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Society Guidelines

The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation

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ABSTRACT

The Canadian Cardiovascular Society (CCS) atrial fibrillation (AF) guidelines program was developed to aid clinicians in the management of these complex patients, as well as to provide direction to policy makers and health care systems regarding related issues. The most recent comprehensive CCS AF guidelines update was published

RÉSUMÉ

Le programme de lignes directrices de la Société canadienne de cardiologie (SCC) en matière de fibrillation auriculaire (FA) a été élaboré pour aider les cliniciens à prendre en charge ces patients complexes, ainsi que pour orienter les décideurs politiques et les systèmes de soins de santé sur des questions connexes. La dernière édition

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*For a full listing of primary and secondary panel members, see Supplemental Appendix S1.

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

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

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in 2010. Since then, periodic updates were published dealing with rapidly changing areas. However, since 2010 a large number of developments had accumulated in a wide range of areas, motivating the committee to complete a thorough guideline review. The 2020 iteration of the CCS AF guidelines represents a comprehensive renewal that integrates, updates, and replaces the past decade of guidelines, recommendations, and practical tips. It is intended to be used by practicing clinicians across all disciplines who care for patients with AF. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to evaluate recommendation strength and the quality of evidence. Areas of focus include: AF classification and definitions, epidemiology, pathophysiology, clinical evaluation, screening and opportunistic AF detection, detection and management of modifiable risk factors, integrated approach to AF management, stroke prevention, arrhythmia management, sex differences, and AF in special populations. Extensive use is made of tables and figures to synthesize important material and present key concepts. This document should be an important aid for knowledge translation and a tool to help improve clinical management of this important and challenging arrhythmia.

complète des lignes directrices de la SCC en matière de FA a été publiée en 2010. Depuis lors, des mises à jour périodiques ont été publiées, traitant de domaines en évolution rapide. Cependant, en 2020, un grand nombre de développements s'y étaient ajoutés, couvrant un large éventail de domaines, ce qui a motivé le comité à créer une refonte complète des lignes directrices. L'édition 2020 des lignes directrices de la SCC en matière de FA représente un renouvellement complet qui intègre, met à jour et remplace les lignes directrices, les recommandations et les conseils pratiques des dix dernières années. Elle est destinée à être utilisée par les cliniciens praticiens de toutes les disciplines qui s'occupent de patients souffrant de FA. L'approche GRADE (Gradation des Recommandations, de l'Appréciation, du Développement et des Évaluations) a été utilisée pour évaluer la pertinence des recommandations et la qualité des résultats. Les domaines d'intérêt incluent : la classification et les définitions de la FA, son épidémiologie, sa physiopathologie, l'évaluation clinique, le dépistage de la FA, la détection et la gestion des facteurs de risque modifiables, l'approche intégrée de la gestion de la FA, la prévention des accidents vasculaires cérébraux, la gestion de l'arythmie, les différences entre les sexes et la FA dans des populations particulières. Des tableaux et figures ont été largement utilisés pour synthétiser les éléments importants et présenter les concepts clés. Ce document devrait représenter une aide importante pour l'intégration des connaissances et un outil pour aider à améliorer la gestion clinique de cette arythmie importante et difficile à traiter.

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is associated with reduced quality of life (QOL), functional status, cardiac performance, and survival. The contemporary management of AF is centred on symptomatic improvement, diminution in morbidity and mortality (particularly the prevention of cardiomyopathy, and stroke/systemic embolism), and reduction in AF-related emergency department (ED) visits or hospitalizations (Fig. 1).

The Canadian Cardiovascular Society (CCS) AF guidelines program was developed to aid clinicians in the management of these complex patients, as well as to provide direction to policy makers and health systems regarding the management of patients with AF. Beginning with the 1994 CCS consensus conference on AF, the CCS AF guidelines program has provided comprehensive guideline updates in 2004 and 2010, with focused updates on the basis of emerging evidence in 2012, 2014, 2016, and 2018.[1-8] The 2020 iteration of the CCS AF guidelines is a comprehensive renewal that integrates, updates, and replaces the past decade of guidelines, recommendations, and practical tips. It is intended to be used by practicing clinicians across all disciplines who care for patients with AF.

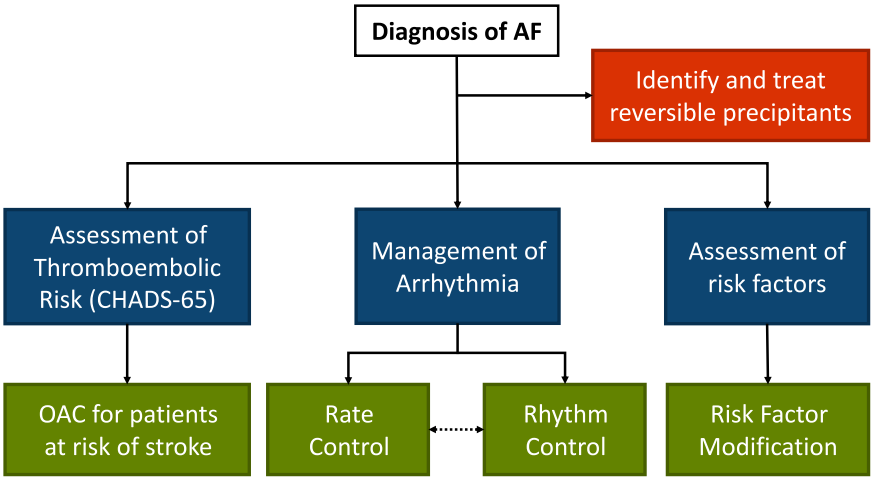
The 2020 comprehensive AF guidelines address the following topics:

1. Classification and Definitions
2. Epidemiology
3. Pathophysiology
4. Clinical Evaluation
5. Screening and Opportunistic AF Detection
6. Detection and Management of Modifiable Risk Factors
7. Integrated Approach to AF management
8. Stroke Prevention
9. Arrhythmia Management
10. Sex Differences
11. AF and Special Populations

Preamble and Guideline Development Methodology

This document was developed in accordance with CCS best practices and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[9] The primary panelists developed the scope of the document, identified topics for review, performed the literature review, evaluated the quality of the evidence, and drafted the recommendations. A systematic search was performed to identify relevant studies within each topic, including systematic reviews and meta-analyses. Draft recommendations were presented, reviewed, and refined by the primary panel. Final review was performed by the primary and secondary panels, with each recommendation achieving more than 90% agreement.

Strength of recommendations and quality of evidence were evaluated according to the GRADE approach.



Major Goals of AF Management	Anticipated Outcome
Prevent stroke or systemic thromboembolism	Improvement in survival
Cardiovascular Risk Reduction	
Improve symptoms, functional capacity, and QOL	Reduction in healthcare utilisation (e.g. ED visits or hospitalizations)
Prevent complications (e.g. LV dysfunction, falls)	

Figure 1. General overview of the management of atrial fibrillation (AF). CHADS-65, Canadian Cardiovascular Society algorithm; ED, emergency department; OAC, oral anticoagulation; LV, left ventricular; QOL, quality of life.

Evidence derived from randomized clinical trials (RCTs) was initially estimated as high-quality evidence, with observational evidence initially deemed low-quality evidence. These estimates were further refined through detailed appraisal into 4 categorical grades ("high," "moderate," "low," and "very low") after consideration of the risk of bias, confounding, consistency of results, directness of evidence, precision, publication bias, magnitude of effect, and dose-response gradient. After this evaluation, the strength of recommendation was determined by considering the balance between desirable and undesirable effects (ie, risk-benefit), confidence in the magnitude of effect (quality of evidence), patient values and preferences, as well as resource considerations. The strength of recommendation was graded as "strong" (the desirable effects outweigh the undesirable effects, and therefore, most individuals will be best served by the recommended course of action) or "weak" (the desirable effects probably outweigh the undesirable effects, indicating that there is a need to consider the individual patient's clinical details, circumstances, values, and preferences).

Peer review of the guideline document was provided by external content experts, patient partners, and the CCS Guidelines Committee (outlined in the *Acknowledgements* section). The final draft was presented and approved by the CCS Executive Committee. For the constitution and roles of the primary and secondary panels, systematic review strategy, methods for formulating the recommendations, and evidence see the Supplementary Material and www.ccs.ca.

1. Classification and Definitions

1.1. Classification on the basis of clinical pattern of AF

AF pattern is defined on the basis of clinical assessment of episode persistence. These patterns have been used to characterize the severity of disease, define patient populations in clinical trials, and are used to form the basis of therapeutic recommendations regarding pharmacological and invasive arrhythmia management.[10]

Four main clinical patterns of AF have been described. Paroxysmal AF is defined as a continuous AF episode lasting longer than 30 seconds but terminating within 7 days of onset. Persistent AF is defined as a continuous AF episode lasting longer than 7 days but less than 1 year. "Longstanding" persistent AF is defined as continuous AF $\geq$ 1 year in duration, in patients in whom rhythm control management is being pursued. Permanent AF is defined as continuous AF for which a therapeutic decision has been made not to pursue sinus rhythm restoration. The mode of termination (spontaneous vs pharmacological/electrical cardioversion) does not influence the classification.

In many patients, AF progresses from short episodes of self-terminating paroxysmal AF to more frequent exacerbations of longer-lasting persistent AF. In the event that both paroxysmal and persistent episodes are present, the classification should be defined on the basis of the predominant AF pattern.

Although valuable, there are limitations to classifying AF patterns by clinical assessment. First, the distinction between paroxysmal and persistent AF is often inaccurate, because clinical assessment often underestimates the

temporal persistence of AF/AF burden compared with long-term electrocardiogram (ECG) monitoring.[11-13] Second, although the AF patterns have been associated with adverse outcomes (eg, heart failure [HF], stroke, and death), there remains uncertainty regarding their independent role of these clinical patterns to predict response to therapy (eg, antiarrhythmic drugs or catheter ablation).[13-17]

1.2. Classification on the basis of pathophysiological pattern of AF

The likelihood of developing AF varies across physiological and pathological states. Despite similar clinical patterns the mechanisms underpinning AF vary substantially between patients. Within this context AF may be considered "primary" if the AF represents an established pathophysiological process or "secondary" if caused by a self-limited or acutely reversible precipitant (Figs. 2 and 3A).[18] "Primary AF" should not be considered analogous to the antiquated term, "lone AF," which previously defined AF without known cause.[19] Common causes of secondary AF include surgery, sepsis, acute myocardial infarction (MI), thyrotoxicosis, or acute pulmonary disease. Secondary AF can be further dichotomized on the basis of the underlying cardiac substrate and risk for AF recurrence into "reversible" or "provoked" AF.[20] Specifically, "reversible AF" defines AF that occurs solely secondary to an acute illness, with little to no abnormal underlying substrate and therefore limited future risk of AF. In contrast, "provoked AF" represents AF that is unmasked by the acute illness, occurring in patients with significant abnormal underlying substrate, and therefore ongoing risk for AF recurrence (Fig. 3, B and C). Examples of the former category include patients with hyperthyroidism or alcohol intoxication ("holiday heart") in the absence of previous heart disease or risk factors, and the latter would include patients developing AF after mitral valve surgery or in the context of a chronic obstructive pulmonary disease (COPD) exacerbation. These concepts are explored in greater depth in section 8.3.6.

