



Society Guidelines

2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

Jason G. Andrade, MD (Co-chair),^{a,b} Atul Verma, MD (Co-chair),^c L. Brent Mitchell, MD,^d Ratika Parkash, MD,^e Kori Leblanc, ACPR, PharmD,^f Clare Atzema, MD,^{g,h} Jeff S. Healey, MD,^{i,j} Alan Bell, MD,^h John Cairns, MD,^a Stuart Connolly, MD,^{i,j} Jafna Cox, MD,^e Paul Dorian, MD,^k David Gladstone, MD,^{g,h} M. Sean McMurtry, MD,^l Girish M. Nair, MBBS,^m Louise Pilote, MD,ⁿ Jean-Francois Sarrazin, MD,^o Mike Sharma, MD,^{i,j} Allan Skanes, MD,^p Mario Talajic, MD,^b Teresa Tsang, MD,^a Subodh Verma, MD,^k D. George Wyse, MD, PhD,^d Stanley Nattel, MD,^b and Laurent Macle, MD (Co-chair);^b for the CCS Atrial Fibrillation Guidelines Committee*

^a University of British Columbia, Vancouver, British Columbia, Canada; ^b Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; ^c Southlake Regional Health Centre, Newmarket, Ontario, Canada; ^d Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada; ^e QEII Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia, Canada; ^f University Health Network, University of Toronto, Toronto, Ontario, Canada; ^g Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; ^h University of Toronto, Toronto, Ontario, Canada; ⁱ McMaster University, Hamilton, Ontario, Canada; ^j Hamilton General Hospital, Hamilton, Ontario, Canada; ^k St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; ^l University of Alberta, Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada; ^m University of Ottawa Heart Institute, Ottawa, Ontario, Canada; ⁿ McGill University Health Centre, Montréal, Quebec, Canada; ^o Institut universitaire de cardiologie et pneumologie, Quebec, Quebec, Canada; ^p London Heart Institute, Western University, London, Ontario, Canada

ABSTRACT

The Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines Committee provides periodic reviews of new data to produce focused updates that address clinically important advances in atrial fibrillation (AF) management. This 2018 Focused Update addresses: (1) anticoagulation in the context of cardioversion of AF; (2) the management of antithrombotic therapy for patients with AF in the context of coronary artery disease; (3) investigation and management of subclinical AF; (4) the use of antidotes for the reversal of non-vitamin K antagonist oral anticoagulants; (5) acute pharmacological cardioversion of AF; (6) catheter ablation for AF, including patients with concomitant AF and heart failure; and (7) an integrated approach to

RÉSUMÉ

Le comité des lignes directrices en matière de fibrillation auriculaire de la Société canadienne de cardiologie (SCC) procède à des examens périodiques des nouvelles données pour produire des mises à jour thématiques portant sur des avancées cliniquement importantes de la prise en charge de la fibrillation auriculaire (FA). La mise à jour ciblée 2018 porte sur les aspects suivants : 1) l'anticoagulation dans le contexte de la cardioversion de la FA; 2) la prise en charge du traitement antithrombotique des patients atteints de FA dans le contexte d'une coronaropathie; 3) la recherche et la prise en charge de la FA sub-clinique; 4) les antidotes aux anticoagulants oraux non-vitamine K; 5) cardioversion pharmacologique aiguë de la FA; 6) l'ablation par

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*For a full listing of primary and secondary panel members, see the [Supplementary Material](#).

Corresponding author: Dr Laurent Macle, Electrophysiology service, Montreal Heart Institute, Université de Montréal, 5000 est, rue Bélanger, Montréal, Québec H1T 1C8, Canada. Tel.: +1-514-376-3330.

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.

the patient with AF and modifiable cardiovascular risk factors. The recommendations were developed 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 and evidence tables are included as [Supplementary Material](#) and are available on the CCS Web site. 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 2018 Focused Update, which is provided in the [Supplementary Material](#).

The contemporary management of atrial fibrillation (AF) is centred on a reduction in the morbidity and mortality associated with AF, as well as on symptomatic improvement with consequent reduction in AF-related emergency room visits or hospitalizations.¹ The Canadian Cardiovascular Society (CCS) Atrial Fibrillation Guidelines committee provides periodic reviews of new data to produce focused updates that address clinically important advances in AF management. The committee reviewed data published since the 2016 Focused Update for the management of AF. This 2018 Focused Update addresses:

1. Anticoagulation in the context of cardioversion of AF;
2. The management of antithrombotic therapy for patients with AF in the context of coronary artery disease (CAD);
3. Investigation and management of subclinical AF (SCAF);
4. The use of antidotes for the reversal of non-vitamin K antagonist oral anticoagulants (NOACs);
5. Acute pharmacological cardioversion of AF;
6. Catheter ablation for AF, including patients with concomitant AF and heart failure (HF);
7. Integrated approach to the patient with AF and modifiable cardiovascular risk factors.

The recommendations were developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) standards with strength of recommendations now classified as “strong” or “weak.” Details of the updated recommendations are presented, along with their background and rationale. The literature review process and evidence tables are included as [Supplementary Material](#), along with an updated summary of all CCS AF Guidelines Recommendations on the CCS Web site.

I. Anticoagulation in the Context of Cardioversion

There have been no randomized clinical trials of oral anticoagulation (OAC) therapy vs placebo for prevention of thromboembolic events at the time of cardioversion. Because of the stroke risk associated with cardioversion in the absence of anticoagulation, it is unlikely that such a study will be done.²⁻¹⁴ Contemporary estimates of the risk of thromboembolic events around the time of cardioversion can be obtained from analysis of the results of the pivotal randomized

cathéter de la FA, y compris chez les patients atteints d'insuffisance cardiaque; 7) une approche intégrée du patient présentant une FA et des facteurs de risque cardiovasculaire modifiables. Les recommandations ont été élaborées à l'aide du système GRADE (*Grading of Recommendations, Assessment, Development, and Evaluation*). Chaque étude et chaque publication ont été soumises à un examen visant à évaluer leur qualité et leurs biais; le processus d'examen des publications et les tableaux de données probantes sont présentés sous la forme d'un [supplément](#) accessible sur le site Web de la SCC. Les détails des recommandations mises à jour sont présentés, ainsi que leur contexte et leur justification. Ce document comporte un lien vers un sommaire mis à jour de toutes les lignes directrices en matière de FA de la SCC, de 2010 à la présente mise à jour ciblée 2018, qui est offerte dans le [supplément en ligne](#).

trials of adjusted-dose warfarin vs NOACs,¹⁰⁻¹³ reports of outcomes of cardioversions performed during these pivotal trials,²⁻⁵ and reports of randomized trials of adjusted-dose warfarin therapy vs NOAC therapy before cardioversion.⁶⁻⁸ Using these sources, the 1-month risk of stroke or systemic embolism (SSE) after cardioversion is estimated to be 0.46% for those treated with adjusted-dose warfarin and 0.31% for those treated with a NOAC. These risks are approximately twofold greater for a thromboembolic event in the month after cardioversion compared with the background risk (0.14% and 0.12% per month baseline stroke risk in those treated with adjusted-dose warfarin and with a NOAC, respectively). For those not receiving anticoagulant therapy the risk of a thromboembolic event is increased approximately fourfold (1.9% for the month after cardioversion vs 0.5% per month baseline risk).⁹⁻¹³

The thromboembolic risk in the pericardioversion period can be conceptually separated into 2 mechanistic phenomena. The first is the generation of thrombi during persistent AF, with subsequent embolization after restoration of an organized atrial contraction.¹⁵ The second relates to a period of transient atrial mechanical dysfunction after the restoration of sinus rhythm.¹⁶⁻¹⁸ This “atrial stunning” is responsible for the development of new thromboembolism post cardioversion despite the restoration of sinus rhythm.^{19,20} This atrial mechanical dysfunction has been reported with all modes of conversion (pharmacologic, electrical, and spontaneous) and is at maximal in the period immediately after cardioversion.¹⁹⁻²² The duration and severity of atrial stunning varies depending on the duration of the atrial arrhythmia, the atrial size, as well as the presence of comorbid structural heart disease.¹⁹⁻²²

OAC use before and after cardioversion

Patients who present with acute (episode duration < 48 hours) nonvalvular AF (NVAF; ie, AF in the absence of rheumatic mitral stenosis, moderate-severe nonrheumatic mitral stenosis, or a mechanical heart valve) have long been considered to have a low risk of thromboembolic events after cardioversion on the basis of the rationale that left atrial thrombi have not yet had time to form. This practice has been supported by observational reports of short-term outcomes after cardioversion in patients with acute AF/atrial flutter (AFL).²³⁻³⁶ In these reports the post cardioversion

30-day risk of SSE was reported to be 0.19% (4047 patients who underwent 4503 spontaneous, pharmacologic, or electrical cardioversions). Although this risk is comparable with that of elective cardioversion in more persistent AF/AFL patients who receive anticoagulation therapy, it is important to recognize that these reports describe cohorts of stable patients at low risk of thromboembolism for whom cardioversion was considered to be an appropriate therapeutic option by their treating physician. Specifically, these patients had a low baseline stroke risk (69% of patients with a Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack [CHADS₂] score of 0-1; 28% receiving chronic OAC therapy) and presented early in the 48-hour window (mean duration of acute AF/AFL of 8.0 hours). Nevertheless, these data suggest that it might be possible to identify a population of patients with acute AF/AFL who are at low risk of a thromboembolic event associated with cardioversion.

