

Dual antiplatelet therapy for secondary stroke prevention

Use of clopidogrel and acetylsalicylic acid after noncardioembolic ischemic stroke

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Approximately 62 000 Canadians suffer a stroke or transient ischemic attack (TIA) each year,¹ and despite a reduction in mortality and hospitalization owing to improved acute management and implementation of preventive measures, the rate of stroke is on the rise owing to the aging population.² The number of incident strokes is expected to double over the next 4 decades, with the largest increase in those aged 75 or older.³ For years, antiplatelet agents, such as acetylsalicylic acid (ASA), clopidogrel, or dipyridamole with ASA, have played a key role in secondary stroke prevention, as these medications reduce the risk of stroke, myocardial infarction, and death by 22%.⁴ Studies evaluating dual antiplatelet therapy (DAPT) for noncardioembolic ischemic stroke have been conducted to assess whether taking clopidogrel with ASA provides greater benefit than taking ASA or clopidogrel alone.⁵⁻⁹ The initial studies failed to show a benefit⁶⁻⁸; however, new data have emerged suggesting that DAPT might provide additional risk reduction, although there are some concerns regarding the generalizability of the evidence.⁵

The objective of this article is to review the current literature and guidelines surrounding the use of DAPT after noncardioembolic ischemic stroke, and to address questions such as when should DAPT be used, what is the optimal duration of therapy, which agent should be continued when stepping down to single antiplatelet therapy (SAPT), and who should receive gastroprotection. Practical tips to facilitate the intended duration of therapy are also shared.

Case description

Mrs K.M., an 84-year-old white woman who is known to you, comes in today for a refill of pantoprazole, which was started 4 weeks ago during a hospital admission for a stroke. The discharge summary in her chart indicates that she presented to the emergency department with acute onset of right-sided weakness and speech impairment. The computed tomography scan of her brain confirmed an ischemic stroke in the left middle cerebral artery and ruled out a hemorrhagic process. Further investigations included the following: Holter monitoring, which showed normal sinus rhythm; an echocardiogram, which indicated preserved left ventricular function with an ejection fraction of 60%; and a carotid ultrasound, which

demonstrated no hemodynamically significant stenosis. Laboratory test results revealed normal complete blood count, renal function, and blood glucose levels. However, her lipid panel findings were elevated (total cholesterol of 6.9 mmol/L, low-density lipoprotein level of 3.8 mmol/L, high-density lipoprotein level of 1.1 mmol/L, and triglyceride level of 4.2 mmol/L). Her body mass index is 28 kg/m². Before discharge, her blood pressure was above her target of 150/90 mm Hg. Today, her blood pressure is 146/84 mm Hg.

Her past medical history includes a TIA 3 years ago, a nonsteroidal anti-inflammatory drug-induced gastric ulcer treated with an 8-week course of omeprazole 5 years ago, poorly controlled isolated systolic hypertension, hypercholesterolemia, and osteoarthritis. There is no known history of coronary artery disease. Before admission, she was taking the following medications: 81 mg of ASA daily, 10 mg of atorvastatin at bedtime, 25 mg of hydrochlorothiazide daily, 1300 mg of extended-release acetaminophen twice daily, and 500 mg of calcium carbonate chewable antacid tablets as needed (approximately 1 to 2 times per month for symptoms of heartburn associated with spicy foods). Within 24 hours of being hospitalized, 75 mg of clopidogrel daily and 40 mg of pantoprazole daily were started. Hydrochlorothiazide was discontinued and replaced with the combination of 4 mg of perindopril and 1.25 mg of indapamide daily, and her dose of atorvastatin was increased to 20 mg at bedtime. Her other medications remained the same.

Mrs K.M. did not suffer any serious deficits after her stroke and continues to live independently in a seniors' complex with her husband. She receives support from her 2 adult children who live in the city and help with transportation and the occasional meal. She uses a dosette to manage her medications and her adherence is reliable. She has no history of smoking and only occasionally has an alcoholic beverage with supper.

You note on the discharge summary that pantoprazole and DAPT with clopidogrel plus ASA were prescribed for 21 days. Thereafter, Mrs K.M. was to continue taking clopidogrel and stop using ASA. However, Mrs K.M. is still taking ASA because she assumed she was supposed to. She questions whether there is any harm in continuing to take ASA as it is only an over-the-counter medication and she is fearful of having another stroke.

