Society Guidelines

The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines

Alan D. Bell, MD, CCFP,a André Roussin, MD, FRCPC,b Raymond Cartier, MD, FRCPC,c Wee Shian Chan, MD, FRCPC,d James D. Douketis, MD, FRCPC,e Anil Gupta, MD, FRCPC,f Maria E. Kraw, MD, FRCPC,g Thomas F. Lindsay, MD, CM, FRSCS,h Michael P. Love, MB, ChB, MD, MRCP,i Neesh Pannu, MD, SM, FRCPC,j Rémi Rabasa-Lhoret, MD, PhD,k Ashfaq Shuaib, MD, FRCPC,l Philip Teal, MD, FRCPC,m Pierre Théroux, MD, CM, FACC, FAHA,n Alexander G. G. Turpie, MD, FRCP, FACC, FRCPC,o Robert C. Welsh, MD, FRCPC, FACC,p and Jean-François Tanguay, MD, CSPQ, FRCPC, FACC, FAHA, FESCq

a From the Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada; b Internal and Vascular Medicine, Centre Hospitalier Universitaire de Montréal, Montréal, Québec, Canada; c Department of Surgery, Montréal Heart Institute, Montréal, Québec, Canada; d Department of Medicine, Women’s College Hospital, Toronto, Ontario, Canada; e Department of Medicine, St. Joseph’s Healthcare, Hamilton, Ontario, Canada; f Department of Clinical Cardiology, Trillium Health Centre, Mississauga, Ontario, Canada; g Division of Endocrinology, St. Michael’s Hospital, Toronto, Ontario, Canada; h Division of Vascular Surgery, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; i Division of Cardiology, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; j Division of Nephrology, University of Alberta, Edmonton, Alberta, Canada; k Institut de Recherches Cliniques de Montréal, Département de Nutrition, Université de Montréal, Montréal, Québec, Canada; l Division of Neurology, University of Alberta, Edmonton, Alberta, Canada; m Department of Neurology, University of British Columbia, Vancouver, British Columbia, Canada; n Coronary Care Unit, Montréal Heart Institute, Montréal, Québec, Canada; o Division of Hematology & Thromboembolism (Emeritus), McMaster University, Hamilton, Ontario, Canada; p Department of Interventional Cardiology, University of Alberta, Edmonton, Alberta, Canada; q Department of Medicine, Montréal Heart Institute, Université de Montréal, Montréal, Québec, Canada

ABSTRACT
Antiplaeee 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.

RÉSUMÉ
Les agents antiplaquettaires sont une des pierres angulaires du traitement des patients ayant une maladie vasculaire athérosclérotique. Les lignes directrices qui portent sur l’utilisation des médicaments antiplaquettaires chez les patients qui manifestent ou qui sont à risque élevé de...
The Canadian Antiplatelet Therapy Guidelines Committee reviewed existing 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 full document has been summarized in an Executive Summary published in the Canadian Journal of Cardiology and may be found at [http://www.ccs.ca/](http://www.ccs.ca/). 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 following acute coronary syndromes, post-percutaneous coronary intervention, post-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/lactation, and perioperative management. Recommendations are provided regarding pharmacologic interactions that may occur during combination therapy with warfarin, clopidogrel and proton-pump inhibitors, or acetylsalicylic acid and nonsteroidal anti-inflammatory drugs, as well as for the management of bleeding complications.

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### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>S1</td>
</tr>
<tr>
<td>Introduction</td>
<td>S4</td>
</tr>
<tr>
<td>Identification of Relevant Clinical Guidelines</td>
<td>S5</td>
</tr>
<tr>
<td>Appraisal of Guidelines Using the AGREE Instrument</td>
<td>S5</td>
</tr>
<tr>
<td>Literature Search</td>
<td>S6</td>
</tr>
<tr>
<td>Preparation of Guidelines</td>
<td>S6</td>
</tr>
<tr>
<td>Regular Updates</td>
<td>S6</td>
</tr>
<tr>
<td>Antiplatelet Therapy for Secondary Prevention in the First Year Following an Acute Coronary Syndrome</td>
<td>S6</td>
</tr>
<tr>
<td>Evidence for Antiplatelet Therapy Post ACS</td>
<td>S6</td>
</tr>
<tr>
<td>Platelet P2Y12 Receptor Antagonants</td>
<td>S7</td>
</tr>
<tr>
<td>Clopidogrel as an Alternative to ASA Post ACS</td>
<td>S7</td>
</tr>
<tr>
<td>Clopidogrel in Addition to ASA Post NSTEACS</td>
<td>S7</td>
</tr>
<tr>
<td>Clopidogrel in Addition to ASA Post STEMI</td>
<td>S7</td>
</tr>
<tr>
<td>Clopidogrel in Addition to ASA Post ACS</td>
<td>S8</td>
</tr>
<tr>
<td>Prasugrel vs Clopidogrel Post ACS</td>
<td>S8</td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel Post ACS</td>
<td>S8</td>
</tr>
<tr>
<td>Recommendation</td>
<td>S9</td>
</tr>
<tr>
<td>Antiplatelet Therapy for Secondary Prevention in the First Year Following Percutaneous Coronary Intervention</td>
<td>S10</td>
</tr>
<tr>
<td>ASA in Patients Undergoing PCI</td>
<td>S10</td>
</tr>
<tr>
<td>Dual-Antiplatelet Therapy in Patients With ACS Who Undergo PCI</td>
<td>S10</td>
</tr>
<tr>
<td>Dual-Antiplatelet Therapy in Patients With Stable CAD Who Undergo Nonurgent PCI</td>
<td>S11</td>
</tr>
<tr>
<td>Dual-Antiplatelet Therapy After BMS Implantation</td>
<td>S12</td>
</tr>
<tr>
<td>Dual-Antiplatelet Therapy After DES Implantation</td>
<td>S12</td>
</tr>
<tr>
<td>Recommendation</td>
<td>S13</td>
</tr>
<tr>
<td>Antiplatelet Therapy Beyond 1 Year After Acute Coronary Syndrome or Percutaneous Coronary Intervention</td>
<td>S14</td>
</tr>
<tr>
<td>ASA Therapy Beyond 1 Year Following a Medically Managed ACS</td>
<td>S15</td>
</tr>
<tr>
<td>Clopidogrel vs ASA for Long-Term Management of Patients With ACS</td>
<td>S15</td>
</tr>
<tr>
<td>Antiplatelet Therapy in Addition to ASA Beyond 1 Year for Patients With Medically Managed ACS</td>
<td>S15</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>S15</td>
</tr>
<tr>
<td>Prasugrel and Ticagrelor</td>
<td>S16</td>
</tr>
<tr>
<td>Post-ACS and Post-PCI Dual-Antiplatelet Therapy Beyond 1 Year</td>
<td>S16</td>
</tr>
<tr>
<td>Recommendation</td>
<td>S16</td>
</tr>
</tbody>
</table>
Antiplatelet Therapy for Secondary Prevention Following Coronary Artery Bypass Grafting

Alternative Antithrombotic Therapy for Preventing Saphenous Vein Graft Occlusion

Optimal Dose of ASA Post CABG

Optimal Timing of Antiplatelet Therapy Initiation Post CABG

Clopidogrel in CABG

ACS, PCI, and CABG

Recommendation

Antiplatelet Therapy for Secondary Prevention of Cerebrovascular Disease

Antithrombotic Therapy for Prevention of Stroke in Patients With a History of TIA or Ischemic Stroke

ASA Compared With Placebo

Comparison of Different Doses of ASA

Other Antiplatelet Agents

Summary

Recommendation

Antiplatelet Therapy for Vascular Prevention in Patients With Peripheral Artery Disease

PAD: The Asymptomatic and the Symptomatic Patient

Patients With Asymptomatic PAD

Patients With Symptomatic PAD, Including Claudication, Critical Limb Ischemia, or Amputation

Antiplatelet Therapy for Patients With PAD Who Undergo Endovascular Intervention

Antiplatelet Agents Following Peripheral Surgical Bypass

Antiplatelet Therapy for the Treatment of AAA

Recommendation

Antiplatelet Therapy for Primary Prevention of Vascular Events

Studies of Primary Prevention in Men

Studies in Subjects With Risk Factors for Vascular Disease

The Effect of Sex in Primary Prevention

Meta-analysis

Summary

Recommendation

Use of Antiplatelet Therapy in Patients With Diabetes

Primary Prevention

Observational Cohorts

Subgroup and Post-Hoc Analyses of Clinical Trials

Randomized Clinical Trials Conducted in Patients With Diabetes

Meta-analyses

Secondary Prevention

Observational Cohorts

Subgroup, Post-Hoc, and Meta-analyses of Randomized Trials

Ongoing Trials

Specific Subgroups and Situations

Optimal ASA Dose for Patients With Diabetes

Other Antiplatelet Therapy

ASA Resistance in Diabetes

Summary

Recommendation

Use of Antiplatelet Therapy in Patients With Heart Failure

Randomized Studies Assessing Antiplatelet Therapy With Warfarin or No Therapy

Nonrandomized Studies

Adverse Effects of ASA on HF

Summary

Recommendation

Use of Antiplatelet Therapy in Patients With Chronic Kidney Disease

Primary Prevention

Secondary Prevention

ASA

Clopidogrel

Prasugrel

Bleeding Risk

Summary

Recommendation
Use of Antiplatelet Therapy in Women Who Are Pregnant or Breastfeeding

ASA in Pregnancy
ASA in Breastfeeding
Dipyridamole
Clopidogrel
Available Recommendations From Existing Guidelines
Recommendation

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

Patient Profile
Diagnostic Testing
Joint Injections
Minor Dental, Eye, and Skin Procedures
Noncardiac Surgery
CABG
Noncardiac Surgery in Patients With Cardiac Stents
Recommendation

Management of Antiplatelet Therapy in Association With Minor Bleeding

Ecchymosis and Petechiae
Oral Mucosal Bleeding
Subconjunctival Bleeding
Recommendation

Combination Therapy With Warfarin and Acetylsalicylic Acid: When to Use, When to Consider, When to Avoid

Evidence for Therapeutic Benefit With Combination Warfarin/ASA Therapy
When to Consider Combination Warfarin/ASA Therapy
Patient Groups in Which There Is Good Evidence for Warfarin/ASA Therapy
Patient Groups in Which There Is Weak Evidence for Warfarin/ASA Therapy
Patient Groups in Which Warfarin/ASA Therapy Is Reasonable Despite the Lack of Supportive Evidence
Recommendation

Interaction Between Clopidogrel and Proton Pump Inhibitors

Studies
Observational Studies
Randomized Controlled Trial
Post-Hoc Analysis of Randomized Controlled Trials
Meta-analysis
Regulatory Guidance
Current Guidelines
Genetic Polymorphisms
Recommendation

Interaction Between Acetylsalicylic Acid and Nonsteroidal Anti-inflammatory Drugs

Platelet Function Studies
Observational and Epidemiologic Studies
Specific COX-2 Inhibitors, Traditional NSAIDs, and Vascular Events
Summary
Recommendation

Funding Sources

References

Appendix I. Composite Domain Scores for Guidelines Assessed Using the AGREE Instrument

Appendix II. External Expert Reviewers of the Canadian Cardiovascular Society Antiplatelet Therapy Guideline

Appendix III. Author Relationships With Industry—CCS Antiplatelet Therapy Guideline Committee

Introduction

Antiplatelet agents are a cornerstone therapy for patients with documented atherosclerotic vascular disease, including those with coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD). The most commonly used antiplatelet agents include acetylsalicylic acid (ASA), ticlopidine, clopidogrel, and dipyridamole. Emerging agents include prasugrel, which was recently approved for marketing, and ticagrelor, which is awaiting approval by Health Canada. Despite clear evidence showing its benefit in preventing adverse cardiovascular events in patients with vascular disease, antiplatelet therapy is underused in clinical practice. In an evaluation of the first and second Canadian Acute Coronary Syndrome (ACS) Registries, discharge
Of 29.5 million patient visits in 2003.4

One of the factors that may contribute to the underuse of antiplatelet therapy, particularly among those outside academic hospital or research settings, is the increasing complexity of regimens for the various vascular risk situations. Unlike other vascular preventive strategies, including control of hypertension and hyperlipidaemia, Canadian physicians lack clear, easily accessible, evidence-based guidance on which to base antiplatelet therapy management decisions. Existing Canadian documents addressing antiplatelet therapy do so as part of guidelines and statements encompassing overall treatment recommendations for specific disease entities (eg, PAD), diabetes, drug-eluting stent (DES) implantation, and stroke). Therefore, there is limited discussion on antiplatelet therapy and no easily accessible, single Canadian source of antiplatelet therapy recommendations.

To create a concise, therapeutic-based statement on managing antiplatelet therapy in Canadian outpatients who have existing, or are at risk of developing, vascular disease, the Canadian Antiplatelet Therapy Consensus Committee was formed. The processes used to develop the guideline recommendations reported herein included the following:

- A search for existing guidelines and new data on the identified topics of interest
- Evaluation of the quality of existing guidelines using the AGREE (Appraisal of Guidelines for REsearch & Evaluation) Instrument
- Development of recommendations via consideration of existing guidelines and their associated AGREE score
- Literature published subsequent to existing guidelines
- Expert opinion
- Creation of graded recommendations using a system set forth by the Canadian Cardiovascular Society (CCS)
- External review by Canadian experts in their respective fields who were not involved in the writing process

Identification of relevant clinical guidelines

Based on the conditions for which antiplatelet therapy is used in the outpatient setting, the working group identified the following topics to be addressed in the guideline: post ACS; post PCI; post CABG; long-term secondary prevention in patients with CAD and cerebrovascular disease; vascular prevention in patients with asymptomatic or symptomatic PAD, including those who undergo endovascular or surgical procedures in the peripheral vasculature; patients with abdominal aortic aneurysm (AAA); primary prevention; women who are pregnant or breastfeeding; patients with chronic kidney disease (CKD), heart failure (HF), and diabetes; perioperative setting; patients with a requirement for oral anticoagulation; and potential interactions between ASA and nonsteroidal anti-inflammatory drugs (NSAIDs) and clopidogrel and proton-pump inhibitors (PPIs). Antiplatelet therapy for the management of atrial fibrillation, valvular heart disease, and pediatrics was not addressed.

The initial search for existing guidelines that might address these topics was performed by searching the National Guidelines Clearinghouse Web site (http://www.guideline.gov). A manual search of the 367 guidelines listed in the “Cardiovascular Diseases” group identified 79 possibly relevant guidelines. A manual search of these individual guidelines identified 67 relevant guidelines published by 24 different associations. To ensure that the most recent guidelines were obtained, the Web sites of the sponsoring associations were searched for updates.

Appraisal of guidelines using the AGREE instrument

The AGREE instrument is a generic tool designed to assess the quality of clinical practice guidelines published by local, regional, national, or international groups. Application of the AGREE instrument ensures that recommendations put forth in this guideline are based on a validated, structured, and rigorous development process. The instrument itself is designed to assess 6 factors associated with guideline quality: (1) scope and purpose (assesses the overall aim of the guideline, the specific clinical questions, and the target patient population); (2) stakeholder involvement (focuses on the extent to which the guideline represents the views of its intended users); (3) rigour of development (relates to the process used to gather and synthesize the evidence and the methods used to formulate the recommendations and to update them); (4) clarity and presentation (assesses the language and format of the guidelines); (5) applicability (pertains to the likely organizational, behavioural, and cost implications of applying the guidelines); and (6) editorial independence (assesses the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline development group).

The writing group applied the AGREE instrument to 63 of the 67 identified guidelines, with most guidelines scored by ≥ 2 members. (The composite domain scores for each of these guidelines are provided in Appendix I.) Overall, most guidelines scored high in the domains of scope and purpose and editorial independence, particularly those published by national societies (eg, those published by the American College of Chest Physicians or European Society of Cardiology). Scores for rigour of development tended to be ~50% because many guidelines did not include information on items such as identification of relevant data or processes for updating the guidelines. Finally, scores for stakeholder involvement and applicability tended to be ≤50%, mainly because most guidelines failed to identify a target audience or consider/consult with patients when formulating recommendations.
Literature search

To identify clinical data not included in existing guidelines, the MEDLINE, Embase, and Cochrane databases were searched using the following parameters:

- Timeframe: January 2007 through March 2010 (January 2007 was chosen because most existing guidelines would include data published prior to this)
- Indications: cardiovascular disease, cerebrovascular disease, coronary artery disease, ischemic heart disease, ischemic stroke, peripheral arterial disease, transient ischemic attack
- Agents: aspirin, acetylsalicylic acid, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine
- Limiters: case-control study, clinical outcome, efficacy, meta-analysis, prospective study, observational study, randomized clinical trial, retrospective study, safety, systematic review
- Keywords: abdominal aortic aneurysm, carotid endarterectomy, carotid stenting, coronary artery bypass grafting, coronary stenting, centesis, chronic kidney disease, congestive heart failure, dental procedure, dermatologic procedure, ecchymosis, epistaxis, joint injection, lactation, peripheral bypass grafting, peripheral stenting, pregnancy, surgery (cardiac and noncardiac)

Due to the paucity of data on the use of antiplatelet therapy for ischemic event protection among patients with CKD and women who are pregnant or breastfeeding, the searches for these conditions were repeated without use of the limiters just outlined above. This allowed identification of data that provided a safety profile of antiplatelet therapy in these patients.

Preparation of guidelines

Individual working groups of ≥ 2 committee members formulated graded summary recommendations for their specific topics. The summary recommendations were based on a synthesis of recommendations from existing guidelines, newly identified clinical data, and, where appropriate, expert clinical opinion and cost-benefit considerations. Whenever possible, the relative, absolute, and net clinical benefits of an intervention were considered when making recommendations. Because of the heterogeneity of the various interventions and the consequences of the events being avoided, no formal cutoffs in terms of numbers needed to treat were established. In situations where absolute benefit is very small, an intervention is not recommended regardless of the relative risk reduction. The grading system used to score the individual recommendations was the 2-tiered system (Class and Level of Evidence) recommended by the CCS (Table 1).

Upon completion, the summary recommendations for each individual topic were reviewed by the entire working group. Once a group consensus was achieved (ie, two-thirds of the committee as a whole agreed on the recommendations put forth by the individual working groups), the individual sections were sent to external reviewers considered to be experts in the field. All sections were reviewed by ≥ 1 external reviewer with the exception of the section entitled “Use of Antiplatelet Therapy in Patients With Chronic Kidney Disease.” (The external reviewers who provided feedback are listed in Appendix II.) When necessary, individual recommendations were revised following the external review process.

### Table 1. Grading system used in the preparation of the Canadian Cardiovascular Society antiplatelet consensus statement

<table>
<thead>
<tr>
<th>Class of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective</td>
<td>A: Data derived from multiple randomized clinical trials or meta-analyses</td>
</tr>
<tr>
<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>
<td>B: Data derived from a single randomized clinical trial or large nonrandomized studies</td>
</tr>
<tr>
<td>IIb: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the usefulness/efficacy less well established</td>
<td>C: Consensus of opinion by experts and/or small studies, retrospective studies, and registries</td>
</tr>
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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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</tr>
</tbody>
</table>

Regular updates

The Antiplatelet Consensus Committee intends to reconvene within 2 years to evaluate the need to update the recommendations.

### Antiplatelet Therapy for Secondary Prevention in the First Year Following an Acute Coronary Syndrome

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

Despite major advances in the medical and invasive management of CAD, ACSs continue to cause substantial morbidity. Platelets play a pivotal role in the pathophysiology of ACSs. The triggering event is typically rupture or erosion of an atherosclerotic coronary artery plaque, which results in platelet activation and intracoronary thrombosis. Therapeutic platelet inhibition is consequently a crucial aspect of ACS management and secondary prevention.

Contemporary classification of ACS is based on the appearance of the presenting electrocardiogram (ECG) and subsequent measurement of cardiac biomarkers, most commonly troponin. Patients who present with ST-segment elevation on their surface ECG usually have underlying complete occlusion of a coronary artery. The majority of these patients manifest biochemical evidence of myocardial necrosis and are typically labelled as having ST-elevation myocardial infarction (STEMI). Patients who present without ST-segment elevation usually have nonocclusive intracoronary thrombosis. Patients with NSTEACS are usually further subclassified according to their cardiac biomarkers. Those with biochemical evidence of myocardial necrosis are labelled as having non–ST-elevation myocardial infarction (NSTEMI) and those with negative biomarkers are labelled as having unstable angina (UA).

**Evidence for antiplatelet therapy post ACS**

A multitude of large, randomized clinical trials have evaluated the effects of ASA alone and in combination with oral P2Y12 receptor antagonists in patients with ACS. The following section reviews the key evidence supporting antiplatelet therapy in the postdischarge phase of ACS management.

The Antithrombotic Trialists’ Collaboration provides the clearest evidence for the secondary preventive benefits of antiplatelet therapy following an ACS. In 19,288 patients treated
with antiplatelet therapy during the acute phase of myocardial infarction (MI), most of whom participated in the ISIS-2 (Second International Study of Infarct Survival) trial and received ASA 162 mg once daily.\textsuperscript{13} Antiplatelet therapy resulted in large reductions in nonfatal recurrent MI (57% relative and 1.3% absolute risk reductions; \(P < 0.0001\)) and vascular death (20% relative and 2.3% absolute risk reductions; \(P < 0.0001\)). There was a smaller but still significant reduction in nonfatal stroke (50% relative and 0.3% absolute risk reductions; \(P = 0.02\)).

Overall, 1 month of antiplatelet therapy resulted in 38 fewer serious events for every 1000 patients treated (number needed to treat [NNT], 26). In the ISIS-2 trial, the benefit of ASA accrued over the first month of therapy and persisted for >10 years.\textsuperscript{13,14} In the Antithrombotic Trialists’ Collaboration meta-analysis of the 18,788 patients with a history of previous MI, treatment with antiplatelet therapy for a mean of 27 months resulted in large reductions in nonfatal recurrent MI (28% relative and 1.8% absolute risk reductions; \(P < 0.0001\)) and vascular death (15% relative and 1.4% absolute risk reductions; \(P = 0.0006\)).\textsuperscript{12} There was again a small but significant reduction in nonfatal stroke (36% relative and 0.5% absolute risk reductions; \(P = 0.002\)). Overall, antiplatelet therapy resulted in 36 fewer serious events for every 1000 patients treated (NNT 26).

Large short- and long-term benefits of ASA have been demonstrated in randomized trials of patients with UA. The Veterans Administration Cooperative Study tested the effect of 12 weeks of ASA 324 mg daily vs placebo in 1266 men with UA.\textsuperscript{15} ASA use resulted in 50% relative and 5% absolute risk reductions in death or MI (\(P = 0.0005\)). In a multicenter Canadian trial of 555 patients with UA, Cairns and colleagues\textsuperscript{16} showed that ASA 325 mg 4 times daily continued for 2 years resulted in 51% relative and 8.4% absolute risk reductions in cardiac death and nonfatal MI (\(P = 0.008\)) after a mean follow-up of 18 months.

