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, FRCSC,[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, FESC[q]

[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

Antiplatelet agents are a cornerstone of therapy for patients with atherosclerotic vascular disease. There is presently a lack of comprehensive guidelines focusing on the use of antiplatelet drugs in patients currently manifesting or at elevated risk of cardiovascular disease.

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

plinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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/. 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.

maladie cardiovasculaire sont à l'heure actuelle incomplètes. Le comité canadien sur les directives pour le traitement antiplaquettaire a passé en revue les lignes directrices des maladies et, subséquemment la littérature publiée, et les revues et l'opinion des experts pour développer des lignes directrices sur l'utilisation de traitements antiplaquettaires dans la prise en charge externe des patients. Ce document entier a été présenté dans un sommaire exécutif du *Journal canadien de cardiologie* et peut être consulté au http://www.ccs.ca/. Le traitement antiplaquettaire semble généralement sous-utilisé, peut-être en partie en raison de l'absence de directives claires et prouvées. Ici, nous donnons des lignes directrices spécifiques pour la prévention secondaire chez les patients en soins externes à la suite de syndromes coronariens aigus, d'une intervention coronaire percutanée, d'un pontage aortocoronarien; chez les patients avec une histoire d'ischémies cérébrales transitoires ou d'accidents vasculaires cérébraux et chez les patients avec une maladie artérielle périphérique. Les questions liées à la prévention primaire sont aussi abordées, en plus des contextes cliniques particuliers comme le diabète, l'insuffisance cardiaque, la maladie rénale chronique, la grossesse et l'allaitement, et la gestion périopératoire. Des recommandations sont données tant pour les interactions pharmacologiques qui peuvent survenir durant un traitement combiné avec la warfarine, le clopidogrel et les inhibiteurs de la pompe à protons, ou l'acide acétylsalicylique et les médicaments anti-inflammatoires non stéroïdaux, que pour la gestion des complications hémorragiques.

TABLE OF CONTENTS

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

use of ASA was reported for 90.4%, 87.9%, and 83.2% of low-, intermediate-, and high-risk patients with non–ST-segment elevation acute coronary syndrome (NSTEACS), respectively.[1] Even in the recently published SYNTAX (SYNergy between PCI with TAXus and cardiac surgery) randomized clinical trial, in which ASA was to be used indefinitely in all patients postprocedure, only 91.2% of patients who underwent percutaneous coronary intervention (PCI) and 84.3% of patients who underwent coronary artery bypass grafting (CABG) were taking ASA 12 months after the procedure.[2] The underuse of antiplatelet therapy is observed among outpatients treated by both specialists and general practitioners. In the international REACH (REduction of Atherothrombosis for Continued Health) Registry of approximately 68,000 patients who had established, or were at risk for developing, cardiovascular disease, 74.8% of patients treated by general practitioners were receiving ≥ 1 antiplatelet agent, compared with 89.5% of patients treated by cardiologists.[3] It is important to note that neither the REACH Registry nor the Canadian ACS Registries recorded information on medication contraindications. In an analysis of US outpatients with established cardiovascular disease and no known contraindication, ASA use was reported in only 32.8% 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,[5] diabetes,[6] drug-eluting stent [DES] implantation,[7] and stroke[8]). 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[9]
- 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

Class of Recommendation	Level of Evidence
I: Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective	A: Data derived from multiple randomized clinical trials or meta-analyses
IIa: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the weight of evidence in favour	B: Data derived from a single randomized clinical trial or large nonrandomized studies
IIb: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the usefulness/efficacy less well established	C: Consensus of opinion by experts and/or small studies, retrospective studies, and registries
III: Evidence that the treatment is not useful and in some cases may be harmful	

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.[10] 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.[11] 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 $P2Y_{12}$ 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.[12] 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,[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.[13,14] In the Antiplatelet 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; $P = 0.0006$).[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.[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[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.[12,17-19]

Platelet P2Y$_{12}$ receptor antagonists. Thienopyridines inhibit platelet aggregation via blockade of platelet P2Y$_{12}$ adenosine diphosphate (ADP) receptors.[20] Currently, the oral thienopyridines ticlopidine, clopidogrel, and prasugrel are approved for use in Canada. An application for marketing approval of the novel P2Y$_{12}$ 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.[21-23] However, clopidogrel is a prodrug that requires a 2-stage oxidation process mediated by cytochrome P450 to generate its active metabolite,[20] 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.[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.[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$_{12}$ receptor blocker, appears to have a potency and speed of onset similar to those of prasugrel.[26] In contrast with clopidogrel and prasugrel, ticagrelor does not require metabolic activation and is a reversible inhibitor of the platelet P2Y$_{12}$ receptor. Because of its half-life (7-8.5 hours) and reversibility,[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 Ischaemic 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.[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%; $P = 0.66$).[28]

Clopidogrel in addition to ASA post NSTEACS. The CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial[29] transformed the global use of clopidogrel and represents the key evidence for thienopyridine therapy in NSTEACS. 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.[30] Thus, controversy regarding the implications of the CURE trial for the optimal duration of clopidogrel post NSTEACS persists. However, pharmacoeconomic analyses have indicated that clopidogrel plus ASA for 1 year post NSTEACS is highly cost-effective in both Canadian[31] and global[32] 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.[33] 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%; $P = 0.03$). 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 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 ≥ 1 intracoronary stents.

Clopidogrel in addition to ASA post ACS. In the CURRENT-OASIS (Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-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 × 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% ab-

solute 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 (1.04% vs 0.95%, 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 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial 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 ≥ 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 the 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 ≥ 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%

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

Agent	Recommended Dose and Duration of Therapy	Class (Level of Evidence)
ASA	Use 75-162 mg/d indefinitely	I (A)
	75-162 mg/d is recommended to minimize bleeding complications	IIa (B)
Clopidogrel	75 mg/d indefinitely in ASA allergy or intolerance	IIa (B)
ASA + clopidogrel	*Post STEMI*	
	Medically managed	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for a minimum of 14 d	I (B)
	Clopidogrel 75 mg/d may be continued for 12 mo in the absence of excess bleeding risk	IIa (C)
	Post PCI	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for 12 mo	I (B)
	ASA 75-162 mg/d and clopidogrel 75 mg/d may be continued beyond 12 mo in patients with a high risk of thrombosis and a low risk of bleeding	IIa (C)
	Post NSTEACS	
	Medically managed	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for a minimum of 1 mo	I (A)
	Clopidogrel 75 mg/d may be continued for 12 mo in the absence of excessive bleeding risk	I (B)
	Post PCI	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for 12 mo	I (A)
	ASA 75-162 mg/d and clopidogrel 75 mg/d may be continued beyond 12 mo in patients with a high risk of thrombosis and a low risk of bleeding	IIb (C)
	Post CABG	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for a minimum of 1 mo and up to 12 mo	I (B)
ASA + prasugrel	ASA 75-162 mg/d and prasugrel 10 mg/d for 12 mo in patients who undergo stent implantation and have an increased risk of thrombosis (eg, STEMI, history of diabetes mellitus, prior documented stent thrombosis)	IIa (B)
	ASA 75-162 mg/d plus prasugrel 10 mg/d should be avoided in patients at a high risk of bleeding, likely to undergo CABG within 7 d, with a history of stroke or TIA, aged ≥75 y, or weight <60 kg	III (B)
ASA + ticagrelor*	ASA 75-162 mg/d plus ticagrelor* 90 mg twice daily for 12 mo	I (B)

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.

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 ≥ 14 days (Class I, Level B) and up to 12 months in the absence of an excessive risk of bleeding (Class IIb, Level C).

For patients presenting with STEMI who are managed by PCI, clopidogrel 75 mg daily is recommended in addition to ASA 75-162 mg daily for 12 months (Class I, Level B).

Continuation of combined therapy beyond 12 months may be considered in patients with a high risk of thrombosis and a low risk of bleeding (Class IIb, Level C).

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

For patients with ACS who undergo stent implantation and have an increased risk of stent thrombosis (eg, STEMI, history of diabetes mellitus, or prior documented stent thrombosis), prasugrel 10 mg daily may be considered in addition to ASA 75-162 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 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,

Postdischarge Management of Acute Coronary Syndrome
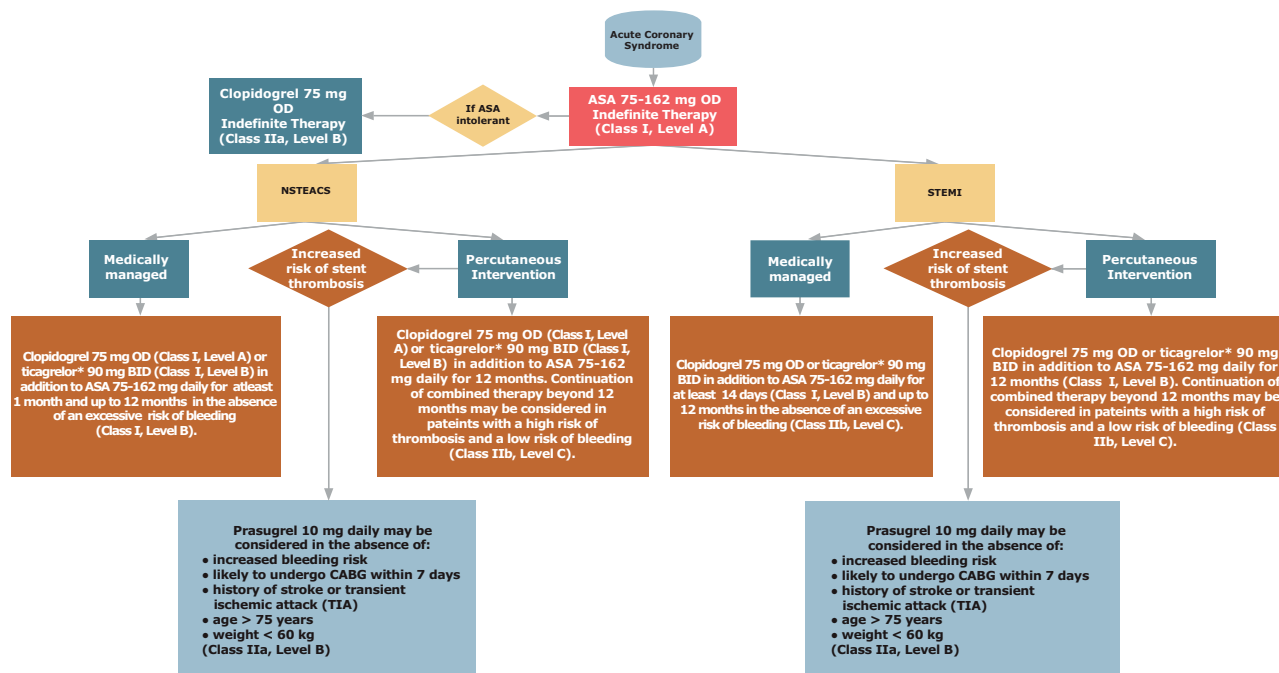
Figure 1. Postdischarge management of acute coronary syndrome. After an acute coronary syndrome, the outpatient antiplatelet therapy recommendations after ST-elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndrome (NSTEACS) in medically managed or after percutaneous intervention. In general, the ADP P2Y$_{12}$ 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.

Level B). (Ticagrelor is currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.)

In general, the ADP P2Y$_{12}$ receptor antagonist added to ASA in the acute setting should be maintained for the duration of therapy (Class I, Level C).

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

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

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.

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 P2Y$_{12}$ 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,

Postdischarge Management of ST Segment Elevation Myocardial Infarction
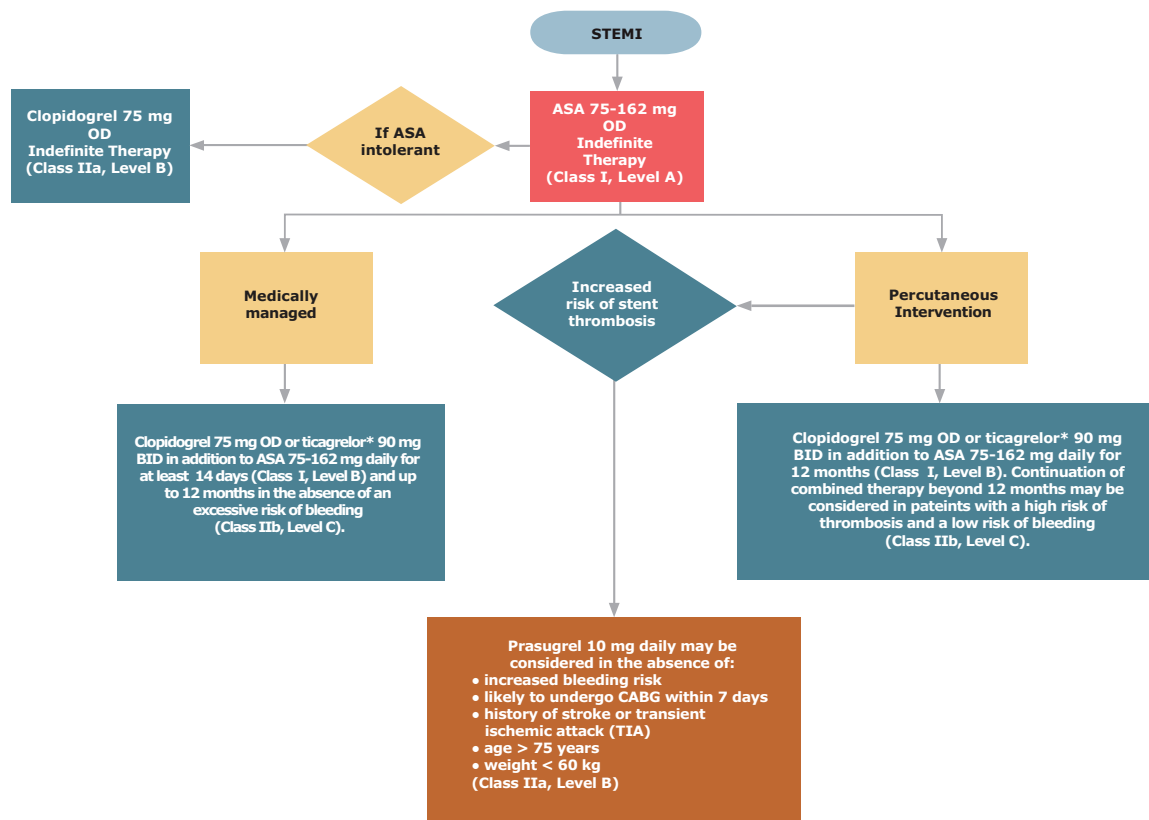
Figure 2. Postdischarge management of ST-elevation myocardial infarction (STEMI). The outpatient management after a STEMI is outlined for patients medically managed or after percutaneous intervention. In general, the ADP $P2Y_{12}$ receptor antagonist added to ASA in the acute setting should be maintained 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 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%; $P = 0.008$).[45] The benefit of adding the ADP $P2Y_{12}$ 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%; $P < 0.05$).[36] Similar reductions were observed for the 3534 patients with STEMI (relative risk reduction 21%, 10.0% vs 12.4%, absolute risk reduction 2.4%; $P < 0.05$).[36] 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%; $P < 0.05$).[46] 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.[47] 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.[47]

