The Technology
Long term use of antiplatelet drugs results in a relative-risk reduction of ischemic stroke (IS), myocardial infarction (MI) and vascular death.\(^1,2\) Clopidogrel biphosphate, a thienopyridine antiplatelet agent structurally similar to ticlopidine, produces irreversible platelet inhibition.\(^3,4\) It produces its antiplatelet effect probably by modifying adenosine diphosphate (ADP) binding sites on platelets. Unlike ticlopidine, clopidogrel seems to carry a minimal or no risk of neutropenia.

Regulatory Status
Clopidogrel has recently been approved in Canada for the secondary prevention of vascular ischemic events (MI, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease.\(^4\)

Patient Group
Patients with atherothrombotic diseases such as transient ischaemic attacks or mild stroke, moderate or severe stroke, unstable angina, acute and remote MI and atherosclerotic peripheral arterial disease (PAD) may benefit from antiplatelet therapy with clopidogrel.\(^1,2,3,4\) Currently there is no available information on the prevalence of the above cardiovascular diseases (CVDs) in the Canadian population. According to a recent Health Canada report, CVDs are the leading cause of death in Canada.\(^4\) In 1995 ischemic heart disease, stroke and other CVDs were responsible for 21%, 7% and 9%, respectively, of the total deaths reported in Canada.\(^5\)

Current Treatments
ASA is the most widely studied and used antiplatelet agent. ASA, as well as ticlopidine, dipyridamole and sulfinpyrazone, are available in Canada for the treatment and prevention of cardiovascular and/or cerebrovascular diseases.\(^1,2\) Each of these agents has limitations in terms of their safety or efficacy. This includes (a) ASA: severe bleeding (gastrointestinal and cerebrovascular); (b) Ticlopidine: 1 to 2% incidence of reversible neutropenia and a high incidence of diarrhea (20-22%) and rash (12%-15%); (c) Dipyridamole and Sulfipyrazone: lack of sufficient evidence of clinical efficacy.\(^8,9\)

Potential Cost
Clopidogrel (PlavixR) 75 mg tablets are available in cartons containing a blister card of 28 tablets.\(^4\) Based on the information provided by the hospitals and community pharmacies in the Ottawa area, the cost of a clopidogrel tablet varies from $2.47 to $3.21 per tablet. The recommended dose for clopidogrel is 75 mg (1 tablet) once daily.
Clopidogrel has a better safety profile than ticlopidine. Unlike ticlopidine, clopidogrel is not associated with neutropenia and thrombocytopenia and does not require routine hematological monitoring. Due to potentially serious side effect of ticlopidine, its use has been limited to patients who are aspirin intolerant and in some instances, to patients in whom aspirin therapy has failed.

Both ticlopidine and clopidogrel are more expensive than aspirin and do not offer any significant advantage over it as first line therapy. Clopidogrel will likely compete for the ticlopidine market. According to IMS data, the annual ticlopidine sales exceeded $22 million in 1998, which is equivalent to approximately 20 million tablets ($1.09/250 mg tablet). Recently, a generic ticlopidine tablet has been introduced at 75% of the cost of the brand name drug. Based on the lowest available cost for clopidogrel ($2.47/day) the cost of this new therapy would increase expenditures for this class of drugs by $3 million annually. Compared to the lowest generic price of ticlopidine available, the annual cost of therapy would be approximately $10 million more for clopidogrel. Finally, increasing use of ticlopidine in Canada (annual consumption has risen greater than 10% annually) and possible increased indications may result in higher anticipated costs.

Clopidogrel was found to be effective in preventing coronary artery stent thrombosis in animal studies and this effect of clopidogrel was substantially enhanced by the addition of aspirin. This effect of combining two antithrombotic agents to prevent stent thrombosis has been demonstrated clinically for ticlopidine-aspirin combination.

Numerous oral glycoprotein IIb/IIIa inhibitors are being studied for their efficacy in occlusive vascular diseases. The most significant adverse effect associated with glycoprotein IIb/IIIa inhibitors is an increased risk of major bleeding complications.

In a randomized, double-blind, multinational study known as CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), the efficacy and safety of once daily administration of clopidogrel, 75 mg, and aspirin, 325 mg, were compared. Approximately 20,000 patients with atherosclerotic vascular disease manifested as either recent IS, recent MI, or symptomatic PAD were randomized to one of the two drugs. During the follow up period of 1 to 3 years (mean 1.9 years), clopidogrel was significantly more effective than aspirin in reducing the annual combined rate of MI, IS or vascular death (clopidogrel, 5.32 % vs. aspirin, 5.83%; p=0.043). However, the annual rate of mortality was not significantly different in the two treatment groups (clopidogrel, 3.05 % vs aspirin, 3.11%; p=0.71). The safety of clopidogrel was comparable to aspirin. In patients treated with clopidogrel severe rash (6% vs. aspirin, 5%) and diarrhea (4% vs. aspirin, 3%) were more common. In the group treated with aspirin dyspepsia (18% vs. clopidogrel,15%) and gastrointestinal hemorrhage (3% vs. clopidogrel, 2%) were more common. Like ASA, the incidence of severe neutropenia with clopidogrel was negligible (clopidogrel, 0.10% vs. aspirin 0.17%).

