

New Guidelines for Outpatient Antiplatelet Therapy in Canada

Highlights from the Canadian Cardiovascular Congress, Montreal, October 2010

At the 2010 Canadian Cardiovascular Congress (CCC), held in Montreal from October 23-27, attendees were offered a wealth of valuable information, including posters and presentations on new research, practical seminars on popular topics in cardiovascular (CV) medicine, and presentations of new clinical practice guidelines. The range of guidelines or position papers presented included the Canadian Cardiovascular Society (CCS) atrial fibrillation guidelines; the CCS position statement on smoking cessation; the CCS refractory angina guidelines; the CCS/Canadian Association of Cardiac Rehabilitation (CACR) position paper on inpatient referral to cardiac rehabilitation; the CCS position paper on the standardized approaches to the investigation of syncope; and—the focus of this report—the CCS antiplatelet therapy guidelines.

The CCS antiplatelet guidelines were presented in a case-based workshop at the CCC. As explained by one of the meeting's co-chairs, Dr. Alan Bell, there had up until now been no Canadian guidelines for the use of antiplatelet therapies. The CCS guidelines, to be published in the *Canadian Journal of Cardiology* in 2011 (and the full set of recommendations available now on the CCS website at www.ccs.ca), therefore represent a valuable new addition to the library of clinical practice guidelines in CV medicine in Canada.

The mandate of the guideline authors was to provide an evidence-based, treatment-focused

guideline for the use of antiplatelet drugs in the outpatient setting. The target audience for these guidelines is all healthcare professionals who manage patients with or at risk of ischemic vascular disease, including primary-care physicians.

The guidelines were broken down and presented in condition-specific sub-topics, each with a number of associated recommendations made based on the best available evidence: acute coronary syndromes (ACS)/percutaneous coronary intervention (PCI);

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stable coronary artery disease (CAD); cerebrovascular disease; peripheral arterial disease (PAD); surgical vascular disease; diabetes; primary prevention; and other special topics (*i.e.*, heart failure, chronic kidney disease, surgical/bleeding management, drug interactions, etc.). This report focuses on the guidelines dedicated to the management of ACS patients. A

TABLE 1. Recommendations for Medically Managed ACS: CCS Antiplatelet Guidelines

Patient Group	Recommendation	Strength of Recommendation
All patients with ACS who survive to hospital discharge	Indefinite therapy with low-dose aspirin (75-162 mg daily)	Class I, Level A
Patients with ACS who survive to hospital discharge and who are allergic to or intolerant of aspirin	Indefinite therapy with clopidogrel 75 mg daily	Class IIa, Level B
Patients presenting with STEMI who are medically managed	Clopidogrel 75 mg + aspirin 75-162 mg daily for at least 14 days	Class I, Level B
	Clopidogrel 75 mg + aspirin 75-162 mg daily for up to 12 months in the absence of an excessive risk of bleeding	Class IIb, Level C
Patients presenting with NSTEMI ACS who are medically managed	Clopidogrel 75 mg + aspirin 75-162 mg daily for at least 1 month	Class I, Level A
	Clopidogrel 75 mg + aspirin 75-162 mg daily for up to 12 months in the absence of an excessive risk of bleeding	Class I, Level B
All patients with ACS who are medically managed and have a low risk of bleeding	Consider continuing clopidogrel 75 mg daily + aspirin 75-162 mg daily beyond 12 months	Class IIb, Level C

complete listing of the CCS guidelines sub-topics is provided in Appendix 1.