1.3. Valvular and nonvalvular AF

The term, "nonvalvular AF" (NVAF) dates back to the late 1970s and was used interchangeably with nonrheumatic AF. This early distinction was on the basis of the observation of the high risk of stroke/systemic embolism associated with severe mitral stenosis. More recently this distinction was used to define candidacy for participation in the landmark phase III trials in which non-vitamin K direct-acting oral anticoagulants (DOACs) were compared with vitamin K antagonists (VKAs) for stroke prevention in patients with NVAF.[21-25] Although previous iterations of the CCS AF guidelines have considered rheumatic mitral stenosis, mitral valve repair, mechanical heart valves, and bioprosthetic heart valves to constitute valvular heart disease, the definition of "valvular AF" has continued to evolve on the basis of emerging evidence.[6,26-28,884] The current definition of "valvular AF" is limited to AF in the presence of any mechanical heart valve, or in the presence of moderate to severe mitral stenosis (rheumatic or nonrheumatic).

2. Epidemiology

2.1. Incidence and prevalence

AF is the most common sustained arrhythmia encountered in clinical practice.[29] Current evidence suggests that the prevalence of AF is 1%-2% in the general population, and increases significantly with age (< 1.0% up to 50 years of age, to 4% at 65 years, and 12% of those 80 years of age or older).[29,30] Although the incidence has been relatively stable over time (approximately 28 per 1000 person-years), the overall prevalence of AF is increasing because of changing population demographics (eg, from 41 cases per 1000 in 1993 to 85 cases per 1000 in 2007).[29,31]

However, the true prevalence of AF is likely to be substantially higher than 1-2%, as these historical estimates were derived from populations with AF diagnosed using ECG, and did not routinely account for patients with paroxysmal AF (which is estimated to be approximately two-thirds of the AF population) or patients with silent AF.[32-35] When factoring in patients with paroxysmal and silent AF, the prevalence of AF increases from 500,000 to nearly 1 million Canadians.[36,37]

2.2. Morbidity and mortality

Although rarely acutely life-threatening, AF is associated with significant impairments in functional capacity and health-related quality of life (HRQOL), as well as with an increased morbidity and mortality. These impairments have been noted across multiple HRQOL domains, with a magnitude comparable or worse than that observed in patients with HF or who are on long-term hemodialysis.[38-42] Even in the absence of perceived symptoms, AF patients objectively experience reduced global life satisfaction.[38]

AF is independently associated with a 1.5- to 4-fold increased risk of mortality, which is predominantly due to increased risk of thromboembolic events and ventricular dysfunction.[31,40,43-46] Nonanticoagulated patients with AF have a 3- to 5-fold increased risk of stroke, which are generally more severe (greater resource utilization, long-term disability, and mortality) and more recurrent than strokes unrelated to AF.[43,47-50] To date, the only therapeutic intervention that has been consistently and definitively shown to improve survival in the AF population is the use of oral anticoagulation (OAC; see section 8).[51,52] Strategies targeting modifiable cardiovascular risk factors and relevant comorbid conditions offer potential opportunities to further improve survival (see sections 3 and 6).

2.3. Health care resource utilization

The economic burden of AF care is substantial. A significant proportion of AF health care expenses are attributed to the direct costs associated with hospitalization and the provision of acute care.[29,53-59] In Canada, AF resulted in 8815 same-day procedures, 76,964 ED visits, and 64,214 acute care admissions (25,892 with AF as the principal diagnosis and

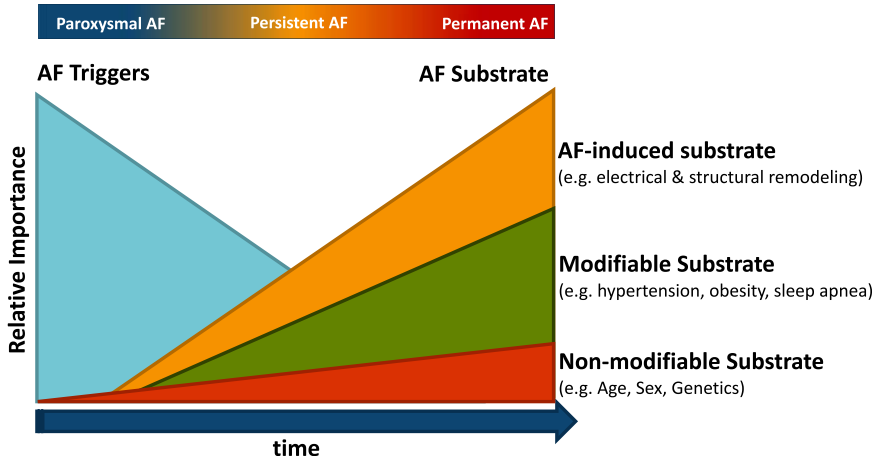


Figure 2. A conceptual model of the life cycle of atrial fibrillation (AF). Early in its course AF is a disease of focal triggers that can be genetically determined. As patients grow older the contribution of abnormal substrate predominates, including nonmodifiable substrate related to age, sex, and genetically determined factors, modifiable substrate related to reversible risk factors (eg, hypertension), as well as substrate induced by the AF episodes themselves. In this model, control of the arrhythmia and therapies directed at cardiovascular risk reduction are complementary for control of the arrhythmia.

38,222 with AF as a comorbid diagnosis) in the 2007-2008 fiscal year. The annual direct cost of AF care adjusted to 2020 Canadian dollars (CAD$) was $956 million: $66 million for ED visits with AF as the principal diagnosis and $20 million with comorbid AF; $204 million for hospitalization with AF as the principal diagnosis and $634 million with comorbid AF; and $32 million for AF-related day procedures.[58] On a per-patient basis, the excess annual direct cost of AF has been estimated to be $16,944-$19,529 (adjusted 2020 US dollars).[55,56] In addition to these direct costs, the annual indirect costs (eg, days of work missed because of illness) have been estimated to be $3082 higher for AF patients compared with those without AF.[57]

It is important to recognize that the cost of care is not uniform across the spectrum of AF. Specifically, the annual inpatient and outpatient direct costs are more than twice as high for patients with "primary AF" compared with patients with "secondary AF" (see section 1.2).[57]

3. Pathophysiology and Risk Factors

AF is a complex and multifaceted condition ranging from an isolated electrophysiological disorder or, more commonly, a manifestation or consequence of other cardiac and noncardiac pathologies (Table 1, Fig. 2).[19] AF generally results from a combination of focal ectopic activity and reentry.[29,60] Ectopic atrial foci arise from perturbations that cause cells to spontaneously depolarize, either secondary to enhanced automaticity or, more frequently, to triggered activity from afterdepolarizations. Discrete abnormalities in Ca^{2+} handling have been identified as centrally involved in afterdepolarization generation in paroxysmal and persistent AF, as well as postoperative AF (POAF).[61,62] There is emerging evidence that inflammatory signalling plays a key role in promoting afterdepolarization generation, as well as other components of AF pathophysiology.[63] These repetitive rapid discharges predominantly originate from the pulmonary veins (PVs), which are a vulnerable region for triggered activity and micro reentry due to the shorter action potential duration, lower resting membrane potentials, and nonuniform myofibril arrangement.[64] When triggered, AF can be maintained by sustained rapid firing of focal impulses that disorganize into fibrillatory waves at their periphery or, in most cases, AF perpetuating reentry. Reentry requires specific conditions for initiation and maintenance. Although reentry is not sustained in the normal atrium, the presence of a vulnerable substrate can perpetuate AF through electrical heterogeneity (eg, regional differences in resting membrane potentials, refractory periods, action potential duration, and conduction velocities). In addition, conduction abnormalities can promote reentrant activity and stabilize reentrant circuits by creating functional barriers that allow recovery of tissue excitability. Structural abnormalities such as atrial fibrosis promote reentry through localized conduction slowing and structural conduction barriers, with atrial chamber dilatation promoting reentry through maintenance of the balance between rotor formation and rotor annihilation.

Recently, there has been a renewed focus on the contribution of modifiable cardiovascular risk factors to the causation of AF, because an improved understanding of this relationship is key to providing effective personalized primary and secondary prevention measures.[29,65,66] Although the precise mechanistic links between risk factors and AF occurrence remain somewhat uncertain, information available from the literature provides many potential insights.[29] 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 and autonomic remodelling. Tobacco use promotes AF through a combination of the direct effects of nicotine on the atrium (eg,

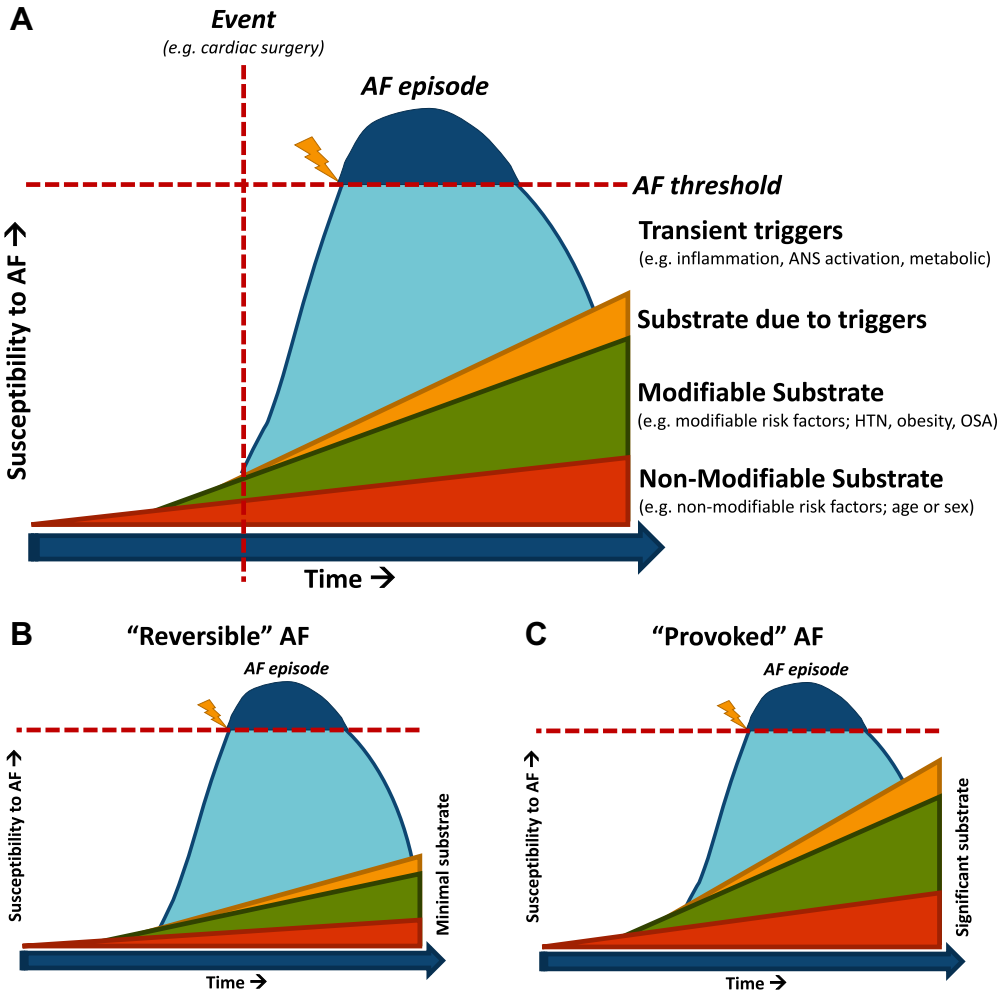


Figure 3. Secondary atrial fibrillation (AF). (**A**) Components of AF susceptibility include the baseline modifiable substrate, nonmodifiable substrate, and substrate induced by AF triggers (as outlined in Fig. 2), as well as new substrate/transient triggers induced by the reversible event (eg, cardiac surgery). A reversible event might only transiently induce substrate or lead to new permanent substrate. In this model, if the sum of the substrate allows the trigger to reach threshold then an AF event might occur. Whether or not the AF recurs is a function of the baseline substrate and any new permanent substrate added by the trigger event. (**B**) "Reversible AF" defines AF that occurs solely secondary to an acute illness, with little to no abnormal underlying substrate and, therefore, limited future risk of AF. (**C**) In contrast, "provoked AF" represents AF that is unmasked by the acute illness, occurring in patients with significant abnormal underlying substrate and, therefore, ongoing risk for AF recurrence. ANS, autonomic nervous system; HTN, hypertension; OSA, obstructive sleep apnea.

altered atrial conduction and refractoriness) along with 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 (changes in atrial dimensions and interstitial fibrosis) and electrophysiological remodelling (conduction slowing and shortening of the effective refractory period), autonomic dysfunction, and inflammation. Obstructive sleep apnea (OSA) promotes AF acutely through strongly negative intrathoracic pressures leading to increased venous return (AF-promoting left atrial [LA] volume loading) and hypoxia-induced pulmonary vasoconstriction. Chronic OSA induces electrical and structural remodelling of the atria, autonomic dysregulation, oxidative stress, and inflammation. Regular exercise protects against AF by combating risk factors like obesity and metabolic syndrome but sustained intense exercise might promote AF occurrence (see section 11.3).