Bringing evidence to practice

The 2014 Canadian Stroke Best Practice Recommendations (CSBPR) for secondary stroke prevention recommend antiplatelet therapy for all patients with ischemic stroke or TIA, unless there is an indication for anticoagulation (eg, atrial fibrillation) (level A evidence).¹ Acetylsalicylic acid, dipyridamole with ASA, or clopidogrel are all appropriate options for long-term secondary prevention (level A evidence).¹ Antiplatelet therapy should be tailored to the individual based on the risk of recurrent stroke and bleeding, as well as medication cost, coverage, and adherence.¹

As for recurrent strokes, both the CSBPR and the 2014 American Heart Association–American Stroke Association (AHA-ASA) guidelines⁴ state there is insufficient evidence to guide medication selection when a patient has a subsequent stroke while taking an antiplatelet agent. Both guidelines also note that short courses of DAPT, with clopidogrel plus ASA, can be used for secondary stroke prevention.^{1,4} If used, clopidogrel with ASA should be started within 24 hours of the stroke or TIA, and it can be continued for up to 21 days.^{1,4} (CSBPR: level A evidence; AHA-ASA: class IIb, level B evidence), based on the CHANCE (Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events) study.⁵ The CSBPR adds that clopidogrel with ASA should not be used routinely in all patients (level C evidence), as the CHANCE study was conducted in a Chinese population.¹ Long-term use of DAPT with clopidogrel plus ASA (ie, >90 days) is not recommended owing to the increased risk of bleeding and all-cause mortality, unless there is another indication (eg, coronary stent) (CSBPR: level A evidence; AHA-ASA: class III, level A evidence).^{1,4,6,8} The following paragraphs will review the primary literature that forms the basis of the above guideline recommendations (**Table 1**).⁵⁻⁸

The CHANCE study evaluated if early administration of clopidogrel with ASA was superior to the use of ASA alone for reducing subsequent strokes.⁵ This randomized, double-blind, placebo-controlled trial included 5170 patients from China who presented with minor ischemic stroke or TIA within 24 hours of symptom onset.⁵ Participants were randomized to receive either 75 mg/d of clopidogrel with 75 mg/d of ASA for the first 21 days then clopidogrel alone for days 22 to 90, or 75 mg/d of ASA with placebo.⁵ By day 90, DAPT reduced the risk of recurrent stroke (number need to treat of 29), without increasing the risk of major bleeding or all-cause mortality.⁵ Approximately three-quarters (77%) of the participants had no history of ischemic stroke or TIA before the index event.⁵

Although the results of the CHANCE study are promising, it has limited generalizability outside of the Chinese population, and the rate of stroke in China is approximately 5 times higher than in North America.⁵ The POINT (Platelet-Oriented Inhibition in New TIA and

minor ischemic stroke) study is currently under way, which is a randomized, double-blind, multicentre North American trial comparing use of 75 mg/d of clopidogrel plus 50 to 325 mg of ASA daily with ASA alone for 90 days in participants presenting within 12 hours of stroke symptoms.¹⁰ The results of this study will help shed light on the role of DAPT for ischemic stroke in Canada, and should be released in the next few years.

The guideline recommendations to avoid long-term use of DAPT with clopidogrel come from the MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients) and SPS3 (Secondary Prevention of Small Subcortical Strokes) trials.^{6,8} The MATCH trial evaluated the use of 75 mg/d of clopidogrel plus 75 mg/d of ASA with use of clopidogrel alone for secondary stroke prevention.⁸ The study failed to show a benefit with DAPT for reducing serious vascular events, and there was an increased risk of bleeding.⁸ The numbers needed to harm (NNHs) for life-threatening bleeding and major bleeding were 50 and 100, respectively, over 18 months.⁸ However, the increased risk of life-threatening bleeding occurred later in the study, and the Kaplan-Meier curves for intracranial bleeding did not separate until after 3 months, suggesting that DAPT during the first 90 days might be safe.⁸ The SPS3 study compared 75 mg/d of clopidogrel plus 325 mg/d of ASA with ASA alone.⁶ Similar to the MATCH trial, DAPT failed to show a benefit in reducing the risk of recurrent stroke, and not only increased the risk of major bleeding (NNH=32) but also all-cause mortality (NNH=44) over 3.4 years.⁶