Similarly, the optimal maintenance dose of ASA following ACS has not been definitively established by randomized clinical trials. The Antithrombotic Trialists’ Collaboration and other post-hoc trial analyses provide indirect support that lower doses of ASA (ie, 75–100 mg daily) may offer the optimal balance between efficacy and safety.\textsuperscript{12,17-19}

**Platelet P2Y\textsubscript{12} receptor antagonists.** Thienopyridines inhibit platelet aggregation via blockade of platelet P2Y\textsubscript{12} adenosine diphosphate (ADP) receptors.\textsuperscript{20} Currently, the oral thienopyridines ticlopidine, clopidogrel, and prasugrel are approved for use in Canada. An application for marketing approval of the novel P2Y\textsubscript{12} receptor blocker ticagrelor has been submitted to global regulatory agencies.

Clopidogrel is preferred over ticlopidine for patients with ACS or undergoing PCI because of the similar efficacy and enhanced safety and tolerability of clopidogrel.\textsuperscript{21-23} However, clopidogrel is a prodrug that requires a 2-stage oxidation process mediated by cytochrome P450 to generate its active metabolite,\textsuperscript{24} and varying absorption and reduced metabolism to its active compound secondary to loss-of-function polymorphisms and drug-drug competition for the relevant enzymes of the cytochrome P450 system may decrease and delay the antiplatelet effects of clopidogrel.\textsuperscript{24}

The third-generation agent prasugrel is also a prodrug that requires metabolic conversion, but it is converted to its active form more efficiently and predictably than clopidogrel.\textsuperscript{25} As a result, prasugrel has a faster onset of action, is more potent, and demonstrates less interindividual variability compared with clopidogrel. Ticagrelor, the second novel P2Y\textsubscript{12} receptor blocker, appears to have a potency and speed of onset similar to those of prasugrel.\textsuperscript{26} In contrast with clopidogrel and prasugrel, ticagrelor does not require metabolic activation and is a reversible inhibitor of the platelet P2Y\textsubscript{12} receptor. Because of its half-life (7-8.5 hours) and reversibility,\textsuperscript{27} ticagrelor requires twice-daily dosing (vs once-daily dosing for clopidogrel and prasugrel).

**Clopidogrel as an alternative to ASA post ACS.** In the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) trial, 19,185 patients with a history of MI within 35 days of randomization, ischemic stroke at 1 week to 6 months of randomization, or symptomatic PAD were randomized to ASA 325 mg daily or clopidogrel 75 mg daily.\textsuperscript{28} In the overall population and after a mean follow-up period of 1.9 years, clopidogrel reduced the relative risk of the primary composite endpoint of vascular death, MI, or ischemic stroke by 8.7% compared with ASA (5.3% vs 5.8%, absolute risk reduction 0.5%; \(P = 0.043\)). Statistical testing for heterogeneity was significant, suggesting that the small benefit of clopidogrel over ASA may not have been equivalent across subgroups. The relative risk reductions in the prespecified subgroups were 7.3% for the 6431 patients with a history of ischemic stroke (95% CI −5.7% to 18.7%; \(P = 0.26\)), 23.8% for the 6452 patients with a history of PAD (95% CI 8.9% to 36.2%; \(P = 0.0028\)), and −3.7% for the 6302 patients with a history of MI (95% CI −22.1% to 12.0%; \(P = 0.66\)).\textsuperscript{28}

**Clopidogrel in addition to ASA post NSTEMI.** The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial\textsuperscript{29} transformed the global use of clopidogrel and represents the key evidence for thienopyridine therapy in NSTEMI. In the CURE trial, 12,562 patients with either UA (75%) or NSTEMI (25%) given ASA 75–325 mg daily were randomized within 24 hours of presentation to receive clopidogrel (300-mg loading dose followed by 75 mg daily) or placebo for a mean of 9 months (range 3-12 months). The relative risk of the primary composite endpoint of cardiovascular death, nonfatal MI, or stroke was reduced by 20% in patients receiving clopidogrel compared with placebo (9.3% vs 11.4%, absolute risk reduction 2.1%; \(P < 0.001\)). Clopidogrel treatment was associated with an increased risk of trial-defined major (3.7% vs 2.7%; \(P = 0.001\)) and minor (5.1% vs 2.4%; \(P < 0.001\)) bleeding but not life-threatening bleeding (2.2% vs 1.8%; \(P = 0.13\)).

A landmark analysis of the CURE trial showed that the majority of clopidogrel benefit was manifest within the first 30 days of treatment.\textsuperscript{30} Thus, controversy regarding the implications of the CURE trial for the optimal duration of clopidogrel post NSTEMI persists. However, pharmacoeconomic analyses have indicated that clopidogrel plus ASA for 1 year post NSTEMI is highly cost-effective in both Canadian\textsuperscript{31,32} and global\textsuperscript{33} contexts.

**Clopidogrel in addition to ASA post STEMI.** Despite the results of the CURE trial and the similar underlying pathophysiology of all ACSs, clopidogrel was not used widely in patients with STEMI until clinical trials were conducted specifically in this patient population.

In the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion TherapY–Thrombolysis In Myocardial Infarction 28)
trial, 3491 patients aged < 75 years receiving thrombolysis and ASA 162 mg within 12-48 hours of an acute STEMI were randomized to clopidogrel (300-mg loading dose followed by 75 mg daily) or placebo.\(^{34}\) Study drug was continued until coronary angiography; for patients who did not undergo angiography, study drug was continued until day 8 or hospital discharge, whichever came first. For patients who underwent angiography, open-label clopidogrel (300-mg loading dose and 75 mg daily) was recommended. The relative risk of the primary composite endpoint of angiographic occlusion of the infarct-related artery, all-cause death, or recurrent MI at 30 days was reduced by 36% in those receiving clopidogrel vs placebo (15.0% vs 21.7%, absolute risk reduction 6.7%; \(P < 0.001\)).

In COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial), 45,852 patients presenting within 24 hours of suspected acute STEMI were randomized to clopidogrel 75 mg daily (no loading dose) or placebo in addition to ASA 162 mg daily.\(^{34}\) Patients undergoing primary PCI were excluded, and \(~50\) of those randomized received thrombolytic therapy. The study drug was continued for up to 4 weeks or until death or hospital discharge, whichever came first. After a mean treatment duration of 15 days, the relative risk of the first coprimary endpoint of the composite of death, MI, or stroke was reduced by 9% in clopidogrel vs placebo recipients (9.2% vs 10.1%, absolute risk reduction 0.9%; \(P = 0.002\)). The second coprimary endpoint of all-cause mortality was also significantly reduced by clopidogrel (7.5% vs 8.1%, absolute risk reduction 0.6%; \(P = 0.05\)). There was no significant increase in trial-defined bleeding associated with clopidogrel.\(^{34}\)

Although the CLARITY-TIMI 28 trial and COMMIT demonstrated the short-term benefits of acute clopidogrel administration, no randomized trials have specifically evaluated the effects of longer-term clopidogrel administration following STEMI. In the absence of specific evidence for long-term dual-antiplatelet therapy in STEMI, the findings of \(\text{CURE}^{29}\) and the common underlying pathophysiology of all types of ACS are typically cited as 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 PCI and, therefore, continuation of dual-antiplatelet therapy after discharge is often mandated by the implantation of \(\geq 1\) intracoronary stents.

**Clopidogrel in addition to ASA post ACS.** In the CURRENT-OASIS (Clopidogrel optimal loading dose Usage to Reduce Recurrent EventN’s-Organization to Assess Strategies in Ischemic Syndromes) 7 trial, 25,087 patients with ACS (70.8% UA/NSTEMI and 29.2% STEMI) undergoing an early invasive management strategy with intended PCI were randomized in a \(2 \times 2\) factorial fashion to receive double-dose (600-mg loading dose followed by 150 mg daily for 7 days, then 75 mg daily) or standard-dose (300-mg loading dose followed by 75 mg daily) clopidogrel and high-dose (300-325 mg daily) or low-dose (75-100 mg daily) ASA.\(^{35}\) After 30 days, the primary composite outcome of cardiovascular death, MI, or stroke did not differ between the double-dose and standard-dose clopidogrel recipients (4.2% vs 4.4%, absolute risk reduction 0.2%; \(P = 0.30\)). However, a significant interaction associated with PCI was observed such that patients who underwent PCI experienced a significant 0.6% absolute risk reduction (3.9% vs 4.5%; \(P = 0.039\)), whereas patients who did not undergo PCI experienced a nonsignificant 0.6% absolute risk increase (4.9% vs 4.3%; \(P = 0.23\)). An interaction by ASA dose was also observed such that double-dose clopidogrel significantly reduced the risk of the primary outcome in recipients of high-dose ASA but not in recipients of low-dose ASA. When assessed using the TIMI criteria, double-dose clopidogrel did not significantly increase the risk of major bleeding (1.0% vs 0.9%, absolute risk increase 0.09%; \(P = 0.50\)); however, when assessed using trial-defined criteria, the risk of major bleeding was significantly increased by double-dose clopidogrel (2.5% vs 2.0%, absolute risk increase 0.5%; \(P = 0.01\)).

**Prasugrel vs clopidogrel post ACS.** In TRITON-TIMI 38 (TIRial to assess Improvement in Therapeutic Outcomes by optimiz- ing platelet inhibitionN with prasugrel–Thrombolysis In Myo-cardial Infarction 38), 13,608 patients with ACS (74% NSTEACS and 26% STEMI) scheduled to undergo PCI were randomized to receive prasugrel (60-mg loading dose followed by 10 mg daily) or clopidogrel (300-mg loading dose followed by 75 mg daily) following coronary angiography, in addition to ASA 75-162 mg daily.\(^{36}\) After a median 14.5-month follow-up, the relative risk of the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 19% in patients receiving prasugrel vs clopidogrel (9.9% vs 12.1%, absolute risk reduction 2.2%; \(P < 0.001\)). Prasugrel significantly reduced the risk of MI, urgent target vessel revascularization, and stent thrombosis, but these benefits occurred at the expense of significant increases in TIMI-defined major, life-threatening, and fatal bleeding. Secondary analysis revealed that the risk-benefit ratio was not favourable for patients aged \(\geq 75\) years with a low body weight or history of stroke or transient ischemic attack (TIA).\(^{36}\) A landmark analysis of TRITON-TIMI 38 showed that prasugrel significantly reduced the rate of MI compared with clopidogrel during the first 3 days of treatment (4.27% vs 5.24%, absolute risk reduction 0.97%; \(P = 0.008\)) and from day 3 through the end of follow-up (3.40% vs 4.79%, absolute risk reduction 1.39%; \(P < 0.0001\)).\(^{37}\) In a prespecified analysis of 3534 patients with STEMI and planned PCI enrolled in TRITON-TIMI 38, prasugrel reduced the relative risk of the primary composite endpoint by 21% compared with clopidogrel (10.0% vs 12.4%, absolute risk reduction 2.4%; \(P = 0.0221\)),\(^{38}\) notably, the study drug could be initiated before coronary angiography in this subgroup. The risks of major, life-threatening, or fatal bleeding were not significantly increased by prasugrel in the STEMI cohort. Prasugrel has been approved for use in patients with ACS who are to be managed with PCI based on the TRITON-TIMI38 findings. However, the product monographs indicate that prasugrel is contraindicated in patients with a known history of TIA or stroke and include a boxed warning highlighting the bleeding risks and recommending avoidance of prasugrel in patients aged \(\geq 75\) years or with a body weight \(< 60\) kg.\(^{39}\)

**Ticagrelor vs clopidogrel post ACS.** In the PLATO (PLATelet inhibition and patient Outcomes) trial, 18,624 patients with ACS (62% NSTEACS and 38% STEMI) were randomized to ticagrelor (180-mg loading dose followed by 90 mg twice daily) or clopidogrel (300- to 600-mg loading dose followed by 75 mg daily) in addition to ASA 75-100 mg daily.\(^{40}\) The relative risk of the primary composite endpoint of vascular death, MI, or stroke at 12 months was reduced by 16%
in patients receiving ticagrelor vs clopidogrel (9.8% vs 11.7%, absolute risk reduction 1.9%; \( P < 0.001 \)). Unexpectedly, ticagrelor was associated with a 21% relative reduction in both cardiovascular (4.0% vs 5.1%, absolute risk reduction 1.1%; \( P < 0.001 \)) and all-cause (4.5% vs 5.9%, absolute risk reduction 1.4%; \( P < 0.001 \)) mortality. Ticagrelor did not increase trial-defined major bleeding overall but was associated with a 19% relative increase in non-CABG-related, trial-defined major bleeding (4.5% vs 3.8%, absolute risk increase 0.7%; \( P = 0.03 \)). Ticagrelor was associated with some unusual side effects, including transient dyspnea and bradycardia, although these rarely required study drug discontinuation.^^40^^

### RECOMMENDATION (Summarized in Table 2 and Figs. 1-3)

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 75-162 mg daily for \( \geq 14 \) 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 medically managed, ticagrelor* ASA 75-162 mg/d plus ticagrelor* 90 mg twice daily for 12 mo I (B)

For patients presenting with NSTEACS who are medically managed, clopidogrel 75 mg daily is recommended in addition to ASA 75-162 mg daily for \( \geq 1 \) 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 75-162 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 with ACS who undergo stent implantation and have an increased risk of thrombosis (eg, STEMI, history of diabetes mellitus, prior documented stent thrombosis), prasugrel 10 mg daily may be considered in addition to ASA 75-162 mg daily for \( \geq 1 \) 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 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 75-162 mg daily for 12 months (Class I, 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 \( \geq 75 \) y, or with a weight < 60 kg (Class III, Level B).

For patients with ACS, ticagrelor 90 mg twice daily may be added to ASA 75-162 mg daily for 12 months (Class I, Level A).

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### Table 2. Recommendations for antiplatelet therapy following hospital discharge for acute coronary syndrome

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommended Dose and Duration of Therapy</th>
<th>Class (Level of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Use 75-162 mg/d indefinitely</td>
<td>I (A)</td>
</tr>
<tr>
<td>ASA</td>
<td>75-162 mg/d is recommended to minimize bleeding complications</td>
<td>Ia (B)</td>
</tr>
<tr>
<td>ASA + clopidogrel</td>
<td></td>
<td>Ia (B)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75 mg/d indefinitely in ASA allergy or intolerance</td>
<td>IIa (B)</td>
</tr>
</tbody>
</table>

ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; NSTEACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

* Currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.
**Postdischarge Management of Acute Coronary Syndrome**

**Figure 1.** Postdischarge management of acute coronary syndrome. After an acute coronary syndrome, the outpatient antiplatelet therapy recommendations after ST-elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndrome (NSTEACS) in medically managed or after percutaneous intervention. In general, the ADP P2Y12 receptor antagonist added to ASA in the acute setting should be maintained for the duration of therapy (Class I, Level C). ADP, adenosine diphosphate; ASA, acetylsalicylate acid; CABG, coronary artery bypass graft. *Currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.*

The optimal duration of long-term dual-antiplatelet therapy (ie, > 1 year) post PCI remains an area of current investigation.

**ASA in patients undergoing PCI**

ASA was the first antiplatelet agent used after coronary stenting. The initial studies exploring single antiplatelet therapy with ASA in combination with oral anticoagulation with warfarin reported a very high rate of stent thrombosis that ranged from 15% to 20%.41-43 Despite these shortcomings, ASA remains the cornerstone of antiplatelet therapy post-coronary stenting. Based on the results of a meta-analysis of 200 trials, low-dose ASA (75-150 mg daily) provides a benefit similar to that of higher ASA doses (160-325 mg daily) but is associated with a lower incidence of bleeding.12

**Dual-Antiplatelet therapy in patients with ACS who undergo PCI**

The efficacy and safety of dual-antiplatelet therapy with ASA and an ADP P2Y12 antagonist in patients with ACS who undergo PCI have been assessed in prespecified analyses of large ACS trials. For patients with NSTEACS who undergo PCI, the benefit of dual ASA and clopidogrel therapy was demonstrated in the PCI-CURE trial (N = 2658), in which ASA plus clopidogrel reduced the relative risk of the primary composite endpoint by 30% vs ASA alone (4.5% vs 6.4%, absolute risk reduction 1.9%; P = 0.03).44 Similarly,

**Antiplatelet Therapy for Secondary Prevention in the First Year Following Percutaneous Coronary Intervention**

**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

During PCI, mechanically induced plaque rupture and vessel injury, combined with the implantation of a metallic stent scaffolding, require effective antiplatelet therapy to prevent thrombosis. Dual-antiplatelet therapy with ASA and either ticlopidine, clopidogrel, prasugrel, or ticagrelor is critical at the time of the procedure, as well as in the month following BMS implantation and the 6-12 months after DES implantation, because it allows time for vessel healing, plaque stabilization, and reendothelialization.10 Importantly, premature discontinuation of dual-antiplatelet therapy post PCI is associated with increased risks of subacute (1-30 days) and late (30 days to 1 year) stent thrombosis.
Postdischarge Management of ST Segment Elevation Myocardial Infarction

**STEMI**

- **Clopidogrel 75 mg OD or ticagrelor 90 mg BID in addition to ASA 75-162 mg daily for at least 14 days (Class I, Level C)**
  - if ASA intolerant

**Increased risk of stent thrombosis**

- **Clopidogrel 75 mg OD or ticagrelor 90 mg BID in addition to ASA 75-162 mg daily for at least 14 months (Class I, Level B)**
  - if patient with high risk of thrombosis and low risk of bleeding (Class IIb, Level C)

**Medically managed**

- **ASA 75-162 mg OD, Indefinite Therapy (Class I, Level A)**
  - if ASA intolerant

**Percutaneous Intervention**

- **Prasugrel 10 mg daily may be considered in the absence of:**
  - increased bleeding risk
  - likely to undergo CABG within 7 days
  - history of stroke or transient ischemic attack (TIA)
  - age > 75 years
  - weight < 60 kg (Class IIa, Level B)

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**Figure 2.** Postdischarge management of ST-elevation myocardial infarction (STEMI). The outpatient management after a STEMI is outlined for patients medically managed or after percutaneous intervention. In general, the ADP P2Y12 receptor antagonist added to ASA in the acute setting should be maintained for the duration of therapy (Class I, Level C). ADP, adenosine diphosphate; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft. *Currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.

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The PCI-CLARITY study (N = 1863) demonstrated benefit for ASA and clopidogrel in patients with STEMI (relative risk reduction 46%, 3.6% vs 6.2%, absolute risk reduction 2.6%; P = 0.008). The benefit of adding the ADP P2Y12 receptor blockers prasugrel and ticagrelor to ASA in patients with ACS undergoing PCI has also been shown. Among the 10,074 patients with NSTEACS in TRITON-TIMI 38, all of whom were randomized after coronary angiography and underwent PCI, prasugrel plus ASA reduced the relative risk of the primary composite endpoint by 19% vs clopidogrel plus ASA (9.9% vs 12.1%, absolute risk reduction 2.2%; P < 0.05). Similar reductions were observed for the 3534 patients with STEMI (relative risk reduction 21%, 10.0% vs 12.4%, absolute risk reduction 2.4%; P < 0.05). In the PLATO invasive study of 13,408 patients scheduled to undergo an invasive management strategy, ASA plus the reversible, direct-acting ADP receptor antagonist ticagrelor reduced the risk in patients with STEMI (N = 6575; relative risk reduction 14%, 8.1% vs 9.5%, absolute risk reduction 1.4%; P = ns) and NSTEACS (N = 6805; relative risk reduction 17%, 9.7% vs 11.8%, absolute risk reduction 2.1%; P < 0.05). Importantly, a reduction in cardiovascular mortality was also demonstrated in the overall PLATO invasive population (relative risk reduction 18%, 3.4% vs 4.3%, absolute risk reduction 0.9%; P = 0.0250).

**Dual-Antiplatelet therapy in patients with stable CAD who undergo nonurgent PCI**

Only 1 randomized study, the CREDO (Clopidogrel for the Reduction of Events During Observation) trial, has examined the benefit of dual-antiplatelet therapy in 2116 patients with stable CAD who underwent nonurgent PCI with bare-metal stent (BMS) placement. In addition to ASA 325 mg daily, patients were randomly assigned to receive a 300-mg clopidogrel loading dose or no loading dose before PCI. Thereafter, all patients received clopidogrel 75 mg daily until day 28. From day 29 to 12 months, patients in the loading-dose group continued to receive clopidogrel 75 mg daily, whereas those in the control group received placebo. At 12 months, the relative risk of the primary composite endpoint of death, MI, or stroke was reduced by 26.9% in the group that received a clopidogrel loading dose and long-term treatment (8.5% vs 11.5%, absolute risk reduction 3.0%; P = 0.02). Although it is not possible to separate the benefit of clopidogrel preloading from the prolonged duration of dual-antiplatelet therapy, a sustained benefit of the prolonged dual-antiplatelet strategy was observed after nonurgent PCI.
In several studies, dual-antiplatelet therapy with ASA and ticlopidine significantly reduced cardiac events after implantation of a BMS compared with either ASA alone or ASA plus oral anticoagulation. This protective effect mainly resulted from a reduction of acute and subacute stent thrombosis, which had an incidence of < 1%. Moreover, most studies showed a dramatic reduction of hemorrhagic complications with ASA plus ticlopidine compared with combined ASA and oral anticoagulant therapy. In the FANTASTIC (Full ANTicoagulation vs ASpirin and Ticlopidine) study, hemorrhagic events occurred in 13.5% of ASA-plus-ticlopidine recipients and 21% of ASA–plus–vitamin K antagonist recipients. Despite its superiority to ASA and oral anticoagulation, the clinical use of ticlopidine was limited due to its hematologic toxicity, which subsequently led to substitution with clopidogrel. Indeed, 3 randomized studies and a meta-analysis showed that clopidogrel was at least as effective as ticlopidine and was a well-tolerated, much safer antiplatelet therapy choice.

### Dual-Antiplatelet therapy after DES implantation

DESs have diminished the need for repeat revascularization secondary to in-stent restenosis, the main limitation associated with BMS implantation. Currently, DES usage varies across regions, but their use is predicted to increase with the availability of later-generation DES that are associated with decreased costs, improved deliverability, and enhanced clinical outcomes.

