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Society Guidelines

Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology 2023 Focused Update of the Guidelines for the Use of Antiplatelet Therapy

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ABSTRACT

Antiplatelet therapy (APT) is the foundation of treatment and prevention of atherothrombotic events in patients with atherosclerotic cardiovascular disease. Selecting the optimal APT strategies to reduce

RÉSUMÉ

Le traitement antiplaquettaire est la base du traitement et de la prévention des manifestations athérothrombotiques chez les patients atteints d'une maladie cardiovasculaire athéroscléreuse. Le choix du

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary 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 judgement 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.

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major adverse cardiovascular events, while balancing bleeding risk, requires ongoing review of clinical trials. Appended, the focused update of the Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology guidelines for the use of APT provides recommendations on the following topics: (1) use of acetylsalicylic acid in primary prevention of atherosclerotic cardiovascular disease; (2) dual APT (DAPT) duration after percutaneous coronary intervention (PCI) in patients at high bleeding risk; (3) potent DAPT ($P2Y_{12}$ inhibitor) choice in patients who present with an acute coronary syndrome (ACS) and possible DAPT de-escalation strategies after PCI; (4) choice and duration of DAPT in ACS patients who are medically treated without revascularization; (5) pretreatment with DAPT ($P2Y_{12}$ inhibitor) before elective or nonelective coronary angiography; (6) perioperative and longer-term APT management in patients who require coronary artery bypass grafting surgery; and (7) use of APT in patients with atrial fibrillation who require oral anticoagulation after PCI or medically managed ACS. These recommendations are all on the basis of systematic reviews and meta-analyses conducted as part of the development of these guidelines, provided in the Supplementary Material.

traitement antiplaquettaire approprié pour réduire les événements cardiovasculaires majeurs, tout en tenant compte du risque de saignement, demande un suivi constant des essais cliniques. En annexe, la mise à jour ciblée des lignes directrices de la Société cardiovasculaire du Canada/Association canadienne de cardiologie d'intervention pour l'utilisation du traitement antiplaquettaire formule des recommandations sur les sujets suivants : 1) l'emploi de l'acide acétylsalicylique dans la prévention primaire des maladies cardiovasculaires athéroscléreuses; 2) la durée du traitement antiplaquettaire double après une intervention coronarienne percutanée (ICP) chez les patients qui présentent un risque élevé de saignement; 3) le choix d'un puissant traitement antiplaquettaire double (inhibiteur de $P2Y_{12}$) chez les patients qui présentent un syndrome coronarien aigu et les stratégies éventuelles de désescalade du traitement antiplaquettaire double après une ICP; 4) le choix et la durée du traitement antiplaquettaire double chez les patients atteints du syndrome coronarien aigu qui reçoivent un traitement médical sans revascularisation; 5) le prétraitement par un traitement antiplaquettaire double (inhibiteur de $P2Y_{12}$) avant une coronarographie non urgente ou urgente; 6) la prise en charge par un traitement antiplaquettaire périopératoire et à long terme chez les patients qui ont besoin d'un pontage aortocoronarien; et 7) l'utilisation du traitement antiplaquettaire chez les patients qui présentent une fibrillation auriculaire et qui ont besoin d'un traitement anticoagulant par voie orale après une ICP ou qui présentent un syndrome coronarien aigu traité médicalement. Toutes les recommandations reposent sur les analyses des publications et les méta-analyses menées dans le but de formuler ces lignes directrices, fournies dans le matériel supplémentaire.

Scope of the 2023 Antiplatelet Therapy Guideline Update

To place into context, the Canadian Cardiovascular Society (CCS) released the original practice guidelines on the use of antiplatelet therapy (APT) in the outpatient setting in 2010, and updates were published in 2012 and 2018.[1-3] Since then, a number of randomized controlled trials (RCTs) on the use of antiplatelet agents in primary and secondary prevention of atherosclerotic cardiovascular (CV) disease (ASCVD) have been published.

We provide updated recommendations on the basis of recent evidence to inform clinical practice. The 2023 CCS/Canadian Association of Interventional Cardiology (CAIC) recommendations focus on the following key topics:

1. Use of acetylsalicylic acid (ASA) in primary prevention of ASCVD;
2. Dual APT (DAPT) treatment duration after percutaneous coronary intervention (PCI) in patients at high bleeding risk (HBR);
3. Potent DAPT ($P2Y_{12}$ inhibitor) choice in patients who presenting with an acute coronary syndrome (ACS) and possible DAPT de-escalation strategies after PCI;
4. Choice and duration of DAPT in ACS patients who are medically treated without revascularization;
5. Pretreatment with DAPT ($P2Y_{12}$ inhibitor) before elective or nonelective coronary angiography;
6. Perioperative and longer-term APT management in patients who require coronary artery bypass grafting (CABG) surgery; and
7. Use of APT in patients with atrial fibrillation (AF) who require oral anticoagulation (OAC) after PCI or medically managed ACS.

Guideline Development

The guideline development process is described in detail in the Supplemental Appendix S1. The CCS Guidelines Committee approved the co-chairs of the guidelines, and the co-chairs identified CCS members and additional experts from the broader community to be considered as primary and secondary panel members. Two methodologists from the methodology subcommittee of the CCS Guidelines Committee joined the primary panel to conduct a systematic review and meta-analysis of the literature for each clinical question addressed. The topics were selected by the co-chairs and approved by the CCS Guidelines Committee. Each topic was addressed in the form of "PICO" questions: patient population of interest (P), intervention (I), comparator (C), and outcomes (O). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to synthesize evidence. Members of the primary panel voted and reached a majority (75%) agreement for all recommendations. A summary of the systematic reviews and meta-analyses conducted for this guideline document are available online as Supplementary Material. The guideline manuscript was peer-reviewed by the secondary panel and the CCS Guidelines Committee before submission.

Use of ASA in Primary Prevention of ASCVD

Although ASA has historically been the cornerstone of secondary prevention of ASCVD, its role in patients without established ASCVD is less clear. Since the publication of the 2011 CCS APT guidelines,[1] major trials on the role of ASA in primary prevention involving > 50,000 participants have been published.[4-7] Our updated meta-analysis of 14 RCTs (n = 167,587 patients) showed a consistent reduction in major adverse cardiac events (MACE) with ASA in primary prevention (risk ratio [RR], 0.90; 95% confidence interval [CI], 0.86-0.94), mainly driven by a reduction in nonfatal myocardial infarction (MI; no significant reduction in all-cause mortality; Supplemental Appendix S2). However, these benefits were offset by an increase in extracranial major bleeding (RR, 1.67; 95% CI, 1.36-2.06), gastrointestinal bleeding (RR, 1.59; 95% CI, 1.32-1.91), and intracranial hemorrhage (RR, 1.33; 95% CI, 1.13-1.56). These risk reductions translate to 4 fewer (95% CI, 2-6 fewer) MACE events, and 5 more (95% CI, 3-8 more) extracranial major bleeding events per 1000 patients treated with ASA over 5 years. None of the prespecified subgroups (sex, age, or diabetes status) per outcome of interest showed a clear net benefit with ASA in primary prevention (Supplemental Appendix S2).[8] Other meta-analyses support these results.[9,10] In this context, we endorse a ***patient-centred informed shared decision-making approach*** to enhance care of patients who might choose ASA for primary prevention, weighing the individual risks and benefits. We provide a visual risk representation of absolute risk reduction and absolute risk increase for key events with ASA in primary prevention (Fig. 1), along with a newly created, transparent, patient-centred decision aid tool to help patients and clinicians explore their values and preferences when contemplating the use of ASA for primary prevention (Supplemental Appendix S3).

RECOMMENDATION

1. We recommend against the **routine** use of ASA for primary prevention of ASCVD regardless of sex, age, or diabetes, in patients without ASCVD (Strong Recommendation; High-Quality Evidence).

BEST PRACTICE STATEMENT

1. The use of ASA for primary prevention of ASCVD might be appropriate in certain individuals deemed to be at high ASCVD risk but with low bleeding risk in the context of a patient-centred, informed, shared decision-making process (Fig. 1; Supplemental Appendix S3).

Values and preferences:

- In the absence of a mortality benefit with ASA in primary prevention, we valued nonfatal ischemic and major bleeding events equally, to provide more flexibility to patients' values. In such circumstances, consideration of patients' preferences for nonfatal outcomes is essential.

Practical tips:

- Prescription of ASA on the basis of CV risk stratification tools has not been prospectively validated in clinical trials, hence the lack of endorsement.
- Clinicians should emphasize optimization of CV risk factors before initiation of ASA treatment in primary prevention.
- Most of the recent trials were carried out with enteric-coated ASA tablets. Whether newer formulations of ASA, such as extended-release capsules, pharmaceutical lipid-aspirin complex tablets, or plain aspirin, will change the risk/benefit balance of ASA in primary prevention remains to be established through dedicated clinical trials.
- The role of ASA in subclinical ASCVD remains undefined and would encourage a patient-centred, informed, shared decision-making process (eg, in patients with asymptomatic atherosclerosis seen on computed tomography angiogram).
- Patients who opt for ASA in primary prevention could be offered screening for *Helicobacter pylori* with eradication therapy as appropriate, be co-prescribed a proton pump inhibitor, and prescribers should preferentially consider gastroprotective formulations of ASA.

DAPT Duration After PCI in Patients at HBR

In the 2018 antiplatelet guidelines, DAPT with ASA and a $P2Y_{12}$ inhibitor was recommended for a minimum of 1 year as a standard and can be considered up to 3 years in patients at high ischemic/low bleeding risk.[3] For elective PCI with a drug-eluting stent (DES), a minimum of 3-6 months was recommended (depending on bleeding risk).[3] Further randomized studies have been performed, which continue to explore shortened DAPT durations. Certainly, DAPT protects against ischemic events, yet patients with major bleeding post-PCI have a 3- to 5-fold increase in mortality risk, potentially offsetting the beneficial role of DAPT, especially in HBR patients.[11] In the recent years, innovative DES platforms have been shown to be associated with low risks of stent thrombosis in the HBR population,[12,13] allowing even shorter DAPT durations. The Academic Research Consortium put forth major and minor criteria to ***objectively*** **and** ***homogeneously*** define HBR patients, whose risk of a Bleeding Academic Research Consortium 3 or 5 major bleed is ≥ 4%, or intracranial hemorrhage is ≥ 1%, at 1 year (Fig. 2).[14] Conversely, we have also developed criteria for identifying complex PCI, for which ischemic risk might dictate longer DAPT duration—as shown in various clinical trials (Fig. 3).[15-20]

In the **Ma**nagement of High Bleeding Risk Patients Post Bioresorbable Polymer Coated **Sten**t Implantation With an Abb**r**eviated Versus Standard **DAPT** Regimen (MASTER DAPT) trial (n = 4434) 2 short DAPT duration strategies (1 month vs ≥ 3 months) were compared in patients at HBR after PCI with biodegradable polymer sirolimus-eluting stents (Ultimaster [not available in Canada]; Terumo, Tokyo, Japan) for ACS or stable coronary artery disease (CAD). In this study,