Of note, 2 other trials assessed DAPT with clopidogrel for reducing the risk of ischemic stroke. The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic, Stabilization, Management, and Avoidance) study evaluated 75 mg/d of clopidogrel plus 75 to 162 mg of ASA daily with ASA alone for 28 months in patients with or at risk of cardiovascular disease.⁹ Overall, DAPT failed to show a benefit. However, in individuals with a history of stroke, DAPT was favoured over SAPT for the prevention of the primary outcome (composite of cardiovascular death, myocardial infarction, or stroke).¹¹ The FASTER (Fast Assessment of Stroke and TIA to prevent Early Recurrence) study compared 75 mg/d of clopidogrel plus 81 mg/d of ASA with ASA alone for 90 days in patients with stroke presenting within 24 hours.⁷ This trial was stopped early because it failed to meet the required recruitment rate, likely owing to its design that also investigated the use of statins.⁷ The results gathered before termination found no statistically significant reduction of recurrent stroke with DAPT, but they did show an increased risk of symptomatic bleeding (NNH=34).⁷

Ticagrelor and prasugrel, the newer antiplatelet agents, are not indicated for secondary stroke prevention. Ticagrelor failed to show a benefit in this population,

Table 1. Summary of randomized controlled trials investigating use of clopidogrel with ASA for secondary stroke prevention

TRIAL	POPULATION	INTERVENTION OR COMPARATOR	OUTCOMES	COMMENTS
CHANCE, ⁵ 2013	<ul style="list-style-type: none"> • N = 5170 • Age ≥ 40 y with acute minor ischemic stroke or TIA within 24 h 	<ul style="list-style-type: none"> • Both groups had open-label ASA (75–300 mg) on d 1 • LD of 300 mg of clopidogrel; then 75 mg/d of clopidogrel with 75 mg/d of ASA for 21 d then 75 mg/d of clopidogrel alone for d 22–90 vs 75 mg/d of ASA alone for 90 d • Treatment with DAPT for 21 d 	<ul style="list-style-type: none"> • Primary end point: any stroke (ischemic or hemorrhagic); 8.2% vs 11.7%; HR = 0.68 (95% CI 0.57–0.81); <i>P</i> < .001; NNT = 29 • Moderate-severe hemorrhage: not statistically significant 	<ul style="list-style-type: none"> • Use of PPI within 90 d: about 1% • Supports short-term (21 d) DAPT immediately following ischemic stroke
SPS3, ⁶ 2012	<ul style="list-style-type: none"> • N = 3020 • Age ≥ 30 y with recent (2 wk to 180 d [mean 62 d]) symptomatic lacunar infarct 	<ul style="list-style-type: none"> • 325 mg/d of ASA with 75 mg/d of clopidogrel vs 325 mg/d of ASA alone • Treatment for a mean of 3.4 y 	<ul style="list-style-type: none"> • Primary end point: any stroke (ischemic or intracranial hemorrhage including subdural hematoma); not statistically significant • Severe hemorrhage 2.1% vs 1.1% per y; HR = 1.97 (95% CI 1.41–2.71); <i>P</i> < .001; NNH = 32 • All-cause mortality: HR = 1.52 (95% CI 1.14–2.04); <i>P</i> = .004; NNH = 44 	<ul style="list-style-type: none"> • Most major bleeding was GI: 1.1% vs 0.52% per y; HR = 2.14 (95% CI 1.36–3.36); <i>P</i> < .001 • Supports avoiding long-term use of DAPT poststroke owing to increased risk of harm
FASTER, ⁷ 2007	<ul style="list-style-type: none"> • N = 392 • Age ≥ 40 y with stroke or TIA within 24 h 	<ul style="list-style-type: none"> • LD of 162 mg of ASA (if ASA naïve) • LD of 300 mg of clopidogrel then 75 mg/d of clopidogrel daily with 81 mg/d of ASA vs 81 mg/d of ASA alone • Treatment for 90 d 	<ul style="list-style-type: none"> • Primary end point: composite of any stroke (ischemic or hemorrhagic); not statistically significant • Total symptomatic bleeding: 3% vs 0%, risk difference 3% (95% CI 0.6%–5.4%); <i>P</i> = .03; NNH = 34 • Total asymptomatic bleeding (eg, bruising): 30.8% vs 13.9%, risk difference 16.9% (95% CI 8.8%–25%); <i>P</i> = .0001; NNH = 6 	<ul style="list-style-type: none"> • Trial stopped early owing to failure to reach recruitment rate • Supports avoiding long-term (90 d) use of DAPT poststroke owing to increased risk of harm
MATCH, ⁸ 2004	<ul style="list-style-type: none"> • N = 7599 • Age > 40 y with stroke or TIA within 180 d (mean 26.5 d) with at least 1 of 5 risk factors for stroke (ie, previous ischemic stroke, previous MI, angina pectoris, DM, or symptomatic PAD) within the past 3 y 	<ul style="list-style-type: none"> • 75 mg/d of ASA with 75 mg/d of clopidogrel vs 75 mg/d of clopidogrel alone • Treatment for 18 mo 	<ul style="list-style-type: none"> • Primary end point: composite of ischemic stroke, MI, vascular death, rehospitalization for acute ischemic event; not statistically significant • Life-threatening bleed: 3% vs 1%, risk difference 1.26% (95% CI 0.64%–1.88%); <i>P</i> < .0001; NNH = 50 • Major bleed: 2% vs 1%, risk difference 1.36% (95% CI 0.86%–1.86%); <i>P</i> < .0001; NNH = 100 	<ul style="list-style-type: none"> • GI bleeds most common cause of life-threatening (1.4% vs 0.6%) and major (1.12% vs 0.29%) bleeds • Supports avoiding long-term use of DAPT poststroke owing to increased risk of harm

