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Society Guidelines

2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

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ABSTRACT

Atrial fibrillation (AF) is an extremely common clinical problem with an important population morbidity and mortality burden. The management of AF is complex and fraught with many uncertain and contentious issues, which are being addressed by extensive ongoing basic and clinical research. The Canadian Cardiovascular Society AF Guidelines Committee produced an extensive set of evidence-based AF management guidelines in 2010 and updated them in the areas of anticoagulation and rate/rhythm control in 2012. In late 2013, the committee judged that sufficient new information regarding AF management had become available since 2012 to warrant an update to

RÉSUMÉ

La fibrillation auriculaire (FA) est un problème clinique très fréquent représentant un fardeau important de la morbidité et de la mortalité de la population. La prise en charge de la FA est complexe et comporte plusieurs questions incertaines et controversées, qui sont actuellement abordées par la recherche fondamentale et clinique approfondie. En 2010, le comité des lignes directrices sur la FA de la Société canadienne de cardiologie a produit un vaste ensemble de lignes directrices sur la prise en charge de la FA fondées sur des données probantes et les a mises à jour en 2012 dans les domaines de l'anticoagulation du contrôle de la fréquence et du rythme. À la fin

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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 judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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the Canadian Cardiovascular Society AF Guidelines. After extensive evaluation of the new evidence, the committee has updated the guidelines for: (1) stroke prevention principles; (2) anticoagulation of AF patients with chronic kidney disease; (3) detection of AF in patients with stroke; (4) investigation and management of subclinical AF; (5) left atrial appendage closure in stroke prevention; (6) emergency department management of AF; (7) periprocedural anticoagulation management; and (8) rate and rhythm control including catheter ablation. This report presents the details of the updated recommendations, along with their background and rationale. In addition, a complete set of presently applicable recommendations, those that have been updated and those that remain in force from previous guideline versions, is provided in the Supplementary Material.

de 2013, le comité a estimé que les nouvelles informations sur la prise en charge de la FA qui sont disponibles depuis 2012 étaient suffisantes pour justifier une mise à jour des lignes directrices sur la FA de la Société canadienne de cardiologie. Après l'évaluation approfondie des nouvelles données probantes, le comité a mis à jour les lignes directrices sur : 1) les principes de prévention de l'accident vasculaire cérébral; 2) l'anticoagulation des patients atteints d'une maladie rénale chronique qui ont une FA; 3) la détection de la FA chez les patients qui subissent un accident vasculaire cérébral; 4) l'évaluation et la prise en charge de la FA subclinique; 5) la fermeture de l'appendice auriculaire gauche dans la prévention de l'accident vasculaire cérébral; 6) la prise en charge de la FA par le service des urgences; 7) la prise en charge péri-interventionnelle de l'anticoagulation; 8) le contrôle de la fréquence et du rythme, y compris l'ablation par cathéter. Ce rapport présente de manière détaillée les recommandations mises à jour, ainsi que leur fondement et leurs justifications. De plus, l'ensemble des recommandations actuellement applicables, celles qui ont été mises à jour et celles des versions précédentes des lignes directrices qui demeurent en vigueur, est fourni dans une *Liste complète des lignes directrices* comme documentation complémentaire.

The management of atrial fibrillation (AF) has changed dramatically over the past 5-10 years, with the introduction of novel direct oral anticoagulants (NOACs), the wide application of AF ablation as an effective therapeutic approach, and the development of new technologies to detect AF. These innovations have the potential to lead to substantially reduced morbidity and mortality among AF patients. Since the 2012 iteration of the Canadian Cardiovascular Society (CCS) AF guidelines, progress has shifted somewhat from the introduction of new therapies to a more refined understanding of how to better apply recent innovations. New developments have nevertheless occurred, including the successful development of another NOAC, edoxaban. There have also been important studies showing the benefits of various monitoring technologies to detect AF in high-risk populations, such as patients with cryptogenic stroke.

The 2014 Focused Update of the CCS Guidelines deals with advances in oral anticoagulant (OAC) therapy and presents a new "CCS algorithm" that will allow clinicians to easily determine which AF patients will benefit from OAC therapy. The update also outlines the optimal approach to perioperative OAC management and updates rate and rhythm management in AF including catheter ablation.

This document is also linked to the *Complete Guidelines Listing* as Supplementary Material, which summarizes all presently applicable CCS AF guidelines including the most recently updated version for recommendations that have changed, and recommendations that remain in force unmodified since 2010.

I. Stroke Prevention Principles

In the 2010 and 2012 CCS guidelines[1,2] it was recommended that the **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) schema[3] be used to estimate stroke risk, because of its simplicity, familiarity, and extensive validation. However, in the 2012 guidelines, elements of the **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) schema[4] were incorporated in an algorithm for the selection of antithrombotic therapy, particularly for patients with a $CHADS_2$ score of 0.

For 2014, the CCS continues to recommend that the $CHADS_2$ schema be used to estimate stroke risk, complemented by the inclusion of some, but not all, of the CHA_2DS_2-VASc criteria. We are recommending an updated simple "CCS algorithm" (Fig. 1) to select appropriate antithrombotic therapy. Based on clinical significance of age $\geq$ 65 years as a risk factor, the clinician should use OAC for most patients who are aged $\geq$ 65 years or have a $CHADS_2$ score $\geq$ 1. Acetylsalicylic acid (ASA) should be used for patients aged $<$ 65 years with $CHADS_2$ score $=$ 0 who have vascular disease. No antithrombotic therapy should be given for patients aged $<$ 65 years with $CHADS_2$ score $=$ 0 and no vascular disease. We do not consider female sex or vascular disease alone as sufficient reasons to prescribe OAC therapy, in contrast to the European Society of Cardiology guideline to use OACs for anyone with a CHA_2DS_2-VASc score $\geq$ 1. We do, however, recommend OAC therapy for patients $\geq$ 65 years old in agreement with the European Society of Cardiology guidelines, but different from the American Heart Association guidelines which suggests a choice of no antithrombotic, ASA, or OAC therapy[5] in these patients. Our simplified "CCS algorithm" differs from the 2012 algorithm in only 1 respect: women with vascular disease no longer qualify for OAC therapy unless they are age $\geq$ 65 or have an additional $CHADS_2$ risk factor.

The rationale for our choice to exclude female sex and vascular disease but include age $\geq$ 65 years as an indication

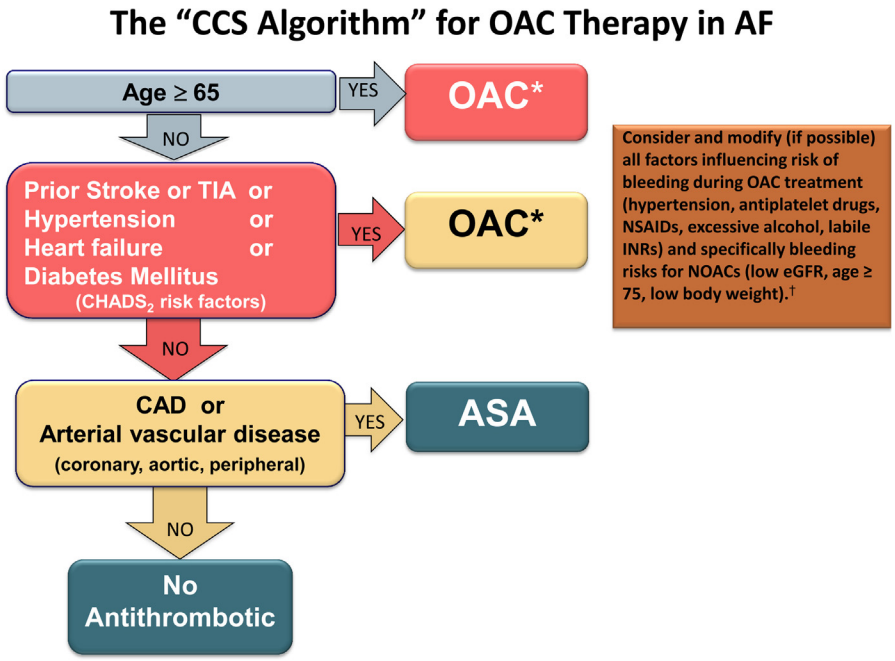

Figure 1. The simplified "CCS algorithm" for deciding which patients with atrial fibrillation (AF) or atrial flutter (AFL) should receive oral anticoagulation (OAC) therapy. * We suggest that a NOAC be used in preference to warfarin for non-valvular AF. † Might require lower dosing. ASA, acetylsalicylic acid; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NOAC, novel oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

for OAC therapy is based on a Danish national cohort study,[6] which delineated the annual stroke risk associated with individual risk factors of the $CHADS_2$ and CHA_2DS_2-VASc schemes. The main limitation to $CHADS_2$ is that no points are given for age 65-74 years, yet the annual risk of stroke in this group is 2.1% compared with an annual risk of stroke of 1.6% for hypertension which does contribute 1 point to the $CHADS_2$ score. However, female sex alone has a 0.9% annual stroke risk (hazard ratio, 1.25; $P = 0.10$ compared with men) and the risk with vascular disease alone is approximately 1.4%. The Guidelines Committee concluded that female sex should not factor into antithrombotic therapy selection because of the low associated stroke risk and the nonsignificant hazard ratio compared with men.

