ABSTRACT

Antiplatelet agents are a cornerstone of therapy for patients with atherosclerotic vascular disease. There is presently a lack of comprehensive guidelines focusing on the use of antiplatelet drugs in patients currently manifesting or at elevated risk of cardiovascular disease. The Canadian Antiplatelet Therapy Guidelines Committee reviewed exist...
ing disease-based guidelines and subsequently published literature and used expert opinion and review to develop guidelines on the use of antiplatelet therapy in the outpatient setting. This Executive Summary provides an abbreviated version of the principal recommendations. Antiplatelet therapy appears to be generally underused, perhaps in part because of a lack of clear, evidence-based guidance. Here, we provide specific guidelines for secondary prevention in patients discharged from hospital after acute coronary syndromes, percutaneous coronary intervention, or coronary artery bypass grafting; patients with a history of transient cerebral ischemic events or strokes; and patients with peripheral arterial disease. Issues related to primary prevention are also addressed, in addition to special clinical contexts such as diabetes, heart failure, chronic kidney disease, pregnancy or lactation, and perioperative management. Recommendations are provided regarding pharmacologic interactions that may occur during combination therapy with warfarin, clopidogrel, and proton-pump inhibitors, or aspirin and nonsteroidal anti-inflammatory drugs, as well as for the management of bleeding complications. The complete guidelines document is published as a supplementary issue of the Canadian Journal of Cardiology and is available at http://www.ccs.ca/.

Unlike other vascular preventive strategies, physicians lack clear, easily accessible, evidence-based guidance on which to base antiplatelet therapy management decisions. Existing documents addressing antiplatelet therapy do so as part of guidelines and statements encompassing overall treatment recommendations for specific disease entities (eg, peripheral arterial disease [PAD], diabetes, drug-eluting stent (DES) implantation, and stroke). Therefore, there is no single easily accessible source of antiplatelet therapy recommendations.

To create a concise, therapeutic-based statement on managing antiplatelet therapy in outpatients who have existing, or are at risk of developing, vascular disease, the Canadian Antiplatelet Therapy Consensus Committee was formed by the Canadian Cardiovascular Society. As outlined in more detail in the full guideline, also available at http://www.ccs.ca/, the processes used to develop the consensus recommendations reported herein included (1) a search for existing guidelines and new data on topics pertinent to antiplatelet therapy use in the outpatient setting; (2) evaluation of the quality of existing guidelines using the AGREE (Appraisal of Guidelines for REsearch and Evaluation) instrument; (3) development of recommendations via consideration of existing guidelines and their associated AGREE score, literature published subsequent to existing guidelines, and expert opinion; (4) creation of graded recommendations through the 2-tiered system recommended by the Canadian Cardiovascular Society (Table 1); and (5) external review by experts in their respective fields who were not involved in the writing process. (The external reviewers are listed in Appendix II of the full guideline document.) When necessary, individual recommendations were revised after the external review process.

In 2 years, the Antiplatelet Consensus Committee intends to reconvene to evaluate the need to update the recommendations.

Role of the Funding Source

Funding for the preparation of the Canadian Antiplatelet Therapy Guideline was provided by the Thrombosis Interest Group of Canada (TIGC), a registered nonprofit, non-commercial organization dedicated to furthering education and research in the prevention and treatment of thrombosis. Although several members of the working group are members of the TIGC, the TIGC as an entity had no input into the content of the guideline. The funding provided by the TIGC was used to support the creation of a password-protected Web site where group members could upload and download references, guidelines, and draft statements; the administrative services of Sharon O’Doherty of the TIGC; and the editorial assistance of Melanie Leiby, PhD, of in-Science Communications, a Wolters Kluwer business. Au-

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<tr>
<th>Table 1. Grading system used in the preparation of the Canadian Cardiovascular Society Antiplatelet Therapy Guideline</th>
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<td>Class of recommendation</td>
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<td>I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective</td>
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<td>IIa: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the weight of evidence in favour</td>
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<td>III: Evidence that the treatment is not useful and in some cases may be harmful</td>
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Antiplatelet Therapy for Secondary Prevention in the First Year Following an Acute Coronary Syndrome

Working Group: Jean-François Tanguay, MD, CSPQ, FRCP, FACC, FAHA, FESC, Michael P. Love, MB, ChB, MD, MRCP, and Robert C. Welsh, MD, FRCP, FACC

Data from randomized clinical trials that compared those with acetylsalicylic acid (ASA) alone, combination therapy with oral P2Y12 receptor antagonists improves clinical outcomes in patients with acute coronary syndrome (ACS), although the combination therapy does increase the risk of bleeding. Evidence from the CURE Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial supports the use of ASA plus clopidogrel for up to 12 months after non–ST-elevation ACS (NSTEACS), regardless of the management strategy, whereas the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 trial and Clopidogrel and Metoprolol in Myocardial Infarction trial support up to 30 days of ASA plus clopidogrel after ST-elevation myocardial infarction (STEMI). In the absence of specific evidence for long-term dual antiplatelet therapy in STEMI, the findings of CURE and the common underlying pathophysiology of all types of ACS are the basis for continuing therapy in patients with STEMI after hospital discharge. The current reality is that an increasing proportion of patients with STEMI undergo in-hospital percutaneous coronary intervention (PCI), and therefore, continuation of dual antiplatelet therapy after discharge is often mandated by the implantation of one or more intracoronary stents. Data from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition and a low risk of bleeding (Class IIb, Level C).