Although stent thrombosis occurs following only 0.5%-2% of stent placements, it is a major safety concern and limits the efficacy of PCI. Stent thrombosis occurs most frequently in the first month after stent implantation (subacute), but numerous cases of late (30 days to 1 year) and very late (> 1 year) stent thrombosis have been described, particularly in DES recipients. Furthermore, stent thrombosis is associated with rates of mortality as high as 45%. Predictors of late stent thrombosis include stenting of small vessels, presence of multiple lesions, long segments implanted with overlapping stents, stenting of ostial bifurcation lesions, suboptimal stent deployment, decreased left ventricular function, advanced age, diabetes mellitus, renal failure, and ACS.
Premature discontinuation of dual-antiplatelet therapy is associated with a marked increased risk of stent thrombosis, and in multivariate analysis, premature discontinuation of dual-antiplatelet therapy is an independent predictor of stent thrombosis. However, the optimal duration of dual-antiplatelet therapy post stenting is unknown. Registry data derived from DES recipients have demonstrated a protective effect of continuing dual-antiplatelet therapy beyond 24 months. In a recent analysis of 2 randomized clinical trials, 2701 patients who had received a DES and were free of major adverse cardiac or cerebrovascular events and major bleeding for a period of ≥ 12 months were randomized to receive clopidogrel 75 mg daily plus ASA 100-200 mg daily or ASA 100-200 mg daily alone. In this study, the use of dual-antiplatelet therapy for a period ≥ 12 months post stenting was not significantly more effective than ASA monotherapy in reducing the rate of the primary composite endpoint of MI or death from cardiac causes (hazard ratio [HR] 1.65, 95% CI 0.80-3.36; P = 0.17). The Dual Anti-Platelet Therapy (DAPT) study, a large multicenter, randomized controlled trial comparing the efficacy and safety of 1 vs 2 years of dual-antiplatelet therapy with ASA and either clopidogrel or prasugrel with ASA following successful DES placement (ClinicalTrials.gov Identifier NCT00977938), is under way and may provide more information on the optimal duration of dual-antiplatelet therapy in this setting.

Thus, in patients perceived to be at increased risk for stent thrombosis or in whom stent thrombosis could be related to dire consequences, continuation of dual-antiplatelet therapy beyond 1 year may be considered with the ideal duration remaining unknown. The individual patient decision to continue beyond 1 year must also take into account perceived bleeding risks of such an individual.

RECOMMENDATION (Summarized in Table 3 and Fig. 4)

Indefinite therapy with ASA 75-162 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 BMS implantation should be given clopidogrel 75 mg daily in addition to ASA 75-162 mg daily for ≥ 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 75-162 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 75-162 mg daily for 12 months (Class I, Level A). Continuation of dual-antiplatelet therapy with ASA 75-162 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 75-162 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 of weight < 60 kg (Class III, Level B).

### Table 3. Recommendations for antiplatelet therapy following hospital discharge for Percutaneous Coronary Intervention (PCI)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommended dose and duration of therapy</th>
<th>Class (level of evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>75-162 mg/d indefinitely</td>
<td>I (A)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75 mg/d indefinitely in ASA allergy or intolerance</td>
<td>Ia (C)</td>
</tr>
<tr>
<td>ASA + clopidogrel</td>
<td><strong>Post-BMS</strong>&lt;br&gt;ASA 75-162 mg/d and clopidogrel 75 mg/d for ≥ 1 mo&lt;br&gt;ASA 75-162 mg/d and clopidogrel 75 mg/d for up to 12 mo in the absence of an excessive risk of bleeding&lt;br&gt;For patients with a high risk of bleeding, a BMS should be implanted and ASA 75-162 mg/d and clopidogrel 75 mg/d continued for a minimum of 2 wk&lt;br&gt;ASA 75-162 mg/d and clopidogrel 75 mg/d beyond 1 y may be considered if the risk of stent thrombosis is high and the risk of bleeding is low</td>
<td>I (B)&lt;br&gt;I (B)&lt;br&gt;I (B)&lt;br&gt;I Ib (C)</td>
</tr>
<tr>
<td>ASA + prasugrel</td>
<td><strong>Post-ACS</strong>&lt;br&gt;ASA 75-162 mg/d and prasugrel 10 mg/d may be considered in patients with increased risk of stent thrombosis (eg, STEMI, history of diabetes mellitus, or prior documented stent thrombosis)&lt;br&gt;ASA 75-162 mg/d plus prasugrel 10 mg/d should be avoided in patients with an increased bleeding risk, likely to undergo CABG within 7 d, with a history of stroke or TIA, aged ≥ 75 y, or weight &lt; 60 kg</td>
<td>Ia (B)&lt;br&gt;III (B)</td>
</tr>
<tr>
<td>ASA + ticagrel*</td>
<td><strong>Post-ACS</strong>&lt;br&gt;ASA 75-162 mg/d and ticagrel* 90 mg twice daily for 12 mo</td>
<td>I (B)</td>
</tr>
</tbody>
</table>

The clinical reason for PCI must be taken into consideration. Specifically, if there is a discrepancy in the suggested duration of therapy, the longer duration of dual antiplatelet therapy is preferred.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

* Currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.
For patients with ACS who undergo stent implantation, ticagrelor 90 mg twice daily may be added to ASA 75-162 mg daily for at least 1 month and up to 12 months (Class I, Level B). (Ticagrelor is currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.)

**Antithrombotic Therapy Beyond 1 Year After Acute Coronary Syndrome or Percutaneous Coronary Intervention**

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

Antithrombotic therapy is a mainstay in the management of patients with CAD, whether acute or chronic. Other sections of this document clearly define the evidence and recommendations for the use of antithrombotic agents in the short-term management of patients with ACS or those who undergo PCI or CABG. In this section, the available data supporting long-term antithrombotic therapy in patients with stable CAD will be presented and consensus recommendations provided. However, before presenting the evidence for long-term antithrombotic therapy, it is important to note that no clinical trial can truly provide sufficient data to recommend indefinite use of medical therapy. Many of the studies quoted are indeed longer-term extensions of studies initiated during or very shortly after the acute phase and are discussed in the previous sections. Thus, “indefinite” recommendations are based on extrapolations from trials based on the data available and a contemporary understanding of CAD pathophysiology. Accordingly, therapy with certain agents (e.g., lipid-lowering agents, renin-angiotensin-aldosterone system [RAAS] inhibitors) is generally accepted as life-long treatments despite the finite duration of...
clinical trials. Additionally, the optimal balance among efficacy, safety, cost-effectiveness, and affordability must be individualized.

ASA therapy beyond 1 year following a medically managed ACS

Some of the initial evidence suggesting a benefit for long-term ASA therapy is from a multicenter Canadian trial conducted by Cairns and colleagues. In this randomized trial of 555 patients with UA, those treated with ASA 325 mg 4 times daily (alone or with sulfipyrazone 200 mg 4 times daily) for a mean of 18 months experienced a 51% reduction in the relative risk of the primary composite endpoint of cardiac death or nonfatal MI compared with patients who received sulfipyrazone alone or placebo (8.6% vs 17.0%, absolute risk reduction 8.4%; P = 0.008). The most comprehensive data supporting the long-term benefit of ASA following ACS come from the Antithrombotic Trialists’ Collaboration 2002 update. Among 18,788 patients with a history of previous MI, treatment with ASA vs control for a mean of 27 months prevented 36 vascular events (vascular death, MI, or stroke) per 1000 patients treated (13.5% vs 17.0%; P < 0.0001). Specifically, treatment with ASA prevented 18 nonfatal MIs (P < 0.0001), 5 nonfatal strokes (P = 0.002), and 14 vascular deaths (P = 0.0006) per 1000 patients treated.

A more recent update of the Antithrombotic Trialists’ Collaboration that reported results by an intention-to-treat analysis for ASA recipients only shed new light on the role of ASA in the secondary prevention of CAD. This meta-analysis included 16 secondary prevention trials and a total of 17,000 individuals, 43,000 person-years, and 3306 serious vascular events. The trials were highly variable regarding the dose of ASA used (50 mg once daily to 500 mg 3 times daily) and length of follow-up (averages ranged from 1 year to > 3 years). ASA appeared to reduce vascular mortality (rate ratio [RR] 0.91, 95% CI 0.82-1.00; P = 0.06) but had no significant effect on other mortality (RR 0.85, 95% CI 0.66-1.08; P = 0.2), leading to a 10% reduction in total mortality (RR 0.90, 95% CI 0.82-0.99; P = 0.02). A nonsignificant increase in hemorrhagic stroke was observed in the secondary prevention trials, but reductions of about one-fifth in total stroke (2.08% vs 2.54% per year; P = 0.002) and coronary events (4.3% vs 5.3% per year; P < 0.0001) were observed. No heterogeneity of effect between men and women was observed for any of the secondary prevention outcomes. Despite the potential for an increased risk of hemorrhagic stroke, hypothetical calculations of the absolute effects of ASA allocation on 5-year outcomes suggest a substantial net benefit of ASA in reducing nonfatal vascular events that is irrespective of age or sex.

The optimal ASA dose has not been definitively established by directly comparing different dosing regimens in large, randomized clinical trials. However, most evidence suggests that low-dose ASA is preferable to higher doses for long-term secondary prevention of CAD. In the 2002 Antithrombotic Trialists’ Collaboration update, an analysis of 3 trials (n = 3570) that directly compared ASA ≥ 75 mg daily with ASA < 75 mg daily failed to demonstrate a significant difference in vascular events between the dose regimens. Considering both direct and indirect comparisons of ASA dose, the odds of a vascular event were reduced by 19% with ASA 500 mg to 1500 mg daily, by 26% with ASA 160 mg to 325 mg daily, and by 32% with ASA 75 mg to 150 mg daily. Authors of another meta-analysis specifically addressing the optimal ASA dose concluded that there is little evidence supporting increased efficacy of ASA doses > 75-81 mg daily but much evidence to suggest that larger doses significantly increase the risk of gastrointestinal bleeding.

Clopidogrel vs ASA for long-term management of patients with ACS

The CAPRIE study compared clopidogrel 75 mg daily with ASA 325 mg daily in 19,185 patients with MI experienced within 35 days, ischemic stroke experienced between 1 week and 6 months of enrollment, or symptomatic PAD. After a mean follow-up of 1.91 years, clopidogrel reduced the relative risk of the primary composite endpoint of vascular death, MI, or ischemic stroke by 8.7% vs ASA (5.32% vs 5.83% per year, absolute risk reduction 0.51% per year; P = 0.043). No major differences in safety between the 2 groups were observed. However, heterogeneity by enrolling condition was observed such that patients with a history of symptomatic PAD had improved outcomes with clopidogrel but patients with a history of stroke had only a marginal benefit and patients with a history of MI had none (relative risk increase 3.7%, 5.03% vs 4.84% per year, absolute risk increase 0.19% per year; P = 0.66).

Antiplatelet therapy in addition to ASA beyond 1 year for patients with medically managed ACS

Clopidogrel. Overall, there is a paucity of a priori data evaluating the long-term (ie, > 1 year) use of clopidogrel in addition to ASA. Much of the evidence supporting its long-term use comes from the CURE trial of patients with NSTEACS. In analysis of outcomes by treatment strategy (medical management, PCI, or CABG), medically managed patients (n = 7985) experienced a significant 20% relative reduction in the risk of the primary composite endpoint of cardiovascular death, nonfatal MI, or stroke at 12 months, the same benefit observed in the overall patient population. However, the optimal duration of clopidogrel therapy within 1 year of the event remains controversial given that most of the benefit associated with clopidogrel in the CURE trial was observed within the first month, although it persisted for the entire 12-month follow-up.

Additional data on the relative benefits of long-term dual-antiplatelet therapy with ASA and clopidogrel in patients with CAD come from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial. The CHARISMA trial was a prospective, randomized, blinded, placebo-controlled study that compared the efficacy and safety of clopidogrel 75 mg once daily plus ASA 75-162 mg once daily vs ASA 75-162 mg once daily alone in patients with clinically evident cardiovascular disease or multiple cardiovascular risk factors. In the overall trial of 15,603 patients, there was no statistical difference in the primary composite endpoint of cardiovascular death, MI, or all-cause stroke in the group treated with clopidogrel and ASA vs ASA alone after a median 28 months of follow-up (RR 0.93, 95% CI 0.83-1.05; P = 0.22). However, in the predefined subgroup of patients with established cardiovascular disease (n = 12,153), the relative risk of the primary endpoint was reduced by 12% (6.9% vs 7.9%, RR 0.88, 95% CI 0.77-0.998; P = 0.046) with no excess of GUSTO (Global Utilization of
Strategies to prevent Thrombosis-defined severe bleeding.

Conversely, no benefit was observed for the 3284 patients with multiple risk factors only (RR 1.20, 95% CI 0.91-1.59; P = 0.20), and a higher rate of GUSTO-defined severe bleeding was observed for clopidogrel-plus-ASA recipients. In a post-hoc analysis of the more narrowly defined "CAPRIE-like" subgroup of 9478 patients with documented prior MI (median time from event 23.6 months), ischemic stroke (median time from event 3.5 months), or symptomatic PAD (median time from diagnosis 23.6 months), the relative risk of the primary composite endpoint was significantly lower for clopidogrel plus ASA vs ASA alone after a median 27.6-month follow-up (HR 0.83, 95% CI 0.72-0.96; P = 0.02).

A slightly larger benefit was observed for the 3846 patients who had a prior MI (HR 0.77, 95% CI 0.61-0.98; P = 0.031). In neither the CAPRIE-like subgroup nor the prior MI subgroups was the risk of GUSTO-defined severe bleeding significantly increased.

**Prasugrel and ticagrelor.** There is even less clinical evidence to support the long-term use of prasugrel and ticagrelor in patients with stable CAD. TRITON-TIMI 38 compared the effect of prasugrel (60-mg loading dose, 10 mg daily), another thienopyridine, with clopidogrel (300-mg loading dose, 75 mg daily) in 13,608 patients with moderate- to high-risk ACS scheduled to undergo PCI. All patients also received ASA 75-162 mg daily. After a median 14.5 months of follow-up, prasugrel was associated with a 19% relative reduction and a 2.2% absolute reduction in the risk of the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (HR 0.81, 95% CI 0.73-0.90; P < 0.001), mainly due to a reduction of nonfatal MI (HR 0.76, 95% CI 0.67-0.85; P < 0.001). However, an increase in TIMI-defined major (HR 1.32, 95% CI 1.03-1.68; P = 0.03) and fatal (0.4% vs 0.1%; P = 0.002) bleeding was observed with prasugrel. A landmark analysis of TRITON-TIMI 38 showed that the benefit of prasugrel over clopidogrel emerged within the first 3 days of therapy and was maintained over the median 15-month follow-up period.

Notably, the significant increase in TIMI-defined major bleeding associated with prasugrel in the primary analysis emerged only on the third day of treatment but continued throughout the study.

The PLATO trial examined, in addition to ASA 75-100 mg daily, the effect of ticagrelor (180-mg loading dose, 90 mg twice daily), an oral, reversible P2Y12 antagonist, vs that of clopidogrel (300- to 600-mg loading dose, 75 mg once daily) in 18,624 patients admitted to the hospital with ACS. A 16% relative reduction and 1.9% absolute reduction in the risk of the primary composite endpoint of vascular death, MI, or stroke were demonstrated at 12 months (HR 0.84, 95% CI 0.77-0.92; P < 0.001). All individual components of the primary endpoint were significantly reduced, including vascular death. In contrast with TRITON-TIMI 38, the bleeding risks observed in the PLATO trial appeared similar throughout the study duration, although ticagrelor was associated with a higher rate of non-CABG-related, trial-defined major bleeding (4.5% vs 3.8%; P = 0.03). In a landmark analysis of the PLATO trial, significant benefits for ticagrelor over clopidogrel emerged within the first 30 days and appeared to diverge in further favour of ticagrelor as treatment continued through the 1-year follow-up.

**Post-ACS and post-PCI dual-antiplatelet therapy beyond 1 year**

The evidence derived from large clinical trials that support the use of dual-antiplatelet therapy beyond 1 year post stenting is limited. Anecdotal pathophysiological reports, various DES trial meta-analyses, and BASKET-LATE (Basel Stent Kosten Efektivitäts Trial–LaTe Thrombotic Events) raised concern about an increase in late and very late stent thrombosis in DES recipients. A recent report from South Korea combined the results of 2 very similar randomized clinical trials in which 2701 patients who had received a DES and had been free of major adverse cardiac or cerebrovascular events and major bleeding for a period of 12 months were randomized to receive clopidogrel 75 mg daily plus ASA 100-200 mg daily or ASA 100-200 mg daily alone. The 2 studies were open-label, but excellent study drug adherence was reported. In this analysis, the use of dual-antiplatelet therapy for a period > 12 months was not significantly more effective than ASA monotherapy in reducing the rate of MI or death from cardiac causes as an opposite trend toward higher event rates was observed (HR 1.65, 95% CI 0.80-3.36; P = 0.17). It should be noted that due to a lower than expected rate of the primary endpoint, the study was underpowered to detect a clinically significant difference in outcomes.

The US Food and Drug Administration (FDA) confirmed a significant reduction of long-term restenosis when DESs are used as recommended (ie, “on-label”), whereas “off-label” use of DES may be associated with an increased risk of very late stent thrombosis, MI, and death. However, more recent data suggest that off-label use of DES does not incur a greater risk than on- or off-label use of BMS.

Based on the preponderance of evidence, the Canadian Association of Interventional Cardiology recommends that all patients treated with DES should remain on ASA and clopidogrel for ≥ 12 months. They further suggest that dual-antiplatelet therapy of a longer duration should be considered in patients treated with DES or in those whom stent thrombosis is likely to have fatal consequences (eg, recipients of multiple stents or stents for bifurcation lesions, or left main disease). Because this statement was published in 2007, no new, compelling data have led to any need to deviate from these recommendations.

**RECOMMENDATION (Summarized in Fig. 5)**

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 75-162 mg daily and clopidogrel 75 mg daily may be considered beyond 1 year in patients with ACS (see post-ACS recommendations) who are medically managed provided the risk of bleeding is low (Class IIb, Level C).

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

Antiplatelet Therapy for Secondary Prevention Following Coronary Artery Bypass Grafting

Working Group: Raymond Cartier, MD, FRCPC

For 30 years, antiplatelet therapy has been the gold standard for preventing saphenous vein graft closure after CABG. ASA is recognized as the standard of care and is generally continued indefinitely given its benefit in preventing subsequent clinical events, although there is no evidence in the literature that antiplatelet therapy improves arterial graft patency.

Alternative antithrombotic therapy for preventing saphenous vein graft occlusion

Although ASA is the standard of care in preventing venous graft occlusion post CABG, other antiplatelet agents have been shown to be effective. Prospective randomized trials have shown ticlopidine 250 mg twice daily to be an effective means of preventing graft closure, with a benefit that on indirect comparison appears to be similar to that of ASA. In contemporary clinical practice, clopidogrel is recommended instead of ticlopidine for patients allergic to or intolerant of ASA because clopidogrel is safer. If ticlopidine is used, white cell count monitoring is mandatory after 1 to 2 weeks and monthly thereafter. Note, however, that no randomized trial has specifically studied the efficacy of clopidogrel in prevention of post-CABG vein graft closure. Indobufen, a reversible inhibitor of platelet cyclooxygenase, and the combination of ASA and dipyridamole were once used to prevent early graft failure at 1 year but are no longer used due to side effects and a lack of documented efficacy.

Warfarin appears to be as effective as antiplatelet therapy in preventing saphenous graft closure post CABG, but it is associated with a higher risk of bleeding complications. However, there is clinical evidence that reduced-intensity anticoagulation could maintain the antithrombotic effect with less anticoagulant-related bleeding. The combination of warfarin and ASA 330 mg 3 times daily plus dipyridamole 75 mg 3 times daily was shown to be superior to warfarin alone, but no trial has directly compared ASA plus warfarin with ASA alone. (Further information on the long-term use of warfarin and ASA is available in “Combination Therapy With Warfarin and ASA: When to Use, When to Consider, When to Avoid.”)
Optimal dose of ASA post CABG. The optimal dose of ASA after CABG has been a topic of debate. Following their extensive review of 114 manuscripts, Dunning and Das suggested that ASA 325 mg daily was the optimal dose for providing the best balance among saphenous vein graft patency, patient survival, and adverse events. In a meta-analysis of 17 studies, Fremes and colleagues concluded that low (≤100 mg) and medium (325 mg) daily doses of ASA were more effective than high-dose (7975 mg) ASA in preventing saphenous vein graft occlusion and caused less gastrointestinal side effects.

Optimal timing of antiplatelet therapy initiation post CABG. In their meta-analysis, Fremes and colleagues established that to be effective, ASA had to be initiated within the first 24 hours after surgery. There was evidence that the greatest benefit was obtained when ASA was initiated in the hour immediately following surgery, although increased postoperative bleeding was reported. They concluded that the optimal benefit of ASA administration was observed when it was started 6 hours after surgery completion. They found no advantage for starting ASA prior to surgery in regard to graft occlusion prevention.

Clopidogrel in CABG

To date, no prospective, randomized trial has shown that adding clopidogrel to ASA after CABG improves saphenous vein graft closure prevention. There is observational evidence that dual-antiplatelet therapy may be helpful in the first month after off-pump CABG but not beyond. For conventional on-pump surgery, the ongoing CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) trial was recently published. Approximately 100 post-CABG patients were randomized to receive either ASA 162 mg daily plus placebo or ASA 162 mg daily plus clopidogrel 75 mg daily for 1 year, after which intravascular ultrasound and angiography was performed to assess graft patency. No difference in the primary outcome of graft intimal hyperplasia was noted for dual-antiplatelet therapy over ASA alone. No statistical differences were noted in the secondary vascular or graft patency outcomes, nor were differences noted in major bleeding.

In a direct comparison of clopidogrel 75 mg daily vs clopidogrel 75 mg plus ASA 100 mg daily conducted among 197 patients, angiographic patency at 1 and 12 months post surgery was similar in the 2 groups, suggesting the absence of benefit for adding clopidogrel to ASA following CABG.

ACS, PCI, and CABG. Although there is no proven benefit for the postoperative use of clopidogrel plus ASA in improving graft patency, dual-antiplatelet therapy might benefit specific subsets of patients in regard to general thrombotic complications. Several randomized clinical trials, including the CURE and CREDO trials, have provided randomized data to clinicians. In the CURE trial of patients with NSTEACS, the majority of benefit observed for clopidogrel (300-mg loading dose, 75 mg daily) plus ASA (75 mg to 325 mg daily) in the overall population was maintained in the 2072 patients who underwent CABG as part of their revascularization strategy (relative risk reduction in the composite endpoint of cardiovascular death, nonfatal MI, or stroke, 11%; 14.5% with clopidogrel vs 16.2% with ASA; absolute risk reduction 1.7%).

Most of this benefit was derived from those patients who underwent CABG during the initial hospitalization period (relative risk reduction 19%, 13.4% vs 16.4%, absolute risk reduction 3.0%). The significant benefit of clopidogrel was limited to the period prior to CABG. In the CREDO trial of patients undergoing non-urgent PCI, the subgroup of patients who underwent CABG instead of PCI showed some reduction in the risk of sudden death, new MI, or stroke over the following 12 months. However, the cohort of surgical patients was small (n = 83) and the results were not significant.

There is some evidence that the in-stent thrombosis could be as high as 20% in patients undergoing CABG shortly after PCI. Therefore, patients requiring CABG after PCI should remain on clopidogrel and ASA for 9 to 12 months as recommended per the post-PCI guidelines, particularly if the stented vessel is not bypassed during surgery. Clopidogrel can be suspended if the stented vessel is bypassed unless other preoperative conditions that suggest its use are not met.

