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Society Guidelines

2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

Laurent Macle, MD (Co-chair),[a] John Cairns, MD,[b] Kori Leblanc, PharmD,[c] Teresa Tsang, MD,[b] Allan Skanes, MD,[d] Jafna L. Cox, MD,[e] Jeff S. Healey, MD,[f] Alan Bell, MD,[g] Louise Pilote, MD,[h] Jason G. Andrade, MD,[a] L. Brent Mitchell, MD,[i] Clare Atzema, MD,[j] David Gladstone, MD,[j] Mike Sharma, MD,[f,k] Subodh Verma, MD,[l] Stuart Connolly, MD,[f] Paul Dorian, MD,[l] Ratika Parkash, MD,[e] Mario Talajic, MD,[a] Stanley Nattel, MD,[a] and Atul Verma, MD (Co-chair);[m] for the CCS Atrial Fibrillation Guidelines Committee*

[a] Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; [b] University of British Columbia, Vancouver, British Columbia, Canada; [c] University Health Network, University of Toronto, Toronto, Ontario, Canada; [d] London Heart Institute, Western University, London, Ontario, Canada; [e] QEII Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada; [f] McMaster University and Hamilton General Hospital, Hamilton, Ontario, Canada; [g] University of Toronto, Toronto, Ontario, Canada; [h] McGill University Health Centre, Montréal, Québec, Canada; [i] Libin Cardiovascular Institute of Alberta, University of Calgary, and Alberta Health Services, Calgary, Alberta, Canada; [j] Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Ontario, Canada; [k] The Canadian Stroke Network, Ottawa, Ontario, Canada; [l] St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [m] Southlake Regional Health Centre, Newmarket, Ontario, Canada

ABSTRACT

The Canadian Cardiovascular Society (CCS) Atrial Fibrillation (AF) Guidelines Committee provides periodic reviews of new data to produce focused updates that address clinically important advances in AF management. This 2016 Focused Update deals with: (1) the management of antithrombotic therapy for AF patients in the context of the various clinical presentations of coronary artery disease; (2) real-life data with non-vitamin K antagonist oral anticoagulants; (3) the use of antidotes for the reversal of non-vitamin K antagonist oral anticoagulants; (4) digoxin as a rate control agent; (5) perioperative anticoagulation management; and (6) AF surgical therapy including the prevention and treatment of AF after cardiac surgery. The recommendations were developed with the same methodology used for the initial 2010 guidelines and the 2012 and 2014 Focused Updates. Using the Grading of Recommendations, Assessment, Development,

RÉSUMÉ

Le comité des lignes directrices sur la fibrillation auriculaire (FA) de la Société canadienne de cardiologie (SCC) procède régulièrement à l'examen des nouvelles données probantes afin de produire des mises à jour portant sur les avancées d'importance clinique dans ce domaine. Cette mise à jour 2016 porte sur 1) la prise en charge du traitement antithrombotique chez les patients atteints de FA en association avec une maladie cardiaque athérosclérotique (MCAS). 2) les données de la vie réelle relatives aux anticoagulants oraux non-vitamine K; 3) les antidotes aux anticoagulants oraux non-vitamine K; 4) la digoxine pour le contrôle de la fréquence; 5) la prise en charge de l'anticoagulothérapie en contexte périopératoire; et 6) le traitement chirurgical de la FA, y compris la prévention et le traitement de la FA après une chirurgie cardiaque. Ces recommandations ont été élaborées à l'aide de la même méthodologie que celle utilisée pour

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*For a full listing of the primary panel members of the Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines Committee, see the *Canadian Cardiovascular Society Atrial Fibrillation Primary Panel* section of the Supplementary Material, and the secondary panel members of the CCS Atrial Fibrillation Guidelines Committee, see the *Canadian Cardiovascular Society Atrial Fibrillation Secondary Panel* section of the Supplementary Material.

Corresponding author: Dr Laurent Macle, Electrophysiology Service, Montreal Heart Institute, Department of Medicine, Université de Montréal, 5000 est, rue Bélanger, Montréal, Québec H1T 1C8, Canada. Tel.: +1-514-376-3330; fax: +1-514-593-2581.

E-mail: lmacle@mac.com

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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and Evaluation (GRADE) standards, individual studies and literature were reviewed for quality and bias; the literature review process and evidence tables are included in the Supplementary Material, and on the CCS Web site. The section on concomitant AF and coronary artery disease was developed in collaboration with the CCS Antiplatelet Guidelines Committee. Details of the updated recommendations are presented, along with their background and rationale. This document is linked to an updated summary of all CCS AF Guidelines recommendations, from 2010 to the present 2016 Focused Update.

l'établissement des lignes directrices 2010 et des mises à jour 2012 et 2014. Les données probantes de la littérature scientifique ont été évaluées à l'aide de la méthodologie GRADE (Grading of Recommendations, Assessment, Development, and Evaluation). La section portant sur la FA en association avec une MCAS a été rédigée en collaboration avec le comité de la SCC chargé des lignes directrices relatives aux traitements antiplaquettaires. Les plus récentes recommandations sont accompagnées de leur mise en contexte et de leur justification. Cette mise à jour est liée à un résumé de l'ensemble des recommandations des lignes directrices sur la FA de la SCC de 2010 à 2016.

The Canadian Cardiovascular Society (CCS) Atrial Fibrillation (AF) Guidelines Committee provides periodic reviews of new data to produce focused updates that address clinically important advances in AF management. This 2016 Focused Update deals with: (1) the management of antithrombotic therapy for AF patients in the context of the various clinical presentations of coronary artery disease (CAD); (2) real-life data with non-vitamin K antagonist (VKA) oral anticoagulants (NOACs); (3) the use of antidotes for the reversal of NOACs; (4) digoxin as a rate-control agent; (5) perioperative anticoagulation management; and (6) AF surgical therapy including the prevention and treatment of AF after cardiac surgery. The recommendations were developed with the same methodology used for the initial 2010 guidelines and the 2012 and 2014 focused updates.[1-4] Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards, individual studies and literature were reviewed for quality and bias; the literature review process is outlined in the evidence tables, which are included in the Supplementary Material and on the CCS Web site. The section on concomitant AF and CAD was developed in collaboration with the CCS Antiplatelet (APT) Guidelines Committee (a member of the 2010 and 2012 consensus panels and the actual co-chairs of the committee, both of them interventional cardiologists), see the *Acknowledgements* section for details. This document is linked to an updated summary of all CCS AF Guidelines, from 2010 to the present 2016 Focused Update (see the *Management of Atrial Fibrillation: Complete CCS AF Guidelines Listing* section of the Supplementary Material).

I. Management of Antithrombotic Therapy in Patients With Concomitant AF and CAD

The extensive evidence for antithrombotic therapy for the prevention of stroke and systemic embolism (SSE) among patients with AF and atrial flutter (AFL) has been thoroughly reviewed in previous CCS guidelines.[2-4] Current CCS AF guidelines recommend that AF patients be stratified using the "CCS algorithm" ("CHADS-65"; Fig. 1).[3] The definitions of the CCS algorithm stroke risk factors are provided in *Part 6,* Supplemental Table S5 of the Supplementary Material.[5] In general, oral anticoagulation (OAC) therapy is recommended for all patients with AF except those younger than 65 years of age with a **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score of 0. In the latter group, aspirin (acetylsalicylic acid; ASA) is recommended in patients with CAD/vascular disease, and there is no indication for antithrombotic treatment in the absence of CAD/vascular disease. When OAC is indicated, a NOAC is recommended in preference to a VKA for non-valvular AF (NVAF).[3] The definition of NVAF was recently revisited.[5] The use of NOACs is contraindicated in the presence of mechanical heart valves, rheumatic mitral stenosis, or moderate and severe nonrheumatic mitral stenosis (see *Part 6,* Supplemental Table S6 of the Supplementary Material). It is also recommended that patients who refuse warranted OAC therapy should receive the combination of ASA and clopidogrel.[3] The current CCS APT guidelines[6,7] provide detailed recommendations for patients with no evidence of manifest vascular disease, and for those with stable CAD (defined by the absence of acute coronary syndrome [ACS] for the preceding 12 months), non-ST elevation ACS (NSTEACS), ST segment elevation myocardial infarction (STEMI), or for elective percutaneous coronary intervention (PCI).