For patients presenting with NSTEACS who are medically managed, clopidogrel 75 mg daily is recommended in addition to ASA 75 to 162 mg daily for at least 1 month (Class I, Level A) and up to 12 months in the absence of an excessive risk of bleeding (Class I, Level B).

For patients presenting with NSTEACS who are managed by PCI, clopidogrel 75 mg daily is recommended in addition to ASA 75 to 162 mg daily for 12 months (Class I, Level A). Continuation of combined therapy beyond 12 months may be considered in patients with a high risk of thrombosis and a low risk of bleeding (Class IIb, Level C).

For patients presenting with NSTEACS who are managed by coronary artery bypass grafting (CABG), clopidogrel 75 mg daily is recommended in addition to ASA 75 to 162 mg daily for a minimum of 1 month and up to 12 months (Class I, Level B).

For patients with ACS who undergo stent implantation and have an increased risk of stent thrombosis (eg, STEMI, history of diabetes mellitus, or prior documented stent thrombosis), prasugrel 10 mg daily may be considered in addition to ASA 75 to 162 mg daily for 12 months (Class IIa, Level B). Prasugrel should be avoided in patients with an increased bleeding risk, likely to undergo CABG within 7 days, with a history of stroke or transient ischemic attack (TIA), aged ≥75 years, or weighing <60 kg (Class III, Level B).

For patients with ACS, ticagrelor 90 mg twice daily may be added to ASA 75 to 162 mg daily for 12 months (Class I, Level B). (This recommendation assumes that ticagrelor, which is under review by Health Canada, will be approved as requested in early 2011.)

In general, the adenosine diphosphate P2Y12 receptor antagonist added to ASA in the acute setting should be maintained for the duration of therapy (Class I, Level C).

RECOMMENDATION

For all patients with ACS who survive to hospital discharge, indefinite therapy with low-dose ASA (75-162 mg daily) is recommended (Class I, Level A). For patients allergic to or intolerant of ASA, indefinite therapy with clopidogrel 75 mg daily is recommended (Class IIa, Level B).

For patients presenting with STEMI who are medically managed, clopidogrel 75 mg daily is recommended in addition to ASA 75 to -162 mg daily for at least 14 days (Class I, Level B) and up to 12 months in the absence of an excessive risk of bleeding (Class IIb, Level C).

For patients presenting with STEMI who are managed by PCI, clopidogrel 75 mg daily is recommended in addition to ASA 75 to 162 mg daily for 12 months (Class I, Level B). Continuation of combined therapy beyond 12 months may be considered in patients with a high risk of thrombosis and a low risk of bleeding (Class IIb, Level C).

Antiplatelet Therapy for Secondary Prevention in the First Year Following PCI

Working Group: Jean-François Tanguay, MD, CSPQ, FRCP, FACC, FAHA, FESC, Michael P. Love, MB, ChB, MD, MRCP, and Robert C. Welsh, MD, FRCP, FACC

Similar to what is observed in ACS, combination therapy with an oral P2Y12 receptor antagonist and ASA is superior to ASA alone in patients who undergo PCI. Evidence from the PCI-CURE12 and PCI-Clopidogrel as Adjunctive Reperfusion Therapy13 studies established the efficacy of dual ASA and clopidogrel therapy in patients with NSTEACS and STEMI, respectively, whereas the Clopidogrel for the Reduction of Events During Observation study14 established its efficacy in patients with stable coronary artery disease (CAD) undergoing nonurgent PCI. The combinations of ASA plus prasugrel or ticagrelor in patients with ACS undergoing PCI were shown to be superior to ASA plus clopidogrel in the TRITON-TIMI 3810 and Platelet Inhibition and Patient Outcomes-Invasive trials,15 respectively. However, major bleeding rates were noted to be higher. The optimal duration of dual ASA/oral P2Y12 receptor antagonist therapy poststenting, particularly among DES recipients, is unknown. Registry data suggest a protective effect of continuing dual antiplatelet therapy beyond 24 months.16-18 but a recent analysis of 2 randomized clinical trials did not show a benefit for con-
Continuing ASA plus clopidogrel for 24 months over ASA plus clopidogrel for 12 months followed by ASA alone for an additional 12 months.\textsuperscript{19}

**RECOMMENDATION**

Indefinite therapy with ASA 75 to 162 mg daily should be used in all patients with acute or chronic ischemic heart disease without contraindications to its therapy (Class I, Level A). This includes patients who have undergone PCI.

All patients who have undergone PCI with bare-metal stent (BMS) implantation should be given clopidogrel 75 mg daily in addition to ASA 75 to 162 mg daily for at least 1 month (Class I, Level B) and up to 12 months in the absence of an excessive risk of bleeding (Class I, Level B) after stent implantation.

For patients with recent bleeding or at increased risk for bleeding, a BMS should be implanted, and clopidogrel 75 mg daily should be added to ASA 75 to 162 mg daily for a minimum of 2 weeks (Class I, Level B).

All patients who have undergone PCI with DES implantation should be given clopidogrel 75 mg daily in addition to ASA 75 to 162 mg daily for 12 months (Class I, Level A).