The relationship between key risk factors and AF are outlined in Table 2.

4. Clinical Evaluation

The purpose of the initial evaluation of a patient with AF is to establish the magnitude and severity of symptoms attributable to AF, identify the underlying etiology and precipitants

of AF, establish prognosis, and develop a therapeutic strategy for symptom relief and morbidity mitigation (Fig. 4).

4.1. AF history

A comprehensive AF history should include the date of first symptomatic attack as well as the date of first ECG documentation. For patients in AF at the time of assessment, the timing of onset for the current AF episode should be determined.

The duration and frequency of episodes should be used to establish the predominant pattern of AF (paroxysmal vs persistent; see section 1). Of note, in some cases the symptom evaluation might be insufficient for the determination of AF pattern and additional monitoring might be required.[12,13]

The presence and nature of AF-related symptoms, their severity, and their effect on QOL should be determined (see section 4.3). Symptoms might be absent or manifest as palpitations, dyspnea, dizziness, weakness, fatigue, or chest pain.[67] In addition, it is important to elicit any history of regular palpitations because any supraventricular tachycardia (SVT) can lead to the development of AF, and ablation of the SVT might eliminate or substantially reduce the likelihood of recurrent AF (see section 11.7).[68,69] Symptoms at the termination of AF episodes, such as presyncope or syncope, should be determined because significant sinus pauses might limit the use of rate- or rhythm-controlling medications and might require the use of permanent pacing or prompt early ablation.

Table 1. Risk markers and comorbid conditions associated with AF

Established risk factors
- Advancing age
- Male sex
- Hypertension
- HF with reduced ejection fraction
- Valvular heart disease
- Overt thyroid disease
- Obstructive sleep apnea
- Obesity
- Excessive alcohol intake
- Congenital heart disease (eg, early repair of atrial septal defect)

Emerging risk factors
- Prehypertension and increased pulse pressure
- Chronic obstructive pulmonary disease
- HF with preserved ejection fraction
- Subclinical hyperthyroidism
- Coronary artery disease
- Morphometric (increased height, increased birth weight)

Potential risk factors
- Familial/genetic factors
- Tobacco use
- Left atrial dilatation
- LV hypertrophy
- Inflammation
- Diabetes
- Pericardial fat
- Subclinical atherosclerosis
- Chronic kidney disease
- Excessive endurance exercise
- Electrocardiographic (atrial conduction delay, PR interval prolongation)

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

Precipitating factors ("triggers for AF episodes"), reversible causes, and coexisting cardiovascular risk conditions should be determined. These include modifiable cardiovascular risk factors and comorbid conditions, which if treated, might reduce or eliminate AF recurrence and improve the overall outcome of the patient, independent of AF (see section 6).[32,70]

Past evaluations and treatments should be explored, including a record of all previous pharmacologic and nonpharmacologic AF interventions (eg, cardioversion and catheter ablation).

AF-related health care utilization should be documented, including a record of emergency department (ED) visits, hospital admissions, and cardioversions.

Risk factors for stroke (see section 8.1) and bleeding (see section 8.5.1) should be elicited.

The precise frequency, duration, and intensity of sports participation (current and previous) needs to be assessed carefully for all AF patients (see section 11.3).

In addition, the evaluation should include: a comprehensive review of all prescription, over the counter, and nonprescription medications; a social history with a focus on alcohol, tobacco, and recreational drug intake; and a family history of cardiac dysrhythmia or relevant risk conditions.

4.2. Investigations

In addition to a comprehensive physical examination several routine investigations are warranted for all patients who present with AF (Fig. 4):

- AF must be electrocardiographically documented, because the perception of "irregularly irregular" palpitations might be the result of a variety of arrhythmias, including atrial tachycardia, atrial flutter (AFL), premature atrial and/or ventricular contractions, or nonarrhythmic causes.
- An ECG is useful in AF and sinus rhythm to identify LA enlargement, left ventricular (LV) hypertrophy (LVH), preexcitation, conduction disease, or evidence of MI.
- A transthoracic echocardiogram should also be performed in all patients to identify LVH or systolic dysfunction, significant valvular or congenital heart disease (CHD), LA enlargement, and rarely, complications such as intracardiac thrombus. LA dimension provides important information about the likelihood of AF recurrence or progression to persistent AF, which can help guide therapeutic decision-making.
- Transesophageal echocardiography (TEE) might be indicated for more detailed evaluation of valvular or CHD, or for the exclusion of LA appendage (LAA) thrombus.
- Routine blood biochemistry should be obtained at the time of the initial AF evaluation. A complete blood count and coagulation studies will inform decisions about the use of antithrombotic medications. Serum electrolytes and creatinine should be measured, and renal function determined to guide drug dosing (eg, creatinine clearance [CrCl], see section 8.3.1). Liver

Table 2. The relationship between AF and modifiable and nonmodifiable risk factors

Risk factor	Role in AF	Mechanism
Hypertension	Hypertension is a strong and independent predictor of incident AF[30] AF incidence is linearly related to BP, with increased risk noted even in the prehypertensive range (adjusted HR, 1.3 for systolic BP 130-139 mm Hg vs < 120 mm Hg)[119,834] Increased pulse pressure has been associated with an increased AF risk (adjusted HR, 1.25 per 20 mm Hg increase)[119]	Hypertension might induce AF through: • Neurohormonal activation (sympathetic nervous system and the renin-angiotensin-aldosterone system) • Structural remodelling (atrial fibrosis) • Electrical remodelling (conduction disturbances)
Diabetes	Diabetes has been associated with approximately a 1.5 times increased risk of AF[835,836] AF risk is independently associated with a longer duration of treated diabetes (3% increased risk for each additional year of diabetes) and with worse glycemic control (13% increased risk with each 1% increase in HbA1c; and 33% increased risk with each 1 mmol/L increase in fasting glucose)[836-840] Coexistence of AF and diabetes portends a worsened prognosis, increasing all-cause mortality, cardiovascular death, and HF[841]	Diabetes might induce AF through: • Structural remodelling (atrial fibrosis) • Electrical remodelling (conduction slowing) • Autonomic remodelling
Tobacco	Tobacco use has been associated with increased risk[30,842-844] • Active smokers have a higher risk than former smokers • Risk is linked to cumulative exposure (greatest risk in the highest tertile, > 675 cigarette-years) Continued tobacco use is associated with worse outcomes after catheter ablation[845] Pooled analyses have not established a relationship between smokeless tobacco products and AF, and there are limited data regarding electronic cigarettes or secondhand smoke[846]	Tobacco use might induce AF through: • Electrical remodelling (altered atrial conduction and refractoriness [direct effects of nicotine]) • Structural remodelling (atrial fibrosis) • Inflammation and oxidative stress
Alcohol	Acute paroxysms of AF have been reported after binge consumption (> 5 standard drinks on a single occasion; "holiday heart" syndrome)[847-849] Heavy habitual consumption has been associated with risk of incident AF in a dose-dependent relationship (8% increase in incident AF with each additional drink per day)[847,849,850] Patients with established AF who continue to consume alcohol have higher rates of progression (eg, paroxysmal to persistent AF), and experience more AF recurrences after cardioversion or ablation[851]	Alcohol use might induce AF through: • Neurohormonal activation (increased sympathetic activity, impairment of vagal tone) • Electrical remodelling (increase in inter- and intra-atrial conduction time, shortening of atrial effective refractory period) • Structural remodelling (atrial fibrosis)
Physical inactivity	Habitual moderate-intensity exercise is inversely associated with risk of incident AF, with a graded inverse relationship shown between increasing fitness and AF (7% lower risk of incident AF with every additional metabolic equivalent achieved on exercise testing)[711,714,716]	Exercise might protect against AF through: • Potentiation of parasympathetic tone • Improved cardiovascular risk factor profile (weight loss; improved BP, glucose, and lipids) • Improved endothelial function
Intense exercise	Intense exercise practices have been associated with an increased incidence of AF, and a greater rate of AF recurrence after cardioversion or catheter ablation[714,721] In this athletic population, AF paroxysms are more than 3 times as likely to occur in vagal contexts (postprandial, sleep, at rest) compared with healthy controls[852]	Vigorous activity might induce AF through: • Acute catecholamine fluxes • Parasympathetic enhancement (baroreflex enhancement and acetylcholine sensitization) • Long-term structural remodelling (atrial dilatation with associated atrial fibrosis) • Electrical remodelling (heterogenous refractoriness)
Obesity	Compared with people with a normal BMI (< 25), overweight (25-30) and obese (> 30) individuals are at increased risk for AF development, with a linear relationship between BMI and AF incidence (AF incidence increasing 3%-7% for each unit increase in BMI)[120,853] Weight gain has been associated with AF risk independent of BMI (34% increased AF with a 16%-35% weight gain, and 61% increased AF with > 35% weight gain)[121] Coexistence of AF and obesity confers worsened prognosis, increasing all-cause mortality and thromboembolism[854]	Obesity might induce AF through: • Structural remodelling (atrial dilatation and fibrosis) • Electrical remodelling (conduction slowing) • Autonomic dysfunction • Inflammation and epicardial fat infiltration • Left ventricular diastolic dysfunction
Sleep apnea	OSA is highly prevalent among those with AF, with a rate that is double that of the general population[855] Patients with moderate to severe OSA have a three- to sixfold increased risk of developing AF[856] CPAP reduces the risk of AF, supporting a causal role of OSA in AF pathogenesis[125,855,857,858] Coexistence of AF and OSA confers worsened prognosis, with higher recurrence after cardioversion and ablation[125,857,858]	Acute OSA might induce AF through: • Left atrial volume loading • Hypoxia-induced pulmonary vasoconstriction Long-term OSA might induce AF through: • Structural remodelling (atrial dilatation and fibrosis) • Electrical remodelling (conduction anisotropy) • Autonomic dysregulation • Oxidative stress and inflammation
Dyslipidemia	The association between dyslipidemia and incident AF is unclear[859,860]	Unclear
Age	Age is one the most powerful predictors of incident AF The lifetime risk of developing AF for individuals 40-55 years of age has been estimated to be 22%-26%[36,861]	Aging might induce AF through: • Structural remodelling • Electrical remodelling

Table 2. Continued.