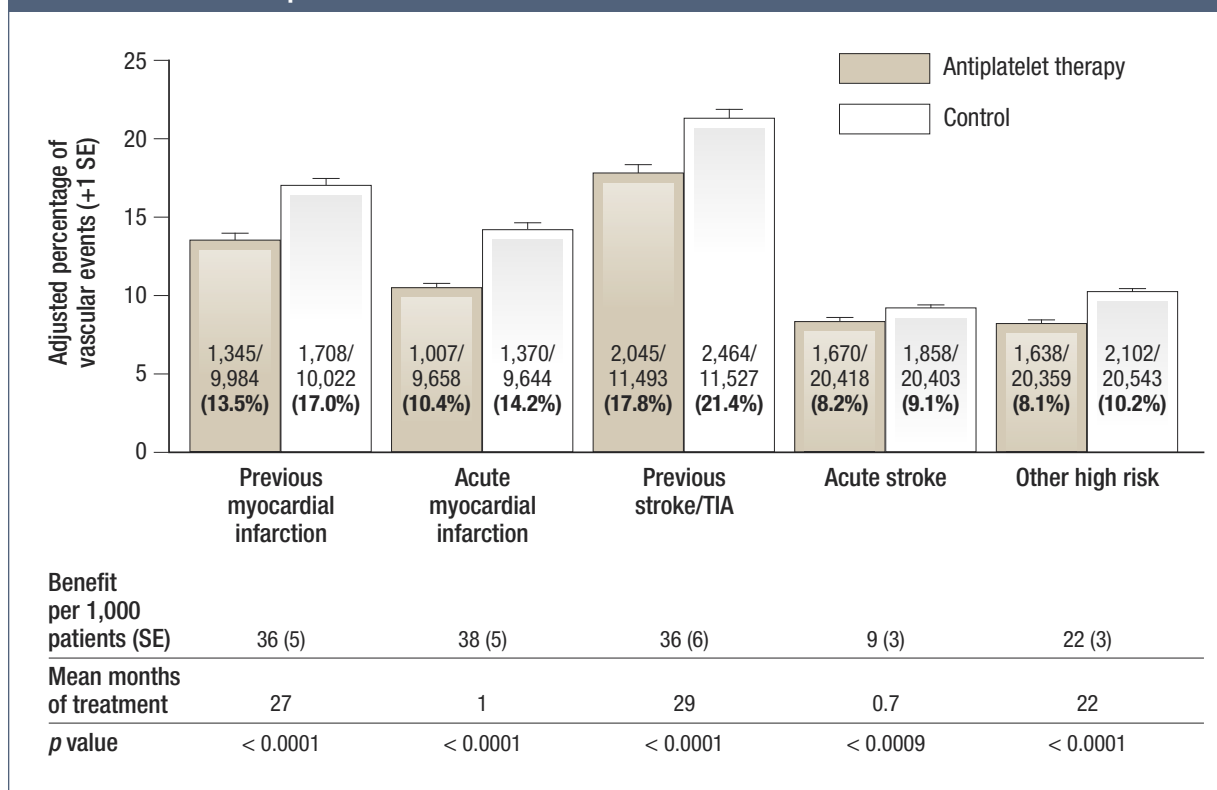
Antiplatelet Therapy for Medically Managed ACS

The first specific subgroup addressed within the ACS/PCI topic concerned medically managed ACS. The key recommendations are summarized in Table 1. In short, the authors recommend the use of aspirin for all medically managed patients with ACS, a recommendation based largely on the findings of the Antithrombotic Trialists' Collaboration.¹ This meta-analysis showed that the rate of subsequent CV events among patients with previous MI was significantly lower for those taking antiplatelet therapy (mostly aspirin) compared to controls (13.5% vs. 17.0%), which translated to 38 fewer serious vascular events per 1,000 treated patients (Figure 1).

To support their recommendation to use aspirin in combination with clopidogrel in patients who do not have an excessive risk of bleeding, the presenters cited the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study.² For the composite endpoint of death from CV causes, nonfatal MI, or stroke, clopidogrel + aspirin in the CURE study was associated with a statistically significant 20% risk reduction compared to aspirin alone over the entire study period. Also, as shown in Figure 2, there was a 20% reduction in risk for this endpoint during the first 24 hours and a 21% reduction over the first 30 days. These benefits were, however, somewhat offset by a modest but significant increase in major bleeding risk (3.7% vs. 2.7%) during the trial.

In addition to the antiplatelet therapies recommended in medically managed ACS (aspirin and clopidogrel), the presenters at the CCC also ac-

FIGURE 1. Evidence for Aspirin: Antithrombotic Trialists' Collaboration¹



knowledge of two newer antiplatelet agents, prasugrel (approved in Canada) and ticagrelor (not yet approved in Canada). While prasugrel has demonstrated benefit in addition to aspirin in patients undergoing PCI (see below),³ there has yet to be any evidence of benefit demonstrated in medically managed ACS.

