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2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy

December 2017

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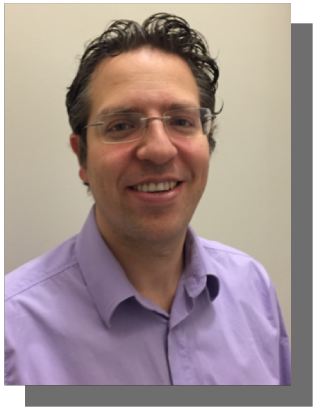

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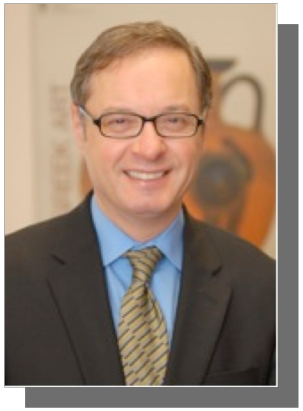

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Overview of 2018 Guideline Topics

- Duration of DAPT
  - ACS and non-ACS patients
- Management of DAPT in patients undergoing:
  - Non-cardiac surgery
  - Elective or semi-urgent CABG
- When and how to switch between oral antiplatelet therapies
- PCI + need for OAC
  - Atrial Fibrillation
  - VTE
  - Mechanical or Bioprosthetic heart valves (Including TAVR)
  - Established or possible LV thrombus

2018 Recommendations

Duration of DAPT

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

Recommendations

1. We **recommend** dual antiplatelet therapy (DAPT) with ASA 81 mg daily plus 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)**.
2. 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.

Duration of DAPT for patients treated with PCI in ACS settings

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.
- 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).

High-risk clinical and angiographic features for thrombotic events

Clinical	Angiographic
Prior myocardial infarction or troponin positive acute coronary syndrome	Multiple stents (≥ 3 stents implanted, ≥ 3 lesions stented)
Diabetes Mellitus treated with oral hypoglycemics or insulin✚	Long lesion length (> 60 mm total stent length)
Chronic kidney disease (creatinine clearance ≤ 60 ml/min)	Complex lesions (bifurcation treated with 2 stents, stenting of chronic occlusion)
Prior stent thrombosis	Left main or proximal LAD stenting
	Multivessel PCI

✚Net benefit to diabetics in the absence of any of other high risk features is unclear

Factors associated with increased bleeding risk

1.	Need for OAC in addition to DAPT
2.	Advanced age (> 75 years)
3.	Frailty
4.	Anemia with hemoglobin < 110 g/dL
5.	Chronic renal failure (creatinine clearance < 40 mL/min)
6.	Low Body Weight (< 60 kg)
7.	Hospitalization for bleeding within last year
8.	Prior stroke/intracranical bleed
9.	Regular need for NSAIDS or prednisone

Risk scores for DAPT duration decisions

Score Name	Online calculator	Patient Population	Score Description	DAPT duration periods	Score variables	Validation	Comments
PRECISE-DAPT[19]	www.precisedaptscore.com/predapt/index.html	PCI with or without ACS	Estimates 1 year rates of ischemic and bleeding events for patients treated with PCI. Patients with PRECISE-DAPT score>25 have lower predicted rates of bleeding events and similar rates of ischemic events with shortened DAPT (3-6 months versus 12-24 months)	3-6 months vs. 12-14 months	Age, previous bleeding, white-blood-cell count, haemoglobin, creatinine clearance	Validated in two separate cohorts (total patients involved in the development: 29,730) c-statistic in the two validation cohorts = 0.66 and 0.70	Discrimination lower for patients on prasugrel Angiographic and PCI variables not included Does not provide guidance to support the decision to prolong DAPT over one year following PCI
CALIBER[130]	https://farr-data-lab.shinyapps.io/caliber-prolonged_dapt_benefits_harms_risks/	Patients surviving 1 year post MI including those treated with or without PCI	Estimates ischemic and bleeding events 2-6 years post MI with and without prolonged DAPT	12 months vs. >12 months	Ischemic prediction score includes 20 variables and bleeding prediction score includes 18 variables	Validated in two cohorts (total patients involved in the development: 19,784) c-statistic in the validation cohort = 0.75 for ischemic endpoints, and 0.72 for major bleeding	High number of variables included in the model Angiographic and PCI variables not included Did not include any patients treated with prasugrel
DAPT[16]	http://tools.acc.org/DAPTriskapp/#!/content/calculator/	Patients 1 year after PCI without bleeding or ischemic events	Estimates the net benefit between ischemic and bleeding events with prolonged DAPT. Patients with DAPT score ≥ 2 had fewer ischemic and bleeding events with prolonged dual antiplatelet therapy (>12 months)	12 months vs. >12 months	Age, cigarette smoking, diabetes mellitus, MI at presentation, prior PCI or prior MI, paclitaxel-eluting stent, stent diameter <3 mm, CHF or LVEF <30%, vein graft stent	Validated in a separate retrospective cohort (total patients involved in the development: 19,784) c-statistic in the validation cohort = 0.64 in both the ischemic and bleeding models	Incorporates angiographic and PCI data <50% of the patients in the derivation cohort were implanted second-generation DES Did not include any patients treated with ticagrelor

