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Society Guidelines

2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy

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ABSTRACT

Antiplatelet therapy (APT) has become an important tool in the treatment and prevention of atherosclerotic events, particularly those associated with coronary artery disease. A large evidence base has evolved regarding the relationship between APT prescription in various clinical contexts and risk/benefit relationships. The Guidelines Committee of the Canadian Cardiovascular Society and Canadian Association of Interventional Cardiology publishes regular updates of its recommendations, taking into consideration the most recent clinical evidence. The present update to the 2011 and 2013 Canadian

RÉSUMÉ

Le traitement antiplaquettaire (TAP) constitue désormais un outil important dans le traitement et la prévention des événements athérosclérotiques, particulièrement ceux qui sont associés à la coronaropathie. Le vaste corpus de données scientifiques a évolué sur la relation entre l'ordonnance de TAP dans les divers contextes cliniques et les rapports bénéfices/risques. Le comité des lignes directrices de la Société canadienne de cardiologie et de l'Association canadienne de cardiologie d'intervention actualise et publie régulièrement ses recommandations en tenant compte des données probantes cliniques

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

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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Cardiovascular Society APT guidelines incorporates new evidence on how to optimize APT use, particularly in situations in which few to no data were previously available. The recommendations update focuses on the following primary topics: (1) the duration of dual APT (DAPT) in patients who undergo percutaneous coronary intervention (PCI) for acute coronary syndrome and non-acute coronary syndrome 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; (4) when and how to switch between different oral antiplatelet therapies; and (5) management of antiplatelet and anticoagulant therapy in patients who undergo PCI. For PCI patients, we specifically analyze the particular considerations in patients with atrial fibrillation, mechanical or bioprosthetic valves (including transcatheter aortic valve replacement), venous thromboembolic disease, and established left ventricular thrombus or possible left ventricular thrombus with reduced ejection fraction after ST-segment elevation myocardial infarction. In addition to specific recommendations, we provide values and preferences and practical tips to aid the practicing clinician in the day to day use of these important agents.

les plus récentes. La mise à jour des lignes directrices sur le TAP de la Société canadienne de cardiologie de 2011 et 2013 intègre de nouvelles données probantes sur la façon d'optimiser l'utilisation du TAP, particulièrement dans les situations où il existait peu ou pas de données. La mise à jour des recommandations porte principalement sur les sujets suivants : 1) la durée du double TAP (DTAP) chez les patients qui subissent l'intervention coronarienne percutanée (ICP) en raison d'un syndrome coronarien aigu ou d'un syndrome coronarien non aigu ; 2) la prise en charge du DTAP chez les patients qui subissent une intervention chirurgicale non cardiaque ; 3) la prise en charge du DTAP chez les patients qui subissent un pontage aortocoronarien non urgent ou semi-urgent ; 4) le moment et la façon de passer d'un traitement antiplaquettaire par voie orale à un autre ; 5) la prise en charge du TAP et de l'anticoagulothérapie chez les patients qui subissent une ICP. Chez les patients qui subissent l'ICP, nous analysons notamment les considérations particulières chez les patients qui souffrent de fibrillation auriculaire, qui portent des valves mécaniques ou bioprothétiques (y compris ceux qui ont subi un remplacement valvulaire aortique par cathéter), qui souffrent d'une maladie thromboembolique veineuse et dont le diagnostic de thrombus ventriculaire gauche est établi ou dont le diagnostic de thrombus ventriculaire gauche avec fraction d'éjection réduite après l'infarctus du myocarde avec sus-décalage du segment ST est possible. En plus des recommandations particulières, nous donnons des valeurs, des préférences et des conseils pratiques pour aider le clinicien praticien dans l'utilisation quotidienne de ces importants agents.

Scope of the 2018 Antiplatelet Therapy Guideline Update

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.[1,2] 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).

Development of the Guidelines

The CCS appointed co-chairs, a primary panel, and a secondary panel to develop this guideline update. The primary panel developed the scope of the document, identified topics for review, performed the literature review and critical appraisal of the identified literature, drafted the recommendations, and voted on the recommendations. Peer review was provided by the secondary panel and the CCS Guidelines Committee. The final draft was presented and approved by the CCS Executive Committee.

The committee used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, which started by defining the question or issue of interest, including the patient population, intervention, comparator, and outcomes.[3,4] A systematic search was performed to identify all relevant studies, including systematic reviews and meta-analyses. The committee reviewed the information from the systematic search and evaluated the quality of evidence for each outcome across the studies. Recommendations were then formulated according to the factors outlined in the GRADE approach. Summaries of the literature review are provided online at www.ccs.ca.

1. Duration of DAPT in Patients Who Undergo PCI

1.1. Duration of DAPT in patients treated with PCI for ACS

The recommended duration of DAPT after ACS and PCI was 12 months on the basis of the results of **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents (CURE) and **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent Ischemic **E**vents in Patients Undergoing **P**ercutaneous **C**oronary **I**ntervention (PCI-CURE), respectively.[1,2,5,6] Although a number of recent randomized trials have suggested that DAPT duration may be shortened to 3-6 months after

PCI,[7-12] particularly with the use of newer generation drug-eluting stents (DESs), most patients enrolled had stable coronary artery disease (CAD) or low-risk ACS with fewer patients having high-risk ACS or STEMI. In one meta-analysis, 67% of ACS patients had biomarker-negative ACS.[6] Despite the enrollment of low-risk ACS patients in these trials, shorter durations of DAPT compared with 1 full year of DAPT were still associated with higher rates of myocardial infarction (MI) and stent thrombosis at 1 year.[6] This suggests that ACS patients who are not at high risk of bleeding should receive at least 12 months of DAPT (Fig. 1).

Clopidogrel or prasugrel, in addition to acetylsalicylic acid (ASA), beyond 1 year after PCI was studied in the DAPT trial[13] and the use of ticagrelor long-term after previous MI was studied in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial.[14] In the DAPT trial, 9961 patients with a DES who received PCI (43% for ACS) who did not have a bleeding event within the first year were randomly assigned to continue thienopyridine treatment beyond 1 year or to receive placebo. Continued treatment with thienopyridine, compared with placebo, reduced the rates of stent thrombosis (0.4% vs 1.4%; hazard ratio [HR], 0.29; $P < 0.001$) and major adverse cardiovascular (CV) and cerebrovascular events (4.3% vs 5.9%; HR, 0.71; $P < 0.001$). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (HR, 1.36; 95% confidence interval [CI], 1.00-1.85; $P = 0.05$). The rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% vs 1.6%; $P = 0.001$).