Finally, according to the CCS guidelines, dual antiplatelet therapy with clopidogrel + aspirin may be considered beyond 12 months in patients with ACS who are medically managed and have a low risk of bleeding. This recommendation is based largely on results observed for the population of patients with clinically evident atherothrombosis within the CHARISMA study.⁷ For these patients, compared to aspirin alone, clopidogrel + aspirin was associated with a significant 12% risk reduction for the primary compos-

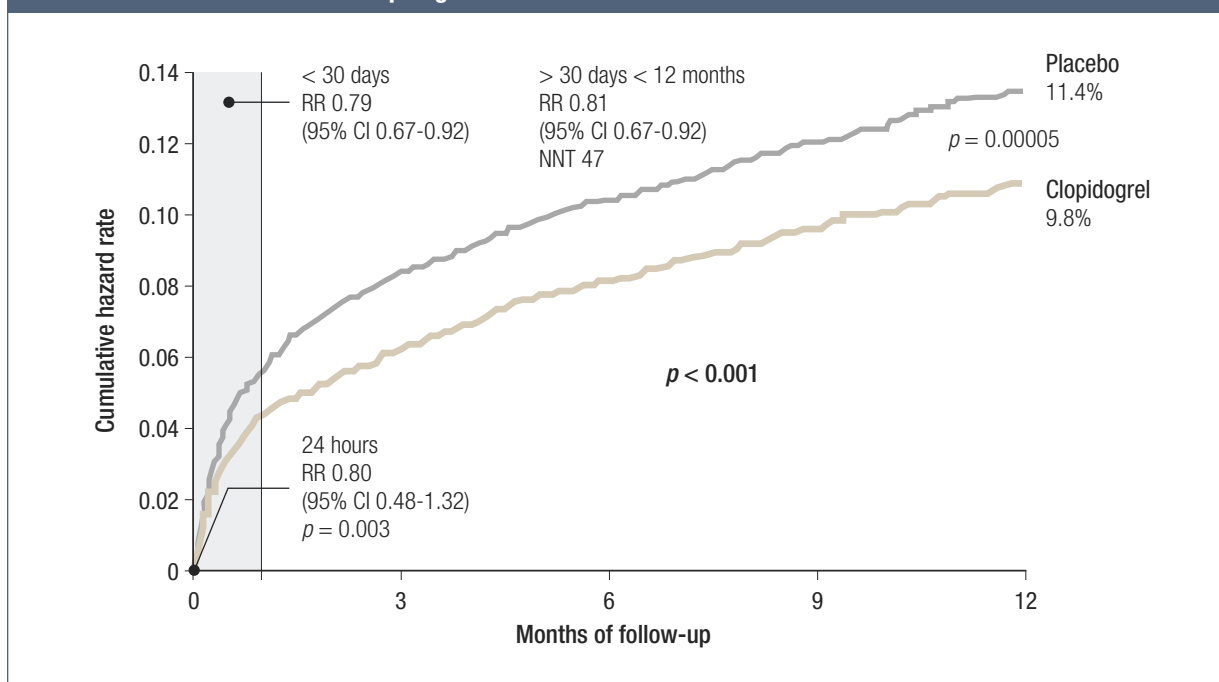
ite outcome (MI, stroke, CV death) after a median follow-up of 28 months.

Antiplatelet Therapy Following PCI for ACS

ACS patients who are managed with percutaneous intervention represent a distinct subset of the ACS population. In turn, there are several subgroups within the PCI-managed population with distinct requirements for antiplatelet therapy.