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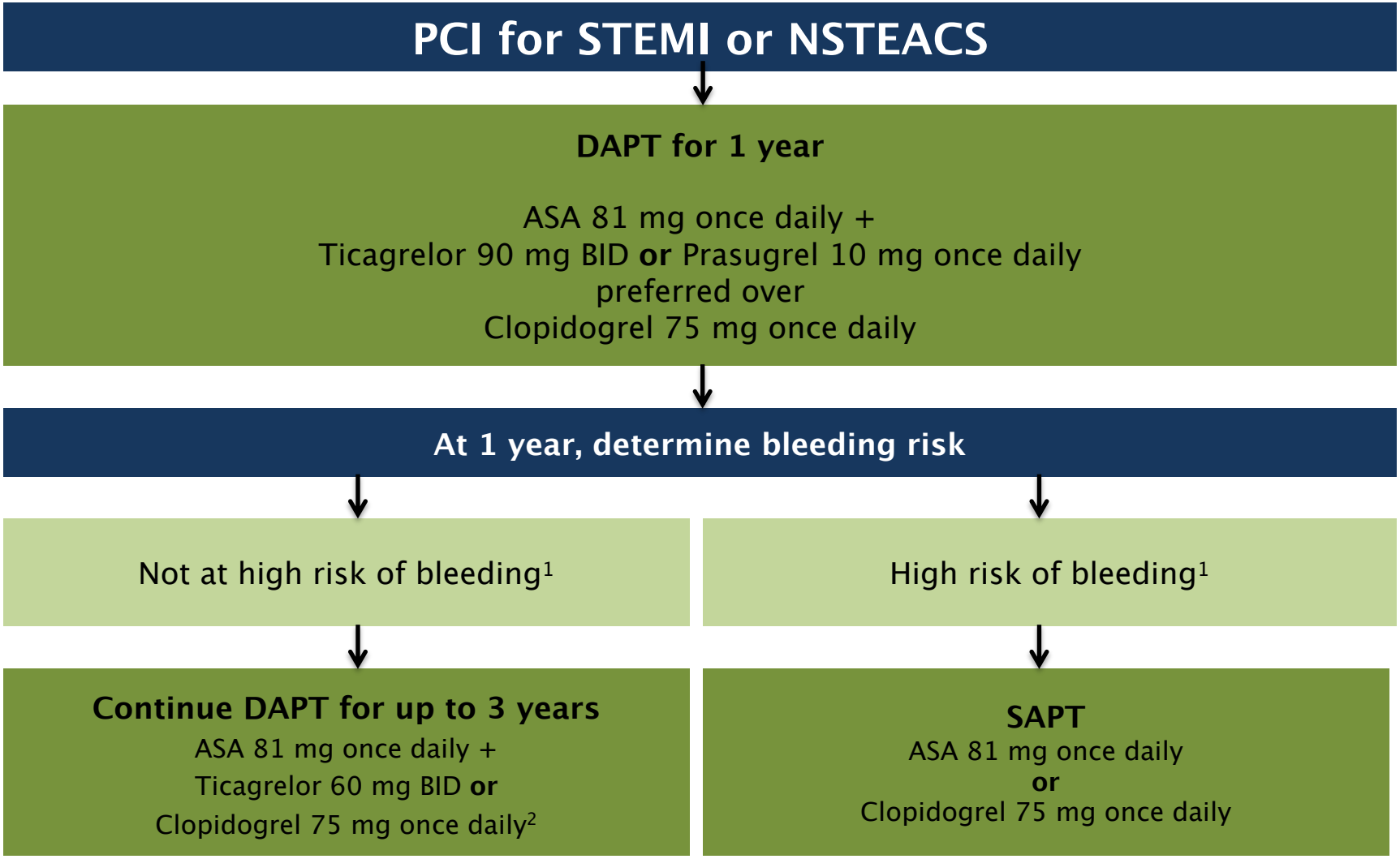

1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior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

Strong recommendation

Weak recommendation

In patients undergoing PCI for a non-ACS indication (e.g., stable ischemic heart disease):

Recommendations

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

4. 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)**.
5. 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 BMS was used) or 3 months (if a DES was used); **(Weak Recommendation, Low Quality Evidence)**.

Duration of DAPT in patients treated with PCI for non-ACS

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 experiencing 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.

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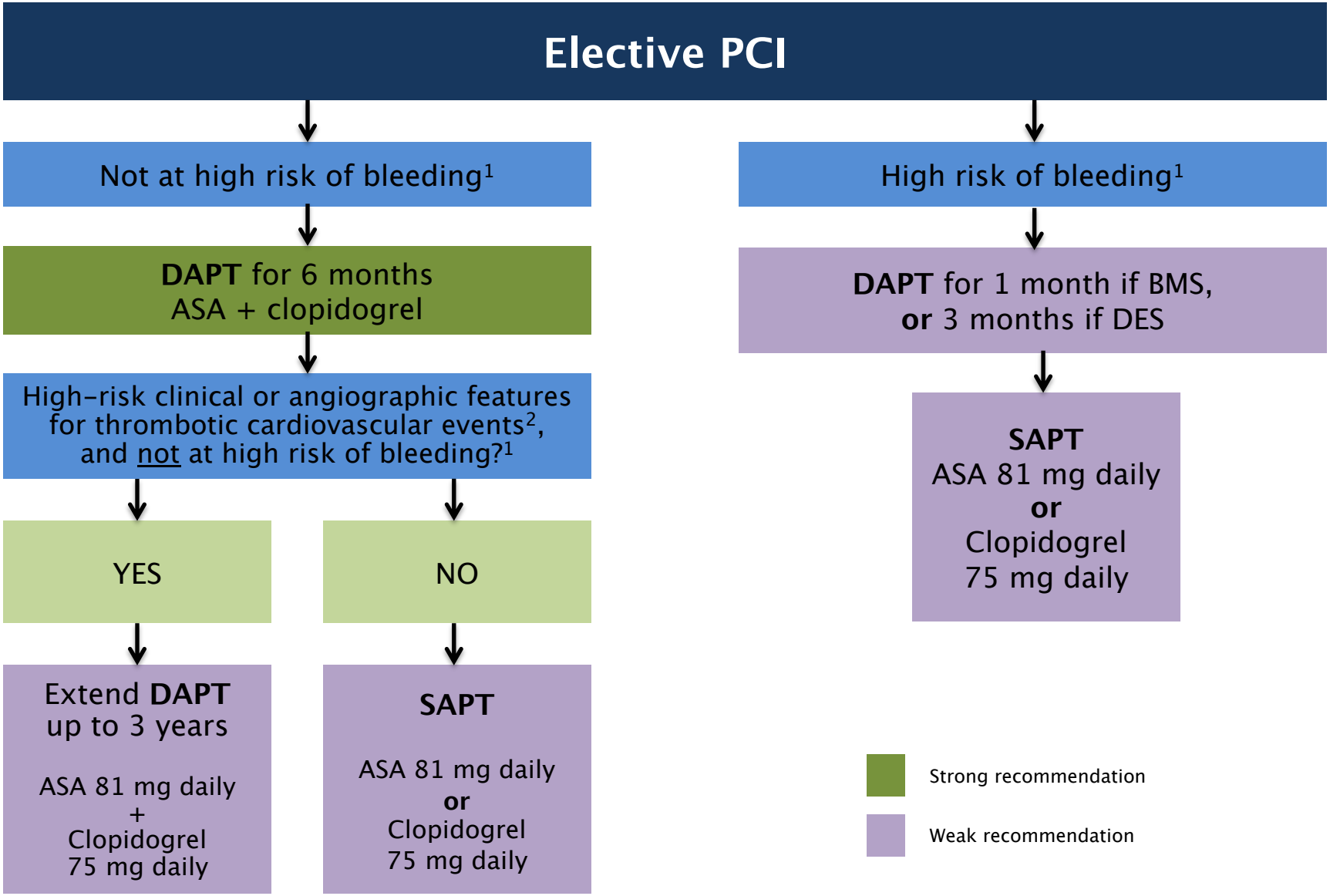


