

A practical approach to prescribing antiplatelet therapy in patients with acute coronary syndromes

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After an acute coronary syndrome, as many as 1 in 5 patients will have a second ischemic event within 5 years.^{1,2} Residual risk is related to several factors that may be mitigated by pharmacologic and nonpharmacologic interventions.² Antiplatelet therapy is a cornerstone in the management of acute coronary syndrome.^{1,3} Acetylsalicylic acid (ASA) — a cyclooxygenase-1 inhibitor — was introduced as an effective treatment for myocardial infarction almost 5 decades ago and remains the most widely used antiplatelet therapy.^{4,5} Although ASA is effective in reducing mortality rates,⁶ combining ASA with a second antiplatelet agent, a P2Y₁₂ receptor inhibitor (known as dual antiplatelet therapy [DAPT]) provides additional benefit and is now the preferred initial strategy for acute coronary syndromes over ASA alone.⁷

We review emerging evidence regarding the use of antiplatelet therapy in acute coronary syndromes, as well as updates to the Canadian and European Society of Cardiology guidelines that highlight adjustments in the choice and duration of antiplatelet therapy, in addition to ASA (Box 1). We particularly focus on strategies to reduce bleeding risk after percutaneous coronary intervention (PCI).^{3,8}

What are the options for oral antiplatelet therapy?

Clopidogrel is a second-generation thienopyridine that has a better safety profile than ticlopidine, a first-generation thienopyridine.⁹ Clopidogrel reduces ischemic events by almost 20% when added to ASA for patients presenting with acute coronary syndromes,

Box 1: Literature search

We conducted a targeted, nonsystematic MEDLINE search from its inception until August 2021 using the terms “antiplatelet,” “clopidogrel,” “prasugrel,” “ticagrelor,” “acute coronary syndrome,” “myocardial infarction” or “bleeding.” We limited the search to articles in English and focused on randomized clinical trials or systematic reviews, although we did not apply any restriction on study type.

Key points

- Prasugrel and ticagrelor are P2Y₁₂ inhibitors that are more effective than clopidogrel at preventing ischemic events in patients presenting with acute coronary syndrome, although they cause more bleeding.
- Dual antiplatelet therapy (acetylsalicylic acid and a P2Y₁₂ inhibitor) is indicated for patients with acute coronary syndrome, usually for at least 1 year.
- The type and duration of dual antiplatelet therapy is determined by a patient’s risk of recurrent ischemia and major bleeding.
- Most patients with atrial fibrillation and acute coronary syndrome should be treated with a direct oral anticoagulant and clopidogrel for 12 months; acetylsalicylic acid should be added for up to 1 month after percutaneous coronary intervention.

with or without ST-segment elevation.^{7,10,11} It irreversibly antagonizes the receptor for platelet adenosine diphosphate (ADP)-P2Y₁₂. The use of clopidogrel may be associated with gastrointestinal symptoms and skin rashes.

Prasugrel and ticagrelor are more potent P2Y₁₂ inhibitors than clopidogrel. Prasugrel is a third-generation thienopyridine that exerts its antiplatelet properties by irreversibly antagonizing the ADP-P₂Y₁₂ receptor; similar to clopidogrel, it requires hepatic conversion to its active metabolites. Ticagrelor is part of the cyclopentyltriazolopyrimidine family and does not require hepatic conversion to its active metabolites before reversibly inhibiting the ADP-P₂Y₁₂ receptor. Ticagrelor may cause shortness of breath or increased levels of uric acid, which leads to gout.

Both prasugrel and ticagrelor provide faster and more consistent inhibition of platelet aggregation and are associated with a further 15%–20% relative risk reduction of ischemic events compared with clopidogrel.^{12,13} Ticagrelor also reduces cardiovascular and all-cause mortality rates.¹² Although ticagrelor and prasugrel are associated with greater bleeding risk than clopidogrel, both are recommended over clopidogrel in patients with low bleeding risk. Recently, the

ISAR-REACT-5 (Intracoronary Stenting and Antithrombotic Regimen 5) study reported fewer ischemic events associated with prasugrel, with no difference in the incidence of major bleeding, when compared with ticagrelor.¹⁴ However, a number of uncertainties preclude definitively recommending one drug over the other.¹⁵ Prasugrel is not recommended in patients older than 75 years of age and in those with a body weight less than 60 kg because of an increased risk of fatal and intracranial bleeding.¹³ A recent meta-analysis summarized the relative differences in ischemic and bleeding risks among the 3 different P2Y₁₂ inhibitors (Table 1).¹⁶

Clopidogrel is currently recommended for patients with acute coronary syndromes who are at high bleeding risk or those who cannot take a potent P2Y₁₂ inhibitor because of adverse effects or cost.^{3,8} Guidelines recommend treatment with clopidogrel as the initial antiplatelet drug for patients with ST-segment elevation myocardial infarction who are treated with fibrinolytic therapy. However, results of the TREAT (Ticagrelor in Patients With ST-Elevation Myocardial Infarction Treated With Pharmacological Thrombolysis) study indicated that switching from clopidogrel to ticagrelor within 24 hours did not lead to an increase in major bleeding in the first 30 days postlysis, compared with continuing clopidogrel.¹⁷

Current guidelines recommend the use of DAPT after an acute coronary syndrome, irrespective of the revascularization strategy, including for medically managed patients and those who undergo coronary artery bypass grafts.^{3,18} A subgroup analysis of 7985 patients from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial who did not undergo revascularization after randomization showed that adding clopidogrel to ASA reduced ischemic events by an absolute 1.9% after 12 months of follow-up, compared with placebo and ASA.⁷ Ticagrelor provides consistent benefit over clopidogrel in reducing ischemic events, irrespective of revascularization strategy.^{12,19}