Postdischarge Management of Non-ST Segment Elevation Acute Coronary Syndrome
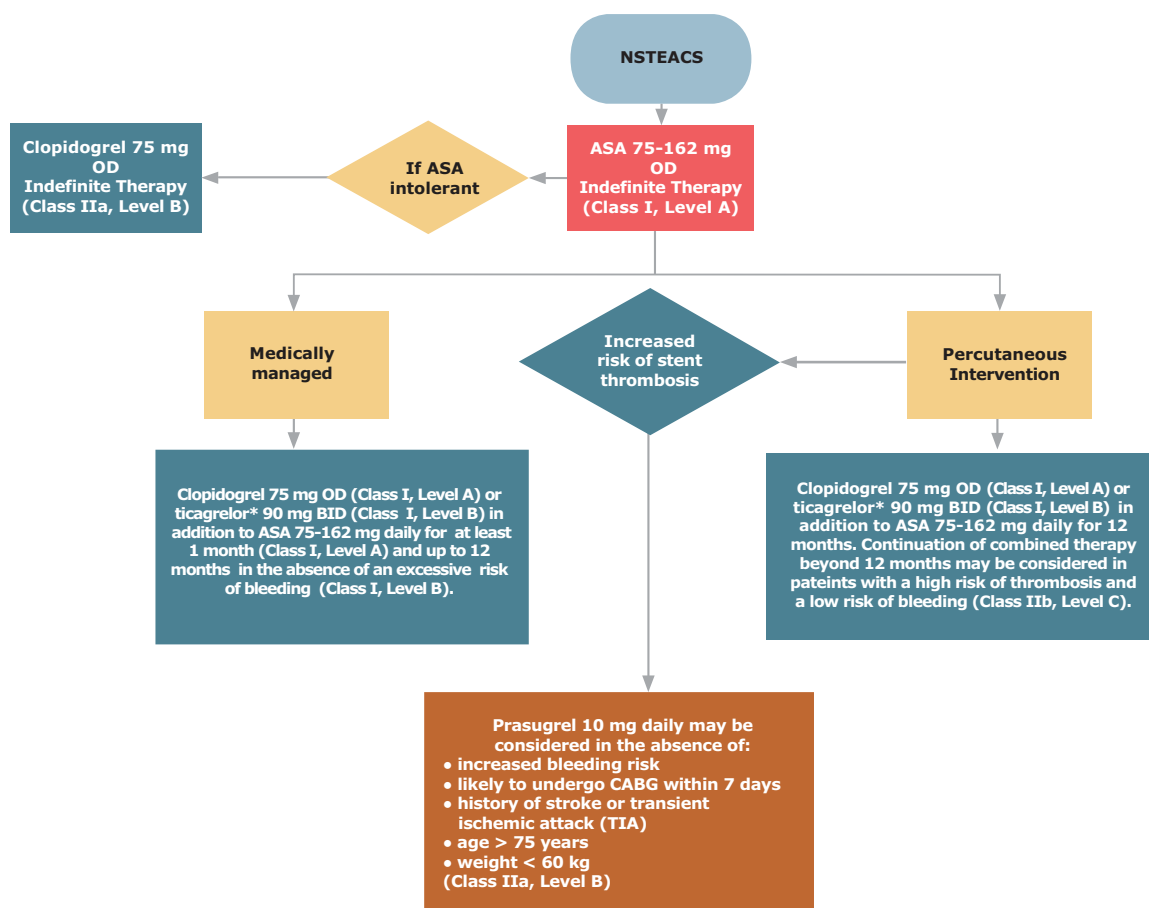
Figure 3. Postdischarge management of non-ST-segment elevation acute coronary syndrome (NSTEACS). The outpatient management after a NSTEACS is outlined for patients medically managed or after percutaneous intervention. In general, the ADP P2Y$_{12}$ receptor antagonist added to ASA in the acute setting 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.

Dual-Antiplatelet therapy after BMS implantation

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.[48-51] 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.[50] Despite its superiority to ASA and oral anticoagulation, the clinical use of ticlopidine was limited due to its hematologic toxicity,[52] which subsequently led to substitution with clopidogrel. Indeed, 3 randomized studies[21,53,54] and a meta-analysis[22] 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.[55] 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.[56]

Although stent thrombosis occurs following only 0.5%-2% of stent placements,[57] 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.[58-61] Furthermore, stent thrombosis is associated with rates of mortality as high as 45%.[61-63] 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.[57]

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

Agent	Recommended dose and duration of therapy	Class (level of evidence)
ASA	75-162 mg/d indefinitely	I (A)
Clopidogrel	75 mg/d indefinitely in ASA allergy or intolerance	IIa (C)
ASA + clopidogrel	*Post-BMS*	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for ≥ 1 mo	I (B)
	ASA 75-162 mg/d and clopidogrel 75 mg/d for up to 12 mo in the absence of an excessive risk of bleeding	I (B)
	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	I (B)
	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	IIb (C)
	Post-DES	
	ASA 75-162 mg/d and clopidogrel 75 mg/d for 12 mo	I (A)
	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	IIb (C)
ASA + prasugrel	*Post-ACS*	
	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)	IIa (B)
	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 < 60 kg	III (B)
ASA + ticagrelor*	*Post-ACS*	
	ASA 75-162 mg/d and ticagrelor* 90 mg twice daily for 12 mo	I (B)

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.

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.[57] 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.[61,63,64] 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.[65] 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).

Postdischarge Management of Patients Undergoing Percutaneous Coronary Intervention
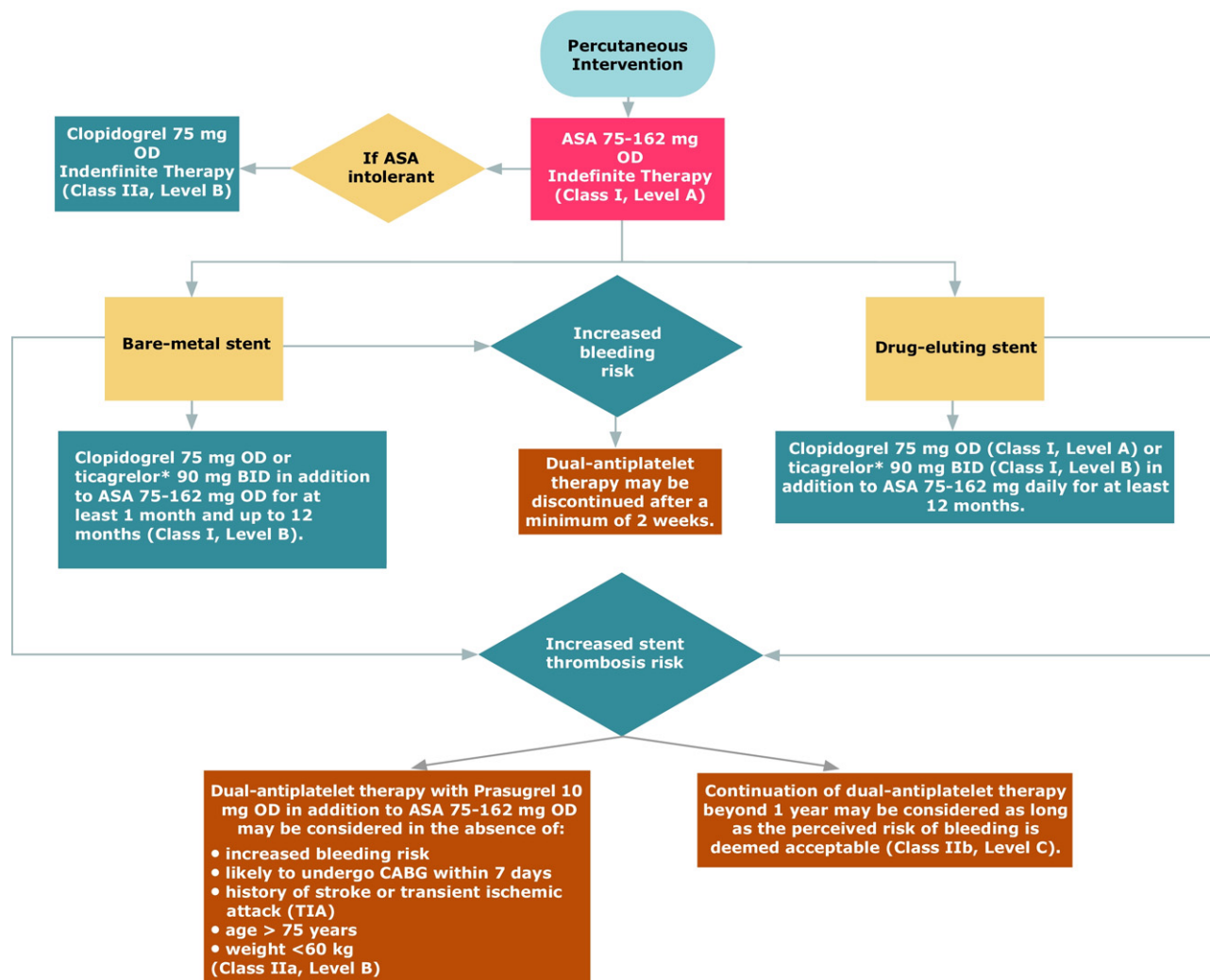
Figure 4. Postdischarge management of patients undergoing percutaneous coronary intervention (PCI). The outpatient management after a PCI is outlined for patients receiving a bare-metal stent or drug-eluting stent. ASA, acetylsalicylate acid; CABG, coronary artery bypass graft. *Currently under review by Health Canada. All recommendations concerning ticagrelor are conditional on approval by Health Canada.

> For patients with ACS who undergo stent implantation, ticagrelor 90 mg twice daily may be added to ASA 75-162 mg daily for 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.)

Antiplatelet 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

Antiplatelet 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 recommenda-

tions for the use of antiplatelet 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 antiplatelet therapy in patients with stable CAD will be presented and consensus recommendations provided. However, before presenting the evidence for long-term antiplatelet 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 (eg, 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 sulfinpyrazone 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 sulfinpyrazone alone or placebo (8.6% vs 17.0%, absolute risk reduction 8.4%; $P = 0.008$).[16] The most comprehensive data supporting the long-term benefit of ASA following ACS come from the Antithrombotic Trialists' Collaboration 2002 update.[12] 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.[66] 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.[66]

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.[12] 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.[17]

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.[28] 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.[29] 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.[67] 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.[30]

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.[68] 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.[68] 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; $P = 0.02$).[69] A slightly larger benefit was observed for the 3846 patients who had a prior MI (HR 0.77, 95% CI 0.61-0.98; $P = 0.031$).[69] 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.[36] 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.[37] Notably, the significant increase in TIMI-defined major bleeding associated with prasugrel in the primary analysis[36] emerged only on the third day of treatment but continued throughout the study.[37]

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 $P2Y_{12}$ 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.[40] 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.[40]

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,[58-60] and BASKET-LATE (Basel Stent Kosten Effektivitäts Trial–LAte Thrombotic Events)[61] 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.[65] 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.[70] 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.[71-73] 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.[7] 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).

Management of Stable Coronary Artery Disease
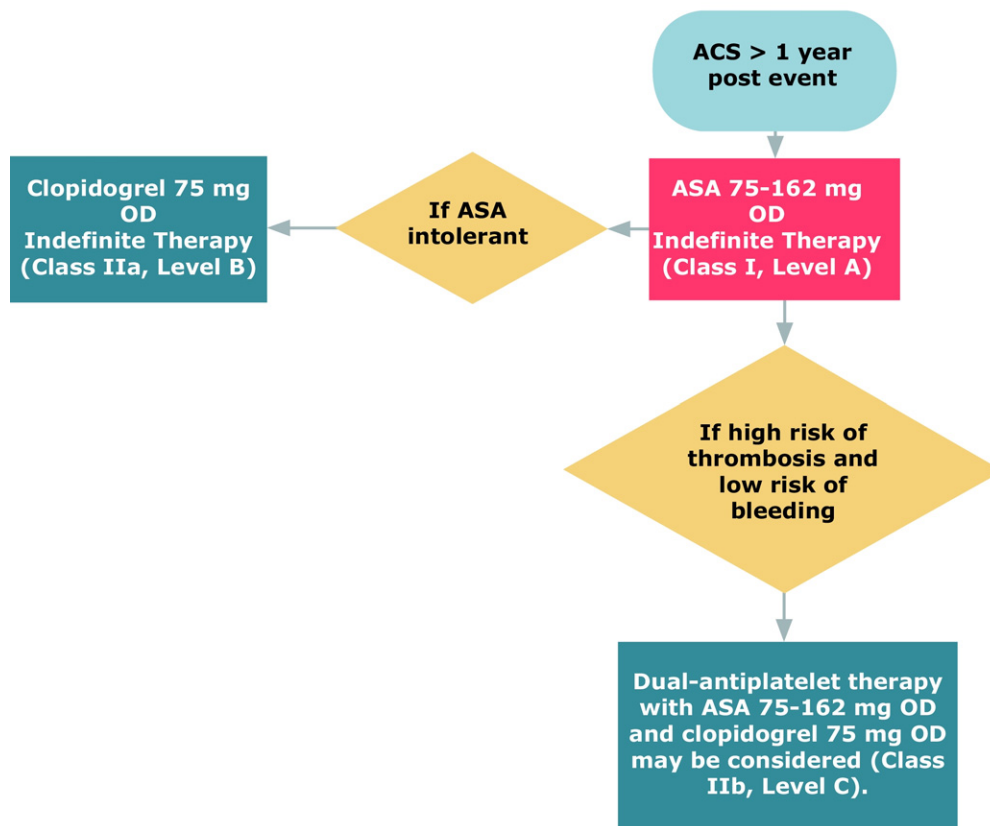
Figure 5. Management of stable coronary artery disease. The outpatient management of patients with stable coronary artery disease or more than one year after an acute coronary syndrome may consider dual-antiplatelet therapy if high risk of thrombosis and low risk of bleeding. ACS, acute coronary syndrome: ASA, acetylsalicylate acid.

> 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.[74] ASA is recognized as the standard of care and is generally continued indefinitely given its benefit in preventing subsequent clinical events,[75,76] 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,[77,78] 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.[75] If ticlopidine is used, white cell count monitoring is mandatory after 1 to 2 weeks and monthly thereafter.[52] 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[79] but are no longer used due to side effects and a lack of documented efficacy.[80,81]

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.[82] However, there is clinical evidence that reduced-intensity anticoagulation could maintain the antithrombotic effect with less anticoagulant-related bleeding.[83] 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,[84,85] 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[86] 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[82] concluded that low (~100 mg) and medium (~325 mg) daily doses of ASA were more effective than high-dose (~975 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[82] 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.[87] For conventional on-pump surgery, the ongoing CASCADE (Clopidogrel After Surgery for Coronary Artery Disease) trial was recently published.[88] 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.[89]

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.[90]

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%).[67]

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 nonurgent 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.[47] 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.[91] 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.[92] Clopidogrel can be suspended if the stented vessel is bypassed unless other preoperative conditions that suggest its use are

---

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.[93] Overall, the risk of stroke at 90 days is ~17% (95% CI 9%-25%) when the outcome is actively ascertained,[94] and the risk of combined vascular complications (ie, MI, stroke, and vascular death) is ~44% (95% CI 42%-46%) at 10 years.[95] The ABCD2 score is often used to classify the risk of subsequent stroke.[96] 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.[97] Recently updated consensus statements from the Canadian Stroke Network,[8] the American Heart Association (AHA)/American Stroke Association,[98] and the American College of Chest Physicians[99] incorporate newer data on the use of antiplatelet agents in secondary ischemic stroke prevention.

Management Post Coronary Artery Bypass Graft
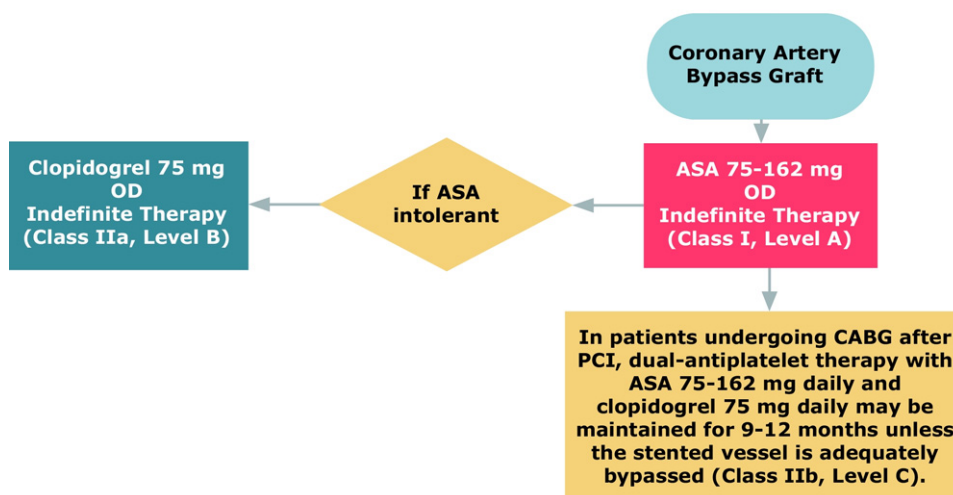
Figure 6. Management of post-coronary artery bypass graft. The outpatient management of patients after coronary artery bypass graft is outlined in this figure and may include dual-antiplatelet therapy when a recently stented vessel is not adequately bypassed. ASA, acetylsalicylate acid; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

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 ~13% (95% CI 6%-19%) compared with controls.[100] In 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.[12] 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.[101]

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.[102] 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.[103] 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.[104] 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.[105] 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 $P2Y_{12}$ 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.[106] In this study, ticlopidine 250 mg twice daily was compared with placebo. The risk of the primary composite endpoint of stroke, MI, or vascular death was 15.3% per year in the placebo group and 10.8% per year in the ticlopidine group (relative risk reduction 30.2%, 95% CI 7.5%-48.3%). In TASS (Ticlopidine ASpirin Stroke trial), 3069 subjects who experienced cerebral or retinal ischemia or TIA within the previous 3 months were randomized to ticlopidine 250 mg twice daily or ASA 650 mg twice daily.[107] Compared with ASA, ticlopidine 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.[28] 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-naive 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.