Conversely, previous CCS AF guidelines have suggested that it is might be possible to identify a population of patients with acute AF/AFL in whom immediate cardioversion without preprocedural anticoagulant therapy presents an unacceptably high risk of thromboembolic complication. Such patients were considered, in previous CCS AF guidelines, to include those with a stroke or transient ischemic attack within the previous 6 months, those with moderate to severe rheumatic mitral stenosis, and those with a mechanical heart valve.³⁷

The Finnish Cardioversion (FinCV) study was a retrospective, observational study that determined outcomes in consecutive patients who underwent cardioversion of acute AF (duration < 48 hours). This study included 7660 cardioversions in 3143 patients (mean age, 62.2 ± 12.3 years; 36.5% female, median Congestive Heart Failure, Hypertension, Age (≥ 75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female) [CHA₂DS₂-VASc] score, 2 (interquartile range, 1-3)).³⁸⁻⁴¹ To date, several analyses have been performed and showed the following key findings. First, the incidence of definite SSE was lower in patients receiving anticoagulation therapy.⁴⁰ In an analysis of the total patient population, the incidence of SSE in patients who were receiving anticoagulation therapy at the time of their cardioversion attempt (0.1% in 2298 encounters) was significantly lower than in patients not receiving anticoagulation therapy (0.7% in 5362 encounters; 82% relative risk [RR] reduction; *P* = 0.001).⁴⁰ In patients with a CHA₂DS₂-VASc score ≥ 2, the risk of SSE after a cardioversion attempt was significantly lower in patients receiving anticoagulation therapy (3 of 1708 encounters; 0.2%) than in patients not receiving anticoagulation therapy (28 of 2590 encounters; 1.1%; *P* = 0.001). In patients with a CHA₂DS₂-VASc score of 0-1, the risk of SSE after a cardioversion attempt was quantitatively lower in patients receiving anticoagulation therapy (0 of 509 encounters; 0.0%) than in patients not receiving anticoagulation therapy (10 of 2772 encounters; 0.4%), but this trend was not statistically significant despite the relatively large number of subjects.⁴⁰ Second, longer durations of AF before cardioversion, even in the 48-hour window of acute AF, were associated with a

significantly increased risk of SEE.^{38,41} In a cohort restricted to the 5116 successful cardioversions performed in the absence of periprocedural or postprocedural anticoagulation in 2481 patients, multivariable logistic regression analysis showed an increased incidence of SSE in patients cardioverted in the time window after AF onset of 12-24 hours (21 of 1840 encounters; 1.1%; odds ratio [OR], 3.3; 95% confidence interval [CI], 1.3-8.9; *P* = 0.001) or in the time window after AF onset of 24-48 hours (9 of 836 encounters; 1.1%; OR, 4.0; 95% CI, 1.7-9.1; *P* = 0.02) compared with those cardioverted in < 12 hours after AF onset (8 of 2400 encounters; 0.3%).³⁸ Third, the statistically significant independent predictors of an increased incidence of SSE in the month after cardioversion of acute AF in the complete cohort were increasing age (per year; OR, 1.05; 95% CI, 1.02-1.09; *P* < 0.001), AF episode duration > 12 hours (OR, 3.89; 95% CI, 1.76-8.60; *P* = 0.001), HF (OR, 3.37; 95% CI, 1.39-8.19; *P* = 0.007), diabetes mellitus (OR, 2.66; 95% CI, 1.25-5.69; *P* = 0.012), and female sex (OR, 2.11; 95% CI, 1.04-4.28; *P* = 0.038).^{39,40}

A recent report from the Swedish National Patient Registry⁴² described outcomes in 10,722 patients who underwent direct current (DC) cardioversion of AF (the duration of AF being unavailable) between January 1, 2006 and December 1, 2010. The 30-day incidence of thromboembolic complication in patients not receiving periprocedural anticoagulation therapy was significantly higher than those receiving anticoagulation therapy (0.9% vs 0.3%; OR, 2.54; 95% CI, 1.70-3.79; *P* < 0.001); the increased OR persisted even after matching patients on the basis of the components of the CHA₂DS₂-VASc and Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly (> 65 Years), Drugs/Alcohol Concomitantly (HAS-BLED) scores (OR, 2.51; 95% CI, 1.69-3.75; *P* < 0.001). Similar findings were observed in a recent observational analysis of the Danish National Patient Registry.¹⁴ This analysis included 16,274 patients discharged from hospital after a first-time DC cardioversion for AF between 2000 and 2008. The 30-day incidence of a thromboembolic event after DC cardioversion was 0.29% (32 of 11,190 patients) in those who received a preprocedure OAC compared with 1.1% (54 of 5084) in patients who did not receive a preprocedure OAC.¹⁴ Although age > 75 years, previous SSE, and rehospitalization for AF were significant risk factors for thromboembolism, the CHADS₂ and CHA₂DS₂-VASc scores offered no discriminative ability in those not receiving OAC therapy (hazard ratio [HR], 2.21; 95% CI, 0.79-6.77 and 2.40; 95% CI, 1.46-3.95 with CHA₂DS₂-VASc score 0-1 and CHA₂DS₂-VASc score 2 or more). Conversely, the risk of thromboembolism was low in patients who initiated OAC therapy only after cardioversion and was comparable with those who received OAC therapy before and after cardioversion (HR, 0.97 for those with only post cardioversion OAC therapy vs those who received OAC therapy pre/post cardioversion; 95% CI, 0.33-2.86).

Overall, the available evidence suggests that the incidence of a definite SSE in the month after cardioversion from acute AF/AFL (< 48 hours) in patients who were not receiving anticoagulation is approximately 0.7%,⁴⁰ which is above the

thromboembolic risk threshold that the CCS uses to recommend anticoagulation therapy.

The comprehensive recommendations regarding cardioversion follow and are summarized in Figure 1.

RECOMMENDATION

1. We recommend that in addition to appropriate rate control, most hemodynamically stable patients with AF or AFL for whom elective electrical or pharmacological cardioversion is planned should receive therapeutic anticoagulation for 3 weeks before cardioversion (Strong Recommendation, Moderate-Quality Evidence).
2. We suggest that pharmacological or electrical cardioversion of symptomatic AF or AFL without at least 3 weeks of previous therapeutic anticoagulation be reserved for patients with the following characteristics (Weak Recommendation, Low-Quality Evidence):
 - i. Patients with NVAF who present with a clear AF onset within 12 hours in the absence of recent stroke or transient ischemic attack (within 6 months);
 - ii. Patients with NVAF and a CHADS₂ score < 2 who present after 12 hours but within 48 hours of AF onset.
3. We suggest that, as an alternative to at least 3 weeks of therapeutic anticoagulation before cardioversion, transesophageal echocardiography (TEE) may be used to exclude cardiac thrombus (Weak Recommendation, Moderate-Quality Evidence).

Practical tip. NVAF is defined as AF in the absence of mechanical heart valves, rheumatic mitral stenosis, or moderate to severe nonrheumatic mitral stenosis.

RECOMMENDATION

4. We recommend that immediate electrical cardioversion be considered for patients whose recent-onset AF/AFL is the direct cause of instability with hypotension, acute coronary syndrome (ACS), or pulmonary edema (Strong Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation places a high value on immediately addressing instability by attempting cardioversion, and a lower value on reducing the risk of cardioversion-associated stroke with a period of anticoagulation before cardioversion. Therapeutic anticoagulation therapy should be initiated as soon as possible.

5. When a decision has been reached that a patient will be undergoing unplanned cardioversion of AF/AFL, we suggest that therapeutic anticoagulation therapy be initiated immediately (preferably before cardioversion) with either a NOAC, or with heparin followed by adjusted-dose warfarin (Weak Recommendation, Low-Quality Evidence).

6. We suggest that, in the absence of a strong contraindication, all patients who undergo cardioversion of AF/AFL receive at least 4 weeks of therapeutic anticoagulation (adjusted-dose warfarin or a NOAC) after cardioversion. (Weak Recommendation, Low-Quality Evidence). Thereafter, we recommend that the need for ongoing antithrombotic therapy should be on the basis of the risk of stroke as determined by the CCS Algorithm (“CHADS-65”; Strong Recommendation, Moderate-Quality Evidence).

Values and preferences. This approach places relatively greater emphasis on the benefits of stroke prevention compared with the risks of bleeding with a short course of anticoagulation therapy. Although it might be possible to parse these risks either on the basis of patient characteristics or the duration of acute AF/AFL, the CCS AF Guidelines Committee at this point has chosen to simplify by recommending anticoagulation for 1 month after cardioversion for all such patients in the absence of a strong contraindication.

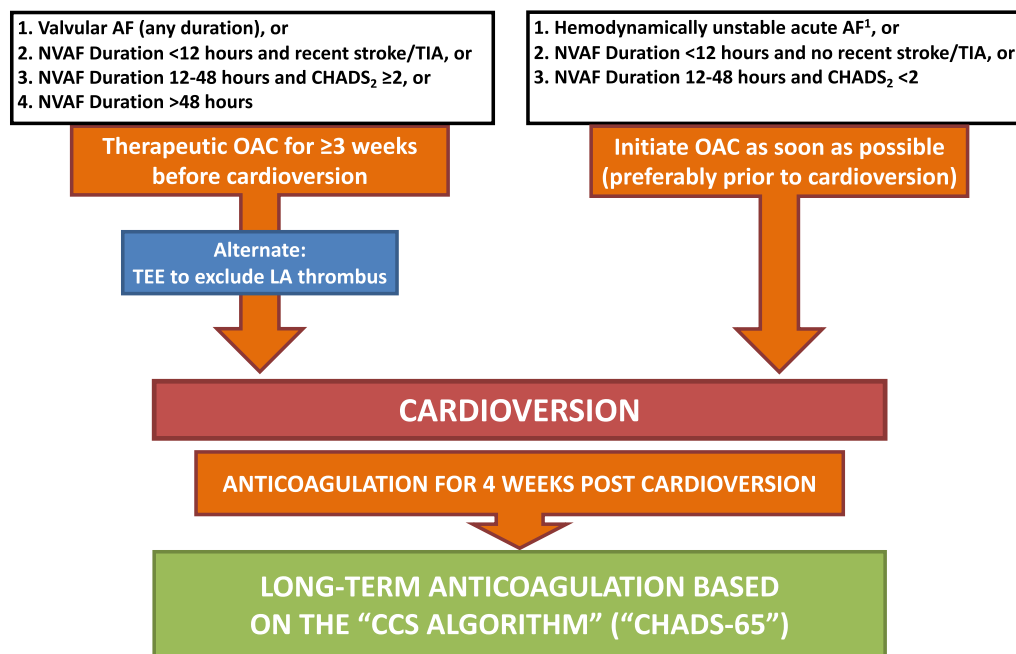
Practical tip. When oral anticoagulation is to be used for only a short period (< 2 months) current evidence does not substantiate either an efficacy or safety advantage for use of a NOAC over adjusted-dose warfarin. Nevertheless, the convenience of use of a NOAC over adjusted-dose warfarin in the pericardioversion period is substantial and the onset of therapeutic anticoagulation is nearly immediate with a NOAC whereas it is delayed in the case of adjusted-dose warfarin. Accordingly, it is reasonable to use NOAC therapy in the pericardioversion period.

The use of TEE to exclude left atrial thrombus

When early cardioversion is desired (ie, without a preceding period of therapeutic OAC treatment) TEE can be performed to exclude left atrial thrombi. The utility of this approach was shown by Klein et al., who randomized 1222 patients with AF of > 48-hour duration and assigned them to TEE-guided cardioversion, or conventional treatment (eg, pretreatment with warfarin for 3 weeks before cardioversion).⁴⁵ Although there was no significant difference in the rate of embolic events (0.8% in the TEE group vs 0.5% in the conventional group; $P = 0.50$), the TEE group had a significantly lower rate of hemorrhagic events (2.9% vs 5.5%; $P = 0.03$), a significantly shorter time to cardioversion (3.0 ± 5.6 vs 30.6 ± 10.6 days, $P < 0.001$), and a greater success rate (sinus rhythm restoration of 71.1% vs 65.2%; $P = 0.03$).

NOACs vs warfarin for cardioversion

Each of the pivotal trials that compared NOACs with adjusted-dose warfarin reported short-term, prospective, non-randomized efficacy and safety outcomes after DC cardioversion in study participants with persistent AF/AFL.²⁻⁵ Similarly, prospective, randomized trials have been completed that compared 3 of the currently available NOACs with adjusted-dose warfarin in the setting of planned cardioversion.^{7,8} The data of the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY),¹⁰ Rivaroxaban Once Daily Oral Direct Factor Xa



¹Hemodynamically unstable acute AF is defined as AF causing hypotension, cardiac ischemia, or pulmonary edema

Figure 1. Oral anticoagulation pathway in the context of cardioversion for atrial fibrillation or flutter. AF, atrial fibrillation; CCS, Canadian Cardiovascular Society; CHADS₂, Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; LA, left atrial; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; TEE, transesophageal echocardiogram.

Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF),¹¹ Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE),¹² Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48),¹³ Explore the Efficacy and Safety of Once-Daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Patients With Non-Valvular Atrial Fibrillation Scheduled for Cardioversion (X-VerT),⁶ and Edoxaban vs Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation (ENSURE-AF)⁷ trials formed the basis of a comparative meta-analysis reported by Renda et al.⁴⁴ In these trials, 6148 patients underwent 6854 cardioversions for AF and were followed for a mean of 42 days. Collectively, there were no significant differences between NOACs and adjusted-dose warfarin with respect to either efficacy (RR, 0.82; 95% CI, 0.38-1.75 for SSE) or safety (RR, 0.98; 95% CI, 0.51-1.87 for major bleeding).

Published after the meta-analysis by Renda et al., Eliquis Evaluated in Acute Cardioversion Compared to Usual Treatments for Anticoagulation in Subjects With Atrial Fibrillation (EMANATE)⁸ randomized 1500 patients who were not receiving OAC therapy to receive apixaban (753 patients) or heparin followed by VKA (747 patients) before DC cardioversion of persistent AF/AFL. Mean time to cardioversion was 3.4 days in the apixaban loading dose group, 25.7 days in the apixaban (no loading dose) group, and 17.8 days in the VKA group. In an intention-to-treat analysis, no patient randomized to receive apixaban had a SSE (0%) whereas 6 patients randomized to receive heparin/VKA therapy (0.8%) had a stroke (log rank $P = 0.016$). In patients who had received at least 1

dose of their assigned anticoagulant therapy there were 3 major bleeding events and 11 clinically relevant nonmajor bleeding events in 735 patients (total of 1.9%) in the apixaban group and 6 major bleeding events and 13 clinically relevant nonmajor bleeding events in 721 patients (2.6%) in the heparin/VKA group ($P =$ not significant).

It should be noted that these trials, individually and in their aggregate, were not sufficiently powered to exclude a clinically meaningful difference in either safety or efficacy. In the absence of a signal suggesting inferiority in safety or efficacy outcomes, the committee considered that NOAC therapy has advantages over dose-adjusted warfarin therapy (rapidity of onset and offset, standard dosages, and lack of need for therapeutic monitoring). Accordingly, NOAC therapy is preferred over adjusted-dose warfarin in the peri-cardioversion period in anticoagulation-naive patients.

II. Management of Antithrombotic Therapy in Patients With AF and CAD

Up to 20%-30% of AF patients also have concomitant CAD, with a significant proportion requiring percutaneous coronary intervention (PCI).^{45,46} An OAC is indicated for the prevention of AF-related SSE, whereas antiplatelet therapy is required for the prevention of coronary events after ACS or PCI. Each offers a relative efficacy benefit (eg, dual antiplatelet therapy [DAPT] is more effective than an OAC alone in reducing ischemic coronary events in an ACS population, but is inferior to an OAC for the prevention of SSE in an AF/AFL population at increased risk of AF-related stroke).⁴⁷ As such, management requires a careful and balanced assessment of the

individual risks of bleeding against the anticipated effect on thrombotic outcomes.

The extensive evidence for antithrombotic therapy for the prevention of SSE among patients with AF/AFL has been thoroughly reviewed in previous CCS guidelines and is not reviewed in depth herein.⁴⁸⁻⁵² This section specifically focuses on antithrombotic regimens for AF patients with coronary or peripheral arterial disease, with an emphasis on the evidence published since the previous AF guideline update in 2016.⁴⁹ The recommendations for patients who undergo PCI with AF are consistent with the 2018 CCS/Canadian Association of Interventional Cardiology (CAIC) focused update of the guidelines for the use of antiplatelet therapy.⁵²

To clarify potentially confusing terminology in this area, single-agent antiplatelet therapy (SAPT) refers to the use of a single antiplatelet drug (eg, acetylsalicylic acid [ASA]), DAPT refers to the concomitant use of 2 antiplatelet agents (eg, ASA with clopidogrel), dual pathway therapy refers to the concomitant use of a SAPT with an OAC agent (eg, VKA with clopidogrel), and triple antithrombotic therapy (TT) the combination of DAPT with an OAC (eg, VKA with ASA and clopidogrel).

RECOMMENDATION

7. We recommend that patients who have concomitant AF and coronary/arterial vascular disease (peripheral vascular disease or aortic plaque), receive an antithrombotic therapy regimen that is on the basis of a balanced assessment of their risk of AF-related stroke, ischemic coronary event, and clinically relevant bleeding associated with the use of antithrombotic agents (Strong Recommendation, High-Quality Evidence [Fig. 2]).

Practical tip. For patients who require combinations of antiplatelet and OAC agents for concomitant AF and coronary/arterial vascular disease, we suggest that measures be used to reduce the risk of bleeding, including careful consideration of modifiable bleeding risk factors with vigorous efforts to mitigate them; consideration of proton pump inhibitor use; avoidance of prasugrel and ticagrelor in conjunction with OACs; the use of warfarin in the lower target international normalized ratio (INR) range (eg, 2.0-2.5); consideration of the lower effective doses of NOACs in selected patients (Fig. 3); specific measures during coronary invasive procedures (radial access, small-diameter sheaths, early sheath removal from femoral site, and minimized use of acute procedural antithrombotic therapies); delaying nonurgent procedures until dual pathway therapy is no longer required; use of walking aids for those with gait or balance disorders; avoidance of nonsteroidal anti-inflammatory drugs or other drugs that might increase bleeding risk; and, strict blood pressure control.

Stable vascular disease and AF in patients at low risk of SSE

SAPT (eg, ASA 81 mg/d) is recommended for patients with AF who are at low risk of SSE (age < 65 years and CHADS₂ score of 0) if vascular disease is present (CAD, peripheral arterial disease, or aortic plaque). This is on the basis of the efficacy of ASA therapy for the prevention of coronary events among patients with stable CAD (RR reduction of 18% for primary prevention and 20% for secondary prevention of MI), rather than the small reduction in stroke observed in AF patients (RR reduction, 22% vs placebo).^{9,53} Although there is extensive evidence for the efficacy of OAC therapy for prevention of ischemic coronary events in patients with stable CAD (eg, VKA), the CCS AF guidelines recommend SAPT in preference

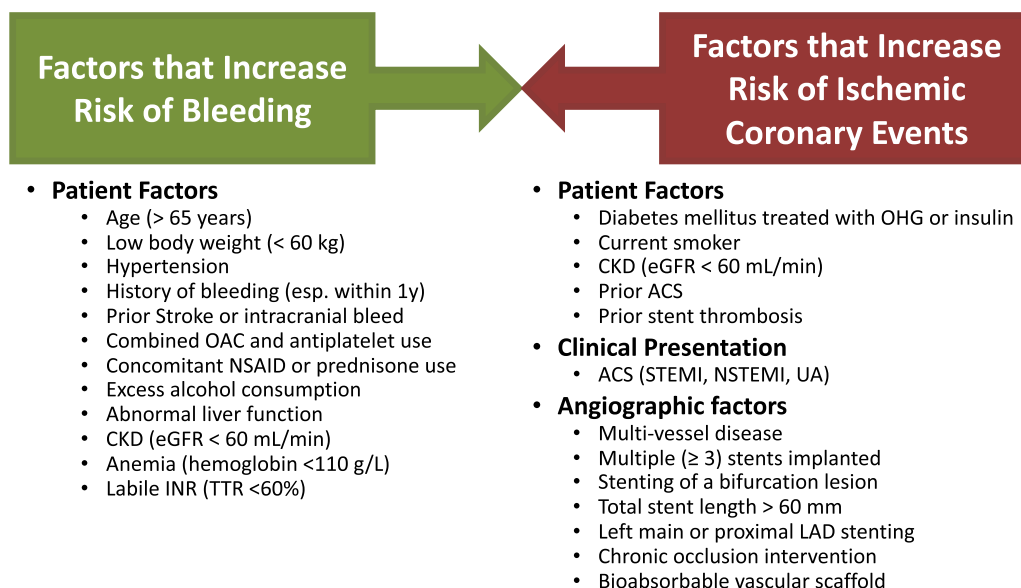


Figure 2. Risk factors associated with an increased risk of bleeding, and an increased risk of ischemic coronary outcomes (recurrent myocardial infarction, stent thrombosis). ACS, acute coronary syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LAD, left anterior descending artery; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non-ST-elevation myocardial infarction; OHG, oral hypoglycemic agents; STEMI, ST-elevation myocardial infarction; TTR, Time in Therapeutic Range; UA, unstable angina.

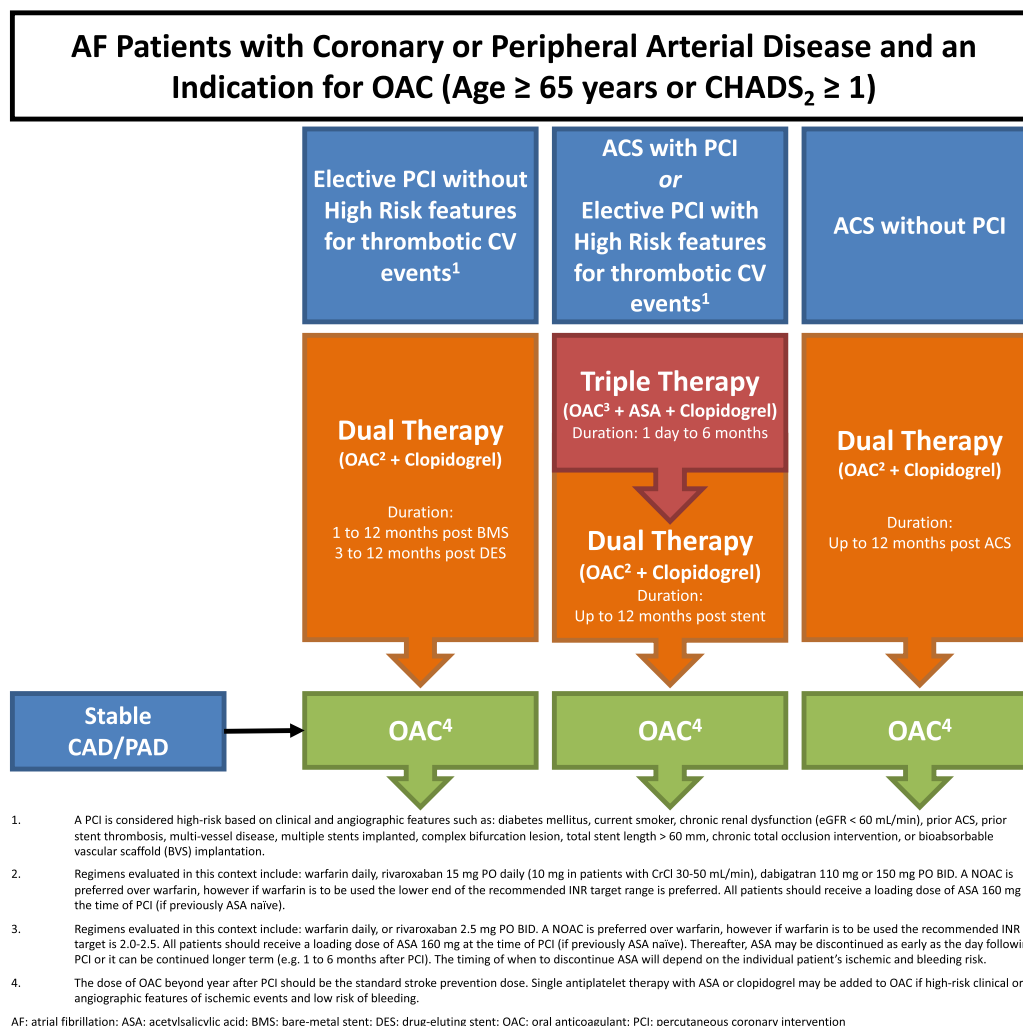


Figure 3. Management of antithrombotic therapy in patients with atrial fibrillation (AF) and coronary artery disease (CAD)/peripheral artery disease (PAD). ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice per day; BMS, bare metal stent; BVS, bioabsorbable vascular scaffold; CCS, Canadian Cardiovascular Society; CHADS₂, Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; CrCl, creatinine clearance; CV, cardiovascular; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; PO, orally.