The benefit of anticoagulant therapy must be weighed against the risk of hemorrhage. The rationale for choosing OAC therapy for all patients with age $\geq$ 65 years or $CHADS_2 \geq 1$ is based on the effects of OAC on the absolute risk reduction of stroke compared with the increase in major hemorrhage. In patients aged $\geq$ 65 years and without other risk factors for stroke, warfarin decreased the annual risk of stroke from 2.1% to 0.7% and increased the risk of major bleeding by approximately 0.5% per year to 1.0%.[7,8] Although the risk of major bleeding increases with increasing $CHADS_2$ scores, the rate of increase is not as steep as that for stroke; therefore, the benefit to risk ratio for OAC actually increases as stroke risk factors accumulate. Furthermore, although 70% of strokes result in death or major disability,[9] most patients survive major hemorrhage without long-term effects. Thus, these results favour the use of OAC in patients with age $\geq$ 65 years or $CHADS_2 \geq 1$. The relative importance of a stroke prevented and major bleed caused is a subjective judgement. There is considerable scope for physician-patient discussion (ie, shared decision-making) to ensure that patient values are concordant with the decision to prescribe OAC therapy, particularly when the annual risk of stroke is in the 2% per year range. Physician-patient discussions are necessary to ensure the patient understands the importance of long-term adherence to OAC therapy.

For patients with an annual stroke risk of approximately 1%-1.5%, for example, patients with vascular disease in the absence of other risk factors, the CCS recommends ASA in preference to OAC based on 2 lines of evidence. ASA reduces the risk of stroke in AF by approximately 20% with only a minor increase in the risk of major bleeding.[10-12] Although warfarin is more efficacious than ASA for stroke prevention (relative risk [RR], 0.6)[7] in this population, it clearly causes more major bleeding (RR, 1.5 in trials of AF,[7,8] but up to 2.5 in non-AF trials[8]).

When the annual risk of stroke is $<$ 1%, the risk of increased major bleeding even with ASA and the inconveniences associated with regular medication might outweigh its benefit, and no antithrombotic therapy might be appropriate. Recent randomized controlled trials (RCTs) among AF patients,[13,14] for example, have found higher rates of major bleeding with ASA, likely because the mean age is older than in the earlier trials. The greater safety of NOACs might alter the risk-benefit calculation for OAC use further, but data to allow this are presently insufficient.

RECOMMENDATION

1. We recommend that all patients with AF or atrial flutter (AFL), whether paroxysmal or persistent, should be stratified using a predictive index for stroke risk (for example, the "CCS algorithm" based on the $CHADS_2$ model) (Strong Recommendation, High-Quality Evidence).
2. We recommend that OAC therapy be prescribed for most patients aged $\geq$ 65 years or $CHADS_2$ score $\geq$ 1 (the "CCS algorithm"; Fig. 1) (Strong Recommendation, Moderate-Quality Evidence).
3. We suggest that ASA (81 mg/d) be prescribed for patients with none of the risks outlined in the "CCS algorithm" (age $<$ 65 years and no $CHADS_2$ risk factors) who have arterial disease (coronary, aortic, or peripheral) (Conditional Recommendation, Moderate-Quality Evidence).
4. We suggest no antithrombotic therapy for patients with none of the risks outlined in the "CCS algorithm" (age $<$ 65 and no $CHADS_2$ risk factors) and free of arterial vascular disease (coronary, aortic, peripheral) (Conditional Recommendation, Low-Quality Evidence).

The NOACs apixaban, dabigatran, edoxaban, and rivaroxaban were developed to overcome the major limitations associated with warfarin and other vitamin K antagonists. All 4 agents have been evaluated in large, blinded, RCTs involving $>$ 70,000 patients.[15-18] The trials of apixaban, dabigatran, and rivaroxaban were summarized in the 2012 CCS update[2] and since then numerous publications have provided details about interactions with age, time in the therapeutic range, renal dysfunction, and previous stroke or transient ischemic attack (TIA). Edoxaban, the most recent agent, was compared with warfarin in the **E**ffective A**n**ti-coa**g**ulation With Factor X**a** Next **Ge**neration in **A**trial **F**ibrillation-**T**hrombolysis **i**n **M**yocardial **I**nfarction 48 (ENGAGE AF-TIMI 48) trial.[18] There were 21,105 patients (mean $CHADS_2$ score = 2.8) randomized double blind to edoxaban 30 mg once daily, edoxaban 60 mg once daily, or warfarin. The principal outcome rates (stroke or systemic embolism) were noninferior to warfarin for both doses of edoxaban and neither dose was superior to warfarin, although there was a trend toward benefit with the higher dose. Bleeding rates were significantly lower for both doses of edoxaban. Intracranial bleeding was significantly less with both doses of edoxaban than warfarin.

Each of the NOACs was found to be noninferior to warfarin for the outcome of all stroke or systemic embolism. None of them caused more major bleeding and all were superior for the outcome of intracranial hemorrhage. A meta-analysis of the 4 RCTs[19] found the following for the higher-dose regimens vs warfarin: stroke or systemic embolism (RR, 0.81; 95% confidence interval [CI], 0.73-0.91; $P < 0.0001$), intracranial hemorrhage (RR, 0.48; 95% CI, 0.39-0.59; $P < 0.0001$), gastrointestinal bleeding (RR, 1.25; 95% CI, 1.01-1.55; $P = 0.04$), all-cause mortality (RR, 0.90; 95% CI, 0.85-0.95; $P = 0.0003$). Comparison of the lower-dose regimens with warfarin showed similar rates of stroke or systemic embolism, significantly less intracranial bleeding, and significantly less mortality. Based on these observations coupled with greater convenience for patients and physicians, the Guidelines Committee continues to recommend NOACs over warfarin for nonvalvular AF.

There have been no published trials directly comparing the various NOACs, and it is unlikely that any will be conducted in the near future. In the absence of any such direct comparative data, the CCS expert panel discussed the possibility that the balance of efficacy and safety might influence clinicians to choose one agent over another. Indirect comparisons using appropriate statistical methods have been performed but their limitations have to be acknowledged.[20,21] Differences in baseline populations and in the designs of the key RCTs affect the ability to make any definitive comparisons between the NOACs. Any differences in efficacy that might exist among the NOACs, and even the difference in efficacy between warfarin and each of the NOACs, is very small compared with the reduction of stroke with any OAC compared with no OAC.

The panel also reviewed the data within various subgroups of patients in the RCTs. It appears that the benefit-to-risk ratio of dabigatran 150 mg vs warfarin is more favourable among patients aged $<$ 75 years, but less favourable in those aged $\geq$ 75 years, among whom dabigatran 110 mg is the better choice.[22] For apixaban and rivaroxaban, the balance of efficacy and safety does not differ between patients $\geq$ 75 vs $<$ 75 years. Dabigatran elimination is more dependent on renal clearance, so rivaroxaban and apixaban might be preferred for estimated glomerular filtration rates (eGFRs) of 30-50 mL/min/1.73 m^2. The initial publication from the **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY) trial showed an excess of myocardial infarction with dabigatran over warfarin but the difference was insignificant when additional events were considered. Meta-analyses have consistently shown more myocardial infarction with dabigatran, although less total mortality, but a recent Food and Drug Administration study showed equivalent rates of myocardial infarction in patients taking dabigatran compared with patients taking warfarin.[23] Gastrointestinal bleeding is more common in patients taking dabigatran 150 mg twice daily and rivaroxaban vs warfarin. The finding for dabigatran was confirmed by a large Food and Drug Administration cohort study.[23] Patients taking dabigatran also had significantly more dyspepsia and earlier discontinuation of study therapy.

RECOMMENDATION

5. We recommend that when OAC therapy is indicated for patients with nonvalvular AF, most patients should receive dabigatran, rivaroxaban, apixaban, or edoxaban (when approved) in preference to warfarin (Strong Recommendation, High-Quality Evidence).

Practical tip. Nonvalvular AF refers to AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

A major challenge for clinicians in following this recommendation is that the current reimbursement systems in Canada are not aligned with it.

