ANTIPLATELET THERAPY

2018 UPDATE

The Canadian Cardiovascular Society's

ANTIPLATELET THERAPY

GUIDELINES

ANTIPLATELET THERAPY

Canadian Cardiovascular Society
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About this Pocket Guide

This pocket guide is a quick-reference tool that features diagnostic and management recommendations based on the 2018 CCS Antiplatelet Therapy Guidelines.

These recommendations are intended to provide a reasonable and practical approach to the care for primary care physicians, specialists, nurses and allied health professionals. Recommendations are subject to change as scientific knowledge and technology advance and practice patterns evolve, and are not intended to be a substitute for clinical judgment. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

For the complete CCS Guidelines on Antiplatelet Therapy, or for additional resources, please visit www.ccs.ca. A summary of all standing CCS APT recommendations, from 2010 to the present 2018 Focused Update is available on the CCS e-Guidelines website: www.ccs.ca/eguidelines.

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Introduction and Rationale

This update to the 2011 and 2013 Canadian Cardiovascular Society (CCS) antiplatelet therapy guidelines incorporates new evidence on how to optimally use antiplatelet therapy, particularly in conditions in which few to no data were previously available. The recommendations focused on the following topics:

1. The duration of dual antiplatelet therapy (DAPT) in patients who undergo percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) and non-ACS indications

2. Management of DAPT in patients who undergo noncardiac surgery

3. Management of DAPT in patients who undergo elective and semiurgent coronary artery bypass graft surgery (CABG)

4. When and how to switch between oral antiplatelet therapies

5. Management of antiplatelet and anticoagulant therapy in patients who undergo PCI with atrial fibrillation (AF), mechanical or bioprosthetic valves (including transcatheter aortic valve replacement [TAVR]), venous thromboembolic disease, and established left ventricular (LV) thrombus (LVT) or possible LVT with reduced ejection fraction after ST-segment elevation myocardial infarction (STEMI).

Duration of DAPT in Patients who Undergo PCI

In patients with ACS (STEMI or NSTEMI) who receive PCI:

- We recommend dual antiplatelet therapy (DAPT) with ASA 81 mg daily with either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily over clopidogrel 75 mg once daily for 1 year (*Strong Recommendation, High-Quality Evidence*).

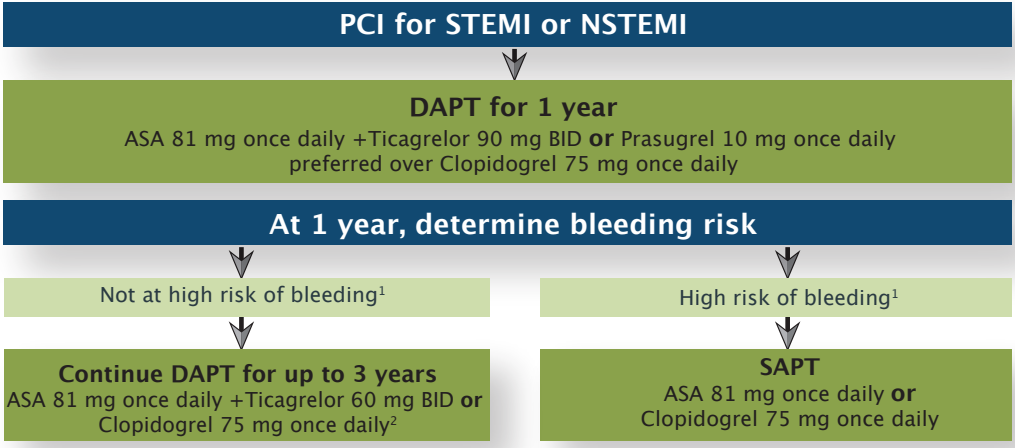
- We recommend that in patients who tolerate 1 year of DAPT without a major bleeding event and who are not at high risk of bleeding, DAPT should be extended beyond 1 year (*Strong Recommendation, High-Quality Evidence for up to 3 years of treatment*). After 1 year, we recommend a DAPT regimen of ASA 81 mg daily plus either ticagrelor 60 mg twice daily or clopidogrel 75 mg once daily (*Strong Recommendation, High-Quality Evidence*) or prasugrel 10 mg once daily (*Weak Recommendation, Moderate-Quality Evidence*).

Values and preferences - These recommendations place greater emphasis on reduction of major cardiovascular events and stent thrombosis versus an increase in bleeding complications.

Practical tips:

- Recommendations on duration of DAPT apply specifically to duration of $P2Y_{12}$ inhibitor therapy. ASA should be continued indefinitely in most patients with CAD who are not on oral anticoagulant therapy.
- Patients who have clinical or angiographic features for an increased risk of a thrombotic cardiovascular event may derive greater absolute benefit from extended DAPT beyond 1 year.
- Quantitative risk scores have been developed. These scores may help identify higher risk patients with greater absolute benefit of extended DAPT.
- An ongoing assessment of bleeding and ischemic risk should be performed at least annually to determine whether DAPT should be continued.
- Prasugrel should be avoided in patients with previous TIA or stroke.
- For those patients who have a bleeding event on ticagrelor or prasugrel, but where continuation of a $P2Y_{12}$ agent is felt to be warranted, please refer to the de-escalation recommendations in section 2.3 of the 2018 APT guidelines.
- In patients with STEMI who receive fibrinolytic therapy, clopidogrel is currently the recommended $P2Y_{12}$ inhibitor within the first 24 hours. A recent randomized trial demonstrated a higher level of platelet inhibition with ticagrelor compared with clopidogrel. On-going trials are evaluating clinical outcomes with ticagrelor in this setting (clinicaltrials.gov NCT02298088).