Continuation of dual antiplatelet therapy with ASA 75 to 162 mg daily and clopidogrel 75 mg daily beyond 1 year may be considered in patients with an increased risk of stent thrombosis as long as the perceived risk of bleeding is deemed acceptable (Class IIb, Level C).

For patients with ACS who undergo stent implantation and have an increased risk of stent thrombosis (eg, STEMI, history of diabetes mellitus, or prior documented stent thrombosis), prasugrel 10 mg daily may be considered in addition to ASA 75 to 162 mg daily for 12 months (Class IIa, Level B). Prasugrel should be avoided in patients with an increased bleeding risk, likely to undergo CABG within 7 days, with a history of stroke or TIA, aged ≥75 years, or weighing <60 kg (Class III, Level B).

For patients with ACS who undergo stent implantation, ticagrelor 90 mg twice daily may be added to ASA 75 to 162 mg daily for 12 months (Class I, Level B). (This recommendation assumes that ticagrelor, which is under review by Health Canada, will be approved as requested in early 2011.)

**Antplatelet Therapy for Secondary Prevention Beyond 1 Year Following ACS or PCI**

**Working Group:** Anil Gupta, MD, FRCPC, and Pierre Théroux, MD

As shown in the post-ACS and post-PCI sections of the guideline, combination therapy with an oral P2Y\textsubscript{12} antagonist and ASA is recommended for up to 1 year following the event. Beyond this timeframe, the most studied, commonly used antiplatelet therapy is ASA monotherapy,\textsuperscript{20-22} with the evidence suggesting that doses greater than 75 to 81 mg once daily do not provide additional clinical benefit but increase the risk of bleeding.\textsuperscript{23} Clopidogrel monotherapy is another treatment option for long-term management of patients with CAD.\textsuperscript{24} The overall results of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial do not support the long-term use of combined ASA-clopidogrel therapy in patients with, or at risk of, ischemic vascular events.\textsuperscript{24} However, use in the predefined subgroup of stable patients with prior atherothrombotic events, reduced the relative risk of the primary endpoint.

**RECOMMENDATION**

For all patients with ACS who survive to hospital discharge, indefinite therapy with low-dose ASA (75-162 mg daily) is recommended (Class I, Level A).

For patients allergic to or intolerant of ASA, indefinite therapy with clopidogrel 75 mg daily is recommended (Class IIa, Level B).

Dual antiplatelet therapy with ASA 75 to 162 mg daily and clopidogrel 75 mg daily may be considered beyond 1 year in patients with ACS (see the recommendations in the section titled Antplatelet Therapy for Secondary Prevention in the First Year Following an Acute Coronary Syndrome) who are medically managed, provided the risk of bleeding is low (Class IIb, Level C).

For all post-PCI patients, indefinite therapy with ASA 75 to 162 mg daily is recommended, regardless of type of stent (Class I, Level A).

Dual antiplatelet therapy with ASA 75 to 162 mg daily and clopidogrel 75 mg daily may be considered beyond 1 year in patients with ACS who receive a BMS or DES, provided their risk of bleeding is low (Class IIb, Level C).

**Antplatelet Therapy for Secondary Prevention Following CABG**

**Working Group:** Raymond Cartier, MD

ASA is recognized as the standard of care for preventing saphenous vein graft closure after CABG and is generally continued indefinitely, given its benefit in preventing subsequent clinical events.\textsuperscript{25} A large meta-analysis showed that low (approximately 100 mg) and medium (approximately 325 mg) daily doses of ASA were more effective than high-dose (approximately 975 mg) ASA in preventing saphenous vein graft occlusion and caused less gastrointestinal side effects.\textsuperscript{26} Although ticlopidine provides a benefit similar to that of ASA in preventing graft closure,\textsuperscript{27,28} it is not recommended for use because of its relatively poor safety and tolerability profile. Despite a lack of direct clinical trial evidence, clopidogrel is recommended for patients who have undergone CABG and who are allergic to or intolerant of ASA. Evidence from the CURE and Clopidogrel for the Reduction of Ischemic Events During Observation clinical trials suggests that although combination ASA-clopidogrel therapy may decrease the risk of cardiovascular events in patients who undergo CABG, it also significantly increases the risk of bleeding.\textsuperscript{13,29} There is no evidence in the literature that antiplatelet therapy, including combination ASA-clopidogrel,\textsuperscript{30} improves arterial graft patency.

**RECOMMENDATION**

For all patients who undergo saphenous vein CABG surgery, ASA 75 to 162 mg daily is recommended as lifelong therapy unless contraindicated (Class I, Level A). ASA
should be initiated within 24 hours of surgery completion (Class IIa, Level B).

For all patients who undergo saphenous vein CABG surgery and have a contraindication to ASA, clopidogrel 75 mg daily is preferred over ticlopidine 250 mg twice daily because of the superior safety profile of clopidogrel (Class IIa, Level C). In patients undergoing CABG after PCI, dual antiplatelet therapy with ASA 75 to 162 mg daily and clopidogrel 75 mg daily may be maintained for 9 to 12 months unless the stented vessel is adequately bypassed (Class IIb, Level C).