For patients with non-ST segment elevation acute coronary syndrome, (NSTACS) the timing of coronary angiography is a factor in the choice of antiplatelet treatment. For patients scheduled for coronary angiography within 24 hours of presentation, there is debate regarding whether patients should be preloaded with a potent P2Y₁₂

inhibitor. Preloading with prasugrel or ticagrelor did not reduce ischemic events in patients with NSTACS scheduled for early coronary angiography.^{20,21} Thus, the European guidelines discourage routine preloading of P2Y₁₂ inhibitors in patients with NSTACS who are planned for an early coronary angiogram and suggest starting DAPT once the need for angioplasty or stents is confirmed.³ This does not apply for patients presenting with ST-segment elevation myocardial infarction in whom preloading with DAPT is recommended. Preloading should also be considered in non-PCI centres because coronary angiography may be delayed. Further, given that, in Canada, most patients with NSTACS do not routinely undergo angiography within the first 24 hours of presentation, preloading with DAPT in patients with moderate-to-high risk of ischemia is reasonable.⁸ If there is suspicion of left main disease or possible aortic dissection, DAPT should not be given.³

How long should dual antiplatelet therapy be continued?

Current guidelines recommend DAPT for 1 year after an acute coronary syndrome, particularly in patients with heightened ischemic risk (Box 2 and Figure 1).^{3,8} However, patients at high risk of bleeding may be considered for shorter treatment duration. Two large randomized controlled trials evaluated extending the duration of DAPT beyond 12 months, using ticagrelor in patients with a history of myocardial infarction in the PEGASUS-TIMI 54 (Prevention with Ticagrelor of Secondary Thrombotic Events in High-Risk Patients with Prior Acute Coronary Syndrome – Thrombolysis In Myocardial Infarction 54) trial, and using clopidogrel or prasugrel in stable patients and patients with acute coronary syndromes who received a PCI in the Dual Antiplatelet Therapy trial.^{22,23} Both trials reported significant relative reductions in ischemic events of 15%–30%, but these benefits were offset by a significant increase in major bleeding.^{22,23} A recent meta-analysis confirmed these findings; DAPT extension beyond 12 months was associated with a 32% reduction in myocardial infarction and a 63% increase in major bleeding among patients who received a PCI.²⁴

Table 1: Relative difference in ischemic and bleeding risks* among different P2Y₁₂ inhibitors¹⁶

Drugs compared	No. of studies (no. of patients)	Ischemic risk	Bleeding risk
Ticagrelor v. clopidogrel	6 RCTs (21 828)†	Ticagrelor associated with 18% reduction in cardiovascular mortality, 28% reduction in stent thrombosis and no difference in MI	Ticagrelor associated with 27% increase in major bleeding
Prasugrel v. clopidogrel	4 RCTs (25 740)	Prasugrel associated with 10% reduction in cardiovascular mortality (95% CI 0.80–1.01), 50% reduction in stent thrombosis and 19% reduction in MI	Prasugrel associated with 26% increase in major bleeding
Prasugrel v. ticagrelor	2 RCTs (5248)	Prasugrel associated with 32% reduction in stent thrombosis and no difference in cardiovascular mortality or MI	No difference in major bleeding

Note: CI = confidence interval, RCT = randomized controlled trial, MI = myocardial infarction.

*The reported ischemic and bleeding risks were all statistically significant except for the reduction of cardiovascular mortality of prasugrel compared with clopidogrel.

†PLATO trial provided 85% of patients to total number.

Box 2: Features of patients at high risk of ischemic events

- Previous stent thrombosis on adequate antiplatelet therapy
- Stenting of the last remaining patent coronary artery
- Diffuse multivessel disease, especially in patients with diabetes
- Chronic kidney disease (i.e., creatinine clearance < 60 mL/min)
- At least 3 stents implanted
- At least 3 lesions treated
- Bifurcation with 2 stents implanted
- Total stented length greater than 60 mm
- Treatment of a chronic total occlusion
- History of ST-segment elevation myocardial infarction

Improvements in stent design and increased recognition of the importance of preventing bleeding led researchers to evaluate shorter durations of DAPT; the findings of noninferiority studies of stable patients and patients with acute coronary syndrome after

PCI have supported this approach.²⁵ Meta-analyses found comparable incidences of stent thrombosis and adverse ischemic events; however, myocardial infarction was more frequent in the shortened DAPT group.²⁵ Recently, the MASTER-DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Prolonged DAPT Regimen) study randomized 4434 patients at high risk of bleeding who were free of cardiovascular events at 1 month after PCI to receive 1 month of DAPT or standard DAPT of at least 3 months after PCI.²⁶ The measure of adverse clinical events (defined as a composite of death from any cause, myocardial infarction, stroke or major bleeding) was comparable between the 2 groups.²⁶ Importantly, the incidence of major bleeding or clinically relevant, nonmajor bleeding was significantly lower in the shorter treatment group (6.5% v. 9.4%, $p < 0.001$).²⁶

The use of a single antiplatelet agent was recently tested in an open-label, multicentre randomized study of 5438 patients who had completed 6–18 months of DAPT without any clinical events, compared with ASA alone. Over a mean follow-up of 24 months, clopidogrel reduced the composite outcome of all-cause death,