Duration of DAPT in Patients with ACS (STEMI or NSTEMI) who Undergo PCI



1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranical bleed, regular need for NSAIDS or prednisone

2 Instead of ticagrelor or clopidogrel, prasugrel 5-10 mg daily is also an option (weak recommendation)

DAPT=dual antiplatelet therapy SAPT=single antiplatelet therapy STEMI=ST segment elevation myocardial infarction NSTEMI=non-ST segment elevation myocardial infarction BID=twice daily

Duration of DAPT for Patients Treated with PCI in Non-ACS Settings

In patients undergoing PCI for a non-ACS indication (eg stable ischemic heart disease):

- We recommend 6 months (and up to 1 year) of DAPT with ASA and clopidogrel (*Strong Recommendation, Moderate-Quality Evidence*).

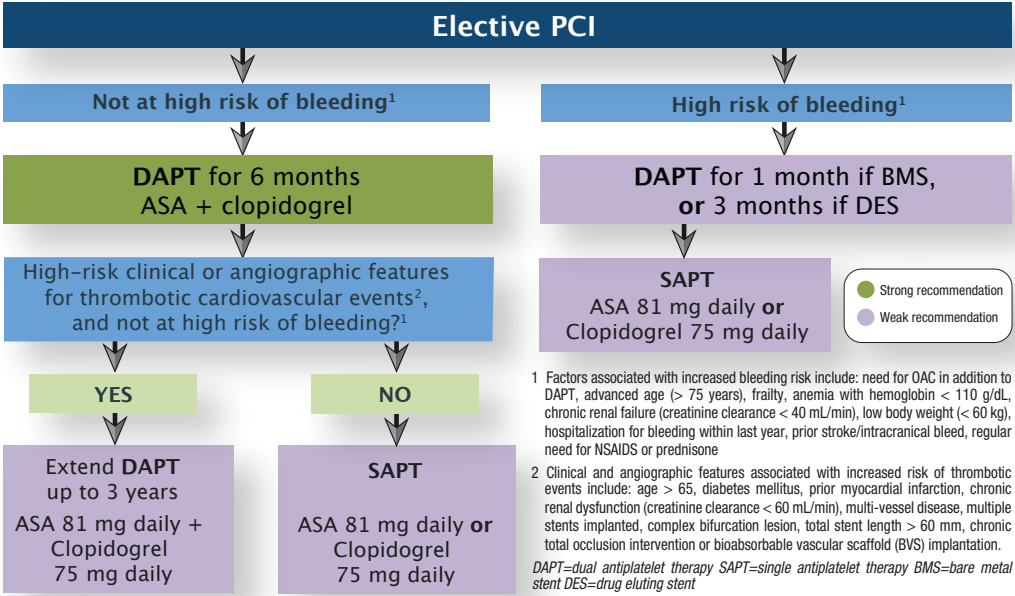
- We suggest that in patients who have additional high-risk clinical or angiographic features for thrombotic cardiovascular events and who are at low risk of bleeding, it is reasonable to extend the duration of DAPT to greater than 1 year (*Weak Recommendation, Moderate-Quality Evidence for up to 3 years of treatment*).
- We suggest that in patients who are at high risk of bleeding, the duration of DAPT be shortened to a minimum of 1 month (if a bare-metal stent [BMS] is used) or 3 months (if a DES is used) (*Weak Recommendation, Low-Quality Evidence*).

Values and preferences - These recommendations place greater emphasis on reduction of major cardiovascular thrombotic events and stent thrombosis versus an increase in bleeding complications. These recommendations presume that patients who experience a clinically significant bleed or at high risk of bleeding would be reassessed for the appropriateness of continuation of DAPT at 1 year.

Practical tips:

- A general principle to consider when deciding on the duration of DAPT is a balanced assessment of the risk of thrombotic cardiovascular events and bleeding. Patients at lower risk of thrombotic events and higher risk of bleeding can be considered for a shorter-duration of DAPT while patients at higher risk of thrombotic events and lower risk of bleeding should be considered for a longer duration of DAPT.
- As in the ACS setting, patients undergoing PCI for a non-ACS indication may derive greater absolute benefit of extended DAPT if they have clinical or angiographic features associated with increased risk of thrombotic cardiovascular events.

Duration of DAPT in Patients who Undergo Elective PCI



1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranical bleed, regular need for NSAIDS or prednisone

2 Clinical and angiographic features associated with increased risk of thrombotic events include: age > 65, diabetes mellitus, prior myocardial infarction, chronic renal dysfunction (creatinine clearance < 60 mL/min), multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold (BVS) implantation.

DAPT=dual antiplatelet therapy SAPT=single antiplatelet therapy BMS=bare metal stent DES=drug eluting stent

- In patients undergoing PCI who are treated with a bare metal stent who require elective non-cardiac surgery, we recommend delaying surgery for at least 1 month after PCI (*Strong Recommendation, Moderate-Quality Evidence*).
- In patients undergoing PCI who are treated with a drug eluting stent who require elective non-cardiac surgery, we recommend delaying surgery for at least 3 months after PCI (*Strong Recommendation, Moderate-Quality Evidence*). If there is a need for semiurgent non-cardiac surgery, we suggest delaying surgery for at least 1 month after PCI (*Weak Recommendation, Low-Quality Evidence*).