In the PEGASUS-TIMI 54 trial, 21,162 patients who experienced an MI 1-3 years earlier were randomized in a double-blind fashion to ticagrelor 90 mg twice daily (BID), ticagrelor 60 mg BID, or placebo.[14] All the patients were to receive low-dose ASA and were followed for a median of 33 months. The 2 ticagrelor doses each reduced the composite of CV death, MI or stroke (7.85% ticagrelor 90 mg, 7.77% ticagrelor 60 mg, 9.04% placebo; HR 90 mg ticagrelor vs placebo: 0.85; $P = 0.008$; HR 60 mg ticagrelor vs placebo: 0.84; 95% CI, 0.74-0.95; $P = 0.004$). Rates of **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%; $P < 0.001$ for each dose vs placebo); the rates of intracranial hemorrhage or fatal bleeding in the 3 groups were 0.63%, 0.71%, and 0.60%, respectively. Because the reduction in ischemic events was offset by an increase in bleeding in DAPT and PEGASUS, patients who have risk factors for recurrent ischemic events might have a more favourable benefit to risk ratio. Clinical and angiographic variables that place a patient at higher risk of ischemia are shown in Table 1.[14,15,19]

Factors associated with increased risk of bleeding are shown in Table 2. Other strategies to improve the benefit-risk ratio currently being evaluated in randomized trials include using $P2Y_{12}$ inhibitor monotherapy without ASA to reduce the risk of bleeding after PCI.[20,21]

Recommendations

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

1. We recommend DAPT with ASA 81 mg daily with either ticagrelor 90 mg BID 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 BID 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 CV events and stent thrombosis vs an increase in bleeding complications.

Practical tip. 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 receiving oral anticoagulant therapy.

Practical tip. Patients who have clinical or angiographic features for an increased risk of a thrombotic CV event might derive greater absolute benefit from extended DAPT beyond 1 year (Table 1).

Practical tip. Quantitative risk scores have been developed.[19,21-24] These scores might help identify higher-risk patients with greater absolute benefit of extended DAPT (Table 3).

Practical tip. An ongoing assessment of bleeding and ischemic risk should be performed at least annually to determine whether DAPT should be continued.

Practical tip. Prasugrel should be avoided in patients with previous transient ischemic attack or stroke.

Practical tip. For patients who have a bleeding event during ticagrelor or prasugrel treatment, but for whom continuation of a $P2Y_{12}$ agent is believed to be warranted, please refer to the de-escalation recommendations in section 2.3.

Practical tip. 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 showed a higher level of platelet inhibition with ticagrelor compared with clopidogrel.[25] Ongoing trials are evaluating clinical outcomes with ticagrelor in this setting (ClinicalTrials.gov NCT02298088).

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

1.2.1. Shortened-duration DAPT. Several recent randomized trials of patients treated with newer-generation

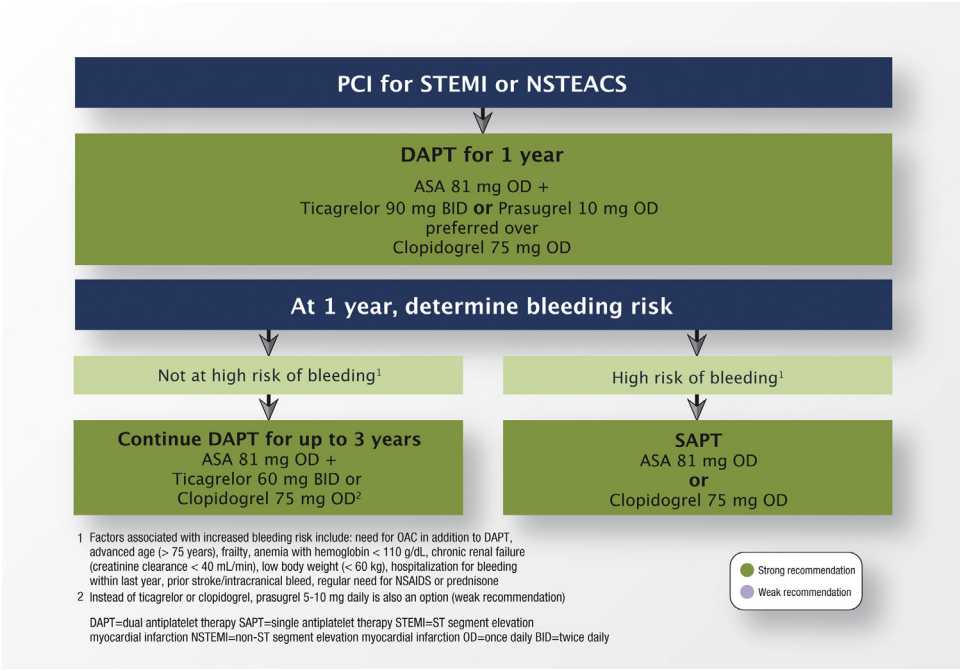

Figure 1. Recommendations for duration of DAPT in patients with ACS (STEMI or NSTEACS) who undergo PCI. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice daily; DAPT, dual antiplatelet therapy; NSAID, nonsteroidal anti-inflammatory drug; NSTEACS, non ST-segment elevation acute coronary syndrome; OAC, oral anticoagulant; OD, once daily; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; STEMI, ST-segment elevation myocardial infarction.

DESs, particularly for a non-ACS indication, have evaluated shortening DAPT to less than 1 year (Fig. 2).[7,9-12,26,27] Fifteen published meta-analyses compared 3-6 months vs 12 months of DAPT.[28-39] A consistent finding was that lower rates of bleeding were associated with shorter courses of DAPT.[28-35,38] Thirteen meta-analyses showed no difference in ischemic or thrombotic end points with shorter courses of DAPT.[29,31-36] Meta-analyses have also evaluated longer vs shorter durations of DAPT in various patient subgroups, in which a consistent finding was that a shorter duration of DAPT might give rise to an increased risk of ischemic outcomes. These groups include previous ACS,[40] multivessel disease,[17] and complex PCI.[15]

Table 1. High-risk clinical and angiographic features for thrombotic events

Feature
Clinical[14]
Before myocardial infarction or troponin-positive acute coronary syndrome
Diabetes mellitus treated with oral hypoglycemics or insulin*
Chronic kidney disease (creatinine clearance $\leq$ 60 mL/min)
Previous stent thrombosis
Current smoker
Angiographic
Multiple stents ($\geq$3 stents implanted, $\geq$ 3 lesions stented)[15] or use of a biodegradable vascular scaffold
Long lesion length (>60 mm total stent length)[15]
Complex lesions (bifurcation treated with 2 stents, stenting of chronic occlusion)[15]
Left main or proximal LAD stenting[16]
Multivessel PCI[17]

LAD, left anterior descending artery; PCI, percutaneous coronary intervention.