**Antiplatelet Therapy for the Secondary Prevention of Cerebrovascular Disease**

**Working Group:** Ashfaq Shuaib, MD, FRCP, and Philip Teal, MD, FRCP

For secondary prevention in patients with TIA or ischemic stroke, antiplatelet therapy regimens with proven efficacy include ASA monotherapy,  ticlopidine monotherapy, clopidogrel monotherapy, and the combination of ASA and dipyridamide. As demonstrated in both the Management of Atherothrombosis for Continued Health and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance studies, combined ASA-clopidogrel therapy should not be used for long-term secondary prevention following stroke or TIA because it does not significantly improve ischemic event prevention but significantly increases the risk of bleeding. Some evidence suggests that combination therapy may provide benefit in the period immediately following stroke or TIA.

**RECOMMENDATION**

Patients who suffer a TIA or ischemic stroke of noncardiac origin should be treated with an antiplatelet agent (Class I, Level A). Initial therapy should be ASA 75 to 162 mg once daily, clopidogrel 75 mg once daily, or ER dipyridamole 200 mg twice daily plus ASA 25 mg twice daily (Class I, Level A). The choice of antiplatelet therapy regimen is determined by consideration of cost, tolerance, and other associated vascular conditions. Available data do not allow for differentiation of antiplatelet regimen by specific stroke subtype (Class IIb, Level C).

The combination of ASA 75 to 162 mg daily plus clopidogrel 75 mg daily in the first month after TIA or minor ischemic stroke may be superior to ASA alone in patients not at a high risk of bleeding (Class IIb, Level C). The combination of ASA 75 to 162 mg daily plus clopidogrel 75 mg daily should not be used for secondary stroke prevention beyond 1 month unless otherwise indicated and the risk of an ankle-brachial index ≤ 0.9), the limited evidence does not support a benefit for antiplatelet therapy. Data do suggest a benefit for ASA monotherapy and clopidogrel monotherapy in patients with symptomatic PAD (ie, patients with claudication, rest pain, or ischemic lesions). Adding dipyridamole to ASA does not improve outcomes over ASA alone, and the combination of ASA and clopidogrel does not appear to provide significant clinical benefit.

Based on studies conducted mostly in patients undergoing infrainguinal bypass surgery, low-dose ASA therapy is recommended for patients who undergo arterial reconstruction, including aortobiliomural reconstructions, axillofemoral or bifemoral bypass, iliopopliteal bypass, common femoral repair, and profundaplasty.

Epidemiologic evidence suggesting that abdominal aortic aneurysm (AAA) may be a marker of subclinical atherosclerosis and the fact that many AAA risk factors are also atherosclerotic risk factors indicate that antiplatelet therapy may be a valuable treatment for preventing cardiovascular events in patients with AAA. In one study, low-dose ASA was associated with a reduced expansion rate and a reduced risk of AAA surgery in patients whose aortic size was 40 to 49 mm. Low-dose ASA is recommended for those with an AAA, with the evidence stronger for those with clinical or subclinical PAD.

**RECOMMENDATION**

For patients with asymptomatic PAD with an ankle-brachial index <0.9, low-dose ASA (75-162 mg daily) may be considered for those at high risk because of associated atherosclerotic risk factors in the absence of risk factors for bleeding (Class IIb, Level C). For patients with symptomatic PAD without overt CAD or cerebrovascular disease, low-dose ASA (75-162 mg daily) or clopidogrel 75 mg daily is recommended, providing the risk for bleeding is low (Class IIb, Level B). The choice of drug may depend on patient preference and cost considerations.

For patients allergic or intolerant to ASA, use of clopidogrel is suggested (Class IIa, Level B).

For patients with intermittent claudication, dipyridamole should not be used in addition to ASA (Class III, Level C). For patients with intermittent claudication, using clopidogrel 75 mg daily in addition to ASA 75 to 162 mg daily is not recommended unless the patient is judged to be at high vascular risk along with a low risk of bleeding (Class IIb, Level B).

For patients with symptomatic PAD with overt CAD or cerebrovascular disease, antiplatelet therapy as indicated for the CAD and/or cerebrovascular status is recommended (Class I, Level A). For patients with symptomatic PAD without compelling indications for oral anticoagulation such as atrial fibrillation or venous thromboembolism, oral anticoagulation should not be added to antiplatelet therapy (Class III, Level B). For patients with symptomatic PAD with an indication for oral anticoagulation such as atrial fibrillation, venous thromboembolism, heart failure (HF), or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (Class III, Level A).
Antiplatelet Therapy for the Primary Prevention of Vascular Events

**Working Group:** Alan D. Bell, MD, CCFP, and James D. Douketis, MD, FRCP

For the purpose of this guideline, primary prevention is defined as antiplatelet strategies administered to individuals free of any evidence of manifest atherosclerotic disease in any vascular bed, to prevent clinical vascular events or manifestations thereof. These include, but are not limited to, syndromes of angina pectoris, myocardial infarction, ischemic stroke, TIA, intermittent claudication, and critical limb ischemia.