- In patients undergoing PCI who are treated with a bare metal or drug eluting stent who require elective non-cardiac surgery, we suggest continuing ASA perioperatively whenever possible (*Weak Recommendation, Low-Quality Evidence*).
- In patients undergoing PCI who are treated with a bare metal or drug eluting stent who require elective non-cardiac surgery, we suggest withholding clopidogrel and ticagrelor for 5-7 days pre-operatively, and prasugrel for 7-10 days pre-operatively (*Weak Recommendation, Low-Quality Evidence*).
- In patients undergoing PCI who are treated with a bare metal or drug eluting stent who have undergone non-cardiac surgery, we suggest restarting maintenance dose DAPT after surgery, as soon as it is deemed safe by the surgeon (*Weak Recommendation, Very Low-Quality Evidence*).

Practical tip - The risk and consequences of peri-operative bleeding will vary considerably depending on the type of surgery performed. Some minor surgical procedures carry a low risk of bleeding, while others a very high risk of bleeding. For example, some dental, opthalmological and endoscopic procedures carry a low risk of bleeding and can be performed without stopping antiplatelet therapy.

Elective or Semiurgent CABG Surgery after ACS

- We recommend continuation of ASA in all patients with ACS who require CABG surgery (*Strong Recommendation, Moderate-Quality Evidence*).

- To minimize the risk of bleeding, for patients with an ACS who are receiving ticagrelor and need semiurgent CABG, we suggest a minimum interruption of ticagrelor for 48-72 hours before CABG (*Weak Recommendation, Low-Quality Evidence*) and recommend an ideal interruption period of 5 days before elective CABG (*Strong Recommendation, Moderate-Quality Evidence*).
- To minimize the risk of bleeding, for patients with an ACS who are receiving clopidogrel and need semiurgent CABG, we suggest a minimum interruption of clopidogrel for 48-72 hours before CABG (*Weak Recommendation, Low-Quality Evidence*) and recommend an ideal interruption period of 5 days before elective CABG (*Strong Recommendation, Moderate-Quality Evidence*).
- To minimize the risk of bleeding, for patients with an ACS who are receiving prasugrel and need semiurgent CABG, we suggest a minimum interruption of prasugrel for 5 days before CABG (*Weak Recommendation, Very Low-Quality Evidence*) and recommend an ideal interruption period of 7 days before elective CABG (*Strong Recommendation, Moderate-Quality Evidence*).

Practical tip - Antiplatelet therapy management in the perioperative period should be based on a balanced assessment of the risks of coronary thrombotic complications versus the risk of perioperative bleeding in discussion with the surgeon, interventional cardiologist, attending physician/cardiologist, and the patient.

Examples of some common clinical scenarios for switching between antiplatelet drugs.

Intensification from clopidogrel to prasugrel or ticagrelor	Switching between prasugrel and ticagrelor	De-escalation from prasugrel or ticagrelor to clopidogrel
In patients: - with ACS, who are initially treated with clopidogrel at presentation - admitted with thrombotic event (e.g., stent thrombosis or ACS), who have been treated with clopidogrel - who are known poor metabolizer of clopidogrel (e.g., CYP2C19 loss-of-function)	In patients: - with intolerance or side effects, who have additional high-risk clinical or angiographic features for thrombotic events warranting completion of the prescribed course of DAPT - admitted with thrombotic event (e.g., stent thrombosis or ACS), who have been treated with the initial P2Y12 receptor inhibitor agent - Interactions between CYP3A inducers and ticagrelor which affect its pharma-codynamics	In patients with: - major bleeding complication that has resolved, who have additional high-risk clinical or angiographic features for thrombotic events, warranting completion of the prescribed course of DAPT - clinically relevant nuisance bleeding that interferes with patient's ability to continue with prasugrel or ticagrelor - intolerance or side effects to prasugrel / ticagrelor in patients who do not have additional high-risk clinical or angiographic features for thrombotic events - a new indication for requiring concurrent treatment with an oral anticoagulant

$P2Y_{12}$ Inhibitor

- We suggest against switching the $P2Y_{12}$ inhibitor initially selected at hospital discharge unless there is a compelling clinical reason to do so (eg, stent thrombosis, cardiovascular event, bleeding, or significant side effects/intolerance) (*Weak Recommendation, Low-Quality Evidence*).

Intensification Strategies

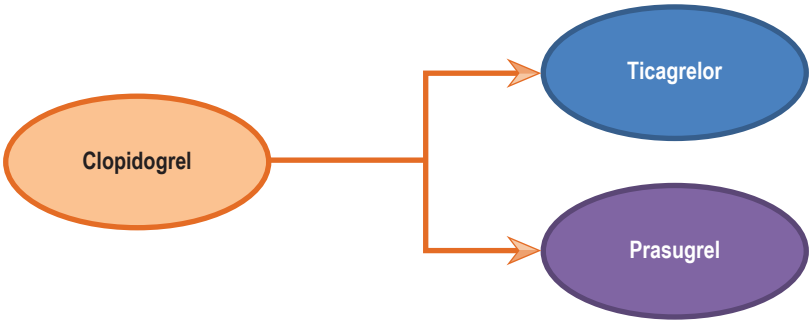
Switching from clopidogrel to ticagrelor

- For patients requiring a switch from clopidogrel to ticagrelor, we recommend a ticagrelor loading dose of 180 mg followed by 90 mg twice daily, regardless of the timing of the last clopidogrel dose (*Strong Recommendation, Moderate-Quality Evidence*).