*Net benefit to diabetic patients in the absence of any of other high risk features is unclear.[18]

1.2.2. Extended duration of DAPT after PCI for a non-ACS indication. Extending DAPT duration beyond 12 months might have benefit in certain patients who receive DES for non-ACS indications.[13] In the DAPT trial, 57% of patients had a non-ACS indication for their index PCI. Three meta-analyses showed consistent results with decreased MI and stent thrombosis, but increased bleeding when DAPT was extended beyond a year after PCI.[18,35,41]

Recently, the **C**ardiovascular **O**utcom**e**s for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial[42] randomized 27,395 patients with stable CAD or peripheral arterial disease to: (1) rivaroxaban 2.5 mg BID with ASA 100 mg daily vs (2) rivaroxaban 5 mg BID vs (3) ASA 100 mg daily. Over a mean follow-up of 23 months, rivaroxaban 2.5 mg with ASA reduced the composite outcome of CV death, MI, or stroke by 24% (4.1% vs 5.4%; HR, 0.76; 95% CI, 0.66-0.86; $P < 0.001$), reduced all-cause mortality by 18% (3.4% vs 4.1%; HR, 0.82; 95% CI, 0.71-0.96; $P = 0.01$), increased major bleeding by 70% (3.1% vs 1.9%; HR, 1.70; 95% CI, 1.40-2.05; $P < 0.001$), but did not significantly increase intracranial or fatal

Table 2. Factors associated with increased bleeding risk

Need for OAC in addition to DAPT
Advanced age (older than 75 years)
Frailty
Anemia with hemoglobin < 110 g/L
Chronic renal failure (creatinine clearance < 40 mL/min)
Low body weight (<60 kg)
Hospitalization for bleeding within past year
Previous stroke/intracranial bleed
Regular need for NSAIDs or prednisone

DAPT, dual antiplatelet therapy; NSAIDs, nonsteroidal anti-inflammatory drugs; OAC, oral anticoagulation.

Table 3. Published risk assessment tools for determining duration of DAPT

Score name	Online calculator	Patient population	Score description	DAPT duration periods	Score variables	Validation	Comments
PRECISE-DAPT[22]	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 higher predicted rates of bleeding events and similar rates of ischemic events with shortened DAPT (3-6 months vs 12-24 months)	3-6 Months vs 12-14 months	Age, previous bleeding, white blood cell count, hemoglobin, creatinine clearance	Validated in 2 separate cohorts (total patients involved in the development: 29,730); c-statistic in the 2 validation cohorts = 0.66 and 0.70	Discrimination lower for patients receiving prasugrel; Angiographic and PCI variables not included; Does not provide guidance to support the decision to prolong DAPT over 1 year after PCI
CALIBER[17]	https://farr-data-lab.shinyapps.io/caliber-prolonged_dapt_benefits_harms_risks	Patients surviving 1 year after MI including those treated with or without PCI	Estimates ischemic and bleeding events 2-6 years after 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 2 cohorts (total patients involved in the development: 19,784); c-statistic in the validation cohort = 0.75 for ischemic end points, 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[19]	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 DAPT (>12 months)	12 Months vs >12 months	Age, cigarette smoking, diabetes mellitus, MI at presentation, previous PCI or 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 the ischemic as well as bleeding model	Incorporates angiographic and PCI data; < 50% of the patients in the derivation cohort received a second-generation DES; Did not include any patients treated with ticagrelor

ACS, acute coronary syndrome; CALIBER, **Ca**rdiovascular Disease Research Using **Li**nked **B**espoke Studies and **E**lectronic Health **R**ecords; CHF, congestive heart failure; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRECISE-DAPT, **PRE**dicting bleeding **C**omplications **I**n patients undergoing **S**tent implantation and subs**E**quent **D**ual **A**nti **P**latelet **T**herapy.

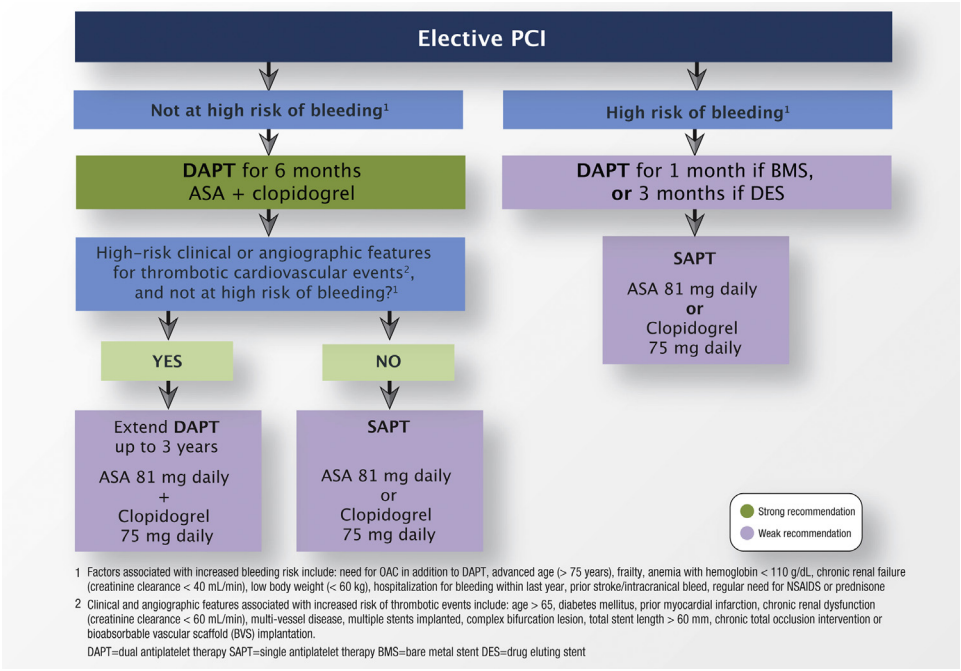

Figure 2. Recommendations for duration of DAPT in patients who undergo elective PCI. ASA, acetylsalicylic acid; BMS, bare-metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

bleeding.[42] Rivaroxaban 5 mg BID led to a nonsignificant 10% reduction in the composite outcome. The combination of rivaroxaban 2.5 mg BID and low dose ASA offers another option for secondary prevention in patients with chronic stable CAD.

Recommendations

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

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 CV events and who are at low risk of bleeding, it is reasonable to extend the duration of DAPT to >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 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 CV thrombotic events and stent thrombosis vs 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 tip. A general principle to consider when deciding on the duration of DAPT is a balanced assessment of the risk of thrombotic CV events and bleeding. Patients at lower risk of thrombotic events and higher risk of bleeding can be considered for a shorter duration of DAPT whereas patients at higher risk of thrombotic events and lower risk of bleeding should be considered for a longer duration of DAPT.

Practical tip. As in the ACS setting, patients who undergo PCI for a non-ACS indication might derive greater absolute benefit of extended DAPT if they have clinical or angiographic features associated with increased risk of thrombotic CV events (Table 1).

1.3. Risk scores to inform DAPT duration after PCI

Three risk scores to quantify bleeding and/or ischemic events have been published and retrospectively validated.[19,22,23] To date, no score has been prospectively validated. Table 3 provides a summary of these scores and links to online calculators for each. Scores combining bleeding and ischemic events assume equal clinical importance to each type of event. Risk scores should complement available clinical and angiographic data, and are not a substitute for clinical judgement.

1.4. Interrupting DAPT for noncardiac surgery

In patients who are being treated with DAPT after a PCI with a BMS or DES, 2 issues need to be addressed: timing of surgery and perioperative DAPT management.