to OACs in those at low risk of SSE because of its safety profile and ease of use.

More recently, in a non-AF population, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial showed that dual pathway therapy with ASA and “vascular dose” rivaroxaban (2.5 mg twice per day [BID]) was associated with a significant reduction in cardiovascular mortality and ischemic stroke, albeit with a significantly increased risk of major bleeding.⁵⁴ As such the combination of ASA and very low dose rivaroxaban might be a reasonable alternative to ASA alone for NVAf patients at low risk of stroke (age < 65 years and CHADS₂ score of 0) who also have coronary or arterial vascular disease.

Practical tip. For patients with NVAf/AFL aged < 65 years with no CHADS-65 risk factors, the risk of stroke

RECOMMENDATION

8. For patients with NVAf/AFL aged < 65 years with no CHADS₂ risk factors, we suggest no antithrombotic therapy for stroke prevention (Weak Recommendation, Moderate-Quality Evidence), with management of their coronary or arterial vascular disease as directed by the 2018 CCS/CAIC focused update of the guidelines for the use of antiplatelet therapy.⁵²

associated with AF is not sufficiently elevated to justify OAC therapy. For this group treatment should be directed at the underlying coronary/peripheral arterial disease as outlined in

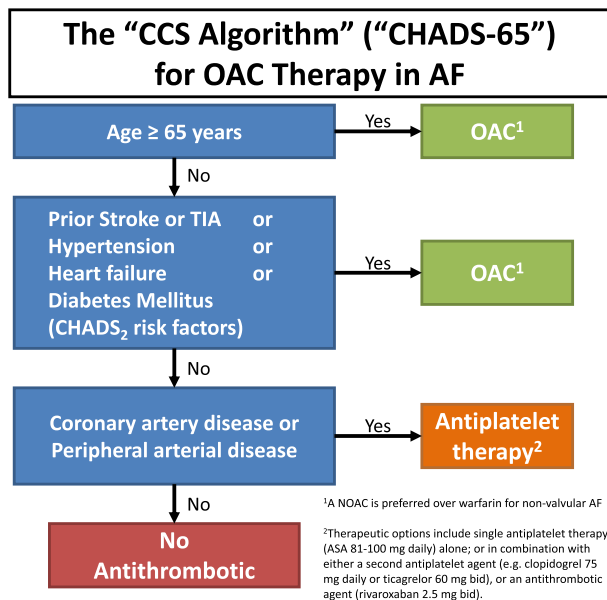


Figure 4. The simplified Canadian Cardiovascular Society (CCS) algorithm (CHADS-65) for deciding which patients with atrial fibrillation (AF) or atrial flutter should receive oral anticoagulant (OAC) therapy. It recommends an OAC for most patients ≥ 65 years of age and for younger patients with a Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS₂) score ≥ 1 ; aspirin (acetylsalicylic acid [ASA]) for patients < 65 years of age with a CHADS₂ score = 0 with arterial vascular disease (coronary, aortic, or peripheral); and no antithrombotic therapy for patients < 65 years of age with a CHADS₂ 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.

the 2018 CCS/CAIC focused update of the guidelines for the use of antiplatelet therapy.⁵² Therapeutic options include ASA 81 mg daily alone; or ASA in combination with either clopidogrel 75 mg daily, ticagrelor 60 mg BID, or rivaroxaban 2.5 mg BID.

Stable vascular disease and AF in patients at high risk of SSE

In patients with AF who are aged ≥ 65 years or with CHADS₂ score ≥ 1 , an OAC is indicated for stroke prevention (Fig. 4). When such a patient also has stable CAD (defined by the absence of ACS for the preceding 12 months), OAC therapy provides protection against stroke and ischemic coronary events.⁵⁵⁻⁶⁰ The Warfarin-Aspirin Reinfarction Study (WARIS)-II indicates that the additional use of antiplatelet therapy with an OAC offers minimal beneficial effect on ischemic or thrombotic coronary outcomes (eg, combined end point of death, myocardial infarction [MI], and stroke, 16.7% with an OAC vs 15.0% with combination OAC and ASA treatment; $P = 0.18$), while conferring an increased risk of adverse bleeding outcomes (overall bleeding 2.82% per year with an OAC alone vs 3.27% per year with combination OAC and ASA treatment).^{59,60}

The comprehensive recommendations regarding antithrombotic treatment in AF patients indicated for an OAC with concomitant coronary/peripheral arterial disease are summarized in Figure 3.

RECOMMENDATION

9. For patients with AF aged ≥ 65 years or with a CHADS₂ score ≥ 1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), we recommend long-term therapy with an OAC alone (Strong Recommendation, High-Quality Evidence).

Values and preferences. For patients with AF and stable coronary or arterial vascular disease, the CCS AF Guidelines Committee believed that routine use of combination therapy (an OAC with a single antiplatelet agent) was not justified because of the increased risk of bleeding without a significant reduction in ischemic coronary and cerebrovascular thrombotic events.

Practical tip. For patients with high-risk clinical or angiographic features for ischemic coronary outcomes (Fig. 2) who are at low risk of bleeding, some clinicians prefer a combination of an OAC and single antiplatelet therapy (either aspirin or clopidogrel) in preference to OAC therapy alone.⁵²

RECOMMENDATION

10. When an OAC is indicated in the presence of coronary or arterial vascular disease, we suggest a NOAC in preference to warfarin (Weak Recommendation, Moderate-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, as well as the data from randomized controlled trials of NOACs vs warfarin for NVAF (eg, equal or greater reduction of stroke, equal or greater reduction in all-cause mortality, equal or less major bleeding, less intracranial bleeding, and no net increase in CAD outcomes).

PCI or ACS in patients with AF

Patients who undergo PCI are generally prescribed DAPT for a period that varies from 4 weeks with bare metal stent (BMS) to more than 12 months after drug-eluting stent (DES) implantation. Shorter durations of DAPT decrease the risk of major bleeding, whereas premature DAPT discontinuation might increase the risk of stent thrombosis and MI. There has been a trend to shorten DAPT duration as second-generation DESs with sustained antiproliferative action and reduced thrombogenicity have become available.

For patients with AF and low stroke risk (age < 65 years and CHADS₂ score of 0), the post-PCI therapeutic DAPT regimen should be provided as outlined in the 2018 CCS/CAIC antiplatelet guidelines, because an OAC is not recommended for stroke prevention in these patients.⁵²

For a patient at higher risk of AF-related stroke (age ≥ 65 years or with CHADS₂ score ≥ 1) combination OAC and antiplatelet therapy is required. In these patients the optimal therapeutic regimen should be individualized on the basis of a balanced assessment of their risk of AF-related stroke, ischemic coronary event, and clinically relevant bleeding. The risk of AF-related SSE can be estimated from the CHADS-65 illustrated in Figure 4.^{48,49} The risk of ischemic coronary events is modulated by the clinical presentation (eg, ACS being higher risk than elective PCI), clinical characteristics (higher risk with comorbid diabetes mellitus or chronic kidney disease, current tobacco use, or previous stent thrombosis), as well as PCI-related factors (higher risk with multivessel disease, multiple stent implantation, total stent length > 60 mm, bifurcation lesion, chronic total occlusion intervention, and stent type; Fig. 2).^{52,61} The risk of bleeding can be estimated from clinical risk scores such as HAS-BLED, Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Anti Platelet Therapy (PRECISE-DAPT), and Cardiovascular Disease Research Using Linked Bespoke Studies and Electronic Health Records (CALIBER), with the former validated in a VKA-treated population, and the latter two in a population with CAD treated with PCI and DAPT.⁵²

The population of patients with ACS who do not undergo revascularization (PCI or coronary artery bypass grafting), represents a heterogenous group. This population includes patients with thrombotic plaque rupture (type I MI) as well as those with supply-demand mismatch due to tachycardia, infection, sepsis, etc (type II MI). For patients with type II MI it is unclear if there is an advantage to routine use of combined OAC and antiplatelet therapy. For patients who have true ACS (type I MI) and are not revascularized, the management should take into consideration the relative risks and benefits of combination therapy.