Switching from clopidogrel to prasugrel

- For patients requiring a switch from clopidogrel to prasugrel, we recommend a prasugrel loading dose of 60 mg followed by 10 mg daily, regardless of the timing of the last clopidogrel dose (*Strong Recommendation, Moderate-Quality Evidence*).

Loading dose: 180 mg
Maintenance dose: 90 mg twice daily
Timing: regardless of the timing of the last clopidogrel dose



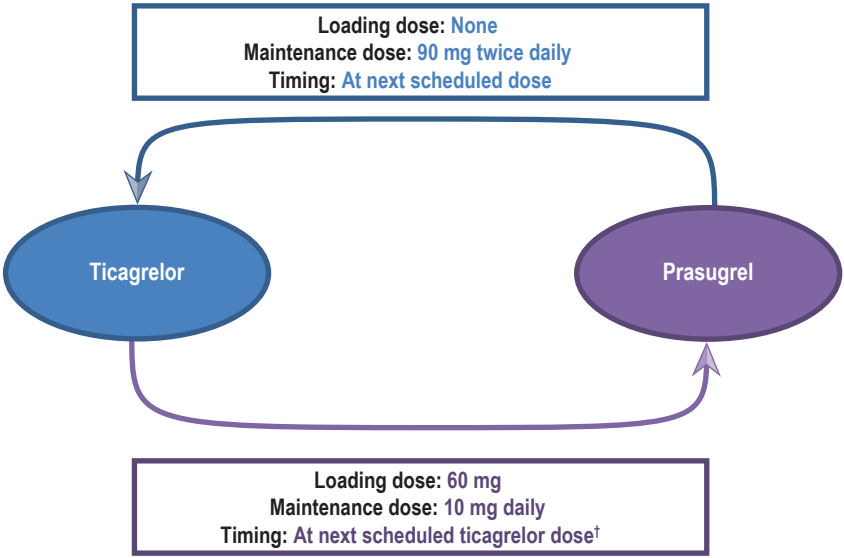
Loading dose: 60 mg
Maintenance dose: 10 mg daily
Timing: regardless of the timing of the last clopidogrel dose

Switching from prasugrel to ticagrelor

- For patients requiring a switch from prasugrel to ticagrelor, we suggest ticagrelor 90 mg BID, without a loading dose, to be initiated at the time of the next scheduled prasugrel dose (*Weak Recommendation, Very Low-Quality Evidence*).

Switching from ticagrelor to prasugrel

- For patients requiring a switch from ticagrelor to prasugrel, we suggest a prasugrel loading dose of 60 mg followed by 10 mg daily, to be initiated at the timing of the next scheduled ticagrelor dose (*Weak Recommendation, Very Low-Quality Evidence*).



† Extending to the following morning (i.e. 24h post last ticagrelor dose) may also be reasonable

De-Escalation Strategies

- For patients receiving ticagrelor or prasugrel who experience a clinically significant bleeding complication that has resolved, we suggest de-escalating to clopidogrel 75 mg daily (*Weak Recommendation, Very Low-Quality Evidence*).

Switching from ticagrelor to clopidogrel

- For patients receiving ticagrelor who are experiencing significant side effects (excluding bleeding) or who are unable to tolerate the drug (and where prasugrel is not an option), we suggest de-escalating to clopidogrel with a loading dose of 600 mg followed by 75 mg daily, to be initiated at the time of the next scheduled ticagrelor dose (*Weak Recommendation, Very Low-Quality Evidence*).

Practical tips:

- The loading dose of 600 mg conveys a short-term (48 hours) pharmacodynamic advantage following the switch to clopidogrel that might be relevant in the early post-ACS/PCI period. In patients who are stable, a loading dose of 300 mg or switching directly to 75 mg daily with no loading dose are also reasonable options, especially for patients felt to be at high risk for bleeding. In the TOPIC study, switching from ticagrelor directly to clopidogrel 75 mg daily one month following ACS was found to decrease bleeding without an increase in ischemic events, with the caveat that the study was not powered for ischemic outcomes.
- The optimal time for the initiation of clopidogrel has not been studied extensively. In OPTI-CROSS, the switch was made at the next scheduled ticagrelor dose; extending to the following morning (i.e. 24h post last ticagrelor dose) may also be reasonable based on pharmacodynamics data from the RESPOND study.

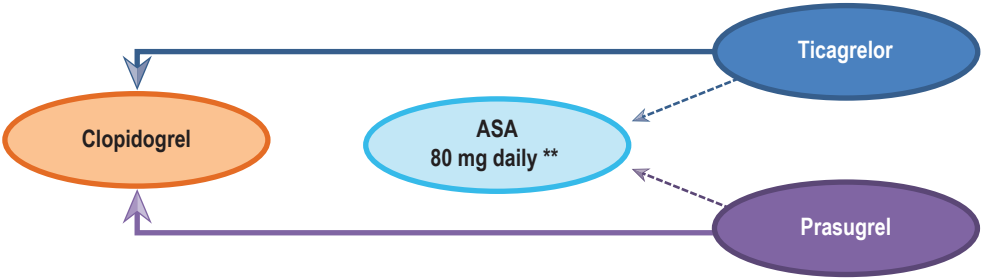
Switching from prasurgel to clopidogrel

- For patients receiving prasugrel who are experiencing significant side effects (excluding bleeding) or who are unable to tolerate the drug (and for whom ticagrelor is not an option), we suggest de-escalating to clopidogrel directly at 75 mg daily (without a loading dose) at the time of the next scheduled prasugrel dose (*Weak Recommendation, Moderate-Quality Evidence*).

