Update on Formulary Use of Clopidogrel in Ontario: Revised ODB Code for Limited Use

by Sol Stern, BSc, MSc, MD, MCFP

Introduction

Effective May 20, 2009, the Ontario Ministry of Health and Long-term Care has updated its Ontario Drug Benefit (ODB) program to include formulary coverage for three important uses of clopidogrel (Plavix®). The update to Edition 41 of the ODB formulary adds to the existing coverage for clopidogrel use and should help clinicians employ this treatment approach in the wide range of patients for whom it is indicated.

The table on the right of this column presents the limited-use (LU) coding for clopidogrel under the updated ODB index. LU codes 375 and 376 have been expanded beyond the indications for which clopidogrel was already covered under previous editions of the ODB index, while LU code 411 adds three new clinical criteria for clopidogrel coverage.

LU code 375, which previously applied to patients immediately post hospitalization for a non-ST-elevation acute coronary syndrome (ACS) and had an LU authorization period of one year, now covers patients immediately post hospitalization for any ACS (any myocardial infarction or unstable angina), in combination with aspirin, and has an indefinite LU authorization period. LU code 376 continues to cover patients immediately pre- or post-percutaneous coronary intervention (PCI), with therapy initated up to 10 days prior to the procedure, but now also has an indefinite LU authorization period (expanded from one year).

The clinical criteria included under the new LU code 411 are established, evidence-based indications for clopidogrel. These include: patients who suffer a cerebrovascular event while being treated with aspirin or the aspirin + dipyridamole combination (Aggrenox®); patients with ongoing severe symptomatic peripheral arterial disease (PAD) following a vascular event while taking aspirin; and patients in whom antiplatelet therapy is required with a documented severe allergy to aspirin.

It should be noted that, for patients new to clopidogrel therapy, the prescription for clopidogrel should include a corresponding LU code whenever applicable. Patients who have received approval for clopidogrel coverage through the Exceptional Access Program (EAP) prior to May 20, 2009 will maintain this approval indefinitely and will not require provision of an LU code on future prescriptions. Indications for use in patients who do not meet the above LU criteria require a patient-specific funding request submitted through the EAP. More information about the expanded LU coding for clopidogrel can be found in the "Questions and Answers" document on the Ministry website (available at: *www.health.gov.on.ca/english/providers/program/drugs/opdp_eo/notices/notices_docs/plavix_faq.pdf*).

This piece presents two brief case studies aimed at helping physicians incorporate the new ODB formulary coverage into their practices. Each represents one of the clinical situations outlined under the new LU code 411.

Clopidogrel Limited Use Codes: Ontario Drug Benefit Formulary Index (May 20, 2009 Update)

Expanded: Reason for Use Code 375

- For patients immediately post-hospitalization for acute coronary syndrome (ACS; defined as any myocardial infarction or unstable angina), in combination with ASA.
- Limited-use authorization period: indefinite.

Expanded: Reason for Use Code 376

- For patients immediately pre- or post-percutaneous coronary intervention (PCI; therapy may be initiated up to 10 days prior to PCI).
- Limited-use authorization period: indefinite.

NEW: Reason for Use Code 411

- For patients who experience a stroke or transient ischemic attack (TIA) while taking Aggrenox® (dipyridamole and aspirin) or ASA alone; or
- For patients experiencing ongoing severe symptomatic peripheral vascular disease (*i.e.,* with ankle-brachial index < 0.5) after a vascular event while taking ASA (ASA should not be used concomitantly); or
- For patients requiring ASA with documented severe allergy to ASA, such as anaphylactic reaction or bronchospasm; gastrointestinal events, including GI bleeds, are excluded.
- Limited-use authorization period: indefinite.

Sol Stern, BSc, MSc, MD, MCFP
Chairman of Palliative Care,
Halton Healthcare Services

Case Study 1: Mrs. J

Mrs. J is a 66-year-old retired woman. Her husband passed away three years ago, and she has two adult children.

Medical history. Mrs. J is a lifetime non-smoker and rarely consumes alcohol. She has no documented allergies to medications. She has a 15-year history of type 2 diabetes, hypertension and dyslipidemia, and a 10-year history of widespread osteoarthritis (OA).

For her hyperglycemia, Mrs. J is taking metformin 500 mg twice daily. Her antihypertensive regimen consists of irbesartan 300 mg and hydrochlorothiazide 12.5 mg once daily. She is also taking atorvastatin 20 mg once daily for her dyslipidemia. Over the years, each of these risk factors has been well controlled. Mrs. J is also taking aspirin 81 mg once daily for cardiovascular risk reduction.