The CCS antiplatelet recommendations for PCI-managed patients are presented in Table 2. The authors recommend using a combination of aspirin and clopidogrel for up to one year in patients with bare-metal-stent (BMS) implantation. The evidence upon which this recommendation is based comes primarily from two major clinical trials published in the early 2000s: the PCI-CURE⁴ and CREDO⁵ studies. PCI-CURE was a Canadian-led substudy of

FIGURE 2. Evidence for ASA and Clopidogrel: CURE Trial²



the CURE study, isolating the 2,658 patients in that trial with non-ST-elevation ACS undergoing PCI. These patients had been randomized to double-blind treatment with clopidogrel (n = 1,313) or

ACS patients who are managed with percutaneous intervention represent a distinct subset of the ACS population.

placebo (n = 1,345). All were pre-treated with aspirin and study drug for a median of six days before PCI during the initial hospital admission, and for a median of 10 days overall. After the PCI, most patients (> 80%) in both groups received open-label thienopyridine antiplatelet therapy for about

four weeks, after which the study drug was restarted for a mean of eight months.

For the primary endpoint (composite of CV death, MI, or urgent target-vessel revascularization within 30 days of PCI), there was a 31% relative risk reduction in favor of clopidogrel + aspirin vs. aspirin alone.

The CREDO study assessed the long-term (12 months) effects of antiplatelet therapy in patients following PCI. In this study, a total of 2,116 patients were randomized to clopidogrel (300-mg loading dose) or placebo three to 24 hours before PCI. Subsequently, up to day 28, all patients received clopidogrel 75 mg daily. From day 29 to one year, patients in the initial clopidogrel loading-dose group received clopidogrel 75 mg daily, while those in the initial control group received placebo. Both groups received aspirin throughout the study.

For the primary endpoint (one-year incidence of death, MI or stroke), long-term clopidogrel therapy was associated with a 26.9% relative reduction vs. placebo (p = 0.02; Figure 3).

TABLE 2. Recommendations for Post-PCI-Managed ACS: CCS Antiplatelet Guidelines

Patient Group	Recommendation	Strength of Recommendation
All patients with acute or chronic ischemic heart disease without contraindications to aspirin therapy	Indefinite therapy with low-dose aspirin (75-162 mg daily)	Class I, Level A
Patients who have undergone PCI with bare-metal-stent (BMS) implantation	Clopidogrel 75 mg daily + aspirin 75-162 mg daily for at least 1 month	Class I, Level B
	Clopidogrel 75 mg daily + aspirin 75-162 mg daily for up to 12 months in the absence of an excessive risk of bleeding	Class I, Level B
Patients with recent bleeding or at increased risk for bleeding	BMS should be implanted and clopidogrel 75 mg daily should be added to aspirin 75-162 mg daily for a minimum of 2 weeks	Class I, Level B
All PCI patients with drug-eluting-stent (DES) implantation	Clopidogrel 75 mg daily + aspirin 75-162 mg daily for 12 months	Class I, Level A
Patients with an increased risk of stent thrombosis and an acceptable perceived risk of bleeding	Consider continuing clopidogrel 75 mg daily + aspirin 75-162 mg daily beyond 12 months	Class IIb, Level C
Patients with ACS who undergo stent implantation and have an increased risk of stent thrombosis (e.g., STEMI, history of diabetes mellitus, or prior documented stent thrombosis)	Prasugrel 10 mg daily may be considered in addition to aspirin 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 \geq 75 years; or weighing $<$ 60 kg	Class III, Level B

Among patients who have a DES implanted, the CCS guidelines clearly recommend dual antiplatelet therapy with aspirin and clopidogrel for one year. This recommendation is supported by the results of an observational study by Eisenstein et al, published in *JAMA* in 2007.⁶ The study included 3,165 patients undergoing PCI with BMS insertion and 1,501 undergoing PCI with DES. The population was also divided by use (or non-use) of clopidogrel, making four groups overall. The investigators observed that, among patients with DES insertion, the use of clopidogrel predicted lower mortality at six and 12 months. The

same was not found for those with BMS insertion (Figure 4).

Given that the risk reduction in this study was shown out to 24 months, with the curves continuing to diverge considerably past the one-year mark, the CCS guidelines state that consideration can be given to extending the dual regimen of clopidogrel and aspirin beyond one year, as long as the risk of bleeding is deemed to be acceptable.