Risk factor	Role in AF	Mechanism
Sex	Sex is one of most powerful predictors of incident AF After adjustment, male sex is associated with a 1.5-fold risk of developing AF[31-34,36,861]	Male sex might predispose to AF through: • Electrical and structural differences (greater atrial dimensions)
Valve disease	Valvular heart disease has been associated with a 1.8- to 3.4-fold increased risk for AF[30] AF risk is greatest for stenotic left-sided valvular lesions, with the highest risk among those with severe stenosis[862] AF risk is increased with complexity of rheumatic heart disease (15% isolated MR, 30% isolated MS, 50% mixed MR and MS, to 70% with mixed mitral and tricuspid valve disease)[863]	Valvular disease might induce AF through: • Structural remodelling
Cardiomyopathy	AF increases with severity of HF symptomatology (< 5% in NYHA class I, 10%-25% in NYHA class II-III, and > 50% in NYHA class IV)[864] Although AF prevalence increases with worsening systolic dysfunction, AF is more common in patients with HFpEF compared with those with HFrEF[864-866] AF prevalence varies depending on the cause of cardiopathy[300]: • Prevalence > 20% with nonischemic, ischemic, and restrictive cardiomyopathies • Prevalence 15%-20% with amyloid, hypertrophic, Keshan, and LV noncompaction • Prevalence < 15% with Takotsubo, Chagas, and arrhythmogenic RV cardiomyopathies	HF might induce AF through: • Structural remodelling • Electrical remodelling (abnormal Ca^{2+}-handling and increased triggered activity) • Neurohormonal activation (increased sympathetic activity, impairment of vagal tone)
Thyroid dysfunction	AF increases with decreasing levels of thyroid stimulating hormone[867,868] • RR, 1.1 with high-normal euthyroidism • RR, 1.2-4 with subclinical hyperthyroidism • RR, 3-6 with overt hyperthyroidism	Hyperthyroidism might induce AF through: • Neurohormonal activation (increased sympathetic tone) • Structural remodelling • Electrical remodelling • Promotion of PV automaticity/triggered activity (thyroid hormone)
Genetic factors	AF is more common in those with a family history of AF in a first-degree relative[869] Monogenic and polygenic inheritance has been described, with multiple susceptibility signals identified at the chromosome 4q25 locus[870-875]	Genetic causes of AF typically result from cardiac ion channel alterations (promoting reentry or ectopic activity), alterations in cellular coupling, or increasing susceptibility to AF

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CPAP, continuous positive airway pressure; HbA1c, hemoglobin A1c; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; NYHA, New York Heart Association; OSA, obstructive sleep apnea; PV, pulmonary vein; RR, relative risk; RV, right ventricular.

function should be assessed before the prescription of potentially hepatotoxic medications, such as amiodarone. Lipid profile, hemoglobin A1c, and fasting blood sugar are recommended in most patients as part of a comprehensive cardiovascular risk assessment. Thyroid function should be assessed because hyperthyroidism remains an important treatable cause of AF.[71] In select cases N-terminal pro-B-type natriuretic peptide (NT pro-BNP) and inflammatory biomarkers might aid in patient management.

- Ambulatory ECG monitoring might aid in the documentation of AF, the identification of other arrhythmias, the assessment of ventricular rate control, and to correlate patient symptoms with heart rhythm or heart rate. In selected patients long-term monitoring using external loop recorders, wearable patch monitors, and cardiac implantable electronic devices (CIEDs) might be useful.[12,13,72,73] In addition, consumer-facing devices (eg, handheld or wearable ECG devices) may be used to document heart rate or cardiac rhythm, potentially providing symptom-rhythm correlation and a measure of AF burden.
- Sleep study or overnight oximetry should be performed in most patients because typical symptoms are less prevalent and screening questionnaires are less accurate in the AF population.
- Exercise testing can be used to supplement ambulatory monitoring in certain patients with exercise-related symptoms and might be helpful to exclude significant ischemia before class Ic antiarrhythmic drug prescription.
- Invasive electrophysiological studies may be considered in patients who are candidates for catheter ablation of AF or with suspected SVT, which could be triggering AF (see sections 9.4 and 11.7).

4.3. Evaluation of the effect of AF on well-being, symptoms, and QOL

Traditional rhythm-based outcome parameters, such as freedom from AF recurrence, are insufficient to evaluate the clinical effect of AF.[74,75] Although rarely life-threatening, AF causes a greater degree of impairment of QOL than is generally appreciated. AF can cause moderate and sometimes severe distress, and substantially alter

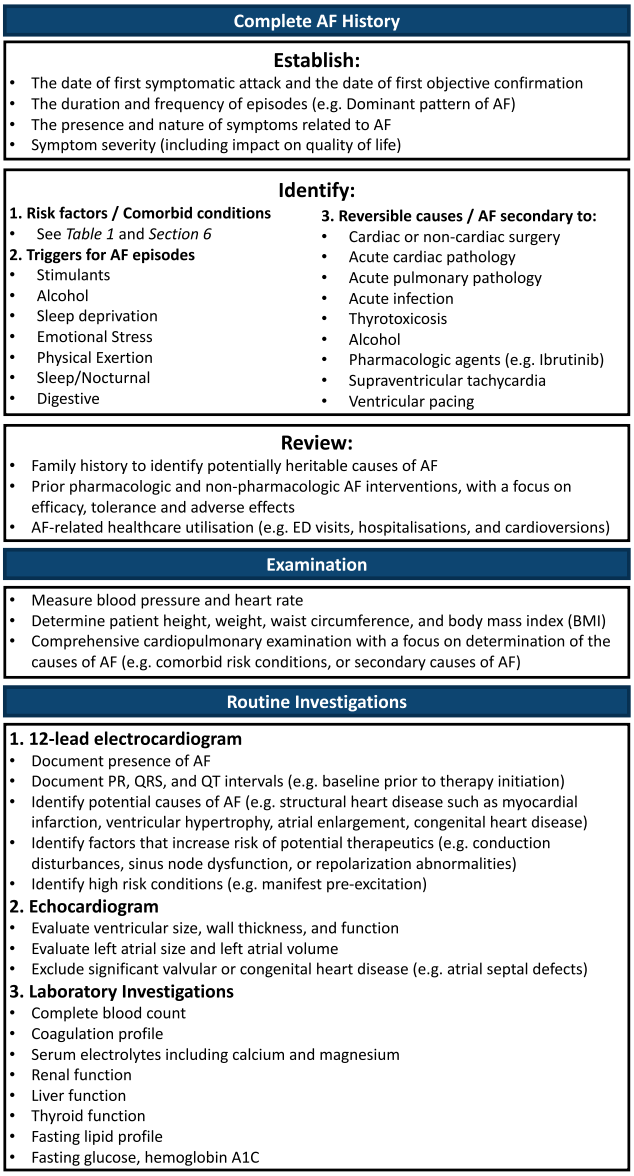


Figure 4. Evaluation of the atrial fibrillation (AF) patient. ED, emergency department.

everyday functioning.[76] Impaired QOL is primarily the result of AF-associated symptoms but can be influenced by AF therapies, illness perceptions, and patient factors such as anxiety or depression.[74,75] A consistent and standardized assessment of the effect of AF on HRQOL is recommended to evaluate the clinical effect of AF and quantitatively assess the changes in well-being resulting from therapeutic interventions. Specifically, multidimensional HRQOL instruments can be used to determine if an intervention had a beneficial effect across all domains concurrently or if a benefit in one domain (eg, physical health) was offset by a negative effect in another (eg, mental health). As such, the assessment of patient-reported outcomes with validated multidimensional instruments offers a relevant and complementary means to evaluate the consequences of AF and the effect of therapeutic interventions on patients' functional status and health.

To date, a large number of instruments have been used to evaluate HRQOL (Table 3). In broad terms, these instruments can be dichotomized into generic and disease-specific questionnaires. Generic instruments, such as the **E**uro**Q**ol-**5D** (EQ-5D) and **S**hort **F**orm-**36** Health Survey (SF-36), are used to assess valuations of health and functioning across a predefined set of health-related domains. Generic instruments have the advantages of extensive

Table 3. Instruments for the assessment of QOL and symptoms in patients with AF

Instrument	Type	Domains	Administration	Comments
SF-36[876]	Generic QOL	Vitality Physical functioning Bodily pain General health perceptions Physical role functioning Emotional role functioning Social role functioning Mental health	Patient	Extensive validation Widespread clinical use Good for comparing between diseases Can be used to evaluate cost-effectiveness Insensitive AF
EQ-5D[877]	Generic QOL	Mobility Self care Usual activities Pain/discomfort Anxiety/depression	Patient	
AFEQT[878]	Specific QOL	Symptoms Daily activities Treatment concerns Treatment satisfaction	Patient	Good reliability Good validity Fair responsiveness (sensitive to change)
AFQOL[879]	Specific QOL	Physical Psychological Sexual activity	Patient	Poor reliability Good validity Poor responsiveness
AFSS[880]	Symptom	Symptom frequency, duration, and severity	Patient	
AFS/B[881]	Symptom	Symptom severity and burden	Patient and caregiver	
EHRA[882]	Classification	Impact of AF on ability to complete daily activities	Caregiver	Simple classification
CCS SAF[77]	Classification	Effect of AF on ability to complete daily activities	Caregiver	Detailed classification Effect of symptoms on QOL

Reliability refers to the extent to which the instrument is free of measurement error (eg, internal consistency, test-retest reliability, and measurement error); validity refers to the extent to which the instrument measures the construct it purports to measure (eg, content, construct, and criterion validity); responsiveness refers to extent to which the measure can detect change over time.[883]

AF, atrial fibrillation; AFEQT, **A**trial **F**ibrillation **E**ffect on **Q**uali**T**y-of-Life questionnaire; AFQOL, **A**trial **F**ibrillation **Q**uality **o**f **L**ife; AFS/B, **A**trial **F**ibrillation **S**ymptom Severity and **B**urden; AFSS, **A**trial **F**ibrillation **S**everity **S**cale; CCS SAF, **C**anadian **C**ardiovascular **S**ociety **S**ymptoms of **A**trial **F**ibrillation; EHRA, **E**uropean **H**eart **R**hythm **A**ssociation; EQ-5D, EuroQol-5D; QOL, quality of life; SAF, **S**ymptoms of **A**trial **F**ibrillation; SF-36, **S**hort **F**orm-**36** Health Survey.

validation across a wide range of populations and health conditions but lack precision for assessing the effect of AF. Disease-specific instruments include symptom-specific scales (eg, the University of Toronto **A**trial **F**ibrillation **S**everity **S**cale [AFSS]), and AF-specific QOL symptom scales (eg, the **A**trial **F**ibrillation **E**ffect on **Q**uali**t**y-of-Life [AFEQT] questionnaire). These instruments do not provide for the ability to compare between disease states (eg, the HRQOL of AF patients relative to HF patients) but are more sensitive to changes in AF patients' health status (spontaneous or as a result of intervention).

The **S**everity of **A**trial **F**ibrillation (SAF; Table 4) is a semiquantitative scale ranging from 0 (no effect of AF or its treatment on overall QOL and patient functioning) to 4 (resulting in a severe impairment of functioning and overall QOL).[77] A multicentre Canadian study has shown that the results of this scale correlate well with previously validated symptom scores and generic measures of QOL and that it can be easily applied by a variety of caregivers at the bedside.[67,78]

Equally important is consideration of advanced age, frailty, cognitive impairment, and mood disorders. Identifying these factors might substantially affect anticipated QOL benefits of various AF therapies and can also help to identify potential challenges in adherence to therapy and self-care (see section 7.2).[79,80]

RECOMMENDATION

1. We recommend that the initial evaluation of a patient with newly diagnosed AF include: a complete history and physical examination, a 12-lead ECG, a transthoracic echocardiogram, and basic laboratory investigations as outlined in Figure 4 (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on a comprehensive evaluation of patients with AF and a lower value on initial costs to the health care system.