RECOMMENDATION

6. We recommend that when OAC is indicated, warfarin be used rather than a NOAC for patients with a mechanical prosthetic valve, rheumatic mitral stenosis or eGFR of 15-30 mL/min/1.73 m^2 (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Patients should generally receive the higher of the 2 doses of the NOACs evaluated in the RCTs unless there is a specific reason to use the lower dose (eg, advanced age, renal failure, small body weight).

Practical tip. Among patients aged $\geq$ 75 years who receive dabigatran, the dose should be 110 mg twice per day, because of better balance between risks of stroke and major bleeding.

RECOMMENDATION

7. We recommend that patients whose risk of stroke warrants OAC therapy, but who refuse any OAC, should receive ASA 81 mg/d with clopidogrel 75 mg/d (Strong Recommendation, High-Quality Evidence).

II. Patients With Chronic Kidney Disease

In the **R**ivaroxaban **O**nce Daily Oral Direct Factor Xa Inhibition **C**ompared With Vitamin **K** Antagonist for Prevention of Stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation (ROCKET AF) trial (n = 14,264) and the **Ant**icoagulation and **R**isk Factors **i**n **A**trial Fibrillation (ATRIA) cohort (n = 13,559) chronic kidney disease (CKD) with a creatinine clearance < 60 mL/min was independently associated with risk for stroke after adjusting for $CHADS_2$ or CHA_2DS_2-VASc parameters.[24] Similar results were obtained in 547 nonvalvular AF patients after catheter ablation: an eGFR < 60 mL/min/1.73 m^2 was independently associated with stroke after adjustment for CHA_2DS_2-VASc parameters.[25] However, renal dysfunction was not found to be independently predictive in at least 3 other cohorts, including a cohort of 978 patients,[26] the 4576 patients of the **A** **M**ulticenter, Randomized, Open-label, **A**ssessor Blin**d**, Non-inferiority Study **E**valuating the **U**se of **S**R34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) trial,[27] and 5912 patients in the Loire Valley Atrial Fibrillation Project.[28]

Whether CKD is an independent stroke risk factor or not, patients with CKD have high rates of AF-related stroke. For example, in patients not taking OAC therapy, the stroke rate was 7.5% per year for patients with an eGFR of 30-59 mL/min/1.73 m^2 and 8.1% for patients with an eGFR < 30 mL/min/1.73 m^2.[29] Because randomized trials have demonstrated efficacy and safety of OACs for subjects with nonvalvular AF and eGFR > 30 mL/min/1.73 m^2,[30] most subjects with nonvalvular AF and CKD benefit from oral anticoagulation. However, there are no randomized trials data for nonvalvular AF patients who are dialysis-dependent, and we therefore cannot recommend their routine anticoagulation (Supplementary Material).

Practical tip. Most patients with nonvalvular AF and CKD who are not dialysis-dependent have sufficient risk for stroke to consider oral anticoagulation.

Practical tip. Among patients with an eGFR of 30-50 mL/min/1.73 m^2, the lower dose forms of the NOACs are preferred. Therefore, patients taking one of the NOACs should have their renal function repeatedly monitored (at least once per year).

III. Detection of AF in Patients With Stroke

Identification of AF has particular importance in patients with acute ischemic stroke or TIA because of the treatment implications for secondary stroke prevention. Without AF, the usual secondary stroke prevention treatment is antiplatelet therapy. However, when AF is documented in stroke/TIA patients (whether paroxysmal or persistent/permanent), OAC therapy is superior to antiplatelet therapy and strongly recommended for recurrent stroke prevention.

Diagnostic evaluation of patients with ischemic stroke or TIA aims to determine the most likely etiology, which can be broadly divided into 5 categories: cardio-embolism, large artery atherosclerosis, small vessel occlusion, other determined etiologies, and undetermined. AF is the leading cardiac cause of stroke, but can be difficult to detect when paroxysmal and asymptomatic. Diagnosed cases of AF account for more than 1 in 6 ischemic strokes, with this proportion increasing with age.[31] However, the true proportion of strokes related to AF is likely even larger, considering that embolic strokes might result from subclinical or "covert" AF, which might represent one of the most commonly underdiagnosed and untreated risk factors for recurrent strokes.

Cardiogenic brain embolism might be the first manifestation of previously-unrecognized AF, appearing on electrocardiogram (ECG) at the time of stroke or detected later during the post-stroke investigation. A 24-hour Holter monitor will detect a new diagnosis of paroxysmal AF in 5% of stroke patients, and prolonged monitoring (for up to 30 days) detects new AF in an additional 5%-20% of patients.[32-34]

In practice, post-stroke screening for AF is usually limited to 12-lead ECG and/or short duration (eg, 24-hour) ECG monitoring, and therefore the diagnosis of AF can be missed. As many as 1 in 4 ischemic strokes, with no cause identified after the usual post-stroke diagnostic evaluation, is classified as 'cryptogenic stroke' or 'embolic stroke of undetermined source.'[35] Undetected AF is likely the cause of a substantial number of these.

Three RCTs comparing different AF detection strategies after a stroke have recently been completed. A UK randomized trial (n = 100) showed that a strategy of 7-day ECG monitoring in the acute phase post-stroke was superior to standard care for AF detection (18% vs 2%; $P < 0.05$) and significantly increased OAC use.[36] The 30-Day Cardiac **E**vent **M**onitor **B**elt for **R**ecording **A**trial Fibrillation After a **C**erebral Ischemic **E**vent (EMBRACE) trial (n = 572) in patients with recent cryptogenic ischemic stroke found that the 30-day monitoring strategy significantly improved AF detection at 90 days (16% vs 3%; $P <$ 0.001) and nearly doubled OAC treatment rates. The **Cry**ptogenic **S**troke **a**nd Under**l**ying **A**trial **F**ibrillation Trial

(CRYSTAL AF) trial (n = 441) randomized patients after an acute cryptogenic stroke to longer-term monitoring with an implantable device or conventional follow-up.[37] At 6 months, AF detection was significantly greater in the intervention group (9% vs 1%; $P = 0.0006$) and OAC rates were doubled; by 3 years, AF was detected in 30% of the intervention group vs 3% of the control group ($P < 0.0001$).

Note that none of the available trials were powered to assess effects of prolonged monitoring on stroke or death rates. The minimum clinically significant duration of AF is uncertain and there was considerable debate among our committee members regarding the clinical significance and therapeutic implications of finding only very brief subclinical AF (SCAF). The optimal device and monitoring duration has not been established. Future studies are needed to determine the most clinically and cost effective strategy. Limited availability or access to ambulatory ECG monitoring is an acknowledged barrier in some regions.

RECOMMENDATION

8. For patients being investigated for an acute embolic ischemic stroke or TIA, we recommend at least 24 hours of ECG monitoring to identify paroxysmal AF in potential candidates for OAC therapy (Strong Recommendation, Moderate-Quality Evidence).
9. For selected older patients with an acute, nonlacunar, embolic stroke of undetermined source for which AF is suspected but unproven, we suggest additional ambulatory monitoring (beyond 24 hours) for AF detection, where available, if it is likely that OAC therapy would be prescribed if prolonged AF is detected (there are currently insufficient data to indicate what the minimum AF duration should be for OAC to be instituted, and expert opinion varies widely) (Conditional Recommendation, Moderate-Quality Evidence).

Practical tip. The yield of monitoring for AF detection depends on many factors including the type and duration of monitoring, patient adherence to monitoring, patient age[38] and other characteristics. The presence of frequent atrial premature beats during a 24-hour Holter recording is a strong independent predictor of AF in this population.[39-41]

IV. Investigation and Management of SCAF

The **As**ymptomatic Atrial Fibrillation and **S**troke **E**valuation in Pacemaker Patients and the Atrial Fibrillation **R**eduction Atrial Pacing **T**rial (ASSERT) and A Prospective Study of the Clinical Significance of A**tr**ial Arrhythmias D**e**tected by Impla**n**ted **D**evice Diagnostic**s** (TRENDS) studies demonstrated that episodes of SCAF as short as 5-6 minutes are common among patients with implanted devices and that SCAF is associated with a 2- to 2.5-fold increased risk of stroke.[42,43] Clinical risk factors influenced the absolute stroke risk among patients with SCAF; however, this risk appeared lower than among patients with clinical AF.[44] The duration and burden of SCAF were less clearly associated with stroke risk and uncertainty remains regarding the AF duration below which stroke risk is not increased. Finally, TRENDS and ASSERT showed no temporal association between SCAF and stroke in most patients.[45,46] Most patients with SCAF do not presently receive OAC,[47] because of uncertainty about their risk-benefit ratio for treatment. The only randomized evaluation of OAC in this setting is the recently-presented but as yet unpublished IMPACT (The **IMPACT** of Biotronik Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With ICD and CRT-D Devices) study. In the absence of publication, its results are difficult to interpret. Uncertainty regarding the role of oral anticoagulation in this population will remain until the completion of **A**pixaban for the **R**eduction of **T**hrombo-**E**mbolism Due to **S**ub-Clinical **A**trial Fibrillation (ARTESiA) (ClinicalTrials.gov NCT01938248) and other trials addressing this question.