Key trials of dual pathway therapy vs triple therapy in AF with ACS/PCI

The Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) randomized 2124 patients with NVAf who underwent PCI for ACS (51%) or for stable CAD to receive, in a 1:1:1 ratio: (1) A P2Y12 inhibitor (94% clopidogrel) with rivaroxaban 15 mg/d (dual pathway) for 12 months; (2) DAPT with rivaroxaban 2.5 mg BID (reduced-dose TT) for 1, 6, or 12 months; or, (3) TT with warfarin (target INR, 2-3) with DAPT for 1, 6, or 12 months.⁶² The primary safety end point of clinically significant bleeding (eg, Thrombolysis in Myocardial Infarction [TIMI] major bleeding and minor bleeding), was lower in the dual pathway and reduced-dose TT groups compared with TT with warfarin (16.8% in patients treated with dual pathway therapy, 18% in patients treated with reduced-dose TT, and 26.7% in patients treated with traditional TT [HR, 0.59 (95% CI, 0.47-0.76); and HR, 0.63 (95% CI, 0.50-0.80, respectively)]). For the 2 TT groups the relative reduction in bleeding with reduced-dose TT persisted across all 3 durations of DAPT use (1 month: 19.4% vs 25.7% [HR, 0.68; 95% CI, 0.38-1.23]; 6 months: 17.5% vs 31.2% [HR, 0.51; 95% CI, 0.34-0.75]; 12 months: 17.9% vs 23.9% [HR, 0.74; 95% CI, 0.52-1.04]). There was a

nonsignificant reduction in major bleeding with the dual pathway and reduced-dose TT groups compared with the group that received traditional TT with warfarin (HR, 0.66 [95% CI, 0.33-1.31]; and HR, 0.57 [95% CI, 0.28-1.16], respectively). In a post hoc analysis, there was a reduction in the composite of all-cause death and rehospitalizations with rivaroxaban-based strategies compared with traditional TT with warfarin.⁶³

The Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial randomized 2725 patients with NVAf who underwent PCI for ACS (51%) or stable CAD to: (1) dual pathway therapy with dabigatran 110 mg BID with a P2Y12 inhibitor (D110); (2) dual pathway therapy with dabigatran 150 mg BID with a P2Y12 inhibitor (D150); or (3) traditional TT with warfarin (target INR, 2-3) with a P2Y12 inhibitor (predominantly clopidogrel) and ASA.⁶⁴ In the TT group aspirin was discontinued after 1 month (BMS) or after 3 months (DES), however, the P2Y12 inhibitor was continued for 12 months post-PCI. The primary outcome was International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant nonmajor bleeding, which was significantly reduced in both dual pathway therapy groups compared with the TT group (11.5% absolute reduction with D110 [HR, 0.52; 95% CI, 0.42-0.63], and 5.5% absolute reduction with D150 [HR, 0.72; 95% CI, 0.58-0.88]). In secondary analyses both dual pathway therapy groups had significant reduced ISTH major bleeding (4.2% absolute reduction with D110 [HR, 0.52; 95% CI, 0.37-0.74], and 2.8% absolute reduction with D150 [HR, 0.64; 95% CI, 0.43-0.94]), and TIMI major bleeding (2.4% absolute reduction with D110 [HR, 0.37; 95% CI, 0.20-0.68], and 1.8% absolute reduction with D150 [HR, 0.51; 95% CI, 0.28-0.93]).

There are several notable limitations to these trials. First, a large proportion of patients underwent elective PCI (44%-72%), meaning the relative risk of coronary outcomes might be underestimated. Second, measures to decrease bleeding risk were underutilized, suggesting that the bleeding rate might have been increased in the TT arm relative to contemporary practice. Third, these trials compared dual pathway therapy using a NOAC with TT using warfarin. It is unknown whether the results would have been similar had the dual pathway therapy groups used a VKA, or the TT group used a therapeutic-dose NOAC. Last, each of the trials was powered to address safety outcomes (ie, bleeding). Although each of these trials were individually underpowered to assess efficacy outcomes (eg, mortality, stroke, and coronary outcomes) a limited meta-analysis of the What Is the Optimal Antiplatelet and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST), PIONEER AF-PCI, and RE-DUAL PCI trials showed that the use of dual pathway therapy was associated with a significant reduction in major bleeding events, without an excess in the occurrence of MI, definite stent thrombosis, and stroke.⁶⁵ Studies of apixaban (Apixaban Versus Warfarin in Patients with AF and ACS or PCI [AUGUSTUS] trial; NCT02415400) and edoxaban (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention [ENTRUST-AF-PCI] trial; NCT02866175) are ongoing.

Duration of TT

The benefit of TT (reduction of recurrent MI and stent thrombosis) must be balanced against the increased bleeding risk with this therapeutic regimen. Importantly, the rate of bleeding with TT peaks within the first month of treatment, and thereafter the risk of bleeding is relatively stable for the duration of TT.

In the AF population, it is possible that shorter durations of DAPT might be reasonable when concomitant OAC therapy will be used for the prevention of SSE. This concept was demonstrated in the **Intracoronary Stenting and Antithrombotic Regimen: Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE)** study, which showed no significant difference in the primary end point of “net clinical benefit” (combination of death, MI, stent thrombosis, stroke, or TIMI major bleeding) between those who received 6 weeks vs 6 months of TT. A post hoc landmark analysis from 6 weeks to 9 months (ie, excluding the period in which both groups had received TT) showed a significant reduction in any **Bleeding Academic Research Consortium (BARC)** bleeding in the abbreviated TT group.⁶⁶ Likewise, the **PIONEER AF-PCI** and **RE-DUAL PCI** trials showed no relationship between major adverse cardiovascular events and TT duration or clinical presentation (ACS vs stable CAD).^{62,64} On balance, these findings suggest that shortening the TT course to ≤ 6 months and thereafter continuing therapy with an OAC and a single antiplatelet agent, might be reasonable in the context of elevated bleeding risk.

AF patients at higher risk of stroke who undergo PCI without high-risk features

RECOMMENDATION

- For patients with AF aged ≥ 65 years or with a CHADS₂ score ≥ 1 , we suggest dual pathway therapy (an OAC with clopidogrel 75 mg/d) for at least 1 month after BMS implantation and at least 3 months after DES implantation (Weak Recommendation, Moderate-Quality Evidence).

AF patients at higher risk of stroke who undergo PCI for ACS or elective PCI with high-risk features

RECOMMENDATION

- For patients with AF aged ≥ 65 years or with a CHADS₂ score ≥ 1 , we recommend an initial regimen of TT (ASA 81 mg/d with clopidogrel 75 mg/d with an OAC) up to 6 months after PCI (Strong Recommendation, Moderate-Quality Evidence). After ASA discontinuation, which may occur as early as the day after PCI, we suggest that dual pathway therapy (an OAC with clopidogrel 75 mg/d) be continued for up to 12 months after PCI (Weak Recommendation, Moderate-Quality Evidence).

Practical tip. For some patients < 65 years of age with CHADS₂ score of 1 at the lower end of the stroke risk spectrum (eg, isolated hypertension), some clinicians prefer DAPT (eg, aspirin and ticagrelor or prasugrel) in preference to triple therapy (an OAC with DAPT).

Practical tip. A PCI is considered high risk for ischemic coronary outcomes on the basis of the clinical presentation (eg, ACS), patient characteristics (comorbid diabetes mellitus treated with oral hypoglycemics or insulin, chronic kidney disease (estimated glomerular filtration rate < 60 mL/min), current tobacco use, previous ACS, or previous stent thrombosis), as well as PCI-related factors (multivessel PCI, multiple $[\geq 3]$ stents implanted, total stent length > 60 mm, complex bifurcation lesion, chronic total occlusion intervention, and stent type (eg, bioabsorbable vascular scaffold; Fig. 2).

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. ASA may be continued as part of TT for up to 6 months for patients with a high risk of thrombotic coronary events and low risk of bleeding. ASA can be discontinued as early as the day after PCI for patients with a low risk of thrombotic coronary events and a high risk of bleeding. For patients at intermediate risk of thrombotic coronary events and intermediate risk of bleeding ASA can be continued as part of TT for 1-3 months.

AF patients at higher risk of stroke in association with medically managed type 1 MI

RECOMMENDATION

- For patients with AF aged ≥ 65 years or with a CHADS₂ score ≥ 1 , we suggest that dual pathway therapy (an OAC with clopidogrel 75 mg/d, rather than prasugrel or ticagrelor) be given without concomitant ASA for 12 months after ACS (Weak Recommendation, Low-Quality Evidence).

Values and preferences. For patients with AF and type 1 MI who do not undergo revascularization, the CCS AF Guidelines Committee places relatively greater emphasis on the reduction in ischemic coronary and cerebrovascular thrombotic events, rather than the increase in bleeding observed with combination therapy. When combination therapy is used the preference for clopidogrel rather than ASA is on the basis of the findings from the **Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events (CAPRIE)** study, in which clopidogrel was shown to be superior to ASA (0.5% absolute reduction in composite of vascular death, MI, or ischemic stroke; $P = 0.043$), well as the substantial efficacy and safety data for combination therapy using clopidogrel and an OAC (clopidogrel used in 88% of patients in RE-DUAL PCI and 95% in PIONEER AF-PCI).^{62,64,67}

III. Investigation and Management of SCAF

The **Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)** and **A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics (TRENDS)**

studies showed that episodes of SCAF as short as 5-6 minutes occur in 30%-40% of patients with implanted devices, and is associated with a 2- to 2.5-fold increased risk of stroke.^{68,69} Although clinical risk factors influence the stroke risk among patients with SCAF, this risk appeared lower than among patients with clinical AF.⁷⁰ Because patients with SCAF tend to be older and at higher risk of OAC-associated bleeding,⁷¹ the risk-benefit ratio of using an OAC is uncertain.

It appears that an increasing duration or burden of SCAF is associated with an increase in the absolute risk of stroke.^{69,72} One study suggested that there was no increased risk of stroke among patients with SCAF when their longest daily burden in the past 30 days was < 5.5 hours.⁶⁹ A more recent analysis from the ASSERT trial suggests that the increased risk of stroke with SCAF is driven by patients whose episodes exceed 24 continuous hours.⁷² There is also uncertainty about the temporal relationship between SCAF and stroke, because TRENDS and ASSERT showed no temporal association between SCAF and stroke in most patients.^{73,74}

The only randomized evaluation of an OAC in this setting is the Combined Use of BIOTRONIK Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk (IMPACT) study.⁷⁵ IMPACT did not show any benefit from remote monitoring for SCAF with protocol-driven initiation and cessation of OAC therapy.⁷⁵ There are currently 2 randomized trials ongoing, which are randomizing patients with SCAF to treatment with an OAC vs either aspirin or placebo: Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH-AF-NET-6) trial⁷⁶ and the Apixaban for the Reduction of Thrombo-Embolic Due to Sub-Clinical Atrial Fibrillation (ARTESiA) trial.⁷⁷ These 2 trials, due to complete in 2019 and 2021, respectively, will determine if and when patients with SCAF should be treated with an OAC.

RECOMMENDATION

14. We suggest that it is reasonable to prescribe OAC therapy for patients who are aged 65 years or older or with a CHADS₂ score of ≥ 1 (CHADS-65) who have episodes of SCAF lasting > 24 continuous hours in duration. Additionally, high-risk patients (such as those with a recent embolic stroke of unknown source) with shorter-lasting episodes might also be considered for OAC therapy (Weak Recommendation, Low-Quality Evidence).

IV. Antidotes for NOACs/NOAC Reversal Agents

NOACs are the preferred agents for stroke prevention in NVAF patients who merit anticoagulation. Although there was less life-threatening bleeding with NOACs than with warfarin in the randomized controlled trials,¹⁰⁻¹³ bleeding remains an important risk. The availability of specific reversal agents has the potential to mitigate the risks associated with major bleeding events (eg, severe active hemorrhage, or bleeding in the context

of emergent surgery) and, with it, patient and physician acceptance of OAC therapy.