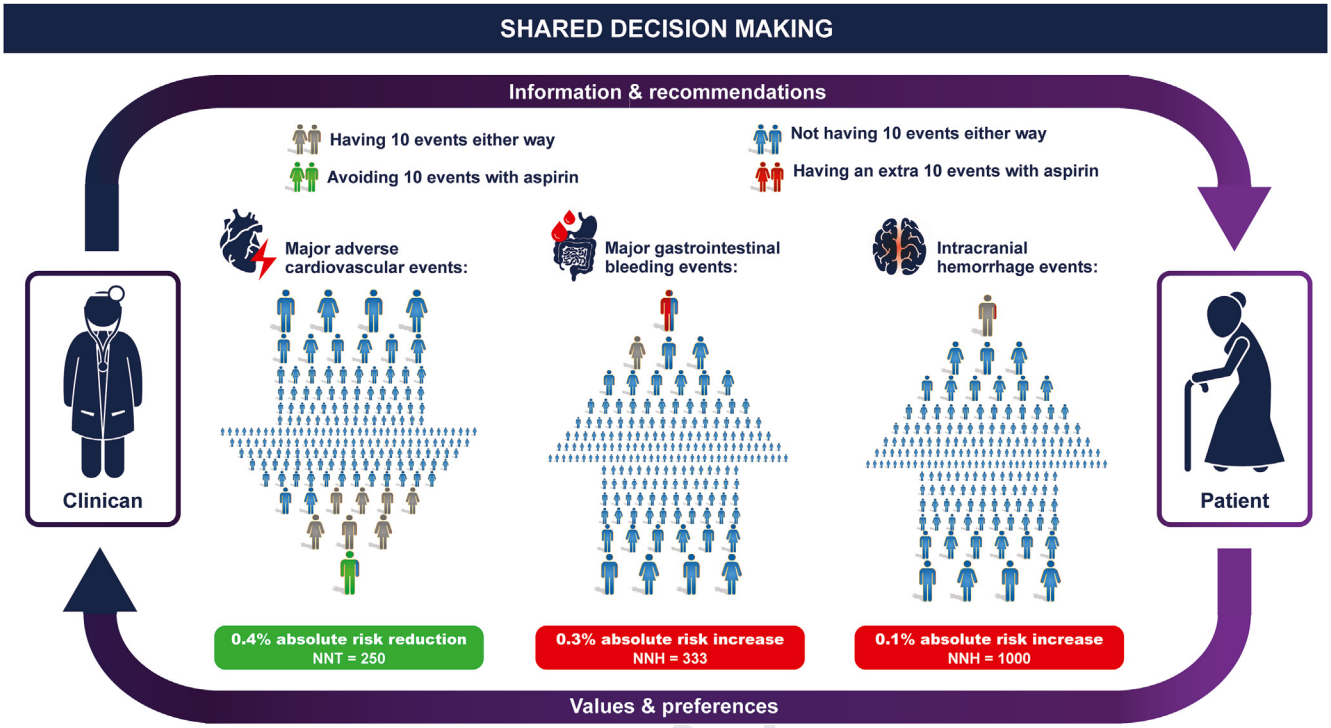

Figure 1. Shared decision-making regarding aspirin for primary prevention of atherosclerotic cardiovascular disease. Consideration of patient preferences for nonfatal outcomes is essential as part of a **shared decision-making process** (decision aid tool available in the Supplemental Appendix S3). In this illustration, each (male and female) is equivalent to 10 patients. Outcomes exhibited were over a 5-year period. NNH, number needed to harm; NNT, number needed to treat.

36% of participants were treated with long-term OAC. Participants who were free from an ischemic and bleeding event were screened between 30 and 44 days after index PCI, and were randomized to open-label immediate DAPT discontinuation (shorter DAPT; thereafter maintaining single APT [SAPT] alone with either ASA or a $P2Y_{12}$ inhibitor), vs DAPT continuation for at least 2 additional months (standard short DAPT; thereafter maintaining SAPT alone with either ASA or a $P2Y_{12}$ inhibitor). Clopidogrel was the $P2Y_{12}$ inhibitor used most frequently in both groups. Shorter DAPT was noninferior to standard short DAPT for net adverse clinical events and major adverse cardiac or cerebral events, but was associated with a significant reduction in major or clinically relevant nonmajor bleeding.[21] These results have now been extended to 15-month follow-up.[22] It does appear the shortest limit to DAPT is 1 month, as shown in **Sh**ort and **Op**timal Duration of **D**ual **A**ntip**l**atelet **T**herapy (STOPDAPT)-3, in which hazard was shown in stopping aspirin immediately after PCI.[23]

To investigate the use of short-duration (1-3 months) DAPT vs standard-duration DAPT (6-12 months) in HBR patients who underwent PCI, we performed a meta-analysis of 5 randomized trials (including 4 HBR subgroups of trials that enrolled HBR and non-HBR patients) involving 7242 patients with a median follow-up of 12 months (Supplemental Appendix S4). Differences in short- and standard-duration DAPT were not statistically significant for MACE, death, or stent thrombosis (definite or probable). Short DAPT duration reduced major bleeding (RR, 0.34; 95% CI, 0.13-0.90) and the composite of major or clinically relevant nonmajor bleeding (RR, 0.60; 95% CI, 0.44-0.81) compared with standard DAPT, translating to 21 and 34 fewer events per 1000 patients, respectively. This finding of reduced bleeding risk with short-duration DAPT was consistent regardless of clinical presentation (ACS vs non-ACS), concomitant indication for OAC, or choice of $P2Y_{12}$ inhibitor.[24]

After the decision to shorten DAPT in HBR patients, it remains unclear which SAPT (ASA or $P2Y_{12}$ inhibitor) should be subsequently chosen. Although further randomized studies are needed, our meta-analysis suggests either may be a choice (Supplemental Appendix S4). However, although not in HBR patients, in the **H**armonizing **O**ptimal **S**trategy for **T**reatment of Coronary Artery Stenosis- **Ex**tended **A**ntiplatelet **M**onotherapy (HOST-EXAM) trial, conducted in South Korea, the use of chronic SAPT with either ASA or clopidogrel monotherapy after 6-18 months of DAPT in all-comers who underwent DES PCI was evaluated. Clopidogrel-based SAPT reduced the risk of MACE and major bleeding compared with ASA-based SAPT.[25] Moreover, modest vascular event reductions with clopidogrel compared with ASA-based SAPT have also been reported in the subgroup of patients with CAD in the **C**lopidogrel vs **A**spirin in **P**atients at **R**isk of **I**schaemic **E**vents (CAPRIE) trial.[26] In a meta-analysis of 7 trials (24,325 patients) that compared $P2Y_{12}$ inhibitor monotherapy (62% clopidogrel, 38.0% ticagrelor) vs ASA in patients with coronary disease, the 2-year risk of CV death, MI, and stroke was lower with $P2Y_{12}$ inhibitors (hazard ratio [HR], 0.88; 95% CI, 0.79-0.97; $P = 0.012$; driven mainly by a reduction in MI) and the major bleeding risk was similar (HR, 0.87; 95% CI, 0.70-1.09; $P = 0.23$).[27] Until further studies are available, it seems logical to use $P2Y_{12}$ inhibitor SAPT.

As a guideline writing group, we recognize that the decisions for DAPT duration can be complex after an ACS or elective PCI. Moreover, recent terminology highlighting DAPT strategies can differ, which might lead to further confusion. In 2023, the Academic Research Consortium published standardized definitions of APT strategies for modulating therapy.[28] Consistently, we provide direction on the use of DAPT for ACS or elective PCI with provisions for extending[29,30] and de-escalating DAPT, incorporating previous CCS/CAIC recommendations (Fig. 4).

RECOMMENDATION

2. We suggest using short dual APT for 1-3 months rather than 6-12 months in patients at HBR who undergo PCI for ACS or elective PCI with maintenance SAPT thereafter, in patients who do not have any ischemic or bleeding events in the first month (Fig. 4; Weak Recommendation; Moderate-Quality Evidence).

Values and preferences:

- We value a shared decision-making approach weighing the risks of bleeding vs ischemic events when considering a short DAPT duration and transitioning to a SAPT strategy in HBR patients.
- We put a high value on the results of the MASTER DAPT trial in favour of a shorter DAPT duration, and less value on the fact that participants were treated with a stent platform that is not available in Canada, and that results might not be generalizable to other stents. However, the use of short DAPT durations in HBR patients has been shown to be safe with several DESs commonly used in routine clinical practice in Canada.[12,13] As well, it appears safe to use 1 month of DAPT (followed by SAPT) with either the biodegradable-polymer or permanent-polymer DES in HBR patients.[31]

Practical tips:

- In patients at HBR, after 1-3 months of DAPT, current practice emphasizes consideration of SAPT with a $P2Y_{12}$ inhibitor over ASA monotherapy (ASA-free strategy; Fig. 4).
- The risk of stent thrombosis must be considered when contemplating short DAPT of 1-3 months. Patients who undergo complex PCI or with a history of stent thrombosis might not be suitable for short DAPT. Complex PCI is defined by the presence of at least 1 of the criteria as shown in Figure 3.
- Only a small percentage of the patients included in the trials underlying this recommendation had an ST-elevation MI (STEMI) as the indication for PCI. Therefore, the strength of evidence for shorter DAPT in this population is less clear.
- After PCI, interventional cardiologists should provide *clear* recommendations (Fig. 4) to the treating physicians regarding DAPT duration to favour an efficient adoption of the selected DAPT strategies (recognizing this can be dynamic throughout the patient's APT treatment).
- In patients at HBR, bleeding avoidance strategies can be adopted to reduce the risk of bleeding (Table 1).
- Clopidogrel is less potent than ticagrelor and prasugrel, which should be considered when selecting a $P2Y_{12}$ inhibitor in patients at HBR.

Potent DAPT ($P2Y_{12}$ Inhibitor) Choice in Patients Who Present With an ACS, and Possible DAPT De-escalation Strategies After PCI

Potent $P2Y_{12}$ inhibitor in patients with ACS

The 2018 antiplatelet guidelines recommended DAPT with the more potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel over clopidogrel after ACS,[3] because these agents have stronger platelet inhibition activity and reduce ischemic end points compared with clopidogrel.[32,33] However, the previous guidelines did not make specific recommendations favouring one potent $P2Y_{12}$ inhibitor over another. Subsequently, the **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen: **R**apid **E**arly **A**ction for **C**oronary **T**reatment (ISAR-REACT) 5 trial compared prasugrel with ticagrelor in patients with ACS and a planned invasive management.[34] In a randomized study of 4018 ACS patients, the primary composite of death, MI, or stroke was more frequent with ticagrelor vs prasugrel (9.3% vs 6.9%, respectively; HR, 1.36; 95% CI, 1.09-1.70) and the risk of BARC bleeding type 3-5 was similar in both groups (5.4% vs 4.8% respectively; HR, 1.12; 95% CI, 0.83-1.51).[34]

We performed an updated meta-analysis of RCTs that compared prasugrel with ticagrelor in ACS patients who underwent PCI (8 RCTs, n = 6212 patients), and an increased risk of MACE with ticagrelor compared with prasugrel was shown (RR, 1.23; 95% CI, 1.01-1.49). However, there were no significant differences in death, stent thrombosis, or major bleeding for both drugs (Supplemental Appendix S5). Although these results need to be acknowledged, they were largely driven by ISAR-REACT 5. The limitations of ISAR-REACT 5 include that it was an open-label study, that approximately one-third of the patients were not receiving assigned therapy at the end of the clinical trial, and that more patients discontinued ticagrelor because of the side effects (5.6% vs 2.4%). Moreover, 11.6% (233 patients) of participants randomized to prasugrel were excluded from the bleeding analysis (for unknown reasons) compared with 1.1% (23 patients) of participants randomized to ticagrelor. These findings in favour of prasugrel could not be replicated in the **S**wedish **W**eb-System for **E**nhancement and **D**evelopment of **E**vidence-Based Care in **H**eart Disease **E**valuated **A**ccording to **R**ecommended **T**herapies (SWEDEHEART) registry.[35] The Q5 second largest trial, Comparison of Prasugrel and Ticagrelor in the Treatment of Acute Myocardial Infarction (PRAGUE-18) in primary PCI, did not show a significant difference in any outcome with ticagrelor- or prasugrel-based DAPT at 30 days or at 1 year.[36,37] The ongoing Switching From Ticagrelor to Prasugrel in Patients With Acute Coronary Syndrome-SWEDEHEART (SWITCH-SWEDEHEART) trial (NCT05183178), a registry-based, step-wedge, cluster randomized study to evaluate the use of ticagrelor vs prasugrel in ACS patients, is expected to provide more definitive insight on the relative efficacy of both agents.[38] Until further studies are performed, we support the use of potent DAPT in patients