1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior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

Management of patients undergoing elective or semi-urgent surgery

Interrupting DAPT for non-cardiac surgery

Recommendations

6. In patients 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).**

7. In patients 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 semi-urgent non-cardiac surgery, we **suggest** delaying surgery for at least 1 month after PCI **(Weak Recommendation, Low Quality Evidence)**.

Interrupting DAPT for non-cardiac surgery

Recommendations

8. In patients 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).**

9. In patients 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).**

10. In patients 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).**

Interrupting DAPT for non-cardiac surgery

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 semi-urgent CABG surgery after ACS

Recommendations

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

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

Elective or semi-urgent CABG surgery after ACS

Recommendations

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

14. To minimize the risk of bleeding, for patients with an ACS who are receiving prasugrel and need semi-urgent CABG, we **suggest** a minimum interruption of prasugrel for 5 days prior to CABG **(Weak Recommendation, Very Low Quality Evidence)** and **recommend** an ideal interruption period of 7 days prior to elective CABG **(Strong Recommendation, Moderate Quality Evidence).**

Elective or semi-urgent CABG surgery after ACS

Practical tip:

- Antiplatelet therapy management in the peri-operative 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.

Switching Therapy

Examples of common clinical scenarios for $P2Y_{12}$ inhibitor switching

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 pharmacodynamics	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

Switching therapy

$P2Y_{12}$ Inhibitor

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

Intensification strategies

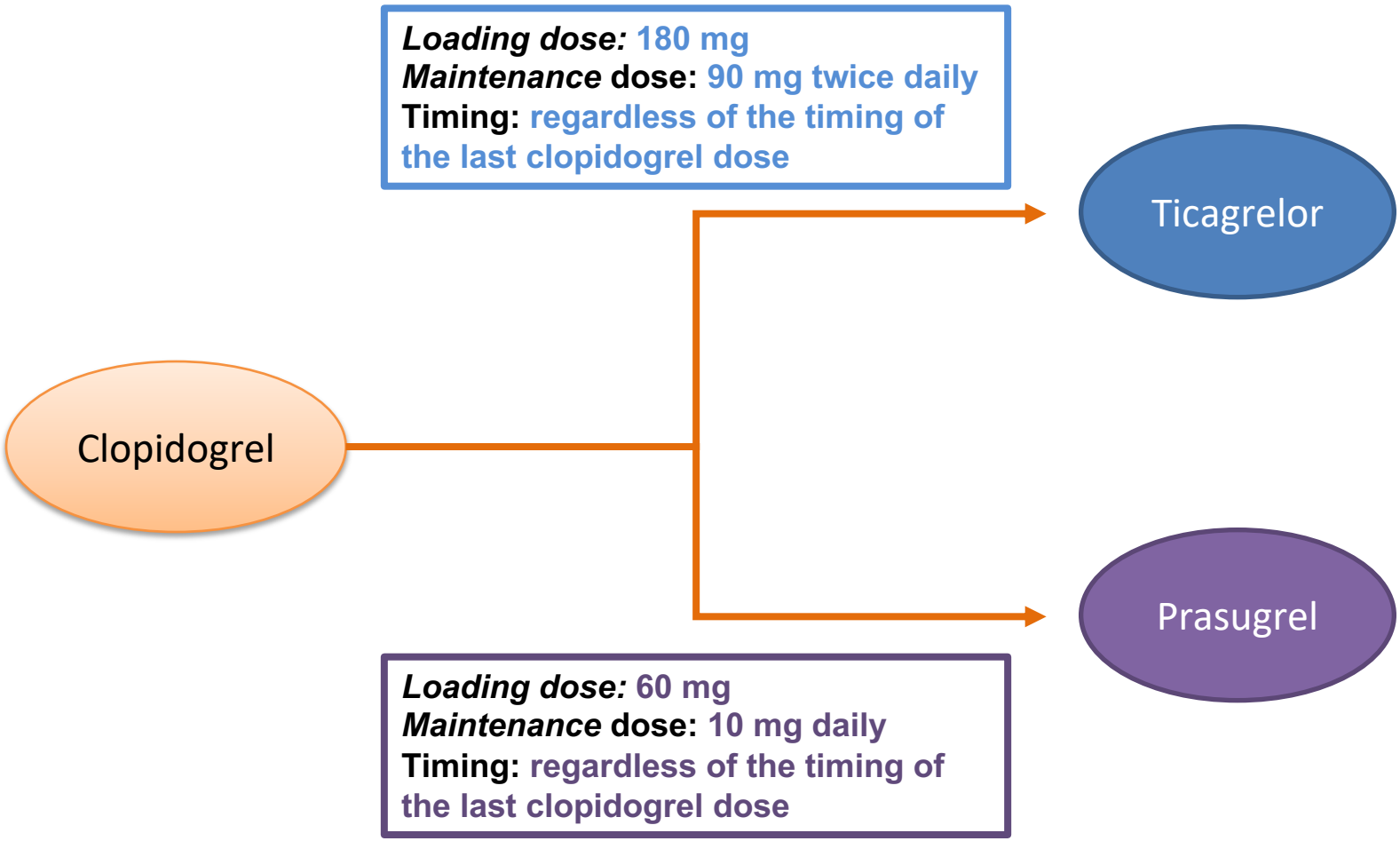
Switching from clopidogrel to ticagrelor