2. We recommend that reversible and secondary causes of AF should be identified and treated (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on evidence supporting a reduction in AF recurrence with treatment of the underlying condition or reversible precipitating event, such as infection, surgery, or thyroid disease.

Practical tip. Elimination of the precipitating event does not completely eliminate the possibility of AF recurrence, meaning patients with secondary AF should be regularly screened for arrhythmia recurrence (see section 11.5.3).

3. We suggest that all individuals with AF should be assessed for their sports and exercise history, with special attention to frequency, duration, intensity, and type of sport (Weak Recommendation; Low-Quality Evidence).
4. We recommend that patient-reported AF-related symptoms and QOL be assessed with validated instruments as part of the longitudinal management of patients with AF (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the recognition that symptom control has a powerful influence on disability and health care resource utilization. The assessment of patient-reported outcomes with validated multidimensional instruments offers a relevant and complementary means to evaluate the effect of therapeutic interventions.

Practical tip. The caregiver-administered CCS SAF scale can be used to assess functional status and the symptomatic effect of AF, and the self-administered disease-specific AFEQT questionnaire can be used to assess the effect of AF on QOL. Consideration can also be made to assess QOL using generic instruments such as the EQ-5D questionnaire.

5. We recommend that patients with AF should be assessed for multimorbidity, frailty, cognitive impairment, dementia, and depression (Strong Recommendation; Low-Quality Evidence).

Practical tip. In this population a structured, integrated, multidisciplinary, patient-focused approach to care can be particularly beneficial because these factors might have an effect on treatment decisions and might improve adherence to therapy and self-care.

Table 4. The CCS SAF scale for the assessment of quality of life[77]

CCS SAF score	Effect on quality of life
Class 0	Asymptomatic with respect to AF
Class 1	Symptoms attributable to AF have minimal effect on patient's general quality of life: • minimal and/or infrequent symptoms, or • single episode of AF without syncope or heart failure
Class 2	Symptoms attributable to AF have a minor effect on patient's general quality of life: • mild awareness of symptoms in patients with persistent/permanent AF, or • rare episodes (eg, less than a few per year) in patients with paroxysmal or intermittent AF
Class 3	Symptoms attributable to AF have a moderate effect on patient's general quality of life: • moderate awareness of symptoms on most days in patients with persistent/permanent AF, or • more common episodes (eg, more than every few months) or more severe symptoms, or both, in patients with paroxysmal or intermittent AF
Class 4	Symptoms attributable to AF have a severe effect on patient's general quality of life: • very unpleasant symptoms in patients with persistent/paroxysmal AF, and/or • frequent and highly symptomatic episodes in patients with paroxysmal or intermittent AF, and/or • syncope thought to be due to AF, and/or • congestive heart failure secondary to AF

CCS-SAF, **C**anadian **C**ardiovascular **S**ociety **S**everity of **A**trial **F**ibrillation Scale; AF, atrial fibrillation.

5. Screening and Opportunistic AF Detection

5.1. Opportunistic AF detection in the general population

AF screening initiatives have emerged with the availability of safe and effective stroke prevention therapy, well defined stroke risk schemes, and new technologies that have simplified AF monitoring. Because a large number of patients with AF might be asymptomatic, screening might provide an opportunity for AF detection with early initiation of stroke prevention therapy to reduce the risk of AF-related complications.

The effects of screening (eg, opportunistic case finding or systematic screening) has been examined in numerous studies in various populations (eg, general population or high-risk subgroups) and settings (eg, community, outpatient clinics, or inpatient).[81,82] Taken together, the rate of new AF detection was 0.9% (95% confidence interval [CI], 0.7-1.1) across 23 prospective cross-sectional studies, yielding a number needed to screen (NNS) of 111 individuals to detect 1 patient with AF.[81] However, the prevalence of AF varies as a function of age and sex. When age and sex adjustment was performed the AF detection rate after a single time point screen was noted to be 1.44% (95% CI, 1.13-1.82) for those 65 years of age or older, but 0.41% (95% CI, 0.31-0.53) for those younger than 65 years in a multicountry, patient level meta-analysis of 141,220 individuals. This yields a NNS of 69 to identify 1 new AF case for patients 65 years of age or older.[82] The choice of screening methodology, device, geographical region, or setting did not influence the AF detection rate.

There is some debate regarding the utility of systematic screening compared with opportunistic case-finding. A comparison of the 2 approaches was addressed in 2 RCTs performed in a United Kingdom primary care setting.[83,84] In the first study 3001 patients older than 65 years of age were randomized to single time point nurse-led systematic screening vs prompted opportunistic case finding.[83] Despite substantially more patients who underwent assessment in the systematic screening arm (73% vs 29%) there was no significant difference in the identification of new AF cases (systematic 0.8% vs opportunistic 0.5%; odds ratio [OR], 1.72; 95% CI, 0.68-4.37).[83] The **S**creening for **AF** in the **E**lderly (SAFE) study was larger in scale (50 primary care practices, 14,802 patients), including 2 interventional groups (single time point systematic screening and opportunistic case finding) as well as a usual care control group. The SAFE study showed that both interventional groups identified significantly more new AF cases compared with usual care (OR, 1.6; 95% CI, 1.1-2.3; $P = 0.009$);

Table 5. AF Screening

Technique	Device	Method	Advantage/disadvantage	Accuracy
Pulse-based	Pulse palpation	Pulse irregularity detected using manual palpation	Time efficient High sensitivity Cost effective Easy to apply across health care settings Easy to perform at home	Sensitivity 84%-97% Specificity 69%-75%
	Blood pressure monitor (eg, M6 Comfort, Blood Pressure Analyzer, or WatchBP)	Algorithm on the basis of pulse irregularity	Time efficient High sensitivity Easy to apply across health care settings Easy to perform at home	Sensitivity 92-100% Specificity 86-97%
	Plethysmography (eg, finger probe, Apple Watch, smartphone photoplethysmograph app)	Algorithm on the basis of pulse irregularity	Capable of intermittent (Smartphone Camera) and extended monitoring (watch-based) Easy to perform at home Potentially costly	Sensitivity 92-96% Specificity 92-98% (lower in continuous watch-based application)
Rhythm-based	Single-lead ECG (eg, Kardia, MyDiagnostick, Zenicor-ECG)	Automated algorithm on the basis of RR irregularity	Capable of intermittent (symptom-based) monitoring ECG can be reviewed by health care professional	Sensitivity 94%-99% Specificity 92%-97%

The blood pressure monitor, M6 Comfort is manufactured by Omron Healthcare (Kyoto, Japan), and the Blood Pressure Analyzer and Watch BP are manufactured by Microlife USA, Inc (Clearwater, FL). The Apple Watch is from Apple Inc (Cupertino, CA). The Kardia is manufactured by AliveCor, Inc (Mountain View, CA), the MyDiagnostick by Applied Biomedical Systems BV (Maastricht, The Netherlands), and the Zenicor-ECG by Zenicor Medical Systems AB (Stockholm, Sweden).

ECG, electrocardiogram.

however, only opportunistic case finding was deemed to be cost-effective.[84]

There is concern that single time point screening offers too finite a window of observation, which is particularly problematic in the context of intermittent AF. This limitation of single time point screening was shown in the STROKESTOP study, in which twice-daily intermittent ambulatory ECG recordings were used over a 2- week period. The authors reported newly diagnosed AF in 3.0% of 75- and 76-year-old subjects, with repeated rhythm assessments leading to a fourfold increase in AF detection over single time point screening (initial single-lead ECG recording [SL-ECG]).[85]

Although effective in AF case-finding, the utility of screening is dependent on population engagement. In the studies outlined above,[81-85] only 50%-75% of eligible patients participated in systematic screening. Alternative screening environments might leverage existing health initiatives (eg, at time of influenza vaccination)[86] or other health care professionals (eg, pharmacy).[87,88]

An economic evaluation of an AF screening program requires consideration of several key factors: (1) participation rate; (2) rate of undiagnosed AF in a targeted population; (3) difference in AF detection between screening and usual care; (4) stroke risk in a targeted population; (5) stroke risk reduction and increase in bleeding risk from OAC; and (6) acceptable threshold for willingness to pay.[89] Intermittent opportunistic case finding was estimated to cost between 10€ and 108€ per patient (depending on the device, calculation method, and intensity of screening), which was lower than that of systematic screening.[81,87,90] A 2-part decision model to evaluate short- and long-term costs and quality-adjusted life years (QALYs) as part of the **P**rogram for the **I**dentification of "**A**ctionable" **AF** (PIAAF) in the pharmacy setting showed an incremental cost per QALY gained of CAD$7480 compared with no screening.[91] When different screening strategies were compared in a Canadian family practice study, screening with pulse check had the lowest expected costs (CAD$202) and screening with (SL-ECG) had the highest expected costs (CAD$222). The no-screening arm resulted in the lowest number of QALYs, whereas pulse check and SL-ECG resulted in the highest expected QALYs.[92]

In a pooled analysis, the sensitivity of pulse palpation, blood pressure (BP) monitors, non-12-lead ECG, and smart phone applications were similar, but specificity was lower with pulse palpation. Because of the simplicity and ease of use, pulse palpation remains the cornerstone for AF detection. Downstream confirmatory testing with a 12-lead ECG should be pursued after pulse palpation, when screening is performed with non-rhythm-based devices (Table 5), or when the diagnosis of AF remains uncertain after rhythm acquisition.[92-94]

Additional studies with robust methodology are needed to identify optimal screening strategies, screening tools, population, and settings with health outcomes for different health care systems. An approach to AF screening is shown in Figure 5.

RECOMMENDATION

6. We recommend that opportunistic screening for AF should be conducted in people 65 years of age and older at the time of medical encounters (Strong Recommendation; Low-Quality Evidence).

Practical tip. Screening can be efficiently and cost-effectively performed using opportunistic pulse checks during routine medical encounters; consideration can also be made to use rhythm-based devices (eg, SL-ECG rhythm device).

7. We recommend downstream confirmatory testing when AF is suspected but not documented, or when the documentation method does not include electrocardiographic rhythm acquisition (Strong Recommendation; Low-Quality Evidence).

Values and preferences. Confirmatory testing for AF is highly dependent on the type of AF. The effectiveness of the various AF screening methods depends on duration of monitoring (eg, single 12-lead ECG vs continuous monitoring). The use of new technologies for screening require validation before implementation.

5.2. Opportunistic AF detection in patients with a CIED

Advances in CIED (pacemaker or defibrillator) technology, which allow for long-term cardiac monitoring, have enabled detection of atrial high-rate episodes (AHREs) in patients with an atrial lead.[50,95,96] Because of the possibility of false positive results, a careful review of the electrograms should be performed.[97] Observational and registry data have shown at least a doubling of thromboembolic risk when AHREs are present compared with their absence.[50,98-101] However, the adjusted stroke rates observed with AHREs appear to be lower than reported among patients with similar risk profiles and clinically apparent AF.[50,99] Although evidence suggests a link between AHREs and elevated stroke risk, many uncertainties exist regarding relevant stroke risk factors, optimal atrial rate cut-off, minimum significant AF burden, and importantly, if OAC reduces AHRE-related stroke (see section 11.1).[50,95,96]

RECOMMENDATION

8. We recommend that AHREs be assessed at the time of CIED (loop recorders, pacemakers, or implanted cardioverter-defibrillators) interrogation (Strong Recommendation; Low-Quality Evidence).