ASA—acetylsalicylic acid, CHANCE—Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events, DAPT—dual antiplatelet therapy, DM—diabetes mellitus, FASTER—Fast Assessment of Stroke and TIA to prevent Early Recurrence, GI—gastrointestinal, HR—hazard ratio, LD—loading dose, MATCH—Management of ATherothrombosis with Clopidogrel in High-risk patients, MI—myocardial infarction, NNH—number needed to harm, NNT—number needed to treat, PAD—peripheral arterial disease, PPI—proton pump inhibitor, SPS3—Secondary Prevention of Small Subcortical Strokes, TIA—transient ischemic attack.

compared with ASA.¹² Prasugrel is contraindicated in individuals with a history of stroke or TIA, as it was found to increase the risk of harm in this subset of patients in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) study (NNH=15 for death, myocardial infarction, stroke, or major bleeding over 14.5 months).¹³

Addressing some questions

What is the optimal duration of DAPT? The optimal duration of DAPT is unknown, but the only trial to show benefit was based on a regimen of DAPT for 21 days.⁵ However, patients who are initiated on DAPT might inadvertently remain on this regimen for an extended period of time. As discussed, prolonged therapy does not provide benefit and increases the risk of harm. Neurologists, primary care prescribers, pharmacists, and patients all play a role in ensuring DAPT is used for the intended duration. (For more information, see the RxFiles newsletter and chart on DAPT duration available from **CFPlus**.)^{*} Communication and documentation are key. **Table 2** provides practical tips on facilitating the intended duration of DAPT.

Which agent should be continued when stepping down from DAPT to SAPT? The antiplatelet selected for ongoing secondary prevention once DAPT is complete depends on which agent was used before the stroke or TIA; however, there is little evidence to guide step-down therapy. In the CHANCE study, patients were stepped down to clopidogrel monotherapy after completing 21 days of DAPT.⁵ Approximately 11% of the patient population had taken a dose of ASA within 24 hours of their hospital admission.⁵ If a patient was not taking an antiplatelet before his or her event, therapy could be stepped down to ASA or clopidogrel, or dipyridamole with ASA. If a patient was taking an antiplatelet before a stroke or TIA, it would be reasonable to switch to an alternative agent. Medication adherence should be assessed before concluding antiplatelet failure. Clopidogrel and dipyridamole with ASA have both shown marginal benefit over ASA monotherapy for secondary prevention of cerebrovascular events.¹⁴⁻¹⁶ In clinical practice, however, clopidogrel or dipyridamole with ASA are often reserved for recurrent cerebrovascular events, as provincial formulary drug plans might only cover these agents if the patient has had a stroke while taking ASA.¹⁷

*The RxFiles newsletter and chart on Duration of Dual Antiplatelet Therapy and Triple Therapy for Cardiovascular and Cerebrovascular Indications is available at www.cfp.ca. Go to the full text of this article online and click on **CFPlus** in the menu at the top right-hand side of the page.

Table 2. Practical tips for facilitating patient adherence to the intended duration of clopidogrel with ASA use in practice

ITEM	PRACTICAL TIPS
Initial prescription and consultation note	Write the indication and intended duration of DAPT Specify which antiplatelet agent should be stopped once DAPT is complete Note the intended duration if a PPI is used for gastroprotection
Patient chart (paper or EMR) or patient profile in the pharmacy system	Document the intended duration of DAPT with the indication and instructions for step-down therapy
Prescription label	Include instructions for the duration of DAPT (eg, "Continue until [date], then stop")
Patient education	Educate the patient on the importance of medication adherence for the intended duration Ensure the patient understands which antiplatelet agent is to be continued when DAPT is complete

ASA—acetylsalicylic acid, DAPT—dual antiplatelet therapy, EMR—electronic medical record, PPI—proton pump inhibitor.