RECOMMENDATION

10. We suggest that it is reasonable to prescribe OAC therapy for patients with age $\geq$ 65 years or $CHADS_2$ score $\geq$ 1 ("CCS algorithm") who have episodes of SCAF lasting $>$ 24 hours, or for shorter episodes in high-risk patients (such as those with a recent cryptogenic stroke) (Conditional Recommendation, Low-Quality Evidence).

V. Left Atrial Appendage Closure in Stroke Prevention

The concept of left atrial appendage (LAA) removal or occlusion to prevent ischemic stroke in AF has existed for many years. This can be achieved surgically at the time of another cardiac surgical procedure or as a stand-alone surgery. It can also be achieved through a transvenous LAA occlusion device. Such devices are approved in Europe, but not in Canada. There are no major trials of surgical removal and there is only one reported randomized trial of a LAA occlusion device, Watchman Left Atrial Appendage System for Embolic **Protect**ion in Patients With **A**trial **F**ibrillation (PROTECT-AF).[48] The 2.3-year follow-up data of PROTECT-AF were published in January 2013.[49] Patients with AF and an indication for warfarin (n = 707) were randomized 2:1 to either receive the Watchman LAA occlusion device (Boston Scientific, Marlborough, MA) or continue warfarin. After device implantation, warfarin was continued for 45 days followed by clopidogrel for 4.5 months and eventually long-term aspirin. The primary efficacy outcome included ischemic stroke, hemorrhagic stroke, systemic embolism, and cardiovascular death. The study met its preset noninferiority end point. Of particular importance are the outcomes of ischemic stroke and systemic embolism because device occlusion is designed specifically to prevent these events. At the 2.3-year follow-up there were only 27 occurrences of ischemic stroke and 3 of systemic emboli. The annual rates of ischemic stroke and systemic embolism were 1.9% and 0.3%, respectively, for device therapy vs 1.4% and 0% for warfarin (no significant differences).

Device therapy was also associated with significant acute complications including serious pericardial effusion (4.8%), procedure related ischemic stroke (1.1%), and device embolism (0.6%).[48] At present there is insufficient evidence to recommend LAA occlusion device therapy as an alternative to warfarin or to NOACs. LAA occlusion device therapy might be considered reasonable in rare AF patients at high risk of

stroke who, because of a very high risk of hemorrhage, are not candidates for either warfarin or a NOAC.

RECOMMENDATION

11. We suggest these nonapproved LAA closure devices not be used, except in research protocols or in systematically documented use protocols in patients at high risk of stroke ($CHADS_2$ score $\geq$ 2) for whom antithrombotic therapy is precluded (Conditional Recommendation, Low-Quality Evidence).

VI. Emergency Department Management

This section focuses on stroke prevention for patients with symptomatic, recent-onset AF/AFL, the most common arrhythmia in the Emergency Department (ED). There are 2 competing strategies for ED management; rate-control and rhythm control treatment.[50,51] The rate control approach consists of ventricular rate control, OAC, and delayed cardioversion after 4 weeks if indicated. With the rhythm control approach, attempts are made to cardiovert patients to sinus rhythm in the ED, either pharmacologically or electrically. The rhythm control approach is widely used in Canadian EDs and details of care are provided in the 2010 CCS AF guidelines.[52,53]

Clinical experience and published reports support the general belief that it is safe to proceed with cardioversion if the duration of AF/AFL is clearly less than 48 hours and the patient has no high-risk stroke characteristics.[54-58] A recent Finnish study followed patients who were successfully cardioverted with AF onset < 48 hours, and who had neither oral anticoagulation nor periprocedural heparin therapy.[59] Of 5112 cases, 0.7% developed thromboembolic events within 30 days, with the highest risk in patients with older age, heart failure, or diabetes. Before proceeding with cardioversion, physicians must be aware of the characteristics that put patients at high risk of immediate stroke and how to mitigate that risk. Furthermore, physicians must carefully consider the need to initiate OAC therapy before patient discharge from the ED, based on Figure 1. Early follow-up with a specialist is recommended to review the need for long-term OAC therapy. The updated approach is summarized in a revised ED treatment algorithm (Fig. 2).

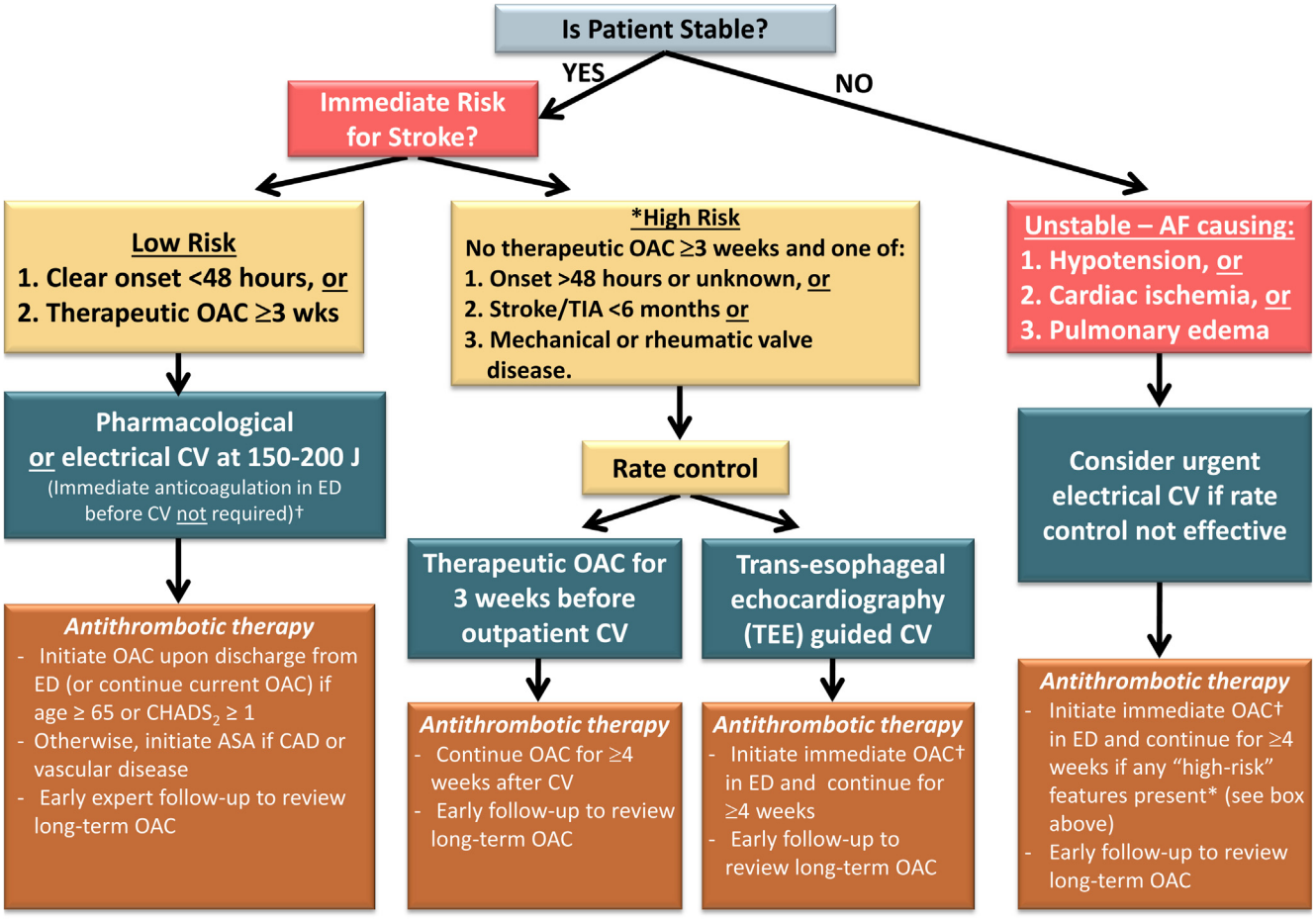

Figure 2. Decision algorithm for management of oral anticoagulation (OAC) therapy for patients who present to the emergency department (ED) with recent-onset atrial fibrillation (AF) requiring rate control or cardioversion (CV) in the ED. † Immediate OAC = a dose of OAC should be given just before cardioversion; either a novel direct oral anticoagulant (NOAC) or a dose of heparin or low molecular weight heparin with bridging to warfarin if a NOAC is contraindicated. ASA, acetylsalicylic acid; CAD, coronary artery disease; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; TIA, transient ischemic attack.