Up to 30% of patients with AF also have CAD.[8] The management of patients with concomitant AF and CAD is challenging because OAC is preferred for the prevention of SSE in AF patients at risk of stroke,[3] and APT therapy (either single or dual APT [DAPT]) is preferred for the prevention of coronary events in CAD patients after NSTEACS, STEMI, or PCI.[6,7] Whereas there is strong evidence supporting recommendations for specific antithrombotic therapies for patients with either AF or CAD alone, there are relatively few high-quality studies of antithrombotic regimens for patients with concomitant AF and CAD. Accordingly, the selection of optimal antithrombotic therapies in such patients has been guided by extrapolations from randomized controlled trials (RCTs) of various antithrombotic therapies among patients with either CAD or AF only, augmented by the results from the available RCTs and observational data from patients with concomitant AF and CAD.[9-12]

RECOMMENDATION

General recommendations regarding antithrombotic therapy in the context of concomitant AF and CAD (asymptomatic, stable CAD [defined by the absence of ACS for the preceding 12 months], elective PCI, NSTEACS, or STEMI) are as follows.

1. We recommend that patients who have concomitant AF and CAD receive a regimen of antithrombotic therapy that is on the basis of a balanced assessment of their risks of stroke, of a coronary event, and of hemorrhage associated

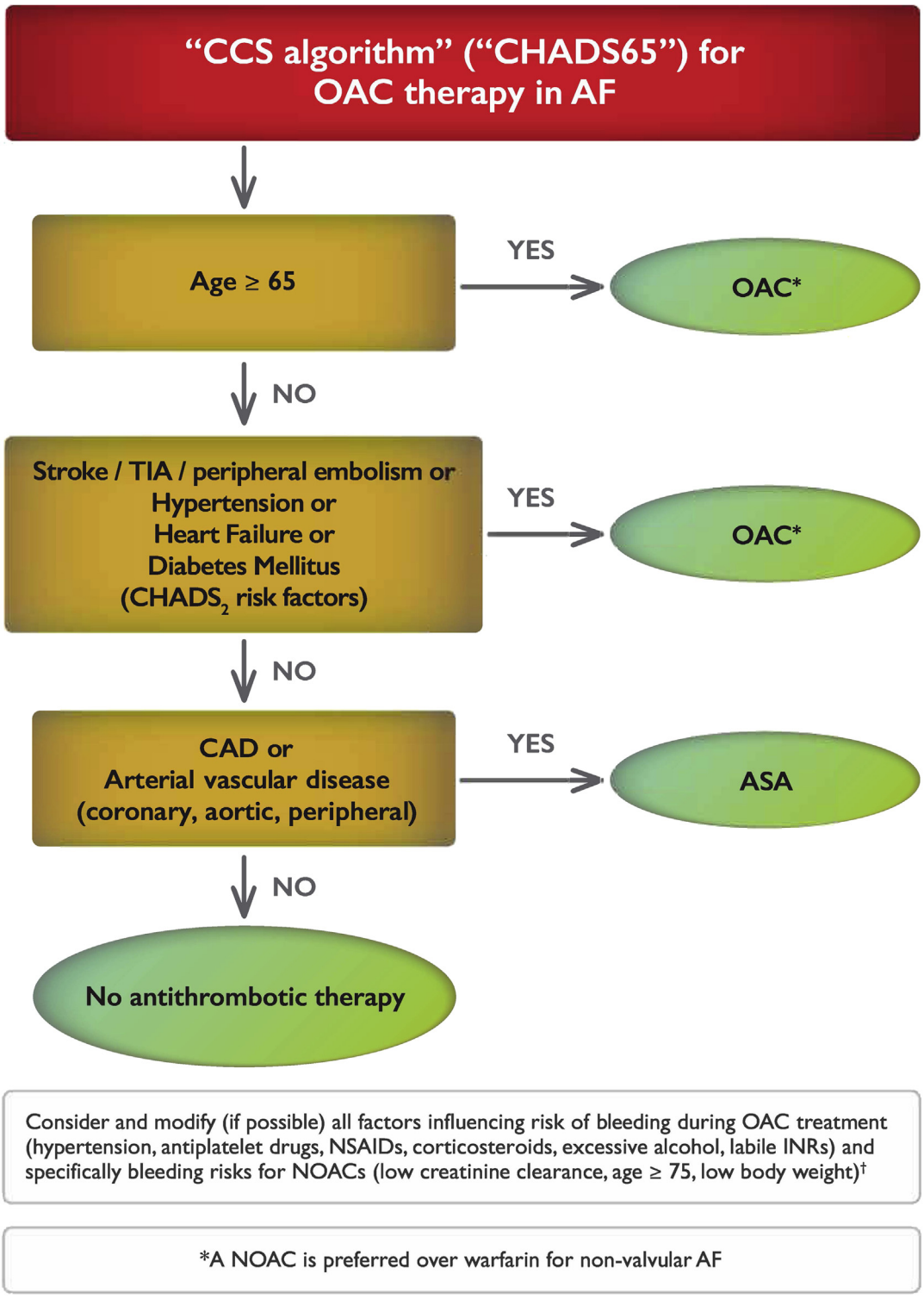

Figure 1. The simplified "Canadian Cardiovascular Society Algorithm" ("CHADS-65") for deciding which patients with atrial fibrillation (AF) or atrial flutter should receive oral anticoagulation (OAC) therapy. It recommends OAC for most patients $\geq$ 65 years of age and for younger patients with a **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score $\geq$ 1; aspirin (acetylsalicylic acid; ASA) for patients $<$ 65 years of age with a $CHADS_2$ score $=$ 0 with arterial vascular disease (coronary, aortic, or peripheral); and no antithrombotic therapy for patients $<$ 65 years of age with a $CHADS_2$ score $=$ 0 and no arterial vascular disease. Bleeding risks should be modified whenever possible. A non-vitamin K antagonist oral anticoagulant (NOAC) is recommended in preference to warfarin for OAC therapy in NVAF patients. CAD, coronary artery disease; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

with use of antithrombotic agents (Strong Recommendation, High-Quality Evidence).
2. When OAC is indicated in the presence of CAD, we suggest a NOAC in preference to warfarin for NVAF (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. The suggestion for use of a NOAC rather than warfarin places relatively greater weight on the ease of use of NOACs vs warfarin and on the data from RCTs of NOACs vs warfarin for NVAF, showing equal or greater reduction of stroke, equal or less major bleeding, less intracranial bleeding, and no net increase in CAD outcomes. It places relatively less weight on the absence of long-term data on the effect of NOACs on coronary outcomes as opposed to the data for efficacy of warfarin.

Practical tip. When CAD is present, some expert clinicians prefer a combination of a NOAC and ASA rather than a NOAC alone in preference to warfarin alone for patients perceived to be at higher risk of coronary events and low risk of major bleeding and might choose a NOAC alone as a reasonable option in those with average to lower risk of coronary events and higher risk of bleeding.

Practical tip. In general, the recommended doses of NOACs are the usual doses studied in the RCTs of NVAF. For patients who require combinations of APT and OAC agents for concomitant AF and CAD, we suggest that measures be used to reduce the risk of bleeding, including careful consideration of **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) risk factors and vigorous efforts to mitigate them; specific measures during invasive procedures (radial access, small-diameter sheaths, early sheath removal from the femoral site, and minimized use of acute procedural antithrombotic therapies); consideration of proton pump inhibitors; avoidance of prasugrel and ticagrelor in conjunction with OAC; the use of warfarin in the lower international normalized ratio (INR) range; consideration of the lower effective doses of NOACs; and delaying nonurgent catheterization until there is clarity about coagulation status and renal function. If the risk of restenosis is relatively low, the option of a bare metal stent (BMS) rather than a second-generation drug-eluting stent (DES) should be considered.