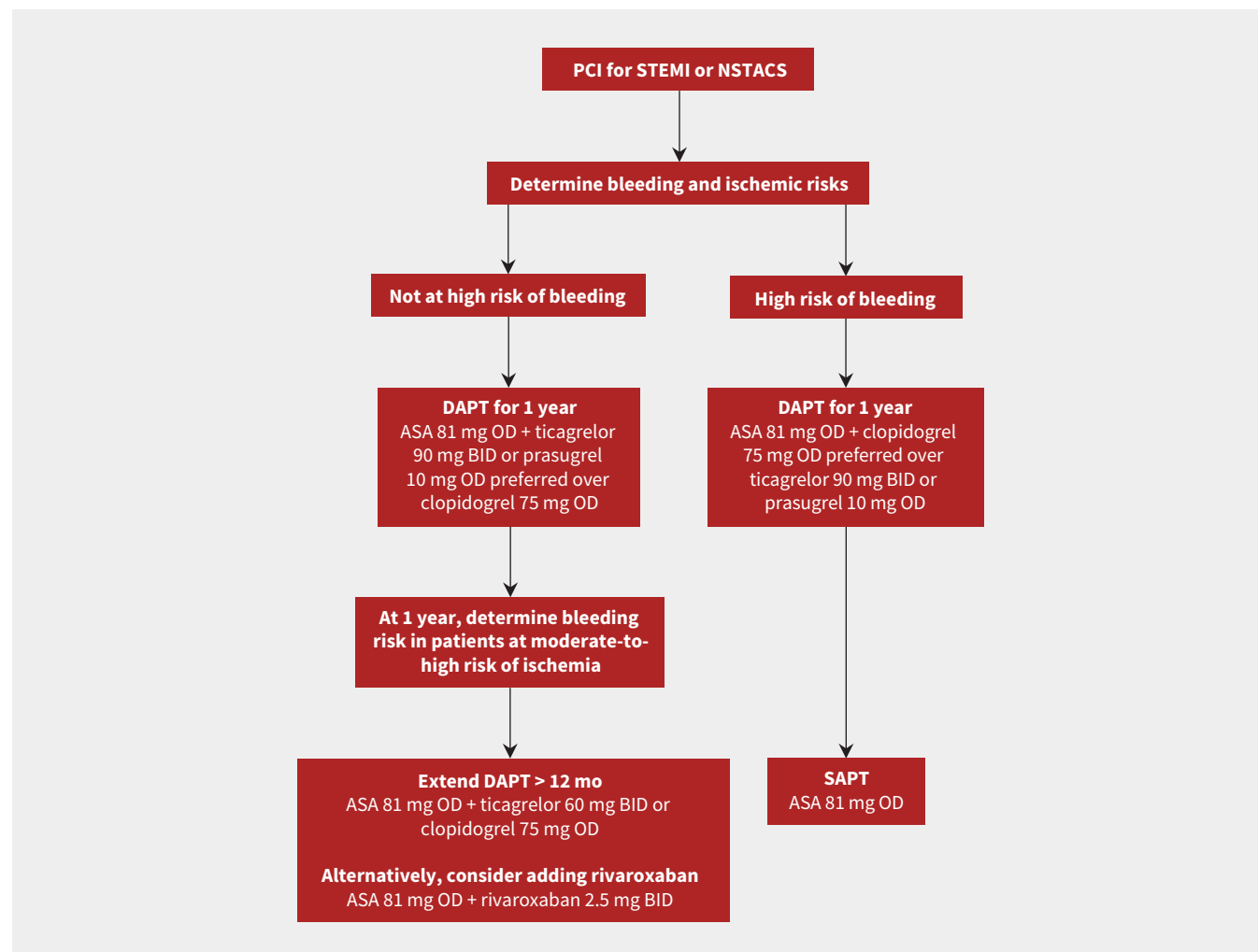


Figure 1: Antiplatelet recommendations in patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI). Note: ASA = acetylsalicylic acid, BID = twice daily, DAPT = dual antiplatelet therapy, NSTACS = non-ST segment elevation acute coronary syndrome, OD = once daily, SAPT = single antiplatelet therapy, STEMI = ST-segment elevation myocardial infarction.

myocardial infarction, stroke, readmission because of an acute coronary syndrome and major bleeding events (5.7% v. 7.7%; hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.59–0.90).²⁷ Both ischemic (3.7% v. 5.5%; HR 0.68, 95% CI 0.52–0.87) and any bleeding events (2.3% v. 3.3%; HR 0.70, 95% CI 0.51–0.98) were reduced with the use of clopidogrel.

Other strategies for extended secondary prevention include the use of a low dose of oral anticoagulant in combination with ASA. This has been used in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial for patients with stable atherosclerotic cardiovascular disease, including previous myocardial infarction, cerebrovascular and peripheral artery disease.²⁸ Compared with ASA alone, rivaroxaban (2.5 mg twice daily) and ASA reduced ischemic events by an absolute 1.3%, but was associated with more major bleeding (3.1% v. 1.9%).²⁸

How is bleeding risk assessed and managed?

Models have been developed to quantify bleeding risk;^{1,29} they include clinical and biomarker variables and have moderate-to-good accuracy (Table 2). The DAPT, PRECISE-DAPT and PRAISE models are accessible online. In a meta-analysis of 88 563 patients, the DAPT score consistently identified patients at high risk of bleeding and ischemia in different cohorts of patients.³⁹ Similarly, the PRECISE-DAPT model effectively identified patients who were not suitable for extended DAPT and were likely to be at risk of bleeding without a decrease in ischemic events.³⁵ The PRECISE-DAPT model was also validated in cohorts of patients with acute coronary syndromes who underwent PCI and were treated with potent P2Y₁₂ inhibitors, and showed moderate accuracy in predicting future bleeding risk.⁴⁰

The PRAISE model used machine learning to predict bleeding, ischemic risk and all-cause deaths.³⁸ The model was derived from 2 cohorts of patients with acute coronary syndromes who were treated with clopidogrel or more potent P2Y₁₂ inhibitors. It accurately predicted major bleeding, as well as acute MI and all-cause mortality. Importantly, machine learning risk-scoring models need to be tested in randomized controlled trials to assess their impact on clinical outcomes.