Evidence from individual randomized clinical trials (eg, the British Doctors’ Study,54 Physician’s Health Study,52 and Women’s Health Study53) and several meta-analyses of these and other primary prevention trials22,54 suggests that ASA monotherapy significantly reduces the relative risk of ischemic cardiovascular events in patients without established cardiovascular disease. The absolute risk reduction, however, is small, resulting in very large numbers needed to treat to prevent a single event. Further, the benefit of ASA is accompanied by a significant increase in the risk of bleeding. Considering that the absolute net benefit of any intervention is dictated by the treatment effect, associated adverse events, and absolute event rates, the low event rate in primary prevention and increased risk of bleeding diminishes or possibly nullifies the absolute net benefit of ASA for primary prevention. Furthermore, most of the studies considered were conducted prior to the widespread use of other primary risk reduction therapies, including statins and inhibitors of the renin-angiotensin-aldosterone system, which would likely further reduce the absolute event rates and net benefit of ASA. Although vascular events are likely to have a greater impact on disability and mortality than is bleeding and although the cost of ASA is low, a clear margin of benefit must apply before recommending a therapy to a vast, healthy population.

**RECOMMENDATION**

For men and women without evidence of manifest vascular disease, the use of ASA at any dose is not recommended for routine use to prevent ischemic vascular events (Class III, Level A).

For men and women without evidence of manifest vascular disease, the use of clopidogrel 75 mg daily plus ASA at any dose is not recommended to prevent ischemic vascular events (Class III, Level B).

In special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk low, ASA 75 to 162 mg daily may be considered (Class IIb, Level C).

**Use of Antiplatelet Therapy in Patients With Diabetes**

**Working Group:** Maria E. Kraw, MD, FRCP, and Rémi Rabasa-Lhoret, MD, PhD

The results of several observational studies55,56 subgroup analyses of randomized clinical trials,52,53,57 the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes,58 and Prevention of Progression of Arterial Disease and Diabetes62 trials conducted specifically in patients with diabetes, and several meta-analyses22,59,60 suggest that ASA therapy for primary prevention may confer similar, or even less, benefit for cardiovascular event reduction in individuals with diabetes than in those without. Even if there was a 10% reduction in the risk of primary events, the number needed to treat in order to prevent 2 major cardiovascular events would be 1000 patients for 1 year. Taking into account rare but well-documented side effects such as major bleeding, such benefit might be questionable, even with a low-cost medication such as ASA.

In observational studies of secondary prevention with ASA, patients with diabetes appear to derive less benefit from ASA than do those without diabetes.66,64,65 No large, randomized clinical trial has specifically examined the use of ASA for secondary prevention exclusively in patients with diabetes. A meta-analysis of trials that assessed antiplatelet vs control therapy in patients with diabetes failed to show a statistically significant reduction in the risk of serious vascular events.63 Because the number of events was much higher in patients with diabetes, the benefit in terms of number of events prevented was comparable in patients with (42 events prevented for every 1000 patients treated) and without (35 events prevented for every 1000 patients treated) diabetes.

ASA appears to be as effective as other antiplatelet agents and may be the best choice given that it is the most widely studied and the most economical. In patients who cannot tolerate ASA or have a clear contraindication (eg, allergy, ASA-induced asthma), an alternate antiplatelet agent may be used. Subgroup analysis of the Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events study showed that clopidogrel significantly reduced the risk of ischemic events compared with ASA in patients with diabetes.62 Combination therapy with ASA and either clopidogrel or prasugrel is beneficial in patients with diabetes who experience ACS,7,63 but not in those who do.
Use of Antiplatelet Therapy in Patients With HF

Recommmendation
There is currently no evidence to recommend routine use of ASA at any dose for the primary prevention of vascular ischemic events in patients with diabetes (Class III, Level A).

For patients with diabetes and aged >40 years and at low risk for major bleeding, low-dose ASA (75-162 mg daily) may be considered for primary prevention in patients with other cardiovascular risk factors for which its benefits are established (Class Ib, Level B).

Low-dose ASA therapy (75-162 mg daily) may be considered for secondary prevention in patients with diabetes and manifest vascular disease for which its benefits are established (Class IIb, Level B).

Clopidogrel 75 mg daily may be considered for secondary prevention in patients with diabetes who are unable to tolerate ASA (Class IIa, Level B).

Use of Antiplatelet Therapy in Women Who Are Pregnant or Breastfeeding

Recommmendation
ASA 75 to 162 mg daily may be considered for primary prevention of ischemic vascular events in patients with ESRD and a low risk of bleeding (Class IIb, Level C).

Antiplatelet therapy should be considered for secondary prevention in patients with CKD and manifest vascular disease for which its benefits are established (Class IIa, Level C).

Use of Antiplatelet Therapy in Patients With Chronic Kidney Disease

Recommmendation
For individuals with HF of ischemic etiology, antiplatelet therapy should be dictated by the underlying CAD (Class IIa, Level A).

For individuals with HF of nonischemic etiology, routine use of antiplatelet agents is not recommended (Class III, Level C).

Low-dose ASA (75 to 162 mg daily) and an ACE inhibitor in combination may be considered for patients with HF when an indication for both drugs exists (Class IIa, Level B).

There is little high-quality evidence to guide the use of ASA or other antiplatelet agents in patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD). A meta-analysis of studies of antiplatelet therapy for maintenance of access patency among dialysis patients demonstrated a significant reduction in the relative risk of serious vascular events associated with antiplatelet therapy, mainly ASA. The small size of the included studies precludes accurate estimation of hazard ratios for bleeding events in this patient population. For secondary prevention, there is conflicting evidence related to whether a positive benefit-to-risk ratio is associated with ASA or combination ASA-clopidogrel therapy in patients with CKD. Conversely, subgroup analysis of TRITON-TIMI 38 revealed that patients with a creatinine clearance < 60 mL per minute were likely to benefit the most from prasugrel vs clopidogrel.