Concomitant AF and stable CAD

The current CCS AF guidelines recommendations for patients with AF who are at low risk of SSE (age < 65 years, $CHADS_2$ score of 0) are no antithrombotic therapy if there is no manifest vascular disease (CAD, peripheral vascular disease, or aortic plaque) and ASA 81 mg/d if vascular disease is present (Fig. 1).[3] The "CCS Algorithm" ("CHADS-65") makes provision for consideration of the **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) risk factors of age 65-74 years and vascular disease but not female sex, about which there is some controversy as to the independence and magnitude of its contribution as a risk factor for stroke in AF.[3] Because of the evidence for the efficacy of ASA for the prevention of coronary events among patients with stable CAD,[6] ASA therapy alone is expected to be adequate for a patient with low stroke risk who has concomitant AF and CAD. There is extensive evidence for the efficacy of VKA treatment for prevention of coronary events in patients who require primary prevention or those with stable CAD.[13] However, in patients with only CAD, ASA is recommended in preference to OAC therapy because of its safety and ease of use.

In patients with AF who are aged ≥ 65 years or with $CHADS_2$ score ≥ 1, OAC is indicated for stroke prevention.[3] When such a patient also has stable CAD, OAC therapy will provide protection against stroke and coronary events. There is sufficient evidence supporting the preference of a NOAC over warfarin for stroke prevention in NVAF.[3] The evidence for the efficacy of OAC for the prevention of coronary events is largely on the basis of studies of VKA.[13-18] There have been no specific RCTs of NOACs vs ASA or vs VKAs among CAD patients. Concerns about using NOACs in CAD patients were raised by an initial finding from the **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY) trial of significantly more occurrences of myocardial infarction (MI) among patients who received dabigatran 150 mg twice per day (bid) vs warfarin.[19] The concern was mitigated by an updated analysis, in which only a trend toward more occurrences of MI with dabigatran 150 mg was reported, although composite ischemic outcomes tended to favour dabigatran over warfarin. There was no interaction between the comparative effects of dabigatran and warfarin and a history of CAD for several ischemic outcomes.[20] Meta-analyses have generally shown more MIs with dabigatran than with warfarin, but trends toward less all-cause mortality.[21,22] There has been no suggestion of excess MI with apixaban,[23] rivaroxaban,[24] or edoxaban[25] vs warfarin, and a meta-analysis of large trials of a NOAC vs warfarin showed no excess of MI with NOACs.[26] Hence, it seems reasonable to recommend a NOAC over warfarin in patients with concomitant NVAF and CAD, because the extensive available data suggest therapeutic equivalence between NOACs and warfarin in terms of ischemic outcomes. Residual concerns about the lack of long-term data for the prevention of coronary events with NOACs vs placebo, in contrast to the availability of such data for VKAs, prompt some clinicians to prescribe a NOAC with ASA for patients with NVAF and vascular disease, although this might not be required.

RECOMMENDATION

For patients with AF with an indication for primary CAD prevention or stable CAD/arterial vascular disease (peripheral vascular disease or aortic plaque), the selection of antithrombotic therapy should be on the basis of their risk of stroke as follows (Fig. 2).

3. If the patient has no evidence of CAD/vascular disease and is aged < 65 years with no $CHADS_2$ risk factors, we suggest no antithrombotic therapy for stroke prevention (Conditional Recommendation, Moderate-Quality Evidence).

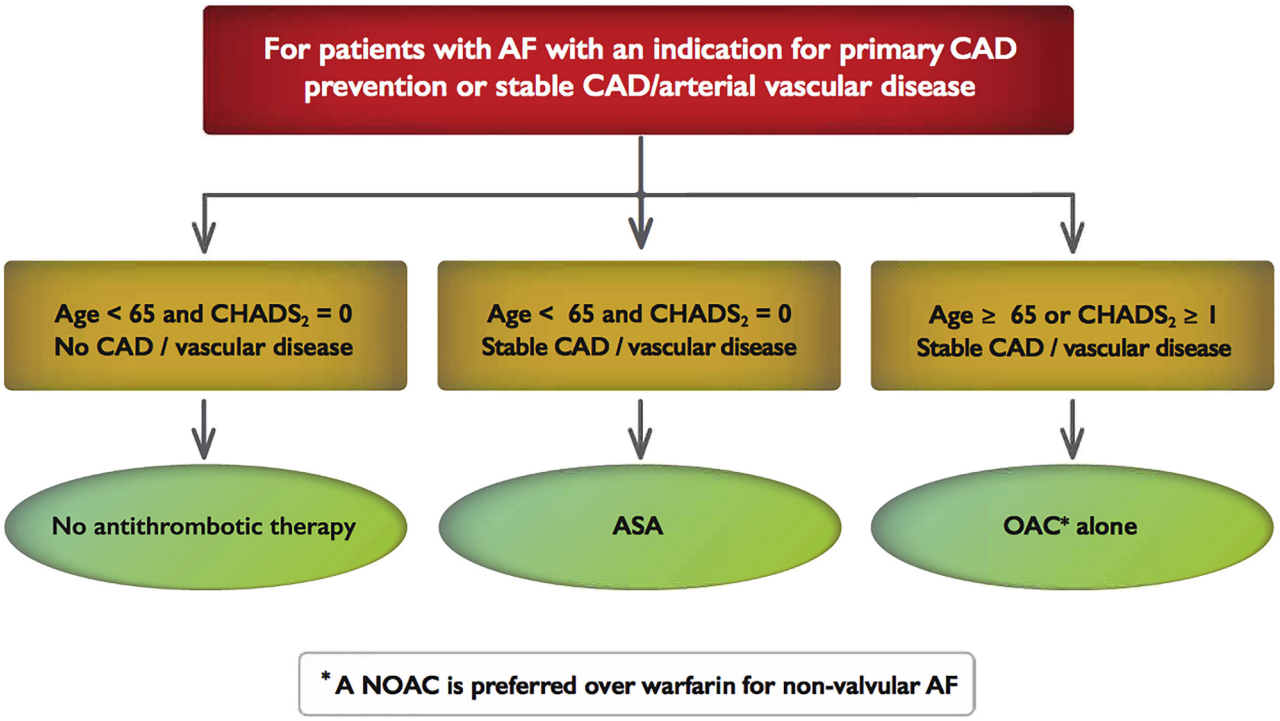

Figure 2. A summary of our recommendations for the management of antithrombotic therapy in patients with concomitant atrial fibrillation (AF) and an indication for primary coronary artery disease (CAD) prevention or stable CAD/arterial vascular disease. ASA, acetylsalicylic acid (aspirin); $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

4. If the patient has stable CAD/vascular disease and is aged < 65 years with no $CHADS_2$ risk factors, we suggest ASA 81 mg/d (Conditional Recommendation, Moderate-Quality Evidence).
5. If the patient has stable CAD/vascular disease and is aged ≥ 65 years or the $CHADS_2$ score ≥ 1, we recommend OAC therapy alone (Strong Recommendation, High-Quality Evidence).

Concomitant AF and Elective PCI

Patients who undergo elective PCI are generally prescribed DAPT for a period that varies from 4 weeks for a BMS to 12 months or more for a DES.[3,6] Whereas shorter durations of DAPT lessen the risk of major bleeding and might lessen all-cause mortality, the risk of stent thrombosis and MI appears to be higher.[27-29] There has been a trend to shorten DAPT duration as second-generation DESs with sustained antiproliferative action and no greater thrombogenicity than BMSs have become available.[30,31] For patients with AF and low stroke risk, the post-PCI therapeutic regimen of DAPT is all that is needed because OAC is not required. However, for a patient at higher risk of AF-related stroke (age ≥ 65 years or $CHADS_2$ score ≥ 1) who requires elective PCI, the combination of OAC with APT therapy must be considered. There is evidence for lower risk of coronary events in patients with elective PCI compared with PCI in the setting of ACS,[32] for markedly increased risk of major bleeding with triple therapy (TT) vs DAPT[33] and for the advantages of combined OAC with clopidogrel vs TT.[34,35] The **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**tent**t**ing (WOEST) study randomized 573 PCI patients using VKA to TT vs VKA with clopidogrel.[35] The primary outcome of thrombolysis in myocardial infarction [TIMI] bleeding at 1 year was reduced with VKA with clopidogrel from 44.4% to 19.4% (hazard ratio [HR], 0.36; $P < 0.0001$), Bleeding Academic Research Consortium (BARC) bleeds were reduced from 12.7% to 6.5% (HR, 0.49; $P = 0.011$), and major adverse cardiac and cerebrovascular events (MACCE) were reduced from 17.6% to 11.1% (HR, 0.6; $P = 0.025$). Based on this evidence, the CCS AF Guidelines Committee recommends a modified WOEST regimen for patients with concomitant AF and elective PCI at higher risk of stroke. The increasing evidence supporting shorter duration DAPT with current generations of DESs[31] prompts consideration of shorter duration of combined OAC with clopidogrel when the bleeding risk is high.