Strategies to reduce bleeding risk at the time of PCI include the use of radial access (preferable to accessing a more central artery), using fluoroscopy or ultrasonography guidance to access the common femoral artery⁴¹ and selecting the right stent platform that is indicated for patients with high bleeding risk or is considered safe for early discontinuation of DAPT.^{26,42} Bleeding risk can also be reduced with the use of clopidogrel rather than prasugrel or ticagrelor in patients who are at high risk.⁴¹ After hospital discharge, several strategies should be used to reduce bleeding risk (Box 3).

The management of acute bleeding events is discussed elsewhere.⁴⁴ Current guidelines categorize patients according to the type of bleeding event and recommend management according to severity (Table 3).¹⁸ Reversal agents are currently available for some oral anticoagulants, and antidotes to P2Y₁₂ inhibitors are being developed.⁴⁵ A ticagrelor reversal agent, bentracimab (PB2452), is a human monoclonal antibody that provides immediate and sustained reversal of the antiplatelet effects of ticagrelor in healthy volunteers.⁴⁵ It is currently being studied in the REVERSE-IT (Rapid

Box 3: Strategies to reduce bleeding risk following hospital discharge

- Shorter duration of dual antiplatelet therapy
- Use of clopidogrel rather than ticagrelor or prasugrel
- Avoidance of nonsteroidal anti-inflammatory drugs
- Optimal blood pressure management
- Abstinence from alcohol
- Use of mobility aids, when appropriate
- Use of proton pump inhibitor for all patients after percutaneous coronary intervention, as recommended by current guidelines.¹⁸
- Screening and eradication of *Helicobacter pylori* (a large randomized controlled trial is underway to assess this strategy in patients with acute myocardial infarction)⁴³
- Correction of anemia to reduce the impact of bleeding

and Sustained Reversal of Ticagrelor–Intervention Trial) trial (NCT04286438). Management of bleeding events in patients on DAPT can be challenging and involvement of specialists should be considered (Box 4).

Can treatment with acetylsalicylic acid be stopped early?

Early stopping of ASA while maintaining P2Y₁₂ inhibition has recently been tested, based on experimental data that suggested the synergistic effect of inhibiting cyclooxygenase-1 with ASA and P2Y₁₂ inhibitors is less relevant in the presence of potent P2Y₁₂ inhibitors.⁴⁶ A recent meta-analysis of data from 16 898 patients with acute coronary syndromes showed that P2Y₁₂ inhibitor monotherapy after 1–3 months of DAPT reduced bleeding events by 50% with no significant increase in ischemic events, compared with 12 months of DAPT.^{24,47} A recent meta-analysis included individual data from 24 096 patients enrolled in 6 randomized trials and highlighted the superiority of P2Y₁₂ inhibitor monotherapy over DAPT in reducing ischemic events in women, and the reduction of

Box 4: Indications for referral to cardiologist and other specialist regarding antiplatelet treatment

- Bleeding events in patients within 1 year of acute coronary syndrome; advice from a cardiologist about resumption or discontinuation of a second antiplatelet agent should be sought early, and consultation with a gastroenterologist should also be considered, if indicated
- New onset atrial fibrillation
- Patients with planned noncardiac surgery (particularly major surgeries)
- Patients with chronic bleeding diatheses, such as hemophilia or severe liver disease; consultation with a hematologist should be considered
- Patients who develop thrombocytopenia; consultation with a hematologist should be considered
- Patients who develop a cerebrovascular event; consultation with a neurologist should be considered

Table 2 (part 1 of 2): Models to estimate bleeding risk

Model	Derived population	Score variables	Score description	Limitations
CRUSADE ³⁰	71 277 community-treated patients with NSTEMI	Hematocrit, creatinine clearance, baseline heart rate, baseline systolic blood pressure, female sex, signs of CHF on presentation, previous vascular disease and diabetes mellitus	Each independent variable was assigned weighted integers according to its coefficient value in the regression model. The sum of the weighted integers (range 1 to 100 points) estimates the risk of in-hospital major bleeding, with a curvilinear relation between CRUSADE bleeding score and predicted probabilities of major bleeding	Patients who died within 48 hours were excluded and early bleeding events may be underestimated. Patients on oral anticoagulation were excluded; similarly those with previous bleeding events or bleeding disorders were not included. CRUSADE is designed to predict in-hospital bleeding events
ACUITY ³¹	17 421 patients with ACS (UA, NSTEMI and STEMI)	Age, female sex, serum creatinine, white blood cell count, anemia, NSTEMI, STEMI and the use of heparin plus glycoprotein IIb/IIIa inhibitor (rather than bivalirudin alone)	Each independent variable was assigned weighted integers according to its coefficient value in the regression model. The sum of the weighted integers (range 1 to 52 points) estimates the risk of 30-day non-CABG major bleeding, with curvilinear relation between ACUITY bleeding score and predicted probabilities of bleeding	Posthoc analysis of patients included in 2 RCTs. Potential variables of interest were not available to be incorporated in the model. Potent P2Y ₁₂ inhibitors were not studied
REACH ³²	64 589 at risk of CAD or with stable CAD	Age, peripheral arterial disease, CHF, diabetes, hypertension, smoking, antiplatelets, oral anticoagulants, hypercholesterolemia	Each factor was assigned a single point, except for CHF, hypertension, smoking and non-ASA antiplatelet therapy, which were assigned 2 points. Oral anticoagulation or DAPT were assigned 4 points. A score > 10 was associated with 6-fold increase in risk of serious bleeding over 2 years	The definition of serious bleeding used for the analyses was either a hemorrhagic stroke or bleeding leading to both hospitalization and transfusion. This may underestimate the rate of major bleeding events. Data regarding potent P2Y ₁₂ inhibitors were limited. The exposure to oral anticoagulation was extrapolated and did not account for potential changes over study follow-up
DAPT ^{33*}	11 648 patients who tolerated DAPT for 1 year without ischemic or bleeding events	Age, cigarette smoking, diabetes mellitus, MI at presentation, previous PCI or previous MI, paclitaxel-eluting stent, stent diameter < 3 mm, CHF or LVEF < 30%, and vein graft stent	Each variable was assigned a single point except for age (65 to < 75 yr and ≥ 75 yr, for which patients were assigned -1 or -2, respectively). Those with CHF, LVEF or vein graft stent were assigned 2 points. Total scores ranged from -2 to 10, and those with scores ≥ 2 were considered high risk and extended DAPT was recommended. Patients with low scores (< 2) were considered low risk and extended DAPT was not recommended	DAPT score showed moderate accuracy in the derivation and validation cohort. It is designed to inform the duration of DAPT rather than predicting future bleeding events
PARIS ³⁴	4190 patients treated with DES (almost 60% had stable presentation)	Age, body mass index, triple therapy at discharge, anemia, current smoking and renal dysfunction	An integer-based risk score was developed for major bleeding (and ischemic events) at 2 years by assigning each variable a score of 2, except for anemia (score of 3) and age (higher score proportional to older patients). The score ranges from 0 to 14 and ≥ 8 is considered high bleeding risk	Most patients were treated with clopidogrel, which limits generalizability to potent P2Y ₁₂ inhibitors. Duration of DAPT was not randomized and decision to stop antiplatelet was according to the clinician's discretion