Clopidogrel is well tolerated and a safe drug. A major side effect of clopidogrel, like other antithrombotic agents, is bleeding. It should be used with caution in patients with an increased risk for bleeding and trauma. In the CAPRIE trial, the percent of patients who permanently discontinued the drug due to a bleeding disorder in the clopidogrel group was not significantly different from the aspirin group (1.20% vs. 1.37%). Other side effects of clopidogrel including gastrointestinal upset, bleeding, diarrhea and rash are generally mild and transient.
Does clopidogrel replace current therapy?

ASA: Clopidogrel has a marginal but statistically significant advantage over medium dose aspirin in terms of combined relative risk reduction (RRR) of IS, MI and death (RRR 8.7%, 95% CI 0.3% to 16.5%, P=0.043). This represents an absolute risk reduction of 0.51%. In subgroup analysis, the only significant difference in RRR of IS, MI and death with clopidogrel was observed in patients with PAD (RRR 23.8%, 95% CI 8.9% to 36.2%, P=0.0028). (Table 1) In terms of safety, clopidogrel does not have any advantage over aspirin.

One year of therapy with clopidogrel, 75 mg daily, costs $901-1172 ($2.47-3.21/75 mg tab). The annual drug cost for medium dose aspirin 325 mg/day ranges from $2.15 to $5.37 ($0.0059 to $0.0147/325 mg tab). Taking into consideration small differences in efficacy, similar discontinuation rates from clinical trials and substantial differences in cost, ASA would continue to be the first choice for the secondary prevention of stroke, MI and other vascular events.

Ticlopidine: Ticlopidine is only approved for the secondary prevention of IS, although evidence of its benefit in other situations (e.g. prevention of stent thrombosis in combination with ASA) has been demonstrated. No direct study comparing clopidogrel and ticlopidine is available. Further, the study populations where these drugs have been evaluated are sufficiently different that comparing relative or absolute risk reductions is difficult. Ticlopidine 500 mg/day was found to be slightly more efficacious than ASA 1300 mg/day in the secondary prevention of stroke in high risk patients (40 year of age, n=3069) in the Ticlopidine Aspirin Stroke Study (TASS). The three year event rate of nonfatal stroke or death from any cause was 17% for ticlopidine and 19% for aspirin - a 12% relative risk reduction.

Based on the available evidence clopidogrel has a better safety profile than ticlopidine. Clopidogrel, unlike ticlopidine, does not cause neutropenia. In TASS, neutropenia (absolute neutrophil count <1200 cells/mm$^3$) occurred in 2.4% and severe neutropenia (absolute neutrophil counts <450 cells/mm$^3$) occurred in 0.9% of patients receiving ticlopidine compared with none in the patients receiving aspirin. The risk of neutropenia from ticlopidine is generally within the first 3 months of therapy and is reversible upon discontinuation of therapy. Rare but potentially fatal, thrombocytopenia has also been reported with ticlopidine. However, until clopidogrel has been used in a sufficiently large population it is too early to determine whether any advantage exists for clopidogrel in this regard.

Due to these hematological side effects resulting from ticlopidine, all patients should have a white blood count with a differential and platelet count

### Table 1: Results of the CAPRIE Trial

<table>
<thead>
<tr>
<th>Patients with Disease Condition</th>
<th>% Risk Clopidogrel vs. Aspirin</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction (%)</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Arterial Disease</td>
<td>3.71% vs. 4.86%</td>
<td>23.67%</td>
<td>1.15%</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>p=0.0028</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>7.15% vs. 7.71%</td>
<td>7.26%</td>
<td>0.56%</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5.03% vs. 4.84%</td>
<td>-3.92%</td>
<td>-0.19%</td>
<td>526</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Population</td>
<td>5.32% vs. 5.83%</td>
<td>8.74%</td>
<td>0.51%</td>
<td>196</td>
</tr>
<tr>
<td></td>
<td>p=0.043</td>
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performed every two weeks for the first three months of the treatment. Incidences of severe rash and diarrhea are also less with clopidogrel than those reported with ticlopidine in different studies but this potential advantage would require head-to-head studies to be proven. Clopidogrel is administered on a once daily dosing schedule with or without food, whereas ticlopidine is administered on a twice daily dosing schedule with food. Annual treatment costs for ticlopidine 250 mg twice daily ranges from $796-1002 (1.09-1.37/250 mg tab) for the brand name drug and $555-598 (0.76-0.82/250 mg tab) for the generic version. Based on the information from four Ottawa area clinical laboratories the cost of hematological testing every 2 weeks for 12 weeks is $90-112 (14.99-18.61/test). Overall the first year cost for generic ticlopidine plus hematological monitoring is less than the cost of treatment with clopidogrel. The most cost-effective option is reserving the use of clopidogrel for patients developing neutropenia from ticlopidine. Until head to head trials are conducted it is difficult to determine whether any other advantages (reduced incidence of adverse effects) would have an impact on cost and/or quality of life.

This brief was prepared by Vijay Shukla.

References