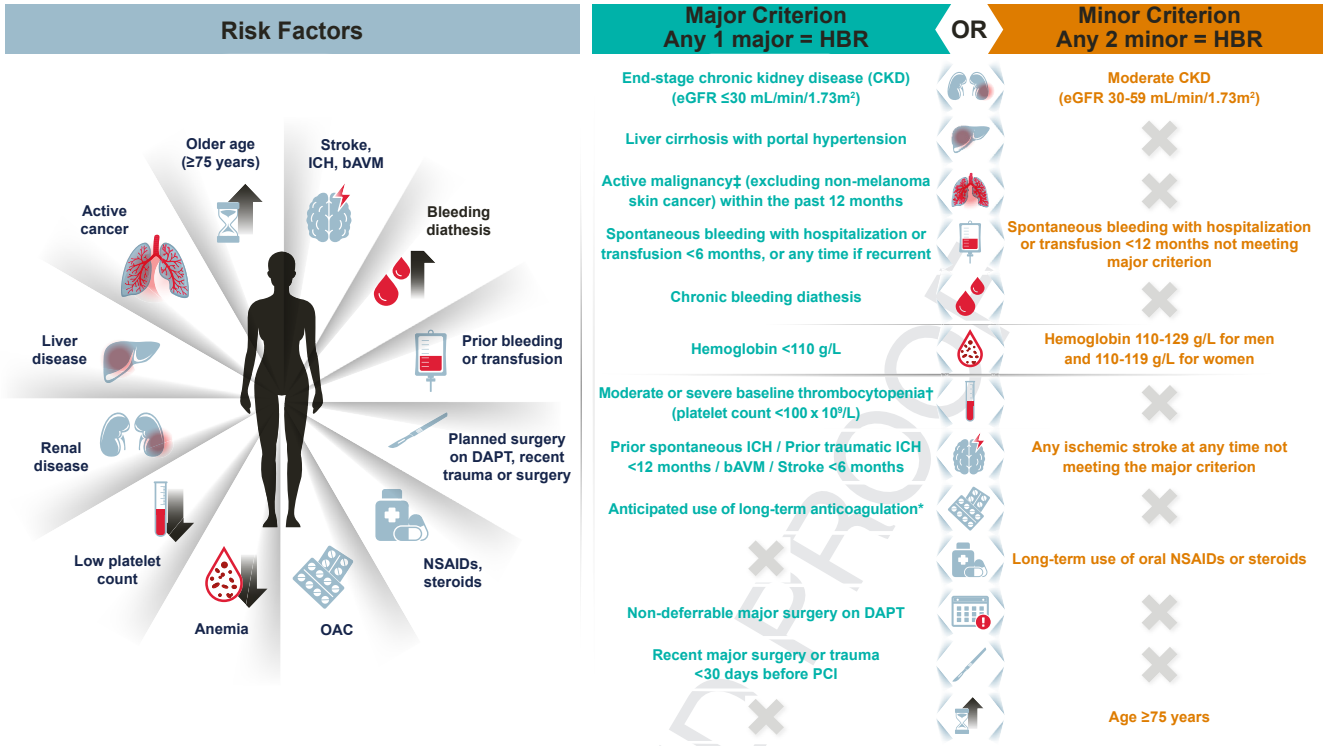

Figure 2. Estimating bleeding risk for antiplatelet decision-making after percutaneous coronary intervention (PCI). This illustration provides criteria Q32 for high bleeding risk (HBR) as defined by the Bleeding Academic Research Consortium (1 major or 2 minor criteria), when short dual antiplatelet therapy (DAPT) should be considered. bAVM, brain arteriovenous malformation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulation. * Excludes vascular protection doses. † Baseline thrombocytopenia is defined before PCI. ‡ Active malignancy is defined as a diagnosis within 12 months and/or ongoing treatment.

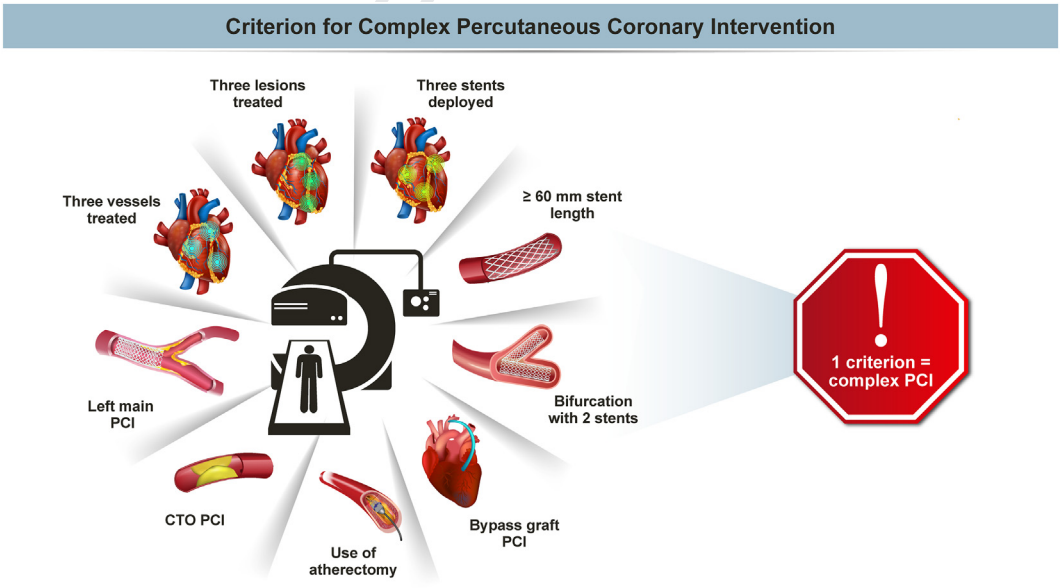

Figure 3. Estimating ischemic risk for antiplatelet decision-making after percutaneous coronary intervention (PCI). This illustration provides criteria Q33 for complex PCI (1 criterion) when longer duration of dual antiplatelet therapy may be considered. CTO, chronic total occlusion.

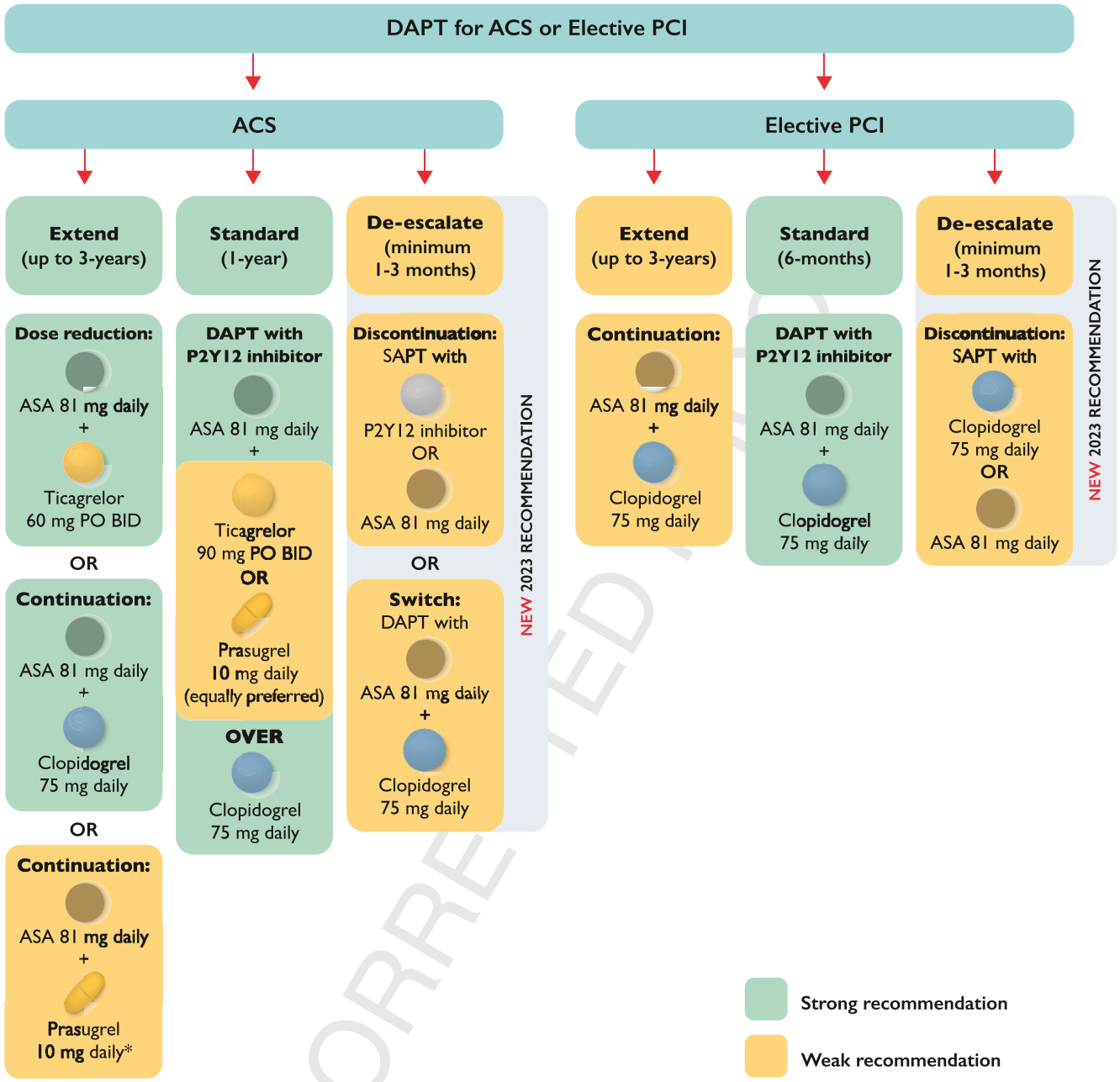

Figure 4. Recommendations for the duration of dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome (ACS) or elective percutaneous coronary intervention (PCI) with provisions for extension or de-escalation of DAPT. This illustration incorporates recommendations from 2018[3] and 2023 regarding duration of DAPT treatment. ASA, acetylsalicylic acid; BID, twice daily; PO, orally; SAPT, single antiplatelet therapy. * Prasugrel 5 mg/d with body weight < 60 kg as was done in the **Ma**nagement of High Bleeding Risk Patients Post Bioresorbable Polymer Coated **Sten**t Implantation With an Abbreviated Versus Standard **DAPT** Regimen (MASTER DAPT) trial.[29]

with ACS and do not discriminate between ticagrelor or prasugrel (Fig. 4).

Potent dual antiplatelet agent de-escalation by switching to clopidogrel

Although potent DAPT might be appropriate for most patients with ACS, some patients might benefit from de-escalation of potent DAPT by switching to clopidogrel-based DAPT. This strategy provides flexibility for the treating physician on the basis of evolving risks/benefits in patients with ACS. Two modest-sized RCTs, the **T**iming **o**f **P**latelet **I**nhibition after Acute **C**oronary Syndrome (TOPIC) and **T**ica**g**relor Versus C**lo**pidogrel in **S**tabilized Patients With **A**cute **M**yocardial **I**nfarction (TALOS-AMI) evaluated de-escalation from potent $P2Y_{12}$ inhibitor DAPT to clopidogrel-based DAPT (switching strategy) at 30 days after PCI.[39,40] The TOPIC trial showed no significant difference in the risk of ischemic events, but a reduction in major bleeding events with this de-escalation by switching strategy.[39] The TALOS-AMI trial showed that de-escalation by switching to clopidogrel-based DAPT significantly reduced the composite

Table 1. Bleeding avoidance strategies

Avoid pretreatment with $P2Y_{12}$ inhibitor
Avoid bridging when interrupting oral anticoagulant
Use radial arterial access for angiograms
Avoid glycoprotein IIb/IIIa inhibitors
Avoid NSAIDs
Use proton pump inhibitors for patients at risk of GI bleeding

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

of CV death, MI, stroke, or major bleeding (driven mainly by a reduction in bleeding), in the setting of an adherence of > 97% to the allocated treatment.[40] We pooled these 2 trials (n = 3343) and de-escalation to clopidogrel-based DAPT was associated with similar rates of MACE, stent thrombosis, and all-cause death, and a significant reduction in major bleeding at 30 days compared with continuation of potent $P2Y_{12}$ inhibitor DAPT (RR, 0.51; 95% CI, 0.28-0.92; Supplemental Appendix S5). We provide this as a reasonable alternative in the care of ACS patients, in whom ischemic and bleeding risks continuously evolve (Fig. 4).

Potent dual antiplatelet agent de-escalation by dose reduction

The **H**armonizing **O**ptimal **S**trategy for **T**reatment of Coronary Artery Diseases Trial - Comparison of **Reduc**tion of Prasugr**el** Dose or **Poly**mer **Tech**nology in **ACS** Patients (HOST-REDUCE-POLYTECH-ACS) trial, was the first trial to assess the safety and efficacy of de-escalation by dose reduction of a potent $P2Y_{12}$ inhibitor-based DAPT 30 days after PCI for ACS.[41] In this study, dose reduction from prasugrel 10 mg daily to prasugrel 5 mg daily was noninferior in preventing the composite of all-cause death, nonfatal MI, stroke, and major bleeding.[41] This strategy has yet to be investigated in non-Asian countries. In this context, no RCT has assessed the efficacy and safety of DAPT de-escalation to low-dose ticagrelor.