The novel antiplatelet, prasugrel, is also included among the recommended choices for certain subgroups of the PCI-managed population. The authors of the CCS guidelines state that pra-

FIGURE 3. CREDO 1-year Primary End-point: Death, MI or Stroke in PCI Patients⁵

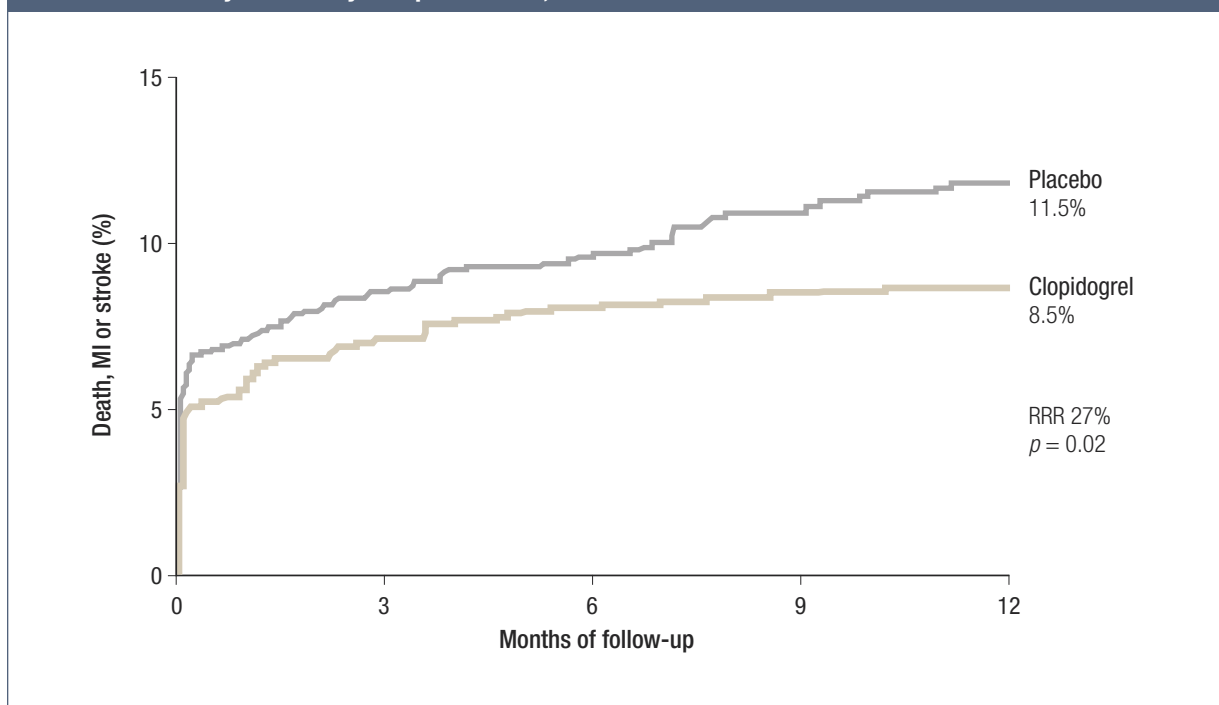


FIGURE 4. 6-Month Landmark Analysis: Adjusted Cumulative Mortality Rates, PCI with Bare-metal or Drug-eluting Stents With or Without Clopidogrel⁶