For her OA-related pain, Mrs. J takes acetaminophen 325 mg as needed. She reports that she has been averaging four to five tablets daily over the past year.

Presentation. Mrs. J presents describing a "spell" one week ago during which she had temporary difficulty with speech, muscle weakness in the left side of her face and transient confusion. She says that the episode lasted approximately one hour and that she has felt perfectly normal since. She wonders if what she experienced was a "small stroke." When questioned about whether or not she has had any sustained muscle weakness or difficulty with ambulation since the episode, she says she has not.

[Mrs. J] is at high risk for a subsequent atherothrombotic event (either another cerebrovascular event or an event in another vascular bed) and requires optimized medical management.

Physical examination. Mrs. J is 168 cm (5'6") tall and weighs 60 kg (132 lbs), for a body mass index (BMI) of 21.3 kg/m^2 (normal range 18.0 to 24.9 kg/m^2). Her current blood pressure (BP) is 128/78 mmHg (target < 130/80 mmHg). The examination reveals no abnormal heart sounds or carotid bruits. Her peripheral pulses are palpable. Her chest is clear, and neurologic and ophthalmologic examinations are normal as well.

Investigations. Laboratory work shows that Mrs. J's lipids and blood glucose (A1C) are at target levels according to current national guideline recommendations. Hemoglobin, creatinine and liver-function tests are also normal. An ECG and a 24-hour Holter monitor are ordered, and both are unremarkable. A CT scan of the head, however, shows multiple small lacunar infarcts. Carotid Doppler shows plaque formation on both sides, but with no significant stenosis.

Discussion of risk factors and diagnosis. Mrs. J's description of her recent symptoms, together with her significant cardiovascular risk factors (longstanding diabetes, hypertension and dyslipidemia), strongly suggests a recent transient ischemic attack (TIA). The evidence from the CT scan shows that this occurred on a background of lacunar infarcts.

Management. Because of the findings of the carotid Doppler, Mrs. J is not a candidate for surgery. She is motivated and compliant with treatment. Her major cardiovascular risk factors (*i.e.*, lipids, BP and hyperglycemia) are currently controlled pharmacologically, and she is already receiving antiplatelet therapy. Despite all of this, she has nevertheless developed cerebrovascular disease and experienced a significant neurologic atherothrombotic event. She is at high risk for a subsequent atherothrombotic event (either another cerebrovascular event or an event in another vascular bed) and requires optimized medical management.

In the CAPRIE trial,[1] clopidogrel 75 mg daily was shown to be superior to aspirin 325 mg daily for overall secondary cardiovascular prevention (relative risk reduction 8.7%, $p = 0.043$). The use of this agent should therefore be considered to provide maximal protection against future events. As well, the results of the PROFESS study[2] should be considered. In this study of secondary stroke prevention, there was no difference observed between patients randomized to receive aspirin + dipyridamole (25 mg and 200 mg, respectively, twice daily) and those randomized to receive clopidogrel 75 mg daily in terms of recurrent stroke (the study's primary endpoint) or in terms of the composite secondary endpoint of stroke, MI and death from vascular causes. Aspirin + dipyridamole therapy was associated with a higher risk of major

hemorrhagic events vs. clopidogrel (HR 1.15, 95% CI 1.00-1.32), including intracranial hemorrhage (HR 1.42, 95% CI 1.11-1.83, $p = 0.006$).

For this clinical situation, clopidogrel should replace the aspirin in the medical regimen (rather than being added as part of a combination approach). This recommendation is based on the findings of the MATCH study,[3] which found that there was no significant additional cardiovascular risk reduction associated with dual clopidogrel-aspirin therapy among patients with recent cerebrovascular events and that the combination was associated with significantly higher bleeding risk compared to clopidogrel alone.

Mrs. J's physician therefore opted to replace her current antiplatelet therapy (aspirin 81 mg daily) with clopidogrel 75 mg daily.

Application of limited use criteria in Ontario. The revised limited use (LU) criteria for clopidogrel in Ontario are outlined on the first page of this piece. In this case, the relevant section of the new LU code 411 is "for patients who experience a stroke or TIA while taking Aggrenox® (dipyridamole plus ASA) or ASA alone."

References:

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348(9038):1329-39.
2. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008; 359(12):1238-51.
3. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004; 364(9431):331-7.

Case Study 2: Mr. N

Mr. N is a 70-year-old retired airline pilot. He is married and has three adult children. He presents for routine follow-up of his chronic conditions.

Medical history. Mr. N quit smoking two years ago. However, throughout his adult life, he was a regular smoker, accumulating approximately 30 pack-years. He regularly consumes alcohol, usually one or two drinks every day. Mr. N has a 15-year history of hypertension and dyslipidemia.