Table 2 (part 2 of 2): Models to estimate bleeding risk

Model	Derived population	Score variables	Score description	Limitations
PRECISE-DAPT ^{35*}	14 963 patients treated with DAPT after PCI were pooled from 8 RCTs with independent adjudication of events	Age, creatinine clearance, hemoglobin, white blood cell count and previous spontaneous bleeding.	Independent predictors of bleeding events that were identified in the multivariate regression model were assigned points based on the magnitude of association of each predictor with bleeding. A score ≥ 25 is considered HBR, and extended DAPT has been associated with increased bleeding in this group, unlike patients with low scores. PRECISE-DAPT showed improved integrated discrimination and reclassification performance compared with the PARIS score	The accuracy of the model in the validation cohort ranged from moderate to good. Frailty was not included as part of the risk model. Most patients were treated with clopidogrel and those on oral anticoagulation were excluded. Prediction of bleeding events in patients on prasugrel was poor
ARC-HBR trade-off model ^{36,37}	6641 patients who underwent PCI and were identified as HBR were pooled from 6 studies	Age, hemoglobin, renal dysfunction, liver disease, cancer, planned major surgery, COPD, current smoker, complex PCI procedure, oral anticoagulation at discharge	Variables were classified as a major or minor criterion for HBR. Major criterion is considered to confer risk of major bleeding of $\geq 4\%$ or $\geq 1\%$ intracranial hemorrhage at 1 year. This score outperformed PARIS and PRECISE-DAPT (alternative model without white blood cell count)	The criteria used were modified from those proposed in the ARC consensus to allow the use of available data. Infrequent, but well-recognized, predictors were pooled as a single variable in the model (i.e., liver disease, cancer and planned surgery)
PRAISE ^{38*}	19 826 patients presenting with ACS from 2 registries	Age, sex, diabetes, hypertension, hyperlipidemia, PAD, eGFR, previous MI, previous PCI, previous CABG, previous stroke, previous bleeding, malignancy, STEMI, LVEF, multivessel disease, complete revascularization, vascular access, DES and treatment with BBs, ACE inhibitors, ARBs, statins, oral anticoagulation and PPIs	Four machine learning models that used different classifiers were developed to predict occurrence of all-cause death, recurrent MI and major bleeding 1 year after discharge. Each model's performance was assessed using a range of learning metrics and the best performing model was selected. When calculated, PRAISE provides 3 outcomes of the calculated score for death, MI, and major bleeding.	It was not possible to fully compare PRAISE with PARIS or PRECISE-DAPT given the insufficient clinical data. Although PRAISE has been prospectively validated in external cohorts, it has not been used in RCTs to aid decision-making of DAPT duration

Note: ACE = angiotensin-converting enzyme, ACS = acute coronary syndrome, ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy, ARB = angiotensin-receptor blocker, ARC = Academic Research Consortium, ASA = acetylsalicylic acid, BB = beta-blocker, CABG = coronary artery bypass graft, CAD = coronary artery disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines, DAPT = dual antiplatelet therapy, DES = drug-eluting stent, HBR = high bleeding risk, eGFR = estimated glomerular filtration rate, LVEF = left ventricle ejection fraction, MI = myocardial infarction, NSTEMI = non-ST segment elevation myocardial infarction, PAD = peripheral artery disease, PARIS = Patterns of Nonadherence to Antiplatelet Regimen In Stented Patients, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, PRAISE = Predicting with Artificial Intelligence Risk after Acute Coronary Syndromes, PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy, RCT = randomized controlled trial, REACH = Reduction of Atherothrombosis for Continued Health Registry, STEMI = ST-segment elevation myocardial infarction, UA = unstable angina.

*DAPT score is available at <https://tools.acc.org/daptriskapp#!/content/calculator/>, PRECISE-DAPT is available at <http://precisedaptscore.com/predapt/> and PRAISE is available at <https://praise.hpc4ai.it/>.

bleeding events when a potent P2Y₁₂ inhibitor was part of the DAPT regime.⁴⁸ Nonetheless, P2Y₁₂ inhibitor monotherapy is still not widely used in the management of patients after PCI.

What are the indications for dual antiplatelet therapy in patients with atrial fibrillation?