**RECOMMENDATION (Summarized in Fig. 6)**

For all patients who undergo saphenous vein CABG, ASA 75-162 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 and have a contraindication to ASA, clopidogrel 75 mg daily is preferred over ticlopidine 250 mg twice daily due to the superior safety profile of clopidogrel (Class IIa, Level C).

In patients undergoing CABG after PCI, dual-antiplatelet therapy with ASA 75-162 mg daily and clopidogrel 75 mg daily may be maintained for 9-12 months unless the stented vessel is adequately bypassed (Class IIb, Level C).

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

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

Patients who present with TIA or ischemic stroke are at an increased risk of recurrent stroke and other vascular events. The risk is highest in the initial 2 days after the event and may remain high for the subsequent 90 days. Overall, the risk of stroke at 90 days is ~17% (95% CI 9%-25%) when the outcome is actively ascertained, and the risk of combined vascular complications (ie, MI, stroke, and vascular death) is ~44% (95% CI 42%-46%) at 10 years. The ABCD2 score is often used to classify the risk of subsequent stroke. Clinical features that should be considered when assessing the risk of ischemic stroke recurrence include age, the type of symptoms (eg, patients presenting with motor and speech impairment are at a high risk of early recurrence), the presence of diabetes or hypertension, and the duration of symptoms. Notably, expedited evaluation and early treatment may lower the risk of recurrence.

Recently updated consensus statements from the Canadian Stroke Network, the American Heart Association (AHA)/American Stroke Association, and the American College of Chest Physicians incorporate newer data on the use of antiplatelet agents in secondary ischemic stroke prevention.
Antithrombotic therapy for prevention of stroke in patients with a history of TIA or ischemic stroke

A number of trials have looked at the efficacy and safety of antithrombotic medications in the prevention of recurrence in patients with TIA and ischemic stroke. The best evidence is for antiplatelet agents, of which ASA has been studied most extensively. Overall, ASA reduces the risk of vascular events by \( \text{13\%} \) (95% CI 6%-19%) compared with controls. The second Antithrombotic Trialists' Collaboration meta-analysis published in 2002, the protective effects of ASA were observed for both young and old subjects and men and women and in patients with and without hypertension or diabetes. In the Algra and van Gijn mini–meta-analysis of trials specifically looking at stroke recurrence in patients with a previous history of TIA or ischemic stroke, the incidence of recurrent stroke was no different in patients taking high-dose (1000 mg daily) or low-dose (100 mg daily) ASA.

ASA compared with placebo. The Canadian Aspirin Trial was the first major study to evaluate the efficacy of ASA for reducing stroke recurrence. In total, 585 patients with TIA were enrolled in a randomized, blinded study comparing ASA 1300 mg daily (alone or in combination with sulfinpyrazone) with placebo. There was a significant 31% reduction in the relative risk of stroke or death in the ASA-treated group. The effect was sex-dependent (48% risk reduction in men vs no effect in women). The absence of an effect in women was likely due to an insufficient number of women enrolled in the trial.

In SALT (Swedish Aspirin Low-dose Trial), ASA 75 mg daily was compared with placebo in 1360 patients with TIA or minor ischemic stroke. There was a significant 18% reduction in the relative risk of recurrent stroke or death, as well as a significant 17% relative reduction in the risk of MI or other vascular death, in the ASA-treated group.

Comparison of different doses of ASA. The Dutch TIA Trial compared ASA 30 mg daily with ASA 283 mg daily in 3131 patients with TIA or minor ischemic stroke. The lower ASA dose was as effective as the higher dose in preventing the primary outcome of recurrent stroke, MI, or vascular death. Furthermore, fewer bleeding events were observed in the low-dose groups. The UK-TIA (United Kingdom Transient Ischaemic Attack) trial treated 2435 patients with TIA or minor ischemic stroke with ASA 600 mg twice daily (\( n = 815 \)), ASA 300 mg once daily (\( n = 806 \)), or placebo (\( n = 814 \)) in a prospective, randomized, and double-blinded fashion. There were no differences in stroke recurrence between the 2 doses of ASA, but the lower dose resulted in significantly fewer gastrointestinal complications. The odds of reaching the primary composite endpoint of stroke, MI, or vascular death were significantly lower (15%) in the 2 actively treated groups compared with the control group.

Other antiplatelet agents. Ticlopidine is a thienopyridine antiplatelet agent that blocks the platelet P2Y12 ADP receptor, resulting in an inhibition of fibrinogen binding to platelets. Two large trials evaluated the efficacy of ticlopidine in preventing recurrent stroke in patients with previous cerebrovascular disease. CATS (Canadian American Ticlopidine Study) enrolled 1072 patients who had sustained a thromboembolic stroke. The ticlopidine group reduced the relative risk of the primary endpoint, recurrent stroke, by 21% (95% CI 4%-38%) at 3 years. A 12%
(95% CI –2% to 26%) decrease in the relative risk of nonfatal stroke or death was also evident in the ticlopidine-treated patients compared with those who were treated with ASA.

Clopidogrel, another thienopyridine antiplatelet agent, was initially evaluated in stroke prevention in the CAPRIE study. The CAPRIE study enrolled 19,185 patients with a history of MI within 35 days of randomization (n = 6302), ischemic stroke between 1 week or 6 months of randomization (n = 6431), or symptomatic PAD (n = 6452) and randomized them to clopidogrel 75 mg daily or ASA 325 mg daily. In the total population, the risk of the primary composite endpoint of ischemic stroke, MI, or vascular death was significantly reduced from 5.83% per year in the ASA group to 5.32% per year in the clopidogrel group (relative risk reduction 8.7%, 95% CI 0.3%-16.5%; \( P = 0.043 \)). In the subgroup of patients with a history of ischemic stroke, clopidogrel reduced the event rate from 7.71% per year to 7.15% per year, although this difference was not significant (relative risk reduction 7.3%; \( P = 0.26 \)). However, the CAPRIE trial was not designed to examine treatment effects in individual patient subgroups.

There are additional studies that have compared the efficacy and safety of clopidogrel with other antiplatelet therapy regimens. These include the MATCH (Management of ATherothrombosis for Continued Health) and PRoFESS (Prevention Regimen For Effectively Avoiding Second Strokes) trials. In the MATCH trial, 7599 patients with ischemic stroke or TIA were treated with clopidogrel 75 mg daily or clopidogrel 75 mg daily plus ASA 75 mg daily for 18 months. \(^{108} \) The primary composite endpoint of ischemic stroke, MI, vascular death, or rehospitalization for an acute ischemic event was evident in 15.7% of patients receiving combination therapy and 16.7% of patients on clopidogrel-alone treatment. The 6.4% relative risk reduction associated with combination therapy was not significantly better than clopidogrel monotherapy (\( P = 0.244 \)). Additionally, there was a significantly higher risk of trial-defined life-threatening bleeds in the combination therapy group (2.6% vs 1.3%; \( P < 0.0001 \)). The PRoFESS trial was a comparison between clopidogrel 75 mg once daily and the combination of extended-release (ER) dipyridamole 200 mg twice daily and ASA 25 mg twice daily in 20,332 patients with ischemic stroke. \(^{109} \) After a mean duration of 2.5 years, no difference in the risk of the primary endpoint, stroke recurrence of any type, was observed (8.8% on clopidogrel vs 9.0% on ASA plus ER dipyridamole; HR 1.01; 95% CI 0.92-1.11). The rate of the secondary composite endpoint of stroke of any type, MI, or vascular death was 13.1% in each treatment group.

The combination of ASA and clopidogrel is recommended for patients post ACS and post PCI (see sections on ACS and PCI for specific recommendations). However, there are limited data on the use of this combination for stroke prevention. As evidenced in the MATCH trial, the long-term combination of ASA and clopidogrel is not superior to the use of clopidogrel alone and may increase the risk of systemic and intracranial hemorrhage (2.6% on combination and 1.3% on clopidogrel alone). \(^{108} \) The FASTER (Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence) trial, a small pilot study (N = 392) on the use of the combination initiated within 24 hours of TIA or minor ischemic stroke onset, suggested a trend toward better 90-day outcomes in the combination group compared with ASA 81 mg once daily alone. \(^{110} \) Six patients treated with clopidogrel and ASA experienced an intracranial or extracranial hemorrhage, whereas none treated with ASA alone did so. A larger study of 633 patients with minor ischemic stroke or TIA noted significantly increased rates of major and life-threatening bleeding in patients treated acutely with ASA plus clopidogrel vs ASA alone. \(^{111} \) Similar to the FASTER study, this effect was only noted in ASA-naïve subjects.

The combination of ER dipyridamole and ASA is considerably better than ASA alone in preventing recurrent stroke in patients with TIA or previous stroke. In ESPS-2 (European Stroke Prevention Study 2), the safety and efficacy of ER dipyridamole 200 mg twice daily plus ASA 25 mg twice daily were compared with ER dipyridamole 200 mg twice daily, ASA 25 mg twice daily, or placebo in 6602 patients with a history of ischemic stroke or TIA. \(^{112} \) After 2 years of follow-up, both ER dipyridamole (16% relative reduction) and ASA (18% relative reduction) were significantly better than placebo in reducing the risk of fatal or nonfatal recurrent stroke. The combination of ER dipyridamole and ASA was significantly better than placebo (37% relative risk reduction) and ASA (23% relative risk reduction). A second trial comparing ASA plus dipyridamole with ASA was ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial). In ESPRIT, 2739 patients with a history of ischemic stroke or TIA in the previous 6 months were randomized to ASA 30-325 mg per day with or without dipyridamole 200 mg twice daily. \(^{113} \) Notably, not all patients received ER preparations of dipyridamole, and the study was not blinded, although event adjudication was. After a mean follow-up of 3.5 years, ASA plus dipyridamole reduced the relative risk of the primary composite outcome of nonfatal stroke, nonfatal MI, vascular death, or nonfatal, trial-defined major bleeding by 20% compared with ASA alone (13% vs 16%, absolute risk reduction 3%). When major bleeding was excluded from the composite endpoint, the relative risk reduction was 22% (11% vs 14%, absolute risk reduction 3%). However, patients in the combination group more often discontinued study medication due to side effects, mainly headache. The most recent trial studying the efficacy and safety of ASA plus ER dipyridamole was the previously described PRoFESS trial. \(^{109} \)

**Summary**

Ischemic stroke comprises multiple mechanisms that include artery-to-artery emboli, cardioembolism, occlusion/damage of small vessels by localized mechanisms (ie, lacunar stroke), and a number of other uncommon conditions. Patients presenting with TIAs have similar underlying pathophysiology but recover earlier than patients who experience an ischemic stroke, likely due to faster reestablishment of blood flow to the ischemic region. The majority of studies examining the use of antiplatelet therapy in secondary stroke prevention enrolled patients with TIA or mild ischemic strokes and excluded patients with a cardioembolic mechanism or a rare cause of ischemic stroke. Treatment algorithms and published guidelines do not generally differentiate between patients with TIA or ischemic noncardioembolic stroke. Early treatment with antiplatelet agents and the appropriate management of associated risk factors remain the best means to prevent recurrent stroke and other vascular complications in patients with TIA or ischemic stroke.
In contrast, the Trans-Atlantic Inter-Society Consensus (TASC II) has recommended antiplatelet therapy, namely ASA or clopidogrel, for all patients with PAD at a grade IA level of recommendation.5 This recommendation is based on the Antithrombotic Trialists’ Collaboration meta-analysis, which concluded that antiplatelet agents as a class are effective in preventing vascular endpoints in patients with PAD.12

In the clinical setting, patients are said to have asymptomatic PAD whenever a bruit is found along major vessels or when peripheral pulsations are reduced or absent. Finding an abnormally enlarged artery, leading to suspicion of an aneurysm, is also evidence of asymptomatic PAD. The formal definition of asymptomatic PAD is usually described in the literature as an ankle-brachial index (ABI) ≤ 0.9.118,119

Patients with asymptomatic PAD usually harbour traditional risk factors; however, patients with asymptomatic PAD and diabetes or coexisting CAD or cerebrovascular disease are a subclass of patients who have different antiplatelet therapy indications. Patients with asymptomatic PAD with an ABI < 0.9 have been shown in many studies to present with a cardiovascular morbidity and mortality rate approximately halfway between that of a patient with a normal ABI and that of a patient with claudication.120

There is only 1 randomized clinical trial assessing the use of antiplatelet agents specifically in asymptomatic PAD.121 This study enrolled 3350 patients with an ABI ≤ 0.95 and randomized them to ASA 100 mg daily or placebo. No reduction in stroke, MI, revascularization, or mortality was demonstrated. A modest, non-significant increase in bleeding was observed in the ASA group. Similarly, a 2 × 2 factorial randomized clinical trial conducted in 1276 patients with diabetes and asymptomatic PAD (defined as ABI < 1.0) revealed an absence of benefit of ASA 100 mg once daily or antioxidant combined or alone compared with placebo after a mean follow-up of 6.7 years.122

The trial was powered to show an efficacy of 25%, and a higher than usual ABI was selected because of the notion that patients with diabetes have harder arteries. It is striking, however, that the median ABI of all patients in the study was ~0.9, which is the standard cutoff point for normality. A subgroup analysis of the 314 patients with an ABI ≤ 0.9 (roughly as many as > 0.9)
showed an odds ratio of 0.81 (0.58-1.14) for the primary endpoint that did not reach statistical significance (P = 0.089).

Patients with symptomatic PAD, including claudication, critical limb ischemia, or amputation. In the clinical setting, symptomatic PAD refers to patients with claudication, rest pain, or ischemic lesions. Other symptoms are less reliable. Most of these patients will have an ABI ≤ 0.9, with a minority showing PAD only by Doppler criteria during a treadmill evaluation. Symptomatic PAD has been shown in many settings to harbour a high risk of cardiovascular events and total mortality, even after multivariate analysis that takes into account the usual risk factors.120

A systematic review of 24 randomized clinical trials of antiplatelet therapy for the prevention of MI, stroke, or vascular death in patients with PAD published between 1990 and 1999 found the number of events to be 6.5% for the antiplatelet therapy treatment group, compared with 8.1% for the placebo group (odds ratio [OR] 0.78, 95% CI 0.63-0.96).123 This analysis included ASA, other cyclooxygenase inhibitors, ticlopidine, and clopidogrel, as well as 2 agents not available in Canada (suloctidil and picotamide).

The Antithrombotic Trialists’ Collaboration reviewed the efficacy of antiplatelet therapy in PAD, including ASA, dipyridamole, ticlopidine, clopidogrel, and picotamide. By including all 42 trials of 9214 patients with claudication or peripheral grafting or angioplasty, there was a 23% odds reduction of vascular events (P = 0.004).12 The same reduction was observed with a nonsignificant heterogeneity test in the 26 trials including 6263 patients with claudication only. Low-dose ASA (75-150 mg daily) was as effective as higher doses. Based largely on this meta-analysis, the Canadian Consensus group arrived at a grade 1A recommendation for the use of ASA or clopidogrel therapy for patients with symptomatic PAD.5

Recently, a new meta-analysis focusing specifically on randomized clinical trials comparing ASA, with or without dipyridamole, with placebo in patients with PAD included 18 studies comprising 5269 patients.124 For the primary endpoint of cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death), the analysis had 88% power to detect a 25% reduction in cardiovascular events and 70% power to detect a 20% reduction in the ASA group compared with the control group. Cardiovascular events were experienced by 251 of 2823 (8.9%) patients taking ASA alone or with dipyridamole and by 269 of 2446 (11.0%) in the control group (pooled RR 0.88, 95% CI 0.76-1.04). ASA therapy was associated with a reduction in the secondary outcome of nonfatal stroke (52 of 2823 [1.8%] vs 76 of 2446 [3.1%], RR 0.66, 95% CI 0.47-0.94) but was not associated with significant reductions in all-cause or cardiovascular mortality, MI, or major bleeding. In the subset of 3019 participants taking ASA alone vs control, ASA was associated with a nonsignificant reduction in cardiovascular events (125 of 1516 [8.2%] vs 144 of 1503 [9.6%], RR 0.75, 95% CI 0.48-1.18), a significant reduction in nonfatal stroke (32 of 1516 [2.1%] vs 51 of 1503 [3.4%], RR 0.64, 95% CI 0.42-0.99) but no statistically significant reductions in all-cause or cardiovascular mortality, MI, or major bleeding. As stated by the authors,124 results for the primary endpoint may reflect limited statistical power due to the small size and scope of the majority of studies.

The largest single study of antiplatelet drugs comprising patients with PAD is the CAPRIE trial, which compared clopidogrel 75 mg once daily with ASA 325 mg once daily in 19,185 patients with MI within 35 days of randomization, ischemic stroke within 1 week to 6 months of randomization, or symptomatic PAD.28 The primary outcome was the composite of MI, ischemic stroke, or vascular death, and patients were followed for a mean of 1.9 years. The results demonstrated that clopidogrel was slightly more effective than ASA in reducing the combined outcome of MI, ischemic stroke, or vascular death (8.7% relative risk reduction, P = 0.043) with a similar safety profile. In the subgroup of 6452 patients with PAD, there was a highly significant reduction in major vascular outcomes of clopidogrel over ASA (23.8% relative risk reduction, P = 0.0028).28

The addition of dipyridamole to ASA produced no significant further reduction in vascular events compared with ASA alone.12

The combined use of low-doses ASA 75-162 mg once daily with clopidogrel 75 mg once daily was not shown to be superior to ASA alone in the CHARISMA trial, which followed 15,603 patients for a median of 28 months.68 The rate of the primary efficacy endpoint of MI, all-cause stroke, or cardiovascular death was 6.8% with clopidogrel plus ASA and 7.3% with placebo plus ASA (RR 0.93, 95% CI 0.83-1.05; P = 0.22). The inclusion criteria led to 21% of patients having risk factors without overt atherosclerotic disease and 78% having documented vascular disease, of whom 23% had symptomatic PAD. In the much larger subgroup of symptomatic patients, the rate of events was 6.9% with clopidogrel and 7.9% with placebo (RR 0.88, 95% CI 0.77-0.998; P = 0.046).68

The possible role of oral anticoagulants, mostly warfarin or acenocoumarol adjusted to an international normalized ratio (INR) of 2.0-3.0, in addition to antiplatelet therapy, namely mostly with ASA 81-325 mg once daily, ticlopidine, or clopidogrel, compared with antiplatelet therapy alone was resolved in the WAVE (Warfarin and Antiplatelet Vascular Evaluation) trial.125 This multicenter, open-label, randomized controlled trial of 2161 patients with PAD (82% with lower limb PAD, others with carotid or subclavian disease) followed for a mean of 35 months demonstrated that in patients with PAD, the combination of an oral anticoagulant and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications. Life-threatening bleeding occurred in 4.0% of patients of receiving combination therapy compared with 1.2% of patients receiving antiplatelet therapy alone (RR 3.41, 95% CI 1.84-6.35; P < 0.001).

Antiplatelet therapy for patients with PAD who undergo endovascular intervention

Angioplasty with or without stent placement is a cornerstone of therapy for treating patients with claudication and increasingly, patients with limb-threatening ischemia. Because ASA is already recommended for all patients with symptomatic PAD, the question is whether the addition of a second agent can improve patency following angioplasty given the data on dual-antiplatelet agents in the coronary circulation.

For patients undergoing lower extremity balloon angioplasty (with or without stenting) for chronic symptomatic PAD, the American College of Chest Physicians recommends long-term ASA 75-100 mg daily (Grade 1C) but recommends against anticoagulation with heparin or vitamin K antagonists (Grade 1A).117 At present, there is no
randomized evidence that dual-antiplatelet therapy improves patency for primary angioplasty in the peripheral circulation. This area is in evolution as angioplasty and recanalization of superficial femoral, popliteal, and tibial vessels are increasing in frequency. Dual-antiplatelet therapy may be beneficial under these conditions; however, this has yet to be subjected to randomized trial comparisons.

**Antiplatelet agents following peripheral surgical bypass**

Antiplatelet agents have been studied most often in those who have undergone infrainguinal bypass surgery. However, low-dose ASA is recommended by the American College of Chest Physicians for all patients who undergo arterial reconstruction, including aortobifemoral reconstructions, axillofemoral or bifemoral bypass, iliofemoral bypass, common femoral repair, and profundaplasty.‡ For those undergoing infrainguinal reconstruction with venous conduits or prosthetic grafts, low-dose ASA is recommended (Grade 1A). Anticoagulation with vitamin K antagonists is not recommended for routine postoperative use (Grade 2A). The recommendation against anticoagulation with vitamin K antagonists (target INR 3.0-4.5) or low-molecular-weight heparins in patients with prosthetic grafts is because these agents have not been associated with improved patency compared with ASA and they significantly increase the risk of bleeding.‡ However, in those with infrainguinal grafts with a high risk of thrombosis and limb loss, combination vitamin K antagonist and ASA therapy may be of benefit in select cases (Grade 2B).†

**Antiplatelet therapy for the treatment of AAA**

There are no randomized trials that have examined the role of antiplatelet agents in the prevention of MI, stroke, or cardiovascular death in patients with AAA. Aortic aneurysms are associated with increasing age, male sex, hypertension, and smoking, suggesting that atherosclerosis may be a component of AAA pathophysiology. In a study in which coronary angiography was performed in 1000 consecutive preoperative vascular surgery patients, 26% of patients had AAA.‡ Of these individuals, 35% had normal coronary arteries (6%) or mild to moderate disease (29%), a further 29% had advanced but compensated CAD, and 31% had correctable CAD. Thus, AAA etiology is likely a spectrum that ranges from pure atherosclerosis to a pure degenerative disease.

It is not a surprise to vascular specialists that a recent study suggested that the presence of an AAA is a measure of subclinical atherosclerosis.³ An analysis of the REACH Registry, which enrolled outpatients with either established atherosclerosis or a high risk thereof, prospectively noted that there was an established diagnosis of AAA in 2.5% of that cohort.³ The prevalence of an AAA was 2.8% in those with symptomatic atherothrombosis compared with 1.2% in those with ≥ 3 atherosclerotic risk factors. When 1-year outcomes were compared between those with and without AAA, rates of fatal and nonfatal coronary and cerebrovascular events did not differ between the cohorts. However, significantly increased rates of cardiovascular deaths and hospitalizations for atherothrombotic events, including coronary, carotid, and peripheral vascular interventions and surgical revascularizations, were observed in patients with AAA. The REACH data support the concept that those with a diagnosis of AAA are at increased risk of adverse atherosclerotic events and that prophylactic use of ASA in this patient population would likely be of benefit. Preliminary evidence for the prophylactic use of antiplatelet therapy comes from a prospective study in which low-dose ASA was associated with a reduced expansion rate and a reduced risk of AAA surgery in patients whose aortic size was 40-49 mm.³ Low-dose ASA is recommended for those with an AAA, with the evidence stronger for those with clinical or subclinical PAD.