RECOMMENDATION

12. For patients with no high-risk factors for stroke (recent stroke or TIA within 6 months; rheumatic heart disease; mechanical valve) and clear AF onset within 48 hours or therapeutic OAC therapy for $\geq$ 3 weeks, we recommend that they may undergo cardioversion in the ED without immediate initiation of anticoagulation. After attempted or successful cardioversion, antithrombotic therapy should be initiated as per the CCS algorithm (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. Either pharmacological or electrical cardioversion may be selected, depending on physician and patient preference. For electrical cardioversion of AF, an initial QRS synchronized energy level of 150-200 J is appropriate.

Practical tip. Patients who are discharged from the ED after receiving or being considered for cardioversion of AF should have early expert follow-up to review the need for ongoing antithrombotic therapy.

RECOMMENDATION

13. For patients at high risk of stroke with cardioversion (not receiving therapeutic OAC therapy for $\geq$ 3 weeks with any of the following: AF episode duration not clearly $<$ 48 hours, stroke or TIA within 6 months, rheumatic heart disease, mechanical valve), we recommend optimized rate control and therapeutic OAC for 3 weeks before and at least 4 weeks after cardioversion (Strong Recommendation, Moderate-Quality Evidence).

Practical tip. When OAC therapy is indicated, a NOAC is preferred over warfarin for most patients.

Practical tip. Before discharge, patients should have their resting heart rate reduced to $<$ 100 beats per minute and their walking heart rate to $<$ 110 beats per minute.

Practical tip. Patients should receive OAC therapy together with appropriate oral rate-controlling agents (β-blocker or nondihydropyridine calcium channel blocker).

RECOMMENDATION

14. We suggest that patients at high risk of stroke (not receiving therapeutic OAC therapy for $\geq$ 3 weeks with any of the following: AF episode duration not clearly $<$ 48 hours, stroke or TIA within 6 months, rheumatic heart disease, mechanical valve) may undergo cardioversion guided by transesophageal echocardiography with immediate initiation of intravenous or low molecular weight heparin (LMWH) before cardioversion followed by therapeutic OAC for at least 4 weeks after cardioversion (Conditional Recommendation, Moderate-Quality Evidence).

Practical tip. If a NOAC is not used after transesophageal echocardiography-guided cardioversion, heparin bridging should be started immediately while warfarin is initiated.

RECOMMENDATION

15. For patients whose recent-onset AF/AFL is the direct cause of instability with hypotension, acute coronary syndrome, or florid pulmonary edema, we recommend that immediate electrical cardioversion be considered with immediate initiation of intravenous or LMWH before cardioversion followed by therapeutic OAC for 4 weeks afterward (unless AF onset was clearly within 48 hours or the patient has received therapeutic OAC for $\geq$ 3 weeks) followed by therapeutic OAC for at least 4 weeks after cardioversion (Strong Recommendation, Low-Quality Evidence).

Practical tip. Caution is required in patients with permanent AF who present with instability because they might not benefit from cardioversion and might be made worse by attempts to do so.

Practical tip. In patients with longstanding AF and hemodynamic instability and a ventricular rate less than 150 beats per minute, the instability is likely from causes other than AF (eg, hypoxia, pain, sepsis) and is unlikely to respond to cardioversion.

Practical tip. Immediate and adequate rate control might alleviate the clinical instability and obviate the need for immediate cardioversion.

VII. Periprocedural Anticoagulation Management

When a patient receiving an OAC or an antiplatelet agent is to undergo a surgical or diagnostic procedure that has a risk of major bleeding, the risk of a thromboembolic event while the antithrombotic agent is reduced or stopped must be weighed against the risk of bleeding during or after the procedure.[60,61] The major patient factors that suggest a greater risk of a thromboembolic event are captured by a higher $CHADS_2$ score, recent ($<$ 3 months) stroke or TIA, mechanical prosthetic heart valve, or rheumatic heart disease. The major patient factors that suggest a higher risk of bleeding are reflected in a higher HASBLED (**H**ypertension, **A**bnormal liver or kidney function, **S**troke, **B**leeding, **L**abile INRs, **E**lderly, **D**rugs) score. The major procedural factors that suggest a higher risk of bleeding are when periprocedural hemostasis might be difficult to achieve and/or when a patient would be placed at significant risk should bleeding occur.

Population risks for major bleeding have been categorized as very low, low, intermediate, and high risk by the Thrombosis Interest Group of Canada (Table 1).[62]

Procedures that have a very low or low probability of major bleeding can generally be safely performed without interruption of antithrombotic therapy (provided, in the case of warfarin, that the international normalized ratio [INR] is not supratherapeutic). Very low-risk procedures include most dental procedures (especially if supplemented with the use of hemostatic mouthwash), minor dermatological procedures, or anterior eye chamber surgery.[61,62,64]

Table 1. Bleeding risks for various invasive/surgical procedures

High risk
Neurosurgery (intracranial or spinal surgery)
Cardiac surgery (coronary artery bypass or heart valve replacement)
Major vascular surgery (abdominal aortic aneurysm repair, aortofemoral bypass)
Major urologic surgery (prostatectomy, bladder tumour resection)
Major lower limb orthopaedic surgery (hip/knee joint replacement surgery)
Lung resection surgery
Intestinal anastomosis surgery
Selected invasive procedures (kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy or biopsies)
Intermediate risk
Other intra-abdominal surgery
Other intrathoracic surgery
Other orthopaedic surgery
Other vascular surgery
Low risk
Laparoscopic cholecystectomy
Laparoscopic inguinal hernia repair
Dental procedures
Dermatologic procedures
Ophthalmologic procedures*
Coronary angiography
Gastroscopy or colonoscopy
Selected invasive procedures (bone marrow aspirate and biopsy, lymph node biopsy, thoracentesis, paracentesis, arthrocentesis)
Cardiac implantable device surgery (pacemaker or implantable defibrillator)†
Very low risk
Dental extractions (1 or 2 teeth) or teeth cleaning
Skin biopsy or skin cancer removal
Cataract removal

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

†Based on results from the **Br**idge or Contin**u**e Coumad**i**n for Device **S**urg**e**ry Randomized **Control**led Trial (BRUISECONTROL) trial.[63]

The recently published **Br**idge or Contin**u**e Coumad**i**n for Device **S**urg**e**ry Randomized **Control**led Trial (BRUISE-CONTROL) trial reported a lower risk of significant hematoma when performing cardiac implantable device (pacemaker or implantable defibrillator) surgery while the patient received uninterrupted, warfarin therapy, as opposed to stopping warfarin and bridging with intravenous unfractionated heparin (UFH) or subcutaneous LMWH in patients with high thromboembolic risk ($CHADS_2$ score $\geq$ 2 or mechanical prosthetic valve). Accordingly, surgery to implant a cardiac device is listed in Table 1 as having a low risk of bleeding. Antithrombotic therapy (whether ASA or warfarin) is continued throughout the implantation procedure in these patients.[63]

For other procedures, interruption of chronic antithrombotic therapy with or without bridging with LMWH or UFH will likely be required.

RECOMMENDATION

16. We recommend that in a patient with AF/AFL, a decision to interrupt antithrombotic therapy for an invasive procedure must balance the risks of a thromboembolic event (as indicated by a higher $CHADS_2$ score, mechanical heart valve, or rheumatic heart disease) with those of a bleeding event (as indicated by a higher HASBLED score and procedures with higher bleeding risks) (Strong Recommendation, Low-Quality Evidence).
17. We suggest that interruption of anticoagulant therapy in a patient with AF/AFL is not necessary for most procedures with a very low risk of bleeding, including cardiac device implantation (pacemaker or implantable defibrillator; Table 1) (Conditional Recommendation, Low-Quality Evidence; High-Quality Evidence for cardiac device implantation).
18. We recommend that interruption of anticoagulant therapy in a patient with AF or AFL will be necessary for most procedures with an intermediate or high risk of major bleeding (Table 1) (Strong Recommendation, Low-Quality Evidence).