Values and preferences - The suggested strategies are formulated on the basis of a systematic review of the literature evaluating pharmacodynamic evidence for optimal platelet inhibition, balanced with an absence of significant bleeding complications. Studies where patients were identified as non-responders using platelet function testing prior to randomization were excluded because of generalizability concerns.

De-Escalation Strategies

Loading dose: Optional loading 300-600 mg *
Maintenance dose: 75 mg daily
Timing: At next scheduled ticagrelor dose†



Loading dose: None
Maintenance dose: 75 mg daily
Timing: At next scheduled dose

* Short-term (48h) PD advantage, might be relevant in the early post-ACS/PCI period, if no bleeding risk
† Extending to 24h post last ticagrelor dose may also be reasonable
** Consider monotherapy with ASA if switch because of bleeding

- We recommend that patients who have concomitant atrial fibrillation (AF) and symptomatic coronary artery disease (CAD) receive a regimen of antithrombotic therapy based on a balanced assessment of their risk of: (1) ischemic stroke; (2) future coronary event(s); and (3) clinically significant bleeding associated with the use of antithrombotic agents (*Strong Recommendation, High-Quality Evidence*).

In Patients With AF Undergoing Elective PCI Without High-Risk Features:

- If age is < 65 years and $CHADS_2$ = 0, we recommend DAPT alone with ASA 81 mg daily with clopidogrel 75 mg daily for 6 months (and up to 1 year) (*Strong Recommendation, High-Quality Evidence*).

Values and preferences - The risk of stroke varies from about 0.7% per year in patients < 65 years of age and $CHADS_2$ score of 0, to about 2.1% per year in patients 65-74 years of age. The risk of stent thrombosis is greatest in the first month after PCI and declines thereafter. In patients with AF at lower risk of stroke, this recommendation gives greater weight to the prevention of future coronary events and less major bleeding with DAPT than with OAC, and less weight to the greater risk of stroke with DAPT than with OAC.

Practical tip - In patients who are at high risk of bleeding, the duration of DAPT should be shortened to a minimum of 1 month (if a BMS was used) or 3 months (if a DES was used) as per recommendation 5 on page 4.

Patients with AF who Undergo PCI

In Patients With AF Undergoing Elective PCI Without High-Risk Features:

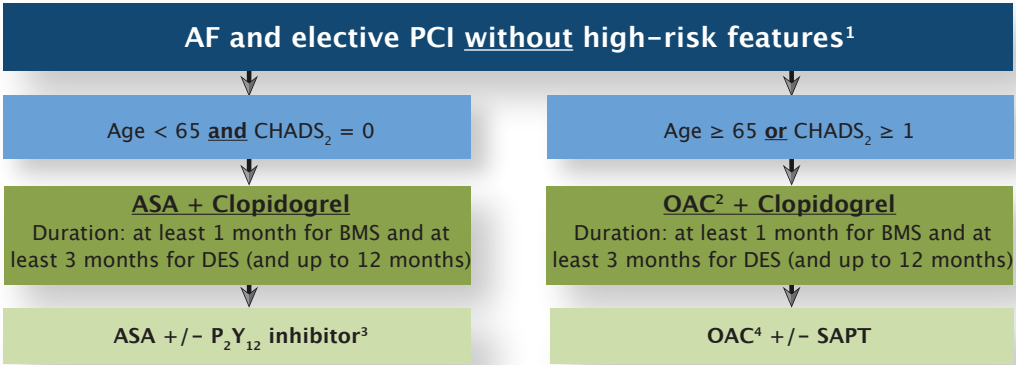
- If age ≥ 65 years or $CHADS_2$ ≥ 1, we suggest OAC plus clopidogrel 75 mg daily for at least 1 month (and up to 12 months) after BMS implantation and for at least 3 months (and up to 12 months) after DES implantation (*Weak Recommendation, Moderate-Quality Evidence*).

Values and preferences - The risk of stroke is increased to 2.1% per year in 65-74 year-old patients and even higher in patients >75 years, providing a rationale for the inclusion of OAC in the regimen. The suggestion for OAC + clopidogrel (and omission of ASA) is based on randomized trials demonstrating a lower risk of bleeding with this regimen versus warfarin plus clopidogrel plus ASA (traditional triple therapy). While the evidence suggests there is unlikely to be a major compromise in efficacy by omitting ASA, it is acknowledged that none of the randomized trials were individually powered to detect moderate differences in thrombotic events. Doses of OAC evaluated in randomized trials of patients with AF undergoing PCI are shown in Table 4. Rivaroxaban 15 mg daily (10 mg daily in patients with renal dysfunction) plus clopidogrel and dabigatran 110 or 150 mg twice daily plus clopidogrel have been evaluated in randomized trials versus traditional warfarin-based triple therapy. At the time this document was written, randomized trials evaluating apixaban and edoxaban based regimens in patients with AF undergoing PCI were in progress, so no dose recommendations with these agents are provided.