Management of TIA and Ischemic Stroke
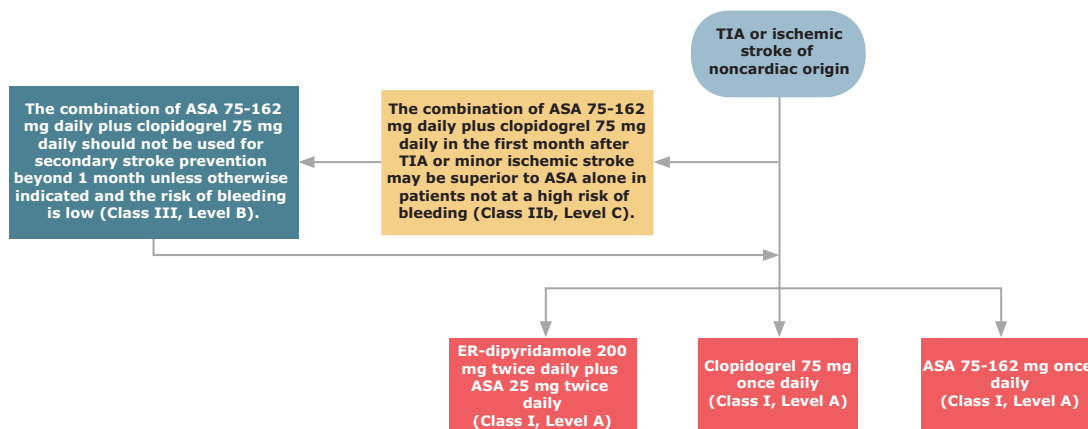
Figure 7. Management of transient ischemic attack (TIA) and ischemic stroke. The outpatient management of TIA or ischemic stroke of noncardiac origin can include dual-antiplatelet therapy for the first month. ASA, acetylsalicylate acid; ER, extended-release; TIA, transient ischemic attack.

RECOMMENDATION (Summarized in Fig. 7)

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

The combination of ASA 75-162 mg daily plus clopidogrel 75 mg daily in the first month after TIA or minor ischemic stroke may be superior to ASA alone in patients not at a high risk of bleeding (Class IIb, Level C).

The combination of ASA 75-162 mg daily plus clopidogrel 75 mg daily should not be used for secondary stroke prevention beyond 1 month unless otherwise indicated and the risk of bleeding is low (Class III, Level B).

Antiplatelet Therapy for Vascular Prevention in Patients With Peripheral Artery Disease

Working Group: André Roussin, MD, FRCP, and Thomas F. Lindsay, MD, CM, FRCSC

Compared with coronary and cerebrovascular disease, antiplatelet therapy in PAD has a disadvantage of much smaller studies in which agents other than ASA are frequently grouped. This leads to recommendations that differ somewhat between scientific societies. For example, the Canadian Consensus recommends 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 contrast, the Trans-Atlantic Inter-Society Consensus (TASC II),[114] the AHA/ACC,[115] the Scottish Intercollegiate Guidelines Network,[116] and the American College of Chest Physicians[117] recommend antiplatelet therapy with varying grade levels of rec-

ommendation depending on whether the patient is symptomatic or has associated coronary or cerebrovascular disease. The present recommendations are based on a review of all existing guidelines and publications, taking into account Canadian expertise.

PAD: The asymptomatic and the symptomatic patient

Patients with asymptomatic PAD. 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) $\leq$ 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 $\leq$ 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 $\times$ 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 $\leq$ 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.[117] 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.[126] 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).[117]

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,[127,128]

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.[129] 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.[130] 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.[131] 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.[132] 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
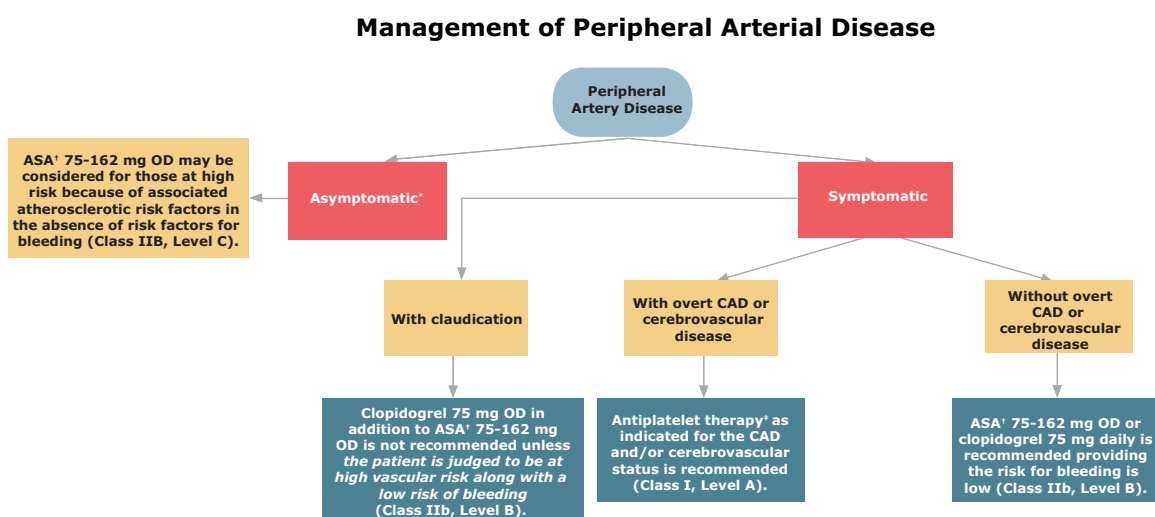
Figure 8. Management of peripheral arterial disease (PAD). The outpatient management of patients with symptomatic or asymptomatic PAD is outlined. ASA, acetylsalicylate acid; CAD, coronary artery disease. *Asymptomatic PAD is defined by ankle-brachial index < 0.9 in the absence of claudication or other 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).

Management Post Peripheral Artery Surgery

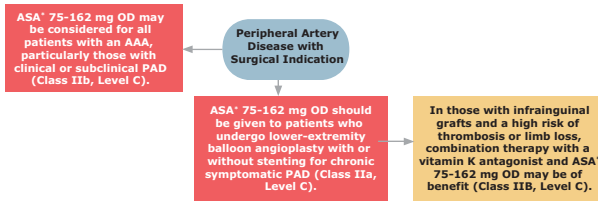**Figure 9.** Management of post peripheral artery surgery. The outpatient management of patients after peripheral artery surgery or percutaneous revascularization or presenting an abdominal aortic aneurysm (AAA). ASA, acetylsalicylate acid; PAD, peripheral arterial disease. *For patients allergic or intolerant to ASA, use of clopidogrel is suggested (Class IIa, Level B).

RECOMMENDATION (Summarized in **Figs. 8 and 9**)

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).

Antiplatelet Therapy for Primary Prevention of Vascular Events

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

For the purpose of these guidelines, "primary prevention" is defined as antiplatelet strategies, administered to individuals free of any evidence of manifest atherosclerotic disease in any vascular bed, to prevent clinical vascular events or manifestations thereof. These include, but are not limited to, syndromes of angina pectoris, MI, ischemic stroke, TIA, intermittent claudication, and critical limb ischemia. Over the past 2 decades, an abundance of well-designed clinical trials and meta-analyses examining the role of ASA and other antiplatelet agents for primary prevention of vascular events have been published or are ongoing.

Studies of primary prevention in men

The British Doctors' Study randomized, in a 2:1 allocation, 5139 male physicians aged < 79 years to open-label ASA 500 mg daily or ASA avoidance.[133] Subjects with a history of MI or stroke were excluded. A history of other ischemic vascular manifestations, including angina pectoris or TIA, was allowed. After a mean of 5.6 years, no statistically significant between-group differences were noted for nonfatal MI, nonfatal stroke, vascular death, or bleeding. A trend for an increased rate of disabling stroke was noted in the ASA group.

As part of a 2×2 factorial study examining the role of ASA in primary vascular protection and β-carotene in cancer prevention, the Physicians' Health Study randomized, in a double-blind fashion, 22,071 US male physicians aged 40-84 years with no history of MI, stroke, or TIA to receive ASA 325 mg every second day or placebo.[134] The study was stopped early after a mean follow-up of 60.2 months due to an observed benefit in the ASA group. The relative risk of MI in ASA recipients was 0.56 (95% CI 0.45-0.70; $P < 0.00001$), although benefit was observed only in those aged > 50 years. With regard to other risk factors, elevated levels of cholesterol reduced the benefit of ASA, while smoking, blood pressure, diabetes mellitus, body mass index, and family history had no effect. A trend toward an increased stroke risk was observed and driven by hemorrhagic stroke (RR 2.14, 95% CI 0.96-4.77; $P = 0.06$). No difference was noted for cardiovascular mortality (RR 0.96, 95% CI 0.60-1.54). Bleeding events requiring transfusion were increased in the ASA group (RR 1.71, 95% CI 1.09-2.69; $P = 0.02$). Although the relative benefit associated with ASA for the prevention of MI was substantial, the absolute risk benefit was only 0.18% per year (NNT of 556 persons for 1 year) due to the low absolute event rate and attenuation by the increased bleeding risk. A subsequent nested case-control study of the Physicians' Health Study demonstrated that the MI benefit derived from ASA appeared to be related to the baseline level of C-reactive protein (CRP).[135] In men in the highest quartile of CRP levels, ASA conferred a 55.7% reduction in the risk of MI ($P = 0.02$), whereas those in the lowest CRP quartile had a nonsignificant 13.9% reduction ($P = 0.77$). Further trials are warranted to assess the po-

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[136]) to low-intensity oral anticoagulation with warfarin (target INR 1.5), controlled-release ASA 75 mg daily, combined ASA plus warfarin, or placebo.[137] 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).[138] 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). Nonsignificant 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). No 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.[68] 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.[139] 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.[140]

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.[141] 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[142] 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.[66] 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,[76,143-145] the benefit in such populations

Primary Prevention
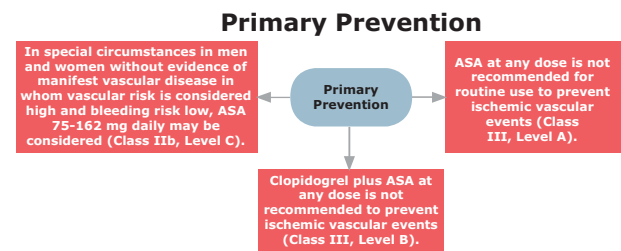
Figure 10. Primary prevention in patients without evidence of manifest vascular disease. For the purpose of this guideline, primary prevention is defined as antiplatelet strategies, administered to individuals free of any evidence of manifest atherosclerotic disease in any vascular bed, to prevent clinical vascular events or manifestations thereof. These include, but are not limited to, syndromes of angina pectoris, MI, ischemic stroke, TIA, intermittent claudication, and critical limb ischemia. ASA, acetylsalicylate acid; TIA, transient ischemic attack.

has not been demonstrated. With regard to individual risk factors, studies of ASA for risk prevention in patients with diabetes have been disappointing.[122,146] For example, compared with the benefit observed in the entire Primary Prevention Project population, lesser benefits were noted in the diabetic cohort.[138] Further, an earlier meta-analysis conducted by the Antithrombotic Trialists' Collaboration[12] 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[141] and the Physician's Health Study,[134] consistent with data indicating that smoking increases ASA resistance.[147] 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.[66]

> **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.[148] In addition to traditional risk factors such as smoking, systemic hypertension, dyslipidemia, and dysglycaemia, atherosclerosis in patients with diabetes can be as-

sociated 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,[149] enhanced platelet aggregation,[150] and increased thromboxane synthesis.[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,[152] various professional organizations, including the Canadian Diabetes Association,[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.[153] In this cohort of 651 patients followed for a mean of 11.6 years, regular use of ASA $\geq$ 75 mg daily at baseline was associated with reduced risks of cardiovascular and all-cause mortality (HR 0.30 [95% CI 0.09-0.95] 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).[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.[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 health women aged $>$ 45 years.[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.[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.[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.[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 $\leq$ 0.99) but no symptomatic cardiovascular disease.[122] Thus, the POPADAD trial can 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 POPAPAD 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).[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.[157] This meta-analysis showed no consistent evidence related to stroke or harm

(eg, bleeding) but suggested that available studies are largely underpowered to detect these clinically major but rare events. Another recent review of 9 randomized controlled trials, 8 of which included relevant endpoints and 6 of which overlapped with the previous meta-analysis, sought to determine if the effect of ASA for primary prevention of cardiovascular events and mortality differs between persons with and without diabetes.[158] When patients with and without diabetes were pooled, the risk of MI was significantly reduced (RR 0.79, 95% CI 0.66-0.95), but the risks of death (RR 0.93, 95% CI 0.85-1.03) and ischemic stroke (RR 0.73, 95% CI 0.43-1.22) were not. The relative risk ratios comparing the benefit of ASA among those with diabetes vs those without for mortality, MI, and ischemic stroke were 1.12 (95% CI 0.92-1.35), 1.19 (95% CI 0.82-1.17), and 0.70 (95% CI 0.25-1.97), respectively, suggesting that the relative benefit of ASA is similar in persons with and without diabetes. Taken together, these studies suggest that ASA therapy may confer similar, or even less, benefit for cardiovascular event reduction in individuals with diabetes than in those without. However, because of the low number of events, current studies cannot rule out a potential 10% risk reduction in primary prevention. Even if there was a 10% reduction in the risk of primary events, the NNT to prevent 2 major cardiovascular events would be 1000 patients for 1 year. Taking into account rare but well-documented side effects such as major bleeding, such benefit might be questionable even with a low-cost medication such as ASA.

Secondary prevention

Observational cohorts. The aforementioned prospective Chinese study also included 723 patients who had cardiovascular disease, 585 (81%) of whom were using ASA.[154] 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).[159] 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.[12] 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

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.[146] 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.[160] 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,[153,156] this has not been confirmed in other trials.[122] Subgroup analysis has also failed to confirm a greater effect in patients at higher risk.[122]

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.[134] Trials using higher ASA doses (eg, ETDRS, which assessed ASA 650 mg daily[146]) 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.[19]

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,[146] nor does it

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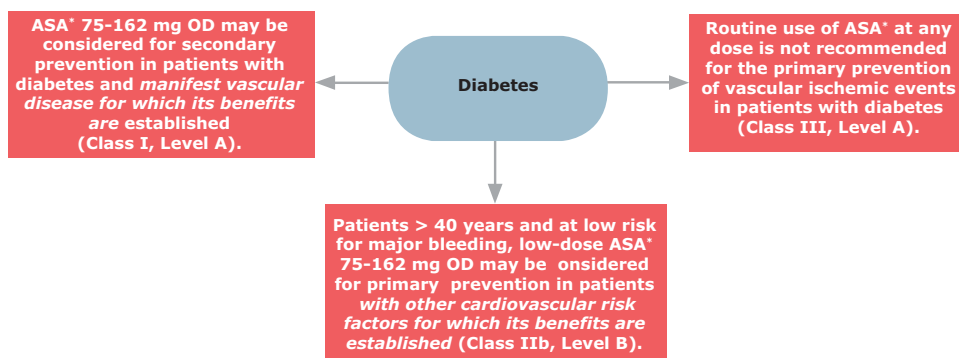
Figure 11. Management of patients with diabetes. The outpatient management for primary and secondary prevention of vascular ischemic events in patients with diabetes. ASA, acetylsalicylate acid. *For patients allergic or intolerant to ASA, use of clopidogrel 75 mg OD is suggested (Class IIa, Level B).