16. 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

17. 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).**

Intensification strategies



Intensification strategies

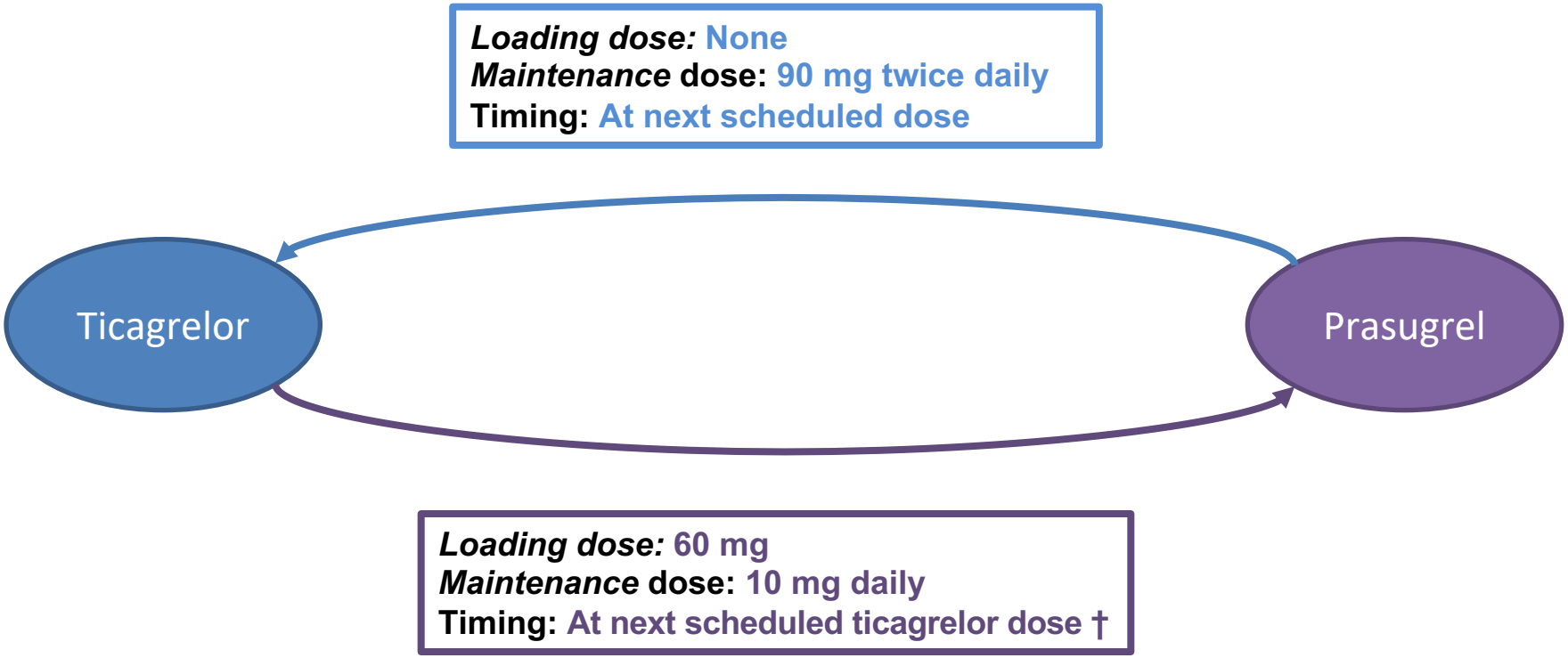
Switching from prasugrel to ticagrelor

18. For patients requiring a switch from prasugrel to ticagrelor, we **suggest** ticagrelor 90 mg twice daily, 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

19. 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).**

Switching between prasugrel and ticagrelor



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

De-escalation strategies

20. For patients on 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

21. For patients on 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).**

De-escalation strategies

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.