The CCS AF Guidelines Committee recommendation for idarucizumab, the dabigatran-specific reversal agent, in patients with active bleeding or those requiring surgery, remains unchanged from the 2016 guidelines update. That recommendation was on the basis of the interim publication of the **Reversal Effects of Idarucizumab on Active Dabigatran** (REVERSE-AD) trial,⁷⁸ now further supported by the data from the full cohort analysis of 301 patients with uncontrollable or life-threatening bleeding (group A) and 202 patients who required urgent surgery (group B).⁷⁹ The median maximum percent reversal of the anticoagulant effect of dabigatran within 4 hours of idarucizumab administration was 100% in those who had a prolonged dilute thrombin time (DTT) or ecarin clotting time (ECT) at baseline. The reversal was rapid and occurred independently of age, sex, renal function, and dabigatran concentration at baseline. Reappearance of dabigatran levels > 20 mg/mL (below which impairment of hemostasis is unlikely) was observed in 23% of patients. This was likely due to redistribution of unbound dabigatran from the extravascular to the intravascular space, and was associated with recurrent or continued bleeding in 10 of the patients in the “life-threatening bleeding” group but none of the patients in the “urgent surgery” group. It was possible to assess time to cessation of bleeding in 134 patients in group A; median time to hemostasis was 2.5 hours after idarucizumab administration and all had confirmed bleeding cessation within 24 hours. Of the 197 patients in group B, periprocedural hemostasis was assessed as normal or mildly abnormal in 98.5%. At 30 days, thrombotic events occurred in 4.8% of all patients, with a mortality rate of 13.5% in group A, and 12.6% in group B.

Another specific reversal agent is andexanet alfa. Andexanet is a recombinant modified human factor Xa decoy protein that binds to the active site of factor Xa inhibitors and sequesters them within the vascular space.⁸⁰ The pharmacodynamic half-life is approximately 1 hour. In the Andexanet Alfa - a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA-4) study, patients with acute major bleeding who had received 1 of 4 factor Xa inhibitors (apixaban, rivaroxaban, edoxaban, or enoxaparin) within the previous 18 hours were treated with a bolus and 2-hour infusion of andexanet, the dose of which was dependent on the timing of the last dose of factor Xa inhibitor.⁸¹ In the published interim analysis of 67 patients the median anti-factor Xa activity decreased by 89% (95% CI, 58%-94%) among the 26 patients who received rivaroxaban and by 93% (95% CI, 87%-94%) among the 20 patients who received apixaban.⁸¹ Four hours after the end of the infusion, there was a relative decrease in anti-factor Xa activity from baseline of 30%-39%. Clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients (78%) at the 12-hour postinfusion mark. At 30 days, the overall mortality rate was 15% (10 patients died) and thrombotic event rate was 18% (12 patients). The US prescribing information provides safety data for 185 patients, citing a 30-day thrombotic event rate of 18% (33 patients) and a mortality rate of 14% (25 deaths).⁸² Although promising, there are insufficient data to recommend andexanet for

Table 1. Characteristics of antiarrhythmic medications used for acute pharmacological cardioversion

Medication	Dose	Time to conversion	Risks
Class Ia			
Procainamide	15-18 mg/kg I.V. over 30-60 minutes	Approximately 60 minutes	Hypotension Bradycardia Ventricular proarrhythmia
Class Ic			
Flecainide	300 mg PO (> 70 kg) 200 mg PO (≤ 70 kg)	2-6 hours	Hypotension Bradycardia and conversion pauses
Propafenone	600 mg PO (> 70 kg) 450 mg PO (≤ 70 kg)	2-6 hours	1:1 Conduction of atrial flutter*
Class III			
Ibutilide	1 mg I.V. over 10 minutes May repeat once	30-60 minutes	QT prolongation Torsades de pointes† Hypotension
Amiodarone	150 mg I.V. bolus then 60 mg/h for 6 hours then 30 mg/h for 18 hours	8-12 hours	Bradycardia Atrioventricular block Torsades de pointes Phlebitis
Vernakalant	3 mg/kg I.V. over 10 minutes, followed by 2 mg/kg I.V. if no conversion	12-30 minutes	Hypotension Bradycardia Nonsustained ventricular tachycardia‡

ACS, acute coronary syndrome; AV, atrioventricular; I.V., intravenous; PO, orally.

* Class Ic drugs (flecainide and propafenone) should be used in combination with AV nodal blocking agents (β-blockers or calcium channel inhibitors). Class Ic agents should be avoided in patients with ischemic heart disease or significant structural heart disease.

† Consider pretreating with 1-4 mg of I.V. MgSO₄. Ibutilide should be avoided in patients with hypokalemia, baseline QT prolongation, or significant structural heart disease.

‡ Vernakalant should be avoided in patients with hypotension, recent ACS, or significant structural heart disease.

reversal of life-threatening bleeding associated with factor Xa inhibitors at this time.

RECOMMENDATION

15. 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.

Practical tip. In acute, life-threatening bleeding situations in which standard resuscitation (such as local measures, transfusion, etc) is anticipated to be insufficient (eg, intracranial hemorrhage), or in situations in which standard resuscitation has not stabilized the patient, 5 g of intravenous (I.V.) idarucizumab should be administered as soon as possible. Activated partial thromboplastin time (aPTT) and thrombin time may be used to qualitatively identify the presence of active dabigatran at baseline in a patient, although they are less sensitive than DTT and ECT; 92% of patients in the REVERSE-AD trial had an elevated DTT or ECT, whereas only 74% had an elevated aPTT. However, obtaining these measures 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.

Practical tip. "Urgent" surgery as defined in the REVERSE-AD trial is surgery that cannot be delayed beyond 8 hours (amended from 4 hours in the initial version of the protocol). The timing of surgery should be on the basis of the clinical indication and stability of the patient. In instances in which delayed surgery is appropriate, clinicians may obtain coagulation parameters (eg, thrombin time or aPTT) to identify patients who would be unlikely to benefit from idarucizumab (see the previous "practical tip").

Practical tip. Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. Oral anticoagulation should be reintroduced as soon as medically appropriate.

V. Acute Pharmacological Rhythm Control

For patients with acute AF/AFL who are eligible for cardioversion, acute rhythm control can be established via either pharmacological or electrical cardioversion. In general, DC electrical cardioversion is more effective, with immediate restoration of sinus rhythm, however, it requires the use of general anaesthesia. Pharmacological cardioversion is less effective, but avoids the risks associated with procedural sedation, and does not require a preceding period of fasting.^{24,28,33,83,84}

Antiarrhythmic medication selection is typically dictated by the patient's comorbidities (eg, structural heart disease), as well as physician preference. Characteristics of antiarrhythmic medications used for acute pharmacological cardioversion are shown in Table 1.

A commonly used I.V. medication for cardioversion of acute AF/AFL in the emergency department setting is the class

Table 2. PIP antiarrhythmic drug therapy

Appropriate candidates for PIP	<ol style="list-style-type: none"> (1) Symptomatic patients (2) Sustained AF episodes (eg, ≥ 2 hours) (3) AF episodes that occur less frequently than monthly (4) Absence of severe or disabling symptoms during an AF episode (eg, fainting, severe chest pain, or breathlessness) (5) Ability to comply with instructions, and proper medication use
Contraindication to PIP	<ol style="list-style-type: none"> (1) Significant structural heart disease (eg, left ventricular systolic dysfunction [left ventricular ejection fraction < 50%], active ischemic heart disease, severe left ventricular hypertrophy) (2) Abnormal conduction parameters at baseline (eg, QRS duration > 120 msec, PR interval > 200 msec, or evidence of pre-excitation) (3) Clinical or electrocardiographic evidence of sinus node dysfunction, bradycardia or advanced AV block (4) Hypotension (systolic BP < 100 mm Hg) (5) Previous intolerance of any of the PIP-AAD medications
PIP administration	Immediate release oral AV nodal blocker (one of diltiazem 60 mg, verapamil 80 mg, or metoprolol tartrate 25 mg) 30 minutes before the administration of a class Ic AAD (300 mg of flecainide or 600 mg of propafenone if ≥ 70 kg; 200 mg of flecainide or 450 mg of propafenone if < 70 kg)
Initial ED monitoring	<p>Telemetry for at least 6 hours</p> <p>Blood pressure monitoring every 30 minutes</p> <p>12-Lead ECG monitoring every 2 hours</p>
Determinants of initial treatment failure	<ol style="list-style-type: none"> (1) AF persistence > 6 hours after PIP-AAD administration or electrical cardioversion required for termination (2) Adverse events including symptomatic hypotension (systolic BP ≤ 90 mm Hg), symptomatic conversion pauses (> 5 seconds), symptomatic bradycardia after sinus rhythm restoration, proarrhythmia (conversion to atrial flutter/tachycardia, or episodes of ventricular tachycardia), severe symptoms (dyspnea, presyncope, syncope), or a > 50% increase in QRS interval duration from baseline
Instructions for subsequent out-of-hospital use	<p>Patients should take the AV nodal agent 30 minutes after the perceived arrhythmia onset, followed by the class Ic AAD 30 minutes after the AV nodal agent.</p> <p>After AAD administration patients should rest in a supine or seated position for the next 4 hours, or until the episode resolves</p> <p>Patients should present to the ED in the event that:</p> <ol style="list-style-type: none"> (1) The AF episode did not terminate within 6-8 hours (2) They felt unwell after taking the medication at home (eg, a subjective worsening of the arrhythmia after AAD ingestion, or if they developed new or severe symptoms such as dyspnea, presyncope, or syncope) (3) More than one episode occurred in a 24-hour period (patients were advised not to take a second PIP-AAD dose within 24 hours) (4) If the AF episode was associated with severe symptoms at baseline (eg, significant dyspnea, chest pain, presyncope, or symptoms of stroke), even in the absence of PIP-AAD use

AAD, antiarrhythmic drug; AF, atrial fibrillation; AV, atrioventricular; BP, blood pressure; ECG, electrocardiogram; ED, emergency department; PIP, “pill-in-the-pocket.”

Ia agent, procainamide.⁸⁵ Procainamide is usually administered over 60 minutes at a dose of 15-18 mg/kg, although a significant amount of the clinical evidence has been on the basis of the infusion of 1 g over 60 minutes.^{24,33,86} Procainamide is more effective for the conversion of acute AF (50% conversion) than for AFL (30% conversion).⁸⁶ Time to cardioversion is approximately 1 hour.⁸⁶ The most common side effect is hypotension (approximately 5%), although QRS widening, premature ventricular contractions, and Torsade de Pointes (TdP) might occur. This medication, like all drugs with class I (Na⁺ channel-blocking) action, should be avoided in patients with Brugada syndrome.⁸⁷

Ibutilide is an I.V. class III agent that has been shown to effectively terminate AFL (50%-75%) and AF (30%-50%), with cardioversion typically occurring within 30-60 minutes.⁸⁴ However, widespread clinical uptake has been limited by a significant risk of TdP, which occurs in approximately 2%-3% of patients. Consequently, ibutilide should not be used in patients with prolonged QTc on electrocardiogram, those with a history of HF or reduced ejection fraction, or those with electrolyte disturbances (low serum potassium or magnesium levels). Pretreatment with high-dose magnesium (≥ 4 g I.V.) might improve ibutilide cardioversion rates and might reduce the risk of TdP.⁸⁸⁻⁹⁰ Patients must be observed with continuous electrocardiogram monitoring for a minimum of 4 hours after ibutilide administration.