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 $P2Y_{12}$–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 ($P = 0.042$).[161] 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 $P2Y_{12}$–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 signifi-

cantly 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 control[163-165] 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, CCPF, 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.[172]

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) vs ASA 300 mg daily vs no antithrombotic therapy in 279 patients with HF who were in sinus rhythm.[178] Because the primary aim was to establish the feasibility of a larger trial, no power calculations were done. After a mean follow-up of 27 months, the study failed to demonstrate significant benefit for either therapy in the primary composite endpoint of death, nonfatal MI, or nonfatal stroke (26%, 32%, and 26% for no therapy, ASA, and warfarin, respectively). Bleeding events were few but trended toward an increase in the warfarin group. Hospitalizations were increased in the ASA group (48%, 64%, and 47% for no therapy, ASA, and warfarin, respectively [$P = 0.044$]), driven largely by worsening HF.

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 $\leq 35\%$.[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 events 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 vs 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 WASH[178] and the WATCH trial,[179] ASA was associated with increased hospitalization for HF, and the aforementioned meta-analysis[180] 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.[186] A retrospective subgroup analysis of data from CONSENSUS II (COoperative New

Scandinavian Enalapril Survival Study II)[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.[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.[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.[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.[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^2 obtained using either the Cock-

Figure 12. Management of heart failure. The outpatient management of patient with ischemic or nonischemic heart failure. CAD, coronary artery disease.

croft-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.[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.[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[191] and following MI.[191-194] Others suggest that ASA may not be beneficial in patients with CKD after ACS[195] and in dialysis patients with a known history of CAD.[196,197]

Clopidogrel. Several large randomized trials evaluating clopidogrel have included patients with an eGFR < 60 mL/min/1.73 m^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,[29] 26.6% of patients in the study had an eGFR < 60 mL/min.[198] Of this group, 24.8% had an eGFR between 30 and 59.9 mL/min, and 1.8% had a eGFR < 30 mL/min. Clopidogrel showed a trend toward a beneficial effect with respect to the primary com-

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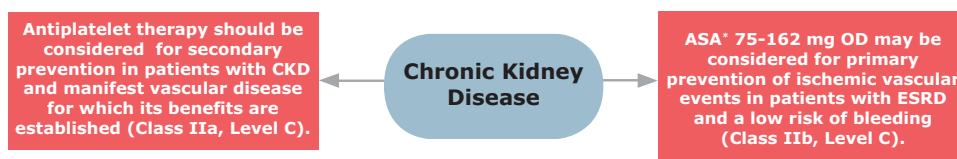
Figure 13. Management of chronic kidney disease. Antiplatelet therapy for primary or secondary prevention of ischemic vascular events in patients with chronic renal disease. ASA, acetylsalicylate acid; CKD, chronic renal disease; ESRD, end-stage renal disease. *For patients allergic or intolerant to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

posite outcome of cardiovascular death, nonfatal MI, or stroke and all of its subcomponents in all groups with impaired renal function (11%, 32%, and 26% reductions from the lowest to highest eGFR tertiles, respectively) without evidence of statistical heterogeneity.[198] In the CHARISMA study, 15,603 patients with established atherosclerotic disease or those at high risk thereof were randomized to clopidogrel 75 mg daily plus ASA 75-162 mg daily vs placebo plus ASA 75-162 mg daily.[68] The primary composite endpoint was the first occurrence of MI, all-cause stroke, or cardiovascular death. Creatinine levels were not reported as a part of this study, although 12.9% of patients had a history of diabetic nephropathy (albuminuria > 30 μg/mL) at baseline. There was a significant increase in both overall (HR 1.8, 95% CI 1.2-2.7) and cardiovascular (HR 1.7, 95% CI 1.1-2.9) mortality in patients with diabetic nephropathy treated with clopidogrel vs placebo, and a significant increase in bleeding was observed.[199] Finally, post-hoc analysis of the CREDO trial, which randomized 2002 patients undergoing nonurgent PCI to clopidogrel (300-mg loading dose, 75 mg daily) plus ASA 325 mg daily or placebo plus ASA 325 mg daily for 1 year postprocedure, found that the incidence of death, MI, or stroke was decreased in the clopidogrel-treated groups with normal or mildly impaired renal function, but a trend toward an increased risk of events was noted in patients with a creatinine clearance < 60 mL/min.[200] No significant difference in TIMI-defined bleeding rates was reported.

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).[36] Among the 1490 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 nonfatal stroke favouring prasugrel over clopidogrel was noted. This is similar to the significant 20% relative risk reduction for those with a creatinine clearance ≥ 60 mL/min. In the subgroup of 12,844 stent recipients enrolled in TRITON-TIMI 38, Academic Research Consortium–defined definite or probably stent thrombosis was reduced by 70% (1.1% vs 3.9%, $P < 0.05$) in those with a creatinine clearance < 60 mL/min, vs 51% (1.1% vs 2.1%, $P < 0.05$) for those with a creatinine clearance ≥ 60 mL/min.[201]

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.[202] 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).[203] The aforementioned subanalysis of the CURE trial reported a 1.5-fold increased risk of minor bleeds in patients with an eGFR < 64 mL/min randomized to clopidogrel plus ASA.[198] 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%).[199] 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).[204] 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).[205]

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).[206] This could represent an increase in absolute risk from 0.8-5.8 per 10,000 births to approximately 23 per 10,000 births.[207-209] 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.[210,211] 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 lose-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.[212-215] 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.[216] 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).[217,218] 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.[210] 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.[219-223] 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 (ie, 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.[224] 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.[225] They also indicate that because clinical experience with breastfeeding with 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 IIb, 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 IIb, Level C).

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

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

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:
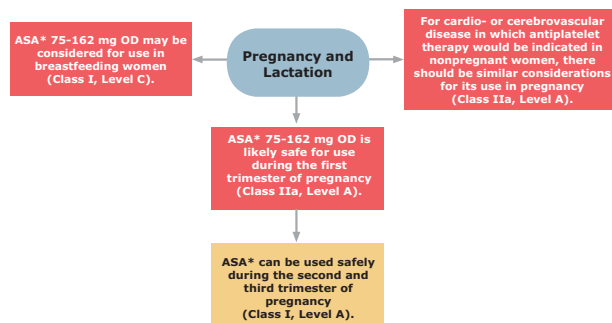
Management in Pregnancy and Lactation

Figure 14. Management in pregnancy and lactation. Antiplatelet therapy during pregnancy and lactation is recommended if maternal benefits clearly outweigh potential fetal/infant risks. ASA, acetylsalicylate acid. *Use of antiplatelet agents other than low-dose ASA for cardio- or cerebrovascular indications during pregnancy and lactation should only be considered if maternal benefits clearly outweigh potential fetal/infant risks (Class IIb, Level C).

(1) ASA alone, (2) clopidogrel alone, (3) ASA and clopidogrel, (4) ASA and dipyridamole, or (5) ASA and cilostazol or pentoxyphylline. The following recommendations will focus on patients who are receiving ASA with or without clopidogrel, which are the 2 most commonly used antiplatelet drug regimens and the regimens in which there are at least some 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, pentoxyphylline, 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 transbronchial 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

Very High Risk
  ○ Neurosurgery (intracranial or spinal surgery)
  ○ Cardiac surgery (coronary artery bypass or heart valve replacement)
High Risk
  ○ Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)
  ○ Major urologic surgery (prostatectomy, bladder tumour resection)
  ○ Major lower limb orthopaedic surgery (hip/knee joint replacement)
  ○ Lung resection surgery
  ○ Intestinal anastomosis surgery
  ○ Permanent pacemaker insertion or internal defibrillator placement
  ○ Selected procedures (kidney biopsy, pericardiocentesis, colonic polypectomy)
Intermediate Risk
  ○ Other intra-abdominal surgery
  ○ Other intrathoracic surgery
  ○ Other orthopaedic surgery
  ○ Other vascular surgery
  ○ Selected procedures (prostate or cervical biopsy)
Low Risk
  ○ Laparoscopic cholecystectomy
  ○ Laparoscopic inguinal hernia repair
  ○ Dental procedures
  ○ Dermatologic procedures
  ○ Ophthalmologic procedures
  ○ Coronary angiography
  ○ Gastroscopy or colonoscopy
  ○ Selected procedures (bone marrow or lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
Very Low Risk
  ○ Single tooth extraction or teeth cleaning
  ○ Skin biopsy or selected skin cancer removal
  ○ Cataract removal

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%).[230] 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%).[231] 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.[232]

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%[233] and 21.6% vs 13.6%,[234] 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%[235] and 0% vs 1.4%,[236] 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%).[237] 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.[238]

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.[239] 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 not an increased risk for bleeding that required medical or other interventions.[240] 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).[241]

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.[81,242] This finding was not replicated in a third study.[243] 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.[243]

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.[244] These patients had a 70% higher risk of needing a transfusion of ≥ 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.[29] The decision of when to perform CABG in patients receiving ASA and clopidogrel is dependent on the relative risks of ischemic events and bleeding.[245] 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.[245]

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).[246]

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.[247] 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.[248] 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.[249] A recent analysis of the Scottish Coronary Revascularisation Register suggests

Perioperative Management of Patients taking ASA
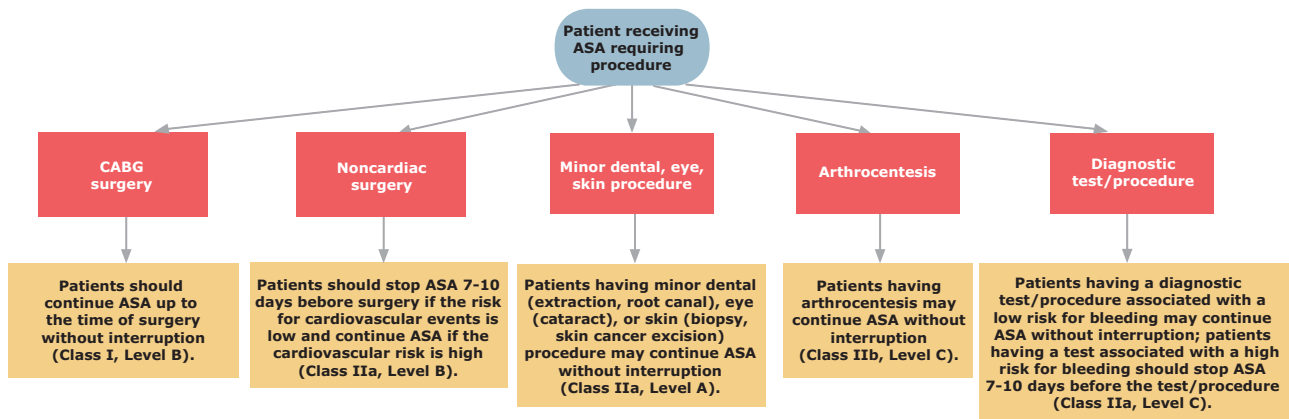
Figure 15. Perioperative management of patients taking ASA. The perioperative antiplatelet management will vary depending on the risk of bleeding related to the diagnostic or surgical procedure and the risk of cardiovascular ischemic event. ASA, acetylsalicylate acid; CABG, coronary artery bypass graft.

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.[250]

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 ≥ 6 weeks after BMS placement and ≥ 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 should continue ASA up to the time of surgery (Class I, Level B). Patients who are receiving ASA and clopidogrel should continue ASA until the time of surgery but discontinue clopidogrel ≥ 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

Perioperative Managementof Patients taking ASA and Clopidogrel
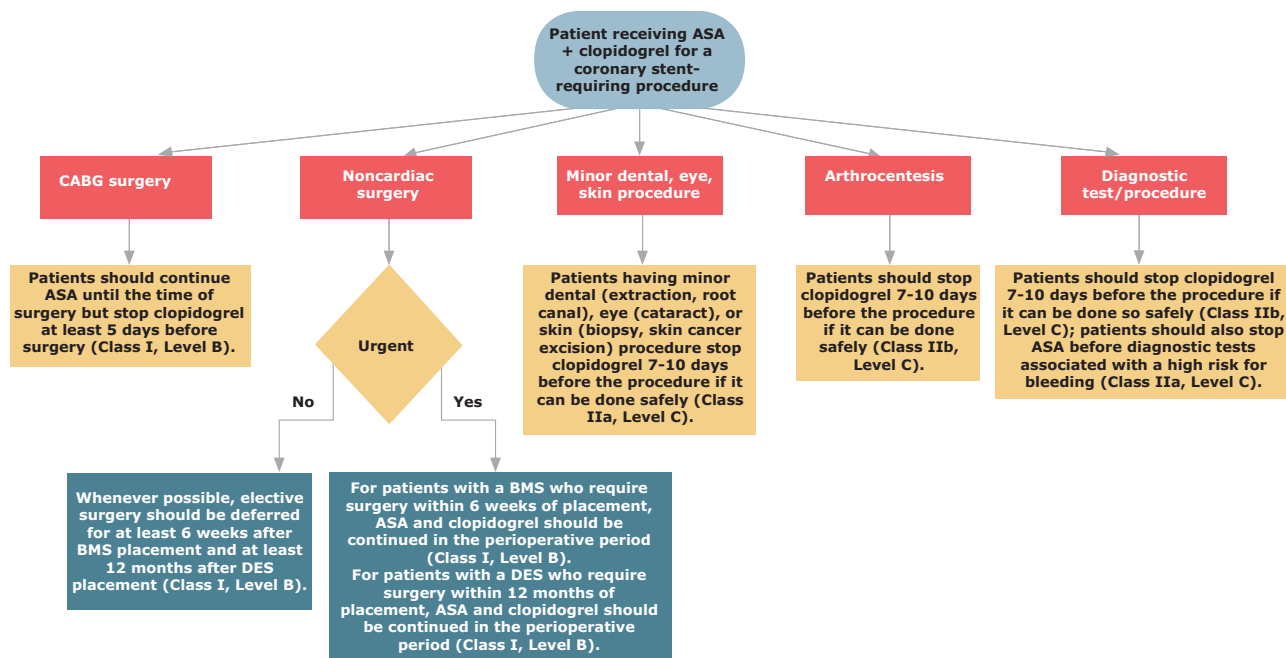
Figure 16. Perioperative management of patients taking ASA and clopidogrel. The perioperative antiplatelet management of patients receiving dual-antiplatelet therapy after a coronary stent will vary depending on the type of stent and the urgency of the surgery. ASA, acetylsalicylate acid; BMS, bare-metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent.

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-

Management of Minor Bleeding

Patients 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).

Patient on antiplatelet therapy with minor bleeding

Patients in whom subconjunctival bleeding develops should continue treatment and be monitored for bleeding
(Class IIa, Level C).

Patients who develop ecchymosis and petechiae should undergo testing with a complete blood count and international normalized ratio (INR) and activated partial thromboplastin time (aPTT)
(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).

Figure 17. Management of minor bleeding. The management of patients on antiplatelet therapy with minor bleeding is outlined and may include further investigation for patients who develop ecchymosis or petechiae. ASA, acetylsalicylate acid.