**Management of Peripheral Arterial Disease**

![Management of Peripheral Arterial Disease](image)

**Figure 8.** Management of peripheral arterial disease (PAD). The outpatient management of patients with symptomatic or asymptomatic PAD is outlined. ASA, acetylsalicylate acid; CAD, coronary artery disease. *Asymptomatic PAD is defined by ankle-brachial index < 0.9 in the absence of claudication or other manifestations of obstructive vascular disease in the extremities. †For patients allergic or intolerant to ASA, use of clopidogrel is suggested (Class IIa, Level B). ‡For patients with PAD with an indication for oral anticoagulation such as atrial fibrillation, venous thromboembolism, heart failure, or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (Class III, Level A).
For patients with **asymptomatic** PAD with an ABI < 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 75-162 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, or mechanical valves, antiplatelet therapy should not be added to oral anticoagulation (Class III, Level A).

Long-term antiplatelet therapy with ASA 75-162 mg daily should be given to patients who undergo lower-extremity balloon angioplasty with or without stenting for chronic symptomatic PAD (Class IIa, Level C). Anticoagulation with heparin or vitamin K antagonists should be avoided in this setting (Class III, Level B).

For all infrainguinal reconstructions, low-dose ASA (75-162 mg daily) should be given (Class IIa, Level B). In those with infrainguinal grafts and a high risk of thrombosis or limb loss, combination therapy with a vitamin K antagonist and ASA may be of benefit (Class IIb, Level C).

**Low-dose ASA (75-162 mg daily) may be considered for all patients with an AAA, particularly those with clinical or subclinical PAD (Class IIb, Level C).**
tential beneficial effects of ASA in selected patient subgroups, such as those with elevated CRP.

Studies in subjects with risk factors for vascular disease

Aside from studies that examined primary prevention in patients with diabetes, which are covered in the section of this guideline entitled “Use of Antiplatelet Therapy in Patients with Diabetes,” 3 studies examined primary prevention of vascular events in high-risk patients. The Thrombosis Prevention Trial randomized 5085 men in the top quintile of ischemic heart disease risk (based on a score derived from the Northwick Park Heart Study) to low-intensity oral anticoagulation with warfarin (target INR 1.5), controlled-release ASA 75 mg daily, combined ASA plus warfarin, or placebo. Subjects with a history of MI or stroke were excluded. Compared with placebo and over a median follow-up of 6.8 years, ASA was associated with nonsignificant relative reductions of 23% in the risk of ischemic heart disease (absolute risk reduction 0.31%, NNT 322 for 1 year) and 36% in the risk of nonfatal ischemic cardiac events (absolute risk reduction 0.32%, NNT 312 for 1 year). No differences in rates of stroke or major bleeding were observed in the ASA-only group. The Primary Prevention Project enrolled 4495 men and women with a mean age of 64.4 years and ≥ 1 major risk factor (age ≥ 65 years, hypertension, diabetes mellitus, hypercholesterolemia, obesity, or history of MI before age 55 in a first-degree relative). Patients with a history of ischemic vascular events or disease were excluded. Subjects were randomized in an open-label, 2 × 2 factorial design to ASA 100 mg daily, vitamin E 300 mg daily, and placebo. The study was stopped after a mean follow-up of 3.6 years when the interim results were consistent with other primary prevention trials that demonstrated a benefit for ASA treatment. ASA reduced the relative risk of cardiovascular death by 44% (RR 0.56, 95% CI 0.31-0.99, NNT 597 for 1 year) and any cardiovascular event by 23% (RR 0.77, 95% CI 0.62-0.95, NNT 189 for 1 year). Non-significant relative risk reductions were observed for the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (RR 0.71, 95% CI 0.48-1.04, NNT 450 for 1 year), MI (RR 0.69, 95% CI 0.38-1.23, NNT 900 for 1 year) and all stroke (RR 0.67, 95% CI 0.36-1.27, NNT 900 for 1 year). Severe bleeding was increased by 3.67-fold in ASA recipients (P = 0.0008; number needed to harm [NNH] 450 for 1 year). Differences were noted in the rate of hemorrhagic stroke. The CHARISMA trial randomized 15,603 men and women with manifest, stable vascular disease or multiple risk factors but no manifest disease to treatment with ASA 75-162 mg daily with or without clopidogrel 75 mg daily. Patients were followed for a mean of 28 months. The primary prevention population did not benefit from dual-antiplatelet therapy as a nonsignificant increased risk of the primary composite endpoint of MI, all-cause stroke, or cardiovascular death was noted (RR 1.20, 95% CI 0.91 to 1.59; P = 0.20). Rates of GUSTO-defined severe and moderate bleeding were also increased by clopidogrel (RR 1.67 and 1.57; P = 0.07 and P = 0.08, respectively).

The value of low-dose ASA in the management of patients with hypertension was examined in the HOT (Hypertension Optimal Treatment) study of 18,790 hypertensive subjects aged 50-80 years. In the HOT study, patients were randomized in a double-blind fashion to ASA 75 mg daily or placebo and followed for a mean of 3.8 years. At study entry, ~16% of subjects had ischemic heart disease. During the study, blood pressure was aggressively managed to diastolic targets of ≤ 90, ≤ 85, or ≤ 80 mm Hg. The use of ASA was associated with significant reductions in major cardiovascular events excluding silent MI (RR 0.85, 95% CI 0.73-0.99, absolute risk reduction 0.16%, NNT 625 for 1 year) and nonsilent MI (RR 0.64, 95% CI 0.49-0.85, absolute risk reduction 0.13%, NNT 769 for 1 year). No significant benefit was noted for stroke, cardiovascular or total mortality, or silent MI. No hazard for cerebral or fatal bleeding was noted, although nonfatal major bleeding was significantly increased (RR 1.84, absolute risk 0.63%; P < 0.001; NNH 606 for 1 year).

Although the studies in patients with risk factors for vascular events indicate, in some cases, a significant relative benefit for ASA in primary prevention, the absolute benefits are small and further attenuated by bleeding events. Despite a lack of requisite evidence, a net therapeutic benefit as primary prevention against cardiovascular events in select patients, particularly those with a low baseline risk for bleeding, cannot be excluded. At the population level, such high-risk asymptomatic patients have not been clearly defined, but they may include patients with multiple cardiovascular risk factors, those with evidence of vascular disease on imaging, and, possibly, patients with elevated levels of inflammatory markers (eg, CRP). At an individual level, clinicians may identify patients who may be at high vascular risk in whom ASA may provide a net therapeutic benefit. Although the risk factors for bleeding tend to mimic those for ischemic events, bleeding risk is greater in women, those with prior bleeds or bleeding diatheses, and with the use of concomitant medications such as NSAIDs.

The effect of sex in primary prevention

To examine the effects of ASA in women in primary vascular prevention, the Women’s Health Study randomized 39,876 women aged ≥ 45 years in a double-blind fashion to ASA 100 mg on alternate days or placebo. All participants were free of any manifestation of ischemic vascular disease. After a mean follow-up of 10.1 years, the relative risk of the primary composite endpoint of nonfatal MI, nonfatal stroke, or cardiovascular death was reduced by a nonsignificant 9% (RR 0.91, 95% CI 0.80-1.03; P = 0.13). However, a significant 17% reduction was seen in the relative risk of all strokes (RR 0.83, 95% CI 0.69-0.99; P = 0.04), driven by a 24% reduction in the relative risk of ischemic stroke (RR 0.76, 95% CI 0.63-0.93; P = 0.009). ASA had no effect on the relative risk of MI (RR 1.02, 95% CI 0.84-1.25; P = 0.83) or death from cardiovascular causes (RR 0.95, 95% CI 0.74-1.22; P = 0.68). A nonsignificant increase in the risk of hemorrhagic stroke was observed with ASA (RR 1.24, 95% CI 0.82-1.87; P = 0.31), whereas a significant increase of 40% in the relative risk of gastrointestinal bleeding requiring transfusion was noted in ASA recipients (RR 1.40, 95% CI 1.07-1.83; P = 0.02). In women aged ≥ 65 years, ASA significantly reduced the relative risks of the primary composite endpoint, ischemic stroke, and MI (by 26%, 30%, and 34%, respectively). As in all of the previously described primary prevention studies, the absolute risk reduction observed with ASA was small. For example, the absolute risk reduction for ischemic stroke was 0.255%, resulting in an NNT to prevent 1 event over 10.1 years of 392. Stated another way, treating 1000 women with ASA for 10 years would prevent ~2.5 ischemic strokes and cause ~1 gastrointestinal bleed requiring transfusion.

Meta-analysis

A meta-analysis by Berger and colleagues examined the sex differences associated with primary prevention by combining the results from 6 of the aforementioned studies. Results of this meta-analysis showed that use of ASA in women was associated with a
17% reduction in the relative risk of ischemic stroke (RR 0.83, 95% CI 0.70-0.97;  \( P = 0.02 \)) but no significant effect on MI. In contrast, men saw a 32% reduction in the relative risk of MI (RR 0.68, 95% CI 0.54-0.86;  \( P = 0.001 \)) but no effect on stroke. Both sexes saw a significant reduction in the relative risk of total vascular events: 12% in women (RR 0.88, 95% CI 0.79-0.99;  \( P = 0.03 \)) and 14% in men (RR 0.86, 95% CI 0.78-0.94;  \( P = 0.01 \)). Major bleeding was significantly increased in women and men (RR of 1.68 in women [95% CI, 1.13-2.52;  \( P = 0.01 \) ] and 1.72 in men [95% CI, 1.35-2.20;  \( P < 0.001 \)]). Of note is the low absolute benefit of ASA in both sexes. Based on this analysis, treatment of 1000 men and 1000 women for a mean of 6.4 years would be required to prevent 8 MIs in men and 3 strokes in women, at a cost of 3 major bleeding events in men and 2.5 such events in women.

A recent Antithrombotic Trialists’ Collaboration meta-analysis of individual participant data from randomized trials of primary and secondary vascular prevention with ASA included > 95,000 individuals and 3554 serious vascular events in the primary prevention analysis. In this analysis, ASA was associated with a 12% relative reduction in the risk of serious vascular events (RR 0.88, 95% CI 0.82-0.94;  \( P = 0.0001 \)). This effect was not altered in any of the prespecified subgroups, including those of individual risk factors and the calculated 5-year risk of CAD. Similar results were noted for coronary events (RR 0.82, 95% CI 0.75-0.90;  \( P = 0.0002 \)) and ischemic stroke (RR 0.86, 95% CI 0.74-1.00;  \( P = 0.05 \)). No mortality benefit was noted. Although the proportional reductions in nonfatal events offered by ASA were similar in the primary and secondary prevention trials, the absolute risk reductions differed by an order of magnitude. Absolute annual risk reductions for vascular events, MI, and ischemic stroke in primary prevention trials were 0.07% (NNT for 1 year 1428), 0.06% (NNT for 1 year 1667), and 0.02% (NNT for 1 year 5000), respectively. ASA was associated with a 32% increase in the relative risk of hemorrhagic stroke (RR 1.32, 95% CI 1.00-1.75;  \( P = 0.05 \); absolute risk increase 0.01%) and a 54% increase in the relative risk of major extracranial bleeding (RR 1.54, 95% CI 1.30-1.82;  \( P < 0.0001 \); absolute risk increase 0.03%). The same factors that increased vascular risk were also noted to increase bleeding risk. Bleeding risk did not differ significantly in the primary and secondary prevention analyses, but the very low absolute vascular benefit of ASA in primary prevention was significantly attenuated by bleeding. In contrast, in secondary prevention, the vascular benefit far outweighed the bleeding risk.

Summary

The absolute net benefit of any intervention is dictated by the treatment effect, associated adverse events, and absolute event rates. Although the proportional treatment effect of ASA is similar in primary and secondary prevention, the low event rate in primary prevention diminishes or possibly nullifies the absolute net benefit. Further, most of the studies considered were conducted prior to the widespread use of other primary risk reduction therapies, including statins and inhibitors of the RAAS, 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 bleeding and the cost of ASA is low, a clear margin of benefit must apply before recommending a therapy to a vast, healthy population. Although many guidelines have recommended ASA for primary prevention based on age or calculated vascular risk, the benefit in such populations has not been demonstrated. With regard to individual risk factors, studies of ASA for risk prevention in patients with diabetes have been disappointing. For example, compared with the benefit observed in the entire Primary Prevention Project population, lesser benefits were noted in the diabetic cohort. Further, an earlier meta-analysis conducted by the Antithrombotic Trialists’ Collaboration failed to demonstrate any benefit for ASA in subjects with diabetes, whereas a 22% relative risk reduction was observed overall. Similarly, smoking, which is used in most risk stratification methods, attenuated the benefit of ASA observed in the Women’s Health Study and the Physician’s Health Study, consistent with data indicating that smoking increases ASA resistance. An Antithrombotic Trialists’ Collaboration prediction model of high-risk subjects (ie, those with a 10-year event rate > 20%) receiving statin therapy suggests that the absolute benefit of ASA in primary vascular protection is small and approximately equivalent to the risk of major bleeding.

RECOMMENDATION (Summarized in Fig. 10)

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 is low, ASA 75-162 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

Cardiovascular disease is a major cause of mortality and morbidity for patients with diabetes. In addition to traditional risk factors such as smoking, systemic hypertension, dyslipidemia, and dysglycemia, atherosclerosis in patients with diabetes can be as-
associated with a procoagulant state, which plays a key role in atherogenesis and its thrombotic complications. Individuals with diabetes have a variety of alterations in platelet function that can predispose them to increased platelet activation and thrombosis. These alterations include increased platelet turnover,\textsuperscript{149} enhanced platelet aggregation,\textsuperscript{150} and increased thromboxane synthesis.\textsuperscript{151} Based on these observations and benefits extrapolated from large trials conducted in high-risk populations, antiplatelet therapy has been widely recommended for primary and secondary prevention in patients with diabetes. However, based on a critical appraisal of new and existing data,\textsuperscript{152} various professional organizations, including the Canadian Diabetes Association,\textsuperscript{6} have recently reduced the level of evidence supporting use of antiplatelet therapy in patients with diabetes. ASA is the antiplatelet agent most commonly studied in the prevention of cardiovascular events in persons with diabetes. While many trials with subgroups of patients with diabetes are available, surprisingly, only a few trials of mixed primary and secondary prevention were designed to investigate antiplatelet therapy specifically in the diabetic population.

**Primary prevention**

**Observational cohorts.** The recently published Fremantle Diabetes study provides one of the largest prospective, observational cohorts assessing the impact of ASA for primary prevention in patients with type 2 diabetes.\textsuperscript{153} In this cohort of 651 patients followed for a mean of 11.6 years, regular use of ASA ≥ 75 mg daily at baseline was associated with reduced risks of cardiovascular and all-cause mortality (HR 0.30 [95% CI 0.20-0.43] and 0.53 [95% CI 0.28-0.98], respectively). Conversely, a prospective study of 5731 Chinese patients with type 2 diabetes and no cardiovascular disease, of whom 1034 (18%) were using ASA, showed that ASA use was associated with an increased risk of vascular death, nonfatal MI, or nonfatal stroke (HR 2.07, 95% CI 1.66-2.59; \(P < 0.001\)).\textsuperscript{154} Because these observational studies are accompanied by many potential biases introduced by the failure to account for changes in antiplatelet therapy throughout the study duration, their results should be interpreted with caution.

**Subgroup and post-hoc analysis of clinical trials.** Several large studies of primary prevention included subgroups of patients with diabetes. The US Physicians’ Health Study was a primary prevention trial that assessed the efficacy and safety of ASA 325 mg taken every 2 days in 22,071 male physicians.\textsuperscript{134} In the subgroup of 533 men with diabetes, ASA use reduced the risk of MI, although the result was not significant, possibly due to the small number of events (11 events in the ASA group [4.0%] vs 26 events [10.1%] in the placebo group; \(P = 0.22\)). The Women’s Health Study was designed to study whether low-dose ASA (100 mg every second day) was beneficial in 39,876 initially healthy women aged > 45 years.\textsuperscript{141} Data from the subgroup of 1027 women with diabetes (only 2.6% of the total population) showed no significant benefit for ASA in preventing the primary endpoint of major cardiovascular events (RR 0.90, 95% CI 0.63-1.29; \(P = 0.57\)). However, a significant reduction in the risk of stroke (RR 0.46, 95% CI 0.25-0.85; \(P = 0.01\)) was observed. Notably, this reduction was much larger than the stroke risk reduction observed for the total population (RR 0.83, 95% CI 0.69-0.99; \(P = 0.04\)). The Primary Prevention Project studied the effect of low-dose ASA (100 mg daily) and/or vitamin E in 4495 people with one or more cardiovascular risk factors for a median of 3.7 years.\textsuperscript{138} Whereas a clear benefit for subjects without diabetes was observed (41% reduction in major cardiovascular events), in the 1031 patients with diabetes, the decrease in major cardiovascular events was not significant (RR 0.90, 95% CI 0.50-1.62), nor was the 23% increase in cardiovascular deaths.\textsuperscript{155} The adherence to therapy in the Primary Prevention Project was low, with 28.2% of persons assigned to ASA stopping therapy before the end of the trial. This low adherence might have affected the statistical power of this trial.

**Randomized clinical trials conducted in patients with diabetes.** Two randomized controlled trials evaluated the efficacy of ASA for primary prevention specifically in patients with diabetes. Using an open-label design, the JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial randomized 2539 patients with type 2 diabetes and no history of atherosclerotic disease to low-dose ASA (81 or 100 mg daily) or no ASA.\textsuperscript{156} After a mean follow-up of 4.37 years, there was no significant difference in the primary endpoint of atherosclerotic events (13.6 per 1000 person-years in the ASA-treated group vs 17.0 per 1000 person years in the nontreated group; HR 0.80, 95% CI 0.58-1.10; \(P = 0.16\)). Among the 1363 patients aged >65 years, secondary endpoint analyses indicated a favourable 32% reduction in the primary endpoint (6.3% vs 9.2%; \(P = 0.047\)), as well as a significant reduction in the incidence of fatal coronary and cerebrovascular events (0.08% vs 0.8%; \(P = 0.0037\)) in the total population. The POPADAD (Prevention Of Progression of Arterial Disease And Diabetes) trial studied ASA 100 mg daily with or without antioxidant therapy in 1276 patients with type 1 or 2 diabetes and asymptomatic PAD (defined as ABI ≤ 0.99) but no symptomatic cardiovascular disease.\textsuperscript{122} Thus, the POPADAD trial could be viewed as a mixed primary and secondary prevention intervention. After a median of 6.7 years of follow-up, there was no difference in primary events among ASA recipients compared with the non–ASA–treated persons (18.2% vs 18.3%, HR 0.98, 95% CI 0.76-1.26). The antioxidant intervention also failed to provide benefit. It should be noted that the number of events in both the JPAD and POPADAD trials was lower than expected, leading to limited statistical power.

**Meta-analyses.** To overcome the aforementioned limitations, 3 recent meta-analyses have examined the use of low-dose ASA in the primary prevention of cardiovascular events. However, none of these meta-analyses have shown a clear benefit for ASA in cardiovascular risk reduction in patients with diabetes. Subgroup analysis of the 5126 patients with diabetes included in the 2009 Antithrombotic Trialists’ Collaboration meta-analysis indicated a nonsignificant trend toward a benefit for prevention of vascular events in patients exposed to ASA (RR 0.88, 95% CI 0.67-1.15).\textsuperscript{66} This is in contrast to subjects without diabetes, in whom a reduction of a similar magnitude was shown to be significant (RR 0.87, 95% CI 0.79-0.96). A meta-analysis looking specifically at patients with diabetes, which included more patients by taking advantage of recently published randomized clinical trials (total of 4-6 trials depending on outcome assessed, providing 8557 to 10,117 participants for analysis), also showed nonsignificant trends for reduction in the risk of major cardiovascular events (RR 0.90, 95% CI 0.81 to 1.00) and all-cause mortality (RR 0.93, 95% CI 0.82 to 1.05) associated with ASA use.\textsuperscript{157} This meta-analysis showed no consistent evidence related to stroke or harm
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. Within this meta-analysis, the ETDRS (Early Treatment Diabetic Retinopathy Study) population largely contributed to the diabetic subgroup analysis. At inclusion, as many as 30% of the 3711 patients had evidence of macrovascular disease; thus, ETDRS should be viewed as a mixed primary and secondary prevention trial in patients with diabetes and severe proliferative retinopathy. The primary outcome of all-cause mortality was analyzed at 5 and 7 years, and no significant differences between ASA and placebo were noted. For the predetermined secondary endpoint of fatal or nonfatal MI, the difference was significant at 5 years (RR 0.72, 99% CI 0.55-0.95) but not at 7 years (RR 0.83, 99% CI 0.66-1.04).

Ongoing trials. Two ongoing trials should clarify some of the uncertainty surrounding the use of ASA in patients with diabetes. ASCEND (A Study of Cardiovascular Events IN Diabetes; ClinicalTrials.gov identifier NCT00135226), which was initiated in 2005, aims to recruit ≥ 10,000 patients and randomize them to ASA 100 mg daily and/or omega-3 fatty acids for ≥ 5 years. ACCEPT-D (Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) randomized 5170 patients aged ≥ 50 years to ASA 100 mg daily and/or simvastatin 20-40 mg daily. Patients will be followed for 5 years, and the study completion date is expected to be September 2013. The anticipated large number of patients that will be enrolled in these 2 trials, and thus, the large number of expected events, should provide adequate power to more conclusively assess the effect of ASA and enable subgroup analyses.

Specific subgroups and situations. In studies of the general population, inconsistent data for the interaction of age and sex with the antiplatelet effect on cardiovascular risk or all-cause mortality have been observed in subgroup analyses of patients enrolled with diabetes. For example, while some studies suggested a significant benefit in older subjects or men, this has not been confirmed in other trials. Group analysis has also failed to confirm a greater effect in patients at higher risk.

Optimal ASA dose for patients with diabetes

As in the general population, the most effective dose of ASA in patients with diabetes remains unknown. It has been suggested that due to increases in platelet turnover and thromboxane synthesis in diabetes, higher single doses or multiple daily doses of ASA may be preferred. Trials using higher ASA doses (eg, ETDRS, which assessed ASA 650 mg daily) have not demonstrated additional benefits, whereas no clinical trials examining multiple daily dosing exist. Low-dose ASA (75-325 mg daily) is often recommended because subgroup analyses have suggested lower risk for bleeding in patients using these doses compared with higher ones.

No data are available to evaluate the benefit of ASA in the context of type 1 diabetes or among those aged < 40 years or with significant insulin resistance or poor glucose control. ASA therapy does not increase the risk of vitreous hemorrhage in patients with diabetic retinopathy, nor does it

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**Secondary prevention**

**Observational cohorts.** The aforementioned prospective Chinese study also included 723 patients who had cardiovascular disease, 585 (81%) of whom were using ASA. In the secondary prevention cohort, ASA had no significant effect on the risk of vascular death, nonfatal MI, or nonfatal stroke (HR 0.91, 95% CI 0.60-1.37). Furthermore, in the overall population, ASA use was associated with a significantly increased risk for upper gastrointestinal bleeding (HR 2.19, 95% CI 1.53-3.15; P < 0.001) and a trend for increased risk of hemorrhagic stroke (HR 1.71, 95% CI 1.00-2.95; P = 0.051). In an analysis of all-cause mortality risk reduction associated with pharmacological agents in a UK cohort of 2499 patients post ACS, of whom 17% had diabetes, ASA was not associated with a mortality benefit in patients with diabetes (HR 0.74, 95% CI 0.50-1.08), whereas a 48% benefit was observed in patients without diabetes (95% CI 0.43-0.63). Interestingly, in this same study, patients with diabetes had similar benefits as patients without for other secondary prevention interventions (eg, statins, angiotensin-converting enzyme [ACE] inhibitors, and β-blockers).