The only randomized trial in noncardiac surgery to assess perioperative antiplatelet drug management is **Perioperative Ischemic Evaluation** (POISE)-2, which showed that perioperative ASA use did not affect the incidence of CV events or mortality but conferred a small but statistically significant

increased risk for major bleeding (4.6% vs 3.8%; $P = 0.04$).[43] However, only 4% of patients had a coronary stent. In a U.S. observational study of 20,590 patients who had noncardiac surgery within 2 years of PCI and 41,180 matched control participants with coronary stents who did not have surgery, there was a clustering of cardiac events within the first 3 months after PCI, with the highest risk if surgery occurred within 4-6 weeks post-PCI.[44] Among patients having surgery between 6 weeks and 6 months post-PCI, the absolute risk for cardiac events was higher after complex surgery than for less complex inpatient surgery or outpatient surgery (5.3% vs 3.7% vs 0.1%). A key limitation of this study was that perioperative DAPT management was not specified. In a Danish study of 4031 patients with drug-eluting coronary stents and 20,232 control participants without CAD having noncardiac surgery, the risk for adverse cardiac events appeared highest within the first month post-PCI.[45] Beyond 1 month post-PCI, the risk for cardiac events was not affected by the time interval between PCI and surgery. However, information on perioperative antiplatelet management was lacking. Finally, in a registry of 880 post-PCI patients who had noncardiac surgery, in whom ASA and DAPT was continued in approximately 70% and approximately 10% of patients, respectively, 30-day rates of perioperative adverse cardiac and major bleeding events were 3.5% and 5.6%, respectively.[46] Overall, in post-PCI patients receiving DAPT having noncardiac surgery, the perioperative increased risk of bleeding with ASA continuation appears modest, and until patient management data are available it is reasonable to suggest continuing ASA, whereas in most patients, interrupting $P2Y_{12}$ therapy.

Recommendations

6. In patients undergoing PCI who are treated with a BMS and who require elective noncardiac surgery, we recommend delaying surgery for at least 1 month after PCI (Strong Recommendation; Moderate-Quality Evidence).
7. In patients undergoing PCI who are treated with a DES and who require elective noncardiac surgery, we recommend delaying surgery for at least 3 months after PCI (Strong Recommendation; Moderate-Quality Evidence). If there is a need for semiurgent noncardiac surgery, we suggest delaying surgery for at least 1 month after PCI (Weak Recommendation; Low-Quality Evidence).
8. In patients undergoing PCI who are treated with either a BMS or DES and who require elective noncardiac surgery, we suggest continuing ASA perioperatively whenever possible (Weak Recommendation; Low-Quality Evidence).
9. In patients undergoing PCI who are treated with a BMS or DES and who require elective noncardiac surgery, we suggest withholding clopidogrel and ticagrelor for 5-7 days preoperatively, and prasugrel for 7-10 days preoperatively (Weak Recommendation; Low-Quality Evidence).
10. In patients undergoing PCI who are treated with a BMS or DES and who have undergone noncardiac 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 perioperative bleeding will vary considerably depending on the type of surgery performed. Some minor surgical procedures carry a low risk of bleeding, whereas others a very high risk of bleeding. For example, some dental, ophthalmological, and endoscopic procedures carry a low risk of bleeding and can be performed without stopping antiplatelet therapy.

1.5. Elective or semiurgent CABG surgery after ACS

Patients who are receiving DAPT and require elective or semiurgent CABG surgery pose a special challenge, especially after an ACS because of the high bleeding risk associated with CABG and the potentially serious consequences of bleeding (eg, pericardial tamponade). The only randomized trial to assess perioperative use of ASA before CABG is **A**ntithrombotic **T**herapy in **A**cute **C**oronary **S**yndromes (ATACAS), which reported that preoperative use of ASA was not associated with an increased risk for bleeding or transfusion requirements but also did not mitigate the risk for ACS or mortality.[47] The neutral findings of this trial might have arisen from the study design whereby ASA was initiated 1-2 hours before CABG, after a $\geq$ 4-day interruption period, which is not done in clinical practice. The findings suggest, in concert with older studies,[48-50] that it is reasonable to continue ASA in patients with or without an ACS who require CABG. In a registry of ASA-treated patients with an ACS who required CABG surgery, of whom 1266 were receiving ticagrelor and 978 receiving clopidogrel, it appeared that stopping ticagrelor for at least 3 days and stopping clopidogrel for 5 days before CABG was needed to mitigate the risk for perioperative bleeding, compared with a shorter interruption interval.[51] Additional

Recommendations

11. We recommend continuation of ASA in all patients with ACS who require CABG surgery (Strong Recommendation; Moderate-Quality Evidence).
12. 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).
13. 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).
14. 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).

observational studies support these interruption intervals for ticagrelor and clopidogrel, with a longer interval for prasugrel.[52-57]

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

2. Switching Therapy

No large randomized trial with definitive clinical outcomes data has been performed to support switching between $P2Y_{12}$ inhibitors.

In large international registries, intensification of therapy from clopidogrel to a more potent $P2Y_{12}$ inhibitor has been reported in 5%-50% of patients, whereas de-escalation from a more potent agent to clopidogrel was undertaken in up to 11% of patients.[58-66] Common reasons for switching are outlined in Supplemental Table S1.

The predominant evidence for switching between $P2Y_{12}$ inhibitors is on the basis of pharmacodynamic data from small, randomized studies, which lack power to definitively assess ischemic or bleeding outcomes. Registry data consisting of > 4000 patients with switching did not show a signal for increased major bleeding complications.[58-65,67]

Recommendations

15. 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, CV event, bleeding, or significant side effects/intolerance) (Weak Recommendation; Low-Quality Evidence).

2.1. Intensification strategies

2.1.1. Switching from clopidogrel to ticagrelor. In the **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial, 47.1% (n = 4396) of patients randomized to ticagrelor received clopidogrel in the 24 hours preceding randomization (Supplemental Table S1).[68] From pharmacodynamic studies, a ticagrelor 180 mg loading dose resulted in early improvement in platelet inhibition compared with 90 mg, among patients receiving clopidogrel; this effect was abrogated by 72 hours.[69,70] No increase in bleeding was observed using the loading dose of 180 mg.

Recommendations

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

2.1.2. Switching from clopidogrel to prasugrel. In **Tr**ial to Assess **I**mprovement in **T**herapeutic **O**utcomes by Optimizing Platelet Inhibitio**n** With Prasugrel (TRITON), pretreatment with clopidogrel before randomization led to exclusion.[71] Consequently, clinical data from a large trial is lacking for a switch from clopidogrel to prasugrel. Accordingly, decision-making must be on the basis of smaller pharmacodynamic studies consisting of > 3000 patients (Supplemental Fig. S1).[64,72-76] Two randomized studies, **Sw**itching **A**nti **P**latelet Study (SWAP; n = 139) and **Tr**ansferring From Clop**i**dogrel Loading Dose to **P**rasugrel **L**oading Dose in Acute Coronary Syndrome Pati**en**t**s** (TRIPLET; n = 282), evaluated the effects of a loading dose of prasugrel.[72,74] The 60-mg loading dose provided a significant increase in platelet inhibition by 2 hours compared with the 10-mg maintenance dose alone. No increase in bleeding outcomes was observed.