Overall, consideration of antiplatelet therapy for primary or secondary prevention of vascular events in patients with CKD and ESRD must include the dramatically increased risk of vascular disease (10- to 100-fold increased risk) vs the risk and potential benefits of treatment.

Use of Antiplatelet Therapy in Patients With Chronic Kidney Disease

Recommmendation
For individuals with HF of ischemic etiology, antiplatelet therapy should be dictated by the underlying CAD (Class IIa, Level A).

For patients with diabetes and aged >40 years and at low risk for major bleeding, low-dose ASA (75-162 mg daily) may be considered for primary prevention in patients with other cardiovascular risk factors for which its benefits are established (Class IIb, Level B).

Low-dose ASA therapy (75-162 mg daily) may be considered for secondary prevention in patients with diabetes and manifest vascular disease for which its benefits are established (Class IIb, Level B).

Clopidogrel 75 mg daily may be considered for secondary prevention in patients with diabetes who are unable to tolerate ASA (Class IIa, Level B).

Regardless of the presence of HF, antiplatelet therapy should be used in all individuals with ischemic heart disease unless specifically contraindicated. Overall, there is no evidence that antiplatelet therapy provides benefit for patients with HF of nonischemic etiology or benefit beyond the known secondary prevention in those with HF due to CAD. There is limited evidence to suggest that ASA may increase the secondary risk of hospitalization for HF.

There are no clinical trials demonstrating the efficacy of antiplatelet therapy or relative superiority of types of antiplatelet therapy in pregnant women with coexisting cardio- or cerebrovascular diseases. Data from randomized trials in which the benefits of ASA were investigated for primary and secondary prevention of preeclampsia and improved pregnancy rates in women who undertake assisted reproductive technology suggest that ASA use does not increase maternal or fetal bleeding risks, placenta abruption, or congenital defects. Similarly, a meta-analysis of observational studies investigating first-trimester ASA exposure reported that ASA use was not associated with an overall increased risk of congenital malformations, although a significantly increased risk of gastrochisis was reported. In several small trials of preeclampsia prevention, dipyridamole was not associated with fetal malformations, and in several case studies, no adverse fetal events were reported when clopidogrel was used throughout pregnancy.

Although maternal ASA ingestion is associated with excretion of salicylate and salicylate metabolites in breast milk, the use of low-dose ASA (50-150 mg daily) during breastfeeding has not been reported to result in adverse infant outcomes and is mostly considered safe. There is no data on the safety of dipyridamole and clopidogrel in breastfeeding.
RECOMMENDATION

For cardio- or cerebrovascular disease in which antiplatelet therapy would be indicated in nonpregnant women, there should be similar considerations for its use in pregnancy (Class IIa, Level A).

Low-dose ASA (75 to 162 mg daily) is likely safe for use during the first trimester of pregnancy (Class IIa, Level A). Low-dose ASA can be used safely during the second and third trimesters of pregnancy (Class I, Level of Evidence A).

Use of antiplatelet agents other than low-dose ASA for cardio- or cerebrovascular indications during pregnancy should be considered only if maternal benefits clearly outweigh potential fetal risks (Class IIb, Level C).

Low-dose ASA (75 to 162 mg daily) may be considered for use in breastfeeding women (Class I, Level C). Use of agents other than low-dose ASA by breastfeeding mothers should be considered only after weighing maternal benefits with potential risks for the newborn (Class IIb, Level C).

Management of Patients on Antiplatelet Therapy Who Require a Surgical or Other Invasive Procedure

Working Group: James D. Douketis, MD, FRCPC, and A. Graham Turpie, MD

The majority of evidence for the management of perioperative antiplatelet therapy comes from case-control studies. These studies suggest that continuing ASA monotherapy is safe for patients undergoing gastrointestinal endoscopy, polyectomy, bronchoscopy, dental procedures, dermatologic procedures, and cataract removal. The evidence for clopidogrel monotherapy or combined ASA/clopidogrel therapy in patients undergoing these procedures is lacking.

In patients who are receiving antiplatelet therapy and require elective noncardiac surgery, there are no randomized trials or nonrandomized studies that compare the benefits and risks of continuing such drugs as opposed to temporarily interrupting their use around the time of surgery. The available evidence suggests a benefit of perioperative ASA continuation but also indicates potential harm related to increased perioperative bleeding. A risk-benefit assessment infers that the benefits of ASA treatment may be limited to patients with prior cardiovascular disease (given reduction in vascular mortality). For stent recipients receiving ASA and clopidogrel who require noncardiac surgery, there is an increased risk for stent thrombosis in the postoperative period. The available evidence suggests the risk of stent thrombosis in BMS and DES recipients is lowest when surgery is performed >3 months or >1 year after stent implantation, respectively.

The preponderance of evidence suggests ASA can be continued in the perioperative period in patients who undergo CABG. In clopidogrel-treated patients who require CABG, no studies have directly assessed clopidogrel use in the perioperative period. The decision of when to perform CABG in patients receiving ASA and clopidogrel is dependent on the relative risks of ischemic events and bleeding. For patients with a low ischemic risk, clopidogrel should be discontinued for 5 days prior to surgery. For patients with a high ischemic risk and low bleeding risk, surgery can be performed immediately. If a patient has both high ischemic and high bleeding risk, clopidogrel should be discontinued for 3 to 5 days prior to CABG. In all cases, preoperative and postoperative strategies that minimize the risk of major bleeding and transfusion should be implemented.