Because of the low-certainty evidence from a single trial, no recommendation for de-escalation by dose reduction of a potent $P2Y_{12}$ inhibitor therapy as part of DAPT in patients with ACS treated with PCI is provided. The ongoing Ticagrelor De-escalation Strategy in East Asian Patients With AMI (EASTYLE; NCT04755387) trial is the first RCT to investigate a ticagrelor de-escalation strategy (in East-Asian patients), with study completion planned for January 2024.

RECOMMENDATION

3. We suggest, when potent dual APT is considered in patients with ACS who receive PCI, either ticagrelor or prasugrel can be used, without preference for either agent (Fig. 4; Weak Recommendation; Low-Quality Evidence).
4. We suggest that the option of de-escalating potent DAPT by switching to clopidogrel-based DAPT be considered in appropriate patients with ACS who receive PCI and tolerate at least 1 month of potent DAPT without a recurrent thrombotic event (Fig. 4; Weak Recommendation; Moderate-Quality Evidence).

Values and preferences:

- Unguided potent $P2Y_{12}$ inhibitor dose de-escalation strategies have mostly been studied in RCTs conducted in East Asia. Whether their results apply to other regions remains unknown.

Practical tips:

- Potential side effects (eg, dyspnea with ticagrelor), dosing frequency (once vs twice daily), drug interactions (eg, CYP3A4 inhibitors or/and inducers for ticagrelor), costs, patient compliance, and availability of each potent $P2Y_{12}$ inhibitor can be considered when individualizing therapy. Potent $P2Y_{12}$ inhibitors can be switched interchangeably (eg, patients having dyspnea with ticagrelor can be switched to prasugrel).
- A clear follow-up strategy needs to be established with the patient at discharge to ensure that DAPT de-escalation by switching (if considered) is performed safely.
- Appropriate patients for DAPT de-escalation by switching to clopidogrel may include patients whose bleeding risk might be higher and the ischemic risk appears minimal (ie, noncomplex PCI).
- If a DAPT de-escalation by switching strategy is chosen, current practice emphasizes de-escalating to clopidogrel directly at 75 mg daily (first dose taken when the next prasugrel/ticagrelor dose would have been scheduled, without a loading dose), because this was the approach undertaken in TOPIC and TALOS-AMI,[39,40] and is least prone to dosing errors.
- Selecting patients for DAPT de-escalation by switching can be supported by an evaluation of the risk of bleeding (Fig. 2) vs PCI complexity (Fig. 3).

Choice and duration of dual APT in patients with ACS treated medically without revascularization

Choice of APT

Patients with ACS who are medically managed without revascularization tend to be heterogeneous in their presentation (Fig. 5). The **T**a**r**geted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**g**y to Medicall**y** Manage **A**cute **C**oronary **S**yndromes (TRILOGY-ACS) trial is the only randomized study of an entirely medically-managed ACS population. In this trial, 9326 ACS patients were randomized to prasugrel 10 mg daily (or to prasugrel 5 mg daily for those aged 75 years or older or weighing < 60 kg) in addition to ASA, or to clopidogrel 75 mg daily in addition to ASA. At a median follow-up of 17 months, prasugrel did not significantly reduce the composite of CV death, MI, or stroke, compared with clopidogrel (13.3% vs 13.9%, respectively; HR, 0.96; 95%: CI, 0.86-1.07)[42] (Fig. 5). In the prespecified analysis of multiple recurrent ischemic events, a lower risk of the primary end point was noted for prasugrel in patients younger than 75 years of age (HR, 0.85; 95% CI, 0.72-1.00),[42] but benefits started appearing after the standard 12-month DAPT duration. Although the rates of severe and life-threatening bleeding events were overall similar in both groups, the risk of **T**hrombolysis **I**n **M**yocardial **I**nfarction (TIMI) major or minor bleeding was increased with prasugrel compared with clopidogrel in patients younger than 75 years (1.9% vs 1.3%; HR, 1.54; 95% CI, 1.06-2.23; Fig. 5). Major and minor bleeding events were not different in the overall population

including in patients aged 75 years or older who received 5 mg daily of prasugrel (HR, 2.1% vs 1.7%; HR, 1.28; 95% CI, 0.95-1.73)[42] (Fig. 5). As such, we maintain our recommendations in favour of clopidogrel over prasugrel in this patient population with support from the results of our systematic review (Supplemental Appendix S6). In Canada, prasugrel is not recommended in patients with ACS treated without PCI and in patients 75 years of age or older or in patients with a body weight < 60 kg (because of the increased risk of major bleeding). Prasugrel is contraindicated in patients with a known history of transient ischemic attack or stroke.

With respect to a ticagrelor-based DAPT strategy in this population, a secondary analysis of the **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial including patients who were intended for a noninvasive management showed a consistent reduction in the primary composite of CV death, MI, or stroke with ticagrelor compared with clopidogrel in this key subgroup.[43] As well, participants from PLATO showed a consistent treatment effect with ticagrelor compared with clopidogrel in an analysis focused on the treatment actually received (medical therapy alone or PCI) in non-ST-elevation ACS (NSTEACS).[44] Although the benefit appeared consistent when ticagrelor was used over clopidogrel in non-revascularized ACS patients (Fig. 5), the certainty of evidence of these results is low because of the post hoc, exploratory nature of these subgroup analyses on the basis of a post-randomization variable (Supplemental Appendix S6). This consideration is now reflected as a change in the strength of our current recommendations compared with previous recommendations. Treatment decisions regarding the choice of APT in medically managed ACS patients need to be guided by clinical evidence (Fig. 5).

DAPT duration

The use of extended DAPT beyond 12 months in patients with medically managed ACS was only indirectly assessed in a prespecified subgroup analysis of the **P**revention of Cardiovascular **E**vents in Patients With Prior Heart Attack Using Tica**g**relor T**a**blet**s** Compared to Placebo on a Backgro**u**nd of A**s**pirin−**T**hrombolysis **i**n **M**yocardial **I**nfarction 54 (PEGASUS-TIMI 54) trial. In 21,162 patients with a previous MI within 1-3 years before randomization and with additional high CV risk features, ticagrelor (at pooled doses of 60 mg or 90 mg twice daily), in addition to ASA 81 mg once daily for 33 months, significantly reduced the composite of CV death, MI, or stroke in patients with and without previous PCI (HR, 0.85; 95% CI, 0.75-0.96 vs HR, 0.82; 95% CI, 0.68-0.99, respectively; interaction $P = 0.76$).[45] However, ticagrelor increased TIMI major bleeding regardless of previous PCI (previous PCI, HR, 1.93; 95% CI, 0.99-3.78 ; no previous PCI, HR, 2.65; 95% CI, 1.90-3.68; interaction $P = 0.41$), but no increase in fatal bleeding or intracranial hemorrhage in either subgroup.[45] Because of the lack of a specific RCT on this topic, the panel believes the certainty of evidence for DAPT duration was too low to issue a specific recommendation (Supplemental Appendix S6).

RECOMMENDATION

5. We recommend clopidogrel over prasugrel (in addition to ASA) as part of a dual APT regimen for patients with medically managed ACS **without** coronary revascularization (Strong Recommendation; Moderate-Quality Evidence).
6. We suggest ticagrelor over clopidogrel (in addition to ASA) as part of a dual APT regimen for patients with medically managed ACS **without** coronary revascularization (Weak Recommendation; Low-Quality Evidence).

Values and preferences:

- We value a patient-centric shared-decision making approach weighing the risks of bleeding vs ischemic events in deciding on type and duration of $P2Y_{12}$ inhibitor-based dual APT.

Practical tips:

- These recommendations should apply to medically-managed patients with type 1 MI, because there are insufficient data to determine the optimal therapy for type 2 MI patients (Fig. 5).
- There is no direct evidence from RCTs to guide DAPT after a MI with nonobstructive CAD or spontaneous coronary artery dissection.
- In selected patients with low bleeding risk, high ischemic risk, and previous MI treated without revascularization and severe coronary disease, extending ticagrelor-based DAPT to 3 years can be considered in clinical practice (because of recurrent ischemic events in this population); however, the panel believes that there was insufficient evidence to make a definitive recommendation on this clinical question.

Pretreatment With DAPT ($P2Y_{12}$ Inhibitor) Before Elective or Nonelective Coronary Angiography

The role of pretreatment (loading doses) with a $P2Y_{12}$ inhibitor, and its timing relative to coronary angiography, has been challenged. A theoretical advantage of pretreating all patients with DAPT before coronary angiography is having effective platelet inhibition at the time of PCI, potentially reducing rates of preprocedural and periprocedural ischemic complications, particularly relevant in the ACS setting. The disadvantages are delaying CABG surgery if required, and increasing perioperative bleeding risk in the small percentage of patients who require emergent/urgent CABG surgery.

STEMI

The 2018 CCS APT guidelines recommend DAPT with ASA 81 mg daily and either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily over clopidogrel 75 mg once daily after STEMI.[3] Dedicated studies that evaluated pretreatment in patients with STEMI treated with primary PCI are

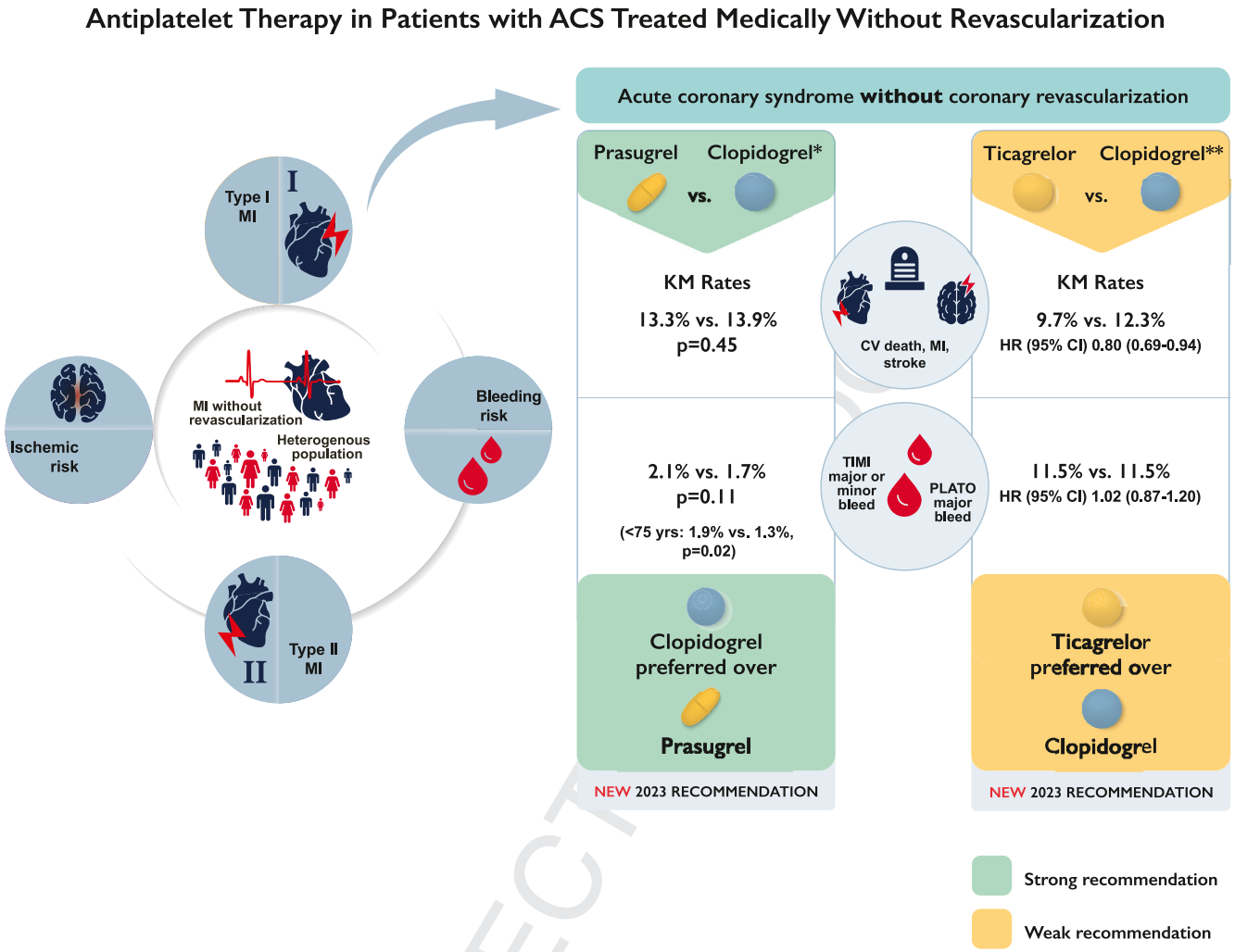

Figure 5. Antiplatelet therapy in patients with acute coronary syndrome (ACS) treated medically without revascularization. In Canada, prasugrel is not recommended in patients with ACS treated without PCI, in patients ≥ 75 years of age or in patients < 60kg. Prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke. * From the **Ta**rgeted Platelet **I**nhibition to **C**larify the **O**ptimal Strate**g**y to Medicall**y** Manage **A**cute **C**oronary **S**yndromes (TRILOGY-ACS) trial in the overall randomized population.[42] ** Subgroup analysis of the **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial, in which the efficacy and safety of randomized $P2Y_{12}$ inhibitor (ticagrelor clopidogrel) treatment and management of non-ST-elevation ACS with or without revascularization was analyzed. Taken from Supplemental Table S2 on the interaction of ticagrelor treatment and revascularization within 10 days for the full study population (ie, all ACS) with Kaplan-Meier (KM) rates 350 days after day 10 postrandomization with a focus on those without revascularization.[44] **Arrow** represents our practical tip of treating those only with type 1 myocardial infarction (MI). CI, confidence interval; HR, hazard ratio; TIMI, **T**hrombolysis **I**n **M**yocardial **I**nfarction. Q36