Recommendations

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).

2.2. Switching between prasugrel and ticagrelor

Switching to another potent $P2Y_{12}$ receptor inhibitor rather than de-escalation to clopidogrel would be preferred for patients deemed at higher risk for ischemic events (Supplemental Fig. S2).

2.2.1. Switching from prasugrel to ticagrelor. SWAP-3 was the only randomized study to evaluate the switch from prasugrel to ticagrelor.[77] In 82 ACS patients initially treated with prasugrel, a loading dose of 180 mg of ticagrelor followed by 90 mg BID vs direct initiation of a 90-mg BID dose was compared with a control arm of patients who continued to receive prasugrel. Both switching groups, irrespective of the use of the 180-mg loading dose, showed an early, but transient greater platelet inhibition present by 2 hours and maintained up to 48 hours. At 1 week, both arms were noninferior compared with patients maintained with prasugrel. There was no major or minor bleeding observed in either switching strategy.

Recommendations

18. 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).

2.2.2. Switching from ticagrelor to prasugrel. The SWAP-2 study randomized 110 patients with stable CAD initially treated with ticagrelor to receive a 60-mg loading dose of prasugrel vs direct initiation of a 10-mg daily dose and compared with a control arm of patients maintained with ticagrelor.[78] In both switching strategies, a transient increase in platelet reactivity was observed in the first 48 hours, an effect that was diminished in patients receiving a 60-mg loading dose of prasugrel. By 7 days, the 2 strategies had

comparable platelet inhibition, with no significant bleeding outcomes observed.

Recommendations

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).

2.3. De-escalation strategies

When de-escalating from ticagrelor or prasugrel to clopidogrel, it is important to consider the rationale for switching to balance bleeding vs thrombotic risks (Supplemental Fig. S3). In patients who have suffered major bleeding during treatment with potent $P2Y_{12}$ inhibitors, there might concerns for further bleeding, which might outweigh ischemic risks and in this context discontinuation might be considered. For patients with high-risk features (Table 1), de-escalation to clopidogrel should be considered to complete the recommended duration of DAPT.

Recommendations

20. 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).

Patients may be switched because of side effects with prasugrel or ticagrelor treatment, in which case thrombotic risks might override concerns of bleeding. In the absence of features associated with high risk for thrombotic events (Table 1), de-escalation to clopidogrel can also be considered (in lieu of switching between potent agents in high-risk patients). Among prasugrel- or ticagrelor-treated patients, who subsequently develop a new indication for requiring concurrent treatment with an oral anticoagulant, de-escalation to clopidogrel should also be considered (refer to Section 3).

2.3.1. Switching from ticagrelor to clopidogrel. The **Opti**mizing **Cross**over from Ticagrelor to Clopidogrel in Patients with Acute Coronary Syndrome (OPTI-CROSS) study evaluated strategies for switching from ticagrelor to clopidogrel.[66] Sixty patients were randomized to receive either a 600 mg loading dose followed by 75 mg daily vs directly starting 75 mg daily. At 48 hours after randomization, a loading dose provided improved platelet inhibition compared with the maintenance dose alone; however, this difference was no longer present by 72 hours, thus suggesting an early protective effect with loading.

Recommendations

21. 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 tip. The loading dose of 600 mg conveys a short-term (48 hours) pharmacodynamic advantage after 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 believed to be at high risk for bleeding. **T**iming **o**f **P**latelet **I**nhibition after Acute **C**oronary Syndrome (TOPIC) study, switching from ticagrelor directly to clopidogrel 75 mg daily 1 month after ACS[79] was reported to decrease bleeding without an increase in ischemic events, with the caveat that the study was not powered for ischemic outcomes.[79]

Practical tip. The optimal time for the initiation of clopidogrel has not been extensively studied. In OPTI-CROSS, the switch was made at the next scheduled ticagrelor dose; extending to the following morning (ie, 24 hours after the last ticagrelor dose) might also be reasonable on the basis of pharmacodynamics data from the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study.[80]

2.3.2. Switching from prasugrel to clopidogrel. Switching from prasugrel to clopidogrel 75 mg daily, without additional loading, was evaluated in the TOPIC study (in patients without adverse events by 1 month after ACS) and in the **T**esting **Respo**nsiveness to **P**latelet **I**nhibition on **C**hronic **Antipl**atelet Treatment for **A**cute **C**oronary **S**yndromes (TROPICAL-ACS) trial (initiated 1 week after ACS and then guided on the basis of platelet function testing).[79,81] There was lower bleeding with no signal for increased ischemic outcomes in the de-escalation groups, but it should be noted that both trials were underpowered to assess ischemic end points.

Recommendations

22. 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 in which patients were identified as nonresponders using platelet function testing before randomization were excluded because of generalizability concerns.

3. Patients With AF Who Undergo PCI

Approximately 20% of patients with AF will require PCI at some time.[82] Up to 21% of ACS patients will have new or established AF.[83] In the absence of clear evidence for the optimal pharmacologic strategy to balance the risks of ischemic stroke and stent thrombosis, the use of "triple therapy" with 2 antiplatelet agents and an oral anticoagulant is commonly used. With PCI alone, DAPT is more effective than warfarin with ASA in reducing coronary events.[84] In ACS, DAPT reduces clinical events.[5,6,68,71,85] In patients with nonvalvular AF, oral anticoagulation (OAC) with warfarin reduces the risk of stroke[86] and is more effective than DAPT in preventing thrombotic complications.[87] Non-vitamin K-dependent oral anticoagulants (NOACs) are preferred to warfarin in AF because of their greater convenience and, with some agents, the lower risks of bleeding events and mortality.[88-90]

Although the rationale for "triple therapy" seems reasonable, the risk of bleeding events is concerning. Analyses from the NOAC AF trials suggest a 30%-60% increased bleeding risk in patients receiving a NOAC plus an antiplatelet agent.[91-94] In a large Danish registry of AF patients, greater nonfatal and fatal bleeds were observed with the combination of warfarin with ASA. Warfarin with clopidogrel as well as triple therapy conferred more than a threefold higher risk of bleeding compared with warfarin alone.[95] In a large meta-analysis (mostly observational studies), a combination of clopidogrel and OAC (a so-called "dual pathway") reduced the risk of bleeding compared with triple therapy with no difference in major adverse cardiac events.[96]