If antithrombotic therapy is to be interrupted for an invasive procedure, aspirin or clopidogrel should be stopped for 5-7 days (7-10 days for procedures with a high risk of major bleeding) and warfarin for 5 days if the INR is in the range of 2-3. After stopping warfarin, the INR before the procedure should be < 1.5 for a procedure with an intermediate risk of major bleeding and < 1.2 for a procedure with a higher risk of major bleeding. In the case of warfarin, if the patient has a higher risk of stroke ($CHADS_2$ score ≥ 3, stroke, or TIA in the previous 3 months, mechanical heart valve, or rheumatic heart disease), the perioperative period should include LMWH or UFH bridging when the INR has decreased to < 2.0. The wisdom of LMWH or UFH bridging in this setting has been recently questioned in a meta-analysis[65] of 33 observational studies and 1 randomized trial involving 7118 patients (slightly less than half of whom were receiving warfarin therapy for stoke prevention in the setting of AF or AFL). This meta-analysis reported that warfarin discontinuation with bridging therapy, compared with warfarin discontinuation without bridging therapy, was associated with an increase in overall bleeding (13.1% vs 3.4%; $P < 0.0001$), an increase in major bleeding (4.2% vs 0.9%; $P = 0.004$), but no reduction in thromboembolic events (0.9% vs 0.6%; $P = 0.50$). Nevertheless, because of the possibility that these observations were confounded by a differential use of bridging in patients at higher bleeding and thromboembolic risk in observational studies, we continue to recommend bridging in patients at higher thromboembolic risk. Two randomized clinical trials (A Safety and Effectiveness Study of **P**ostoperativ**e** LMWH B**ri**dging Therapy versus Placeb**o** Bridging Therapy for **P**atients on Long Term Warfarin [PERIOP2][66] and Effectiveness of **Bridg**ing Anticoagulation for Surgery [the BRIDGE study[67]]) are under way that should provide additional data to inform this recommendation. When bridging heparin therapy is used, it should be stopped 24 hours before the procedure in the case of LMWH and 4-6 hours before the procedure in the case of UFH.

At present, 3 NOACs are approved for the prevention of stroke and systemic thromboembolism in patients with nonvalvular AF in Canada—apixaban, dabigatran, and rivaroxaban. Reported experience with these agents in the periprocedural period is limited. Bleeding and thromboembolic outcomes in the periprocedural period using NOAC vs warfarin have been investigated in the RE-LY and **A**pixaban

for **R**eduction **i**n **St**roke and **O**ther **T**hromboembo**l**ic **E**vents in Atrial Fibrillation (ARISTOTLE) trials.[9,68] There were no statistically significant differences between the dabigatran or the apixaban group and their respective warfarin groups with respect to bleeding or thromboembolic complications in the periprocedural period.[69,70] Comparable data have not yet been published regarding rivaroxaban from the ROCKET AF trial, but an observational analysis from the Dresden NOAC Registry suggests no difference in bleeding or thromboembolic complications in the periprocedural period in a comparison of patients who had been receiving rivaroxaban with patients who received dabigatran.[68]

Because of the limited reported experience with NOACs in the periprocedural period, recommendations regarding their use are necessarily empirical. The offset kinetics of their anticoagulant effects might be reasonably predicted by their elimination half-lives.[71-73] Dabigatran is eliminated to a greater extent by the kidneys, so the time it should be withheld for an invasive procedure depends on renal function. Renal function is less critical to the elimination half-lives of apixaban and rivaroxaban, provided the eGFR is $>$ 30 mL/min/1.73 m^2. We recommend that the withdrawal period for apixaban or rivaroxaban be 1-2 days for a procedure with a lower risk of major bleeding and 2-3 days for a procedure with a higher risk of major bleeding. The same periods are recommended for withdrawal of dabigatran when the eGFR is $\geq$ 80 mL/min/1.73 m^2. The higher end of these ranges is recommended for dabigatran if the eGFR is 50-80 mL/min/1.73 m^2, and an additional day should be added for dabigatran if the eGFR is 30-50 mL/min/1.73 m^2. For eGFR $<$ 30 mL/min/1.73 m^2, yet an additional day should be added for dabigatran, although NOACs are not generally recommended in these patients.

Because of the rapid onset and offset kinetics of the NOACs, bridging with LMWH or UFH is not recommended during the periprocedural period unless the NOAC has been withdrawn for a period longer than that recommended and the patient has a greater risk of thromboembolism ($CHADS_2$ score $\geq$ 3, mechanical heart valve, stroke or TIA within 3 months, rheumatic heart disease).

The absence of a proven "antidote" for the NOACs along with interindividual variability in their respective terminal elimination half-lives, suggest a conservative approach for recommendations regarding the use of these agents around the time of procedures during which any bleeding could confer serious adverse outcomes. Thus, the NOACs should not be used in the perioperative period when neuraxial anaesthesia or lumbar puncture is planned.

After the invasive procedure, antithrombotic therapy is reintroduced after hemostasis has been secured (usually 24-48 hours after a procedure with a lower risk of major bleeding and 48-72 hours after a procedure with a higher risk of major bleeding). Because of the rapid onset of the effects of the NOACs, these agents should be restarted nearer the latter portion of each of these suggested ranges. When bridging LMWH is used, the LMWH should be given in prophylactic dosages for 24-72 hours depending on the risk of procedural bleeding. LMWH may be increased to therapeutic dosages thereafter, providing postoperative bleeding has not occurred. Warfarin therapy is reintroduced after the same time periods, recognizing that several days will be needed for the INR to achieve the therapeutic range at which time bridging LMWH or UFH may be discontinued.

RECOMMENDATION

Before the procedure

19. When a decision to interrupt aspirin or clopidogrel therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 5-7 days before the procedure, except for procedures with a very high risk of bleeding, in which case we suggest interruption 7-10 days before the procedure (Conditional Recommendation, Low-Quality Evidence).
20. When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 5 days before the procedure. A procedure with low bleeding risk may proceed when the INR is $<$ 1.5 and a procedure with an intermediate or high bleeding risk may proceed when the INR is $<$ 1.2 (Conditional Recommendation, Low-Quality Evidence).
21. When a decision to interrupt warfarin therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that bridging therapy with LMWH or UFH be instituted when the INR is below that patient's therapeutic INR target in a patient at high risk of thromboembolic events ($CHADS_2$ score $\geq$ 3, mechanical heart valve, stroke or TIA within 3 months, rheumatic heart disease) (Conditional Recommendation, Low-Quality Evidence).
22. When a decision to interrupt apixaban or rivaroxaban therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 1-2 days before a procedure with low risk of major bleeding and 2-3 days before a procedure with an intermediate or high risk of major bleeding (Conditional Recommendation, Low-Quality Evidence).
23. When a decision to interrupt dabigatran therapy for an invasive procedure has been made for a patient with AF/AFL, we suggest that interruption begin 1-2 days before a procedure with low risk of major bleeding and 2-3 days before a procedure with an intermediate or high risk of major bleeding when eGFR is $\geq$ 80 mL/min/1.73 m^2 (Conditional Recommendation, Low-Quality Evidence). The upper end of these ranges should be used if eGFR is 50-80 mL/min/1.73 m^2, an additional day should be added when eGFR is 30-50 mL/min/1.73 m^2, and in case eGFR is $<$ 30 mL/min/1.73 m^2, yet 1 more day of dabigatran withdrawal should be added (Conditional Recommendation, Low-Quality Evidence).
24. We recommend that when LMWH or UFH bridging is used for an invasive procedure, the therapy should be started before the procedure when the INR is $<$ 2.0 and be stopped 24 hours before the procedure for LMWH and 4-6 hours befolre the procedure for UFH (Strong recommendation, Low-Quality Evidence).

After the procedure

25. When LMWH or UFH bridging is used for an invasive procedure, we suggest that such therapy be restarted after the procedure when hemostasis is established (usually 24 hours for a procedure with a low risk of bleeding and 48-72 hours for a procedure with an intermediate or high risk of bleeding) in prophylactic dosages for the first 24-72 hours and then increased to therapeutic dosages. Bridging is then continued until an OAC is therapeutic (Conditional Recommendation, Low-Quality Evidence).
26. When warfarin, ASA, or clopidogrel therapy has been interrupted for an invasive procedure, we suggest that such therapy be restarted after the procedure when hemostasis is established (usually 24-48 hours for a procedure with a low risk of bleeding and 48-72 hours for a procedure with an intermediate or high risk of bleeding) (Conditional Recommendation, Low-Quality Evidence).
27. When apixaban, dabigatran, or rivaroxaban have been withdrawn for an invasive procedure we suggest that such therapy be restarted after the procedure 1 day after hemostasis is established (usually 48 hours for a procedure with low risk of bleeding and 72 hours for a procedure with an intermediate or high risk of bleeding) (Conditional Recommendation, Low-Quality Evidence).