Following the initial period of antithrombotic therapy for patients with AF undergoing elective PCI without high-risk features:

- If age is < 65 and $CHADS_2$ = 0, we recommend long-term therapy with either ASA alone or, if high-risk clinical or angiographic features of ischemic events develop and low risk of bleeding, ASA + a $P2Y_{12}$ inhibitor (*Strong Recommendation, High-Quality Evidence*); or
- If age is 65 years or older or $CHADS_2$ ≥ 1 we recommend long-term therapy with either OAC alone (*Strong Recommendation, High-Quality Evidence*) or,
- If high-risk clinical or angiographic features for ischemic events develop and low risk of bleeding, OAC plus single antiplatelet therapy with ASA or a $P2Y_{12}$ inhibitor (*Weak Recommendation, Low-Quality Evidence*).

Practical tip - All patients should receive ASA 81 mg (or a minimum of 160 mg if ASA-naive) on the day of the PCI procedure.



1 A PCI is considered high-risk based on clinical and angiographic features such as: diabetes mellitus, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold (BVS) implantation.

2 OAC regimens evaluated in this context include rivaroxaban 15 mg daily (10 mg in patients with renal dysfunction), dabigatran 110 mg or 150 mg BID and warfarin. If warfarin is to be used, recommended INR 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 naïve). Thereafter, ASA can be discontinued as early as the day following PCI.

3 Extended treatment with a P2Y12 inhibitor can be added to ASA if high-risk clinical or angiographic features of ischemic events develop and low risk of bleeding.

4 The dose of OAC beyond the initial period of antithrombotic therapy (up to a year after PCI) should be standard stroke prevention doses as per the CCS Atrial Fibrillation Guidelines. Single antiplatelet therapy with either ASA or clopidogrel may be added to OAC if high-risk clinical or angiographic features of ischemic events develop and low risk of bleeding.

AF: atrial fibrillation; ASA: acetylsalicylic acid; BMS: bare-metal stent; DES: drug-eluting stent; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; SAPT: single antiplatelet therapy

Patients with AF who Undergo PCI

In patients with AF undergoing PCI for ACS or high-risk elective PCI:

- If age < 65 years and $CHADS_2$=0, we recommend DAPT alone with ASA 81 mg daily plus a $P2Y_{12}$ inhibitor (ticagreloror prasugrel recommended for patients with ACS and clopidogrel recommended for patients undergoing elective PCI) for up to 12 months (*Strong Recommendation, High-Quality Evidence*).

Values and preferences - Patients with AF < 65 years and $CHADS_2$ = 0 who undergo PCI require DAPT to reduce thrombotic coronary events. OAC is not recommended in these patients with low risk of stroke.

Practical tip - The duration of treatment with DAPT in patients with ACS (or those undergoing high risk PCI) who also have AF with a low risk of stroke should depend on a balanced assessment of the risk of coronary thrombotic events and bleeding. Patients at lower risk of coronary thrombotic events and higher risk of bleeding can be considered for shorterduration DAPT and patients at higher risk of coronary thrombotic events and lower risk of bleeding should be considered for longer duration of DAPT.

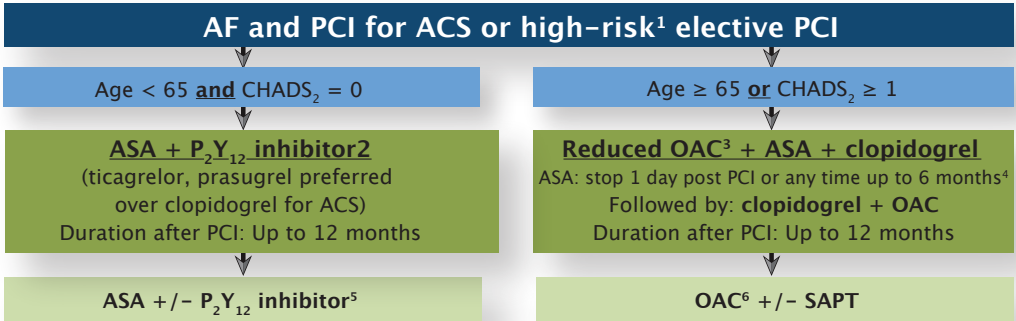
In patients with AF undergoing PCI for ACS or high-risk elective PCI:

- If age ≥ 65 years or $CHADS_2$ ≥ 1*, we recommend an initial regimen of triple therapy with ASA 81 mg daily plus clopidogrel 75 mg daily plus reduced intensity/dose OAC. ASA may be discontinued as early as the day following PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent coronary thrombotic events versus major bleeding (*Strong Recommendation, Moderate-Quality Evidence*).
  **If $CHADS_2$ = 1 and age < 65 years another option for initial treatment (especially if high-risk for ischemic events) is DAPT alone using ASA + ticagrelor or prasugrel for ACS, similar to the recommendation for the $CHADS_2$ = 0 patient.*

- Following ASA discontinuation, we suggest that OAC + clopidogrel 75 mg daily be continued for up to 12 months after the initial PCI (*Weak Recommendation, Moderate-Quality Evidence*).