inconclusive. In the **A**dministration of **T**icagrelor in the Cath **L**ab or in the **A**mbulance for **N**ew ST Elevation Myocardial **I**nfarction to Open the **C**oronary Artery (ATLANTIC) trial Q11 of 1862 STEMI patients, pretreatment with ticagrelor 180 mg in the prehospital setting was associated with similar rates of 30-day MACE and bleeding events compared with delayed administration of ticagrelor in the catheterization laboratory (median time of 31 minutes later).[46] However, the rate of definite stent thrombosis was lower in the pretreatment group (0% vs 0.8%, $P = 0.008$ in the first 24 hours; 0.2% vs 1.2% at 30 days, $P = 0.02$).[46] In the Q12 ATLANTIC-H[24] 24-hour analysis, differences in platelet reactivity, coronary reperfusion rates and ST-segment resolution were in favour of prehospital administration, which translated to a reduction in MI or definite stent thrombosis within 24 hours of PCI.[47] The time from pretreatment to PCI was short in the ATLANTIC trial, and whether its results apply to settings with longer delays remains unknown. In the CIPAMI trial, which compared prehospital vs in- Q13 laboratory clopidogrel loading dose in patients with STEMI, early inhibition was safe but was not associated with a significant reduction in clinical events.[48]

We performed a pooled estimate of both of these studies and there was no difference in MACE at 30 days (RR, 0.76; 95% CI, 0.34-1.70) or major bleeding (RR, 1.10; 95% CI, 0.72-1.67), but we did observe a reduction in definite stent thrombosis (RR, 0.19; 95% CI, 0.04-0.86) with DAPT pretreatment (Supplemental Appendix S7). As shown in

Figure 6, we endorse pretreatment with ASA and $P2Y_{12}$ inhibitors as soon as possible after diagnosis in patients with STEMI, consistent with the 2019 CCS/CAIC guidelines on the acute management of STEMI in the focused update on regionalization and reperfusion.[49]

NSTEACS

Among patients who undergo coronary angiography in the setting of NSTEACS, the benefits of $P2Y_{12}$ inhibitor pretreatment remain unclear. The largest study to address this issue was the **A** **C**omparison of Prasugrel at the Time of Percutaneous **C**oronary Intervention **o**r as Pretreatment **a**t the Time of Diagnosis in Patients With Non-**ST**-Elevation Myocardial Infarction (ACCOAST) trial, a multicentre, randomized blinded study of 4033 patients with NSTEACS randomly allocated to pretreatment with prasugrel or prasugrel administered in the catheterization laboratory if PCI was indicated. At 7 days, there was no difference in MACE (10.0% vs 9.8%, respectively; $P = 0.81$), but there was an increased risk of TIMI major bleeding (2.6% vs 1.4%; $P = 0.006$) with pretreatment.[50] The **D**ownstream Versus **U**pstream Strategy for the Administration of P2Y12 Receptor **B**lockers **I**n Non-ST Elevated Ac**u**te Coronary **S**yndromes With Initial Invasive Indication (DUBIUS) trial was a smaller open-label trial that tested ticagrelor pretreatment vs on-table $P2Y_{12}$ inhibitor immediately before PCI, and showed no difference in a composite of ischemic and bleeding events (3.3% vs 2.9%, respectively; percent absolute risk reduction: −0.46; 95% CI, −2.87 to 1.89) at 30 days.[51] Notably, in both studies, coronary angiography was performed at a median time of 23.3 hours (interquartile range: 4.0-30.0 hours) after *randomization*.[50,51]

In the Canadian context, patients commonly present to community hospitals where access to angiography might be delayed well beyond 24 hours. The **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents in Patients Undergoing **P**ercutaneous **C**oronary **I**ntervention (PCI-CURE) was the only study in which pretreatment with clopidogrel 300 mg followed by 75 mg daily vs placebo before angiography (in addition to baseline ASA) was examined among a large subgroup of 2658 patients with NSTEACS treated with PCI. Patients received the study drug for a median of 6 days before PCI. Those who received clopidogrel pretreatment experienced a lower composite rate of CV death, MI, or urgent target vessel revascularization at 30 days compared with placebo-treated patients (4.5% vs 6.4%; RR, 0.70; 95% CI, 0.50-0.97; $P = 0.03$).[52] More importantly, the reduction in ischemic events was apparent before and after PCI,[52] because clopidogrel reduces ischemic vascular events as early as 24 hours after initiation and continuing out to 12 months.[53]

We performed a meta-analysis of 7 pretreatment RCTs in patients with NSTEACS and no difference was shown in 30-day mortality, MACE, or definite stent thrombosis with $P2Y_{12}$ inhibitor pretreatment compared with a no-pretreatment strategy, with an increase in major bleeding events (RR, 1.48; 95% CI, 1.09-2.02)—driven solely by the potent $P2Y_{12}$ inhibitor pretreatment strategies (Supplemental Appendix S7). However, in patients who experience delays in angiography beyond 24 hours from diagnosis (or if timing is uncertain or unknown at the time pf presentation), as is the case for many patients in Canada, we strongly believe it is prudent to provide pretreatment with $P2Y_{12}$ inhibitor therapy (Fig. 6).

Stable ischemic heart disease

The **A**ntiplatelet Therapy for **R**eduction of **My**ocardial **D**amage during **A**ngioplasty (ARMYDA-5 PRELOAD) trial evaluated the safety and efficacy of high-dose clopidogrel (600 mg) given in the catheterization laboratory, but before PCI, vs routine pretreatment (600 mg) in patients who underwent coronary angiography (61% for stable ischemic heart disease). There was no difference in MACE at 30 days (8.8% without pretreatment vs 10.3% with pretreatment; $P = 0.72$) and no difference in bleeding or vascular complications.[54] A study from the **S**wedish **C**oronary **A**ngiography and **A**ngioplasty **R**egistry (SCAAR) involving nearly 27,000 stable ischemic heart disease patients reported that in-laboratory$P2Y_{12}$ inhibitors administration and pretreatment with $P2Y_{12}$ inhibitors were associated with a similar risk of MACCE at 30 days (2.0% vs 2.7%; adjusted odds ratio [OR], 0.81; 95% CI, 0.57-1.12), but that in-laboratory administration was associated with a reduction in in-hospital bleeding (1.9% vs 2.1%; adjusted OR, 0.70; 95% CI, 0.51-0.96).[55] We performed a meta-analysis of 3 RCTs that evaluated pretreatment with clopidogrel given at a minimum of 2 hours before coronary angiography, and no benefit of this strategy on 30-day MACE was shown (RR, 1.00; 95% CI, 0.69-1.46), including mortality, periprocedural MI, stent thrombosis, and target vessel revascularization. No difference in major bleeding risk was observed (RR, 1.30; 95% CI 0.35-4.84; Supplemental Appendix S7).

As for choice of $P2Y_{12}$ inhibitor for elective PCI in patients with stable ischemic heart disease, the **A**ssessment of **L**oading With the **P**2Y12 Inhibitor Ticagrelor or Clopidogrel to **H**alt Ischemic **E**vents in Patients **U**ndergoing Elective Coronary **S**tenting (ALPHEUS) trial showed that ticagrelor did not reduce periprocedural MI, but increased minor bleeding at 30 days compared with clopidogrel.[56] The Strategies of Loading With Prasugrel Versus Clopidogrel in PCI-Treated Biomarker Negative Angina (SASSICAIA) trial compared a 60 mg prasugrel loading dose with 600 mg of clopidogrel and showed no difference in MACE or bleeding at 30 days.[57]

Overall, the totality of data do not support pretreatment with a $P2Y_{12}$ inhibitor as the standard of care in patients who undergo elective coronary angiography. Clopidogrel should be the standard $P2Y_{12}$ inhibitor to administer in the cardiac catheterization laboratory (600 mg loading dose) for elective PCI (Fig. 6).

RECOMMENDATION
STEMI

7. We suggest routine pretreatment with a $P2Y_{12}$ inhibitor before the procedure in patients who undergo primary PCI for STEMI (Fig. 6; Weak Recommendation; Low-Quality Evidence).

NSTEACS

8. We suggest **against routine** pretreatment with a $P2Y_{12}$ inhibitor before the procedure in patients who undergo coronary angiography for NSTEACS, if the procedure is expected to occur **≤ 24 hours** after admission (Fig. 6; Weak Recommendation; Moderate Quality Evidence).
9. We suggest **routine** pretreatment with a $P2Y_{12}$ inhibitor before the procedure in patients who undergo coronary angiography for NSTEACS, if the procedure is expected to occur **≥ 24 hours** after admission (Fig. 6; Weak Recommendation; Low-Quality Evidence).

Stable Ischemic Heart Disease for Elective PCI

10. We suggest **against routine** pretreatment with a $P2Y_{12}$ inhibitor before the procedure in patients who undergo elective coronary angiography for suspected CAD (Fig. 6; Weak Recommendation; Low-Quality Evidence).

Values and preferences:

- We value nonfatal ischemic and major bleeding events equally in this topic. In such circumstances, consideration of patient preference for nonfatal outcomes is essential, whenever possible.

Practical tips:

- Current practice emphasizes consideration for maintenance of chronic ASA therapy before elective coronary angiography. For elective coronary angiography with possibility of PCI, if a patient is not receiving chronic ASA therapy, a loading dose of ASA is usually administered orally before the procedure.
- For **planned** elective PCI, current practice emphasizes consideration for pretreatment with DAPT at least 2 hours before PCI.
- In patients who undergo elective PCI, clopidogrel (with a loading dose of 600 mg) is the preferred $P2Y_{12}$ inhibitor.
- In patients who undergo PCI for ACS (regardless of need for pretreatment), loading doses are required for $P2Y_{12}$ inhibitors—ticagrelor 180 mg,[33] prasugrel 60 mg,[31] and clopidogrel 600 mg[58-60] (except for STEMI treated with fibrinolysis), with maintenance doses instituted thereafter.
- Clopidogrel is the $P2Y_{12}$ inhibitor that has been the most studied in patients who have undergone elective PCI.
- Pretreatment with $P2Y_{12}$ inhibitors for non-STEMI depends on local practice and needs to be individualized on the basis of access to a catheterization laboratory.
- If the suspicion of a coronary anatomy requiring CABG is high before coronary angiography in patients with ACS, it is reasonable to not pretreat with a $P2Y_{12}$ inhibitor even if the expected delay for the procedure is > 24 hours.
- Routine preloading with clopidogrel-based DAPT (300 mg) at the time of fibrinolysis (the only $P2Y_{12}$ inhibitor of choice) and before coronary angiography is usually performed in patients who undergo reperfusion with a pharmacoinvasive approach for STEMI.