RECOMMENDATION

Patients who are receiving ASA and undergoing a diagnostic test associated with a low risk for bleeding may continue ASA without interruption, whereas patients undergoing a noncardiac procedure associated with a high risk for bleeding should discontinue ASA 7 to 10 days before the procedure (Class IIa, Level C). Patients who are receiving ASA and clopidogrel should discontinue clopidogrel 7 to 10 days before the procedure if it can be done safely (Class IIb, Level C); ASA should also be discontinued before diagnostic tests associated with a high risk for bleeding (Class IIa, Level C).

Whenever possible, elective surgery in patients receiving ASA and clopidogrel secondary to coronary stent implantation should be deferred for at least 6 weeks after BMS placement and at least 12 months after DES placement (Class I, Level B). For patients who are receiving ASA and clopidogrel for a BMS and require urgent surgery within 6 weeks of placement, ASA and clopidogrel should be continued in the perioperative period (Class I, Level B). For patients who are receiving ASA and clopidogrel for a DES and require urgent surgery within 12 months of placement, ASA and clopidogrel should be continued in the perioperative period (Class I, Level B).

Patients who are receiving ASA and are to have arthrocentesis may continue ASA through the time of the procedure (Class IIb, Level C). Patients who are receiving ASA and clopidogrel should discontinue clopidogrel 7 to 10 days before the procedure if it can be done safely (Class IIb, Level C).

Patients who are receiving ASA and undergoing a minor dental, eye, or skin procedure or surgery may continue ASA around the time of the procedure (Class IIa, Level A). Patients who are receiving ASA and clopidogrel should discontinue clopidogrel 7 to 10 days before the procedure if it can be done safely (Class IIa, Level C).

Patients who are receiving ASA and require elective noncardiac surgery should discontinue ASA 7 to 10 days prior to surgery if the risk for cardiovascular events is low but continue therapy if cardiovascular risk is high (Class IIa, Level B). Patients who are receiving ASA and clopidogrel, who are likely to be at high cardiovascular risk, should continue ASA up to surgery (Class IIa, Level C) but discontinue clopidogrel 7 to 10 days before surgery if it can be done safely (Class IIb, Level C).

Patients who are receiving ASA and require CABG should continue ASA up to the time of surgery (Class I, Level B). Patients who are receiving ASA and clopidogrel should continue ASA until the time of surgery but discontinue clopidogrel at least 5 days before surgery (Class I, Level B).

Management of Antiplatelet Therapy in Association With Minor Bleeding

Working Group: James D. Douketis, MD, FRCPC, and A. Graham Turpie, MD

In patients receiving antiplatelet drugs, non-life-threatening minor bleeding is common, particularly in those also re-
ceiving anticoagulant therapy (warfarin or heparin) or systemic corticosteroids or with comorbidities such as chronic renal or hepatic disease. In general, minor bleeding is self-limiting and does not require medical attention. Studies specifically assessing the incidence, consequence, and clinical management of antiplatelet drug–associated minor bleeding are lacking. Therefore, the recommendations herewith are based on expert opinion alone and should be interpreted in this context.

**RECOMMENDATION**

Patients who are receiving ASA or ASA and clopidogrel and who develop ecchymosis and petechiae should undergo testing with a complete blood count and international normalized ratio (INR) and activated partial thromboplastin time monitoring to investigate for thrombocytopenia or a coagulopathy (Class IIa, Level C). In the absence of superimposed abnormalities in haemostatic function, antiplatelet drugs can be continued with clinical observation, whereas in patients with thrombocytopenia or a coagulopathy, ASA (or clopidogrel) should be stopped pending further investigations (Class IIa, Level C).

Patients who are receiving ASA or ASA and clopidogrel and in whom there is excessive bleeding after a dental procedure should receive application of local pressure and/or use of tranexamic acid mouthwash 2 to 4 times daily for 1 to 2 days (Class IIa, Level C).

Patients who are receiving ASA or ASA and clopidogrel and in whom subconjunctival bleeding develops should continue treatment and be monitored for bleeding (Class IIa, Level C).

**Combination Therapy With Warfarin and ASA: When to Use, When to Consider, When to Avoid**

**Working Group:** James D. Douketis, MD, FRCPC, and A. Graham Turpie, MD

In patients with both atrial fibrillation and CAD, relevant data to assess the efficacy of combined warfarin-ASA compared with warfarin alone is derived from a subgroup analysis of warfarin-treated patients in the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation trials, which compared warfarin (target INR, 2.0-3.0) with ximelagatran for stroke prevention in patients with atrial fibrillation. This analysis suggested a lack of benefit for combination warfarin-ASA therapy. In a retrospective cohort study of more than 4000 warfarin-treated patients managed by a specialized anticoagulation clinic, there were no significant differences in rates of coronary events or thromboembolism in patients receiving combination warfarin-ASA therapy compared with those receiving warfarin alone. Taken together, there does not appear to be compelling evidence that combination warfarin-ASA therapy is more effective than warfarin alone in preventing cardiac and other thromboembolic outcomes in patients with either chronic CAD or chronic atrial fibrillation or in patients with both CAD and atrial fibrillation.