**Subgroup, post-hoc, and meta-analyses of randomized trials.** No large, randomized clinical trial has specifically examined the use of ASA for secondary prevention exclusively in patients with diabetes. In the 2002 Antithrombotic Trialists’ Collaboration meta-analysis, a subset of 9 trials included antiplatelet vs control therapy in almost 5000 patients with diabetes. Compared with a 22% reduction in the risk of major cardiovascular events among the > 140,000 high-risk subjects on antiplatelet therapy, patients with diabetes showed a nonsignificant 7% risk reduction for serious vascular events. However, because the number of events was much higher in patients with diabetes, the benefit

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**Optimal ASA dose for patients with diabetes**

As in the general population, the most effective dose of ASA in patients with diabetes remains unknown. It has been suggested that due to increases in platelet turnover and thromboxane synthesis in diabetes, higher single doses or multiple daily doses of ASA may be preferred. Trials using higher ASA doses (eg, ETDRS, which assessed ASA 650 mg daily) have not demonstrated additional benefits, whereas no clinical trials examining multiple daily dosing exist. Low-dose ASA (75-325 mg daily) is often recommended because subgroup analyses have suggested lower risk for bleeding in patients using these doses compared with higher ones.

No data are available to evaluate the benefit of ASA in the context of type 1 diabetes or among those aged < 40 years or with significant insulin resistance or poor glucose control. ASA therapy does not increase the risk of vitreous hemorrhage in patients with diabetic retinopathy, nor does it
Management of Patients with Diabetes

ASA* 75-162 mg OD may be considered for secondary prevention in patients with diabetes and manifest vascular disease for which its benefits are established (Class I, Level A).

Diabetes

ASA* 75-162 mg OD may be considered for primary prevention in patients with other cardiovascular risk factors for which its benefits are established (Class IIb, Level B).

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

Figure 11. Management of patients with diabetes. The outpatient management for primary and secondary prevention of vascular ischemic events in patients with diabetes. ASA, acetylsalicylic acid. *For patients allergic or intolerant to ASA, use of clopidogrel 75 mg OD is suggested (Class IIa, Level B).

increase stroke or fatal bleeds in patients with adequately controlled systemic hypertension.139

Other antiplatelet therapy

If an antiplatelet agent is to be used, 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 or ASA-induced asthma), an alternate antiplatelet agent such as clopidogrel may be used.

Clopidogrel is a receptor antagonist of ADP P2Y12–induced platelet aggregation. The addition of clopidogrel 75 mg daily to ASA 75-162 mg daily was not shown to be of benefit among high-risk patients with diabetes enrolled in the CHARISMA trial.68 Data from 2 trials that investigated clopidogrel in secondary prevention provide additional information for patients with diabetes. In the 3866 patients enrolled in the CAPRIE study who had diabetes, the primary composite endpoint of ischemic stroke, MI, or vascular death occurred in 15.6% per year of those randomized to clopidogrel 75 mg daily and 17.7% per year of those randomized to ASA 325 mg daily (P = 0.042).167 In the subgroup of 2840 patients with diabetes enrolled in the CURE trial, which compared clopidogrel (300-mg loading dose, 75 mg daily) plus ASA (75-325 mg daily) with ASA alone, the rate of the primary composite endpoint of cardiovascular death, nonfatal MI, or stroke was 1.75 times as high as that of the population without diabetes (14.2% vs 7.9% for clopidogrel, 16.7% vs 9.9% for placebo).29 The patients with diabetes experienced a 15% relative risk reduction in the primary endpoint that bordered on significance but was of a similar magnitude as in the entire population. In the dual-antiplatelet therapy arm, there was a significant increase in major bleeding in the overall population (3.7% vs 2.7%; P = 0.001).

Prasugrel is another antagonist of ADP P2Y12–induced platelet aggregation. In TRITON-TIMI 38, the addition of prasugrel (60-mg loading dose, 10 mg daily) to ASA 75-162 mg daily significantly reduced the risk of the primary composite endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke compared with the addition of clopidogrel (300-mg loading dose, 75 mg daily) to ASA 75-162 mg daily in 13,608 patients with ACS scheduled to undergo PCI.36 A prespecified subgroup analysis revealed that the 3146 patients with diabetes experienced significantly more benefit than did the patients without diabetes for the primary composite endpoint (HR 0.70, 95% CI 0.58-0.85; P < 0.0001 for patients with diabetes vs HR 0.86, 95% CI 0.76-0.98; P = 0.02 for patients without).162 In contrast with the results of the overall population, in which TIMI-defined major bleeding was significantly increased in prasugrel recipients, patients with diabetes experienced a similar rate of bleeding with prasugrel and clopidogrel (2.5% vs 2.6%, HR 1.06, 95% CI 0.66-1.69; P = 0.81).

ASA resistance in diabetes

The absence of clear benefits for antiplatelet therapy in patients with diabetes might indicate that patients with diabetes are a specific subgroup of patients in whom mechanisms such as ASA resistance are manifest. Markers of biological activity suggest reduced efficacy of antiplatelet therapy in patients with diabetes, particularly those with poor metabolic control163-165 and obesity.166,167 Depending on the definition and technique used to assess ASA resistance, the prevalence in patients with diabetes varies considerably, from 0% to 50%, although more recent data suggest a prevalence < 5%.168 Unfortunately, no published study has been designed to investigate the implications of biochemical ASA resistance, the impact of improved metabolic control, or the benefit of increased ASA dose or multiple daily dosing in the context of poor metabolic control.

Summary

Despite clear evidence of a procoagulant state in patients with diabetes, the balance between benefits and potential harms of antiplatelet treatment appears less favourable in patients with diabetes compared with those in other high–cardiovascular risk groups.

RECOMMENDATION (Summarized in Fig. 11)

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 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 I, Level A).

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 Patients With Heart Failure
Working Group: Alan D. Bell, MD, CCFP, and James D. Douketis, MD, FRCP

Largely due to reduced cardiac output, HF is associated with an increased risk of thromboembolic events. Relative stasis of blood within the heart, arterial and venous circulation, abnormal cardiac wall motion, as well as the frequent association with CAD, atrial fibrillation, reduced mobility, and other comorbidities, all contribute to a prothrombotic state in patients with HF.169-171 Reported rates of thromboembolic events range from 2 to 3.5 per 100 patient-years.172,173 For example, the incidence of all thromboembolic events in the first (mean follow-up 2.28 years) and second (mean follow-up 2.56 years) Veterans Affairs Vasodilator-Heart Failure Trials was 2.7 per 100 patient-years and 2.1 per 100 patient-years, respectively.

Trials designed to investigate the role of antithrombotic and antiplatelet therapies in reducing thromboembolic events have not consistently demonstrated benefit. Early studies of warfarin in HF demonstrated significant benefit, but results were confounded by the inclusion of large numbers of patients with atrial fibrillation and valvular heart disease.174-177 This chapter will focus on antiplatelet therapy in patients with HF in the absence of these conditions.

Randomized studies assessing antiplatelet therapy with warfarin or no therapy

WASH (Warfarin/Aspirin Study in Heart failure) was an open-label, blinded endpoint, pilot study assessing warfarin (target INR 2.5-3.0) or double-blind to ASA 162 mg daily or clopidogrel 75 mg daily in 279 patients with HF who were in sinus rhythm.178

Low-dose ASA therapy (75-162 mg daily) may be considered for secondary prevention in patients with other cardiovascular risk factors for which its benefits are established (Class Iib, Level B).

The WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart failure) trial was undertaken to determine the optimal antithrombotic agent for patients in sinus rhythm who had HF with an ejection fraction ≤ 35%.179 In the WATCH trial, 1587 patients were randomized to open-label warfarin (target INR 2.5-3.0) or double-blind to ASA 162 mg daily or clopidogrel 75 mg daily and followed for a mean of 1.9 years. Because the majority of patients had ischemic heart disease, no placebo arm was included. Due to slow enrollment, the study was terminated prior to the recruitment of the planned 4500 patients, changing the difference in annual event rates the study was powered to detect from 20% to 40%. No differential benefit of the treatments was noted for the primary composite endpoint of time to first occurrence of death, nonfatal MI, or nonfatal stroke. The hazard ratios were as follows: for warfarin vs ASA, 0.98 (95% CI 0.86-1.12; \( P = 0.77 \)); for clopidogrel vs ASA, 1.08 (95% CI 0.83-1.40; \( P = 0.57 \)); and for warfarin vs clopidogrel, 0.89 (95% CI 0.68-1.16; \( P = 0.39 \)). Warfarin was associated with fewer nonfatal strokes (\( P < 0.01 \) vs either ASA or clopidogrel), although only 21 such events occurred. Major bleeding episodes were more frequent in warfarin recipients compared with clopidogrel (\( P < 0.01 \)) but not ASA (\( P = 0.22 \)) recipients. More admissions for HF were observed in the ASA group compared with warfarin (218 vs 155; \( P < 0.001 \)). Similar results were observed when ischemic or nonischemic etiology of HF was considered. A meta-analysis of WASH and the WATCH trial suggests a weak trend in favour of a lower mortality rate with warfarin compared with ASA (RR 0.91, 95% CI 0.67-1.22).180

The WARCEF (Warfarin vs Aspirin in patients with Reduced Cardiac Ejection Fraction) trial is currently enrolling a target of 2860 patients with an intent to compare the efficacy of warfarin vs ASA in preventing death, ischemic stroke, and intracerebral hemorrhage over 1-6 years of follow-up in patients with HF.181 Follow-up is expected to continue to January 2011.

Nonrandomized studies. Several post-hoc analyses of HF studies have examined the effect of warfarin in preventing cardiovascular events, with mixed and potentially confounded results.182-184 In 1 linked administrative database study of patients with a first MI who did not undergo PCI but developed HF, clopidogrel use was associated with a reduction in all-cause mortality (HR 0.86, 95% CI 0.78-0.95; \( P = 0.002 \)).185 These findings, although promising, are limited by the lack of adjustment for comorbidities and potentially unreliable reporting of clopidogrel adherence.

Adverse effects of ASA on HF

Prostaglandins, including prostacyclin and prostaglandin E1, are upregulated in HF and offer several benefits, including vasodilatory, natriuretic, and antiplatelet effects. This effect is further enhanced by ACE inhibition, which reduces bradykinin breakdown. Bradykinin, a potent vasodilator, acts by stimulating formation of vasodilatory prostaglandins such as prostacyclin, whereas ASA, like other nonsteroidal anti-inflammatory agents, inhibits the enzyme cyclooxygenase, which in turn decreases the production of the prostaglandins.186

In both WASH178 and the WATCH trial,179 ASA was associated with increased hospitalization for HF, and the aforementioned meta-analysis180 is consistent with a substantial increase in the rate of HF-related hospitalization for ASA vs warfarin (RR 0.64, 95% CI 0.48 to 0.85). In a post-hoc analysis of SOLVD (Studies Of Left Ventricular Dysfunction),183 patients who received ASA or dipyridamole at baseline did not receive the survival benefits of the ACE inhibitor enalapril.184 A retrospective subgroup analysis of data from CONSENSUS II (COoperative New
Scandinavian Enalapril Survival Study II\textsuperscript{187} demonstrated that the 6-month mortality rate of patients with acute MI who received enalapril and ASA was higher than the combined mortality rates of patients receiving enalapril or ASA alone.\textsuperscript{186}

Contrary to these results are those of McAlister and colleagues, who conducted a cohort study of patients discharged after a first hospitalization for HF.\textsuperscript{188} In follow-up of 7352 patients hospitalized for HF, ASA use in the absence of ACE inhibitor use did not increase the risk of death or readmission for HF (HR 1.02, 95\% CI 0.91-1.16), even among patients without CAD (HR 0.98, 95\% CI 0.78-1.22) or patients with renal dysfunction (HR 1.13, 95\% CI 0.94 to 1.36). Users of ACE inhibitors were less likely to die or require readmission for HF (HR 0.87, 95\% CI 0.79-0.96), even if they were using ASA (HR 0.86, 95\% CI 0.77-0.95). There were no dose-dependent interactions between ASA and ACE inhibitors. Teo and colleagues undertook a systematic overview of data from 22,060 patients enrolled in 6 long-term randomized trials of ACE inhibitors to assess whether ASA altered the effects of ACE inhibitor therapy on the composite outcome of death, MI, stroke, hospital admission for HF, or revascularization.\textsuperscript{189} Overall, ACE inhibitor therapy significantly reduced the relative risk of the composite outcome by 22\% ($P < 0.0001$), with clear risk reductions observed among both those receiving ASA at baseline (OR 0.80; 99\% CI, 0.73-0.88) and those who were not (OR 0.71; 99\% CI, 0.62-0.81; interaction $P = 0.07$).

### Summary

Heart failure is associated with an increased risk of thromboembolic and other ischemic cardiovascular events. The etiology of HF is ischemic in approximately 70\% of patients, with hypertension and idiopathic causes implicated in the remainder.\textsuperscript{76} 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.

### RECOMMENDATION (Summarized in Fig. 12)

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

### Use of Antiplatelet Therapy in Patients With Chronic Kidney Disease

**Working Group:** Neesh Pannu, MD, SM, FRCP, and Alan D. Bell, MD, CCFP

For the purpose of this guideline, CKD is defined as an estimated glomerular filtration rate (eGFR) or creatinine clearance $< 60$ mL/min/1.73 m\textsuperscript{2} obtained using either the Cockcroft-Gault formula or the Modification of Diet in Renal Disease (MDRD) equation. CKD is associated with an increased risk of cardiovascular disease, as well as a higher risk of bleeding.\textsuperscript{190} There are no randomized controlled trials that have specifically evaluated the effects of ASA or other antiplatelet agents on cardiovascular or cerebrovascular events in patients with advanced CKD or end-stage renal disease (ESRD). A review of the available data is presented next.

### Primary prevention

While there are no randomized controlled trials that have specifically evaluated the effects of ASA on the prevention of cardiovascular or cerebrovascular events in patients with advanced CKD or ESRD, a meta-analysis of studies of antiplatelet therapy for maintenance of access patency among 2632 dialysis patients demonstrated a 41\% reduction in the relative risk of serious vascular events.\textsuperscript{12} The small size of the included studies precludes accurate estimation of hazard ratios for bleeding events in this patient population. No specific information is available regarding patients with CKD stages 1-4.

### Secondary prevention

ASA. All studies evaluating the effectiveness of ASA for secondary prevention in patients with CKD have been retrospective and observational in nature and have reported varying results. Multiple studies have reported ASA use to be associated with a reduction in mortality in patients with CKD and ESRD with HF\textsuperscript{191} and following MI.\textsuperscript{191-194} Others suggest that ASA may not be beneficial in patients with CKD after ACS\textsuperscript{195} and in dialysis patients with a known history of CAD.\textsuperscript{196,197}

**Clopidogrel.** Several large randomized trials evaluating clopidogrel have included patients with an eGFR $< 60$ mL/min/1.73 m\textsuperscript{2}. Post-hoc analysis of such patients has yielded mixed results. In the CURE study of 12,562 patients with NSTEACS randomly assigned to either clopidogrel (300-mg loading dose, 75 mg daily) or placebo in addition to ASA 75-325 mg daily,\textsuperscript{29} 26.6\% of patients in the study had an eGFR $< 60$ mL/min.\textsuperscript{198} Of this group, 24.8\% had an eGFR between 30 and 59.9 mL/min, and 1.8\% had an eGFR $< 30$ mL/min. Clopidogrel showed a trend toward a beneficial effect with respect to the primary com-

![Figure 12. Management of heart failure. The outpatient management of patient with ischemic or nonischemic heart failure. CAD, coronary artery disease.](image-url)
Management of Chronic Kidney Disease

Figure 13. Management of chronic kidney disease. Antiplatelet therapy for primary or secondary prevention of ischemic vascular events in patients with chronic renal disease. ASA, acetylsalicylic acid; CKD, chronic renal disease; ESRD, end-stage renal disease. *For patients allergic or intolerant to ASA, use of clopidogrel 75 mg OD is suggested (Class IIa, Level B).

Prasugrel. TRITON-TIMI 38 randomized 13,608 patients to receive, in addition to ASA 75-162 mg daily, prasugrel (60-mg loading dose, 10 mg daily) or clopidogrel (300-mg loading dose, 75 mg daily). Among the 14,902 patients with a creatinine clearance < 60 mL/min, a nonsignificant 14% reduction in the relative risk of the primary composite endpoint of cardiovascular death, nonfatal MI, or stroke and a trend toward an increased risk of events was noted in patients with a creatinine clearance < 60 mL/min. No significant difference in TIMI-defined bleeding rates was reported.

Bleeding risk

Antiplatelet therapy significantly increases bleeding risk in patients with CKD, and this risk appears to be magnified when dual-antiplatelet therapy is used. A study of clopidogrel 75 mg daily plus ASA 325 mg daily vs double placebo for prevention of hemodialysis access graft thrombosis (n = 200) was prematurely terminated because of the bleeding risk associated with therapy (42% vs 24% over the mean follow-up period of 196 days). The aforementioned subanalysis of the CURE trial reported a 1.5-fold increased risk of minor bleeds in patients with an eGFR < 60 mL/min randomized to clopidogrel plus ASA. There was also a statistically nonsignificant increased risk of severe bleeding among clopidogrel plus ASA recipients in the diabetic nephropathy subgroup of the CHARISMA study (2.6% vs 1.5%). These findings are also supported by a retrospective study of 255 Canadian patients undergoing chronic hemodialysis, which reported a significantly increased bleeding risk in patients receiving ASA (HR 5.24, 95% CI 1.64-16.79). The UK-HARP 1 (First United Kingdom Heart And Renal Prevention) study, which randomized a heterogeneous group of 448 patients with CKD and ESRD to ASA 100 mg daily or placebo, reported a 2-fold increase in bleeding complications in the ASA group (17% vs 8%, P = 0.005), although there was no statistically significant increased risk of major bleeding (2% with ASA vs 3% with placebo).

Summary

There is little high-quality evidence to guide the use of ASA or other antiplatelet agents in patients with CKD. 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. No randomized trial has been sufficiently powered to address the benefits of antiplatelet therapy in patients with CKD; however, the bleeding events reported in the available studies have generally been minor and have not been associated with increased mortality.

RECOMMENDATION (Summarized in Fig. 13)

ASA 75-162 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 Women Who Are Pregnant or Breastfeeding

Working Group: Wee Shian Chan, MD, FRCP

Cardiovascular and cerebrovascular diseases occurring in pregnancy are uncommon, but they do arise. There are no clinical trials...
demonstrating the efficacy of antiplatelet therapy or relative superiority of types of antiplatelet therapy in pregnant women with coexisting cardiovascular or cerebrovascular diseases. Thus, the indications for antiplatelet therapy in pregnant women must be extrapolated from multiple studies performed in the general population. The safety data of specific antiplatelet agents during pregnancy and breastfeeding will be considered next.

ASA in pregnancy

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 (OR 1.33, 95% CI 0.94-1.89), although a significantly increased risk of gastroschisis (ie, the herniation of abdominal contents through an abdominal wall defect) was reported (OR 2.37, 95% CI 1.44-3.88). This could represent an increase in absolute risk from 0.8-5.8 per 10,000 births to approximately 23 per 10,000 births. However, major limitations of this meta-analysis include the possibility of recall bias and the uncertainty surrounding the ASA dose exposure in affected pregnancies.

In the past 15 years, low-dose ASA (50-150 mg daily) has been extensively assessed in randomized controlled studies for the primary and secondary prevention of preeclampsia. In addition to the primary outcome of preeclampsia development, these studies have reported safety events such as maternal and fetal peripartum bleeding risks and childhood developmental outcomes. There were no increased maternal or fetal bleeding risks, placenta abruptions, or adverse childhood development defects observed up to 12-18 months post delivery when ASA was used throughout the latter half of pregnancies. However, it is not certain whether low-dose ASA was consistently initiated in the first trimester in these studies.

Low-dose ASA is frequently prescribed prior to conception or early in conception to improve pregnancy rates in women who undertake assisted reproductive technology. There are several meta-analyses of randomized clinical trials assessing use of low-dose ASA (75-100 mg daily) for this indication. The specific outcomes of congenital malformations were not available from individual studies; however, low-dose ASA was prescribed uniformly in these patients throughout the first trimester of pregnancy.

ASA in breastfeeding

Maternal ingestion of ASA is associated with the excretion of both salicylate and salicylate metabolites into the breast milk. In a few case reports, adverse infant side effects like the development of metabolic acidosis and thrombocytopenia have been reported with the use of high doses of ASA (several grams per day). The theoretical risk of Reye’s syndrome in the infant caused by salicylate in breast milk is unknown. The use of low-dose ASA (75-162 mg daily) during breastfeeding has not been reported to result in adverse infant outcomes and is mostly considered safe.

Dipyridamole

Dipyridamole has been assessed in several small trials (<500 women in total) of preeclampsia prevention. No fetal malformations have been reported. The safety of dipyridamole exposure in the first trimester, however, cannot be specifically determined. The safety of dipyridamole use during breastfeeding is unknown.

Clopidogrel

The experience with clopidogrel use during pregnancy is limited to a few case reports of pregnant women who had coronary artery events during pregnancy. Clopidogrel was given throughout pregnancy in a few of these patients with no reported adverse fetal events. The bleeding risk of clopidogrel in combination with other antiplatelet therapy for neuraxial procedures during delivery cannot be ascertained. As for dipyridamole, there are no safety data on clopidogrel use in breastfeeding women.

Available recommendations from existing guidelines

Due to the uncertain risk associated with use of ASA in the first trimester, the 2006 ischemic stroke and TIA guidelines jointly published by the AHA/American Stroke Association advocate the use of unfractionated heparin or low-molecular-weight heparin in the first trimester for low-risk conditions (i.e., those that would not require anticoagulation but would require antiplatelet therapy if the patient were not pregnant) followed by low-dose ASA for the remainder of the pregnancy. The guidelines published by the Institute for Clinical Systems Improvement state that precautions should be followed for use of all antiplatelet therapy in the third trimester because of bleeding concerns and the risk of placental separation. They also indicate that because clinical experience with breastfeeding and any antiplatelet agent is limited, risks cannot be entirely ruled out.

RECOMMENDATION (Summarized in Fig. 14)

For cardiovascular 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 (75-162 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 cardiovascular or cerebrovascular indications during pregnancy should be considered only if maternal benefits clearly outweigh potential fetal risks (Class IIIb, Level C).