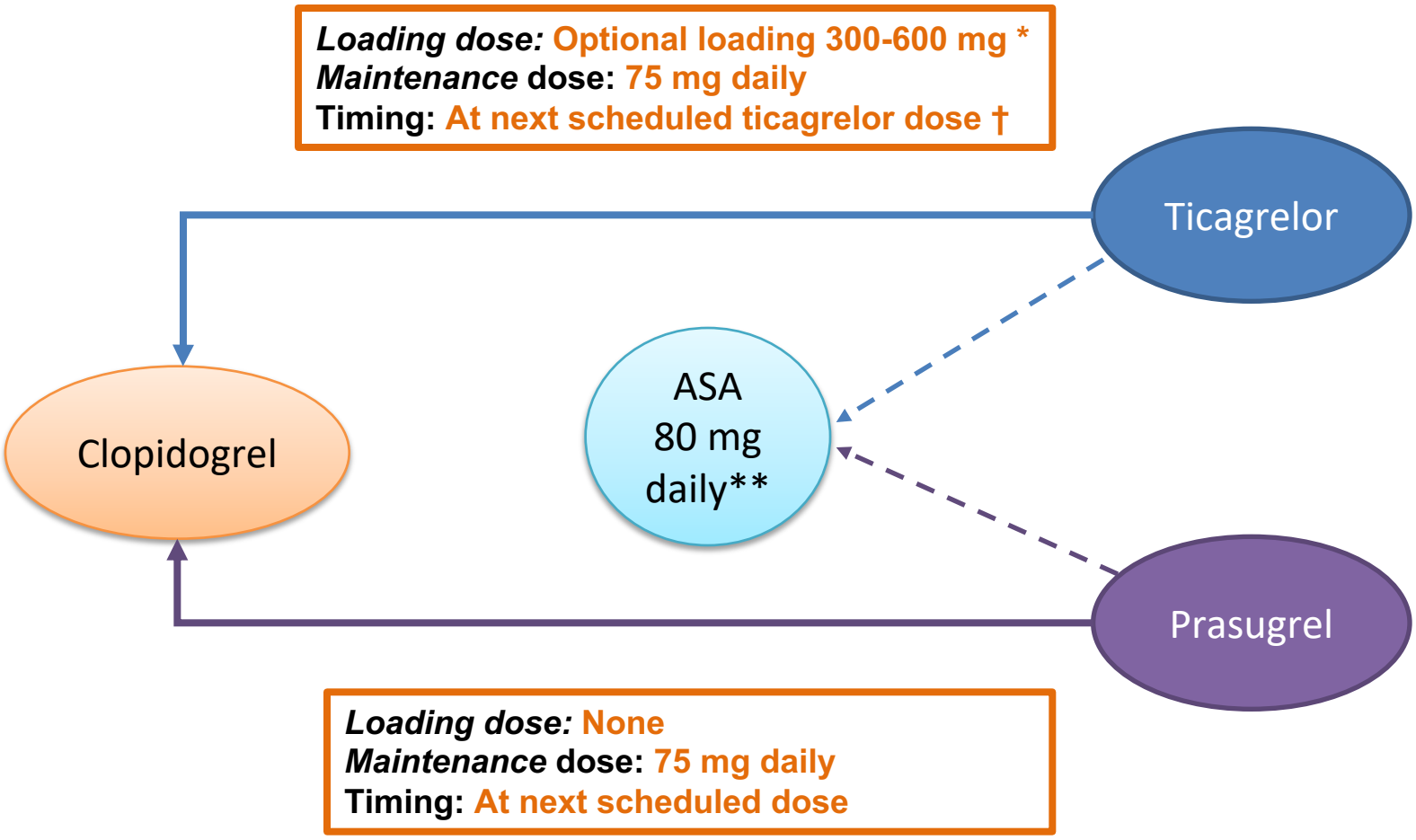
De-escalation strategies

Switching from prasugrel to clopidogrel

22. For patients on prasugrel who are experiencing significant side effects (excluding bleeding) or who are unable to tolerate the drug (and where 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 based on 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



* 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

APT + OAC Therapies in patients with AF and PCI

Patients undergoing PCI with AF

Recommendation

23. We **recommend** that patients who have concomitant **atrial fibrillation** (AF) and **symptomatic coronary artery disease** (CAD) receive a regimen of antithrombotic therapy that is 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:

Recommendation

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

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.

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.

In patients with AF undergoing elective PCI without high-risk features:

Recommendation

25. If **age ≥ 65 years or CHADS$_2$ ≥ 1**, we **suggest** OAC + 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**).

In patients with AF undergoing elective PCI without high-risk features:

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:

Recommendation

26. 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 develop and low risk of bleeding, ASA + a $P2Y_{12}$ 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, High Quality Evidence)** or, if high-risk clinical or angiographic features of ischemic events develop and low risk of bleeding, OAC plus single antiplatelet therapy with ASA or a $P2Y_{12}$ inhibitor **(Strong Recommendation, Moderate and High Quality Evidence).**

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

Practical tip:

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

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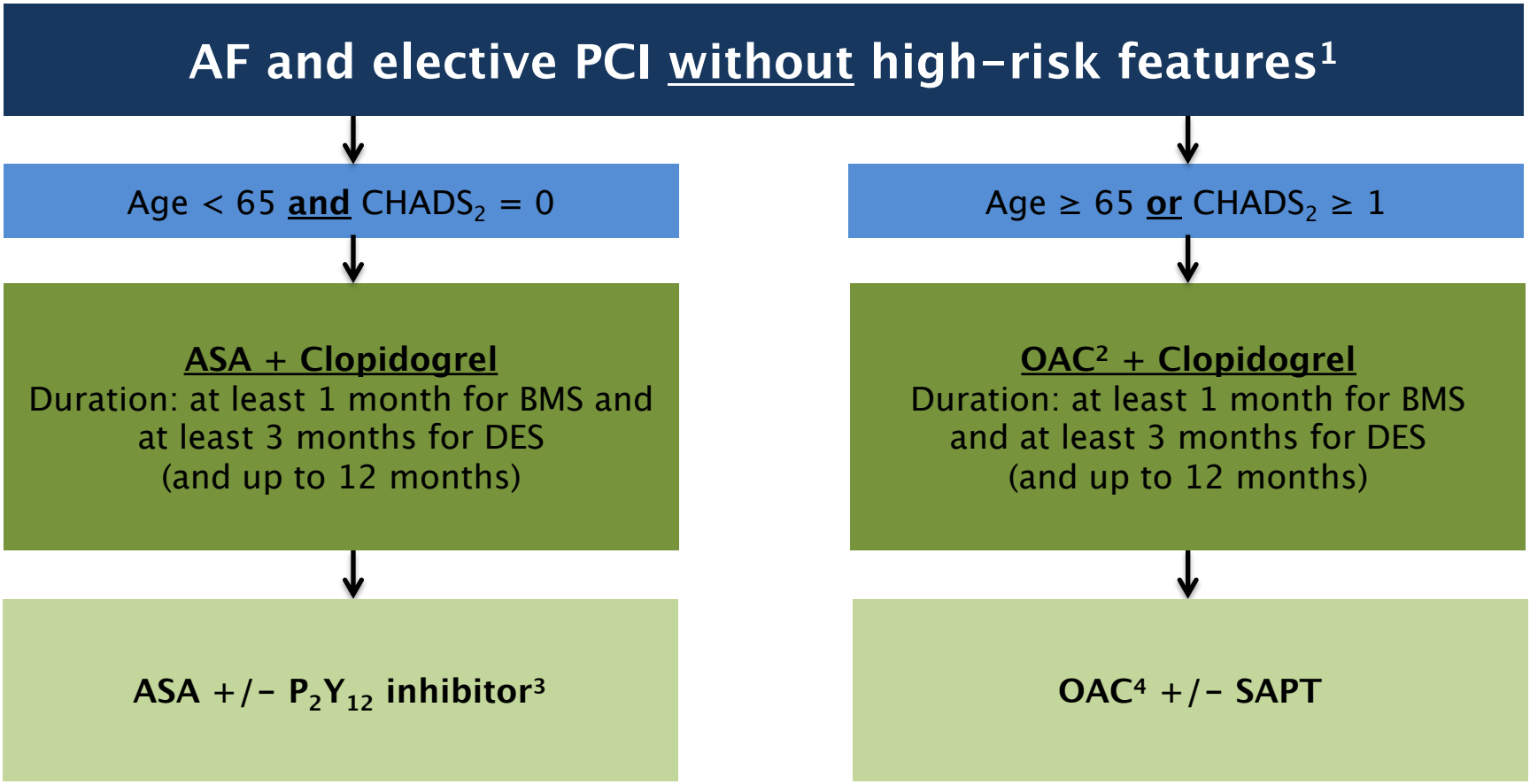