The **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) trial (n = 573) compared clopidogrel and warfarin (dual pathway) with ASA and clopidogrel with warfarin (triple therapy) in patients with a need for anticoagulation who underwent PCI.[97] In this open-label trial, a reduction in bleeding (most of which was minor bleeding) was observed with the dual pathway approach. The trial was not powered for efficacy. The **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen-Testing of a 6-Week Versus a 6-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting (ISAR-TRIPLE) trial (n = 614) randomized patients receiving OAC and PCI during concomitant warfarin and ASA treatment to either 6 weeks of clopidogrel (shorter triple therapy) or 6 months of clopidogrel (longer triple therapy). The trial showed no differences in bleeding or efficacy but was notably underpowered for these outcomes. In a post hoc landmark analysis after 6 weeks (with both arms of the study receiving triple therapy at 6 weeks), the 6-month group seemed to experience more major bleeding events.[98] The An **O**pen-Label, Randomized, Controlled, Multicenter Study Explor**i**ng Tw**o** Treatme**n**t Strat**e**gi**e**s of **R**ivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with **A**trial **F**ibrillation who Undergo **P**ercutaneous **C**oronary **I**ntervention (PIONEER AF-PCI) trial (n = 2124) evaluated 2 recent concepts in antithrombotic therapy: the use of a NOAC in place of warfarin and the dual pathway with elimination of ASA as an alternative to a traditional triple therapy regimen. In this open-label study of AF patients receiving PCI, patients were randomized to a $P2Y_{12}$ inhibitor (94.4% received clopidogrel and only 4.3% ticagrelor and 1.3% prasugrel) with rivaroxaban 15 mg daily (dual pathway) for 12 months, DAPT with rivaroxaban 2.5 mg BID (reduced-dose triple therapy) for 1, 6, or 12 months, or DAPT with warfarin (traditional triple therapy) for 1, 6, or 12 months. The dual pathway as well as the reduced-dose triple therapy strategies reduced clinically significant bleeding compared with traditional triple therapy with warfarin. The main limitation of this trial was that it was not powered to detect moderate differences in efficacy, including stroke or stent thrombosis.[99] In a post hoc analysis, there was a reduction in the composite of all-cause death and rehospitalizations (CV hospitalizations as well as bleeding hospitalizations) with rivaroxaban-based strategies compared with traditional triple therapy with warfarin.[100] The **R**andomized **E**valuation of **D**ual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalv**u**lar **A**tria**l** Fibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (RE-DUAL PCI)[101] trial (n = 2725) evaluated 2 doses of dabigatran in patients with AF who underwent PCI. Patients were randomized to dual pathway with dabigatran (110 mg or 150 mg BID) with a $P2Y_{12}$ inhibitor (88% received clopidogrel and 12% received ticagrelor) vs traditional triple therapy with warfarin with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and ASA. Both dual pathway approaches reduced clinically significant bleeding compared with warfarin triple therapy and was noninferior with respect to risk of thromboembolic events—recognizing this study was also underpowered to detect differences in these events. The trials that evaluated a dual pathway regimen are summarized in Supplemental Table S2. Ongoing studies include AUGUSTUS (NCT02415400), which is evaluating apixaban, and **E**doxaba**nT**reatment Vers**us** Vitamin K Antagonist in Pa**t**ients with **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (ENTRUST-AF-PCI) (NCT02866175), which is evaluating edoxaban.

Recommendations

23. We recommend that patients who have concomitant AF and symptomatic 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 without high-risk features who undergo elective PCI we make the following recommendation (Fig. 3).

Recommendations

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

24. If age is < 65 years and **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) = 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 approximately 0.7% per year in patients younger than 65 years of age and $CHADS_2$ score of 0, to approximately 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.

In patients with AF who undergo elective PCI without high-risk features, we make the following recommendation (Fig. 3).

Recommendations

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

25. If age $\geq$ 65 years or $CHADS_2 \geq 1$, 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- to 74-year-old patients and even higher in patients older than 75 years, providing a rationale for the inclusion of OAC in the regimen. The suggestion for OAC and clopidogrel (and omission of ASA) is on the basis of randomized trials that showed a lower risk of bleeding with this regimen vs warfarin with clopidogrel and ASA (traditional triple therapy). Although the evidence suggests a major compromise in efficacy is unlikely 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 who undergo PCI are shown in Table 4. Rivaroxaban 15 mg daily (10 mg daily in patients with renal dysfunction) with clopidogrel and dabigatran 110 or 150 mg BID and clopidogrel have been evaluated in randomized trials vs traditional warfarin-based triple therapy. At the time this document was written, randomized trials evaluating apixaban- and edoxaban-based regimens in patients with AF who undergo PCI were in progress, so no dose recommendations with these agents are provided.

After the initial period of antithrombotic therapy, we make the following recommendations for patients with AF who undergo elective PCI without high-risk features (Fig. 3).

Recommendations

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

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 plus a $P2Y_{12}$ inhibitor (Strong Recommendation, High Quality Evidence); or

After the initial period of antithrombotic therapy for patients with AF without high-risk features who undergo elective PCI, if age is 65 years or older or $CHADS_2 \geq 1$ 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 and single antiplatelet therapy with aspirin 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.

In patients with AF who undergo PCI for ACS or elective PCI with high risk features (Fig. 4) we make the following recommendation.

Recommendations

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

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 who undergo elective PCI) for up to 12 months (Strong Recommendation; High-Quality Evidence).

Values and preferences. Patients with AF who are younger than 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 who undergo 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 (Table 1) and bleeding (Table 2). 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.

Recommendations

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

28. If age $\geq$ 65 years or $CHADS_2 \geq 1$*, 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 for up to 6 months of treatment, depending on the risk of recurrent coronary thrombotic events versus major bleeding (Strong Recommendation, Moderate Quality Evidence). 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, Moderate Evidence).
*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 prasugrel, similar to the recommendation for the $CHADS_2 = 0$ patient.

Values and preferences. In patients 65-74 years of age, the risk of stroke is approximately 2.1% per year and still higher beyond age 75 years, whereas the risk of coronary events is approximately 6%-10% per year after ACS (STEMI or non-STEMI), 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) vs 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 after 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).

Practical tip. All patients should receive ASA 81 mg (or 160 mg if ASA-naive) on the day of the PCI procedure. Thereafter, ASA can be discontinued as early as the day after PCI.

Practical tip. Factors associated with an increased risk of ischemic and bleeding events are shown in Tables 1 and 2.

Practical tip. 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, because of the higher risk of bleeding in this context.

OAC regimens evaluated in the context of a triple therapy regimen include (Table 4):

- Rivaroxaban 2.5 mg BID with ASA and clopidogrel
- Warfarin (the recommended international normalized ratio target is 2.0-2.5)

The OAC regimens that have been evaluated in the context of a dual pathway regimen include (Table 4):

- Rivaroxaban 15 mg daily (10 mg in patients with renal dysfunction) and clopidogrel 75 mg daily
- Dabigatran 110 mg or 150 mg BID and clopidogrel 75 mg daily. Note that in the RE-DUAL PCI trial, which evaluated dabigatran in patients with AF who underwent PCI, the dabigatran 110 mg BID was associated with a trend to a higher risk of death or thrombotic events (11% vs 8.5%; HR, 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% vs 7.9%; HR, 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), might be preferable
- Trials evaluating apixaban and edoxaban in patients with AF who undergo PCI are ongoing

Practical tip. Consider using a proton pump inhibitor for protection against gastrointestinal bleeding while patients are receiving a triple therapy regimen.