The atrial-selective antiarrhythmic drug vernakalant was recently approved by Health Canada. In an emergency department-based study of acute AF, the conversion rate was 59% and the median time to cardioversion was 12 minutes.⁸³ The major potential adverse effects are hypotension, along with bradycardia after cardioversion. Transient but fairly common side effects include dysgeusia (abnormal taste), paraesthesia, and nausea. Vernakalant should not be used in patients with hypotension, severe HF (New York Heart Association classification III/IV), recent ACS, or severe aortic stenosis. It is less effective in the conversion of typical AFL.⁹¹

With the exception of patients with structural heart disease, amiodarone is not recommended for acute rhythm control because of the delayed action in conversion (approximately 8 hours).⁹²⁻⁹⁴ The most common adverse drug reactions with I.V. administration are phlebitis, hypotension, and bradycardia. Although there is potential for prolongation of the QT interval the incidence of TdP is rare.⁹⁵

An alternate approach is to consider oral administration of flecainide or propafenone in combination with an atrioventricular node-blocking agent (β -blockers or calcium channel inhibitors; Table 2). Although the time to cardioversion (2-6 hours) is longer than with I.V. medications, the major clinical benefit is that patients are able to treat their subsequent AF episodes using the “pill-in-the-pocket” approach, which reduces the need to visit the emergency department. A key

caveat to this approach is that the first dose must be administered in a monitored environment to exclude treatment-related adverse reactions.^{96,97} Indications, contraindications, and monitoring details are presented in [Table 2](#).

VI. Catheter Ablation of AF

The section on catheter ablation of AF was last updated in 2014. Since that time, there have been significant developments in periablation management and clinical trial evidence.

Uninterrupted OAC therapy with a VKA has been the standard of care periablation since clinical trials showed less bleeding and reduced thromboembolic complications compared with VKA interruption with low molecular-weight heparin bridging.⁹⁸ The safety and efficacy of uninterrupted NOAC therapy periablation, was recently explored in 3 randomized trials that compared uninterrupted NOAC with uninterrupted VKA treatment periablation. The **Active-Controlled Multi-Center Study With Blind-Adjudication Designed to Evaluate the Safety of Uninterrupted Rivaroxaban and Uninterrupted Vitamin K Antagonists in Subjects Undergoing Catheter Ablation for Non-Valvular Atrial Fibrillation (VENTURE-AF)** trial was the smallest ($n = 248$) of these trials, which randomized patients to uninterrupted rivaroxaban vs uninterrupted VKA treatment.⁹⁹ The trial showed that there was no difference in major bleeding or thromboembolic events. In contrast, the **Randomized Evaluation of Dabigatran Etxilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Peri-Procedural Anticoagulation Strategy** trial (RE-CIRCUIT; $n = 635$) showed a significant reduction in ISTH bleeding with uninterrupted dabigatran 150 mg BID compared with uninterrupted VKA (1.6% vs 6.9%, $P = 0.0009$).¹⁰⁰ Of note, the number of patients with cardiac tamponade and with groin hematoma was higher in the VKA arm. There was no difference in the number of patients with a thromboembolic event, with only 1 in the VKA arm. Finally, the recently published **Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban During Atrial Fibrillation Catheter Ablation (AXAFA)** trial ($n = 674$) showed no difference between uninterrupted apixaban and uninterrupted VKA treatment for either bleeding or thromboembolic events.¹⁰¹ This trial also performed a substudy of post-ablation cerebral magnetic resonance images to look for subclinical cerebral microemboli and again, there was no difference between strategies. The ongoing **Evaluation of Edoxaban Compared With VKA in Subjects Undergoing Catheter Ablation of Nonvalvular Atrial Fibrillation (ELIMINATE-AF)** trial will report on uninterrupted edoxaban vs uninterrupted VKA treatment (ClinicalTrials.gov NCT02942576). On the basis of these data we make the following recommendation.

RECOMMENDATION

16. We suggest that catheter ablation may be performed using uninterrupted therapeutic oral anticoagulation with either a NOAC or adjusted-dose warfarin (Weak Recommendation, Moderate-Quality Evidence).

Other important clinical trials included **Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF II)**, which compared 3 techniques for ablation of persistent AF.¹⁰² Although guidelines had made the assumption that more extensive ablation was required for treating these patients, the trial showed that strategies of additional use of empiric linear ablation or targeted electrogram ablation in addition to pulmonary vein isolation did not improve freedom from AF over pulmonary vein isolation alone.

Previous iterations of the CCS AF guidelines recommend a trial of antiarrhythmic drugs (AADs) before considering an ablation procedure for most patients, with first-line ablation therapy reserved for highly selected symptomatic patients with paroxysmal AF. These recommendations are on the basis of the results of several randomized controlled studies that showed superior freedom from recurrent arrhythmia, a reduction in the overall AF burden, and improvement in symptoms, exercise capacity, and quality of life with catheter ablation relative to AAD therapy.¹⁰³⁻¹¹¹ The **Catheter Ablation vs Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (CABANA)** trial was designed to evaluate the effect of ablation on mortality, stroke, and bleeding end points.¹¹² This study randomized older, higher-risk patients to ablation ($n = 1108$) or drug therapy ($n = 1096$). At the time of this guideline update, the study had not been published, but the presented results showed no difference in the primary composite outcome (death, disabling stroke, serious bleeding, or cardiac arrest) at 5 years in an intention to treat analysis (HR, 0.86; 95% CI, 0.65-1.15). Despite a high rate of crossover (9.2% not receiving ablation in the intervention arm and 27.5% of drug therapy patients receiving ablation) a significant reduction in the secondary end point of death and cardiovascular hospitalization was observed (HR, 0.83; 95% CI, 0.74-0.93). Moreover, the “on treatment” analysis, which evaluated the patients who received ablation showed a significant reduction in the primary end point (HR, 0.67; 95% CI, 0.50-0.89) with associated significant reductions in all-cause mortality (HR, 0.60; 95% CI, 0.42-0.86) and death and cardiovascular hospitalization (HR, 0.83; 95% CI, 0.74-0.94) compared with drug therapy. Until the full publication is available, however, the Guideline Committee has not changed its recommendation that AF ablation should be second-line therapy for most patients and first-line therapy only for highly selected patients.

Ablation in patients with AF and HF

AF and HF frequently coexist, with AF representing an independent predictor of progression, hospitalization, and death in the HF population.¹¹³⁻¹¹⁹ Although restoring and maintaining sinus rhythm has been considered as a therapeutic target to improve clinical outcomes, large randomized controlled trials of AADs have failed to support this hypothesis.¹²⁰⁻¹²⁴ It is postulated that the attenuated benefit observed with AAD therapy is related to cardiac and noncardiac toxicities (eg, proarrhythmia or negative inotropy). As such, ablation has been proposed as a more efficacious means to improve outcomes.

To date, 7 randomized trials have been performed ([Table 3](#)).¹²⁵⁻¹³¹ Collectively these randomized studies have shown a single-procedure success (eg, elimination of any AF episodes > 30 seconds) in the range of 40%-69%, with

Table 3. Randomized studies of AF ablation in heart failure

	PABA-CHF ¹²⁵	MacDonald et al. ¹²⁶	ARC-HF ¹²⁷	CAMTAF ¹²⁹	AATAC ¹²⁸	CAMERA-MRI ¹³⁰	CASTLE-AF ¹³¹
Comparator	AV node ablation with biventricular pacing	Medical rate control	Medical rate control	Medical rate control	Amiodarone rhythm control	Medical rate control	Medical therapy (rate or rhythm control)
Patient n	81	41	52	55	203	68	179
● Persistent AF	48%	100%	100%	100%	100%	72%	70%
Follow-up, months	6	6	12	12	24	6	37
Outcomes ¹³⁹							
● HF hospitalization, RR (95% CI)	2.93 (0.12-69.83)*	2.71 (0.12-62.70)*	—	—	0.55 (0.39-0.76)	0.20 (0.01-4.01)*	0.58 (0.41-0.81)
● All-cause mortality, RR (95% CI)	—	—	—	0.31 (0.01-7.23)*	0.44 (0.20-0.97)	—	0.54 (0.34-0.84)
Standard mean difference in:							
● LVEF improvement	9.00 (6.26-11.74)	1.70 (-4.17 to 7.57)*	5.5 (0.00-11.00)*	11.70 (5.62-17.78)	1.90 (0.55-3.25)*	14.0 (8.50-19.50)	9.70 (2.57-16.83)
● 6-MW distance	55.0 (26.56-83.44)	-1.30 (-54.75 to 52.15)*	42.34 (-7.51-92.19)*	—	12.0 (0.51-23.49)*	27.0 (-28.0 to 82.0)*	31.60 (-49.03 to 112.23)*

6-MW, 6-minute walk distance; AATAC, Ablation vs Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device; AF, atrial fibrillation; ARC-HF, Catheter Ablation vs Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; AV, atrioventricular; CAMERA-MRI, Catheter Ablation vs Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; CAMTAF, Catheter Ablation vs Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation vs Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction; PABA-CHF, Pulmonary-Vein Isolation for Atrial Fibrillation in Patients With Heart Failure; RR, risk ratio.

* Not statistically significant.

multiple procedures improving the success up to 88%. Beyond arrhythmia recurrence, catheter ablation of AF in HF patients with left ventricular systolic dysfunction appears to be associated with improvement in left ventricular ejection fraction (LVEF; improvement of 4.5%-18%; weighted mean difference [MD] of 7.40; 95% CI, 3.37-11.43; $P < 0.01$), improvement in exercise performance (maximal oxygen uptake or VO_2 max, MD of 3.17 mL/kg/min; 95% CI, 1.05-5.28; $P < 0.01$; $I^2 = 0\%$; and 6-minute walk MD, 26.96 m; 95% CI, 6.39-47.54; $P = 0.01$), and improvement in quality of life (33% average improvement in Minnesota Living with HF Questionnaire score), with no significant increase in risks of serious adverse events (RR, 1.05; 95% CI, 0.96-1.16; $P = 0.30$) compared with medical treatment.¹²⁵⁻¹³¹

However, a more substantial quantification of the utility of catheter ablation in patients with AF and HF with reduced systolic function is the objective outcomes, such as mortality and hospitalization. Although CABANA failed to show significant mortality benefit in unselected populations, recent randomized trials have shown that catheter ablation of AF in HF patients with reduced LVEF results in significant improvement in all-cause mortality as well as fewer HF hospitalizations.^{128,131,132} The first of these studies was the Ablation vs Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device (AATAC) study, which randomized 203 patients with New York Heart Association functional class II-III HF and an LVEF $< 40\%$ to catheter ablation ($n = 102$) or amiodarone rhythm control ($n = 101$).¹²⁸ After 24-27 months of follow-up, patients in the ablation group had a significantly greater freedom from recurrent AF (70% vs 34%; $P < 0.001$). In addition, the secondary end points of unplanned hospitalization and all-cause mortality were both significantly reduced (45% and 56%, respectively), corresponding to number needed to treat of 3.8 for unplanned hospitalization and 10 for all-cause mortality. The second study, Catheter Ablation vs Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF), randomized patients with symptomatic paroxysmal or persistent AF, New York Heart Association class II-IV HF, and an LVEF $\leq 35\%$ to catheter ablation (179 patients) or medical therapy (184 patients).¹³¹ All patients had a cardiac implantable device (implantable cardioverter defibrillator or cardiac resynchronization therapy-implantable cardioverter defibrillator). After a median follow-up of 37.8 months, patients in the ablation group were significantly less likely to meet the primary composite end point of all-cause mortality or HF admission (16.1% absolute reduction; HR, 0.62; 95% CI, 0.43-0.87; $P = 0.006$). Similar to AATAC, there was a 47% relative reduction in all-cause mortality (HR, 0.53; 95% CI, 0.32-0.86) and a 44% reduction in HF hospitalization (HR, 0.56; 95% CI, 0.37-0.83).