RECOMMENDATION

For patients with AF and recent elective PCI, the selection of antithrombotic therapy should be on the basis of their risk of stroke as follows (Fig. 3).

6. If the patient is aged < 65 years with no $CHADS_2$ risk factors, we recommend an APT therapy regimen without OAC, as per *Part 7, Recommendations 6-9* of the Supplementary Material (adapted from the CCS 2012 APT guidelines).

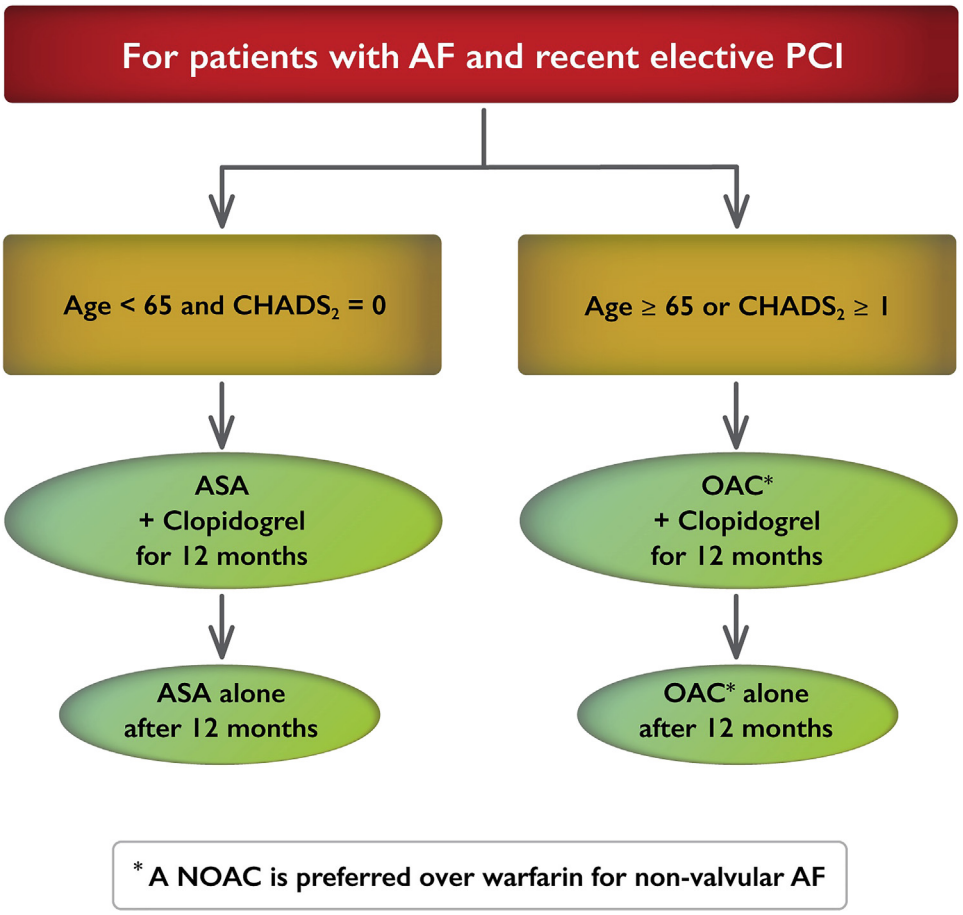

Figure 3. A summary of our recommendations for the management of antithrombotic therapy in patients with atrial fibrillation (AF) and recent percutaneous coronary intervention (PCI). ASA, acetylsalicylic acid (aspirin); $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.

7. If the patient is aged $\geq$ 65 years and the $CHADS_2$ score $\geq$ 1, we suggest that clopidogrel 75 mg/d and OAC be given, without concomitant ASA, for 12 months post-PCI (Conditional Recommendation, Moderate-Quality Evidence), to be followed by OAC alone (Strong Recommendation, High-Quality Evidence).

Practical tip. Some patients who are at high risk of stent thrombosis and whose risk of major bleeding is acceptable may continue OAC with clopidogrel for longer than 12 months after ACS, whereas those at particularly high risk of major bleeding may have their clopidogrel discontinued earlier than 12 months and continue to receive only OAC.

Concomitant AF and NSTEACS or STEMI

The antithrombotic management of these patients is more complex. The CCS APT guidelines recommend that most such patients should receive ASA indefinitely, along with at least 12 months of a P2Y12 inhibitor,[6] on the basis of the results of the clinical trials of clopidogrel, prasugrel, and ticagrelor.[36-38] They also recommend the use of prasugrel or ticagrelor in preference to clopidogrel as a component of DAPT in settings of NSTEACS and STEMI.[6] The greater risk of bleeding with these more potent agents is considered justified in view of the improved coronary outcomes. Clopidogrel is generally recommended only for patients with contraindications to ticagrelor and prasugrel. Subsequent trials of longer-duration P2Y12 inhibition have reported improved cardiac outcomes among patients with previous MI but with an increase in major bleeding.[27,39] The benefit of longer-duration DAPT might be less with second-generation DESs.[27,30] These findings support the use and duration of DAPT among patients with concomitant AF and previous NSTEACS or STEMI. In a patient with AF at low risk of stroke (age < 65 years, $CHADS_2$ score of 0), DAPT would be expected to provide protection not only against recurrent coronary events, but also against stroke/systemic embolism as shown in the **A**trial Fibrillation **C**lopidogrel **T**rial With **I**rbesartan for Prevention of **V**ascular **E**vents—**A**spirin (ACTIVE-A) trial.[40]

For a patient with concomitant NSTEACS or STEMI and AF at higher risk of stroke (age $\geq$ 65 years or $CHADS_2$ score $\geq$ 1) the optimal antithrombotic therapy is uncertain. CCS AF guidelines recommend OAC for stroke prevention[3] and CCS APT guidelines recommend DAPT to prevent coronary events after NSTEACS or STEMI.[7] Accordingly, clinicians have perceived an obligation to treat patients with

concomitant AF and CAD using OAC and also DAPT, so-called triple antithrombotic therapy (or TT). Although there are relatively few rigourous controlled data to guide the selection and duration of TT, its use has become widespread.[9-12]

The most recent meta-analysis of studies that compared DAPT with TT (all observational studies apart from a single very small RCT) showed significantly less major bleeding with DAPT (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.39-0.68), but no increase in composite thrombotic events (all-cause death, MI, stent thrombosis, and stroke; OR, 0.71; 95% CI, 0.46-1.08).[34] There were insufficient data in the trial publications to allow statistical adjustments for baseline risk of thrombotic events. A recent observational study compared TT with DAPT among 4959 AF patients aged $\geq$ 65 years who underwent PCI with stenting.[33] Bleeding requiring hospitalization occurred in 17.6% of patients with TT vs 11% with DAPT (hazard ratio [HR], 1.61; 95% CI, 1.31-1.97), intracranial bleeding occurred in 3.4% vs 1.5% (HR, 2.04; 95% CI, 1.25-3.34), and yet rates of MACE (death or readmission for MI or stroke) were not less with TT. Dans et al. assessed the outcomes of 6952 patients who received ASA or clopidogrel in combination with OAC at some time during the RE-LY study.[41] The HR for major bleeding was 1.60 (95% CI, 1.42-1.82) with the combination of 1 APT agent and 2.31 (95% CI, 1.79-2.98) with the combination of two. The absolute rates of major bleeding were highest with warfarin, then with dabigatran 150 mg bid, and least with dabigatran 110 mg bid. The **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen: **Triple** Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-Triple) RCT compared 6 weeks of TT followed by VKA plus ASA vs 6 months of TT among 614 patients who had been receiving OAC therapy for $>$ 12 months (85% for AF) and then underwent PCI with a DES.[42] The rates of the primary outcome (death, MI, stroke or TIMI major bleed) and composite ischemic events did not differ, nor did the rates of major bleeding.