5.3. AF detection after embolic stroke of undetermined source

AF accounts for a substantial proportion of acute ischemic strokes or transient ischemic attacks (TIAs) of known etiology, and might be responsible for a significant amount of strokes of undetermined etiology (embolic stroke of undetermined source [ESUS] or cryptogenic stroke).[102-104] In those with ESUS and no known history of AF, antiplatelet therapy remains the treatment of choice.[105] This was demonstrated in recent RCT, where empiric initiation of rivaroxaban 15mg daily was not superior to aspirin in preventing recurrent

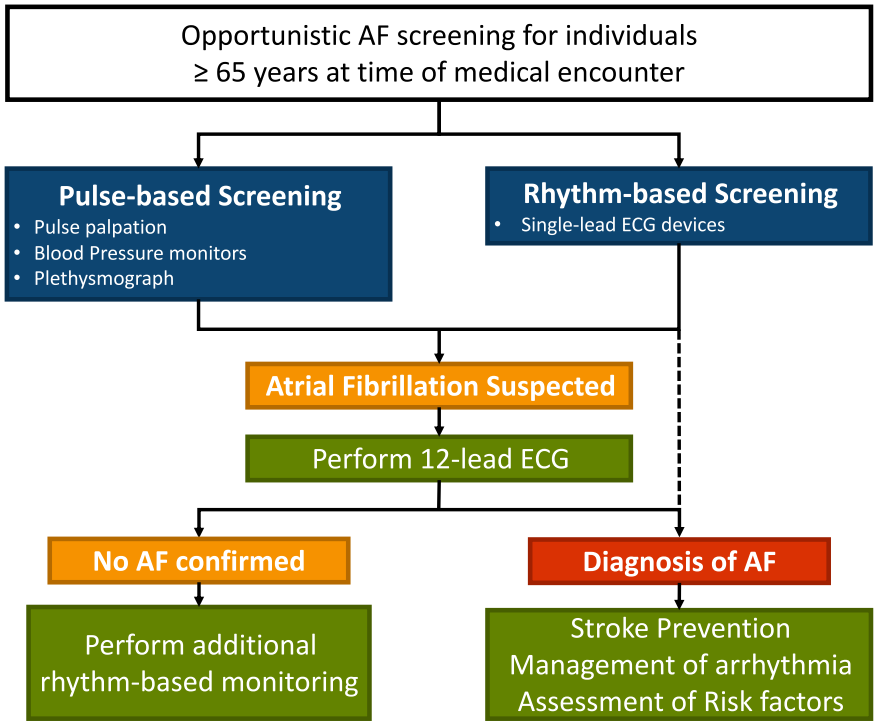


Figure 5. Approach to opportunistic atrial fibrillation (AF) screening. In general, AF screening should be performed in enriched populations, in whom the identification of AF is likely to change management. When screening is pursued pulse-based screening (eg, using manual palpitation) is a reasonable first step, however, electrocardiographic confirmation of AF is required. In contrast, AF might be diagnosed when screening is performed using rhythm-based devices (eg, single-lead electrocardiogram [ECG]).

stroke, and was associated with an almost threefold higher risk of bleeding.[105,106] However, it is known that antiplatelet therapy is inadequate for the treatment of AF-associated strokes (see section 8.2.1).[51,107,108] As such, ESUS patients require extensive AF screening to identify patients who would benefit from OAC for the secondary prevention of AF-associated thromboembolism.[51,107,108]

Detection of AF is related to burden and improves with increasing intensity of monitoring.[109] In a systematic review of inpatient screening, the proportion of stroke patients newly diagnosed with AF on an admission 12-lead ECG was 7.7% (95% CI, 5.0-10.8), with an additional 7.0% (95% CI, 3.9-10.8) diagnosed after inpatient cardiac telemetry, and an additional 4.5% (95% CI, 2.7-6.7) diagnosed after in-hospital Holter monitoring.[110]

Prolonged postdischarge cardiac monitoring strategies (> 24 hours) have been evaluated in 3 RCTs for the purpose of AF detection after stroke.[111] A small United Kingdom study showed that a 7-day event monitoring uncovered new AF in 18% of patients compared with 2% in the control arm ($P < 0.05\%$).[112] 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) showed a 30-day monitor detected AF in 16% of patients compared with 3.2% who underwent a 24-hour Holter monitoring within 90 days ($P < 0.001$; NNS = 8), which led to nearly a doubling in the rate of OAC use.[72] The **Cry**ptogenic **St**roke **a**nd Under**l**ying **A**trial **F**ibrillation (CRYSTAL AF) trial (N = 441) showed a sixfold higher rate of AF detection at 6 months using an implantable cardiac monitor compared with usual care.[73] At 3 years, the rate of AF detection was 30%, with most patients prescribed an OAC.[113]

Prolonged rhythm monitoring was associated with a 51% reduction in the risk of recurrent stroke/TIA,[114] with the rates of recurrent cerebrovascular events or mortality being similar in patients who had known AF before their stroke and patients in whom AF was only diagnosed after their stroke.[115] Substudy analyses from the EMBRACE and CRYSTAL AF trials showed that prolonged rhythm monitoring was cost-effective for the prevention of recurrent stroke in patients with ESUS compared with usual care.[116,117]

Although there is no minimal AF burden threshold stipulated for which long-term OAC should be initiated for secondary prevention,[118] in the EMBRACE study a steep increase in OAC use was observed for patients found to have evidence of at least 30 seconds of AF on monitoring.[72] The authors acknowledged the lack of data to inform this matter but argue that the AF duration threshold at which to begin OAC might reasonably be lower for secondary stroke prevention compared with primary prevention. Further clinical trials are needed to determine the optimal duration and method of rhythm monitoring, the ideal population for extended rhythm monitoring, the minimum AF burden required for OAC initiation, and the efficacy of a prolonged monitoring strategy for the end point of recurrent stroke.

RECOMMENDATION

9. We recommend at least 24 hours of ambulatory ECG monitoring to identify AF in patients with nonlacunar ESUS (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places relatively high value on the fact that stroke might be the first manifestation of previously undiagnosed AF.

10. We suggest additional monitoring for AF detection (eg, prolonged external loop recorder or implantable cardiac monitoring, where available) be performed for selected older patients with nonlacunar ESUS in whom AF is suspected but unproven (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places high value on aggressively investigating selected patients with embolic stroke of unknown source. The main rationale is to improve the identification of patients who would have an evidence-based change in management aimed at preventing recurrent strokes (eg, switching from antiplatelet to OAC) if a clear diagnosis of AF is found. There are currently insufficient data to indicate what the minimum AF duration should be for OAC to be instituted and expert opinion varies widely, therefore treatment decisions should be individualized.

6. Detection and Management of Modifiable Risk Factors

Modifiable cardiovascular risk factors are well recognized contributors to the development and progression of AF.[29,65,66] These established, emerging, and potential risk factors for AF have been summarized in section 3, and Tables 1 and 2. The risk of developing AF increases with the severity and number of modifiable cardiovascular risk factors (such as hypertension, diabetes mellitus, and obesity). In many cases this risk increase is linear within and between risk factors and might be apparent even within the established "normal range." For example, a systolic BP in the prehypertensive range (130-139 mm Hg) has been associated with a 28% higher adjusted risk of developing AF compared with a systolic BP < 120 mm Hg.[119] Similarly, although the corrected AF incidence increases approximately 5% for each unit increase in body mass index (BMI),[120] weight gain has been associated with incident AF independent of BMI (34% increased AF with a 16%-35% weight gain, and 61% increased AF with a > 35% weight gain).[121]

In light of the breadth of data supporting an association between these modifiable cardiovascular risk factors and AF incidence, it has been suggested that the implementation of lifestyle modification and risk factor intervention could significantly decrease the incidence of AF. Unfortunately, the

evidence to support targeted risk factor modification to prevent incident AF is limited, in part because of the observation that the absolute risk increase of incident AF from any individual risk factor is low. As such, two complementary approaches have been proposed. The first is to target preventive intervention in individuals who are at highest risk for AF occurrence. Identification of these individuals could be accomplished through the use of risk prediction models or, potentially, with artificial intelligence-enabled screening algorithms.[122-124] When identified, these high-risk populations could be targeted for comprehensive risk factor modification. However, it is important to recognize that a focus on only those identified as at highest risk of developing AF would miss the opportunity to prevent most incident cases of AF because these occur in the large segment of the population typically considered to be at "lower risk." As such, decreasing the population effect of AF will require broad implementation of lifestyle modification strategies (eg, a focus on physical activity, and avoidance of alcohol and tobacco consumption) in addition to targeted intervention of traditional cardiovascular risk factors (including hypertension, HF, diabetes, OSA, and obesity) in those at highest risk of AF development.

In patients with established AF, the relationship between risk factor intervention and AF outcomes is well recognized. Several studies have shown that continuous positive airway pressure usage in patients with OSA is associated with a lower risk of AF recurrence compared with nonusage, with rates of recurrent AF comparable with those in patients without OSA.[125-127] Many studies have shown that targeted weight loss interventions significantly reduce AF burden (number and cumulative duration of AF episodes) and AF symptom severity scores.[128-130] The **L**ong-Term **E**ffect of **G**oal-Directed Weight Management on **A**trial Fibrillation **C**ohort: A Long-Term Follow-Up Stud**y** (LEGACY) cohort study showed that patients with a weight loss of $> 10\%$ was associated with a sixfold increase in the likelihood of being arrhythmia-free over a 5-year follow-up compared with those with lesser degrees of weight loss.[129] Abed et al. showed that weight reduction with intensive risk factor management resulted in a significant improvement in AF-related QOL, AF symptom scores, and AF burden.[128] The Impact of **Cardio**respiratory **Fit**ness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation (CARDIO-FIT) study showed that a > 2 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 follow-up.[131] AF burden reduction was proportional to the increase in cardiorespiratory fitness, with an adjusted reduction in AF recurrence of 10% for each MET gained (hazard ratio [HR], 0.90; 95% CI, 0.83-1.00).[131] Rienstra et al. showed improved maintenance of sinus rhythm at 1 year with a strategy of cardiac rehabilitation, HF medication optimization, and aggressive BP control (75% maintenance of sinus rhythm on a 7-day Holter vs 63% in the control group; OR, 1.77, $P = 0.042$).[132] The **Agg**ressive **R**isk Factor **R**eduction **St**udy for **A**trial **F**ibrillation and Implications for the Outcome of Ablation (ARREST-AF) single-centre cohort study showed that patients who chose to undergo aggressive risk factor modification had better QOL 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%

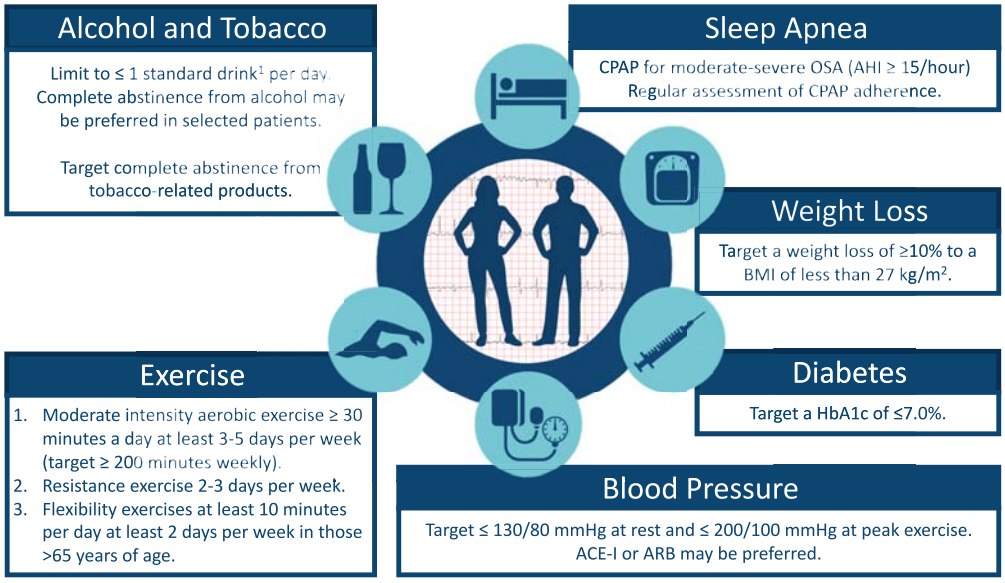


Figure 6. The components of modifiable risk factor management for atrial fibrillation patients. In addition to the key modifiable risk factors and treatment targets outlined in the illustration, consideration should be given to manage coexisting diabetes and dyslipidemia consistent with contemporary guideline recommendations. ACE-I, angiotensin-converting enzyme inhibitor; AHI, apnea-hypopnea index; ARB, angiotensin II receptor blocker; BMI, body mass index; CPAP, continuous positive airway pressure; HbA1c, hemoglobin A1c; OSA, obstructive sleep apnea.