Values and preferences - In patients 65-74 years of age, the risk of stroke is about 2.1%/year and still higher beyond age 75 years, while the risk of coronary events is approximately 6-10%/year after ACS (STEMI or NSTEMI), providing a rationale for the inclusion of OAC in the post-PCI antithrombotic regimen. Because the risk of bleeding is higher with triple therapy, a reduced intensity/dose of OAC is suggested when it is used in this context. The duration of triple therapy will vary depending on an individual patient's risk of ischemic (Table 1) versus bleeding events (Table 2). In patients with a low risk of thrombotic events and a high risk of bleeding, the duration of triple therapy can be short, with omission of ASA as early as the day following PCI. In patients with a very high risk of thrombotic events and low bleeding risk, ASA could be continued longer, for up to 6 months of treatment. For patients at intermediate risk of ischemic and bleeding events the duration of aspirin will be somewhere in between (for example 1 month or 3 months).

Patients with AF who Undergo PCI for ACS or High-Risk Elective PCI



***If $CHADS_2$ = 1 and Age < 65 another option for initial treatment (especially if high-risk for ischemic events) is DAPT alone using ASA+ticagrelor or ASA+prasugrel, similar to the recommendation for the $CHADS_2$=0 patient**

Figure 4

1. A PCI is considered high-risk based on clinical and angiographic features such as: diabetes, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multivessel coronary artery disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold implantation.
2. Ticagrelor and prasugrel are recommended in ACS patients, whereas clopidogrel is recommended for elective PCI.
3. Regimens evaluated in the context of triple therapy include rivaroxaban 2.5 mg BID or warfarin. If warfarin is to be used, recommended INR target is 2.0-2.5. OAC options evaluated in the context of a dual pathway strategy include rivaroxaban 15 mg daily (plus clopidogrel) or dabigatran 110 mg/150 mg BID (plus clopidogrel).
4. DAPT will have been started as part of ACS management or prior to high risk elective PCI. ASA may be discontinued as early as the day following PCI or it can be continued longer term (eg. 1, 3 or maximum 6 months after PCI). The timing of when to discontinue ASA will vary, depending on the individual patient's ischemic and bleeding risk.
5. A P2Y12 inhibitor can be added to ASA if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.
6. The dose of OAC beyond 1 year after PCI should be standard stroke prevention doses as per the CCS Atrial Fibrillation Guidelines. Single antiplatelet therapy with either ASA or clopidogrel may be added to OAC if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.

AF: atrial fibrillation; ACS: acute coronary syndrome; ASA: acetylsalicylic acid; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

Practical tips:

- All patients should receive ASA 81 mg (or 160 mg if ASA naïve) on the day of the PCI procedure. Thereafter, ASA can be discontinued as early as the day following PCI.
- Factors associated with an increased risk of ischemic and bleeding events are shown in tables 1 and 2
- When combining OAC with antiplatelet therapy, consider reducing the dose of OAC (or intensity of warfarin), with possible omission of ASA the day after PCI, given the higher risk of bleeding in this context.
  - OAC regimens evaluated in the context of a triple therapy regimen include:
    - rivaroxaban 2.5 mg BID + ASA + clopidogrel
    - warfarin (the recommended INR target is 2.0-2.5).
  - OAC regimens that have been evaluated in the context of a dual pathway regimen include:
    - rivaroxaban 15 mg daily (10 mg in patients with renal dysfunction) + clopidogrel 75 mg daily
    - dabigatran 110 mg or 150 mg twice daily + clopidogrel 75 mg daily. Note that in the RE-DUAL PCI trial evaluating dabigatran in patients with AF undergoing PCI, the dabigatran 110 mg BID was associated with a trend to a higher risk of death or thrombotic events (11% versus 8.5%, hazard ratio 1.30, 95% CI 0.98-1.73, P=0.07). This risk was not observed with the dabigatran 150 mg BID dose (7.9% versus 7.9%, hazard ratio 0.97, 95% CI 0.68-1.39, P=0.44). Therefore, in patients who are not at high risk of bleeding, the dabigatran 150 mg BID dose, when used in combination with clopidogrel 75 mg daily (ASA omitted), may be preferable.
    - Trials evaluating apixaban and edoxaban in patients with AF undergoing PCI are on-going.
- Consider using a proton pump inhibitor for protection against gastro-intestinal bleeding while patients are on a triple therapy regimen.
- When a $P2Y_{12}$ inhibitor is to be combined with OAC as part of a dual pathway or triple therapy regimen, then clopidogrel is suggested over ticagrelor or prasugrel given its lower risk of bleeding complications and the lack of data on ticagrelor or prasugrel in combination with OAC.
- Several risk scores have been formulated to quantitate ischemic risk. While none of these scores have been validated in a population of patients with AF undergoing PCI, they may still be helpful to the clinician in estimating risk.

Patients with AF who Undergo PCI

Following the initial period of antithrombotic therapy for patients with AF undergoing PCI for ACS or high-risk elective PCI:

- If age < 65 and $CHADS_2$ = 0, we recommend long-term therapy with either ASA alone or, if high-risk clinical or angiographic features of ischemic events and low risk of bleeding, ASA + $P2Y_{12}$ inhibitor (*Strong Recommendation, High-Quality Evidence*); or
- If age ≥ 65 or $CHADS_2$ ≥ 1, we recommend long-term therapy with either OAC alone (*Strong Recommendation, Moderate- and High-Quality Evidence*) or, if high-risk clinical or angiographic features of ischemic events persist and low risk of bleeding, OAC plus single antiplatelet therapy with ASA or a $P2Y_{12}$ inhibitor (*Weak Recommendation, Low-Quality Evidence*).