Combination warfarin-ASA therapy is of known benefit in patients with a mechanical prosthetic heart valve. Other conditions for which combination warfarin-ASA therapy is reasonable include patients with atrial fibrillation or venous thromboembolism who are receiving long-term warfarin and develop an ACS treated with medical therapy alone, patients who have an indication for long-term warfarin therapy and undergo CABG, and patients with atrial fibrillation who develop a stroke syndrome despite therapeutic anticoagulation with warfarin. In patients receiving long-term warfarin who undergo coronary stent implantation, it is reasonable to coadminister warfarin, ASA, and clopidogrel for at least 6 weeks, although patients with a DES may require such therapy for at least 12 months, or possibly longer.  

**RECOMMENDATION**

In patients with a mechanical prosthetic heart valve, combination warfarin (target INR, 2.0-3.0) and ASA 75 to 162 mg daily should be considered, especially in patients with any mechanical mitral valve or in patients with an older caged-ball or bileaflet mechanical aortic valve (Class IIa, Level A).

In patients who have a clinical indication for long-term warfarin and develop an ACS that is treated with medical therapy alone, combination warfarin (target INR, 2.0-3.0) and ASA (75 to 162 mg daily) therapy is reasonable for up to 12 weeks, at which time ASA may be withdrawn if there are no further cardiac events (Class IIb, Level C).

**Interaction Between Clopidogrel and Proton Pump Inhibitors**

**Working Group:** Wee Shian Chan, MD, FRCP, and Alan D. Bell, MD, CCFP

As many as two-thirds of clopidogrel recipients receive a proton pump inhibitor (PPI) for the treatment of a concomitant acid-related disorder. Several pharmacodynamic interaction studies suggest that omeprazole reduces the antiplatelet effect of clopidogrel, and results of observational studies have raised concerns that the dual use of clopidogrel and a PPI might lead to an increased risk of adverse cardiovascular outcomes compared with patients receiving clopidogrel without a concomitant PPI. Product monographs for clopidogrel recommend that concomitant use of clopidogrel and PPIs be discouraged.

However, there is also observational data showing no effect of concomitant clopidogrel and PPI use on adverse outcomes, and a post hoc analysis of the TRITON-TIMI 38 randomized clinical trial revealed no increased risk of adverse cardiovascular outcomes associated with dual use of a PPI and either clopidogrel or prasugrel. Results of the Clopidogrel and the Optimization of Gastrointestinal Events randomized trial showed that during a total follow-up of 180 days, combination clopidogrel-omeprazole therapy did not significantly increase the risk of the adjudicated composite cardiovascular outcome of cardiovascular death, nonfatal myocardial infarction, CABG, PCI, or ischemic stroke (4.9% with clopidogrel plus omeprazole vs 5.7% with clopidogrel alone; hazard ratio, 0.99; 95% CI, 0.68-1.44).

Recent guidance published jointly by the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association recommends the use of PPIs to reduce gastrointestinal bleeding in patients with a history of upper gastrointestinal bleeding and suggests they are appropriate for patients with multiple risk factors for gastrointestinal bleeding who require antiplatelet therapy. Routine prophylactic use of PPIs...
and H2 blockers in patients at lower risk of upper gastrointestinal bleeding is not recommended. The guidance also states that decisions regarding the concomitant use of PPIs and thienopyridines must balance overall cardiovascular and gastrointestinal risks and benefits.

**RECOMMENDATION**

The pharmacodynamic interaction between clopidogrel and PPIs and the initial findings from observational studies suggested an increased risk of cardiovascular events in concomitant users of clopidogrel and PPIs. Recently published data from a randomized clinical trial suggest that this risk is likely clinically insignificant. Nevertheless, because of potential limitations with study design and patients recruited, PPIs that minimally inhibit cytochrome P450 2C19 are preferred for patients taking clopidogrel who are considered to be at increased risk of upper gastrointestinal bleeding (Class IIb, Level B).

**Interaction Between ASA and Nonsteroidal Anti-Inflammatory Drugs**

**Working Group:** Alan D. Bell, MD, CCFP, and Wee Shian Chan, MD, FRCP

Although no randomized trials examining the clinical effect of an interaction between ASA and nonsteroidal anti-inflammatory drugs (NSAIDs) have been completed, laboratory studies and observational and epidemiologic data have suggested an adverse effect. This interaction has important clinical consequences because, unlike coxibs, traditional NSAIDs may inhibit ASA binding to platelet cyclooxygenase-1. The reversible binding of traditional NSAIDs does not offer a consistent antiplatelet effect or the vascular protection afforded by the irreversible binding of ASA.

**RECOMMENDATION**

Individuals taking low-dose ASA (75 to 162 mg daily) for vascular protection should avoid the concomitant use of traditional (non–cyclooxygenase-2 inhibitor) NSAIDs (Class III, Level C).

If a patient taking low-dose ASA (75 to 162 mg daily) for vascular protection requires an anti-inflammatory drug, specific cyclooxygenase-2 inhibitors should be chosen over traditional NSAIDs (Class IIb, Level C).

Both cyclooxygenase-2 inhibitors and traditional NSAIDs increase cardiovascular risk and, if possible, should be avoided in patients at risk of ischemic vascular events (Class III, Level A).

**References**