Because of the greater bleeding risk with the newer APT agents, they are not recommended as a component of TT. In patients at lower risk of stroke from AF, extrapolating from the finding of better stroke prevention with clopidogrel plus ASA compared with ASA alone,[40] some clinicians might prescribe a combination of ASA with either clopidogrel, ticagrelor, or prasugrel in preference to TT, in the expectation that the bleeding risk is likely to be lower.

Direct application of the WOEST results is somewhat limited because AF was the reason for VKA therapy in only 69% of subjects, most PCIs were elective, and measures to decrease bleeding risk (radial approach, proton pump inhibitor, shortened time of TT) were underutilized.[35] A recent meta-analysis of trials of clopidogrel with OAC vs TT, which included the WOEST trial and observational data from 5 studies, showed significantly reduced major bleeding with clopidogrel plus OAC vs TT (OR, 0.79; 95% CI, 0.64-0.98), and no increase in the composite outcome of all-cause death, MI, stent thrombosis, and stroke (OR, 0.90; 95% CI, 0.69-1.23).[34]

NSTEACS/STEMI patients at higher risk of stroke require OAC indefinitely. If no PCI is undertaken, the CCS AF guidelines now recommend a modified WOEST regimen, with clopidogrel and OAC, for 12 months followed by OAC indefinitely. However, if PCI is undertaken, the additional risk of stent thrombosis leads to a recommendation of TT for 3-6 months, followed by OAC with clopidogrel through to 12 months after ACS, followed by long-term OAC alone.

As for concomitant AF and stable CAD, the CCS AF guidelines suggest the use of NOACs in preference to VKAs for concomitant NVAF and NSTEACS or STEMI. Of note, only rivaroxaban has been evaluated in a completed phase III trial, as a complement to DAPT among patients with ACS (most of them had received PCI).[43] The 2.5 and 5 mg bid doses of rivaroxaban significantly reduced ischemic events, but bleeding was increased. These doses are much lower than the doses of 15 and 20 mg daily used in **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation (ROCKET-AF).[24]

RECOMMENDATION

For patients with AF, in association with NSTEACS or STEMI, the selection of antithrombotic therapy should be on the basis of their risk of stroke as follows (Fig. 4).

8. If the patient is aged $<$ 65 years with no $CHADS_2$ risk factors, we recommend an APT therapy regimen without OAC, as per *Part 7, Recommendations 11-19* of the Supplementary Material (adapted from the CCS 2012 APT Guidelines).
9. If the patient is aged $\geq$ 65 or the $CHADS_2$ score $\geq$ 1 and no PCI is undertaken, we suggest the combination of clopidogrel 75 mg daily (rather than prasugrel or ticagrelor) and OAC be given, without concomitant ASA, for 12 months, to be followed by OAC alone (Conditional Recommendation, Low-Quality Evidence).
10. If the patient is aged $\geq$ 65 years or the $CHADS_2$ score $\geq$ 1 and PCI is undertaken, we suggest the combination of ASA 81 mg/d and clopidogrel 75 mg/d and OAC (TT) for 3-6 months (duration depending on the perceived risks of coronary thrombosis and major bleeding). After 3-6 months we suggest the combination of clopidogrel and OAC to be continued until 12 months after ACS, to be followed by OAC alone (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. The suggestion of TT for the first 3-6 months places greater weight on more reduction of coronary events (vs OAC with clopidogrel) and on more SSE prevented (vs DAPT) but less weight on the increased risk of major bleeding. The balance of stroke/systemic embolus prevented and major bleeds caused could be judged as appropriate only for patients with a higher risk of stroke (eg, $CHADS_2$ score $\geq$ 2).

Practical tip. Some patients who are at high risk of stent thrombosis and whose risk of major bleeding is acceptable might continue the combination of OAC with clopidogrel for longer than 12 months after ACS.

Practical tip. Some patients at particularly high risk of major bleeding might have their clopidogrel discontinued earlier than 12 months and continue to receive OAC therapy only.

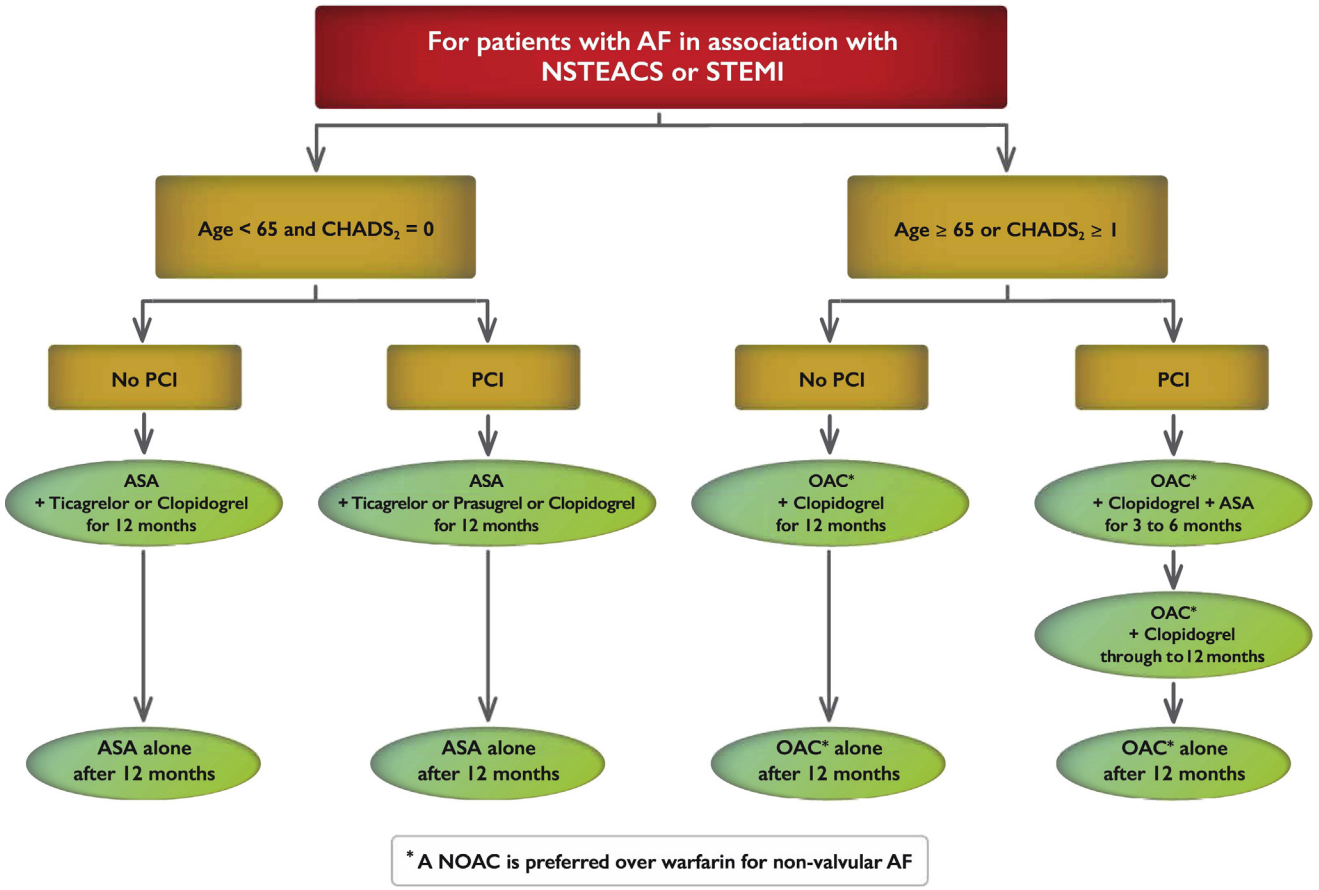

Figure 4. A summary of our recommendations for the management of antithrombotic therapy in patients with atrial fibrillation (AF) in association with Non-ST-elevation acute coronary syndrome (NSTEACS) or ST-elevation myocardial infarction (STEMI). ASA, acetylsalicylic acid (aspirin); $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PCI, percutaneous coronary intervention.