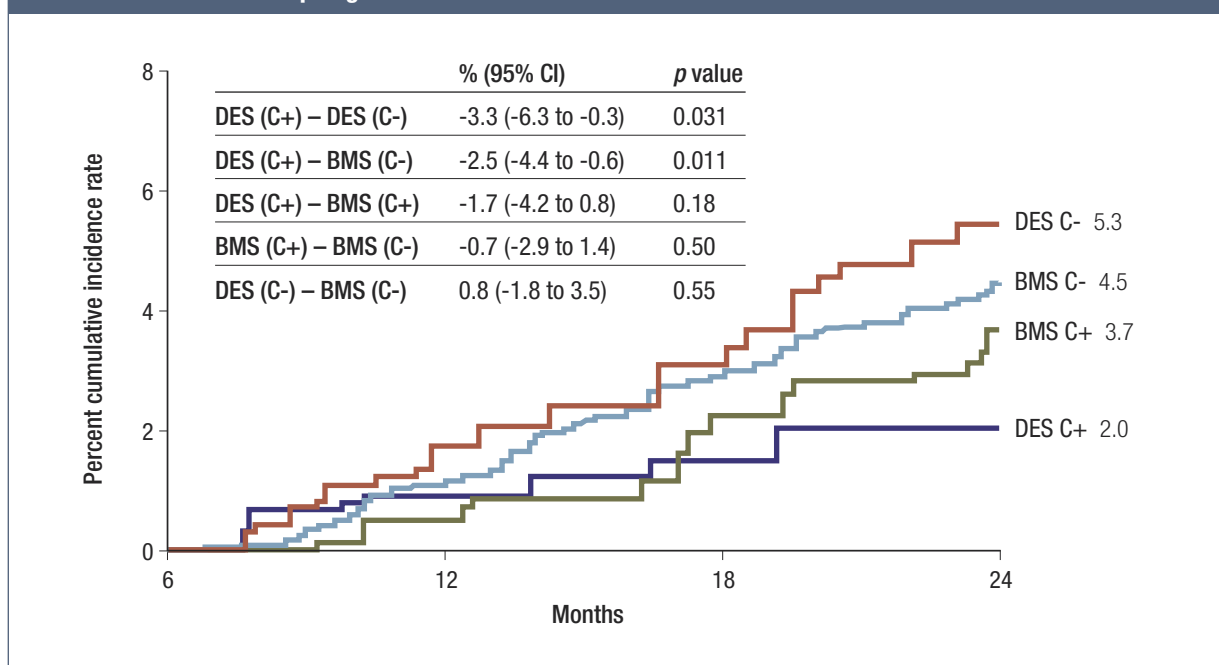
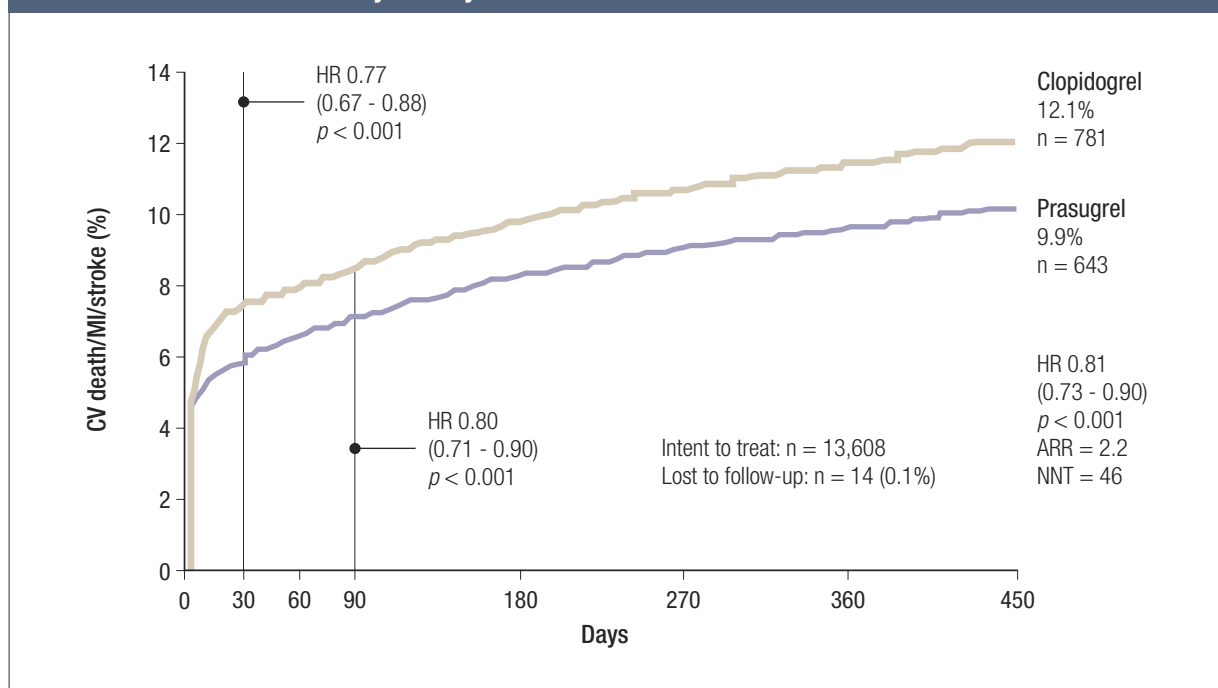