Perioperative and Longer-term APT Management in Patients Who Require CABG Surgery

More than 10% of patients who present with ACS have anatomy that requires revascularization with CABG surgery.[61] This poses a clinical dilemma if patients have been treated with a $P2Y_{12}$ inhibitor because of the risk of perioperative bleeding. Although delaying surgery might mitigate this risk, such a penalty might expose patients to the risk of ischemic events while awaiting surgery (with heightened risks in Canada because of delays to CABG). Adding to this dilemma, a recent meta-analysis that compared more potent antiplatelet strategies with weaker strategies in patients who required CABG suggested an overall survival benefit among patients receiving more potent APT before surgery.[62] Timing is of the essence in discontinuing $P2Y_{12}$ inhibitors before CABG surgery.

Timing of $P2Y_{12}$ inhibitor discontinuation in patients with ACS before CABG: clopidogrel

Pharmacodynamic data show complete offset of $P2Y_{12}$ receptor inhibition by 5 days after clopidogrel cessation.[63] To date, there has only been 1 small randomized study to evaluate timing to surgery among patients treated with clopidogrel.[64] This 3-arm study allocated 38 patients to undergo CABG 5 days after discontinuation, 40 patients to undergo CABG 3 days after discontinuation, and 40 patients to undergo CABG on the day of discontinuation. Although there was a significant increase in intraoperative blood loss and need for blood products among patients who underwent surgery on the day of clopidogrel discontinuation, there were no differences in blood loss in patients with 3 days of clopidogrel discontinuation compared with 5 days. The study had few clinical events, with only 2 patients who required surgical re-exploration surgery (1 in each of the 3-day and 0-day groups) and 1 patient with an MI at 1 month (in the 5-day group).[64] In light of limited evidence (Supplemental Appendix S8), the panel elected to issue a best practice statement rather than a recommendation on this topic. We strongly believe a heart team approach should guide decisions regarding clopidogrel discontinuation before CABG anywhere from 2 to 7 days before surgery (Fig. 7).

BEST PRACTICE STATEMENT

2. Recognizing the limited evidence, the time from clopidogrel discontinuation to CABG surgery should be on the basis of factors such as coronary anatomy, hemodynamic stability, bleeding risk, and surgical team expertise, with ideal timing anywhere between 2 and 7 days for patients who do not require urgent CABG surgery (Fig. 7).

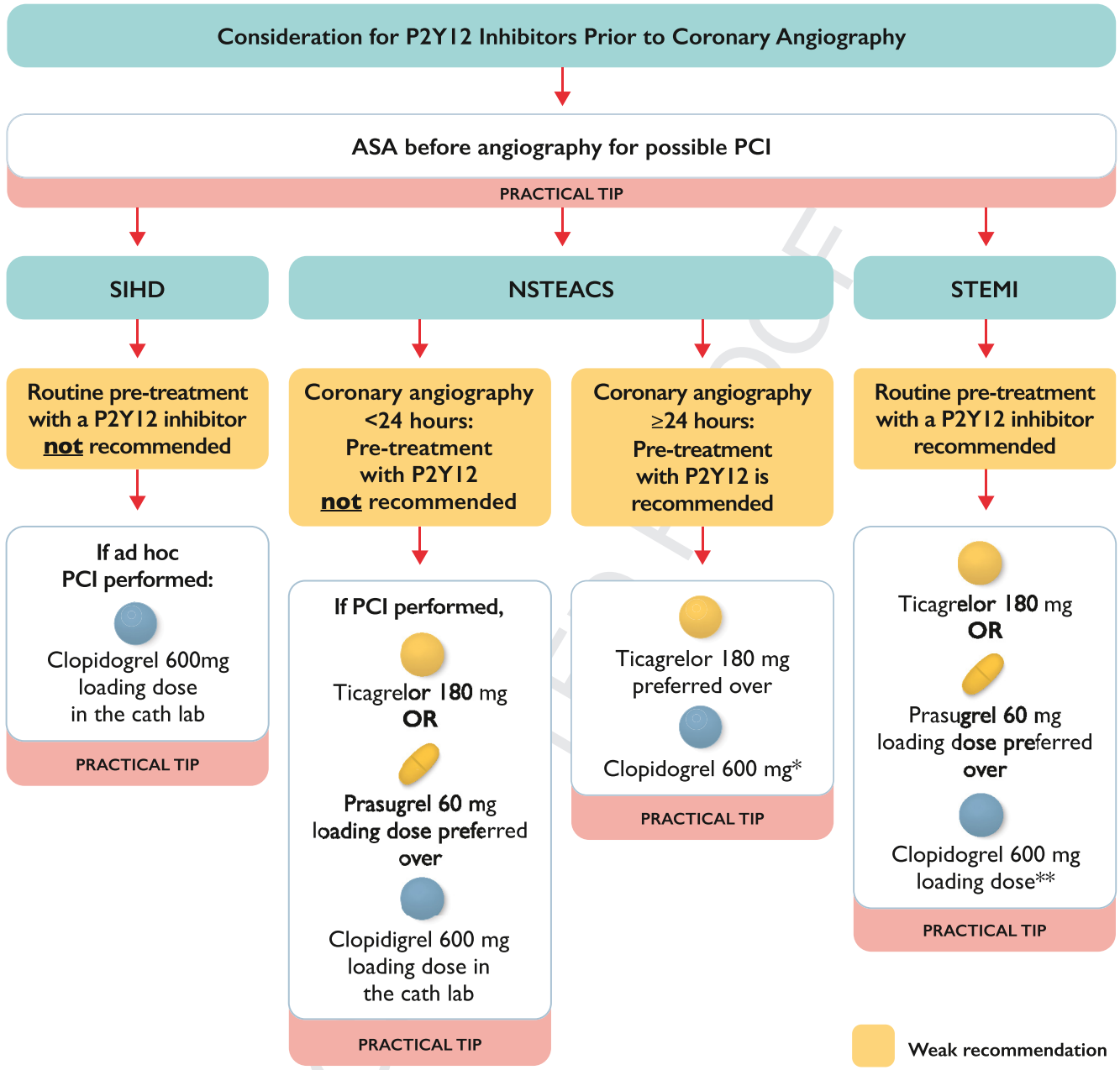

Figure 6. Pretreatment with $P2Y_{12}$ inhibitors in patients before they undergo coronary angiography. ASA, acetylsalicylic acid; cath; catheterization; NSTEACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction. * In the **T**rial to Assess **I**mprovement in **T**herapeutic **O**utcomes by Optimizing Platelet Inhibitio**n** With Prasugrel **T**hrombolysis **i**n **M**yocardial **I**nfarction 38 (TRITON-TIMI 38) prasugrel was only given when PCI was performed for NSTEACS patients (ie, no pre-treatment).[32] ** In STEMI patients receiving fibrinolysis, clopidogrel 300 mg loading dose is the only choice.

Timing of $P2Y_{12}$ inhibitor discontinuation in patients with ACS before CABG: ticagrelor

To date, there has only been 1 randomized study to evaluate the ideal timing from cessation of ticagrelor to CABG among patients with ACS who do not require immediate surgery. The Timing of Coronary Artery Bypass Surgery Among Patients With Acute Coronary Syndromes Initially on Ticagrelor (RAPID CABG) study randomly allocated 143 patients to a strategy of early CABG (2-3 days after cessation of ticagrelor) vs delayed surgery (5-7 days after ticagrelor cessation) in Canada. The early group had a 4.6% rate of severe or massive perioperative bleeding compared with 5.2% in the delayed group (between group difference, −0.6%; 95% CI, −8.3 to 7.1; $P = 0.03$ for noninferiority)[65] (Supplemental Appendix S8).

In addition, several large cohort studies further support the safety of shortening the time from ticagrelor cessation to CABG. In a Swedish cohort of 1266 ticagrelor-treated ACS patients, BARC CABG-related bleeding was similar in

patients who underwent surgery between 3 and 5 days compared with > 5 days (OR, 0.93; 95% CI, 0.53-1.64; $P = 0.80$).[66] Among 2482 ACS patients in a large European registry, no differences in major bleeding were observed in patients with 2-3 days ticagrelor cessation compared with 4-14 days cessation, but discontinuation of ticagrelor within 2 days of CABG was associated with an increased risk of CABG-related bleeding when compared with propensity-matched patients who received ASA alone.[67] Of interest, in an interim analysis of the Rapid and Sustained Reversal of Ticagrelor— Intervention Trial (REVERSE-IT) trial (an ongoing single-arm prospective study), bentracimab was effective in immediately reversing the antiplatelet effect of ticagrelor.[68]

We provide guidance for ticagrelor discontinuation in ACS before nonurgent/emergent CABG surgery in Figure 7. Recommendations were solely on the basis of the RAPID CABG trial.

RECOMMENDATION

11. We suggest holding ticagrelor for 2-3 days rather than 5-7 days before CABG surgery (Fig. 7; Weak Recommendation; Low-Quality Evidence).

DAPT vs SAPT after CABG

The use of ASA-based SAPT at a dose of 75-162 mg daily after CABG is supported by early evidence showing a reduction in bypass graft occlusion[67] and is recommended indefinitely for secondary prevention.[1] The role of DAPT post-CABG has been addressed in 2 recent study-level network meta-analyses,[69,70] and in a later patient-level meta-analysis focused on ticagrelor.[71] In the meta-analysis by Solo et al. involving 20 RCTs and 4803 patients, DAPT using either ticagrelor or clopidogrel was associated with a reduction in saphenous vein graft failure compared with ASA-based SAPT (ticagrelor: OR, 0.50; 95% CI, 0.31-0.79, number needed to treat = 10; clopidogrel: OR, 0.60; 95% CI, 0.42-0.86, number needed to treat = 19).[70] Similarly, Gupta et al. reported in a review of 43 RCTs (15,511 patients) that DAPT using either ticagrelor or clopidogrel was associated with reduced saphenous vein graft stenosis compared with ASA monotherapy (ticagrelor: OR, 0.40; 95% CI, 0.21-0.74; clopidogrel: OR, 0.64; 95% CI, 0.42-0.98).[69] In the meta-analysis by Sandner et al., including 4 ticagrelor RCTs, DAPT was associated with a reduction in saphenous vein graft failure compared with ASA monotherapy (OR, 0.51; 95% CI, 0.35-0.74; $P < 0.001$).[71] The effect of DAPT (vs SAPT) on graft patency post-CABG was consistent in patients with or without ACS. However, to date, there is no compelling evidence that postoperative DAPT improves MACE or mortality outcomes compared with ASA-based SAPT.

We performed a study-level meta-analyses of 10 trials involving 3947 patients and a consistent reduction in graft occlusion per patient (RR, 0.73; 95% CI, 0.58-0.92) and per graft (RR, 0.62; 95% CI, 0.50-0.78) was shown in favour of DAPT vs SAPT. The risk of major bleeding was similar with both strategies (RR, 1.00; 95% CI, 0.68-1.47; Supplemental Appendix S8). For off-pump surgery (without cardiopulmonary bypass), hemostatic pathways were less affected compared with on-pump surgery, inferring a potentially greater benefit of DAPT. In our meta-analysis, DAPT significantly reduced MACE after off-pump surgery (RR, 0.42; 95% CI, 0.21-0.85), but not after on-pump surgery (RR, 0.98; 95% CI, 0.73-1.31) (P for interaction = 0.03; Supplemental Appendix S8).

RECOMMENDATION

12. We suggest the use of dual APT over SAPT after CABG surgery with or without ACS (Fig. 8; Weak Recommendation; Moderate-Quality Evidence).

Practical tips:

- In patients with a concomitant indication for OAC, either SAPT or no APT therapy could be used after CABG.
- It is generally advised to continue ASA until surgery (Fig. 7), to resume ASA early postoperatively (Fig. 8), and to start the second antiplatelet agent when the bleeding risk is acceptable in the postoperative period according to the surgical team (Fig. 8).
- In patients at HBR, abbreviated DAPT might be preferred to SAPT after CABG for ACS, and SAPT could be considered for elective CABG.
- Because DAPT has been shown to reduce MACE after off-pump CABG surgery, but not after on-pump CABG surgery, this weak recommendation to use DAPT over SAPT may be considered more strongly in patients who had off-pump surgery.
- In practice, DAPT duration after CABG for ACS is generally of 1 year, but this duration may be modulated according individual patient ischemic and bleeding risk.