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 WARIS (Warfarin Aspirin ReInfarction Study) II, which randomized 3630 patients with acute MI to warfarin (target INR 2.8-4.2) alone, ASA 75 mg daily alone, or warfarin (target INR 2.0-2.5) plus ASA 75 mg daily, combination therapy significantly reduced the risk of the composite outcome of nonfatal reinfarction and thromboembolic stroke compared with ASA alone, but not warfarin alone;[257] combi-

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.[258] 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.[252]

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).[251] The therapeutic benefit of warfarin/ASA therapy is greatest in patients with a mechanical mitral valve.[259] 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.[259]

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).[253] 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).[260] 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.[261] As many as two-thirds of clopidogrel recipients also receive a PPI for the treatment of a concomitant acid-related disorder.[262] The PPIs lansoprazole, omeprazole, and esomeprazole are strong inhibitors of CYP2C19 activity, whereas pantoprazole is a weak CYP2C19 inhibitor.[263] In the past 2 years, several pharmacodynamic interaction studies suggest that omeprazole reduces the antiplatelet effect of clopidogrel,[264-266] 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

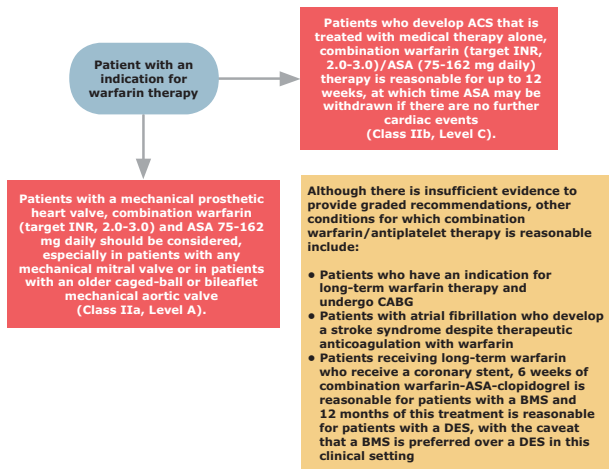**Figure 18.** Management of patients requiring warfarin. The management of patients on antiplatelet therapy requiring warfarin therapy requires an assessment of the risk of bleeding and the medical conditions for which combination therapy may be reasonable. ACS, acute coronary syndrome; ASA, acetylsalicylate 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]; $P < 0.05$).[267] Another pharmacy and medical claims database also showed an increased risk of adverse events in clopidogrel/PPI users.[268] 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).[269] This study also identified diabetes and discharge use of an ACE inhibitor or an angiotensin receptor blocker as significant predictors of reinfarction. Among a cohort of 820 DES recipients discharged with clopidogrel who were randomly selected from a single-center database, the 318 PPI users had a significantly increased risk of all-cause death, MI, or stent thrombosis at 1 year compared with PPI nonusers (13.8% vs 8.0%, HR 1.8, 95% CI 1.2-2.7; $P = 0.009$).[270] In a population-based, nested case-control study of 13,636 patients discharged from the hospital with a diagnosis of MI, current use (within 30 days) of a PPI and clopidogrel was associated with an increased risk of reinfarction (adjusted OR 1.27, 95% CI 1.03-1.57).[271] There was no similar increased risk associated with the use of H_2-receptor antagonists (adjusted OR 0.94, 95% CI 0.63-1.40) or pantoprazole, a specific PPI that does not inhibit CYP2C19 (adjusted OR 1.02, 95% CI 0.70-1.47). This finding was supported in a cohort

study of 8205 patients with ACS taking clopidogrel, of whom 5244 were also using PPI therapy.[262] 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[272] 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[273] 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 gastroduodenal bleeding (HR 0.50, 95% CI 0.39-0.65). Similarly, a study by Zairis and colleagues[274] 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 EveNTs) 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 $\geq$ 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, CABG, 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).[275] 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 [PRasugrel 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.[276] 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[277] 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 is discouraged (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] 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 clopidogrel[284] 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.[281] 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 GRAVITAS (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 cycoloxygenase-1 (COX-1), preventing the conversion of arachidonic acid to thromboxane, a process involved in platelet aggregation.[20] Because the anucleate platelet is unable to reform COX-1, aggre-

Use of Proton-Pump Inhibitiors

```
┌─────────────────────────┐
│  Use of proton-pump     │
│  inhibitors in patients │
│  taking clopidogrel     │
└─────────────────────────┘
            │
            ▼
        ◇─────────◇
       ╱ Patient at  ╲
      ╱  risk of      ╲
      ╲  upper         ╱
       ╲ gastrointestinal ╱
        ╲ bleeding  ╱
         ◇───────◇
            │
            ▼
```

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).
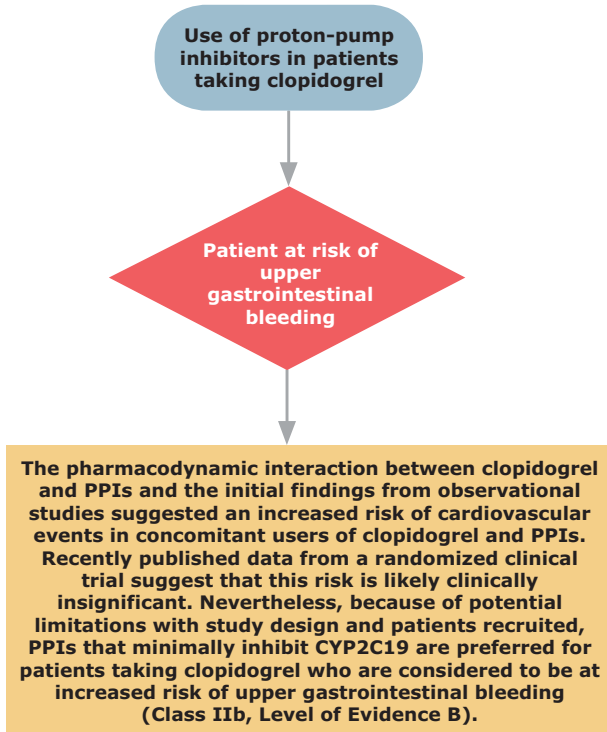
Figure 19. Use of proton-pump inhibitors. The management of patients on dual antiplatelet therapy may include the use of proton-pump inhibitors with minimal inhibition of cytochrome P2C19 in patients considered at increased risk of upper gastrointestinal bleeding. CY, cytochrome; PPIs, proton-pump inhibitors.

gatory function is permanently impaired. Unlike ASA, traditional 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–inhibiting 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-mediated platelet inhibition if the drugs are used concomitantly. Although 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 consecutive days, complete inhibition of platelet aggregation persisted up to 24 hours after dosing.[293] However, when dosed in the reverse 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 prior to 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 conflicting results with naproxen in this regard.[297,298] Capone and colleagues[299] demonstrated that ex vivo, naproxen reversibly 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 function, 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 Wei[300] 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 interaction between ASA and NSAIDs.

Numerous studies have examined the effect of COX-2 inhibitors (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 studies. 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 naproxen.[306] A post-hoc analysis of patients at high cardiovascular risk examined the interaction of these NSAIDs with ASA.[307] Among ASA users, patients in the ibuprofen substudy 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 observational 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 (VIoxx Gastrointestinal Outcomes Research) trial.[297] 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 McGettigan and Henry.[310] 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 IIb, 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).

Funding Sources

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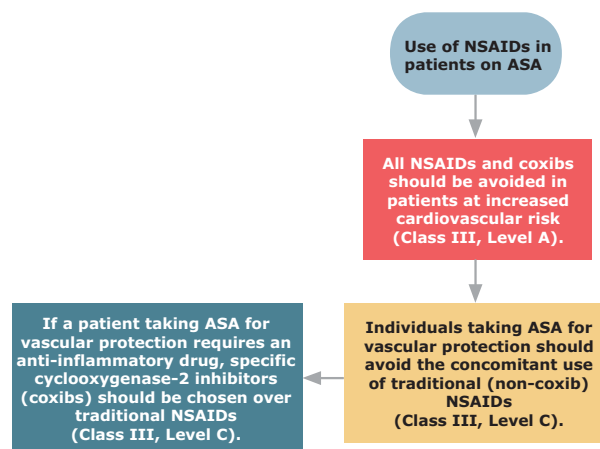
Figure 20. Use of NSAIDs in patients on ASA. In patients on ASA, the use on traditional nonsteroidal anti-inflammatory drugs should be avoided and if an anti-inflammatory drug is required, a specific cyclo-oxygenase-2 inhibitor should be considered. ASA, acetylsalicylate acid; coxib, cyclooxygenase-2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

References

1. Yan AT, Yan RT, Tan M, et al. Management patterns in relation to risk stratification among patients with non-ST elevation acute coronary syndromes. Arch Intern Med 2007;167:1009-16.

2. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention vs coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.

3. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-9.

4. Stafford RS, Monti V, Ma J. Underutilization of aspirin persists in US ambulatory care for the secondary and primary prevention of cardiovascular disease. PLoS Med 2005;2:e353.

5. Abramson BL, Huckell V, Anand S, et al. Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease—executive summary. Can J Cardiol 2005;21:997-1006.

6. Bhattacharyya OK, Shah BR, Booth GL. Management of cardiovascular disease in patients with diabetes: the 2008 Canadian Diabetes Association guidelines. CMAJ 2008;179:920-6.

7. Love MP, Schampaert E, Cohen EA, et al. The Canadian Association of Interventional Cardiology and the Canadian Cardiovascular Society joint statement on drug-eluting stents. Can J Cardiol 2007;23:121-3.

8. Lindsay P, Bayley M, McDonald A, et al. Toward a more effective approach to stroke: Canadian Best Practice Recommendations for Stroke Care. CMAJ 2008;178:1418-25.

9. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care 2003;12:18-23.

10. Libby P, Théroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481-8.

11. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation 2007; 116:e148-304.

12. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.

13. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349-60.

14. Baigent C, Collins R, Appleby P, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. BMJ 1998;316:1337-43.

15. Lewis HD, Jr., Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.

16. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985;313:1369-75.

17. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA 2007;297:2018-24.

18. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108:1682-7.

19. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353: 2373-83.

20. Patrono C, Bachmann F, Baigent C, et al. Expert consensus document on the use of antiplatelet agents. The Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease of the European Society of Cardiology. Eur Heart J 2004;25:166-81.

21. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). Circulation 2000;102:624-9.

22. Bhatt DL, Bertrand ME, Berger PB, et al. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. J Am Coll Cardiol 2002;39:9-14.

23. Steinhubl SR, Tan WA, Foody JM, Topol EJ. Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. JAMA 1999;281:806-10.

24. Momary KM, Dorsch MP. Factors associated with clopidogrel nonresponsiveness. Future Cardiol 2010;6:195-210.

25. Jakubowski JA, Payne CD, Brandt JT, et al. The platelet inhibitory effects and pharmacokinetics of prasugrel after administration of loading and maintenance doses in healthy subjects. J Cardiovasc Pharmacol 2006;47:377-84.

26. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852-6.

27. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral P2Y(12) receptor antagonist, in healthy subjects. Eur J Clin Pharmacol 2010;66:487-96.

28. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel vs aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.

29. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.

30. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. Circulation 2003;107:966-72.

31. Kolm P, Yuan Y, Veledar E, et al. Cost-effectiveness of clopidogrel in acute coronary syndromes in Canada: a long-term analysis based on the CURE trial. Can J Cardiol 2007;23:1037-42.

32. Lyseng-Williamson KA, Plosker GL. Clopidogrel: a pharmacoeconomic review of its use in patients with non-ST elevation acute coronary syndromes. Pharmacoeconomics 2006;24:709-26.

33. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-89.

34. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.

35. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel in acute coronary syndromes. N Engl J Med 2010;363:930-42.

36. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel vs clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

37. Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. J Am Coll Cardiol 2008;51:2028-33.

38. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary interven-

tion for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723-31.

39. Eli Lilly Canada Inc. Product monograph for Effient. Toronto, Ontario, Canada: Eli Lilly Canadia Inc., 2010.

40. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361: 1045-57.

41. de Feyter PJ, DeScheerder I, van den Brand M, et al. Emergency stenting for refractory acute coronary artery occlusion during coronary angioplasty. Am J Cardiol 1990;66:1147-50.

42. Serruys PW, Strauss BH, Beatt KJ, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med 1991; 324:13-7.

43. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701-6.

44. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.

45. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005;294:1224-32.

46. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010;375:283-93.

47. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20.

48. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084-9.

49. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998;339: 1665-71.

50. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation vs antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation vs aspirin and ticlopidine (FANTASTIC) study. Circulation 1998;98: 1597-603.

51. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation vs antiplatelet therapy after coronary stent implantation in high-risk patients: the Multicenter Aspirin And Ticlopidine Trial after Intracoronary Stenting (MATTIS). Circulation 1998;98:2126-32.

52. Love BB, Biller J, Gent M. Adverse haematological effects of ticlopidine. Prevention, recognition and management. Drug Saf 1998;19:89-98.

53. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin vs ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99:2364-6.

54. Müller C, Büttner HJ, Petersen J, Roskamm H. A randomized comparison of clopidogrel and aspirin vs ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000;101:590-3.

55. Brodie BR, Stuckey T, Downey W, et al. Outcomes with drug-eluting stents vs bare metal stents in acute ST-elevation myocardial infarction:

results from the Strategic Transcatheter Evaluation of New Therapies (STENT) Group. Cathet Cardiovasc Interv 2008;72:893-900.

56. Sheiban I, Villata G, Bollati M, et al. Next-generation drug-eluting stents in coronary artery disease: focus on everolimus-eluting stent (Xience V). Vasc Health Risk Manag 2008;4:31-8.

57. Moussa ID, Colombo A. Antiplatelet therapy discontinuation following drug-eluting stent placement: dangers, reasons, and management recommendations. Cathet Cardiovasc Interv 2009;74:1047-54.

58. Roukoz H, Bavry AA, Sarkees ML, et al. Comprehensive meta-analysis on drug-eluting stents vs bare-metal stents during extended follow-up. Am J Med 2009;122:581 e1-10.

59. Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. Am J Med 2006;119:1056-61.

60. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937-48.

61. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting vs bare-metal stents. J Am Coll Cardiol 2006;48:2584-91.

62. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007;297:159-68.

63. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. Circulation 2006;113:2803-9.

64. Tanzilli G, Greco C, Pelliccia F, et al. Effectiveness of two-year clopidogrel + aspirin in abolishing the risk of very late thrombosis after drug-eluting stent implantation (from the TYCOON [two-year ClOpidOgrel need] study). Am J Cardiol 2009;104:1357-61.

65. Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med 2010;362: 1374-82.

66. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373: 1849-60.

67. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004;110:1202-8.

68. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin vs aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.

69. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol 2007;49:1982-8.

70. Pinto Slottow TL, Waksman R. Overview of the 2006 Food and Drug Administration Circulatory System Devices Panel meeting on drug-eluting stent thrombosis. Catheter Cardiovasc Interv 2007;69:1064-74.

71. Ko DT, Chiu M, Guo H, et al. Safety and effectiveness of drug-eluting and bare-metal stents for patients with off- and on-label indications. J Am Coll Cardiol 2009;53:1773-82.

72. Roy P, Buch AN, Javaid A, et al. Impact of "off-label" utilization of drug-eluting stents on clinical outcomes in patients undergoing percutaneous coronary intervention. Am J Cardiol 2008;101:293-9.

73. Carlsson J, James SK, Lindbäck J, et al. Outcome of drug-eluting vs bare-metal stenting used according to on- and off-label criteria. J Am Coll Cardiol 2009;53:1389-98.

74. Chesebro JH, Clements IP, Fuster V, et al. A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med 1982;307:73-8.

75. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 2004;110:e340-437.

76. Becker RC, Meade TW, Berger PB, et al. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:776S-814S.

77. Chevigné M, David JL, Rigo P, Limet R. Effect of ticlopidine on saphenous vein bypass patency rates: a double-blind study. Ann Thorac Surg 1984;37:371-8.

78. Limet R, David JL, Magotteaux P, Larock MP, Rigo P. Prevention of aorta-coronary bypass graft occlusion. Beneficial effect of ticlopidine on early and late patency rates of venous coronary bypass grafts: a double-blind study. J Thorac Cardiovasc Surg 1987;94:773-83.

79. Rajah SM, Nair U, Rees M, et al. Effects of antiplatelet therapy with indobufen or aspirin-dipyridamole on graft patency one year after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1994;107:1146-53.

80. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation 1988;77:1324-32.

81. Sethi GK, Copeland JG, Goldman S, et al. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting. Department of Veterans Affairs Cooperative Study on Antiplatelet Therapy. J Am Coll Cardiol 1990;15:15-20.

82. Fremes SE, Levinton C, Naylor CD, et al. Optimal antithrombotic therapy following aortocoronary bypass: a meta-analysis. Eur J Cardiothorac Surg 1993;7:169-80.

83. Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med 1982;307:1676-81.

84. Brooks N, Wright J, Sturridge M, et al. Randomised placebo controlled trial of aspirin and dipyridamole in the prevention of coronary vein graft occlusion. Br Heart J 1985;53:201-7.

85. Rajah SM, Salter MC, Donaldson DR, et al. Acetylsalicylic acid and dipyridamole improve the early patency of aorta-coronary bypass grafts. A double-blind, placebo-controlled, randomized trial. J Thorac Cardiovasc Surg 1985;90:373-7.

86. Dunning J, Das S. What is the optimal dose of aspirin after discharge following coronary bypass surgery. Interact Cardiovasc Thorac Surg 2003;2:427-30.

87. Gurbuz AT, Zia AA, Vuran AC, Cui H, Aytac A. Postoperative clopidogrel improves mid-term outcome after off-pump coronary artery bypass graft surgery: a prospective study. Eur J Cardiothorac Surg 2006;29:190-5.

88. Kulik A, Le May M, Wells GA, Mesana TG, Ruel M. The clopidogrel after surgery for coronary artery disease (CASCADE) randomized controlled trial: clopidogrel and aspirin vs aspirin alone after coronary bypass surgery [NCT00228423]. Curr Control Trials Cardiovasc Med 2005;6:15.

89. Kulik A, Le May MR, Voisine P, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) Trial. Circulation 2010;122:2680-7.

90. Gao C, Ren C, Li D, Li L. Clopidogrel and aspirin vs clopidogrel alone on graft patency after coronary artery bypass grafting. Ann Thorac Surg 2009;88:59-62.

91. Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol 2000;35:1288-94.

92. Popma JJ, Berger P, Ohman EM, et al. Antithrombotic therapy during percutaneous coronary intervention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:576S-99S.

93. Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 2007;6:1063-72.

94. Wu CM, McLaughlin K, Lorenzetti DL, et al. Early risk of stroke after transient ischemic attack: a systematic review and meta-analysis. Arch Intern Med 2007;167:2417-22.

95. van Wijk I, Kappelle LJ, van Gijn J, et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. Lancet 2005;365:2098-104.

96. Giles MF, Rothwell PM. Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischemic attack risk scores. Stroke 2010;41:667-73.

97. Rothwell PM, Giles MF, Chandratheva A, et al. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet 2007;370:1432-42.

98. Adams RJ, Albers G, Alberts MJ, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39:1647-52.

99. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:630S-69S.

100. Algra A, van Gijn J. Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin. J Neurol Neurosurg Psychiatry 1999;66:255.

101. Algra A, van Gijn J. Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia. J Neurol Neurosurg Psychiatry 1996;60:197-9.

102. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. N Engl J Med 1978;299:53-9.

103. The SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991;338:1345-9.

104. The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg versus. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991;325:1261-6.

105. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom Transient Ischaemic Attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044-54.

106. Gent M, Blakely JA, Easton JD, et al. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Lancet 1989;1:1215-20.

107. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med 1989;321:501-7.

108. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331-7.

109. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole vs clopidogrel for recurrent stroke. N Engl J Med 2008;359:1238-51.

110. Kennedy J, Hill MD, Ryckborst KJ, et al. Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol 2007;6:961-9.

111. Geraghty OC, Kennedy J, Chandratheva A, et al. Preliminary evidence of a high risk of bleeding on aspirin plus clopidogrel in aspirin-naive patients in the acute phase after TIA or minor ischaemic stroke. Cerebrovasc Dis 2010;29:460-7.

112. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13.

113. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole vs aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006;367:1665-73.

114. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33(suppl 1):S1-75.

115. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113:e463-654.

116. Scottish Intercollegiate Guidelines Network, Diagnosis and management of peripheral arterial disease: a national clinical guideline. Edinburgh, Scotland: National Health System Scotland, 2006.

117. Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:815S-43S.

118. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001;344:1608-21.

119. Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol 2005;25:1463-9.

120. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.

121. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;303:841-8.

122. Belch J, MacCuish A, Campbell I, et al. The Prevention Of Progression of Arterial Disease And diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.

123. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. Br J Surg 2001;88:787-800.

124. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. JAMA 2009;301:1909-19.

125. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med 2007;357:217-27.

126. The BOA Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. Lancet 2000;355:346-51.

127. Zankl AR, Schumacher H, Krumsdorf U, et al. Pathology, natural history and treatment of abdominal aortic aneurysms. Clin Res Cardiol 2007;96:140-51.

128. Grootenboer N, Bosch JL, Hendriks JM, van Sambeek MR. Epidemiology, aetiology, risk of rupture and treatment of abdominal aortic aneurysms: does sex matter? Eur J Vasc Endovasc Surg 2009;38:278-84.

129. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.

130. Freiberg MS, Arnold AM, Newman AB, et al. Abdominal aortic aneurysms, increasing infrarenal aortic diameter, and risk of total mortality and incident cardiovascular disease events: 10-year follow-up data from the Cardiovascular Health Study. Circulation 2008;117:1010-7.

131. Baumgartner I, Hirsch AT, Abola MT, et al. Cardiovascular risk profile and outcome of patients with abdominal aortic aneurysm in out-patients with atherothrombosis: data from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. J Vasc Surg 2008;48:808-14.

132. Lindholt JS, Sorensen HT, Michel JB, Thomsen HF, Henneberg EW. Low-dose aspirin may prevent growth and later surgical repair of medium-sized abdominal aortic aneurysms. Vasc Endovasc Surg 2008;42:329-34.

133. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988;296:313-6.

134. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129-35.

135. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.

136. Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986;2:533-7.

137. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998; 351:233-41.

138. de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet 2001;357:89-95.

139. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755-62.

140. Alexander KP, Peterson ED. Minimizing the risks of anticoagulants and platelet inhibitors. Circulation 2010;121:1960-70.

141. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.

142. Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006;295: 306-13.

143. Joint British Societies. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91(suppl 5):v1-52.

144. Pearson TA, Blair SN, Daniels SR, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388-91.

145. U.S. Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150:396-404.

146. ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. JAMA 1992;268:1292-300.

147. Cambria-Kiely JA, Gandhi PJ. Possible mechanisms of aspirin resistance. J Thromb Thrombolysis 2002;13:49-56.

148. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73-8.

149. DiMinno G, Silver MJ, Cerbone AM, Murphy S. Trial of repeated low-dose aspirin in diabetic angiopathy. Blood 1986;68:886-91.

150. Halushka PV, Rogers RC, Loadholt CB, Colwell JA. Increased platelet thromboxane synthesis in diabetes mellitus. J Lab Clin Med 1981;97: 87-96.

151. Davì G, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. N Engl J Med 1990;322: 1769-74.

152. Sirois C, Poirier P, Moisan J, Grégoire JP. The benefit of aspirin therapy in type 2 diabetes: what is the evidence? Int J Cardiol 2008;129:172-9.

153. Ong G, Davis TM, Davis WA. Aspirin is associated with reduced cardiovascular and all-cause mortality in type 2 diabetes in a primary prevention setting: the Fremantle Diabetes study. Diabetes Care 2010;33: 317-21.

154. Leung WY, So WY, Stewart D, et al. Lack of benefits for prevention of cardiovascular disease with aspirin therapy in type 2 diabetic patients—a longitudinal observational study. Cardiovasc Diabetol 2009;8:57.

155. Sacco M, Pellegrini F, Roncaglioni MC, et al. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care 2003;26:3264-72.

156. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134-41.

157. De Berardis G, Sacco M, Strippoli GF, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009;339:b4531.

158. Calvin AD, Aggarwal NR, Murad MH, et al. Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care 2009; 32:2300-6.

159. Cubbon RM, Gale CP, Rajwani A, et al. Aspirin and mortality in patients with diabetes sustaining acute coronary syndrome. Diabetes Care 2008;31:363-5.

160. De Berardis G, Sacco M, Evangelista V, et al. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. Trials 2007;8:21.

161. Bhatt DL, Marso SP, Hirsch AT, et al. Amplified benefit of clopidogrel vs aspirin in patients with diabetes mellitus. Am J Cardiol 2002;90: 625-8.

162. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel—Thrombolysis in Myocardial Infarction 38. Circulation 2008;118:1626-36.

163. Watala C, Golanski J, Pluta J, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin)—its relation to metabolic control. Thromb Res 2004;113:101-13.

164. Friend M, Vucenik I, Miller M. Research pointers: Platelet responsiveness to aspirin in patients with hyperlipidaemia. BMJ 2003;326:82-3.

165. Gasparyan AY, Watson T, Lip GY. The role of aspirin in cardiovascular prevention: implications of aspirin resistance. J Am Coll Cardiol 2008; 51:1829-43.

166. Sibbing D, von Beckerath O, Schömig A, Kastrati A, von Beckerath N. Impact of body mass index on platelet aggregation after administration of a high loading dose of 600 mg of clopidogrel before percutaneous coronary intervention. Am J Cardiol 2007;100:203-5.

167. Bonello-Palot N, Armero S, Paganelli F, et al. Relation of body mass index to high on-treatment platelet reactivity and of failed clopidogrel dose adjustment according to platelet reactivity monitoring in patients undergoing percutaneous coronary intervention. Am J Cardiol 2009; 104:1511-5.

168. Angiolillo DJ. Antiplatelet therapy in diabetes: efficacy and limitations of current treatment strategies and future directions. Diabetes Care 2009; 32:531-40.

169. Davis CJ, Gurbel PA, Gattis WA, et al. Hemostatic abnormalities in patients with congestive heart failure: diagnostic significance and clinical challenge. Int J Cardiol 2000;75:15-21.

170. Jafri SM, Ozawa T, Mammen E, et al. Platelet function, thrombin and fibrinolytic activity in patients with heart failure. Eur Heart J 1993;14:205-12.

171. Sbarouni E, Bradshaw A, Andreotti F, et al. Relationship between hemostatic abnormalities and neuroendocrine activity in heart failure. Am Heart J 1994;127:607-12.

172. Dunkman WB, Johnson GR, Carson PE, et al. Incidence of thromboembolic events in congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87:VI94-101.

173. Fuster V, Gersh BJ, Giuliani ER, et al. The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981;47:525-31.

174. Griffith GC, Stragnell R, Levinson DC, Moore FJ, Ware AG. A study of the beneficial effects of anticoagulant therapy in congestive heart failure. Ann Intern Med 1952;37:867-87.

175. Harvey WP, Finch CA. Dicumarol prophylaxis of thromboembolic disease in congestive heart failure. N Engl J Med 1950;242:208-11.

176. Lip GY, Gibbs CR. Anticoagulation for heart failure in sinus rhythm: a Cochrane systematic review. QJM 2002;95:451-9.

177. Wishart JH, Chapman CB. Dicumarol therapy in congestive heart failure. N Engl J Med 1948;239:701-4.

178. Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. Am Heart J 2004;148:157-64.

179. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. Circulation 2009;119:1616-24.

180. Cleland JG, Ghosh J, Freemantle N, et al. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-Lipids and cardiac resynchronisation therapy in heart failure. Eur J Heart Fail 2004;6:501-8.

181. Pullicino P, Thompson JL, Barton B, et al. Warfarin vs Aspirin in patients with Reduced Cardiac Ejection Fraction (WARCEF): rationale, objectives, and design. J Card Fail 2006;12:39-46.

182. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

183. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

184. Falk RH, Pollak A, Tandon PK, Packer M. The effect of warfarin on prevalence of stroke in patients with severe heart failure [abstract]. J Am Coll Cardiol 1993;21:218A.

185. Bonde L, Sorensen R, Fosbøl EL, et al. Increased mortality associated with low use of clopidogrel in patients with heart failure and acute myocardial infarction not undergoing percutaneous coronary intervention: a nationwide study. J Am Coll Cardiol 2010;55:1300-7.

186. Ahmed A. Interaction between aspirin and angiotensin-converting enzyme inhibitors: should they be used together in older adults with heart failure? J Am Geriatr Soc 2002;50:1293-6.

187. Bonarjee VV, Omland T, Nilsen DW, et al. Left ventricular volumes, ejection fraction, and plasma proatrial natriuretic factor (1-98) after withdrawal of enalapril treatment initiated early after myocardial infarction. CONSENSUS II Multi-Echo Study Group. Br Heart J 1995;73:506-10.

188. McAlister FA, Ghali WA, Gong Y, et al. Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. Circulation 2006;113:2572-8.

189. Teo KK, Yusuf S, Pfeffer M, et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. Lancet 2002;360:1037-43.

190. Wright J, Hutchison A. Cardiovascular disease in patients with chronic kidney disease. Vasc Health Risk Manag 2009;5:713-22.

191. Ezekowitz J, McAlister FA, Humphries KH, et al. The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease. J Am Coll Cardiol 2004;44:1587-92.

192. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol 2003;42:201-8.

193. McCullough PA, Sandberg KR, Borzak S, et al. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. Am Heart J 2002;144:226-32.

194. Shlipak MG, Heidenreich PA, Noguchi H, et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555-62.

195. Keough-Ryan TM, Kiberd BA, Dipchand CS, et al. Outcomes of acute coronary syndrome in a large Canadian cohort: impact of chronic renal insufficiency, cardiac interventions, and anemia. Am J Kidney Dis 2005;46:845-55.

196. Ethier J, Bragg-Gresham JL, Piera L, et al. Aspirin prescription and outcomes in hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2007;50:602-11.

197. Ishani A, Herzog CA, Collins AJ, Foley RN. Cardiac medications and their association with cardiovascular events in incident dialysis patients: cause or effect? Kidney Int 2004;65:1017-25.

198. Keltai M, Tonelli M, Mann JF, et al. Renal function and outcomes in acute coronary syndrome: impact of clopidogrel. Eur J Cardiovasc Prev Rehabil 2007;14:312-8.

199. Dasgupta A, Steinhubl SR, Bhatt DL, et al. Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin vs aspirin alone (a post hoc analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA] trial). Am J Cardiol 2009;103:1359-63.

200. Best PJ, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Am Heart J 2008;155:687-93.

201. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. Lancet 2008;371:1353-63.

202. Hiremath S, Holden RM, Fergusson D, Zimmerman DL. Antiplatelet medications in hemodialysis patients: a systematic review of bleeding rates. Clin J Am Soc Nephrol 2009;4:1347-55.

203. Kaufman JS, O'Connor TZ, Zhang JH, et al. Randomized controlled trial of clopidogrel plus aspirin to prevent hemodialysis access graft thrombosis. J Am Soc Nephrol 2003;14:2313-21.

204. Holden RM, Harman GJ, Wang M, Holland D, Day AG. Major bleeding in hemodialysis patients. Clin J Am Soc Nephrol 2008;3:105-10.

205. Baigent C, Landray M, Leaper C, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis 2005;45:473-84.

206. Kozer E, Nikfar S, Costei A, et al. Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. Am J Obstet Gynecol 2002;187:1623-30.

207. Hobbs CA, Hopkins SE, Simmons CJ. Sources of variability in birth defects prevalence rates. Teratology 2001;64(suppl 1):S8-S13.

208. Godwin KA, Sibbald B, Bedard T, et al. Changes in frequencies of select congenital anomalies since the onset of folic acid fortification in a Canadian birth defect registry. Can J Public Health 2008;99:271-5.

209. Srivastava V, Mandhan P, Pringle K, et al. Rising incidence of gastroschisis and exomphalos in New Zealand. J Pediatr Surg 2009;44:551-5.

210. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet 2007;369:1791-8.

211. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2007CD004659.

212. Gelbaya TA, Kyrgiou M, Li TC, Stern C, Nardo LG. Low-dose aspirin for in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update 2007;13:357-64.

213. Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. Cochrane Database Syst Rev 2009CD004734.

214. Poustie VJ, Dodd S, Drakeley AJ. Low-dose aspirin for in vitro fertilisation. Cochrane Database Syst Rev 2007CD004832.

215. Ruopp MD, Collins TC, Whitcomb BW, Schisterman EF. Evidence of absence or absence of evidence? A reanalysis of the effects of low-dose aspirin in in vitro fertilization. Fertil Steril 2008;90:71-6.