FIGURE 5. TRITON TIMI-38: Primary Efficacy Results³



sugrel 10 mg daily can be considered for patients who undergo stent implantation and have an increased risk of stent thrombosis (e.g., those suffering a STEMI, those with diabetes or those with history of stent thrombosis). This recommendation is based on the results of the TRITON-TIMI 38 study,³ in which 13,608 patients with moderate-to-high-risk ACS and scheduled PCI were randomized to prasugrel (60-mg loading dose and 10-mg daily maintenance dose) or clopidogrel (300-mg loading dose and 75-mg daily maintenance dose), for six to 15 months. The rate of the primary endpoint (composite of CV death, MI or stroke) was significantly lower in the prasugrel group than the clopidogrel group (9.9% vs. 12.1%; $p < 0.001$; Figure 5). Specific support for using prasugrel in patients at increased risk for stent thrombosis, meanwhile, comes from a secondary finding in this study, that prasugrel was also associated with a significantly lower rate of stent thrombosis compared to clopidogrel (1.1%

vs. 2.4%). These benefits were, however, accompanied by a significant increase in life-threatening bleeding with prasugrel vs. clopidogrel (1.4% vs. 0.9%; $p = 0.01$). The CCS guidelines therefore state that prasugrel should be avoided in patients with an increased bleeding risk.

Conclusions

The 2010 CCS guidelines for the use of antiplatelet therapies provide much-needed guidance for healthcare professionals who deal with patients at risk of vascular events, in the outpatient setting. Antiplatelet therapy is one of the cornerstones of pharmacologic therapy in these at-risk patients and, prior to the development of these guidelines, there was no single source of evidence-based guidance for such therapy.

This summary has reviewed the recommendations with respect to patients who have suffered an ACS, giving guidance for the optimal use of antiplatelet therapy to reduce the risk of a subse-

APPENDIX 1. CCS Antiplatelet Guidelines Sub-topic Listing

- Antiplatelet therapy for secondary prevention in the first year following an ACS
- Antiplatelet therapy for secondary prevention in the first year following PCI
- Antiplatelet therapy for secondary prevention beyond 1 year following ACS or PCI
- Antiplatelet therapy for secondary prevention following CABG
- Antiplatelet therapy for the secondary prevention of cerebrovascular disease
- Antiplatelet therapy for vascular prevention in patients with PAD
- Antiplatelet therapy for the primary prevention of vascular events
- Antiplatelet therapy in patients with diabetes
- Antiplatelet therapy in patients with heart failure
- Antiplatelet therapy in patients with chronic kidney disease
- Antiplatelet therapy in women who are pregnant or breastfeeding
- Management of patients on antiplatelet therapy who require a surgical or other invasive procedure
- Management of antiplatelet therapy in association with minor bleeding
- Combination therapy with warfarin and aspirin: when to use, when to consider, when to avoid
- Interaction between clopidogrel and proton pump inhibitors
- Interaction between aspirin and NSAIDs

quent CV event. The well established agents, aspirin and clopidogrel, form the backbone of these recommendations, with the newer agent, prasugrel, also recommended for consideration in specific sub-populations.

The panel at the CCC workshop pointed out that these guidelines are intended to serve as a useful tool in clinical decision-making, which will ultimately be guided by patient-specific considerations and left in the hands of individual prescribing physicians. Furthermore, the panel ack-

nounced that the field is evolving, and that the guideline recommendations may need to be updated as data from clinical trials are published or as new therapies become available.

The full guidelines, including these ACS-related recommendations as well as those concerning other populations, will be published in an upcoming issue of the *Canadian Journal of Cardiology* and are available on the CCS website (www.ccs.ca). For complete details on any recommendation discussed in this review, please refer to those published guidelines.

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