Specific type of $P2Y_{12}$ inhibitor as part of DAPT in ACS after CABG

In the PLATO and the **T**rial to Assess **I**mprovement in **T**herapeutic **O**utcomes by Optimizing Platelet Inhibitio**n** With Prasugrel **T**hrombolysis **i**n **M**yocardial **I**nfarction 38 (TRITON-TIMI 38) trial, only 10.2% (n = 1899) and 2.5% (n = 346) of participants were treated with CABG, respectively. In PLATO, CABG, total mortality was reduced among patients treated with ticagrelor-based DAPT compared with clopidogrel-based DAPT (4.7% vs 9.7%; HR, 0.49; 95% CI, 0.32-0.77; $P < 0.01$).[61] Similarly, in the subgroup of patients who underwent CABG in the TRITON-TIMI 38 study, total mortality with prasugrel-based DAPT was reduced compared with clopidogrel-based DAPT (2.31% vs 8.76%; adjusted OR, 0.26; 95% CI, 0.08-0.85; $P = 0.025$).[72]

We pooled the results of these 2 subgroup analyses and a large reduction in mortality with potent $P2Y_{12}$-inhibitor DAPT was shown compared with clopidogrel-based DAPT

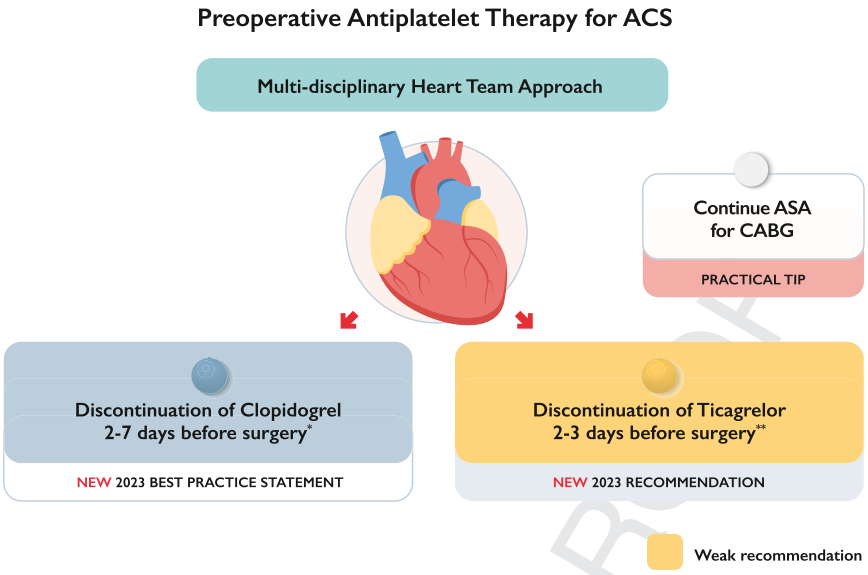

Figure 7. Preoperative antiplatelet strategies in patients scheduled to undergo coronary artery bypass grafting (CABG) surgery. ACS, acute coronary syndrome; ASA, acetylsalicylic acid. * Decision should be on the basis of factors such as coronary anatomy, hemodynamic stability, bleeding risk, and surgical team expertise with value placed on a heart team approach. ** Recommendation solely on the basis of the Canadian study, Timing of Coronary Artery Bypass Surgery Among Patients With Acute Coronary Syndromes Initially on Ticagrelor (RAPID CABG).[65]

(RR, 0.45; 95% CI, 0.28-0.72), with low heterogeneity (I^2 = 11%) between trials (Supplemental Appendix S8). Notably, time to surgery was often delayed and there was poor study drug compliance after CABG in these studies. In PLATO, > 30% of patients had CABG more than 7 days after study drug administration and most patients in TRITON-TIMI 38 had CABG more than 90 days after presentation.[61,72] In these studies, CABG decision was a postrandomization variable, therefore these subgroup analyses should be viewed as potentially biased.

RECOMMENDATION

13. We suggest using dual APT with ticagrelor/prasugrel rather than clopidogrel-based dual APT in patients with a recent ACS who undergo CABG surgery (Fig. 8; Weak Recommendation; Moderate-Quality Evidence).

Values and preferences:

- This recommendation puts a high value on the mortality benefits with intensified $P2Y_{12}$ inhibitors observed in CABG substudies of the PLATO and TRITON-TIMI 38 randomized trials, despite that these were mostly PCI trials (especially TRITON-TIMI 38, in which only 1% underwent CABG) in which CABG was a post-randomization variable.

Practical tip:

- When selecting which potent $P2Y_{12}$ inhibitor to use as part of DAPT after CABG in patients with ACS, ticagrelor might be preferred over prasugrel because of the larger amount of evidence supporting this agent.

Use of APT in Patients With AF Requiring OAC After PCI or Medically Managed ACS

Up to 10% of patients who undergo PCI and 21% of patients who present with ACS require long-term anticoagulation OAC for AF or other indications.[73,74] In patients aged 65 years or older admitted for MI, up to 26.9% have concomitant AF.[73] In the past, these patients would be treated with triple therapy, in a combination of OAC with DAPT. Large-scale trials have compared the efficacy and safety of triple therapy (OAC with DAPT) vs dual pathway (mostly direct OAC with $P2Y_{12}$ inhibitor) in this population, redefining the standard for antithrombotic therapy.[75] In appropriate patients with AF and an indication for OAC who undergo PCI, the 2018 guidelines recommended the dual pathway strategy after PCI, after a course of triple therapy of 1 day up to 6 months (duration depending on indication for PCI and patients' characteristics).[3]

Since then, 2 major RCTs have been published: the AUGUSTUS and the **E**doxaba**n** **T**reatment Versus Vitamin K Antagonist in Patients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (ENTRUST-AF-PCI) trials.[76,77] AUGUSTUS was the only trial with a double-blind, randomized 2 × 2 factorial design comparing ASA 81 mg daily and placebo, and warfarin vs a direct OAC (apixaban). All patients received a $P2Y_{12}$ receptor antagonist (most commonly clopidogrel). This design allows for the treatment effect of both interventions on outcomes to be evaluated separately—with inferences made on 4 combinations. This 6-month trial included ACS patients (treated with or without PCI), and patients who underwent elective PCI. Major or clinically relevant nonmajor bleeding events were reduced in patients who receiving apixaban compared with a vitamin K antagonist (10.5% vs 14.7%, respectively; HR, 0.69; 95% CI, 0.58-0.81), and ASA increased this risk compared with placebo (16.1% vs 9.0%, respectively; HR,

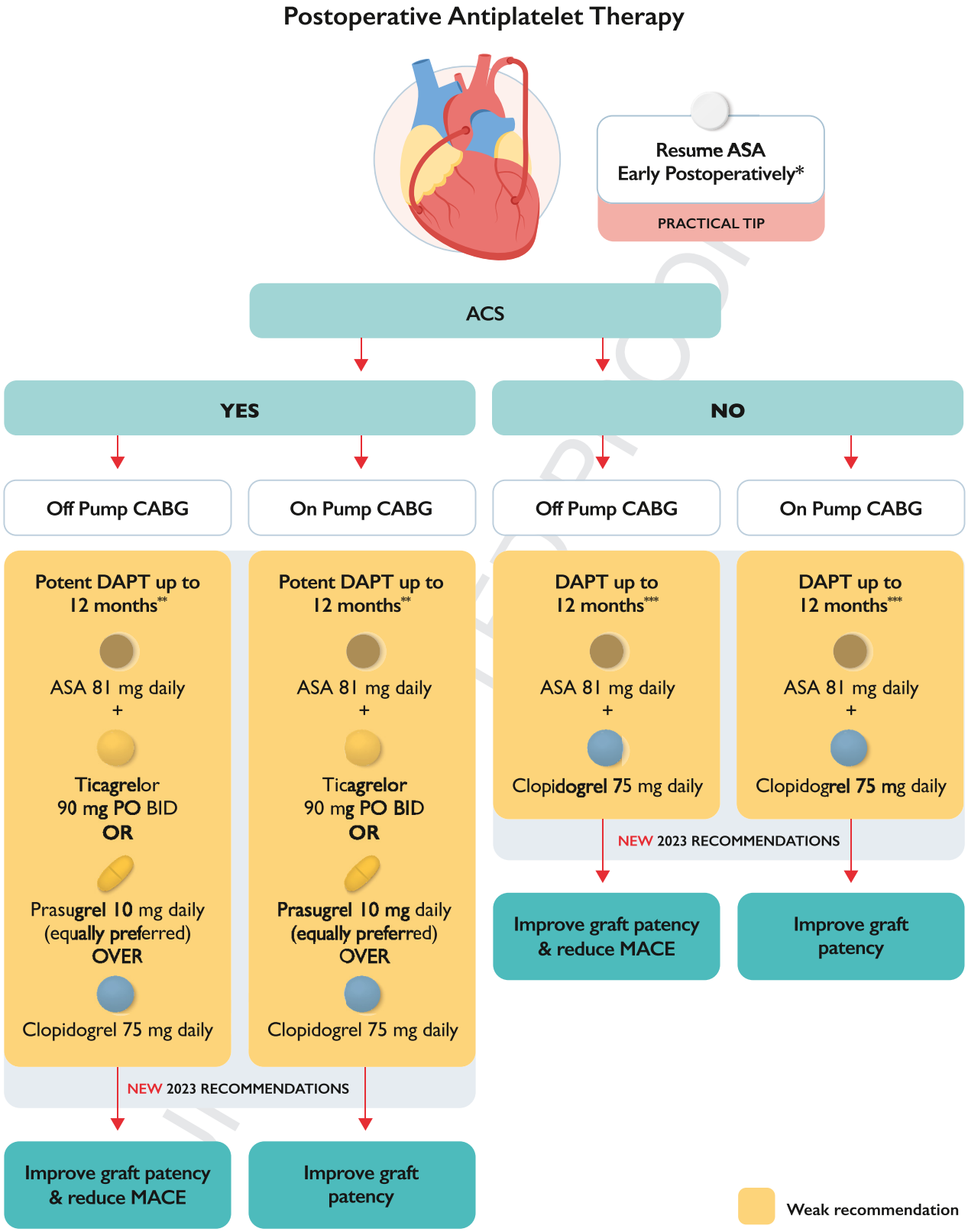

Figure 8. Postoperative antiplatelet strategies in patients who have undergone coronary artery bypass grafting (CABG) surgery. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice daily; DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events; PO, orally. * When deemed clinically safe for bleeding risk as per clinician. ** Ticagrelor may be preferred over prasugrel—both preferred over clopidogrel. *** Predominant evidence for clopidogrel-based DAPT.

1.89; 95% CI, 1.59-2.24). The composite of death or hospitalization was reduced with apixaban compared with vitamin K antagonists (23.5% vs 27.4%, respectively; HR, 0.83; 95% CI, 0.74-0.93) whereas there was no significant difference for ASA and placebo. The combination of $P2Y_{12}$ inhibitor and apixaban (without ASA) had the lowest bleeding risk without compromising ischemic events.[76] In a landmark analysis, the additional use of ASA significantly reduced severe ischemic events from randomization to 30 days (by approximately 0.9% in absolute terms) but not thereafter, and significantly increased the risk of severe bleeding before and after 30 days (by 1.0% and 1.25%, respectively).[78] In the ENTRUST-AF-PCI trial, patients with AF treated with OAC and who underwent successful PCI were randomized to triple therapy with warfarin, or to dual pathway therapy with a $P2Y_{12}$ inhibitor and edoxaban. The dual pathway strategy was noninferior to the triple therapy strategy with regard to the primary composite end point of major bleeding or clinically relevant nonmajor bleeding, without a significant increase in ischemic events.[77]

We performed an updated systematic review and meta-analysis, including 6 trials (11,156 patients), and showed a significant reduction in major bleeding with the dual pathway strategy compared with triple therapy (RR, 0.62; 95% CI, 0.52-0.73; $I^2 = 0\%$). For death and MACE, no significant differences were observed. Although these trials were not individually powered for ischemic events, these pooled results are reassuringly safe. For every 1000 patients treated, dual pathway would be associated with 23 fewer major bleeds (95% CI, from 29 to 16 fewer), 4 more stent thrombosis events (95% CI, from 0 to 9 more), and 8 more MACE (95% CI, from 2 to 19 more; Supplemental Appendix S9). Noteworthy, in the studies included in our meta-analysis, patients received ASA as part of their antithrombotic regimen before randomization, with ASA then being discontinued in participants randomized to the dual pathway strategy. The most appropriate duration of ASA as part of a dual pathway strategy has not been elucidated. However, the allowed maximal interval between PCI (or ACS in the AUGUSTUS trial) and randomization varied between from 3 to 14 days per protocol, with observed mean times to ASA discontinuation ranging from 1.6 to 6.6 days. Furthermore, clopidogrel was the $P2Y_{12}$ inhibitor used in 88%-95% of patients enrolled in these trials. The evidence for combining ticagrelor or prasugrel with OAC therefore remains quite limited.