Taken together, these studies show that catheter ablation is associated with an improvement in all-cause mortality (8.1% vs 15.9%; RR, 0.52; 95% CI, 0.35-0.76; $P < 0.01$), a reduction in HF hospitalization (17.7% vs 31.3%; RR, 0.57; 95% CI, 0.45-0.72; $P < 0.01$) and ejection fraction, compared with medical therapy. Ongoing randomized controlled trials in the AF and HF population will assess the effect of AF ablation on all-cause mortality (Rhythm Control - Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy

and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation [RAFT-AF]; NCT01420393) and HF hospitalization (RAFT-AF, and Catheter Ablation vs. Medical Therapy in Congested Hearts With AF [CATCH-AF]; NCT02686749).

Although these results are compelling, the committee decided not to add a new recommendation for ablation in HF patients. Instead, we believe that the existing recommendation to pursue catheter ablation as a second-line treatment for symptomatic patients applies to this group. Despite the lack of a new recommendation specifically for patients with HF and a reduced LVEF, it is important to recognize that the consideration of patients with structural heart disease as an appropriate ablation candidate does represent a philosophical shift in practice because these patients were previously discouraged from ablation because of concerns regarding potential inefficacy and harm.

VII. Integrated Approach to AF and Modifiable Cardiovascular Risk Factors

There are several care gaps in AF management, specifically in the domains of stroke prevention, in the timing/appropriateness of transitions between rate and rhythm control, as well in the assessment for ablation procedure candidacy.^{133,134} Dedicated multidisciplinary clinics specifically focused on AF care have recently been developed as a means to facilitate patient and provider education, as well as to provide evidence-based care centred on chronic disease management principles. Previous studies have suggested that a combined specialist and nurse-based AF clinic is associated with improved adherence to guideline-based care, enhanced transitions of care (from the emergency room to the specialty clinic and back to community care), and significant improvement in quality of life.^{51,135-138} In addition, systematic multidisciplinary AF clinics have been shown to reduce cardiovascular death (HR, 0.28 vs usual care) and cardiovascular hospitalization (HR, 0.66 vs usual care).¹³⁵

Analogous multidisciplinary models of care, such as HF clinics, have shown similar benefits in cardiovascular outcomes as well as cost-effectiveness.^{139,140} Greater coordination of care with nursing interventions has been shown to result in more efficient use of resources,¹⁴¹ better coordination of heart rhythm procedures,^{142,143} and better implementation of other cardiac therapies for patients with HF.^{144,145} In the Canadian context, reduced wait times, improved implementation of recommendations, and more effective use of tertiary care resources has been shown.¹⁴⁶

Although the genesis of AF clinics in Canada arises from the Calgary model, similar programs now exist across the country.¹⁴⁷ Although individually tailored to the needs of their communities, these Canadian AF clinics are broadly on the basis of the principles of: (1) timely access to specialist care, to reduce adverse outcomes (eg, stroke or rehospitalization) imposed by delays in treatment initiation; (2) knowledge translation, because improved understanding of AF facilitates active participation by the patient in their treatment pathway, with secondary benefits in treatment adherence and persistence; and (3) guideline adherence, in particular in the domains of stroke prevention and comorbidity management (eg, hypertension, obesity, and sleep apnea).^{70,147,148} This last point is especially relevant as a systematic approach to patient care, including protocol-driven management on the basis of

contemporary guidelines, and offers an opportunity for holistic management of the patient beyond the heart rhythm.

Recently, there has been a renewed focus on the contribution of modifiable cardiovascular risk factors to the causation and persistence of AF.¹⁴⁹⁻¹⁵¹ Although the precise mechanistic links between risk factors and AF occurrence remain somewhat uncertain, information available from the literature provides many potential insights. Hypertension, the most significant population-attributable modifiable risk factor for AF, causes activation of the sympathetic and renin-angiotensin-aldosterone systems, as well as structural and electrophysiological atrial remodelling that enhances AF susceptibility. Diabetes mellitus promotes AF via structural remodelling (possibly mediated by advanced glycosylation end-products) and autonomic remodelling. Tobacco use promotes AF through a combination of the direct effects of nicotine on the atrium (eg, altered atrial conduction and refractoriness), as well as structural remodelling, inflammation, and oxidative stress. Alcohol, when consumed in excess, promotes AF through the induction of arrhythmia triggers (increased sympathetic activity/impairment of vagal tone) as well as atrial fibrosis (from the direct toxic effects of alcohol metabolites). Obesity promotes AF through weight-related structural remodelling (changes in atrial dimensions and interstitial fibrosis), weight-related electrophysiological remodelling (conduction slowing and shortening of the effective refractory period), autonomic dysfunction, and inflammation. Obstructive sleep apnea promotes AF acutely through strongly negative intrathoracic pressures leading to increased venous return (AF-promoting left atrial volume loading) and hypoxia-induced pulmonary vasoconstriction. Chronic obstructive sleep apnea induces electrical and structural remodelling of the atria, autonomic dysregulation, oxidative stress, and inflammation.

Previous studies have shown that intensive risk factor management has beneficial effects on AF.^{152,153} Rienstra et al. reported improved maintenance of sinus rhythm at 1 year with a strategy of cardiac rehabilitation, HF medication optimization, and aggressive blood pressure control (75% maintenance of sinus rhythm on a 7-day Holter vs 63% in the control group; OR, 1.77; $P = 0.042$).¹⁵³ The Long-Term Effect of Goal-Directed Weight Management on Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY) cohort study showed that patients with a weight loss of > 10% was associated with a 6-fold increase in the likelihood of being arrhythmia-free over a 5-year follow-up period compared with those with lesser degrees of weight loss (< 10%).¹⁵⁴ Abed et al. reported that weight reduction with intensive risk factor management resulted in a significant improvement in AF-related quality of life and symptom scores, as well as AF burden (episode frequency and duration).¹⁵² Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation (ARREST-AF) was a single-centre cohort study that showed that patients who chose to undergo aggressive risk factor modification had better quality of life and symptom control, a significant reduction in AF burden, and greater arrhythmia-free survival after catheter ablation compared with those who did not (OR, 4.8; 95% CI, 2.04-11.4).¹⁵⁰ The Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation (CARDIO-FIT) study showed that a > 2 peak metabolic equivalents (METs) improvement in cardiorespiratory fitness was associated with a significantly reduced AF burden compared with a gain of < 2 METs over long-term

Table 4. Risk markers and comorbid conditions associated with AF

Conventional risk factors
<ul style="list-style-type: none"> • Advancing age • Male sex • Hypertension • HF with reduced ejection fraction • Valvular heart disease • Thyroid disease • Obstructive sleep apnea
Emerging risk factors
<ul style="list-style-type: none"> • Chronic obstructive pulmonary disease • Excessive alcohol intake • Pre-hypertension • Increased pulse pressure • HF with preserved ejection fraction • Congenital heart disease • Subclinical hyperthyroidism • Obesity • Coronary artery disease • Morphometric (increased height, increased birth weight) • Excessive endurance exercise
Potential risk factors
<ul style="list-style-type: none"> • Familial/genetic factors • Tobacco Use • Echocardiographic <ul style="list-style-type: none"> Left atrial dilatation LV hypertrophy • Inflammation • Diabetes • Pericardial fat • Subclinical atherosclerosis • Electrocardiographic (atrial conduction delay, PR interval prolongation) • Chronic kidney disease

AF, atrial fibrillation; HF, heart failure; LV, left ventricular.

follow-up.¹⁵⁵ This response was proportional to the increase in cardiorespiratory fitness, with an adjusted reduction in AF recurrence of 10% for each MET gained (HR, 0.90; 95% CI, 0.83-1.00).¹⁵⁵ These data suggest that a comprehensive management strategy that includes suppression of triggers (targeted by risk factor modification, AADs, and/or catheter ablation) and amelioration of arrhythmogenic substrate (risk factor modification) might lead to improved outcomes. Further research is required to determine whether these interventions will effectively alter the occurrence or progression of AF, when it is present.

It is the opinion of the AF Guidelines Committee that, for now, the emphasis of risk factor modification should focus on cardiovascular event reduction with the optimal management of risk factors and concomitant disorders (Table 4), following the recommendations of the 2018 Canadian dyslipidemia,¹⁵⁶ hypertension,¹⁵⁷ and diabetes¹⁵⁸ guidelines.

RECOMMENDATION

17. We recommend systematic and strict guideline-adherent management of traditional modifiable cardiovascular risk factors and/or conditions associated with AF, to reduce cardiovascular events (eg, stroke, MI, etc; Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a high value on a systematic approach to providing guideline-directed therapy for any cardiovascular risk factors and/or conditions associated with AF.

Practical tip. The detection and optimal management of risk factors and concomitant disorders together with appropriate rate/rhythm control and stroke prevention might contribute to a reduction in cardiovascular-related emergency department visits and hospitalizations. Addressing such risk factors might be most comprehensively and efficiently accomplished through a specialized clinic or other multidisciplinary management approach, and through use of a standardized, systematic protocol-based approach.

RECOMMENDATION

18. We suggest that, in addition to implementing appropriate rate or rhythm control measures, an approach targeting modifiable risk markers and conditions associated with AF should be applied to prevent recurrence of the arrhythmia and/or decrease its symptom burden (Weak Recommendation, Low-Quality Evidence).

Values and preferences. The aggressive treatment of obesity and cardiometabolic risk markers/conditions (including hypertension, HF, diabetes, and sleep apnea) has been shown to reduce AF burden and improve quality of life. This recommendation places a high value on the recognized association between these potential risk markers and conditions that are known to aggravate AF and the possibility that treatment of these might result in prevention and/or regression of the substrate that causes AF as well as improvement of patient symptoms.

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Secondary Panel Members: David Bewick, MD, Vidal Essebag, MD, PhD, Peter Guerra, MD, Milan Gupta, MD, Brett Heilbron, MBChB, Paul Khairy, MD, Bob Kiaii, MD, George Klein, MD, Simon Kouz, MD, Daniel Ngui, MD, Pierre Pagé, MD, Calum Redpath, MD, Jan Surkes, MD, and Richard Whitlock, MD.

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Supplementary Material

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