Dual antiplatelet therapy does not prevent stroke and systemic thromboembolism in patients with atrial fibrillation as effectively as oral anticoagulation.⁴⁹ Conversely, an oral anticoagulant does not reduce coronary ischemic events, including stent thrombosis, as effectively as DAPT. Thus, triple therapy combining DAPT and OAC is recommended in patients with acute coronary syndromes, either medically managed or after PCI, who also have

atrial fibrillation. Direct oral anticoagulants are associated with a lower rate of bleeding events than vitamin K antagonists, and are therefore preferred in patients with atrial fibrillation,⁵⁰ except in those with mechanical heart valves, moderate-to-severe mitral stenosis or advanced renal disease. Clopidogrel is the P2Y₁₂ of choice in patients receiving triple therapy, rather than ticagrelor or prasugrel, because of the lower risk of bleeding.³

The duration of triple therapy remains a matter of debate, given the increased risk of major bleeding over time. The AUGUSTUS (Open-label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) trial showed that, beyond the first 30 days (the period of

Table 3: Management of bleeding events in patients with acute coronary syndrome receiving antithrombotic therapy

Bleeding event	Event description	Antithrombotic treatment modification	
		Original treatment	Modification
Trivial bleeding	A bleeding event not requiring medical attention or further evaluation (e.g., skin bruising, self-resolving epistaxis, minimal conjunctival bleeding)	DAPT	<ul style="list-style-type: none"> Continue DAPT
		Concomitant OAC*	<ul style="list-style-type: none"> Consider continuation of the regimen or skip a single dose of OAC
Mild bleeding	A bleeding event requiring medical attention without need for hospital admission (e.g., major epistaxis, moderate conjunctival bleeding, genitourinary or gastrointestinal bleeding without substantial blood loss, mild hemoptysis)	DAPT	<ul style="list-style-type: none"> Continue DAPT Consider shortening DAPT or de-escalation to a less potent P2Y₁₂ inhibitor
		Concomitant OAC*	<ul style="list-style-type: none"> In patients on VKA: consider holding drug until INR < 2 In patients on DOAC: skip a single dose In patients on TT: consider switching to dual therapy (clopidogrel and OAC)
Moderate bleeding	A bleeding event requiring hospital admission or associated with substantial blood loss (≥ 3 mmol/L hemoglobin) without hemodynamic instability (e.g., genitourinary, respiratory, upper or lower gastrointestinal bleeding with substantial blood loss or requiring transfusion)	DAPT	<ul style="list-style-type: none"> Consider stopping DAPT and continuing with a single P2Y₁₂ inhibitor Resume DAPT within 3 days if considered safe to do so Consider shortening DAPT or de-escalation to a less potent P2Y₁₂ inhibitor
		Concomitant OAC*	<ul style="list-style-type: none"> Consider stopping OAC or reversing VKA with vitamin K (unless CHA₂DS₂-VASc ≥ 4 or a cardiac assist device or mechanical heart valve is present) If DOAC was taken within 2–4 hours, charcoal or dialysis (for patients on dabigatran) can be used Consider resuming treatment within 1 week, if patient is clinically stable <ul style="list-style-type: none"> In patients on VKA: consider a target INR 2.0–2.5 (unless mechanical heart valve or cardiac assist device is present) In patients on DOAC: consider the lowest effective dose In patients on TT: consider switching to dual therapy (clopidogrel and OAC)
Severe bleeding	A bleeding event associated with severe blood loss (≥ 5 mmol/L hemoglobin) in a hemodynamically unstable patient requiring hospital admission (e.g., severe genitourinary, respiratory or gastrointestinal bleeding, bleeding into critical spaces such as pericardium, retroperitoneum, intraocular spinal or intracranial spaces)	DAPT	<ul style="list-style-type: none"> Consider stopping DAPT and continue with SAPT (preferably with P2Y₁₂ inhibitor) Consider stopping all antithrombotic agents if bleeding persists Once bleeding has ceased, reassess the need for DAPT or SAPT; if DAPT is resumed, consider shortening length of treatment or de-escalating to a less potent P2Y₁₂ inhibitor
		Concomitant OAC*	<ul style="list-style-type: none"> Stop or reverse OAC until bleeding stops (except for patients with an extreme thrombotic risk, i.e., with a mechanical heart valve in mitral position or cardiac assist device) <ul style="list-style-type: none"> In patients on VKA: administer FFP or 4F-PCC In patients on DOAC: administer 4F-PCC In patients on dabigatran: consider administering idarucizumab Consider resuming treatment within 1 week, if clinically stable <ul style="list-style-type: none"> In patients on VKA: consider target INR of 2.0–2.5 (except for patients with mechanical heart valves and cardiac assist devices) In patients on DOAC: consider the lowest effective dose In patients on TT: consider switching to dual therapy (clopidogrel and OAC)
Life-threatening bleeding	Any severe active bleeding that poses a threat to a patient's life (e.g., massive genitourinary, respiratory or gastrointestinal bleeding, active intracranial, spinal or intraocular hemorrhage, any bleeding causing hemodynamic instability)	DAPT	<ul style="list-style-type: none"> Stop all antithrombotic agents immediately Once bleeding has ceased, reassess the need for DAPT or SAPT, preferably with clopidogrel (particularly in patients who had upper GI bleeding)
		Concomitant OAC*	<ul style="list-style-type: none"> Stop and reverse OAC <ul style="list-style-type: none"> In patients on VKA: use FFP or 4F-PCC In patients on dabigatran: consider administering idarucizumab

Note: 4F-PCC = 4-factor prothrombin complex concentrate, ACS = acute coronary syndrome, CHA₂DS₂-VASc = score that evaluates risk of ischemic stroke, DAPT = dual antiplatelet therapy, DOAC = direct oral anticoagulant, FFP = fresh frozen plasma, GI = gastrointestinal, INR = international normalized ratio, OAC = oral anticoagulant, SAPT = single antiplatelet therapy, TT = triple therapy, VKA = vitamin K antagonist.

