setting in the trials was more controlled than the settings in general practice in that patients who did not meet certain inclusion criteria (age, severity of disease, medical history, comorbidities, and compliance) were excluded. Therefore, the generalizability is limited.

Direct comparisons between antiplatelet agents were unavailable for all outcomes and for all pairs of interventions. None of the trials compared quality of life between antiplatelet agents. No reliable data were available to examine the effect of study drugs based on various ASA doses. No available studies assessed the effect of study drugs in patients with ASA intolerance who underwent PCI. As well, the authors did not find any study to assess the benefits and harms of using clopidogrel for patients who are experiencing restenosis, but who are not candidates for re-stenting. Studies to determine if there are certain patient characteristics for which one antiplatelet regimen is preferred compared with another are lacking.

**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 points data (such as death, MI, stroke, revascularization, and major bleeds) suggest 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.

The 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.

References


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