Who should receive gastroprotection? Acetylsalicylic acid can cause direct damage to the lining of the gastrointestinal (GI) tract by inhibiting the production of protective prostaglandins.¹⁸ Conversely, clopidogrel does not cause ulcers or erosions of the GI tract, but its antiplatelet effects might promote bleeding if there is a pre-existing lesion. In the clinical trials investigating DAPT for cerebrovascular indications, more than 50% of major bleeds were GI bleeds.^{6,8} The baseline use of proton pump inhibitors (PPIs) in these studies was often not reported⁶⁻⁸ or low (eg, CHANCE trial reported a baseline use of 1%).⁵ There are no studies explicitly investigating gastroprotection during DAPT in stroke patients; however, management strategies can be extrapolated from studies and recommendations made for cardiovascular indications.^{19,20} Gastroprotection is not recommended for all patients taking DAPT; however, patients with risk factors for GI bleeding might benefit from the addition of an acid-suppressing agent (**Box 1**).¹⁹⁻²¹

Previously, some concerns were raised regarding a potential drug interaction between PPIs and clopidogrel. The initial concern was based largely on an observational study that suggested that omeprazole reduced the conversion of clopidogrel to its active form, resulting in reduced efficacy of the antiplatelet.²² However, data from a 2010 randomized controlled trial suggest a clinically significant interaction is unlikely.²³ If initiating a PPI, consider selecting an agent other than omeprazole

Box 1. Patient risk factors to consider for gastroprotection with a PPI

Prescribe PPIs to patients who are taking DAPT and have risk factors for GI bleeding

- ≥ 1 of the following GI bleeding risk factors:
 - History of a GI ulcer or bleed
 - Anticoagulation therapy use
 - Chronic use of NSAIDs or corticosteroid therapy
- ≥ 2 of the following GI bleeding risk factors:
 - Age of 65 y or older
 - Dyspepsia
 - Gastroesophageal reflux disease
 - Helicobacter pylori* infection
 - Chronic alcohol use

DAPT—dual antiplatelet therapy, GI—gastrointestinal, NSAID—nonsteroidal anti-inflammatory drug, PPI—proton pump inhibitor. Data from Abraham et al,¹⁹ Roffi et al,²⁰ and Andreotti et al.²¹

and esomeprazole for patients who are currently taking clopidogrel, as there are several available that have similar efficacy and less potential for drug interactions.

Back to Mrs K.M.

You explain to Mrs K.M. that the pantoprazole was started to prevent the risk of having a GI bleed while taking DAPT. Now that the duration of DAPT is complete, the pantoprazole is no longer needed. You clarify that she is only to continue taking the clopidogrel for ongoing stroke prevention and that she should stop taking ASA. You add that long-term therapy with both agents does not further reduce her risk of recurrent stroke and increases her risk of bleeding and potentially death. You also advise her to avoid nonsteroidal anti-inflammatory drugs in the future, as these medications might increase her risk of a GI bleed. She is reassured to hear you will work closely with her to manage her other stroke risk factors, such as blood pressure, cholesterol levels, diet, weight, and exercise.

Conclusion

There is some evidence that clopidogrel with ASA reduces the risk of recurrent noncardioembolic ischemic stroke; however, these results might not be generalizable to the Canadian population.⁵ Benefits have only been found with short-term courses (ie, 21 days) of DAPT⁵; long-term use (ie, >90 days) has been associated with an increased risk of mortality and major bleeding.^{6,8} Thus, clear communication and documentation regarding the intended duration of DAPT is important. A PPI should be used in patients taking DAPT who are at high risk of GI bleeds to help reduce the risk of major bleeding.¹⁹⁻²¹ If DAPT is used, there is limited guidance on which agent to use when

stepping down to SAPT; however, which antiplatelet was used before the stroke or TIA, along with medication adherence, should be considered.

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Acknowledgment

We thank **Dr Gary Hunter**, Clinical Assistant Professor of Neurology and Neurocritical Care, and **Dr Tessa Laubscher**, Clinical Associate Professor of Academic Family Medicine, both at the University of Saskatchewan, for their contributions to this article.

Competing interests

RxFiles and contributing authors do not have any commercial competing interests. RxFiles Academic Detailing Program is funded through a grant from Saskatchewan Health to Saskatoon Health Region; additional “not for profit; not for loss” revenue is obtained from sales of books and online subscriptions. No financial assistance was obtained for this publication.

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