VIII. Rate and Rhythm Control

Since the publication of the 2012 focused update of CCS AF guidelines,[2] there have been some new data that reinforce the rate and rhythm control recommendations in the 2010 guidelines and the focused update.[74]

Target for rate control

In the 2010 guidelines, the committee recommended that the goals of ventricular rate control "should be to improve symptoms and clinical outcomes which are attributable to excessive ventricular rates."[74] Although the historical target for rate control was a resting heart rate < 80 beats per minute, the 2010 guidelines liberalized the target to a resting heart rate $<$ 100 beats per minute based on randomized clinical trial data suggesting no difference between strict and lenient rate control targets.

A recent substudy of 608 patients analyzed quality of life with 3 measurement tools in patients randomized to lenient vs strict rate control.[75] After an average of 2 years of follow-up, there was no difference between groups for any of the quality of life measures. This evidence further reinforces the guidelines original recommendation for a more lenient target heart rate of $<$ 100 beats per minute.

Use of digoxin for rate control

In the 2010 guidelines, digoxin was downgraded to second-line therapy for rate control of AF, behind calcium channel blockers and β-blockers. Specifically, we suggested that "digoxin not be used as initial therapy for active patients and be reserved for rate control in patients who are sedentary or who have left ventricular dysfunction."[74] Since that time, additional evidence has further questioned the use of digoxin for rate control. Two substudies from the **A**trial **F**ibrillation **F**ollow-up **I**nvestigation of **R**hythm **M**anagement (AFFIRM) trial comparing rate control with rhythm control were published in 2013.[76,77] In the first substudy, use of digoxin was treated as a time-dependent covariate to take into account that patients might be using therapy or not at various times in follow-up. After controlling for clinical variables and using propensity adjustment, the results showed a significant increase in all-cause mortality associated with digoxin use (hazard ratio, 1.41; 95% CI, 1.19-1.67; $P < 0.001$).[76] In the same journal issue, however, another substudy from the AFFIRM trial showed no increased mortality, but also no benefit, associated with digoxin use (hazard ratio, 1.06; 95% CI, 0.83-1.37; $P = 0.64$).[77] The second study excluded a large number of patients based on inclusion criteria and method of propensity matching, and did not account for changes in digoxin use over time. Furthermore, there has been a greater understanding about drug interactions that might elevate digoxin levels to toxic ranges. Dronedarone, for example, has been shown to increase steady-state digoxin levels by 2.5 times.[78] These data reinforce the 2010 guidelines recommendation that digoxin only be used as second-line therapy in selected cases.

Algorithm for choice of rate vs rhythm control for AF

As mentioned earlier, the main goal of AF treatment is to relieve symptoms, improve functional capacity and quality of life, and where possible, improve left ventricular function. Trial results suggest that this can be accomplished by either rate control or rhythm control, without systematic benefit of either strategy in terms of mortality or morbidity. Thus, the choice of rate vs rhythm control must be individualized for each patient. Furthermore, the preferred treatment strategy might change over time if the patient's symptoms change or if one strategy has not proven effective.

The Guidelines Committee has developed a new practice algorithm (Fig. 3) to help in treatment selection. For patients with recently diagnosed symptomatic AF, rate control to keep the heart rate $<$ 100 beats per minute seems an appropriate first step. If symptoms do not resolve with rate control or therapy-related adverse effects appear, then rhythm control might be considered. The choice of rhythm control relates to AF characteristics. For patients with a low burden of infrequent paroxysmal AF, pill-in-pocket antiarrhythmic therapy might be reasonable. For more frequent paroxysmal AF, daily maintenance antiarrhythmic therapy might be tried, followed by consideration of catheter ablation if the response is not adequate. For patients with persistent AF, a trial of cardioversion might help to determine further treatment strategies. If sinus rhythm restoration substantially improves symptoms and AF does not recur, the patient might simply be observed until AF recurs. If sinus rhythm restoration improves symptoms but AF recurs, maintenance antiarrhythmic drug (AAD) therapy should be considered, with catheter ablation if drugs are not effective. However, if sinus rhythm restoration does not

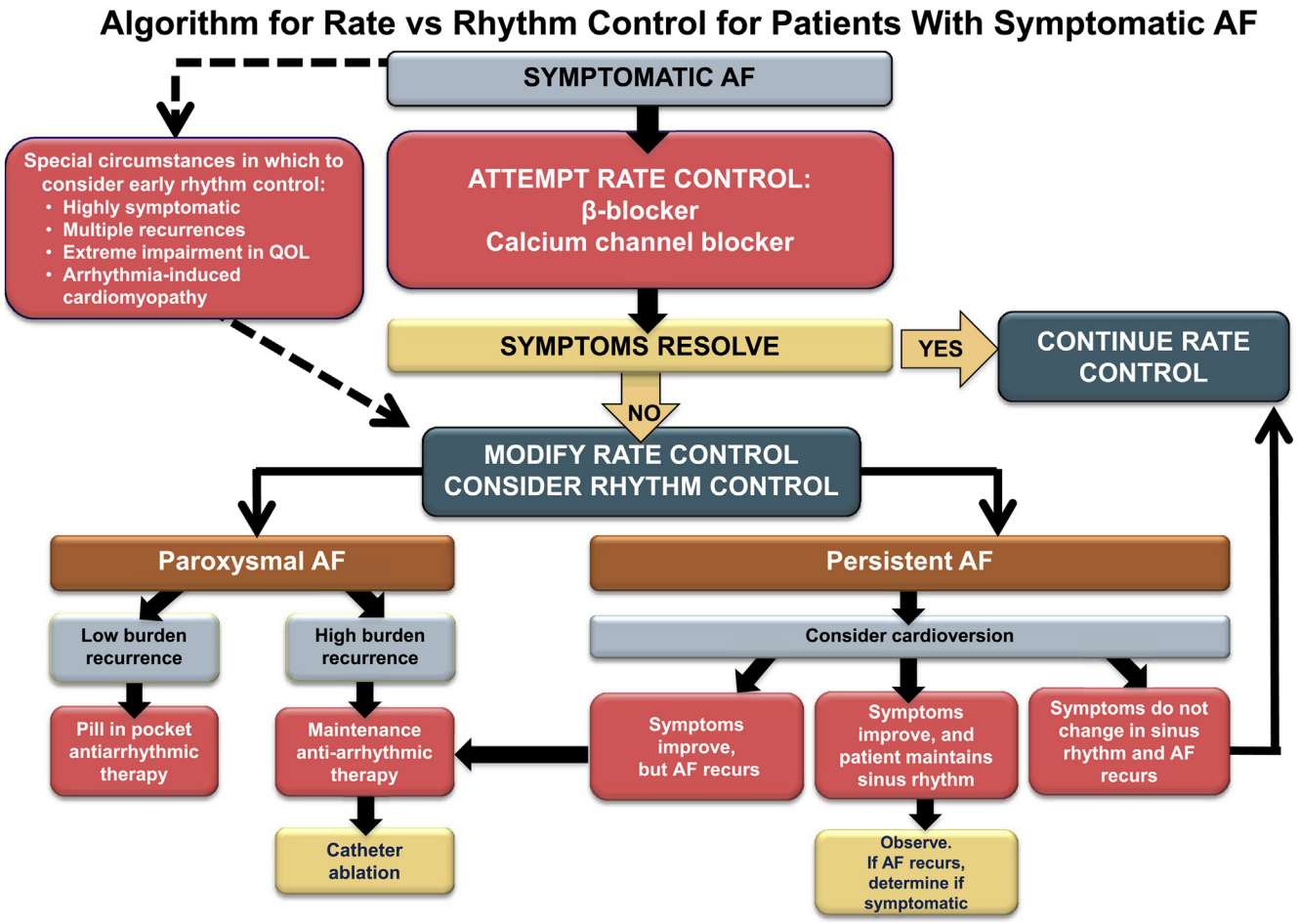

Figure 3. Approach to rate and/or rhythm control of atrial fibrillation (AF) in patients presenting with symptomatic AF. QOL, quality of life.

change symptoms, long-term rate control would be preferred if AF recurs.

In selected cases with highly symptomatic AF, multiple recurrences, or extreme impairment in quality of life, early consideration of rhythm control in conjunction with rate control might be indicated. Patients with arrhythmia-induced cardiomyopathy might also be considered for early rhythm control, although cardiomyopathy might resolve with adequate rate control alone.

For patients with asymptomatic persistent AF, rate control is usually the therapy of choice. However, AF symptoms might be difficult to ascertain because they can be quite nonspecific. Fatigue, declining exercise tolerance, decreased motivation, and exertional dyspnea might all be attributed to aging or other conditions, but might actually be due to AF. When it is difficult to establish whether symptoms are due to AF, a trial of cardioversion might be helpful. Clear symptom relief after restoration of sinus rhythm would encourage a rhythm control approach.