His hypertension has been controlled with a combination of ramipril 10 mg, hydrochlorothiazide 12.5 mg and amlodipine 5 mg, each taken once daily. His dyslipidemia is currently treated and controlled with rosuvastatin 10 mg once daily. He has a documented allergy to aspirin, having experienced drug-related bronchospasm with this agent 10 years ago.

Apart from his chronic conditions and surgery for nasal polyps 10 years ago, Mr. N's medical history is otherwise unremarkable.

Presentation. Mr. N describes calf pain in both legs that he says has developed gradually over the past two to three months. He has noticed that it worsens when he walks and improves with rest. When questioned, he does not recall any numbness or tingling in his legs, nor has he experienced any chest pains or palpitations. However, he does say that his feet feel cold more often than usual and that this has led him to worry that he has problems with circulation in his legs.

Physical examination. Mr. N is 180 cm (5'11") tall and weighs 80 kg (176 lbs), which gives a BMI of 24.7 kg/m^2 (normal range 18 to 24.9 kg/m^2). His BP is currently 136/84 mmHg (target < 140/90 mmHg). Heart sounds are normal and there are no carotid bruits detected, but peripheral pulses are diminished in both legs. Neurologic examination is normal, including normal sensations in both legs. His chest is clear. The ophthalmologic examination is unremarkable.

[Mr. N] has a documented allergy to aspirin, having experienced a drug-related bronchospasm with this agent 10 years ago.

Investigations. Laboratory work ordered for this visit show that Mr. N's lipids are at target and that hemoglobin, creatinine and liver enzymes are normal. A recent ECG was conducted; it was also normal. In the office, an ankle-brachial index (ABI, the ratio of the BP in the lower legs to the BP in the arm) of 0.8 is obtained using a hand-held Doppler device.

Discussion of risk factors and diagnosis. This patient is an older man with long-standing hypertension and dyslipidemia. Furthermore, he has a significant smoking history. Each of these factors significantly increases his risk for vascular disease and associated events (*e.g.*, myocardial infarction, stroke).

Mr. N's symptoms (calf pain, diminished peripheral pulses, cold in the extremities) are consistent with peripheral arterial disease (PAD). This led the physician to assess Mr. N's ABI. The ABI of 0.8 confirmed the diagnosis of PAD (normal value being 0.9 to 1.0). The development of PAD, as well as his background risk factors, not only put Mr. N at risk for continued or worsening symptomatic PAD, but also for atherothrombotic disease and its complications in other vascular beds (*e.g.*, coronary and cerebrovascular events).

Management. Mr. N's BP and lipids are currently controlled to target levels based on current national consensus guidelines. Furthermore, the use of an angiotensin-converting enzyme (ACE) inhibitor (ramipril in this case) has been associated with overall cardiovascular risk reduction independent of BP lowering.

However, Mr. N is still not optimally treated. Given his risk factors and symptomatic PAD, he would also benefit from the addition of an antiplatelet agent to his risk-reducing medical regimen. The Antithrombotic Trialists Collaboration concluded that, among high-risk groups, the use of antiplatelet therapy reduces the odds of major cardiovascular events by 22%.[1] For the subgroup with PAD, the odds reduction was 23%. Because Mr. N has a documented aspirin allergy, this agent is not an option.

Clopidogrel has demonstrated efficacy in reducing the risk of major cardiovascular events in patients with documented atherosclerosis (history of myocardial infarction, stroke or symptomatic PAD). In the CAPRIE study,[2] more than 19,000 patients with atherosclerosis were randomized to clopidogrel 75 mg once daily or aspirin 325 mg once daily. Over a mean follow-up of 1.91 years, there was a statistically significant (p = 0.043) relative risk reduction (RRR) of 8.7% in favor of clopidogrel for the composite outcome of ischemic stroke, myocardial infarction or vascular death. The benefit of clopidogrel was particularly evident in the large subgroup of CAPRIE patients who had documented PAD at baseline (RRR 23.8%, p = 0.0028). Mr. N's physician therefore opts to add clopidogrel 75 mg daily to his treatment regimen.

Application of limited use criteria in Ontario. The revised limited use (LU) criteria for clopidogrel in Ontario are outlined on the first page of this piece. In this case, the relevant section of the new LU code 411 is "for patients requiring ASA with documented severe allergy to ASA, such as anaphylactic reaction or bronchospasm." Mr. N's risk factors and documented PAD are such that he requires antiplatelet therapy and he has a documented allergy to aspirin (bronchospasm).

References:

1. Antithrombotic Trialists' Collaboration. Collaborative metaanalysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71-86.
2. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348(9038):1329-39.