Practical tip. Some clinicians might prefer the combination of clopidogrel and OAC therapy beginning from the time of PCI, placing more weight on the reduced bleeding and no increase of thrombotic events compared with TT in the WOEST trial and less value on the fact that only 25% of patients in this trial had PCI for ACS. A combination of ASA with ticagrelor, ASA with prasugrel, or ASA with clopidogrel might also be used in preference to TT for some patients with a $CHADS_2$ score of 1 at the lower end of the stroke risk spectrum (eg, isolated hypertension), reserving TT or OAC with clopidogrel for patients at higher stroke risk.

II. Real Life Data With NOACs

The CCS AF guidelines recommendation of using a NOAC over warfarin for most patients with NVAF requiring OAC[2,3] was predominantly on the basis of data that compared NOACs with warfarin in RCTs.[19,23,24] As experience with these agents in clinical practice outside carefully-controlled RCTs has increased, published observational data add support to the current CCS recommendation. Observations from large government, insurance, and health system databases, including that of the US Food and Drug Administration Minisentinel database, show that, in widespread clinical use, NOACs are associated with effects on stroke and bleeding consistent with RCT data.[44-50] It is important to note that in some publications,[48] only bleeding event data are provided, without corresponding stroke prevention results. Although these "real world" data are nonrandomized and come with limitations common to administrative databases, consistency with RCT findings provides reassurance regarding the safety of NOACs in general clinical care.

III. Reversal Agents for NOACs

Although use of NOACs showed less life-threatening bleeding than warfarin in RCTs,[19,23,24] their annual rates of major bleeding were 2%-4% and clinicians and patients alike are concerned about bleeding risks with these agents. Despite successful reversal of coagulation parameters (eg, INR) with hemostatic factors and vitamin K in patients receiving warfarin, bleeding-related outcomes are not clearly improved, particularly those of intracranial bleeding.[51,52] Bleeding management protocols for NOACs have included hemostatic factors, such as fresh-frozen plasma, 3- or 4-factor prothrombin complex concentrates, activated prothrombin complex concentrates and recombinant activated factor VII, activated charcoal for overdose or unintentional ingestion, and dialysis or continuous renal replacement therapy.[53,54] Unfortunately, the evidence for benefit from hemostatic factors is inconsistent[55,56] and they add a potential risk of thrombosis.[57,58] In addition, although dialysis has been reported to be successful in case reports of dabigatran-related bleeding, it might be impractical in an actively bleeding patient, and is ineffective in patients with

apixaban-, edoxaban-, and rivaroxaban-associated bleeding because of their protein binding.[55]

Specific reversal agents, "antidotes," are in various stages of clinical development. These include andexanet-α, specific for factor Xa inhibitors, aripazine, a universal reversal agent, and idarucizumab, a specific reversal agent for dabigatran available in Canada since May 2016. Andexanet-α appears to be effective in reversing anticoagulant activity and is well tolerated in healthy volunteers.[59] It is currently being studied in an open-label phase III, single-arm study on its effectiveness in patients taking any factor Xa inhibitor who present with acute major or intracranial bleeding (NCT02329327). Aripazine, a synthetic small molecule that binds to unfractionated heparin (UFH), low molecular-weight heparin (LMWH), fondaparinux, dabigatran, and factor Xa inhibitors, is presently undergoing phase I and II clinical trials.

Idarucizumab is a humanized monoclonal antibody fragment that binds to protein-bound and unbound dabigatran with high affinity, approximately 350-fold greater than the affinity of dabigatran for thrombin, neutralizing dabigatran and its active metabolites.[60] In phase I trials with > 200 volunteers, idarucizumab was well tolerated.[61-63] In the **Revers**al **E**ffects of Idarucizumab on **A**ctive **D**abigatran (REVERSE-AD) trial, adults with overt, life-threatening bleeding (n = 51) or requiring urgent surgery or other invasive procedures (n = 39) during dabigatran treatment received idarucizumab 5 g as two 2.5 g bolus infusions up to 15 minutes apart.[64] Urgent surgery was defined as a procedure that required normal hemostasis that could not be delayed for at least 8 hours. In an interim analysis of patients with elevated dilute thrombin times and ecarin clotting times at presentation (n = 68), reversal of the anticoagulant effect was 100%. The dilute thrombin time was normalized in 98% of the bleeding patients and 93% of the urgent surgery patients, and the ecarin clotting time was normalized in 89% and 88%, respectively. Median time to the cessation of bleeding was reported to be 11.4 hours, but was not systematically evaluated. There were 18 deaths overall (9 per group), including 5 fatal bleeding events. Thrombotic events occurred in 5 patients (including deep vein thrombosis, pulmonary emboli, left atrial [LA] thrombus, MI, and ischemic stroke); none were receiving antithrombotic therapy at the time.

RECOMMENDATION

11. We recommend administering idarucizumab for emergency reversal of dabigatran's anticoagulant effect in patients with uncontrollable or potentially life-threatening bleeding and/or in patients who require urgent surgery for which normal hemostasis is necessary (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places relatively greater value on the ability of idarucizumab to reverse coagulation parameters indicative of dabigatran's effect, its potential to decrease bleeding-related outcomes, and risks of urgent surgery and its safety and tolerability profile, and less value on the absence of a control group in the REVERSE-AD trial and on the cost of the drug.

Table 1. Bleeding risks for various invasive/surgical procedures

High-risk
Neurosurgery (intracranial or spinal surgery)
Cardiac surgery (coronary artery bypass or heart valve replacement)
Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)
Major urologic surgery (prostatectomy, bladder tumour resection)
Major lower limb orthopaedic surgery (hip/knee joint replacement surgery)
Lung resection surgery
Intestinal anastomosis surgery
Selected invasive procedures (kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy or biopsies)
Intermediate risk
Other intra-abdominal surgery
Other intrathoracic surgery
Other orthopaedic surgery
Other vascular surgery
Low risk
Laparoscopic cholecystectomy
Laparoscopic inguinal hernia repair
Dental procedures
Dermatologic procedures
Ophthalmologic procedures*
Coronary angiography
Gastroscopy or colonoscopy (without biopsy)
Selected invasive procedures (bone marrow aspirate and biopsy, lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
Cardiac implantable device surgery (pacemaker or implantable defibrillator)†
Dental extractions (1 or 2 teeth) or teeth cleaning
Skin biopsy or skin cancer removal
Cataract removal

* Selected ophthalmic procedures might be high-risk, such as those with retrobulbar block.

† On the basis of results from **Br**idge or Contin**u**e Coumad**i**n for Device **S**urg**e**ry Randomized **Control**led Trial (BRUISECONTROL).[69]

Practical tip. In the acute, life-threatening bleeding situation in which standard resuscitation (such as local measures, transfusion, etc) is not anticipated to be sufficient (eg, intracranial hemorrhage), or in the situation in which it has not stabilized the patient, idarucizumab should be administered as soon as possible. Although dilute thrombin time and ecarin clotting time were used to identify the presence of dabigatran in REVERSE-AD, these tests are not widely available. Thrombin time and activated partial thromboplastin time are widely available and can qualitatively identify the presence of active dabigatran in a patient,[65] however, obtaining these tests should not delay the administration of idarucizumab. In many instances of life-threatening bleeding, clinicians have to make a treatment decision on the basis of a history of dabigatran use rather than laboratory evidence. Renal function and timing of the last dose of dabigatran provide key information regarding the likely extent of remaining dabigatran effect. The timing of surgery might permit clinicians to obtain coagulation parameters like stat thrombin time or activated partial thromboplastin time to identify patients who no longer have dabigatran present, and who would be unlikely to benefit from idarucizumab. No dose adjustment for idarucizumab is required in patients with renal impairment. In some patients, coagulation parameters might increase between 12 and 24 hours after initial administration of idarucizumab, possibly reflecting redistribution of extravascular dabigatran into the intravascular space.[64] Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease.

OAC should be reintroduced as soon as medically appropriate.