Recent evidence suggests that 4 weeks of antiarrhythmic therapy after cardioversion might reduce the incidence of longer-term AF recurrence beyond the 4 weeks.[79] Patients were randomized after cardioversion to no antiarrhythmic therapy, flecainide for 4 weeks after cardioversion, or flecainide for 6 months after cardioversion. Although short-term flecainide was less effective than long-term treatment, the difference in recurrence was small (56% vs 48%), reflecting the predominant recurrence rate early after cardioversion and suggesting that short-duration antiarrhythmic therapy after cardioversion might produce enduring AF recurrence reduction.

IX. Catheter Ablation for AF

AF ablation as first-line therapy

Recent studies examined the value of AF ablation as first-line therapy. The **M**edical **An**tiarrhythmic **T**reatment or **R**adiofrequency **A**blation in **P**aroxysmal **A**trial **F**ibrillation (MANTRA-PAF) study randomized 294 patients with paroxysmal AF and no history of AAD use to an initial strategy of catheter ablation (n = 146) or AADs (n = 148). After 24 months, AF burden was not different but significantly more patients in the ablation group were AF-free.[80] The **R**adiofrequency **A**blation vs **A**ntiarrhythmic Drugs as **F**irst-Line **T**herapy of Atrial Fibrillation 2 (RAAFT-2) trial randomized 127 AAD-naive patients with paroxysmal AF to first-line ablation (n = 66) vs AAD-therapy (n = 61)[75] and followed them for 2 years: ablation significantly reduced symptomatic and asymptomatic AF vs AADs. This new

evidence supports the 2010 recommendation suggesting catheter ablation as first-line therapy in highly-selected patients with symptomatic paroxysmal AF. In Table 2 the benefit-to-risk ratio for catheter ablation in various situations are summarized.

Alternate energy sources for catheter ablation

AF ablation most commonly uses radiofrequency (RF) energy to isolate pulmonary veins (PVs). However, performing PV isolation (PVI) with a "point-by-point" approach might be technically challenging. Ablation technologies have therefore been developed to achieve PVI with a single circumferential energy application.

The cryoballoon system consists of a steerable catheter that delivers pressurized cryorefrigerant to a distally mounted balloon. The multicentre, randomized **S**ustained **T**reatment **o**f **P**aroxysmal **A**trial **F**ibrillation (STOP AF) trial compared AAD therapy with cryoballoon-based PVI in 245 patients with drug-refractory paroxysmal AF.[81] At 1 year, 69.9% of 163 cryoballoon-ablated patients were AF-free, compared with 7.3% of 82 patients randomized to AADs. Early experience suggests that the efficacy and safety of cryoballoon ablation are comparable to RF energy for paroxysmal AF.[82,83]

The PV ablation catheter (PVAC) consists of a circular catheter that enables mapping and circumferential PV ablation using RF. PVAC ablation efficacy compares favourably with standard RF energy delivery,[82,84,85] but PVAC ablation produced an excessively high rate (38%-45%) of silent cerebral ischemic lesions.[86,87] With procedural modifications, there has been a significant decrease in cerebral ischemic events to rates similar to those obtained using other technologies.[88]

Complications of catheter ablation

In recent studies the important issue of risks associated with AF ablation have been examined.[89-92] In a single-centre study in which risks were assessed during 1190 procedures over 9 years, the major complication rates were 4.7%, including vascular complications (1.5%), tamponade (1.1%), and stroke/TIA (1.1%).[89] In a US inpatient database analysis 93,801 ablations performed between 2000 and 2010 were examined.[91] The overall complication rate was 6.29% (vascular, 1.53%; pericardial, 1.52%; respiratory, 1.3%; stroke/TIA, 1.02%) with a 0.42% in-hospital mortality rate. Annual operator volume (< 25 AF ablation procedures) and hospital volume (< 50 AF ablation procedures) were significant predictors of major adverse outcomes. The experience threshhold for reduced risk seems to be 25-50 procedures per operator per year, which aligns with the 2010 CCS/Canadian Heart Rhythm Society training standards for adult clinical cardiac electrophysiology.[93]

Table 2. Balance of benefit to risk for catheter ablation in patients with symptomatic atrial fibrillation

	Long-standing*	Persistent	Paroxysmal
First line	—	—	+
Failed first drug	—	+	++
Failed second drug	+	++	+++
Failed multiple drugs	++	+++	+++

\+ Indicates balance of benefit to risk in favour of catheter ablation.
*Ongoing symptomatic atrial fibrillation ≥ 1 year.

Long-term efficacy of catheter ablation

Most large-scale observational studies and RCTs had limited follow-up.[94-98] Recently, several studies have demonstrated that very late arrhythmia recurrences (> 1 year) are not uncommon after initial "successful" ablation.[99-102] In 1 study, arrhythmia-free survival rates were 87%, 81%, and 63% after the last catheter ablation procedure at 1, 2, and 5 years, respectively.[99] In another study, the long-term arrhythmia-free outcomes of 123 patients AF-free at 1 year were 85% after 3 years and 71% after 5 years.[100] Catheter ablation of AF should thus be considered an effective treatment rather than a cure. This new evidence reinforces the importance of pursuing oral anticoagulation in patients with high thromboembolic risk, regardless of short- or mid-term procedural success.

Antithrombotic therapy in relation to catheter ablation

AF ablation is associated with a risk of thromboembolism even in patients without stroke risk factors. Therefore, careful anticoagulation is critical before, during, and after AF ablation procedures. Recent studies have demonstrated that performing AF ablation with uninterrupted warfarin (therapeutic INR of 2.0-3.0) is safe and associated with fewer complications (vascular access complications, strokes) compared with bridging with LMWH.[103-105] Evidence for the periprocedural use of NOACs for AF ablation is limited. Nonrandomized studies that evaluated interrupted dabigatran vs uninterrupted warfarin have yielded conflicting results.[106-109] Recently, no differences in periprocedural bleeding or thromboembolic complications were observed between uninterrupted rivaroxaban and uninterrupted warfarin therapy.[110] Results from RCTs of periprocedural NOAC vs warfarin should further define the relative role of these agents. After ablation during warfarin treatment, it should be continued to maintain an INR of > 2.0 to avoid the use of heparin bridging. When NOACs are used, they can be reinitiated within 4-12 hours of sheath removal without the need for heparin bridging. In all cases, oral anticoagulation with warfarin or NOACs should be continued for at least 2 months after AF ablation. Although it has been suggested that AF ablation could lower the long-term stroke risk, this remains unproven.[111-114] In addition to delayed symptomatic AF recurrence discussed previously herein, asymptomatic recurrences are not infrequent; accordingly, evaluation of procedural success according to symptoms alone is unreliable.[115] Therefore, decisions regarding long-term anticoagulation should be based on the patient's stroke risk factors, not on the apparent absence of AF recurrence. A desire to avoid long-term anticoagulation should not be considered an indication for AF ablation. Further long-term studies such as the **O**ptimal Anti**c**oagulation for **E**nhanced Risk Patients Post-Catheter **A**blation for Atrial Fibrillatio**n** (OCEAN) trial (ClinicalTrials.gov NCT02168829) will help to assess the risk of stroke after AF ablation.

RECOMMENDATION

28. We recommend catheter ablation of AF in patients who remain symptomatic after an adequate trial of AAD therapy and in whom a rhythm control strategy remains desired (Strong Recommendation, Moderate-Quality Evidence).
29. We suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in highly selected patients with symptomatic, paroxysmal AF (Conditional Recommendation, Moderate-Quality Evidence).
30. We suggest that catheter ablation of AF should be performed by electrophysiologists with a high degree of expertise and high annual procedural volumes (Conditional Recommendation, Low-Quality Evidence).

Practical tip. The following represents an ideal, but not exclusive, profile of a patient who is referred for consideration of AF ablation today: age < 80 years, symptomatic with their AF, has tried but treatment has failed or is intolerant of AAD therapy, has paroxysmal AF or short-standing persistent AF, and minimal to moderate structural heart disease (such as left ventricular dysfunction or valvular disease).

Practical tip. AF ablation should not be considered as an alternative to oral anticoagulation. If a patient has a high thromboembolic risk profile, then the patient should continue oral anticoagulation even after successful AF ablation. Studies of long-term monitoring have consistently shown asymptomatic episodes of AF before and after ablation. Initiation of oral anticoagulation should also not be delayed when indicated in patients pending referral for AF ablation.

Acknowledgements

For a full list of Guideline Committee Members, see the *Canadian Cardiovascular Society Atrial Fibrillation Guidelines — Primary Panel* and *Canadian Cardiovascular Society Atrial Fibrillation Guidelines — Secondary Panel* sections of the Supplementary Material.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2014.08.001.