Low-dose ASA (75-162 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 IIIb, Level C).

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

Working Group: James D. Douketis, MD, FRCP, and Alexander G. G. Turpie, MD, FRCP, FACC, FRCPCh

The perioperative management of patients who are receiving antiplatelet therapy is a common clinical problem given the large number of patients who are receiving these agents for treatment of CAD, cerebrovascular disease, or PAD. Patients who are taking antiplatelet drugs may be receiving one of the following regimens:
should be weighed against the perioperative risk for bleeding if a recent MI. The risk for cardiovascular events in high-risk patients includes those with a recently implanted BMS or DES or whom it may be preferable to continue antiplatelet drugs perioperatively, such as MI or stroke. Patients at high risk for cardiovascular events, in general, would not be expected to increase the risk for cardiovascular events with continued ASA therapy. In general, patients at low risk for perioperative management is less problematic if they are taking short-acting platelet inhibitors (ie, clopidogrel and ASA). There are no perioperative risk classification schemes that are currently available data regarding perioperative management. In patients taking other antiplatelet drug regimens, data are lacking. In such patients, perioperative management is less problematic if they are taking short-acting platelet inhibitors (eg, dipyridamole, cilostazol, pentoxifylline, NSAIDs) but problematic for users of irreversible platelet inhibitors (ie, clopidogrel and ASA).

Patient profile

Patients who are receiving antiplatelet therapy encompass a broad risk spectrum for cardiovascular events that depends on the clinical indication for antiplatelet therapy and whether patients are receiving treatment for the primary or secondary prevention of disease. There are no perioperative risk classification schemes that consider the benefits and risks of continuing or interrupting antiplatelet therapy. In general, patients at low risk for perioperative cardiovascular events in whom interruption of antiplatelet drugs would not be expected to increase the risk for cardiovascular events include those who are receiving ASA for the primary prevention of MI or stroke. Patients at high risk for cardiovascular events, in whom it may be preferable to continue antiplatelet drugs perioperatively, include those with a recently implanted BMS or DES or a recent MI. The risk for cardiovascular events in high-risk patients should be weighed against the perioperative risk for bleeding if antiplatelet drugs are continued around the time of surgery or invasive procedure. Table 4 lists common procedures and their associated risks of bleeding.

Diagnostic testing

Invasive diagnostic testing spans a wide range of procedures. Procedures associated with a low risk for bleeding include upper and lower gastrointestinal endoscopy, bronchoscopy, and bone marrow biopsy. Procedures associated with a high risk for bleeding include urogenital organ biopsy (kidney, bladder, or prostate) and liver biopsy. Other diagnostic tests, such as cervical and endometrial biopsy, are intermediate in risk.

In patients undergoing gastrointestinal endoscopy, a case-control study of > 20,000 patients who underwent colonoscopy found no increased risk for bleeding in patients who continued ASA around the time of the procedure.226 Similar findings were found in a study of ASA-treated patients undergoing polypectomy.227 In patients undergoing bronchoscopy, 1 case-control study found ASA use did not increase the risk for severe bleeding in patients undergoing bronchoscopy (HR 1.1).228 However, a prospective cohort study found a significantly higher incidence of moderate or severe bleeding after tracheobronchial biopsy in patients who received clopidogrel (61%) or clopidogrel plus ASA (100%) compared with patients who were not taking antiplatelet drugs (1.8%).229

Joint injections

Arthrocentesis that is performed for diagnostic purposes or for treatment (eg, corticosteroid injection) is a common outpatient procedure. To our knowledge, there are no studies assessing the safety of arthrocentesis in antiplatelet drug-treated patients. Based on expert opinion, it is likely that the risk for bleeding is low given the limited tissue damage and small-calibre needle that is typically used for this procedure.

Table 4. Relative risk of bleeding associated with common surgical and nonsurgical procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Very High Risk</th>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
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<tbody>
<tr>
<td>Neurosurgery (intracranial or spinal surgery)</td>
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<td>Cardiac surgery (coronary artery bypass or heart valve replacement)</td>
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<td>Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)</td>
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<td>Major urologic surgery (prostatectomy, bladder tumour resection)</td>
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<td>Major lower limb orthopaedic surgery (hip/knee joint replacement)</td>
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<td>Lung resection surgery</td>
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<td>Intestinal anastomosis surgery</td>
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<td>Permanent pacemaker insertion or internal defibrillator placement</td>
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<tr>
<td>Selected procedures (kidney biopsy, pericardiocentesis, colonic polypectomy)</td>
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<tr>
<td>Single tooth extraction or teeth cleaning</td>
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<tr>
<td>Skin biopsy or selected skin cancer removal</td>
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<tr>
<td>Cataract removal</td>
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Minor dental, eye, and skin procedures

Common dental procedures include single or multiple tooth extractions and endodontic (eg, root canal) procedures. In a randomized trial of 39 patients that compared continuing or discontinuing ASA before a dental procedure, there were no major bleeds in either treatment arm, but the incidence of clinically relevant nonmajor bleeding was higher in patients who continued ASA (21% vs 10%). In a cohort study of 51 patients who continued ASA, there were no major bleeds, and clinically relevant nonmajor bleeding occurred in only 1 patient (2%). Studies are lacking in patients who are receiving clopidogrel and require a dental procedure. It is probable, however, that the continuation of clopidogrel and ASA by patients undergoing dental procedures will increase the risk of minor bleeding above that seen with ASA alone.

Common dermatologic procedures include excisions of basal and squamous cell carcinomas, actinic keratoses, and malignant or premalignant nevi. In 2 cohort studies, moderate and/or minor bleeding was more frequent in patients who continued ASA compared with those who were not receiving ASA (22% vs 13% and 21.6% vs 13.6%, respectively). In 2 other cohort studies, the incidence of minor bleeding appeared comparable in patients who received ASA and those who did not in the periprocedural period (1.9% vs 4.2% and 0% vs 1.4%, respectively). Studies in patients who are receiving clopidogrel and require dermatologic procedures are lacking.

The most common ophthalmologic procedure is cataract removal. In a prospective cohort study involving such patients, there was no apparent important increase in arterial thromboembolic events among 977 patients who had ASA interruption compared with 3363 patients who continued ASA (0.20% vs 0.65%). No clinically important bleeds were noted. There are few data involving the safety of continuing clopidogrel in patients undergoing eye procedures. One study conducted in patients having cataract surgery indicated that although subconjunctival hemorrhage was more common in clopidogrel-treated patients compared with those who were treated with ASA or were not receiving antiplatelet therapy, there were no sight-threatening bleeding complications.

Noncardiac surgery

In patients who are receiving antiplatelet therapy and require elective noncardiac surgery, there are no randomized trials or other nonrandomized studies that compare the benefits and risks of continuing such drugs as opposed to temporarily interrupting their use around the time of surgery. One 17,000-patient randomized trial compared perioperative administration of low-dose ASA (160 mg once daily) with placebo in patients undergoing hip fracture repair or other major orthopaedic surgery. ASA conferred a 43% (95% CI 18%-60%) decrease in the relative incidence of pulmonary embolism and a relative 29% (95% CI 3%-48%) decrease in deep vein thrombosis but no significant effect on MI. In a meta-analysis of > 49,000 patients undergoing noncardiac surgery, perioperative continuation of ASA was associated with an increase in bleeding but no an increased risk for bleeding that required medical or other interventions. Another systematic review found that perioperative interruption of ASA conferred an increased risk for adverse cardiovascular events (OR 3.1, 95% CI 1.8-5.6). Taken together, these findings from randomized trials suggest benefit for perioperative ASA continuation but also indicate potential harm related to increased perioperative bleeding. A risk-benefit assessment infers the benefits of ASA treatment may be limited to patients with prior cardiovascular disease (given reduction in vascular mortality).

CABG

In ASA-treated patients who require CABG, observational studies have shown that continuing ASA in the perioperative period increases the risk for mediastinal bleeding, blood transfusion, and re-operation. This finding was not replicated in a third study. In 1 large cohort study, ASA use within the 5 days prior to CABG was shown to lower the risk for postoperative death without increasing the risk for reoperation due to bleeding or blood transfusion requirements.

In clopidogrel-treated patients who require CABG, no studies have directly assessed clopidogrel use in the perioperative period. In a subanalysis of the CRUSADE Registry that assessed anticoagulation strategies for patients with NSTEACS who underwent CABG, 87% of clopidogrel recipients underwent CABG within 5 days of clopidogrel exposure. These patients had a 70% higher risk of needing a transfusion of 2-4 units of packed red blood cells. In a subanalysis of the CURE trial, which assessed antiplatelet strategies for NSTEACS, patients who received clopidogrel within 5 days of CABG had a 50% increase in trial-defined life-threatening or major bleeding. 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 bleeding risk, clopidogrel should be discontinued for 3-5 days prior to CABG. In all cases, preoperative and postoperative strategies that minimize the risk of major bleeding and transfusion should be implemented.

Noncardiac surgery in patients with cardiac stents

In patients who require noncardiac surgery and are receiving ASA and clopidogrel secondary to BMS or DES implantation, there is an increased risk for stent thrombosis in the postoperative period, especially if surgery is performed in close proximity to stent placement. Stent thrombosis in this clinical setting is associated with a large incidence of MI or death (up to 45% of affected patients). In patients with a BMS, 1 observational study found that the risk for major cardiovascular events was lowest (2.8%) if elective surgery was performed ≥ 3 months after stent implantation, whereas it was 10.5% in patients who underwent surgery within 30 days of stent placement and 3.8% in patients who underwent surgery 31-90 days after stent placement. Another observational study suggested that the risk of stent thrombosis and other adverse events is increased if noncardiac surgery is performed within 30 days of BMS placement or within 6 months of DES placement. In patients with DES implantation, 1 observational study reported that the risk for cardiovascular events in patients undergoing elective surgery was similar throughout the first year after stent placement and diminished thereafter. A recent analysis of the Scottish Coronary Revascularisation Register suggests
that although waiting to perform noncardiac surgery until 6 weeks after DES or BMS placement significantly reduces the risk of adverse ischemic outcomes, the risk can be further reduced by delaying surgery beyond 1 year.\textsuperscript{50}

**RECOMMENDATION (Summarized in Figs. 15 and 16)**

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 7-10 days before the procedure (Class IIa, Level C). Patients who are receiving ASA and clopidogrel should discontinue clopidogrel 7-10 days before the procedure if it can be done so 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 $\geq 6$ weeks after BMS placement and $\geq 12$ 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 7-10 days before the procedure if it can be done safely (Class IIb, Level C).

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

Patients who are receiving ASA and require elective noncardiac surgery should discontinue ASA 7-10 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 7-10 days before surgery if it can be done so safely (Class IIb, Level C).

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

**Management of Antiplatelet Therapy in Association With Minor Bleeding**

**Working Group:** James D. Douketis, MD, FRCP, and Alexander G. G. Turpie, MD, FRCP, FACC, FRCPC

In patients who are receiving antiplatelet drugs, non–life-threatening minor bleeding is common. Minor bleeding is especially common in patients who are also receiving anticoagulant therapy (warfarin or heparin), in those who are receiving systemic corticosteroids, and in those 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.

**Ecchymosis and petechiae**

Both ecchymosis and petechiae can occur in patients who are receiving antiplatelet therapy. Petechiae (ie, pinpoint capillary-based hemorrhages) typically occur in ASA- or clopidogrel-treated patients who have thrombocytopenia, with a
platelet count usually $< 50 \times 10^9/L$. Ecchymosis (ie, subcutaneous venous bleeding) can occur in ASA- and clopidogrel-treated patients who are receiving warfarin or corticosteroids or in patients with a superimposed coagulopathy.

Oral mucosal bleeding

Oral mucosal bleeding may commonly occur after dental procedures, particularly after multiple dental extractions or more extensive oral surgery. In general, such bleeding is self-limiting, although it may appear considerable enough to cause anxiety for patients.

Subconjunctival bleeding

Subconjunctival bleeding is more common in anticoagulant-treated vs antiplatelet-treated patients. It can be precipitated by vigorous coughing or straining during a bowel movement, and although it can cause reddening of the entire sclera, it does not affect visual acuity and is self-limiting, with resolution of the ecchymosis within 1-2 weeks.

**RECOMMENDATION (Summarized in Fig. 17)**

Patients who are receiving ASA or ASA and clopidogrel and develop ecchymosis and petechiae should undergo testing with a complete blood count and INR and activated partial thromboplastin time (aPTT) monitoring to investigate for thrombocytopenia or a coagulopathy (Class IIa, Level C). In the absence of superimposed abnormalities in hemostatic 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 in whom there is excessive bleeding after a dental procedure should receive application of local pressure and/or use of tranexamic acid mouthwash 2-4 times daily for 1-2 days (Class IIa, Level C).

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

Combination Therapy With Warfarin and Acetylsalicylic Acid: When to Use, When to Consider, When to Avoid

**Working Group:** James D. Douketis, MD, FRCP, and Alexander G. G. Turpie, MD, FRCP, FACC, FRCPC

Warfarin and ASA are widely used as separate treatments for the primary and secondary prevention of thromboembolic and atherothrombotic diseases based on their established effects in inhibiting thrombus formation and platelet aggregation, respectively. The potentially complementary therapeutic effects of warfarin and ASA make combination therapy appealing in 2 clinical scenarios. The first is when both the coagulation- and platelet-mediated pathways are involved in 1 disease, such as an ACS. However, in this setting, the anticoagulant, typically heparin, low-molecular-
weight heparin, or fondaparinux, is administered only for 7-10 days whereas the antiplatelet agent, typically ASA, is continued indefinitely. The second scenario is when a patient has 2 different diseases, 1 that is treated with an anticoagulant and 1 with an antiplatelet agent (eg, patients who have both atrial fibrillation and CAD or those with both venous thromboembolism and CAD).

Treatment with combination warfarin/ASA therapy should be limited to patients in whom the evidence for benefit outweighs the risk for harm related to bleeding. In the absence of such benefit from clinical trials, empiric use of combination warfarin/ASA should be used with caution given the established increased risk for bleeding compared with warfarin alone. In 1 meta-analysis, combination warfarin/ASA therapy conferred a 43% higher risk for major (life-threatening) bleeding compared with warfarin alone (OR 1.43, 95% CI 1.00-2.02).251 A large community-based study found a 2-fold higher risk for major bleeding in patients receiving warfarin and ASA compared with those receiving warfarin alone (OR 2.06, 95% CI 1.01-4.36).252 Finally, in a large linked administrative database study, the incidence of bleeding in patients with CAD who received ASA alone, warfarin alone, and combination warfarin/ASA therapy were 2.6%, 4.3%, and 5.1% per person-year, respectively.253 Compared with ASA users, those receiving combination ASA/warfarin had a 1.8-fold higher risk for major bleeding (OR 1.84, 95% CI 1.51-2.23).

The management of patients who have 2 diseases and who may require treatment with both warfarin and an antiplatelet drug arises frequently in clinical practice. For example, atrial fibrillation and CAD occur in ~2.3 million and ~16 million people, respectively, in North America.254,255 Therefore, it would not be uncommon to have a patient who will have both conditions and, thus, a clinical indication for both warfarin and ASA.

Evidence for therapeutic benefit with combination warfarin/ASA therapy

In patients with atrial fibrillation alone, a meta-analysis found no significant reduction in the risk of arterial thromboembolism with combination warfarin/ASA therapy compared with warfarin alone (OR 0.99, 95% CI 0.47-2.07).251 In patients with CAD alone, this meta-analysis found that combination warfarin/ASA therapy did not significantly reduce thromboembolic outcomes (OR 0.69, 95% CI 0.35-1.36). In the ASPECT-2 (Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis 2) trial, which enrolled 999 patients with CAD and randomized them to receive warfarin (target INR, 2.0-2.5) and low-dose ASA or warfarin alone (target INR 3.0-4.0), there was no significant difference in the composite endpoint of MI, stroke, or death in patients who received combination therapy vs warfarin alone (OR 0.92, 95% CI 0.36-1.85).256 In the WARIS (Warfarin Aspirin Reinfarction Study) II, which randomized 3630 patients with acute MI to warfarin (target INR 2.0-2.5) and low-dose ASA or warfarin alone (target INR 3.0-4.0), there was no significant difference in the composite endpoint of MI, stroke, or death in patients who received combination therapy vs warfarin alone (OR 0.92, 95% CI 0.36-1.85).256 In the WARIS (Warfarin Aspirin Reinfarction Study) II, which randomized 3630 patients with acute MI to warfarin (target INR 2.0-2.5) and low-dose ASA or warfarin alone (target INR 3.0-4.0), there was no significant difference in the composite endpoint of MI, stroke, or death in patients who received combination therapy vs warfarin alone (OR 0.92, 95% CI 0.36-1.85).256
nation therapy significantly increased nonfatal major bleeding compared with ASA alone but with not warfarin alone.

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 SPORTIF (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.\(^2\)\(^5\)\(^8\)\(^9\) There were no significant differences in the risk for coronary events (0.6% vs 1.0% per year) or stroke (1.7% vs 1.5% per year) in patients receiving warfarin and ASA or warfarin alone, thereby suggesting a lack of benefit with combination therapy. In a retrospective cohort study of more than 4,000 warfarin-treated patients managed by a specialized anticoagulation clinic, there were no significant differences in rates of coronary events (OR 0.99, 95% CI 0.37-2.62) or thromboembolism (OR 1.48, 95% CI 0.43-5.08) in patients receiving combination warfarin/ASA therapy compared with those receiving warfarin alone.\(^2\)\(^5\)\(^2\)

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. Thus, warfarin is effective to prevent recurrent cardiac events in patients with chronic, stable CAD.

When to consider combination warfarin/ASA therapy

Patient groups in which there is good evidence for warfarin/ASA therapy. Based on well-designed randomized trials, combination warfarin/ASA therapy is indicated in patients with a mechanical prosthetic heart valve. In a meta-analysis of 5 trials of patients with a mechanical aortic or mitral heart valve, warfarin/ASA therapy conferred a 73% reduction in the risk of arterial thromboembolism compared with warfarin alone (OR 0.27, 95% CI 0.15-0.49).\(^2\)\(^5\)\(^1\) The therapeutic benefit of warfarin/ASA therapy is greatest in patients with a mechanical mitral valve.\(^2\)\(^5\)\(^9\) In patients with a mechanical aortic valve, the benefits of combination therapy are less pronounced, but combination therapy should be considered in patients with older caged-ball or tilting disc aortic valve types.\(^2\)\(^5\)\(^9\)

Patient groups in which there is weak evidence for warfarin/ASA therapy. In patients with atrial fibrillation or venous thromboembolism who are receiving long-term warfarin and develop an ACS that is treated with medical therapy alone, combination therapy with warfarin and ASA is reasonable, the latter for up to 12 weeks, with the aim of stabilizing ongoing plaque rupture and preventing coronary rethrombosis. If, during the subsequent 12 weeks the patient has no further coronary events, ASA can be withdrawn given the evidence that warfarin alone is effective for chronic stable CAD. Thus, there is a short-term indication for combination warfarin/ASA therapy.

Patient groups in which warfarin/ASA therapy is reasonable despite the lack of supportive evidence. In patients who are receiving long-term warfarin and who undergo coronary stent implantation, it is reasonable to coadminister warfarin, ASA, and clopidogrel for ≥ 6 weeks. Thereafter, clopidogrel and ASA can be stopped assuming there are no additional coronary events. In patients with a DES, “triple therapy” with warfarin, ASA, and clopidogrel may be required for ≥ 12 months, possibly longer. Observational studies have found that patients who received “triple therapy” are at high risk for bleeding events compared with patients who receive other combinations of antithrombotic therapy. In a large, linked administrative database study, compared with patients with CAD who received ASA alone, the risk for bleeding was 1.8-fold higher in patients receiving combination ASA/warfarin (OR 1.84, 95% CI 1.51-2.23), 3.5-fold higher in patients receiving combination clopidogrel/warfarin (OR 3.52, 95% CI 2.42-5.11), and 4-fold higher in patients receiving “triple therapy” (OR 4.05, 95% CI 3.08-5.33). In another retrospective study, the 1-year risk for major bleeding in patients who had stent implantation was substantially higher in patients receiving “triple therapy” compared with dual–ASA/clopidogrel therapy (14.3% vs 3.0%, OR 9.0, 95% CI 3.1-26.1). In patients who have an indication for long-term warfarin therapy and undergo CABG, ASA is beneficial in preventing graft stenosis, whereas warfarin alone has not been studied and combination therapy is reasonable. Finally, in patients with atrial fibrillation who develop a stroke syndrome despite therapeutic anticoagulation with warfarin, the addition of ASA is reasonable because it may reduce the risk for recurrent stroke.

RECOMMENDATION (Summarized in Fig. 18)

In patients with a mechanical prosthetic heart valve, combination warfarin (target INR 2.0-3.0) and ASA 75-162 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)/ASA (75-162 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

Clopidogrel is a prodrug that requires activation by the cytochrome P450 isozyme CYP2C19 in the liver.\(^2\)\(^6\) Many as many as two-thirds of clopidogrel recipients also receive a PPI for the treatment of a concomitant acid-related disorder.\(^2\)\(^6\)\(^2\) The PPIs lansoprazole, omeprazole, and esomeprazole are strong inhibitors of CYP2C19 activity, whereas pantoprazole is a weak CYP2C19 inhibitor.\(^2\)\(^6\) In the past 2 years, several pharmacodynamic interaction studies suggest that omeprazole reduces the antiplatelet effect of clopidogrel,\(^2\)\(^6\)\(^4\)-\(^2\)\(^6\)\(^5\) 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.
Management of Patients Requiring Warfarin

**Figure 18.** Management of patients requiring warfarin. The management of patients on antiplatelet therapy requiring warfarin therapy requires an assessment of the risk of bleeding and the medical conditions for which combination therapy may be reasonable. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BMS, bare-metal stent; DES, drug-eluting stent.

**Studies**

**Observational studies.** In an analysis of 1010 clopidogrel recipients identified from a medical and pharmacy database, the adjusted 1-year rates of MI were significantly greater in patients who had exposure to PPIs (2.60% for no PPI exposure [n = 384] vs 10.00% for low PPI exposure [n = 90] vs 11.38% for high PPI exposure [n = 536]; *P < 0.05*). Another pharmacy and medical claims database also showed an increased risk of adverse events in clopidogrel/PPI users. In this matched cohort analysis of 2066 patients who had an acute MI or stent placement in the 30 days prior to an index clopidogrel prescription, the number of hospitalizations for MI or stenting were greater among those who also had a PPI prescription (27.6 vs 14.3 events per 100 person-years; adjusted HR 1.64, 95% CI 1.16-2.32; *P = 0.005*). In a retrospective, observational review of 5794 patients who experienced an MI, underwent PCI, and were discharged on clopidogrel, the 1369 PPI recipients had a significantly greater risk of experiencing reinfarction within 1 year (26% vs 16%, OR 1.78, 95% CI 1.55-2.07). This study also identified diabetes and experiencing reinfarction within 1 year (26% vs 16%, OR 1.78, 95% CI 1.55-2.07). This finding was supported in a cohort study of 8205 patients with ACS taking clopidogrel, of whom 5244 were also using PPI therapy. The use of clopidogrel plus a PPI was associated with an increased risk of death or rehospitalization for ACS compared with use of clopidogrel and no PPI (adjusted OR 1.25, 95% CI 1.11-1.41). Based on an analysis of 3 large population cohorts of 18,565 post-ACS or -PCI clopidogrel users, Rassen and colleagues reported that the risk of MI or death was 1.22 (95% CI 0.99-1.51). From this study, the authors hypothesized that the size of the risk increase associated with clopidogrel and PPI dual therapy may be exaggerated by biases inherent in observational studies, and even if an increased risk existed, it likely would not exceed 20%.