IV. Periprocedural Anticoagulation Management

Interruption of antithrombotic therapy

When patients receiving OACs or APT agents need surgery or invasive diagnostic procedures, the risk of SSE while the antithrombotic agent is reduced or stopped must be weighed against the risk of bleeding during or after the procedure[66,67] (see *Part 11, Recommendation 1* of the Supplementary Material). Risks of major bleeding for various procedures have been categorized as very low, low, intermediate, and high by Thrombosis Canada (Table 1).[68] The current AF guidelines no longer differentiate low risk from very low risk. These procedures can generally be safely performed without interrupting antithrombotic therapy, provided the INR is not supratherapeutic in the case of warfarin. In the case of cardiac device implantation, superiority of uninterrupted warfarin has been shown,[69] and an RCT is currently under way to determine the safety of uninterrupted NOACs for such procedures.[70] Interruption of anticoagulation remains recommended for procedures with an intermediate or high risk of major bleeding. Recommendations for preprocedural interruption of various antithrombotic agents are detailed in *Part 11, Recommendations 4-7* of the Supplementary Material.

RECOMMENDATION

12. We suggest that interruption of anticoagulant therapy, particularly for VKAs, in a patient with AF/AFL is not necessary for most procedures with a low risk of bleeding, such as cardiac device implantation (pacemaker or implantable defibrillator), and most dental procedures (Table 1) (Conditional Recommendation, Moderate-Quality Evidence).

Bridging considerations

When a decision to interrupt warfarin therapy has been made for an invasive procedure with an intermediate or high risk of major bleeding, bridging with LMWH or UFH when the INR has decreased below therapeutic levels should be considered for patients with high stroke risk. A meta-analysis[71] of 33 observational studies and 1 RCT involving 7118 patients (< 50% with AF) reported that warfarin discontinuation with bridging therapy, compared with warfarin discontinuation without bridging therapy, was associated with increased overall bleeding (13.1% vs 3.4%; $P < 0.0001$) and major bleeding (4.2% vs 0.9%; $P = 0.004$), but with no reduction in thromboembolic events (0.9% vs 0.6%; $P = 0.50$). More recently, in the randomized double-blinded placebo-controlled Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial[72] the value of bridging in 1884 AF patients needing to interrupt warfarin for an elective surgery/invasive procedure was assessed. Patients were randomized to placebo injections or LMWH from 3 days to 1 day before the procedure, and for 5-10 days after the procedure. The study showed that no bridging was noninferior to bridging for arterial thromboembolism, but was associated with significantly fewer major and minor bleeds. There were no significant differences for any other outcomes. We have therefore increased the threshold for bridging to patients with $CHADS_2$ score ≥ 4, instead of $CHADS_2$ score ≥ 3. Mechanical heart valves and recent transient ischemic attack or stroke are considered very high-risk factors for thromboembolism, and such patients were excluded from the BRIDGE trial. Heparin bridging continues to be recommended for patients with these risk factors as well as for those with rheumatic heart disease. Recommendations for pre- and postprocedural management of heparin bridging are detailed in *Part 11, Recommendations 10 and 11* of the Supplementary Material.

RECOMMENDATION

13. When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that bridging therapy with LMWH or UFH be instituted when the INR is below therapeutic level only in patients at high risk of thromboembolic events ($CHADS_2$, score ≥ 4, mechanical heart valve, stroke/transient ischemic attack within 3 months, rheumatic heart disease) (Conditional Recommendation, Low-Quality Evidence).

Bridging is not generally necessary for NOACs because their half-lives are similar to those of LMWH. Bleeding and thromboembolic outcomes in the periprocedural period using NOACs vs warfarin have been investigated in the RE-LY, ROCKET AF, and **A**pixaban for **R**eduction **i**n **St**roke and **O**ther **T**hromboembo**l**ic **E**vents in Atrial Fibrillation (ARISTOTLE) trials.[73-75] In these studies, NOACs and warfarin were generally interrupted. There were no statistically significant differences between the dabigatran, rivaroxaban, or the apixaban groups and their respective warfarin groups with respect to bleeding or thromboembolic complications. Data are also available from observational studies of NOAC interruption. The **O**utcomes **R**egistry for **B**etter **I**nformed **T**reatment of **A**trial **F**ibrillation (ORBIT-AF) is a prospective, observational registry study of US patients with AF.[76] Of 7372 patients treated with OAC, 2803 interruption events occurred in 2200 patients (30%). Median follow-up was 2 years. OAC interruptions were common for major and minor procedures, with bridging used in one-quarter of the cases. The findings suggested that bridging anticoagulation was associated with increased risk of bleeding and adverse events. In the Perioperative Dabigatran Study,[77] a Canadian multicentre prospective study of perioperative management, 541 adult patients receiving dabigatran for any indication (97% AF) underwent an invasive procedure requiring NOAC interruption. The outcomes of the study included major and minor bleeding, thromboembolism, and death, and suggested

that interruption of dabigatran without bridging is safe. Observational analyses from the Dresden NOAC Registry (76% rivaroxaban, 24% dabigatran) suggested no difference in bleeding or thromboembolic complications in the periprocedural period between rivaroxaban and dabigatran[78] Heparin bridging did not reduce cardiovascular events but led to significantly higher rates of major bleeding. Recommendations for reintroduction of antithrombotic agents after an invasive procedure are detailed in *Part 11, Recommendations 12 and 13* of the Supplementary Material.

RECOMMENDATION

14. We recommend no bridging (LMWH or UFH) for NVAF patients receiving NOACs who undergo elective surgery or invasive procedures requiring interruption of anticoagulation (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Duration of preprocedural interruption of NOACs should be adjusted according to renal function (see *Part 11, Recommendations 6 and 7* of the Supplementary Material). The Thrombosis Canada Perioperative Anticoagulant Management Algorithm is a helpful tool to aid decisions regarding periprocedural anticoagulation (http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm).

V. Digoxin and Mortality

Digoxin is less effective at controlling heart rate than β-blockers or calcium channel blockers during exercise and should therefore be avoided as the sole agent for rate control of AF in active patients.[79,80] Many reports indicate an association between digoxin use for rate control in patients with AF and mortality.[81-83] However, this observation might be because of the comorbidities associated with digoxin use and the inability to adjust sufficiently to control for this. Because of its relative inefficacy and unresolved concerns that it might increase mortality, digoxin should only be used with caution and careful dose selection, as a second-line agent to control rate in symptomatic patients who do not respond to first-line drugs. A recent Canadian study reported that heart rate in AF was not associated with mortality, although rates > 114 beats per minute predicted hospitalizations.[84] In cases in which digoxin must be used for rate control of AF/AFL, a target resting heart rate < 100 beats per minute is recommended (see *Part 3, Recommendation 4* of the Supplementary Material).[85]

RECOMMENDATION

15. We suggest that digoxin can be considered as a therapeutic option to achieve rate control in patients with AF and symptoms caused by rapid ventricular rates whose response to β-blockers and/or calcium channel blockers is inadequate, or in whom such rate-controlling drugs are contraindicated or not tolerated (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. Digoxin is considered a second-line agent because although some published cohort, retrospective, and subgroup studies show no harm, there are others that suggest possible harm.

Practical tip. When digoxin is used, dosing should be adjusted according to renal function and potential drug interactions. With analyses that suggested higher drug concentrations are associated with adverse outcomes, maximum trough digoxin serum concentration of 1.2 ng/mL would be prudent. When digoxin is being used to treat patients with concomitant left ventricular systolic dysfunction, its use should be dictated by the recommendations of the CCS Heart Failure Clinical Guidelines.

VI. Surgical Therapy for AF

Surgical AF ablation procedures

A number of factors need to be considered when contemplating the combination of AF ablation therapy with cardiac surgery, including local expertise, associated risk, and potential benefits of sinus rhythm. Despite the very high reported rates of sinus rhythm after the surgical MAZE procedure, the combination of adjuvant surgical treatment to achieve sinus rhythm in patients who undergo cardiac surgery remains controversial. The decision-making algorithm for surgical MAZE is complex, and many factors, including the type of surgery (mitral valve surgery vs coronary artery bypass graft [CABG]), extent of procedure (left vs biatrial), energy source, and surgeon/institutional experience need to be considered. Despite these heterogeneous factors, studies on the MAZE procedure have grouped mitral, aortic, and coronary artery surgery together to allow sufficient power for analysis. A recent systematic review combined 9 small RCTs and showed a large effect on the maintenance of sinus rhythm at 12 months in 481 patients (OR, 10.41; 95% CI, 5.30-20.44) as well as beyond 12 months (OR, 11.61; 95% CI, 4.53-29.79; 4 studies, 154 patients).[86] Importantly, there were no differences between groups with respect to incidence of stroke, total mortality, or permanent pacemaker implantation. Although no heterogeneity was observed among trials, no individual study randomized more than 95 patients.