CI, 2.04-11.4; $P < 0.001$).[65] Taken together, these data suggest that outcomes might be improved by using a comprehensive management strategy that includes suppression of triggers (targeted by risk factor modification, antiarrhythmic drugs, and/or catheter ablation) and amelioration of arrhythmogenic substrate (risk factor modification). Treatment targets for modifiable risk factor intervention are presented in Figure 6.

RECOMMENDATION

11. In patients with established AF or at high risk of developing AF, we recommend a systematic approach to the identification of traditional modifiable cardiovascular risk factors and/or conditions associated with AF, with strict guideline-adherent management to reduce major cardiovascular events (Strong Recommendation; High-Quality Evidence) and to prevent recurrence of the arrhythmia and/or decrease its symptom burden (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on a comprehensive, holistic, and systematic approach to the management of AF. Because of the contribution of modifiable risk factors to the development and progression of AF, a systematic approach to the identification of modifiable cardiovascular risk conditions offers a potential therapeutic target to improve outcomes in this population. This recommendation recognizes the association between these modifiable cardiovascular risk factors (including but not limited to hypertension, HF, diabetes mellitus, obesity, inactivity, sleep apnea, and alcohol misuse), and major adverse cardiovascular outcomes (eg, stroke, MI, cardiovascular death) and AF outcomes (AF burden/exacerbations, AF-related ED visits/hospitalizations).

Practical tip. Screening for common cardiovascular risk factors and/or conditions (hypertension, obesity, inactivity, sleep apnea, diabetes, and alcohol misuse) should be performed in addition to screening for AF-specific risk conditions (HF, valvular heart disease, thyroid dysfunction).

7. Integrated Approach to AF Management

As with many other chronic cardiovascular conditions, the complex and multifaceted nature of AF necessitates a systematic approach to the management of the AF patient. Much of the initial management of AF can be provided by primary care providers with the support of specialist cardiology input to guide management decisions in selected AF patients who develop problems or complications during therapy. Dedicated multidisciplinary clinics specifically focused on integrated AF care have been developed to facilitate patient and provider education, provide advanced subspecialist treatment options, and deliver evidence-based care centred on chronic disease management principles.

The systematic approach to patient care in integrated multidisciplinary AF clinic networks typically includes holistic protocol-driven management beyond the heart rhythm, with a particular focus on known care gaps in the domains of stroke prevention, transitions between rate and rhythm control, and coordination of heart rhythm procedures.[49,133,134] Although individually tailored to the needs of their communities,[135] multidisciplinary AF clinics are broadly on the basis of the principles of: (1) timely access to specialist care, to reduce adverse outcomes (eg, stroke or hospitalization) imposed by treatment delays; (2) knowledge translation, because improved understanding of AF facilitates active participation by the patient in their care pathway; (3) guideline adherence, in particular in the domains of stroke prevention and comorbidity management; and (4) integration with community care providers to enhance treatment cohesiveness and support care transitions (eg, from the ED to the specialty clinic and back to community care). A conceptual framework for the integrated approach to AF management is presented in Figure 7.

Nonrandomized studies of specialized AF clinics have suggested that the greater coordination of care between specialist, nursing, and allied health interventions are associated with reduced wait times, enhanced transitions of care, improved adherence to guideline-based care, significant improvement in QOL, and more effective use of tertiary care resources.[136-139] These observational findings were supported by the results of a randomized single-centre study, which showed that a nurse-led multidisciplinary integrated care approach reduced cardiovascular death (HR, 0.28 vs usual care) and cardiovascular hospitalization (HR, 0.66 vs usual care), with resultant cost-effectiveness compared with standard care.[140,141] Although these data were not replicated in a multicentre study of nurse-led vs usual care (HR, 0.85; 95% CI, 0.70-1.05; $P = 0.12$ for the composite of cardiovascular death or cardiovascular hospitalization), a prespecified analysis showed significant benefit in experienced centres.[142]

RECOMMENDATION

12. We suggest a structured, integrated, multidisciplinary, patient-focused approach to care should be implemented for patients with AF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes that AF is a multifactorial disease that requires long-term treatment. An integrated patient-focused team-based approach to care has been shown to improve guideline adherence, reduce adverse clinical outcomes such as hospitalization and mortality, and improve QOL.

7.1. Self-management, shared decision-making, and patient education

As with other chronic illness, self-management plays a crucial role in the longitudinal care of AF patients. Self-management can be conceptualized as the "day-to-day management of chronic conditions by individuals over the course of an illness" with an ultimate goal of improving health outcomes by enabling individuals to effectively manage their own illness.[143] Pragmatically, this involves shifting from the traditional provider-patient relationship to one in which the patient takes the responsibility for guiding their care in partnership with their health care providers (eg, shared decision-making).[144] Key areas of focus include medical management (eg, adherence to a therapeutic regimen), behaviour modification (eg, weight loss and exercise), and development of strategies to provide emotional and psychosocial support. Fundamental to the concept of self-management is the patient's perceived understanding about the cause(s), consequences, clinical manifestations, and controllability of their AF. Misalignment of the therapeutic interventions with the patient values and preferences can lead to dissatisfaction with therapy, nonadherence (not taking OAC as directed), and nonpersistence (therapy discontinuation), resulting in an increased risk of stroke.[145]

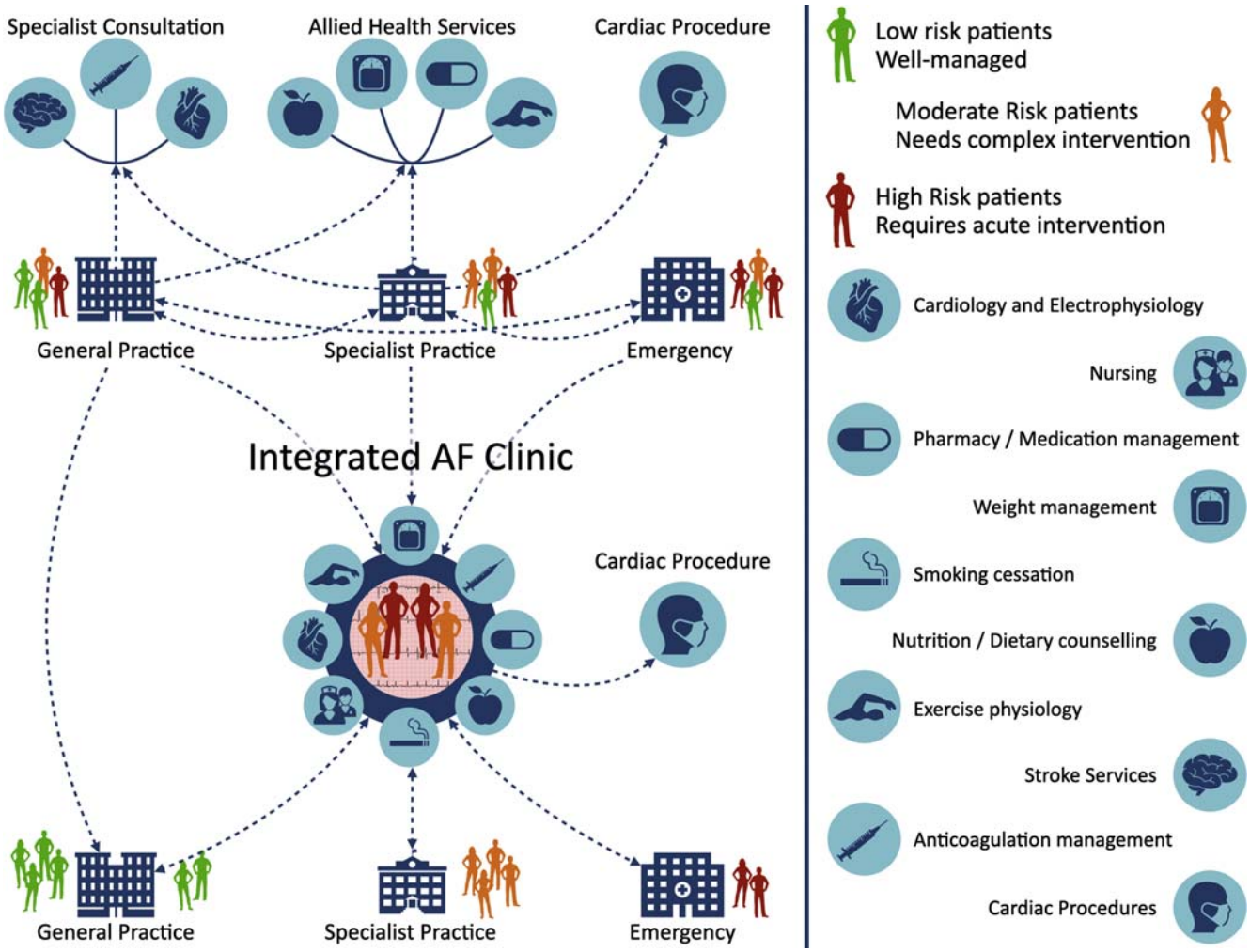


Figure 7. Integrated approach to atrial fibrillation (AF) management. Shown at the top of the illustration is the current paradigm of care for the AF patient, whereby siloed care is delivered across the spectrum of AF patients (low-, moderate-, and high-risk) leading to inconsistent access to specialty care and allied health care providers, inappropriate health care resource utilization (eg, patients seeking nonacute care in the emergency department), and inconsistent management. Shown at the bottom of the illustration is the ideal integrated AF care model, whereby the integrated AF clinic acts as a central hub for the management of AF patients. In this model the AF clinic can act as a peripheral resource for lower risk/well managed patients, who are able to remain with their community providers. For higher-risk patients in need of complex or acute intervention the AF clinic acts as a central access point for comprehensive care from the multidisciplinary heart team.