*Concomitant OAC with antiplatelet therapy, including both SAPT and DAPT.

highest risk for stent thrombosis), ASA and oral anticoagulation increased bleeding events without significantly reducing ischemic events when compared with placebo and oral anticoagulation in patients receiving P2Y₁₂ inhibitors.^{51,52}

Numerous studies, including a recent meta-analysis, found that combining oral anticoagulation and single antiplatelet therapy reduced bleeding risk compared with triple therapy.⁵³ Importantly, these studies were not powered to detect potential differences in ischemic events, and the meta-analysis found an increased risk of stent thrombosis associated with the combination therapy.⁵³ A small study of consecutive patients suggested that the ischemic risk was greater in patients who underwent complex PCI procedures without the use of ASA immediately after a PCI procedure.⁵⁴ Therefore, triple therapy should be considered in patients at high risk of ischemia and of stent thrombosis and low risk of bleeding for up to 1 month after PCI (Figure 2). After 1 month, ASA should be stopped, and oral anticoagulation and a P2Y₁₂ inhibitor (preferably clopidogrel, given its lower bleeding risk) should be continued up to 12 months in patients after acute coronary syndrome. At 1 year, oral anticoagulation monotherapy should be used for secondary prevention of stroke.⁵⁵

How should antiplatelet agents be switched?

De-escalation from a more potent P2Y₁₂ inhibitor to clopidogrel occurs in up to 28% of patients with acute coronary syndromes, most often because of bleeding or high risk of bleeding.⁵⁶ Similarly, switching between potent P2Y₁₂ inhibitors may be required

if specific adverse effects such as shortness of breath or gout develop in patients receiving ticagrelor. An international consensus document and Canadian guidelines provide guidance to physicians when switching between P2Y₁₂ inhibitors (Box 5).^{30,57}

Guided de-escalation therapy by either platelet function testing or CYP2C19-directed genotyping may also be considered in select patients with acute coronary syndromes.⁵⁸

Box 5: Switching between oral P2Y₁₂ inhibitors

Ticagrelor to clopidogrel

Ticagrelor has a relatively fast offset of action. Clopidogrel should be administered 24 hours after the last dose of ticagrelor. A 600 mg loading dose of clopidogrel should be considered unless the patient had a recent bleeding event, in which case clopidogrel 75 mg should be considered.

Prasugrel to clopidogrel

The prolonged offset of prasugrel means that the usual clopidogrel maintenance dose of 75 mg daily should be started 24 hours after the last dose of prasugrel.

Ticagrelor to prasugrel

A 60 mg loading dose of prasugrel should be administered 24 hours after the last dose of ticagrelor.

Prasugrel to ticagrelor

A 90 mg maintenance dose of ticagrelor should be administered twice daily 24 hours after the last prasugrel dose. If it has been fewer than 30 days since the patient's PCI, a loading dose of 180 mg ticagrelor should be considered.