Practical tip. 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 because of its lower risk of bleeding complications and the lack of data on ticagrelor or prasugrel in combination with OAC.

Practical tip. Several risk scores have been formulated to quantitate ischemic risk (Table 3). Although none of these scores have been validated in a population of patients with AF who undergo PCI, they might still be helpful to the clinician in estimating risk.

After the initial period of antithrombotic therapy for patients with AF with high-risk features who undergo PCI for ACS or high-risk elective PCI the following recommendations are made (Fig. 4):

Recommendations

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

29. If age $<$ 65 years 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 with $P2Y_{12}$ inhibitor (Strong Recommendation; High-Quality Evidence); or

If age is 65 years or older or $CHADS_2 \geq 1$ 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 with single antiplatelet therapy with ASA or a $P2Y_{12}$ inhibitor (Weak Recommendation; Low-Quality Evidence).

Practical tip. The COMPASS trial[42] showed that, in patients with stable CAD or peripheral arterial disease who did

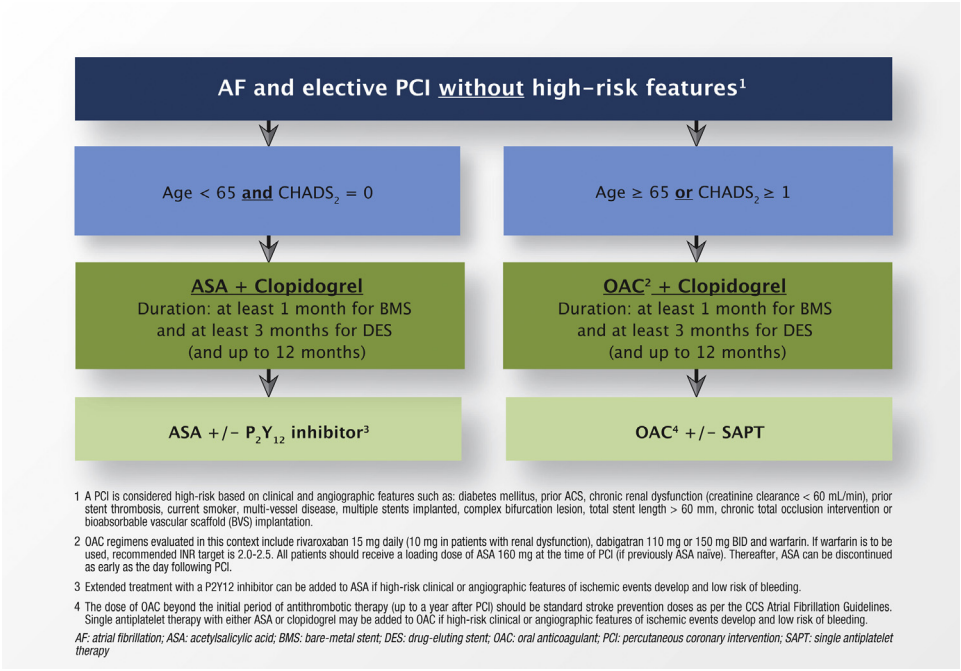

Figure 3. Recommendations for patients with AF without high-risk features who undergo elective PCI. ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; BID, twice daily; BMS, bare-metal stent; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; DES, drug-eluting stent; INR, international normalized ratio; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

not have AF, ASA used in addition to very low dose OAC (rivaroxaban 2.5 mg BID) reduced major CV 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

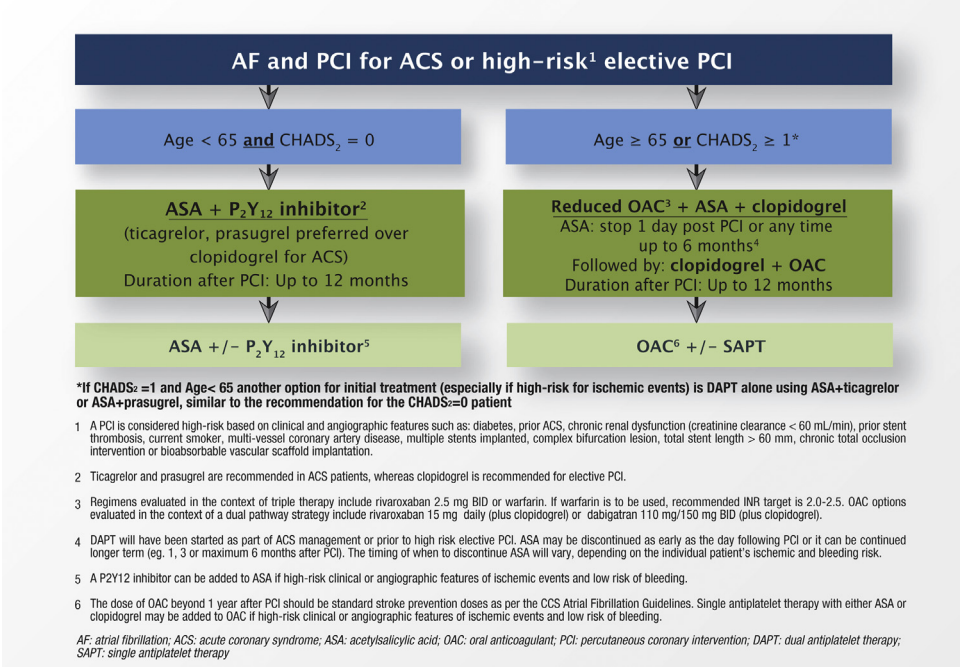

Figure 4. Recommendations for patients with AF who undergo PCI for ACS or high-risk elective PCI. ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; BID, twice daily; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; DAPT, dual antiplatelet therapy; INR, international normalized ratio; OAC, oral anticoagulant; PCI, percutaneous coronary intervention.

given to extending treatment long-term with OAC (at a standard AF stroke prevention dose) and 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.

4. Other Reasons for Anticoagulation

Recommendations

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).

4.1. Prosthetic heart valves

Anticoagulation with vitamin K antagonist (VKA) and/or antiplatelet therapy is indicated to prevent thrombotic complications of a surgically implanted prosthetic heart valve (PHV). A careful assessment of the potential risks of valve thrombosis and systemic bleeding is required when considering a given antithrombotic regimen. As such the optimal combination of agents, duration of antithrombotic therapy, and optimal therapeutic international normalized ratio levels all differ for specific types of valves and are influenced by valvular as well as patient-level characteristics.[102,103] Studies of patients with mechanical[104,105] as well as bioprosthetic heart valves[106,107] have shown an increased risk of valve thrombosis early in the postoperative period, highlighting the importance of adequate antithrombotic regimens early after surgical valve replacement.