However, there are also data showing no impact of concomitant PPI use on outcomes in clopidogrel recipients. An analysis by Ray and colleagues of 20,596 patients hospitalized for MI, coronary revascularization, or UA and treated with clopidogrel, 7593 who were also current users of PPIs failed to show an adverse effect of PPI use on the risk of MI, sudden cardiac death, stroke, or other cardiovascular death in the total population (HR 0.99, 95% CI 0.82-1.19) or those who underwent PCI (HR 1.01, 95% CI 0.76-1.34). As might be expected, users of PPIs also had a lower risk of hospitalization for gastrointestinal bleeding (HR 0.50, 95% CI 0.39-0.65). Similarly, a study by Zairis and colleagues of 588 consecutive patients who underwent successful stent implantation did not reveal a significantly increased risk of cardiac death or rehospitalization for nonfatal MI among the 340 patients who received omeprazole and the 248 who did not (10.0% vs 9.7%, HR 1.1, 95% CI 0.6-1.8; *P = 0.89*).

**Randomized controlled trial.** The COGENT (Clopidogrel and the Optimization of Gastrointestinal EventNTs) study was a randomized, double-blind clinical trial that compared a fixed-dose combination of clopidogrel 75 mg plus omeprazole 20 mg with clopidogrel 75 mg in 3761 patients anticipated to receive clopidogrel plus enteric ASA 75-325 mg for ≥12 months. Results of the COGENT study showed that over 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 MI, CABI, PCI, or ischemic stroke (4.9% with clopidogrel plus omeprazole vs 5.7% with clopidogrel alone; HR 0.99, 95% CI 0.68-1.44). Although these findings suggest that coadministration of clopidogrel and omeprazole does not increase cardiovascular risk, the results are limited by the early termination of the trial due to sponsor bankruptcy and, thus, the shorter-than-planned follow-up duration and low number of adjudicated cardiovascular events (n = 109).

**Post-Hoc analysis of randomized controlled trials.** Post-hoc analysis of 2 randomized controlled trials that compared cardiovascular outcomes (TRITON-TIMI 38) or platelet aggregation (PRINCIPLE-TIMI 44 [Prazugrel IN Comparison to clopidogrel for Inhibition of PLatElet activation and aggregation]) in patients treated with prasugrel and ASA with those of patients treated with clopidogrel plus ASA revealed no increased risk of adverse cardiovascular outcomes associated with dual use of a PPI and either clopidogrel or prasugrel. Some observations from this study of interest are (1) there was attenuation of in vitro antiplatelet effects associated with both clopidogrel and prasugrel use in patients treated with PPI compared with those not treated with
PPI, with patients on clopidogrel showing greater attenuation than those on prasugrel; and (2) for patients randomly assigned to clopidogrel and who had a single reduced-function CYP2C19 allele, the primary endpoint of cardiovascular death, MI, or stroke was not significant after adjusting for the propensity to be treated with a PPI (OR 0.76, 95% CI 0.39-1.48).

**Meta-analysis.** Recently, Kwok and Loke performed a meta-analysis of 23 studies with 93,278 patients that compared outcomes in clopidogrel users who were and were not taking a PPI. Of the 12 studies that reported either MI or ACS events as outcomes, an increased risk was associated with concomitant PPI use (RR 1.43, 95% CI 1.15-1.77; \( P = 0.001 \)). However, the risk varied depending on the type of study, with the highest risk observed for unadjusted observational data and the lowest for propensity-matched and clinical trial data. Similar results were observed when the 19 studies that assessed major adverse cardiac events were analyzed (overall RR 1.25, 95% CI 1.09-1.42; \( P = 0.001 \)). Notably, an analysis of 13 studies that assessed all-cause mortality failed to find a significant effect in the pooled analysis (RR 1.09, 95% CI 0.94-1.26; \( P = 0.27 \)) or in the unadjusted observational data, adjusted observational data, or propensity-matched and clinical trial data. These findings led the authors to conclude that the evidence for the impact of concomitant clopidogrel and PPI use on cardiovascular outcomes is conflicting and inconsistent and that there is no evidence of an effect on mortality.277 They suggest that clinicians carefully weigh the risks of gastrointestinal hemorrhagic events before deciding to completely avoid PPI use in clopidogrel recipients.

**Regulatory guidance**

In the face of this evidence, as well as analyses of several studies published only as abstracts,278-280 the US FDA issued an update on November 17, 2009, stating that the concomitant use of omeprazole and clopidogrel should be avoided.281 The FDA acknowledged that there was insufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their coadministration. However, they stated that there was no evidence that other drugs, including most \( H_2 \) blockers (eg, ranitidine, famotidine, nizatidine, with the exclusion of the CYP2C19 inhibitor cimetidine) or antacids, interfere with the antiplatelet activity of clopidogrel. The statement included in the Canadian product monograph for clopidogrel, which was updated in September 2009, is broader in that it recommends that concomitant use of clopidogrel and PPIs be avoided (ie, it does not limit the warning to omeprazole only).282

**Current guidelines**

Recently, the American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG), and AHA published a joint expert consensus statement on the use of PPIs and thienopyridines.283-285 The statement 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 or \( H_2 \) blockers is not recommended for patients at lower risk of upper gastrointestinal bleeding. The consensus also states that decisions regarding the concomitant use of PPIs and thienopyridines must balance overall cardiovascular and gastrointestinal risks and benefits.

**Genetic polymorphisms**

In light of data suggesting that carriers of CYP2C19 loss-of-function polymorphisms have a reduced antiplatelet response to clopidogrel284 and an increased risk of adverse cardiovascular outcomes,285 the US FDA added a black box warning to the clopidogrel prescribing information highlighting the increased cardiovascular risk in clopidogrel poor metabolizers and the availability of genetic tests for determining the CYP2C19 genotype.286 Further, they recommend that clinicians consider alternative treatment strategies in patients identified as poor metabolizers. However, response to clopidogrel is multifactorial, and data suggest that CYP2C19 genotype, even when combined with clinical factors (eg, diabetes mellitus and age) that contribute to clopidogrel response, explains only 5%-12% of the observed response variability.284,286 Given that genetic testing is typically not available to clinicians outside the research environment and that the relationship between CYP2C19 polymorphism and patient outcomes has not been assessed prospectively, an official recommendation regarding the use of genetic testing in guiding antiplatelet therapy cannot be made at this time. Pending the results of ongoing studies such as the GRAVTAS (Gauging Responsiveness with A VerifyNow assay – Impact on Thrombosis And Safety) clinical trial,287 recommendations may be made in future iterations of the guideline. This echoes a recent joint clinical statement from the ACCF/AHA, which recommends that while clinicians need to be cognizant of the role of genetic polymorphisms in mediating clopidogrel response, the impact of individual polymorphisms on clinical outcomes remains to be determined and clinicians should adhere to existing guidelines and their own clinical judgement as the basis for choosing an antiplatelet therapy regimen.288

**RECOMMENDATION (Summarized in Fig. 19)**

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.275 Nevertheless, because of potential limitations with study design and patients recruited, PPIs that minimally inhibit CYP2C19 are preferred for patients taking clopidogrel who are considered to be at increased risk of upper gastrointestinal bleeding (Class IIb, Level of Evidence B).

**Interaction Between Acetylsalicylic Acid and Nonsteroidal Anti-Inflammatory Drugs**

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

ASA exerts its antiplatelet effect by irreversibly binding to the serine residue at position 529 of platelet cyclooxygenase-1 (COX-1), preventing the conversion of arachidonic acid to thromboxane, a process involved in platelet aggregation.289 Because the anucleate platelet is unable to reform COX-1, aggre-
ASA.290,291 Because ASA has a short serum half-life (45 min), 
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 CYP2C19 are preferred for 
patients taking clopidogrel who are considered to be at 
increased risk of upper gastrointestinal bleeding 
(Class IIb, Level of Evidence B).

The use of proton-pump inhibitors. The management of pa-
tients on dual antiplatelet therapy may include the use of proton-
pump inhibitors with minimal inhibition of cytochrome P2C19 in pa-
tients considered at increased risk of upper gastrointestinal 
bleeding. COX-1, cytochrome; PPIs, proton-pump inhibitors.

Figure 19. Use of proton-pump inhibitors. The management of pa-
tients on dual antiplatelet therapy may include the use of proton-
pump inhibitors with minimal inhibition of cytochrome P2C19 in pa-
tients considered at increased risk of upper gastrointestinal 
bleeding. COX-1–inhbiting NSAIDs do not offer cardioprotective bene-
gatory function is permanently impaired. Unlike ASA, tradi-
tional NSAIDs form a reversible complex with COX-1 that is 
dependent on the serum concentration of the drug. As the 
serum level falls, dissociation occurs and the platelet assumes 
normal function.289 While bound to platelets, COX-1–inhbit-
ing NSAIDs have been shown to prevent binding of ASA.290,291 Because ASA has a short serum half-life (~18 minutes),292 the potential exists for NSAIDs to prevent ASA-medid-
ated platelet inhibition if the drugs are used concomitantly. Al-
though no randomized trials examining the clinical effect of this 
interaction have been completed, laboratory studies, observational 
data, and epidemiologic analysis have suggested an adverse effect.

Platelet function studies

Catella-Lawson and colleagues demonstrated that when a 
single oral dose of ASA 81 mg was administered to healthy 
volunteers 2 hours prior to ibuprofen 400 mg for 6 consec-
tive days, complete inhibition of platelet aggregation persisted 
up to 24 hours after dosing.293 However, when dosed in the re-
verse order, aggregation was noted to resume by 6 hours and was 
virtually uninhibited by 24 hours. When multiple oral daily doses 
of ibuprofen were administered, the platelet-inhibitory effects 
of ASA were antagonized despite ASA being dosed 2 hours 
before the first daily ibuprofen dose. ASA antagonism was not 
observed when acetaminophen, rofecoxib, or extended-release 
diclofenac was used instead of ibuprofen.

Due to their variable and reversible binding to platelet 
COX-1, NSAIDs do not offer cardioprotective bene-
fits.294–296 However, a number of studies have provided con-
flicting results with naproxen in this regard.297,298 Capone 
and colleagues299 demonstrated that ex vivo, naproxen re-
versibly binds platelet COX-1 and blocks irreversible ASA 
binding. They further noted that if naproxen is strictly 
dosed, it will provide an antiplatelet effect similar to that of 
ASA. However, prevention of ASA binding was noted at 
concentrations of naproxen too low to inhibit platelet func-
tion, suggesting that outside the controlled environment of a 
research study, the drug is likely to interfere with the 
reliable antiplatelet effect of ASA.

Observational and epidemiologic studies

In their analysis of 7107 patients discharged from the 
hospital after a cardiovascular event, MacDonald and Wei300 demonstrated a hazard ratio of 1.73 (95% CI 1.05- 
2.84; P = 0.03) for cardiovascular mortality and 1.93 (95% 
CI 1.30-2.87; P = 0.001) for all-cause mortality in patients 
taking ibuprofen in addition to ASA compared with those 
taking ASA alone. In an examination of the primary prevention 
of MI, a subgroup analysis of the 5-year, 22,071-subject Physicians’ Health Study was performed.301 In this 
study, healthy male physicians were randomized to ASA 325 
mg on alternate days or placebo. In the ASA arm, the use of 
NSAIDs on > 60 days per year was associated with a nearly 
3-fold increase in MI compared with no use of NSAIDs (RR 
2.86, 95% CI 1.25-6.56). No significant effect was noted in 
the placebo arm, suggesting this risk is related to the inter-
action between ASA and NSAIDs.

Numerous studies have examined the effect of COX-2 in-
hbitors (ie, coxibs) on the antiplatelet effect of ASA.302–305 
Because COX-2 is absent from platelets, an interaction would 
not be expected and, indeed, has not been observed in these 
projects. The TARGET (Therapeutic Arthritis Research and 
Gastrointestinal Event Trial) study of 18,325 patients with 
osteoarthritis comprised 2 parallel substudies comparing the 
COX-2 inhibitor lumiracoxib with either ibuprofen or 
aproxen.306 A post-hoc analysis of patients at high cardio-
vascular risk examined the interaction of these NSAIDs with 
ASA.307 Among ASA users, patients in the ibuprofen sub-
study experienced significantly more vascular events with 
ibuprofen than with lumiracoxib (RR 9.08, 2.14% vs 
0.25%; P = 0.038), whereas in the naproxen substudy, rates 
were similar for naproxen and lumiracoxib (1.58% and 
1.48%, respectively). Among the patients not taking ASA, 
no increased risk was observed with ibuprofen, suggesting 
the effect is due to the interaction with ASA. Contrary to 
these results, a single case-control study failed to identify an 
interaction between ibuprofen and ASA.308

Specific COX-2 inhibitors, traditional NSAIDs, and 
vascular events

The use of both selective and nonselective COX-2 NSAIDs 
has been associated with an increased risk of vascular events 
compared with placebo in both randomized trials and observa-
tional studies. A meta-analysis of 138 randomized controlled 
trials (N = 145,373) of ≥ 4 weeks’ duration that included a 
comparison of a selective COX-2 inhibitor vs placebo or a 
traditional NSAID or both and information on serious vascular 
events (ie, MI, stroke, or vascular death) was conducted by 
Kearney and colleagues.309 Overall, the incidence of serious
vascular events was similar between selective COX-2 inhibitors and any traditional NSAID (1.0% per year vs 0.9% per year; $P = 0.1$). Individual relative risk increases were 1.42 (95% CI 1.13-1.78) for coxibs, 1.51 (95% CI 0.96-2.37) for ibuprofen, 1.63 (95% CI 1.12-2.37) for diclofenac, and 0.92 (95% CI 0.67-1.26) for naproxen. Heterogeneity was noted for naproxen vs non-naproxen NSAIDs in comparison with coxibs ($P = 0.001$). This heterogeneity was largely driven by a comparison of naproxen with high-dose rofecoxib in the VIGOR (Vloxx Gastrointestinal Outcomes Research) trial. A similar meta-analysis of 17 case-control or cohort studies reporting the incidence of cardiovascular events with selective COX-2 inhibitors, nonselective NSAID use, or both was conducted by McGGettigan and Henry. A dose-related increased cardiovascular risk was evident with rofecoxib $\leq 25$ mg daily (summary RR 1.33, 95% CI 1.00-1.79) and rofecoxib $> 25$ mg daily (summary RR 2.19, 95% CI 1.64-2.91). Conversely, celecoxib was not associated with an elevated risk of ischemic vascular events (summary RR 1.06, 95% CI 0.91-1.23). Among nonselective drugs, diclofenac was associated with the highest risk (summary RR 1.40, 95% CI 1.16-1.70). The other drugs, including naproxen, had summary relative risks close to 1. Overall and with the exception of high-dose rofecoxib, a drug that was removed from worldwide markets in 2004, there is insufficient evidence to suggest that selective COX-2 inhibitors increase the risk of ischemic vascular events compared with traditional, nonselective NSAIDs.

Summary

Because ASA and traditional NSAIDs compete for the binding of platelet COX-1, a potential for a pharmacodynamic drug interaction exists. This interaction has important clinical consequences because the reversible binding of NSAIDs does not offer a consistent antiplatelet effect or the vascular protection afforded by the irreversible binding of ASA. Although no prospective, randomized trials examining the clinical impact of this interaction have been completed, a wealth of observational data supports an association with adverse vascular outcomes.

**RECOMMENDATION (Summarized in Fig. 20)**

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

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

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

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**Use of NSAIDs in Patients on ASA**

**Figure 20.** Use of NSAIDs in patients on ASA. In patients on ASA, the use on traditional nonsteroidal anti-inflammatory drugs should be avoided and if an anti-inflammatory drug is required, a specific cyclooxygenase-2 inhibitor should be considered. ASA, acetylsalicylic acid; coxib, cyclooxygenase-2 inhibitor; NSAID, non-steroidal anti-inflammatory drugs.

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## Appendix I. Composite domain scores for guidelines assessed using the AGREE instrument

<table>
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<th>Guideline (author/group, topic, year)</th>
<th>Scope and purpose*</th>
<th>Stakeholder involvement†</th>
<th>Rigour of development‡</th>
<th>Clarity and presentation§</th>
<th>Applicability¶</th>
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ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACG, American College of Gastroenterology; ACP, American College of Physicians; ACS, acute coronary syndrome; ADA, American Diabetes Association; AHA, American Heart Association; A/P, antiplatelet; ASA, American Stroke Association; ASGE, American Society of Gastrointestinal Endoscopy; BCS, Brazilian Cardiology Society; BSG, British Society of Gastroenterology; CAD, coronary artery disease; CAIC, Canadian Association of Interventional Cardiology; CCS, Canadian Cardiology Society; CDA, Canadian Diabetes Association; CKD, chronic kidney disease; CSANZ, Cardiovascular Society of Australia and New Zealand; CSS, Canadian Stroke Strategy; CV, cardiovascular; CVD, cardiovascular disease; DES, drug-eluting stent; EACTS, European Association of Cardio-Thoracic Surgery; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; ESO, European Stroke Organization; GI, gastrointestinal; HFSA, Heart Failure Society of America; ICSI, Institute for Clinical Systems Improvement; NHFA, National Heart Foundation of Australia; NHLBI, National Heart, Lung, and Blood Institute; NICE, National Institute for Health and Clinical Excellence; NKF, National Kidney Foundation; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non-ST-segment elevation myocardial infarction; NZGG, New Zealand Guidelines Group; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SCAI, Society for Cardiovascular Angiography and Interventions; SIGN, Scottish Intercollegiate Guidelines Network; STEMI, ST-segment elevation myocardial infarction; TASC, Trans-Atlantic Society Consensus; TIA, transient ischemic attack.

* Assesses the overall aim of the guideline, the specific clinical questions, and the target patient population.
† Focuses on the extent to which the guideline represents the views of its intended users.
‡ Relates to the process used to gather and synthesize the evidence and the methods to formulate the recommendations and to update them.
§ Pertains to the language and format of the guidelines.
¶ Pertains to the likely organizational, behavioural, and cost implications of applying the guidelines.
§ Assesses the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline development group.
### Appendix II. External expert reviewers of the Canadian Cardiovascular Society antiplatelet therapy guideline

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Affiliation</th>
<th>Sections reviewed</th>
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<tr>
<td>Paul W. Armstrong, MD, FRCPC</td>
<td>University of Alberta, Edmonton, Alberta, Canada</td>
<td>Antiplatelet Therapy for the Primary Prevention of Vascular Events</td>
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<tr>
<td>Shannon Bates, MD, MSc, FRCPC</td>
<td>McMaster University Medical Centre, Hamilton, Ontario, Canada</td>
<td>Use of Antiplatelet Therapy in Women Who Are Pregnant or Breastfeeding</td>
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<tr>
<td>Stephanie J. Brister, MD, BSc, FRCS</td>
<td>University of Toronto and Toronto General Hospital, Toronto, Ontario, Canada</td>
<td>Antiplatelet Therapy for Secondary Prevention Following Coronary Artery Bypass Grafting</td>
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<tr>
<td>Jean Buithieu, MD</td>
<td>McGill University Health Centre, Montréal, Québec, Canada</td>
<td>Antiplatelet Therapy for Vascular Prevention in Patients With Peripheral Artery Disease</td>
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<tr>
<td>Mark Crowther, MD, MSc, FRCPC</td>
<td>McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada</td>
<td>Management of Antiplatelet Therapy in Association With Minor Bleeding</td>
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<tr>
<td>Diego H. Delgado, MD</td>
<td>Toronto General Hospital, Toronto, Ontario, Canada</td>
<td>Combination Therapy With Warfarin and Acetylsalicylic Acid: When to Use, When to Consider, When to Avoid Interaction Between Clopidogrel and Proton Pump Inhibitors Interaction Between Acetylsalicylic Acid and Nonsteroidal Anti-inflammatory Drugs</td>
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<td>John W. Eikelboom, MD, MSc</td>
<td>McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada</td>
<td>Use of Antiplatelet Therapy in Patients With Heart Failure Interaction Between Clopidogrel and Proton Pump Inhibitors Interaction Between Acetylsalicylic Acid and Nonsteroidal Anti-inflammatory Drugs</td>
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<td>David Fitchett, BChir, MD, MRCP, FRCP, FACC, FESC</td>
<td>University of Toronto and St. Michael’s Hospital, Toronto, Ontario, Canada</td>
<td>Antiplatelet Therapy for Secondary Prevention Following Acute Coronary Syndromes</td>
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<tr>
<td>Thomas L. Forbes, MD</td>
<td>University of Western Ontario, London, Ontario, Canada</td>
<td>Antiplatelet Therapy for Secondary Prevention in Stable Coronary Artery Disease</td>
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<td>Stephen Fremes, MD, MSc, FRCS, FACP, FACC</td>
<td>Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada</td>
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<tr>
<td>Michael D. Hill, MD, MSc, FRCPC</td>
<td>University of Calgary, Calgary, Alberta, Canada</td>
<td>Antiplatelet Therapy for Secondary Prevention of Cerebrovascular Disease</td>
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<tr>
<td>Lawrence A. Leiter, MD, FRCP, FACP</td>
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<td>Use of Antiplatelet Therapy in Patients With Diabetes</td>
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<td>Anil Nigam, MD, MSc, FRCP</td>
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<td>Paul Poirier, MD, PhD, FRCP, FACC</td>
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<td>Erick Schampaert, MD, FRCP</td>
<td>Université de Montréal and Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada</td>
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<td>Alex C. Spyropoulos, MD, FACP, FCCP</td>
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<td>Management of Patients on Antiplatelet Therapy Who Require a Surgical or Other Invasive Procedure</td>
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<td>Theodore H. Wein, MD, FRCP</td>
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### Appendix III. Author relationships with industry—CCS antiplatelet consensus committee

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<th>CV surgery</th>
<th>Congenital heart disease</th>
<th>General cardiology</th>
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Note: The table includes various relationships and categories for each committee member. Categories include: 1 = General cardiology, 2 = Interventional, 3 = Medical devices, 4 = Cardiology research, 5 = Prevention, 6 = Intervention, 7 = Medical devices, 8 = Cardiology research, 9 = Medical education.
### Appendix III. Continued

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