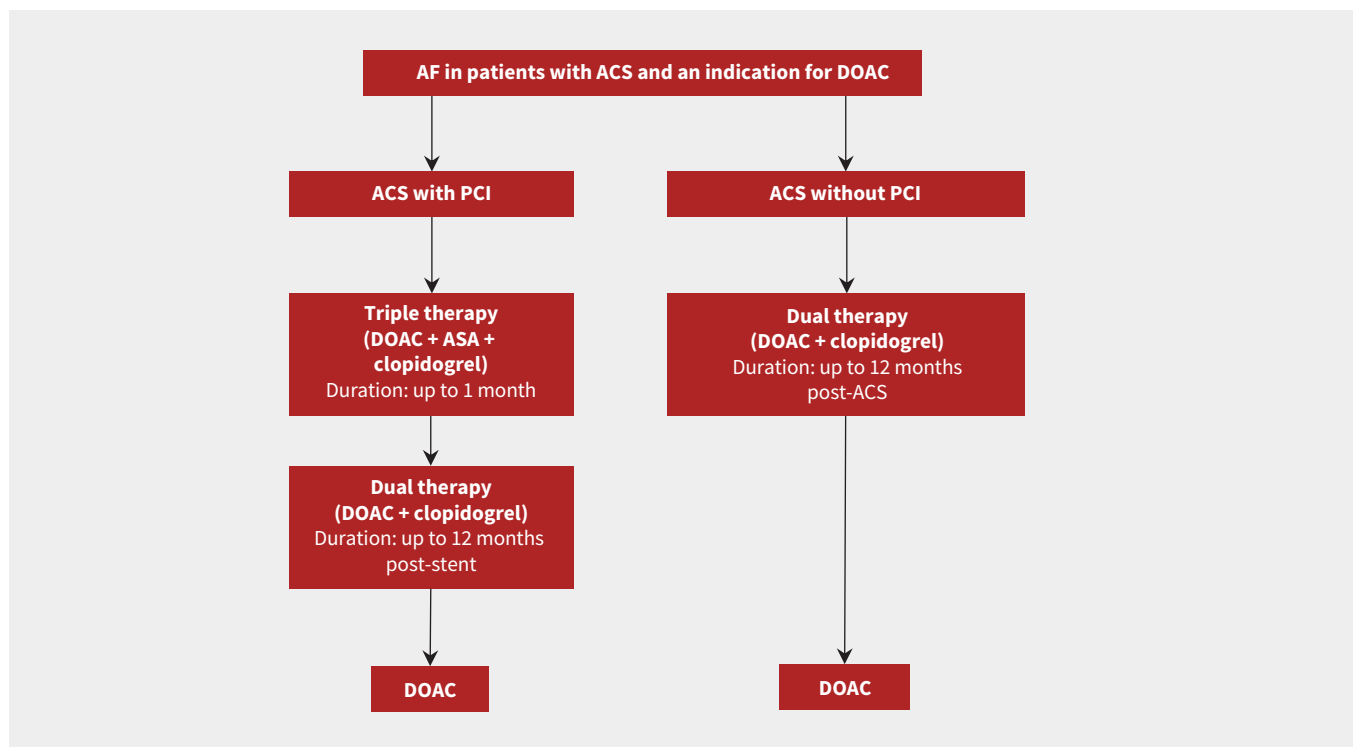


Figure 2: Antiplatelet management in patients with acute coronary syndrome (ACS) and atrial fibrillation (AF). Direct oral anticoagulation (DOAC) is preferred over warfarin; however, if warfarin is to be used the recommended international normalized ratio target is 2.0–2.5. The timing of when to discontinue acetylsalicylic acid (ASA) will depend on the individual patient's ischemic and bleeding risk. Note: PCI = percutaneous coronary intervention.

Conclusion

Prasugrel and ticagrelor are antiplatelet agents that are more effective than clopidogrel at decreasing the future risk of ischemic events in patients with acute coronary syndromes, but

are more likely to cause bleeding. The choice of antiplatelet regimen is influenced by the ischemic and bleeding risk of each patient (Figure 3). Up to a month of triple therapy with ASA, clopidogrel and an oral anticoagulant should be considered in patients with acute coronary syndromes who also have atrial fibrillation.

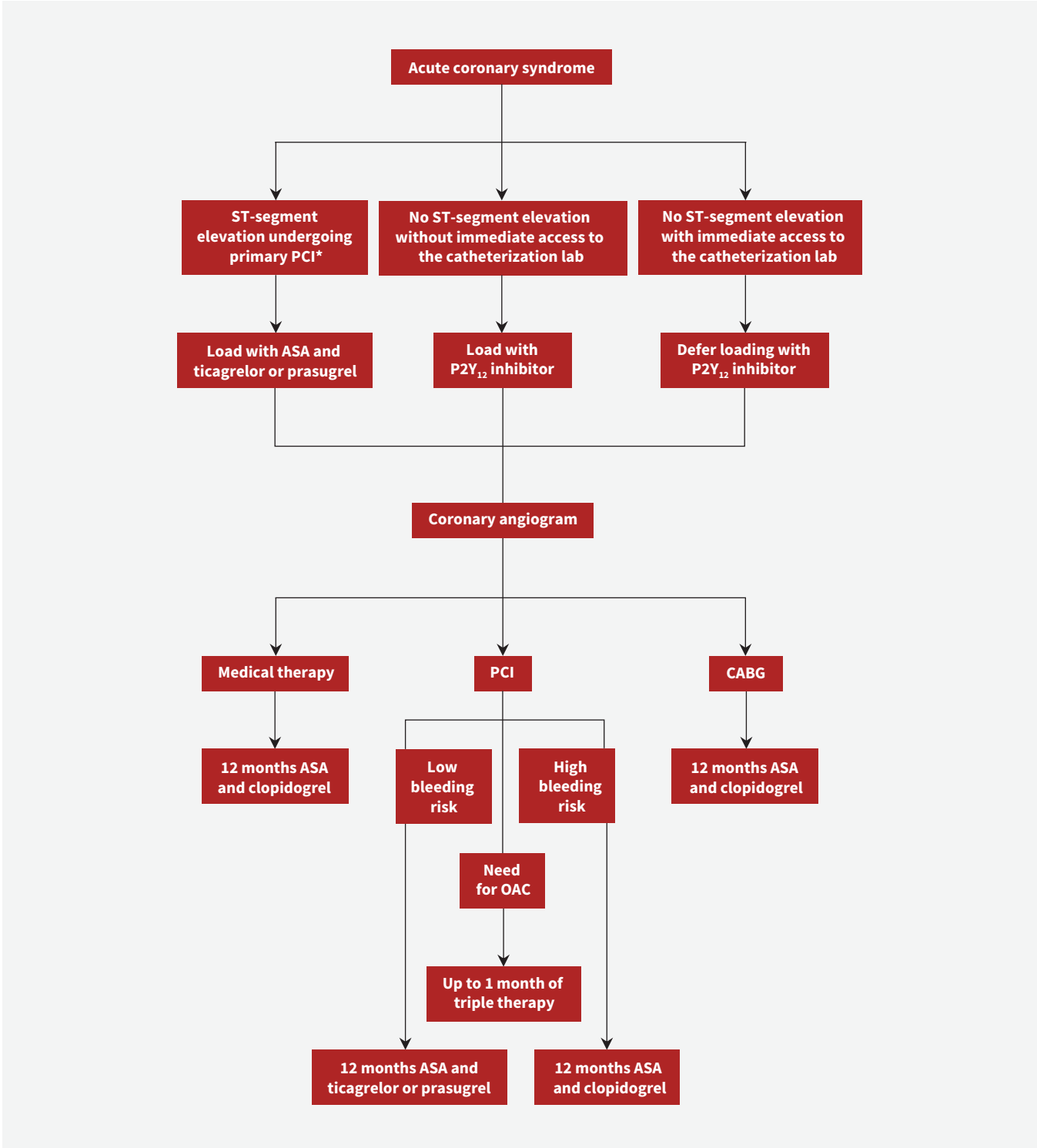


Figure 3: Flowchart for antiplatelet management in patients with acute coronary syndrome. Note: ASA = acetylsalicylic acid, CABG = coronary artery bypass grafting, OAC = oral anticoagulant, PCI = percutaneous coronary intervention. *Patients receiving fibrinolytic therapy should be loaded with ASA and clopidogrel. Switching to ticagrelor within 24 hours should be considered.

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