216. Pütter J, Satravaha P, Stockhausen H. [Quantitative analysis of the main metabolites of acetylsalicylic acid. Comparative analysis in the blood and milk of lactating women (author's transl)]. Z Geburtshilfe Perinatol 1974;178:135-8.

217. Clark JH, Wilson WG. A 16-day-old breast-fed infant with metabolic acidosis caused by salicylate. Clin Pediatr (Phila) 1981;20:53-4.

218. Terragna A, Spirito L. [Thrombocytopenic purpura in an infant after administration of acetylsalicylic acid to the wet-nurse]. Minerva Pediatr 1967;19:613-6.

219. Al-Aqeedi RF, Al-Nabti AD. Drug-eluting stent implantation for acute myocardial infarction during pregnancy with use of glycoprotein IIb/IIIa inhibitor, aspirin and clopidogrel. J Invasive Cardiol 2008;20:E146-9.

220. Boztosun B, Olcay A, Avci A, Kirma C. Treatment of acute myocardial infarction in pregnancy with coronary artery balloon angioplasty and stenting: use of tirofiban and clopidogrel. Int J Cardiol 2008;127:413-6.

221. Cuthill JA, Young S, Greer IA, Oldroyd K. Anaesthetic considerations in a parturient with critical coronary artery disease and a drug-eluting stent presenting for caesarean section. Int J Obstet Anesth 2005;14:167-71.

222. Klinzing P, Markert UR, Liesaus K, Peiker G. Case report: successful pregnancy and delivery after myocardial infarction and essential thrombocythemia treated with clopidrogel. Clin Exp Obstet Gynecol 2001;28:215-6.

223. Kuczkowski KM. Clopidogrel and pregnancy: a situation pregnant with danger? Arch Gynecol Obstet 2009;280:693-4.

224. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577-617.

225. Burnett B, Kopecky S, Morton C, et al. Institute for Clinical Systems Improvement health care guideline: Antithrombotic Therapy, Seventh Edition. Bloomington, MN: Institute for Clinical Systems Improvement, 2009.

226. Yousfi M, Gostout CJ, Baron TH, et al. Postpolypectomy lower gastrointestinal bleeding: potential role of aspirin. Am J Gastroenterol 2004; 99:1785-9.

227. Sawhney MS, Salfiti N, Nelson DB, Lederle FA, Bond JH. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008;40:115-9.

228. Herth FJ, Becker HD, Ernst A. Aspirin does not increase bleeding complications after transbronchial biopsy. Chest 2002;122:1461-4.

229. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest 2006;129:734-7.

230. Ardekian L, Gaspar R, Peled M, Brener B, Laufer D. Does low-dose aspirin therapy complicate oral surgical procedures? J Am Dent Assoc 2000;131:331-5.

231. Madan GA, Madan SG, Madan G, Madan AD. Minor oral surgery without stopping daily low-dose aspirin therapy: a study of 51 patients. J Oral Maxillofac Surg 2005;63:1262-5.

232. Allard RH, Baart JA, Huijgens PC, van Merkesteijn JP. [Antithrombotic therapy and dental surgery with bleeding]. Ned Tijdschr Tandheelkd 2004;111:482-5.

233. Billingsley EM, Maloney ME. Intraoperative and postoperative bleeding problems in patients taking warfarin, aspirin, and nonsteroidal antiinflammatory agents. A prospective study. Dermatol Surg 1997;23:381-3; discussion 4-5.

234. Kargi E, Babuccu O, Hosnuter M, Babuccu B, Altinyazar C. Complications of minor cutaneous surgery in patients under anticoagulant treatment. Aesthet Plast Surg 2002;26:483-5.

235. Shalom A, Wong L. Outcome of aspirin use during excision of cutaneous lesions. Ann Plast Surg 2003;50:296-8.

236. Bartlett GR. Does aspirin affect the outcome of minor cutaneous surgery? Br J Plast Surg 1999;52:214-6.

237. Katz J, Feldman MA, Bass EB, et al. Risks and benefits of anticoagulant and antiplatelet medication use before cataract surgery. Ophthalmology 2003;110:1784-8.

238. Kumar N, Jivan S, Thomas P, McLure H. Sub-Tenon's anesthesia with aspirin, warfarin, and clopidogrel. J Cataract Refract Surg 2006;32:1022-5.

239. Pulmonary Embolism Prevention trial Steering Committee. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355:1295-302.

240. Burger W, Chemnitius JM, Kneissl GD, Rücker G. Low-dose aspirin for secondary cardiovascular prevention: cardiovascular risks after its periop-

erative withdrawal vs bleeding risks with its continuation—review and meta-analysis. J Intern Med 2005;257:399-414.

241. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. Eur Heart J 2006;27:2667-74.

242. Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis 2004;17:21-7.

243. Bybee KA, Powell BD, Valeti U, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. Circulation 2005;112:I286-92.

244. Mehta RH, Roe MT, Mulgund J, et al. Acute clopidogrel use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. J Am Coll Cardiol 2006;48:281-6.

245. Fitchett D, Eikelboom J, Fremes S, et al. Dual antiplatelet therapy in patients requiring urgent coronary artery bypass grafting surgery: a position statement of the Canadian Cardiovascular Society. Can J Cardiol 2009;25:683-9.

246. Vicenzi MN, Meislitzer T, Heitzinger B, et al. Coronary artery stenting and non-cardiac surgery—a prospective outcome study. Br J Anaesth 2006;96:686-93.

247. Nuttall GA, Brown MJ, Stombaugh JW, et al. Time and cardiac risk of surgery after bare-metal stent percutaneous coronary intervention. Anesthesiology 2008;109:588-95.

248. Schouten O, van Domburg RT, Bax JJ, et al. Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol 2007;49:122-4.

249. Rabbitts JA, Nuttall GA, Brown MJ, et al. Cardiac risk of noncardiac surgery after percutaneous coronary intervention with drug-eluting stents. Anesthesiology 2008;109:596-604.

250. Cruden NL, Harding SA, Flapan AD, et al. Previous coronary stent implantation and cardiac events in patients undergoing noncardiac surgery. Circ Cardiovasc Interv 2010.

251. Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med 2007;167:117-24.

252. Johnson SG, Rogers K, Delate T, Witt DM. Outcomes associated with combined antiplatelet and anticoagulant therapy. Chest 2008; 133:948-54.

253. Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009;374:1967-74.

254. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.

255. National Heart, Lung, and Blood Institute. Morbidity and mortality: 2009 chart book on cardiovascular, lung, and blood diseases. Bethesda, MD: Department of Health and Human Services, 2009.

256. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109-13.

257. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347: 969-74.

258. Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trials. Am Heart J 2006;152: 967-73.

259. Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:593S-629S.

260. Olson KL, Delate T, Johnson SG, Wilson ED, Witt DM. Incidence of hemorrhage among anticoagulated patients receiving antiplatelet therapy after percutaneous coronary intervention. J Thromb Thrombolysis 2010;29:316-21.

261. Savi P, Pereillo JM, Uzabiaga MF, et al. Identification and biological activity of the active metabolite of clopidogrel. Thromb Haemost 2000; 84:891-6.

262. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009;301:937-44.

263. Li XQ, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos 2004;32:821-7.

264. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008;51:256-60.

265. Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost 2009;101: 714-9.

266. Cuisset T, Frere C, Quilici J, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. J Am Coll Cardiol 2009;54:1149-53.

267. Pezalla E, Day D, Pulliadath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. J Am Coll Cardiol 2008;52:1038-9; author reply 9.

268. Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. Arch Intern Med 2010;170:704-10.

269. Evanchan J, Donnally MR, Binkley P, Mazzaferri E. Recurrence of acute myocardial infarction in patients discharged on clopidogrel and a proton pump inhibitor after stent placement for acute myocardial infarction. Clin Cardiol 2010;33:168-71.

270. Gaglia MA Jr, Torguson R, Hanna N, et al. Relation of proton pump inhibitor use after percutaneous coronary intervention with drug-eluting stents to outcomes. Am J Cardiol 2010;105:833-8.

271. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-8.

272. Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. Circulation 2009;120:2322-9.

273. Ray WA, Murray KT, Griffin MR, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med 2010;152:337-45.

274. Zairis MN, Tsiaousis GZ, Patsourakos NG, et al. The impact of treatment with omeprazole on the effectiveness of clopidogrel drug therapy during the first year after successful coronary stenting. Can J Cardiol 2010;26:e54-7.

275. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010; Epub ahead of print 06 Oct 2010.

276. O'Donoghue ML, Braunwald E, Antman EM, et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. Lancet 2009;374:989-97.

277. Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. Aliment Pharmacol Ther 2010;31:810-23.

278. Stanek EJ, Aubert RE, Flockhart DA, et al. a national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated wtih clopidogrel following coronary stenting: the Clopidogrel Medco Outcomes Study. Presented at The Society for Cardiovascular Angiography and Interventions 32nd Annual Scientific Sessions. Las Vegas, NV, 2009.

279. Aubert RE, Epstein RS, Teagarden JR, et al. Abstract 3998: Proton pump inhibitors effect on clopidogrel effectiveness: the Clopidogrel Medco Outcomes Study. Circulation 2008;118:S_815.

280. Dunn SP, Macaulay TE, Brennan DM, et al. Abstract 3999: Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. Circulation 2008;118:S-815.

281. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. United States product information for Plavix. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, 2010.

282. Sanofi-aventis Canada Inc., Bristol Myers Squibb Canada. Product monograph for Plavix®. Laval, Québec: sanofi-aventis Canada Inc., 2009.

283. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. J Am Coll Cardiol 2010; Epub ahead of print 08 Nov 2010.

284. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009;302:849-57.

285. Sofi F, Giusti B, Marcucci R, et al. Cytochrome P450 2C19(*)2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. Pharmacogenomics J 2010; Epub ahead of print 31 Mar 2010.

286. Hochholzer W, Trenk D, Fromm MF, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol 2010;55:2427-34.

287. Price MJ, Berger PB, Angiolillo DJ, et al. Evaluation of individualized clopidogrel therapy after drug-eluting stent implantation in patients with high residual platelet reactivity: design and rationale of the GRAVITAS trial. Am Heart J 2009;157:818-24, 824 e1.

288. Holmes DR Jr, Dehmer GJ, Kaul S, et al. ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning". A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation 2010;122:537-57.

289. Pedersen AK, FitzGerald GA. Cyclooxygenase inhibition, platelet function, and metabolite formation during chronic sulfinpyrazone dosing. Clin Pharmacol Ther 1985;37:36-42.

290. Livio M, Del Maschio A, Cerletti C, de Gaetano G. Indomethacin prevents the long-lasting inhibitory effect of aspirin on human platelet cyclo-oxygenase activity. Prostaglandins 1982;23:787-96.

291. Rao GH, Johnson GG, Reddy KR, White JG. Ibuprofen protects platelet cyclooxygenase from irreversible inhibition by aspirin. Arteriosclerosis 1983;3:383-8.

292. Husted SE, Pedersen AK, Petersen T, Geday E. Systemic availability of acetylsalicylic acid in normal men and women and its effect on in vitro platelet aggregability. Eur J Clin Pharmacol 1983;24:679-82.

293. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809-17.

294. García Rodríguez LA, Varas C, Patrono C. Differential effects of aspirin and non-aspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. Epidemiology 2000;11:382-7.

295. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. Lancet 2002;359:118-23.

296. García Rodríguez LA, Varas-Lorenzo C, Maguire A, González-Pérez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation 2004;109:3000-6.

297. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343:1520-8, 2 p following 8.

298. Rahme E, Pilote L, LeLorier J. Association between naproxen use and protection against acute myocardial infarction. Arch Intern Med 2002;162:1111-5.

299. Capone ML, Sciulli MG, Tacconelli S, et al. Pharmacodynamic interaction of naproxen with low-dose aspirin in healthy subjects. J Am Coll Cardiol 2005;45:1295-301.

300. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 2003;361:573-4.

301. Kurth T, Glynn RJ, Walker AM, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. Circulation 2003;108:1191-5.

302. Greenberg HE, Gottesdiener K, Huntington M, et al. A new cyclooxygenase-2 inhibitor, rofecoxib (VIOXX), did not alter the antiplatelet effects of low-dose aspirin in healthy volunteers. J Clin Pharmacol 2000;40:1509-15.

303. Jermany J, Branson J, Schmouder R, Guillaume M, Rordorf C. Lumiracoxib does not affect the ex vivo antiplatelet aggregation activity of low-dose aspirin in healthy subjects. J Clin Pharmacol 2005;45:1172-8.

304. Leese PT, Recker DP, Kent JD. The COX-2 selective inhibitor, valdecoxib, does not impair platelet function in the elderly: results of a randomized controlled trial. J Clin Pharmacol 2003;43:504-13.

305. Renda G, Tacconelli S, Capone ML, et al. Celecoxib, ibuprofen, and the antiplatelet effect of aspirin in patients with osteoarthritis and ischemic heart disease. Clin Pharmacol Ther 2006;80:264-74.

306. Farkouh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675-84.

307. Farkouh ME, Greenberg JD, Jeger RV, et al. Cardiovascular outcomes in high risk patients with osteoarthritis treated with ibuprofen, naproxen or lumiracoxib. Ann Rheum Dis 2007;66:764-70.

308. Patel TN, Goldberg KC. Use of aspirin and ibuprofen compared with aspirin alone and the risk of myocardial infarction. Arch Intern Med 2004;164:852-6.

309. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. BMJ 2006;332:1302-8.

310. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633-44.

311. Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 Chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. Circulation 2007;116:2762-72.

312. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:e418-99.

313. Fleisher LA. Cardiac risk stratification for noncardiac surgery: update from the American College of Cardiology/American Heart Association 2007 guidelines. Cleve Clin J Med 2009;76(suppl 4):S9-15.

314. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009; 120:2271-306.

315. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2008;118:1894-909.

316. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:299S-339S.

317. Colwell JA. Aspirin therapy in diabetes. Diabetes Care 2004;27(suppl 1):S72-3.

318. American Diabetes Association. Standards of medical care in diabetes—2009. Diabetes Care 2009;32(suppl 1):S13-61.

319. Mosca L, Banka CL, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007;115:1481-501.

320. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal anti-inflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115:1634-42.

321. Grines CL, Bonow RO, Casey DE Jr, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007;115:813-8.

322. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113:2363-72.

323. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. Stroke 2006; 37:1583-633.

324. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.

325. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007;115:114-26.

326. Snow V, Barry P, Fihn SD, et al. Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2004;141:562-7.

327. Zuckerman MJ, Hirota WK, Adler DG, et al. ASGE guideline: the management of low-molecular-weight heparin and nonaspirin antiplatelet agents for endoscopic procedures. Gastrointest Endosc 2005; 61:189-94.

328. Caramelli B, Pinho C, Calderaro D, et al. I: Guideline for perioperative evaluation. Arq Bras Cardiol 2007;89:e172-209.

329. Veitch AM, Baglin TP, Gershlick AH, et al. Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures. Gut 2008;57:1322-9.

330. Dunning J, Versteegh M, Fabbri A, et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg 2008;34:73-92.

331. Rosenzweig JL, Ferrannini E, Grundy SM, et al. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2008;93:3671-89.

332. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth

Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007;14(suppl 2): S1-113.

333. Stramba-Badiale M, Fox KM, Priori SG, et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur Heart J 2006;27:994-1005.

334. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388-442.

335. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-660.

336. Silber S, Albertsson P, Avilés FF, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2005; 26:804-47.

337. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J 2009;30:2769-812.

338. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341-81.

339. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909-45.

340. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 2007;28:88-136.

341. The European Stroke Oranization (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of iscaemic stroke and transient ischaemic attack 2008. Heidelburg, Germany: European Stroke Organization, 2008.

342. Albaladejo P, Marret E, Piriou V, Samama CM. Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force. Br J Anaesth 2006;97:580-2.

343. Heart Failure Society of America. Section 13: Evaluation and therapy for heart failure in the setting of ishcemic heart disease. J Card Fail 2006;12: e104-e11.

344. Danielson D, Robrock J, Rothe P, Stultz J, Bjork K; Institute for Clinical Systems, Improvement health care guideline: preoperative evaluation. Bloomington, MN: Institute for Clinical Systems Improvement, 2008.