Practical tip - The COMPASS trial demonstrated that, in patients with stable CAD or PAD who did not have atrial fibrillation, ASA added to very low dose OAC (rivaroxaban 2.5 mg BID) reduced major cardiovascular events. It is important to note that rivaroxaban 2.5 mg BID has not been evaluated for long-term stroke prevention in patients with AF. The standard stroke prevention dose of rivaroxaban in patients with AF is 15 mg or 20 mg daily. Consideration could be given to extending treatment long-term with OAC (at a standard AF stroke prevention dose) plus single antiplatelet therapy (clopidogrel or ASA) in selected patients at low risk of bleeding who have high-risk clinical or angiographic features for ischemic events.

- We recommend that patients who have concomitant symptomatic CAD and another condition requiring OAC receive a regimen of antithrombotic therapy that is based on a balanced assessment of their risk of (1) systemic embolism, (2) future coronary event(s) and (3) clinically significant bleeding associated with the use of antithrombotic agents (*Strong Recommendation, High-Quality Evidence*).

In patients with a previous valve replacement who undergo PCI for an ACS or non-ACS indication:

- For patients with a mechanical valve replacement, we suggest an initial regimen of ASA 81 mg daily plus clopidogrel 75 mg daily plus a vitamin K antagonist (VKA) (triple therapy). ASA may be discontinued as early as the day after PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent thrombotic events versus major bleeding (*Weak Recommendation, Very Low-Quality Evidence*).

- For patients with a mechanical valve replacement, we recommend against the use of a NOAC regardless of whether it is in combination with antiplatelet therapy or used alone (*Strong Recommendation, Moderate-Quality Evidence*).

- For patients with a surgical bioprosthetic valve replacement, (implanted < 6 months), we suggest DAPT with ASA 81 mg daily and clopidogrel 75 mg daily for at least 6 months (and up to 12 months) (*Weak Recommendation, Very Low-Quality Evidence*).
- For patients with a transcatheter aortic valve replacement (TAVR) (implanted < 6 months), we suggest DAPT with ASA 81 mg daily and clopidogrel 75 mg daily for 3-6 months (*Weak Recommendation, Very Low-Quality Evidence*).

Values and preferences - Following PCI, the uninterrupted use of a vitamin K antagonist (warfarin) is critical to minimize the risk of valve thrombosis in patients with a mechanical valve. A NOAC should not be used in this setting. The duration of triple therapy will vary depending on an individual patient's risk of thrombotic versus bleeding events. In patients with low risk of thrombotic events and high risk of bleeding, the duration of triple therapy can be short, with omission of ASA as early as the day following PCI. In patients with high risk of thrombotic events and low bleeding risk, the duration of triple therapy can be longer, for up to 6 months of treatment. Patients at intermediate risk of thrombotic and bleeding events the duration of triple therapy will be somewhere in between.

Practical tip - In patients with a mechanical heart valve, warfarin is specifically indicated. Other OAC's are not recommended.

Patients with Venous Thromboembolism Undergoing PCI

In patients with venous thrombo-embolism undergoing PCI for an ACS or non-ACS indication:

- We suggest an initial regimen of ASA 81 mg daily plus clopidogrel 75 mg daily plus either parenteral **OR** oral anticoagulation (in accordance with DVT/PE recommendations). ASA may be discontinued as early as the day following PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent ischemic events versus major bleeding. Following ASA discontinuation, we suggest that OAC plus clopidogrel 75 mg daily be continued for up to 12 months after the initial PCI (*Weak Recommendation, Very Low-Quality Evidence*).

- For patients requiring an elective PCI, we recommend delaying PCI if appropriate until the completion of parenteral or oral anticoagulation for VTE (*Strong Recommendation, Very Low-Quality Evidence*).

† In selected patients requiring extended VTE prophylaxis (ie orthopedic surgery or surgical oncology), the same recommendations can be followed as for VTE therapy. When VTE prophylaxis is discontinued, DAPT can be resumed if minimum duration has not been completed as per other clinical risk profile.

Values and preferences - This recommendation places emphasis on optimizing the prevention and treatment of DVT and PE with either a parenteral or oral anticoagulant.

In patients with established left ventricular thrombus undergoing PCI for an ACS or non-ACS indication:

- We suggest an initial regimen of triple therapy with ASA 81 mg daily plus clopidogrel 75 mg daily plus OAC. ASA may be discontinued as early as the day following PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent coronary ischemic events versus major bleeding. Following ASA discontinuation, we suggest treatment with OAC plus clopidogrel 75 mg daily for up to 1 year. If there is evidence of LV thrombus resolution ≥ 3 months after PCI, we suggest discontinuation of OAC and treatment with ASA 81 mg daily plus a $P2Y_{12}$ inhibitor for up to 1 year after PCI (*Weak Recommendation, Very Low-Quality Evidence*).

Practical tip - Warfarin is the only anticoagulant evaluated for the treatment of established left ventricular thrombus. While NOACS are generally safer than warfarin, they have not been evaluated specifically in this context.

Patients Undergoing PCI who are at Risk of Left Ventricular Thrombus

In patients undergoing PCI for an ACS indication who are high-risk of developing LV thrombus:

- We recommend dual antiplatelet therapy (DAPT) with ASA 81 mg daily plus either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily for up to 1 year (*Strong Recommendation, Moderate-Quality Evidence*).

- We suggest routine use of triple therapy should be avoided given the weak evidence for prevention of LV thrombus and higher risk of bleeding events (*Weak Recommendation, Moderate-Quality Evidence*).

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