Recently, there have been 2 RCTs to investigate the most appropriate antithrombotic therapy strategy in patients with AF and concomitant stable CAD who requiring long-term OAC. The **O**ptimizing **A**ntithrombotic **C**are in Patients With **A**tria**l** Fibrillati**on** and Coronary St**e**nt (OAC-ALONE) trial was designed to evaluate the safety and efficacy of OAC monotherapy (75.2% warfarin; 24.8% dual OAC) compared with OAC with SAPT beyond 1 year after PCI. The study was prematurely terminated because of slow participant enrollment (696 participants in 38 months). The primary composite end point of all-cause death, MI, systemic embolism, or stroke occurred in 15.7% of patients with OAC alone, compared with 13.6% in the combined OAC and SAPT group (HR, 1.16; 95% CI, 0.79-1.72; P for noninferiority = 0.20, P = for superiority = 0.45).[79] In the more recent **A**trial **F**ibrillation and **I**schemic Events With **R**ivaroxaban in Pati**e**nts With Stable Coronary Artery Disease (AFIRE) trial rivaroxaban monotherapy was evaluated (10 mg or 15 mg once daily, according to the patient's creatinine clearance) compared with rivaroxaban and SAPT for safety and efficacy in 2215 Japanese patients with AF and stable CAD (history of PCI or CABG at $>$ 1 year before enrollment, or coronary stenosis $\geq$ 50% not requiring revascularization). This study was also terminated early, because of the excess risk of mortality in the rivaroxaban with SAPT group compared with the rivaroxaban monotherapy group (HR, 0.55; 95% CI, 0.38-0.81, favouring rivaroxaban monotherapy). The primary efficacy end point (a composite of stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause) was noninferior and superior to OAC with SAPT (HR, 0.72; 95% CI, 0.55-0.95; $P <$ 0.001 for noninferiority, $P = 0.02$ for superiority) with OAC monotherapy. OAC monotherapy also significantly reduced the risk of major bleeding (HR, 0.59; 95% CI, 0.39-0.89; $P = 0.01$ for superiority).[80]

We performed a pooled analysis of both studies and no difference in MACE (RR 0.91; 95% CI, 0.58-1.41) with OAC monotherapy, but a significant reduction in major bleeding in favour of OAC monotherapy (RR, 0.66; 95% CI, 0.49-0.91) was shown (Supplemental Appendix S9).

Figure 9 provides a summary of our recommendations regarding the antithrombotic management of AF patients who undergo PCI, or with an ACS who do not undergo revascularization. The 2020 CCS/Canadian Heart Rhythm Society comprehensive guidelines for the management of AF issued strong recommendations for the use of a dual pathway strategy (OAC and $P2Y_{12}$ inhibitor, without ASA) in patients aged 65 years or older or with a $CHADS_2$ (**C**ongestive Heart Failure, **H**ypertension, **A**ge $\geq$ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack [doubled]) score who underwent PCI without ACS or high-risk features, or with medically managed type 1 MI, but not in patients who underwent PCI for ACS or elective PCI with high-risk features.[81] In our new recommendations, the indications for dual pathway strategy were thus expanded to the latter subgroup.

RECOMMENDATION

14. We suggest dual pathway therapy ($P2Y_{12}$ inhibitor with oral anticoagulant and omit ASA from 1-30 days) rather than triple therapy (dual APT with oral anticoagulant) in most patients with AF with an indication for OAC, and who have undergone PCI or who are medically managed for an ACS (Fig. 9; Weak Recommendation; Moderate-Quality Evidence).

Values and preferences:

- We place greater emphasis on the large reduction in bleeding complications vs the small increase in stent thrombosis with a dual pathway strategy. However, a clinically important difference in death or MI cannot be ruled out on the basis of current data. It is therefore paramount to balance bleeding and thrombotic risks when tailoring treatment for individual patients, and to incorporate patients' and physicians' values regarding the competing risks.

RECOMMENDATION

15. We suggest OAC monotherapy rather than dual-pathway therapy (oral anticoagulant with APT) in patients with CAD and concomitant AF with an indication for long-term OAC, who have not had a coronary revascularization procedure or ACS in the past 12 months (Fig. 9; Weak Recommendation; Very Low-Quality Evidence).

Values and preferences:

- We place a high emphasis on the internal validity of the AFIRE RCT that evaluated this strategy, and a lower emphasis on the external generalizability of its finding, which might potentially be affected because it was conducted exclusively in Japanese individuals, using the rivaroxaban dosing from the Japanese product monograph (15 mg once daily with creatinine clearance > 50 ml/min; 10 mg once daily with creatinine clearance 15-49 ml/min, respectively).

Practical tips:

- When a $P2Y_{12}$ inhibitor is to be combined with OAC, clopidogrel may be used rather than ticagrelor or prasugrel because of its lower risk of bleeding and the limited data on combining ticagrelor or prasugrel with OAC.
- For patients treated with a dual pathway strategy (OAC and SAPT), current practice emphasizes the use of at least 1 dose of ASA at the time of PCI or at admission for ACS.
- When considering the appropriate ASA duration for an individual patient, it is important to consider that ASA duration before switching to dual pathway was on average 1.6-6.6 days after PCI in the large-scale trials. *Landmark analyses showed that ASA use beyond 30 days increased bleeding risk with no apparent benefit.*[33]
- When OAC is combined with a $P2Y_{12}$ inhibitor, current practice emphasizes consideration of a dual OAC over a vitamin K antagonist because of the lower bleeding rates shown in randomized trials.
- Patients at high ischemic risk and who underwent complex PCI (Fig. 3) were under-represented in the randomized trials that compared triple therapy vs dual pathway therapy. Hence, although a dual pathway strategy (OAC and SAPT) might be the standard approach, for selected patients at higher risk for ischemic complications, a duration of triple therapy of up to 1 month (and beyond) might be a reasonable alternative.
- For patients with a high ischemic/thrombotic risk, a history of stent thrombosis or a complex PCI (Fig. 3), clinical judgement should be used in the application of the recommendation to use OAC monotherapy alone after 1 year.
- For patients with AF and PCI or ACS requiring medical management, bleeding avoidance strategies should be considered (Table 1).
- For all patients with AF, the indication for OAC and their dosing of OAC during and after completion of dual pathway treatment should follow the 2020 CCS/Canadian Heart Rhythm Society comprehensive guidelines for the management of AF.[81]

Current Controversies With APT and Future Considerations

APT in the treatment of ASCVD will unequivocally continue to evolve over time. Although we are cognizant of potential sex and gender disparities, we could not issue specific recommendations because of low female representation and inconsistent reporting of many sex-specific analyses. It is incumbent upon the community of trialists to ensure future studies are powered to address the safety and efficacy of APT agents in both sexes and/or gender. With the results of the **C**ardiovascular **O**utcom**e**s for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial and of new antithrombotic agents such as factor XIa inhibitors that are currently being studied, APT might no longer be considered the optimal antithrombotic pathway in the future. In the COMPASS trial, rivaroxaban at a dose of 2.5 mg twice daily in addition to ASA increased major bleeding, but reduced the composite of CV death, stroke, or MI compared with ASA alone in stable patients with ASCVD[82] and those with previous PCI.[83] However, the role of the COMPASS strategy vs DAPT immediately after PCI needs to be addressed. When the decision is made to discontinue DAPT after PCI, the optimal choice of SAPT remains uncertain. In those without $P2Y_{12}$ inhibitor pretreatment (particularly in ACS), the role of short-acting intravenous antiplatelet agents such as cangrelor might be of value to mitigate periprocedural events.[84,85] Finally, pathways targeted on the basis of atherothrombotic disease state and pathophysiology might lead toward therapies individualized tailored for patients.

Ethics Statement

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Patient Consent

The authors confirm that patient consent is not applicable to this article because this is a guidelines document.

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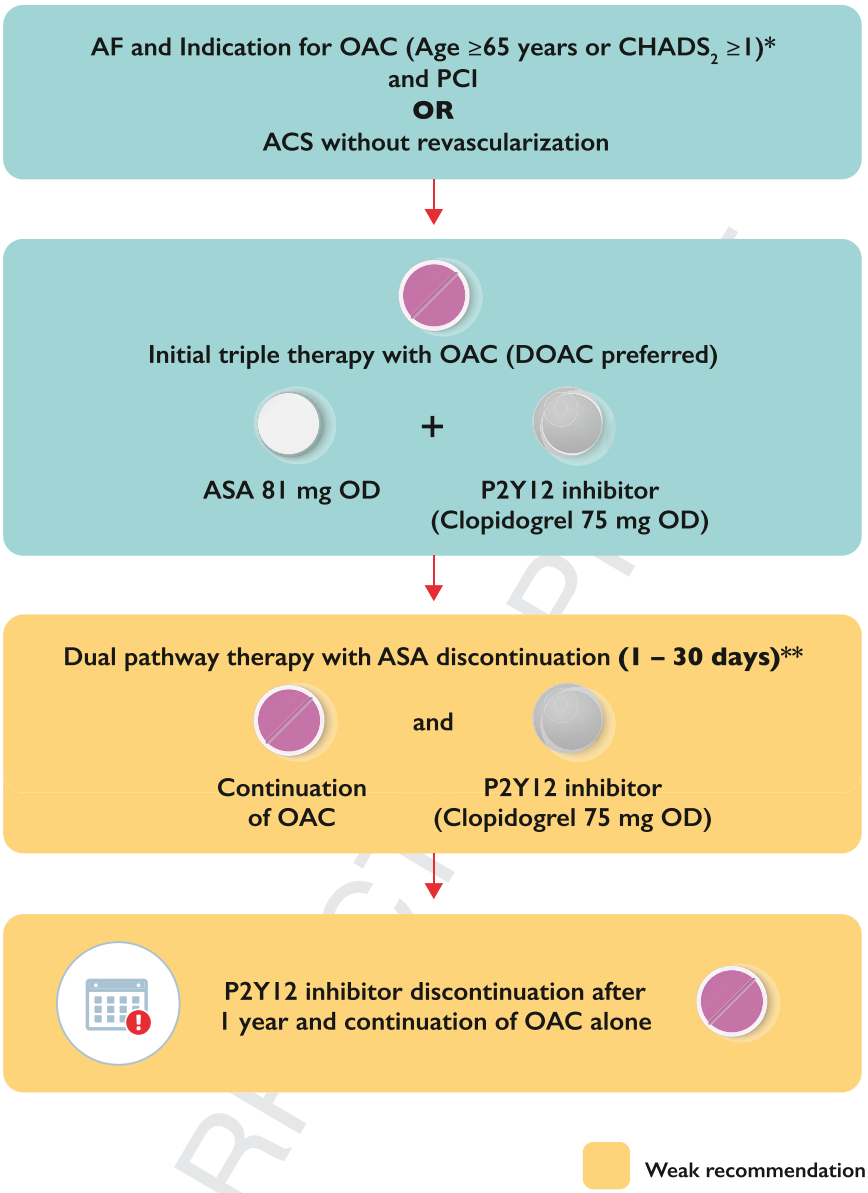

Figure 9. Antiplatelet strategies in patients with concomitant atrial fibrillation (AF) and percutaneous coronary intervention (PCI) and/or acute coronary syndrome (ACS). ASA, acetylsalicylic acid; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack [doubled]; DOAC, dual oral anticoagulation; OAC, oral anticoagulation; OD, once daily. * Patients who do not require OAC for their AF as per the Canadian guidelines for the management of AF would receive dual antiplatelet therapy.[81] OAC regimens evaluated in this context include apixaban 5 mg twice daily (BID; 2.5 mg BID if patients meet 2 or more of the following dosage reduction criteria: older than 80 years of age, < 60 kg in weight, or creatinine > 133 μM/L), dabigatran 110 mg, or 150 mg BID, edoxaban 60 mg daily (30 mg daily if patients with any of the following characteristics: moderate or severe renal impairment [creatinine clearance 15-50 mL/min], < 60 kg in weight, or concurrent use of specific potent P-glycoprotein inhibitors), rivaroxaban 15 mg daily (10 mg in patients with renal dysfunction), and warfarin. If warfarin is to be used, recommended international normalized ratio target is 2.0-2.5. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA-naive). ** ASA duration before switching to dual pathway was an average of 1.6-6.6 days after PCI in the large-scale trials.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2023.10.013.