1 A PCI is considered high-risk based on clinical and angiographic features such as: diabetes mellitus, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent 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 P_2Y_{12} 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

AF and elective PCI without high-risk features[1]

Figure footnotes

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), 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 P_2Y_{12} 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 following 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

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

Recommendation

27. If **age < 65 years and $CHADS_2$=0**, we **recommend** DAPT alone with ASA 81 mg daily plus a $P2Y_{12}$ inhibitor (ticagrelor or 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.

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

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 shorter-duration DAPT and patients at higher risk of coronary thrombotic events and lower risk of bleeding should be considered for longer duration of DAPT.

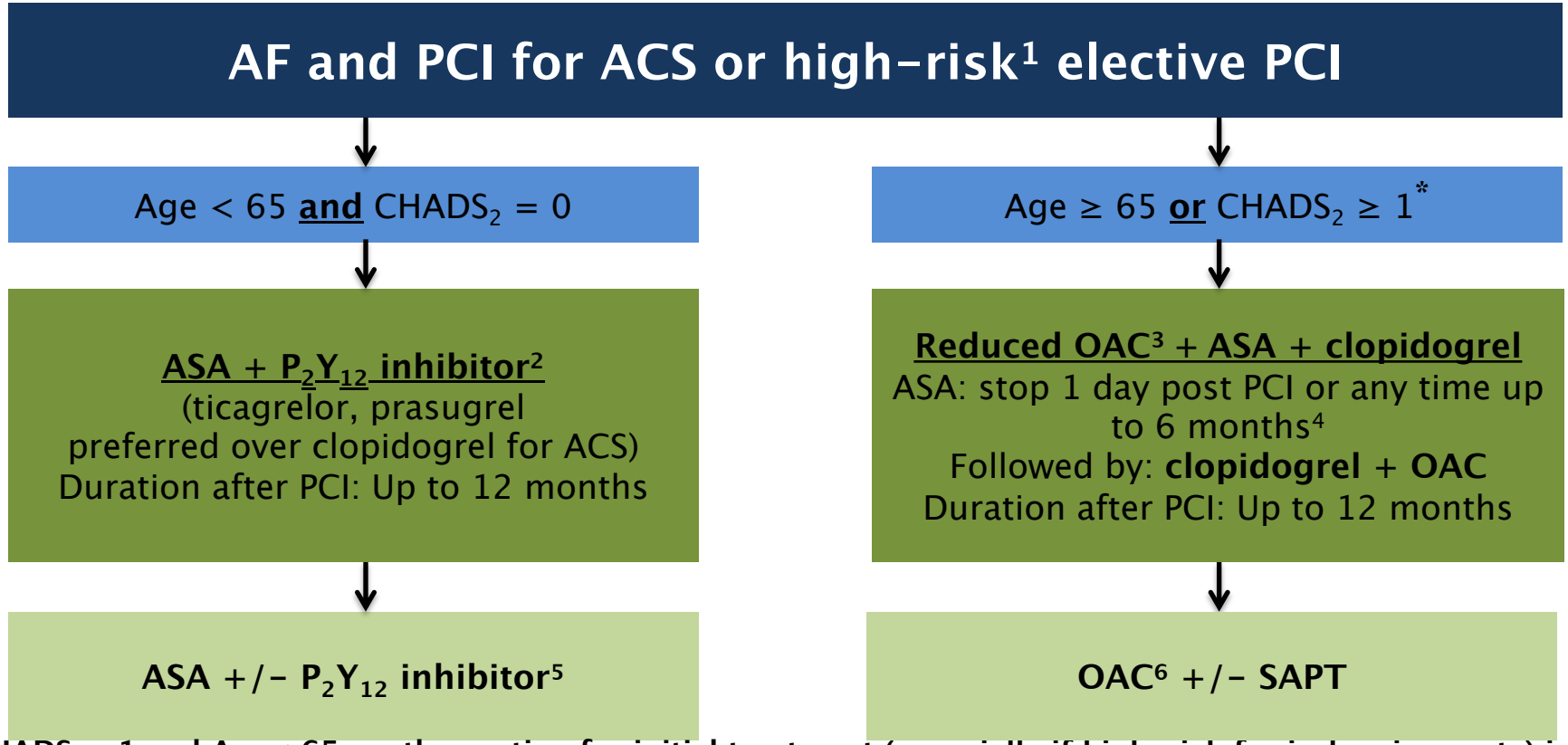
In patients with AF undergoing PCI for ACS or elective PCI with high-risk features:

Recommendation
28. 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 Evidence**).

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

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 approximatley 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).