345. Lehman G, Nguyen JH, Bershow S, et al. Institute for Clinical Systems Improvement health care guidelines: stable coronary artery disease. Bloomington, MN: Institute for Clinical Systems Improvement, 2009.

346. Joslin Diabetes Center. Joslin Diabetes Center & Joslin Clinic clinical guideline for adults with diabetes. Boston, MA: Joslin Diabetes Center, 2009.

347. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Guidelines for the management of acute coronary syndromes 2006. Med J Aust 2006;184:S9-29.

348. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand. Reducing risk in heart disease 2007 (updated 2008). Melbourne, Victoria, Australia: National Heart Foundation of Australia, 2008.

349. Cooper A, Skinner J, Nherera L, et al. Clinical guidelines and evidence review for post myocardial infarction: secondary prevention in primary and secondary care for patients following a myocardial infarction. London, UK: National Collaborating Centre for Primary Care and Royal College of General Practitioners, 2007.

350. National Kidney Foundation. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005; 45:S1-153.

351. New Zealand Guidelines Group. Cardiovascular guidelines handbook: a summary resource for primary care practitioners. Wellington, NZ: New Zealand Guidelines Group, 2009.

352. New Zealand Guidelines Group. Evidence-based best practice guideline: management of type 2 diabetes. Wellington, New Zealand: New Zealand Guidelines Group, 2003.

353. Non ST-Elevation Acute Coronary Syndrome Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand. Non ST-elevation acute coronary syndromes: New Zealand management guidelines. N Z Med J 2005;118:1680.

354. ST-Elevation Myocardial Infarction Guidelines Group and the New Zealand Branch of the Cardiac Society of Australia and New Zealand. ST-elevation myocardial infarction: New Zealand management guidelines. N Z Med J 2005;118:1679.

355. Imiela J, Opolski G, Rydzewska G, et al. Position paper of the working group of three Polish national consultants in internal medicine, gastroenterology, and cardiology on prevention of gastrointestinal complications during antiplatelet treatment. Pol Arch Med Wewn 2009; 119:347-8.

356. Scottish Intercollegiate Guidelines Network. Acute coronary syndromes: a national clinical guideline. Edinburgh, Scotland: National Health System Scotland, 2007.

357. Scottish Intercollegiate Guidelines Network. Diagnosis and management of chronic kidney disease. Edinburgh, Scotland: National Health System Scotland, 2008.

358. Scottish Intercollegiate Guidelines Network. Management of acute upper and lower gastrointestinal bleeding. Edinburgh, Scotland: National Health System Scotland, 2008.

359. Scottish Intercollegiate Guidelines Network. Diagnosis and management of peripheral arterial disease: a national clinical guideline. Edinburgh, Scotland: National Health System Scotland, 2006.

360. Scottish Intercollegiate Guidelines Network. Risk estimation and the prevention of cardiovascular disease: a national clinical guideline. Edinburgh, Scotland: National Health System Scotland, 2007.

361. Scottish Intercollegiate Guidelines Network. Management of stable angina: a national clinical guideline. Edinburgh, Scotland: National Health System Scotland, 2007.

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

Guideline (author/group, topic, year)	Scope and purpose*	Stakeholder involvement†	Rigour of development‡	Clarity and presentation§	Applicability¶	Editorial independence‖
ACC/AHA; chronic stable angina; 2007[311]	100%	42%	100%	67%	100%	100%
ACC/AHA; NSTEMI; 2007[11]	100%	75%	90%	75%	39%	83%
ACC/AHA; PAD; 2005[115]	100%	71%	71%	83%	78%	100%
ACC/AHA; perioperative evaluation of noncardiac surgery; 2007[312]	94%	38%	75%	83%	39%	92%
ACC/AHA; perioperative evaluation of noncardiac surgery; 2009[313]	94%	58%	76%	83%	50%	92%
ACC/AHA/SCAI; STEMI and PCI focused updates; 2009[314]	100%	56%	85%	77%	22%	83%
ACCF/ACG/AHA; reducing GI risk of A/P therapy; 2008[315]	93%	43%	50%	80%	24%	76%
ACCP; CAD; 2008[76]	98%	58%	97%	78%	85%	81%
ACCP; ischemic stroke; 2008[99]	100%	50%	86%	92%	67%	100%
ACCP; PAD; 2008[117]	100%	67%	93%	92%	78%	100%
ACCP; perioperative management; 2008[316]	100%	33%	57%	67%	44%	100%
ADA; aspirin in diabetes; 2004[317]	100%	42%	67%	50%	78%	50%
ADA; diabetes; 2009[318]	100%	50%	67%	75%	56%	83%
AHA; CV disease prevention in women; 2007[319]	96%	61%	79%	69%	63%	89%
AHA; NSAID statement; 2007[320]	100%	33%	36%	71%	17%	83%
AHA/ACC/SCAI/ACS/ADA; prevention of premature discontinuation of antiplatelet therapy; 2007[321]	89%	46%	48%	71%	22%	67%
AHA/ACC; secondary prevention of atherosclerotic disease; 2006[322]	83%	63%	76%	79%	61%	92%
AHA/ASA; prevention of ischemic stroke; 2006[224]	100%	50%	69%	71%	28%	92%
AHA/ASA; primary prevention of ischemic stroke; 2006[323]	100%	50%	69%	46%	33%	92%
AHA/NHLBI; metabolic syndrome; 2005[324]	100%	33%	24%	33%	44%	100%
AHA/ADA; primary prevention in patients with DM; 2007[325]	100%	33%	48%	75%	44%	100%
ACP; stable angina; 2004[326]	89%	58%	83%	75%	39%	100%
ASGE; non-ASA antiplatelets for endoscopy; 2008[327]	78%	33%	36%	64%	11%	33%
BCS; perioperative treatment; 2007[328]	67%	25%	36%	63%	28%	33%
BSG; antiplatelets for endoscopy; 2008[329]	94%	46%	52%	88%	28%	33%
CAIC/CCS; joint statement on DESs; 2007[7]	67%	33%	52%	58%	22%	67%
CCS; PAD; 2005[5]	100%	67%	81%	92%	56%	83%
CSS; stroke care; 2008[8]	100%	50%	90%	83%	33%	100%
CDA; diabetes; 2008[6]	100%	83%	100%	67%	67%	83%
EACTS; antiplatelets in cardiac surgery; 2008[330]	94%	50%	79%	88%	33%	42%
Endocrine Society; prevention of CVD in metabolic risk; 2008[331]	100%	42%	67%	25%	44%	100%
ESC; CV disease prevention; 2007[332]	100%	54%	85%	77%	83%	88%
ESC; CV disease in women; 2006[333]	89%	42%	43%	67%	78%	50%
ESC; heart failure; 2008[334]	100%	42%	40%	54%	44%	100%
ESC; NSTEMI; 2007[335]	89%	50%	81%	67%	33%	72%
ESC; PCI; 2005[336]	94%	46%	76%	75%	22%	63%
ESC; perioperative management; 2006[337]	83%	46%	69%	71%	72%	63%
ESC; stable angina; 2006[338]	92%	48%	89%	79%	38%	92%
ESC; STEMI; 2008[339]	100%	58%	83%	92%	39%	75%
ESC/EASD; diabetes; 2007[340]	100%	42%	81%	42%	56%	67%
ESO; ischemic stroke and TIA update; 2008[341]	78%	50%	71%	83%	33%	100%
French Task Force; perioperative management; 2006[342]	61%	42%	29%	67%	22%	33%
HFSA; heart failure with ischemic heart disease; 2006[343]	100%	54%	76%	75%	33%	100%
ICSI; antithrombotic therapy; 2009[225]	100%	61%	56%	58%	19%	67%
ICSI; preoperative evaluation; 2008[344]	78%	67%	60%	67%	50%	58%
ICSI; stable CAD; 2009[345]	100%	67%	67%	58%	33%	100%
Joslin Diabetes Center; diabetes; 2009[346]	100%	50%	71%	75%	33%	0%
NHFA/CSANZ; ACS; 2006[347]	100%	71%	67%	79%	50%	75%
NHF/CSANZ; secondary prevention; 2007[348]	56%	33%	33%	42%	33%	67%
NICE; secondary prevention after MI; 2007[349]	100%	50%	86%	92%	89%	100%
NKF; management of CVD in CKD; 2005[350]	83%	54%	74%	58%	39%	100%

Appendix I. Continued

Guideline (author/group, topic, year)	Scope and purpose*	Stakeholder involvement†	Rigour of development‡	Clarity and presentation§	Applicability¶	Editorial independence‖
NZGG; CV disease; 2009[351]	67%	67%	57%	92%	33%	100%
NZGG; diabetes; 2003[352]	100%	67%	76%	92%	78%	100%
NZGG; NSTEMI; 2005[353]	100%	67%	38%	50%	44%	17%
NZGG; STEMI; 2005[354]	100%	67%	38%	33%	44%	17%
Polish working group; antiplatelet therapy GI complications; 2009[355]	67%	21%	10%	46%	0%	25%
SIGN; ACS; 2007[356]	100%	92%	90%	75%	78%	50%
SIGN; CKD; 2008[357]	100%	75%	95%	88%	94%	100%
SIGN; upper and lower GI bleeding; 2008[358]	100%	83%	100%	88%	61%	100%
SIGN; PAD; 2006[359]	100%	71%	98%	92%	72%	100%
SIGN; risk estimation for prevention of CV disease; 2007[360]	100%	69%	92%	86%	70%	56%
SIGN; stable angina; 2007[361]	94%	75%	88%	96%	89%	100%
TASC II; PAD; 2007[114]	94%	63%	86%	92%	56%	63%

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 of 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

Reviewer	Affiliation	Sections reviewed
Paul W. Armstrong, MD, FRCPC	University of Alberta, Edmonton, Alberta, Canada	Antiplatelet Therapy for the Primary Prevention of Vascular Events
Shannon Bates, MDCM, MSc, FRCP(C)	McMaster University Medical Centre, Hamilton, Ontario, Canada	Use of Antiplatelet Therapy in Women Who Are Pregnant or Breastfeeding
Stephanie J. Brister, MD, BSc, FRCSC	University of Toronto and Toronto General Hospital, Toronto, Ontario, Canada	Antiplatelet Therapy for Secondary Prevention Following Coronary Artery Bypass Grafting
Jean Buithieu, MD	McGill University Health Centre, Montréal, Québec, Canada	Antiplatelet Therapy for Vascular Prevention in Patients With Peripheral Artery Disease
Mark Crowther, MD, MSc, FRCPC	McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada	Management of Antiplatelet Therapy in Association With Minor Bleeding
		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
Diego H. Delgado, MD	Toronto General Hospital, Toronto, Ontario, Canada	Use of Antiplatelet Therapy in Patients With Heart Failure
John W. Eikelboom, MD, MSc	McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada	Interaction Between Clopidogrel and Proton Pump Inhibitors
		Interaction Between Acetylsalicylic Acid and Nonsteroidal Anti-inflammatory Drugs
David Fitchett, BChir, MD, MRCP, FRCP, FACC, FESC	University of Toronto and St. Michael's Hospital, Toronto, Ontario, Canada	Antiplatelet Therapy for Secondary Prevention Following Acute Coronary Syndromes
		Antiplatelet Therapy for Secondary Prevention in Stable Coronary Artery Disease
Thomas L. Forbes, MD	University of Western Ontario, London, Ontario, Canada	Antiplatelet Therapy for Vascular Prevention in Patients With Peripheral Artery Disease
Stephen Fremes, MD, MSc, FRCSC, FACP, FACC	Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada	Antiplatelet Therapy for Secondary Prevention Following Coronary Artery Bypass Grafting
Michael D. Hill, MD, MSc, FRCPC	University of Calgary, Calgary, Alberta, Canada	Antiplatelet Therapy for Secondary Prevention of Cerebrovascular Disease
Lawrence A. Leiter, MD, FRCPC, FACP	St. Michael's Hospital and University of Toronto, Toronto, Ontario, Canada	Use of Antiplatelet Therapy in Patients With Diabetes
Anil Nigam, MD, MSc, FRCPC	Montréal Heart Institute and University of Montréal, Montréal, Québec, Canada	Antiplatelet Therapy for the Primary Prevention of Vascular Events
Paul Poirier, MD, PhD, FRCPC, FACC	Laval University and Hôpital Laval, Québec, Québec, Canada	Use of Antiplatelet Therapy in Diabetes
Heather J. Ross, MD, MHSc, FRCPC	University of Toronto and Toronto General Hospital, Toronto, Ontario, Canada	Use of Antiplatelet Therapy in Patients With Heart Failure
Erick Schampaert, MD, FRCPC	Université de Montréal and Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada	Antiplatelet Therapy for Secondary Prevention Following Percutaneous Coronary Intervention
		Antiplatelet Therapy for Secondary Prevention in Stable Coronary Artery Disease
Alex C. Spyropoulos, MD, FACP, FCCP	McMaster University and Hamilton General Hospital, Hamilton, Ontario, Canada	Management of Patients on Antiplatelet Therapy Who Require a Surgical or Other Invasive Procedure
Theodore H. Wein, MD, FRCPC	McGill University and Montreal General Hospital, Montréal, Québec, Canada	Antiplatelet Therapy for Secondary Prevention of Cerebrovascular Disease

Appendix III. Author relationships with industry—CCS antiplatelet consensus committee

Committee member	Category*	Relationship <$10,000	Relationship >$10,000	Arrhythmias/ EP	CV surgery	Congenital heart disease	General cardiology	Heart failure	Interventional	Noninvasive	Prevention/ vascular	Other
Alan D. Bell	1, 2	AstraZeneca, Boehringer Ingelheim	None									
Raymond Cartier	1, 2, 9		sanofi-aventis								X	
Wee Shian Chan	13	sanofi-aventis	None									Travel
James Douketis	1	Boehringer Ingelheim, Leo Pharma, Pfizer	None									
Anil Gupta	1	AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, Pfizer, sanofi-aventis, Servier	None									
Maria Kraw												
Thomas Lindsay	1	sanofi-aventis	None									
Michael Love	1	Abbott Vascular, AstraZeneca	None									
Neesh Pannu												
Philip Teal	1	Boehringer Ingelheim, Bristol-Myers Squibb, sanofi-aventis	None									
Rémi Rabasa-Lhoret	1	AstraZeneca, Eli Lilly, GlaxoSmithKline, Novartis, Abbott	Imunotec									Aging
	1, 9	None	Merck, Novo-Nordisk, sanofi-aventis									Diabetes
	9	None	Consortium Québecquois Du Médicament, Cystic Fibrosis Foundation, Quebec Diabetes Association									Diabetes
	9	None	CIHR									Obesity
André Roussin	1	AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer, GlaxoSmithKline, Merck, Pfizer, Schering Plough	sanofi-aventis								X	
	9	Bayer	Bristol-Myers Squibb, sanofi-aventis								X	DVT

Appendix III. Continued

Committee member	Category*	Relationship <$10,000	Relationship >$10,000	Arrhythmias/ EP	CV surgery	Congenital heart disease	General cardiology	Heart failure	Interventional	Noninvasive	Prevention/ vascular	Other
Jean-François Tanguay	1, 2, 9	Abbott Vascular	AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, sanofi-aventis				X		X			
	1, 2	Boehringer Ingelheim	None									
	9	None	Accumetrics				X		X			
Pierre Théroux												
Alexander G. G. Turpie	1	None	sanofi-aventis									Anticoag-ulant Development
	2	None	Bayer, GlaxoSmithKline, Johnson & Johnson, Pfizer, sanofi-aventis									Anticoagu-lants Clinical
Robert Welsh	1	Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly	AstraZeneca, sanofi-aventis				X		X			
	9	None	AstraZeneca, Boehringer Ingelheim, Eli Lilly, sanofi-aventis				X		X			

*Categories: 1: Consulting Fees/Honouraria; 2: Speaker's Bureau; 3: Equity Interests/Stock Options; 4: Equity Interests; 5: Royalty Income; 6: Non-Royalty Payments; 7: Officer, Director, or Any Other Fiduciary Role; 8: Ownership/Partnership/ Principal; 9: Research Grants; 10: Fellowship Support; 11: Salary; 12: Intellectual Property Rights; 13: Other Financial Benefit.