Currently the combination of a VKA and low dose ASA (75-100 mg daily) is recommended for patients with a mechanical heart valve; a truncated dose of VKA followed by continuous use of low-dose ASA is recommended for patients with surgically implanted bioprosthetic valves, although it is reasonable to also consider use of antiplatelet therapy alone without OAC.[108] NOACs are contraindicated among patients with mechanical PHVs.

Approximately 10% of patients in WOEST (49 of 563) and approximately 7% of patients in ISAR-TRIPLE (45 of 614) had a PHV as their indication for OAC[97,98]; the subgroup of patients in WOEST with PHV appeared to derive a similar benefit from double therapy as opposed to traditional triple therapy compared with the main WOEST population (P for interaction = 0.116). Retrospective cohort studies that compared traditional triple therapy to double that have included patients with PHV have not reported separate events among PHV patients because of small numbers (2%-11% of total cohort population).[109-116]

Randomized trials of TAVR compared with traditional surgical aortic valve replacement have used DAPT for at least 1 month postprocedure.[117-119] However, these regimens have not been on the basis of randomized data and as such the use of DAPT after TAVR is given a relatively weak recommendation.[108]

In patients with a previous valve replacement who undergo PCI for an ACS or non-ACS indication the following recommendations are made.

Table 4. Dual pathway and triple therapy regimens evaluated in clinical trials

Dual pathway
1. Rivaroxaban 15 mg OD with clopidogrel 75 mg OD[99]
2. Dabigatran 110* or 150 mg BID with clopidogrel 75 mg OD[101]
3. Warfarin with clopidogrel 75 mg OD[97]

Triple therapy
1. Rivaroxaban 2.5 mg BID with ASA 81 mg OD and clopidogrel 75 mg OD[99]
2. Warfarin (INR, 2.0-2.5) with ASA 81 mg OD and clopidogrel 75 mg OD[98]

ASA, acetylsalicylic acid; BID, twice daily; INR, international normalized ratio; OD, every day.

*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% vs 8.5%; hazard ratio, 1.30; 95% confidence interval, 0.98-1.73; $P = 0.07$). This risk was not observed with the 150 mg BID dose (7.9% vs 7.9%; hazard ratio, 0.97; 95% confidence interval, 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), might be preferable.

Recommendations

In patients with **a previous 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 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 vs major bleeding (Weak Recommendation; Very Low-Quality Evidence).
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).

Values and preferences. After PCI, the uninterrupted use of a VKA (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 vs 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 after 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 OACs are not recommended.

In patients with a previous valve replacement who undergo PCI for an ACS or non-ACS indication, note the following recommendations.

Recommendations

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 **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).

4.2. Venous thromboembolic disease

Venous thromboembolic disease (VTE), comprising deep venous thrombosis and pulmonary embolism, carries a significant risk of short- and long-term mortality if left untreated.[120] In addition, up to 50% of untreated patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) will have recurrent thrombosis within 3 months of the index event.[121,122] Therefore, oral and parenteral anticoagulants are necessary to prevent as well as treat VTE.[123]

Although antiplatelet therapy is not indicated for the initial treatment of VTE, the extended use of ASA is given a weak recommendation for the prevention of recurrent VTE after the initial period of anticoagulant therapy.[123]

Approximately 7.5% of patients in the ISAR TRIPLE trial had VTE as their indication for OAC; no separate outcomes were reported for this subgroup of patients[98]; the WOEST trial did not report the numbers of enrolled patients who had VTE. Relatively few patients with VTE are described among retrospective cohort studies that compared traditional triple therapy with double therapy among patients who require OAC as well as DAPT.[109-116]

The following recommendations are made for patients with venous thromboembolism who undergo PCI for an ACS or non-ACS indication (in selected patients who require extended VTE prophylaxis (ie, orthopaedic 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).

Recommendations

In patients with **venous thromboembolism undergoing PCI for an ACS or non-ACS indication**:

35. We suggest an initial regimen of ASA 81 mg daily plus clopidogrel 75 mg daily with either parenteral or OAC (in accordance with DVT/PE recommendations). 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 ischemic events vs major bleeding. After 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 OAC for VTE (Strong Recommendation; Very Low-Quality Evidence).

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

4.3. LVT formation after MI

LVT formation is a feared complication after acute STEMI, with the risk being highest in the first 3 months after an index event.[124] The risk of LVT formation has remained significant even in the era of primary PCI and DAPT,[125] leading to a class IIa recommendation for anticoagulant therapy for STEMI patients with asymptomatic LVT and a class IIb recommendation for those with anterior/apical akinesis or dyskinesis.[126]

However, several studies have failed to show a clear benefit of routine anticoagulation in addition to DAPT after anterior STEMI. A substudy of the **H**armonizing **O**utcomes With **R**evascular**iz**at**ion** and **S**tents in **A**cute **M**yocardial **I**nfarction (HORIZONS-AMI) trial showed no benefit of triple therapy among STEMI patients treated with primary PCI for the reduction short- or long-term ischemic outcomes but did show significant increases in major bleeding.[127] Udell et al. showed no benefit of warfarin use for up to 3 months among a cohort of elderly patients after acute MI, and furthermore showed no difference in the risk of stroke between patients who presented with an anterior MI compared with those with a non-anterior MI.[128]

Le May et al. identified 460 patients with anterior STEMI who had undergone primary PCI and received DAPT with (n = 131) and without (n = 329) warfarin.[129] Patients in the warfarin group had a higher rate of net adverse clinical events (all-cause mortality, stroke, reinfarction, and major bleeding) at 180 days compared with those in the no-warfarin group (14.7% vs 4.6%; $P = 0.001$). Use of warfarin therapy was an independent predictor of net adverse clinical events after propensity scoring analysis (odds ratio, 4.01; 95% CI, 2.15-7.5). Shavadia et al. recently reported similar results with no benefit for triple therapy in a series of consecutive STEMI patients with anterior LV dysfunction.[130]

In patients with established LVT who undergo PCI for an ACS or non-ACS indication we make the following recommendation.

Recommendations

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

37. We suggest an initial regimen of triple therapy with ASA 81 mg daily with clopidogrel 75 mg daily plus OAC. 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 coronary ischemic events vs major bleeding. After 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 $\geq$ 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 LVT. Although NOACS are generally safer than warfarin, they have not been evaluated specifically in this context.

We make the following recommendations for patients who undergo PCI for an ACS indication who are at high risk of developing LV thrombus.

Recommendations

In patients who undergo **PCI for an ACS indication who are at high risk of developing LV thrombus**:

38. We recommend DAPT with ASA 81 mg daily plus either ticagrelor 90 mg BID or prasugrel 10 mg once daily for up to 1 year (Strong Recommendation; Moderate-Quality Evidence).
39. We suggest routine use of triple therapy should be avoided because of the weak evidence for prevention of LV thrombus and higher risk of bleeding events (Weak Recommendation; Moderate-Quality Evidence).

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Appendix

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Supplementary Material

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