2018 CCS/CAIC Focused Update of the Guidelines for the Use of Antiplatelet Therapy



***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**

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, multi-vessel 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 P_2Y_{12} 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

AF and PCI for ACS or high-risk[1] elective PCI

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, multi-vessel 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 P_2Y_{12} 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.

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.

Practical Tips

- **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.

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

Recommendation

29. 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).**

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

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.

APT + OAC Therapies
Other reasons for OAC

Other reasons for anticoagulation

Recommendation

30. 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 prior valve replacement who undergo PCI for an ACS or non-ACS indication:

31. 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).**

Other reasons for anticoagulation

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

32. 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).**

33. 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).**
34. 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).**

Other reasons for anticoagulation

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.

Other reasons for anticoagulation

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

35. 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).**

36. 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).**

ǂ 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.

Other reasons for anticoagulation

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

Other reasons for anticoagulation

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

37. 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.

Other reasons for anticoagulation

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

38. 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).**

39. We **suggest** 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).**

Conclusions

High-risk clinical and angiographic features for thrombotic events

Clinical	Angiographic
Prior myocardial infarction or troponin positive acute coronary syndrome	Multiple stents (≥ 3 stents implanted, ≥ 3 lesions stented) or use of biodegradable vascular scaffold
Diabetes Mellitus treated with oral hypoglycemics or insulin✚	Long lesion length (> 60 mm total stent length)
Chronic kidney disease (creatinine clearance ≤ 60 ml/min)	Complex lesions (bifurcation treated with 2 stents, stenting of chronic occlusion)
Prior stent thrombosis	Left main or proximal LAD stenting
Current Smoker	Multivessel PCI

✚Net benefit to diabetics in the absence of any of other high risk features is unclear

Factors associated with increased bleeding risk

1.	Need for OAC in addition to DAPT
2.	Advanced age (> 75 years)
3.	Frailty
4.	Anemia with hemoglobin < 110 g/dL
5.	Chronic renal failure (creatinine clearance < 40 mL/min)
6.	Low Body Weight (< 60 kg)
7.	Hospitalization for bleeding within last year
8.	Prior stroke/intracranical bleed
9.	Regular need for NSAIDS or prednisone

Risk scores for DAPT duration decisions

Score Name	Online calculator	Patient Population	Score Description	DAPT duration periods	Score variables	Validation	Comments
PRECISE-DAPT[19]	www.precisedaptscore.com/predapt/index.html	PCI with or without ACS	Estimates 1 year rates of ischemic and bleeding events for patients treated with PCI. Patients with PRECISE-DAPT score>25 have lower predicted rates of bleeding events and similar rates of ischemic events with shortened DAPT (3-6 months versus 12-24 months)	3-6 months vs. 12-14 months	Age, previous bleeding, white-blood-cell count, haemoglobin, creatinine clearance	Validated in two separate cohorts (total patients involved in the development: 29,730) c-statistic in the two validation cohorts = 0.66 and 0.70	Discrimination lower for patients on prasugrel Angiographic and PCI variables not included Does not provide guidance to support the decision to prolong DAPT over one year following PCI
CALIBER[130]	https://farr-data-lab.shinyapps.io/caliber-prolonged_dapt_benefits_harms_risks/	Patients surviving 1 year post MI including those treated with or without PCI	Estimates ischemic and bleeding events 2-6 years post MI with and without prolonged DAPT	12 months vs. >12 months	Ischemic prediction score includes 20 variables and bleeding prediction score includes 18 variables	Validated in two cohorts (total patients involved in the development: 19,784) c-statistic in the validation cohort = 0.75 for ischemic endpoints, and 0.72 for major bleeding	High number of variables included in the model Angiographic and PCI variables not included Did not include any patients treated with prasugrel
DAPT[16]	http://tools.acc.org/DAPTriskapp/#!/content/calculator/	Patients 1 year after PCI without bleeding or ischemic events	Estimates the net benefit between ischemic and bleeding events with prolonged DAPT. Patients with DAPT score ≥ 2 had fewer ischemic and bleeding events with prolonged dual antiplatelet therapy (>12 months)	12 months vs. >12 months	Age, cigarette smoking, diabetes mellitus, MI at presentation, prior PCI or prior MI, paclitaxel-eluting stent, stent diameter <3 mm, CHF or LVEF <30%, vein graft stent	Validated in a separate retrospective cohort (total patients involved in the development: 19,784) c-statistic in the validation cohort = 0.64 in both the ischemic and bleeding models	Incorporates angiographic and PCI data <50% of the patients in the derivation cohort were implanted second-generation DES Did not include any patients treated with ticagrelor

Examples of common clinical scenarios for $P2Y_{12}$ inhibitor switching

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 pharmacodynamics [131]	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