Recently, 2 larger RCTs assessed the effect of LA ablation in addition to coronary artery and valve surgery on maintenance of sinus rhythm at 1 year.[87,88] All patients underwent routine closure of the LA appendage (LAA). In the first study, 224 patients were randomized to LA cryoablation or control; 60.2% of cryoablation patients showed sinus rhythm according to Holter monitoring at 1 year, vs 35.5% ($P = 0.002$) of patients without ablation.[87] There were no adverse consequences, including no increased rate of death, MI, stroke, or renal failure, but there was a nonsignificant trend in

pacemaker requirement in the ablation arm (6% vs 1%).[87] The most recent trial, specifically in patients who underwent mitral valve surgery, reported that 63.2% of 260 patients randomized to ablation (either pulmonary vein isolation or biatrial ablation as a secondary randomization) were in sinus rhythm at 1 year vs 29.4% ($P < 0.001$) without.[88] The ablation method made no difference. Adverse events were unchanged, except for a greater rate of conduction abnormality requiring permanent pacing in the ablation group (21.5% vs 8.1%; $P < 0.01$).

RECOMMENDATION

16. We suggest that a surgical AF ablation procedure should be considered in association with mitral valve, aortic valve, or CABG surgery in patients with AF, when the likelihood of success is deemed to be high, the additional risk is low and sinus rhythm is expected to achieve substantial symptomatic benefit (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes that individual institutional experience and patient considerations best determine for whom the surgical procedure is performed. Importantly, the symptomatic benefit of sinus rhythm needs to be balanced with the attendant risks of ablation surgery, including the need for permanent pacing. This recommendation also recognizes that LA endocardial access is not routinely required for aortic or coronary surgery, limiting ablation to newer epicardial approaches.

Surgical LAA exclusion for stroke prevention

There are few data from RCTs to recommend surgical LAA removal as a primary strategy to reduce stroke. Several cohort studies in patients who underwent surgical MAZE procedures have reported reduced stroke rates, usually attributed to surgical ligation of the LAA.[89-92] This is partly on the basis of data that showed 90% of LA thrombi, when seen on transesophageal echocardiography or at autopsy, occur within the LAA.[93] LAA removal has become a regular part of surgical ablation procedures in many centres, on the basis of cohort studies alone.[87,88] There is increasing evidence from RCTs that percutaneous occlusion of the LAA results in outcomes not inferior to warfarin therapy.[94-96] Although it is reasonable to propose that surgical removal of the LAA will reduce stroke rates, only 1 surgical trial has randomized patients to surgical LAA or ongoing warfarin therapy, as a pilot study to test the feasibility of a large RCT (**L**eft **A**trial **A**ppendage **O**cclusion **S**tudy **II**; LAAOS II).[97] On the basis of this pilot, a large RCT of surgical exclusion of the LAA vs warfarin therapy has been initiated in 4700 patients.[98] The primary end point is stroke or systemic embolism over 4 years. Total mortality and safety end points will also be compared. Until this definitive trial is completed, consensus remains the only basis for surgical LAA removal. As such, we have downgraded the 2010 recommendation[99] to conditional on the basis of low-quality evidence.

RECOMMENDATION

17. In patients with AF, we suggest that closure (excision or obliteration) of the LAA should be considered as part of the surgical ablation of AF associated with mitral, aortic valve, or CABG surgery if this does not increase the risk of the surgery (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the potential for stroke reduction and a lower value on loss of atrial transport function with LAA closure. It places less value on the need to continue OAC therapy even after LAA surgical excision.

VII. Prevention and Treatment of AF After Cardiac Surgery

In 2011, comprehensive CCS guidelines on the management of postoperative AF (POAF) were published.[100] Most of these guidelines remain unchanged, including those regarding β-blockers and amiodarone with strong recommendations for their use on the basis of high-quality evidence. In areas for which high-quality evidence is lacking, recommendations were reviewed and altered. New evidence was also considered.

POAF is common, is associated with adverse consequences, increased length of hospital stay and costs, and is appropriately treated with either a rate control or rhythm control strategy. A very recent randomized trial has appeared, which motivated the committee to change the strength of the 2010 recommendation.[101]

RECOMMENDATION

18. We recommend that POAF might be appropriately treated with either a ventricular response rate control strategy or a rhythm control strategy (Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the RCTs that investigated rate control as an alternative to rhythm control for AF, including 1 trial that specifically addressed the cardiac postoperative period. Choice of strategy should therefore be individualized on the basis of the degree of symptoms experienced by the patient.

Magnesium and atrial pacing

A recent systematic review of 21 trials, none particularly large, using intravenous magnesium in 2988 patients, reported a reduction in POAF from 26.2% to 16.5% (OR, 0.55; 95% CI, 0.41-0.73).[102] Considerable heterogeneity was noted, on the basis of varied dosing regimens. The use of intravenous magnesium remains conditionally recommended, as in 2011, except that the quality of evidence has been downgraded to low. Likewise, the recommendation for the use

of biatrial pacing to prevent POAF remains conditional,[100] because evidence for its use has not changed.[102]

Limiting inflammation and oxidative stress

Agents that suppress inflammation or oxidative stress, including statins, steroids, colchicine, and fish oils (polyunsaturated fatty acids; PUFA), have been used to suppress the proinflammatory and oxidative effect of surgery to reduce POAF. A recent trial that randomized 1922 patients to perioperative rosuvastatin or placebo, showed no reduction in rates of POAF (OR, 1.04; 95% CI, 0.84-1.30), but a statistically significant increase in the rate of acute kidney injury.[103] Statins cannot therefore be recommended to prevent POAF. A previous systematic review on the use of steroids suggested a beneficial effect on the basis of 14 studies.[104] When tested in 2 definitive studies that randomized > 11,000 patients, no benefit was seen,[105] and a potential small signal of harm was noted.[106] As such, steroids cannot be recommended for the prevention of POAF. Likewise, PUFA appear to have limited effect. Two separate meta-analyses on the basis of 8 trials including 2687 patients were recently published: 1 was negative (OR, 0.86; 95% CI, 0.71-1.04),[107] the other positive (OR, 0.84; 95% CI, 0.71-0.99) as a consequence of different trial weighting.[108] Importantly, the largest RCT, which randomized 1516 patients, showed no difference in POAF, including number of sustained, symptomatic, or treated episodes.[109] Thus, preoperative PUFA treatment cannot be recommended to prevent POAF.

A systematic review of the use of colchicine at 1 mg/d in 584 patients from 3 small RCTs reported a significant reduction in POAF (OR, 0.44; 95% CI, 0.29-0.66).[110] A second systematic review of 4 RCTs using colchicine, including patients who underwent ablation, also showed a reduction in postsurgical AF among 1118 patients.[111] A higher rate of discontinuation of colchicine, predominantly because of gastrointestinal upset and diarrhea (OR, 2.30; 95% CI, 1.47-3.62), was also observed.[111] Thus, there is low-quality evidence supporting the use of colchicine if other treatment options are not available.

RECOMMENDATION

19. We suggest that patients who have a contraindication to β-blocker therapy and to amiodarone before or after cardiac surgery be considered for prophylactic therapy to prevent POAF with intravenous magnesium (Conditional Recommendation, Low-Quality Evidence) or colchicine (Conditional Recommendation, Low-Quality Evidence) or with biatrial pacing (Conditional Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on preventing POAF using novel therapies that are supported by lower-quality data; with a higher value on the lower probability of adverse effects from magnesium vs colchicine. The use of biatrial pacing needs to be individualized according to patient and institution, because the potential for adverse effects might outweigh benefit according to local expertise.

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Supplementary Material

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