Doses of OAC evaluated in RCTS of patients undergoing PCI

Trials		Primary endpoint	Comments
WOEST (n=573)	**Clopidogrel 75 mg daily + warfarin** Versus **ASA 80-100 mg + clopidogrel 75 mg daily + warfarin**	Any TIMI bleeding episode (minimal, minor, major) at 12 months Clopidogrel + warfarin: 19.4% ASA+clopidogrel + warfarin: 44.4% (p<0·0001)	-69% had AF/flutter -Most of the reduction in bleeding was in minimial and minor bleeding -Not powered for efficacy (thrombotic events) -Use of PPI: <40%
ISAR-TRIPLE (n=614)	**ASA 75-200 mg daily** **+ clopidogrel 75 mg daily** **+ warfarin (lowest recommended target INR)** for 6 weeks versus 6 months	Composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months 6 weeks triple therapy: 9.8% 30 events) 6 months triple therapy: 8.8% (27 events) (p=0.63)	-The trial was underpowered for its primary endpoint -No differences in efficacy or safety were found -Prevalence of AF: 84% -Use of PPI: 37.2%
PIONEER-AF (n=2124)	**1. Rivaroxaban 15 mg daily + P2Y12 inhibitor (mainly clopidogrel)** **2. Rivaroxaban 2.5 mg twice daily + DAPT (ASA + P2Y12 inhibitor, mainly clopidogrel)** **Step down to rivaroxaban 15 mg daily + P2Y12 inhibitor** **3. Traditional triple therapy: ASA + clopidogrel + warfarin**	Clinically significant bleeding (composite of TIMI major, minor or requiring medical attention) at 12 months 1. Rivaroxaban 15 mg daily+clopidogrel: 16.8% 2. Rivaroxaban 2.5 mg BID + DAPT: 18.0% 3. Traditional triple therapy (ASA+clopidogrel+warfarin): 26.7% (p<0.001 versus both groups 1 and 2)	-Prevalence of AF: 100% -Clopidogrel used as the P2Y12 inhibitor in >93% of patients -Duration of triple therapy for groups and 3 were not randomized (1, 6 or 12 months) -Most of the reduction in bleeding was in bleeding requiring medical attention with no difference in TIMI major or minor bleeding -Not powered to detect differences in efficacy -Use of PPI: <40%
RE-DUAL PCI (n=2725)	**Dabigatan 110 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily)** **Dabigatan 150 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily)** **Traditional triple therapy: ASA+clopidogrel+warfarin**	Time to first major or clinically relevant non-major bleeding event Dual therapy with dabigatran 110 mg twice daily: 15.4% Triple therapy group: 26.9% (p<0.001) Dual therapy with dabigatran 150 mg twice daily: 20.0% Corresponding triple therapy group: 25.7% (p=0.002)	-Prevalence of AF: 100% -Clopidogrel used as the P2Y12 inhibitor in 88% of patients (ticagrelor in 12% of patients); Not powered to detect differences in efficacy; Use of PPI: not provided

Dual Pathway and Triple Therapy Regimens Evaluated in Clinical Trials

Dual Pathway	Triple Therapy
1. Rivaroxaban 15 mg once daily + clopidogrel 75 mg once daily[1]	1. Rivaroxaban 2.5 mg BID + ASA 81 mg once daily + clopidogrel 75 mg once daily[1]
2. Dabigatran 110* or 150 mg BID + clopidogrel 75 mg once daily[2]	2. Warfarin (INR 2.0-2.5) + ASA 81 mg once daily + clopidogrel 75 mg once daily[4]
3. Warfarin + clopidogrel 75 mg once daily[3]	

*In the RE-DUAL PCI trial, the 110 mg BID dabigatran dose 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 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.

1. PIONEER-AF: Gibson CM et al. NEJM 2016;375:2423]
2. RE-DUAL PCI: Cannon CP et a.l. NEJM 2017; 377:1513-1524
3. WOEST: Dewilde et al., Lancet 2013;381:1107-15
4. ISAR Triple :Fiedler et al . J Am Coll Cardiol 2015;65:1619-29

Risk scores for DAPT duration

Scores	Variables	Predicted outcomes
DAPT [1]	Age, MI at presentation, prior MI or PCI, diabetes, stent diameter <3 mm, smoking, paclitaxel-eluting stent, CHF/low EF, SVG PCI	Trade-off between ischemic/bleeding outcomes >1 year after PCI
PRECISE-DAPT [2]	Age, previous bleeding, WBC, hemoglobin, creatinine clearance	Trade-off between ischemic/bleeding outcomes with 3-6 versus 12-24 months of DAPT
CALIBER [3]	Ischemic score: 20 variables Bleeding score: 18 variables	Ischemic and bleeding events 2-6 years post-MI, with or without DAPT

1. Yeh RW et al. JAMA. 2016. 2. Costa F et al. Lancet. 2017. 3. Pasea L et al. Eur Heart J. 2017.

Randomized Trials of OAC Following PCI

Trials	Studied regimens	Primary endpoint	Comments
WOEST (n=573) Lancet 2008	Warfarin (target INR 2.0) + clopidogrel 75 mg daily Versus Warfarin (target INR 2.0) + clopidogrel 75 mg daily + ASA 80-100 mg daily	Any bleeding episode at 12 months Warfarin + clopidogrel: 19.4% Warfarin + clopidogrel + ASA: 44.4% (p<0·0001)	Prevalence of AF/flutter: 69% Use of PPI: <40% Stents used 65% DES, 35% BMS
ISAR-TRIPLE (n=614) JACC 2015	ASA 75-200 mg daily + clopidogrel 75 mg daily + warfarin (lowest recommended target INR) for 6 weeks versus 6 months	Composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months •6 weeks triple therapy: 9.8% •6 months triple therapy: 8.8% (p=0.63)	Prevalence of AF: 84% Use of PPI: 37.2% Stents used 99% DES INR therapeutic range 64%
PIONEER-AF (n=2124) NEJM 2016	Rivaroxaban 15 mg daily + P2Y12 inhibitor (group 1) vs Rivaroxaban 2.5 mg twice daily + DAPT (group 2) vs Warfarin (INR 2.0-3.0) + DAPT (group 3)	Clinically significant bleeding at 12 months Group 1: 16.8% Group 2: 18.0% Group 3: 26.7% (p<0.001 versus both groups 1 and 2)	Prevalence of AF: 100% Clopidogrel used in 93% of patients Use of PPI: <40% Stents used 65% DES, 32% BMS INR therapeutic range 65%
RE-DUAL PCI (n=2725) NEJM 2017	Dabigatran 110 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) vs Dabigatran 150 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) vs Warfarin (INR 2.0-3.0) + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) + aspirin ≤100 mg daily	Time to first major or clinically relevant non-major bleeding event 15.4% in 110mg dual therapy vs 26.9% comparable triple therapy group (P<0.001 for noninferiority; P<0.001 for superiority) 20.2% in 150mg dual therapy vs 25.7% comparable triple therapy group (P<0.001 for noninferiority)	Prevalence of AF: 100% Clopidogrel used in 88% of patients Stents used 83% DES, 35% BMS Use of PPI: unknown INR therapeutic range 64%