Patient-centred care requires collaboration between clinicians and knowledgeable patients, considering the best available evidence in addition to the patient's values and preferences.[145] Unfortunately, AF patients often have a poor understanding of the cause, consequences, and controllability of their AF, with particular deficiencies noted in the domain of stroke prevention.[145-147] Tailored patient education facilitates the construction of an accurate illness representation, improves patients' illness-treatment coherence, corrects beliefs about therapeutic options and goals, improves treatment adherence, relieves disease-associated anxiety and stress, and promotes self-management.[146-148] However, the ideal educational strategy is uncertain. Despite written information, patient decision aids, and in-person education sessions all being commonly used, there is no consensus regarding the most effective structure, setting, or educator.[149]

RECOMMENDATION

13. We recommend that individualized goals of care and specific approaches to management should be developed in collaboration with patients and should consider their values and preferences to enhance engagement and improve adherence to long-term therapy (Strong Recommendation; Low-Quality Evidence).
14. We recommend that patients and care providers be supported with educational resources (in person and print/electronic) to enhance disease awareness and facilitate self-management (Strong Recommendation; Low-Quality Evidence).

7.2. Treatment adherence

Adherence has been defined as the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result,"[150] which, in the case of pharmacotherapy can be further conceptualized as medication adherence (eg, the extent to which patients take their medications as prescribed) and persistence (eg, the duration of continuous use after index prescription). Unfortunately, nonadherence to pharmacotherapy is common for patients across the spectrum of cardiovascular diseases.[151,152] In the AF population, adherence and persistence to stroke prevention therapies are suboptimal. Beyond the observation that approximately one-third of higher-risk AF patients fail to receive appropriate OAC,[153-155] of those who receive OAC approximately one-third of OAC-treated patients demonstrate suboptimal adherence.[156,157] Furthermore, persistence in those who have started OAC treatment has been shown to be inadequate with 10% of those who have started VKA treatment failing to fill a second prescription, one-third discontinuing therapy within a year, and less than one-third continuing OAC after 5 years.[158] Likewise, in those who have started DOAC treatment the rates of discontinuation within a year have been reported to range between 13.6% and 52.7%.[159-161] Unfortunately, lower rates of OAC adherence has been associated with higher rates of all-cause mortality and stroke.[156,157,160-162]

Table 6. Potential interventions to improve adherence and persistence

- Establishment of a "blame-free" health care environment (eg, recognizing that adherence is not exclusively the responsibility of the patient)
- Assess health literacy and provide tailored education
- Use motivational strategies and focus the interventions on behavioural strategies
- Address rational nonadherence
- Modify care delivery (eg, provide more convenient care such as telemedicine; use structured follow-up)
- Simplify dosing regimens (eg, reduce the number of daily doses)
- Consider medication delivery (eg, blister packs)

In consideration of the link between adherence and outcomes, it is paramount to pursue strategies that improve adherence and persistence. Although the focus is often limited to factors related to the patients themselves (eg, behavioural), nonadherence and nonpersistence are often multifactorial in origin. As such, any intervention that targets adherence and persistence must take into consideration factors related to the health care system (eg, lack of access or continuity of care), the patient-provider interaction (eg, a poor provider-patient relationship, poor communication, lack of patient education), the medical condition itself (eg, asymptomatic AF and the need for continued ongoing therapy), medical comorbidities (eg, physical disability, mental health disorders, or cognitive impairment), the therapeutic regimen (eg, complexity, medication side effects), or other socioeconomic factors (eg, low level of literacy, high medication cost, or lack of social support).[163]

Solutions proposed to improve adherence and persistence are presented in Table 6. When used in isolation, these unimodal interventions have limited effect on adherence and clinical outcomes. Multimodal interventions, although complex, have shown the greatest benefit in improving outcomes. In the HF population an intensive pharmacist-led multimodal intervention increased medication adherence (78.8% vs 67.9%) and reduced ED visits/hospitalizations (relative risk [RR], 0.82; 95% CI, 0.73-0.93), saving USD$2960 in annual health care costs compared with usual care.[164] Likewise, a large cluster-randomized study showed that a multimodal intervention improved OAC prescription at 1 year compared with usual care (80% vs 67%).[165] Despite the absolute difference in OAC prescription being 9.1% (95% CI, 3.8-14.4) between groups, there was a $> 50\%$ reduction in stroke (HR, 0.48; 95% CI, 0.23-0.99; $P = 0.04$). However, it is important to consider that the most effective interventions are often complex and time-consuming, which has limited their implementation outside of multidisciplinary clinical environments.

RECOMMENDATION

15. We recommend that adherence and persistence to pharmacotherapy be assessed at each clinical encounter and supported using patient-centred strategies (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation puts high value on the evidence that indicates poor long-term persistence and adherence with OAC treatment, as well as the recognition that strategies to improve persistence and adherence can substantially reduce the risk of stroke/systemic embolism.

7.3. Electronic or mobile health

The term "eHealth" or "mHealth" commonly refers to the use of electronic media or mobile health technologies to provide or enhance the delivery of health care. eHealth can include the use of electronic interfaces (eg, Web sites or digital resources) along with mobile health devices (eg, handheld ECG devices or wearable smart devices).[166,167] There are ample opportunities to incorporate eHealth throughout the provision of AF care (see section 5.1). Innovations in eHealth can improve access to services through outreach and telemedicine.[168] Smartphone applications and smart watches can measure the pulse using photoplethysmography or electrical sensors, providing an estimate of heart rate during daily activity and during arrhythmias. The future of AF care delivery will likely leverage a combination of point-of-care and other mHealth technologies to deliver a patient-centred experience.

8. Stroke Prevention

8.1. Stroke risk assessment

Observations from the Framingham cohort and subsequent clinical trials revealed that NVAF is an independent risk factor for stroke (annual incidence of approximately 4.1%-4.5%) and combined stroke/systemic embolism (annual

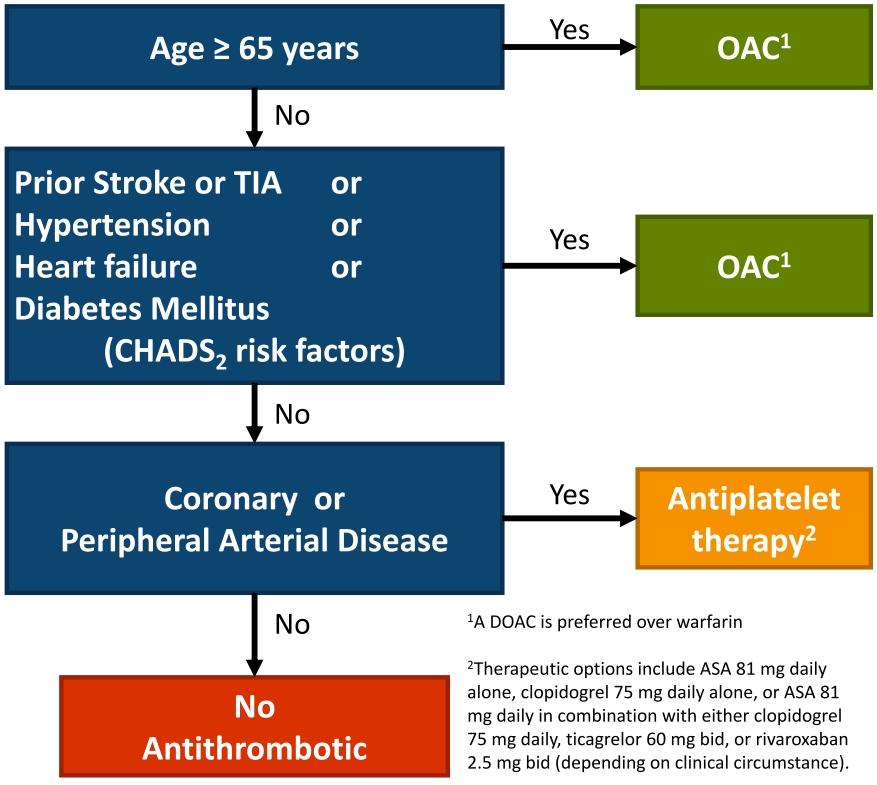


Figure 8. The "CCS algorithm" (CHADS-65) to guide antithrombotic therapy decision-making for patients with nonvalvular atrial fibrillation (AF) or atrial flutter. An oral anticoagulant (OAC) should be prescribed to most patients 65 years of age or older and for younger patients with 1 or more of the other **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) risk factors: history of congestive heart failure, hypertension, diabetes, or stroke/transient ischemic attack (TIA). If none of the previous factors are present, but the patient has coronary or peripheral vascular disease, we recommend acetylsalicylic acid (ASA) 81 mg daily alone or in combination with other antithrombotic therapy. If none of the factors (including vascular disease) are present, no antithrombotic therapy is indicated. When an OAC is prescribed, a non-vitamin K antagonist direct OAC (DOAC) is recommended in preference to warfarin. Bleeding risks should be modified whenever possible. bid, twice daily.

incidence of 50%).[70,169] The risk was further refined by the delineation of various baseline characteristics that might affect the risk of the stroke.[169-173] The first widely adopted tool for stroke risk assessment was the **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) score, which assigns a single point for HF, hypertension, age 75 years or older, and diabetes, and 2 points for previous stroke/systemic embolism.[26,172] Unfortunately, $CHADS_2$ was unable to adequately differentiate very low risk individuals (ie, in whom OAC is associated with a greater risk than benefit) from those at low but still clinically important stroke risk. This led to the development of the expanded **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) score. This score includes the additional risk factors of vascular disease (1 point), female sex (1 point), and age between 65 and 74 years (1 point), and also increases the risk weight to 2 points for age 75 years or older.[26,171]

The 2010 CCS guidelines recommended stroke prevention therapies[4] on the basis of the $CHADS_2$ whereas the 2012 update[5] differentiated among patients at low $CHADS_2$ risk on the basis of risk factors derived from the CHA_2DS_2-VASc.[174] The algorithm for antithrombotic prescription was further revised in 2014,[175] on the basis of data from a Danish national cohort study, which showed that the annual risk of "stroke" (defined as a thromboembolic event precipitating hospitalization or death) was 2.1% for patients aged 65-74 years and 4.4% for those 75 years of age or older.[174] Because age could be reliably determined in all patients, it was agreed that age 65 years or older should be the starting point for a revised algorithm.[175] Likewise, OAC was justified for younger patients with any $CHADS_2$ risk factors (annual risk of stroke: 2.4% with HF, 1.6% with hypertension, 2.3% with diabetes, and 7.9% with previous stroke/systemic embolism). The CCS Guidelines Committee judged that antiplatelet therapy has no role in AF-related stroke prevention and, therefore, no antithrombotic therapy was recommended for patients younger than 65 years with none of the $CHADS_2$ risk factors. However, in the presence of vascular disease daily antiplatelet therapy is indicated to prevent ischemic vascular events independent of the presence of AF.[176] As such, antiplatelet therapy is only indicated in the presence of established vascular disease in NVAF patients aged younger than 65 years with no $CHADS_2$ risk factors (see section 8.3.2.1). The CCS algorithm (CHADS-65) is presented in (Fig. 8).

Among several organizations that publish guidelines for antithrombotic therapies for patients with AF, there are variations in the definitions of the component risk factors, and in the selection and interpretation of data on the stroke risk associated with the individual risk factors according to their preferred risk schemes.[10,26,177] These differences in definitions are unlikely to affect the categorization of patient stroke risk, however, they might provide different point estimates of the annual risk of stroke.

It has also become evident that the risk of stroke varies among cohorts reported from different countries.[178] For similar baseline characteristics, the Taiwanese[179] and Danish cohorts[174] appear to have particularly high stroke risk, whereas cohorts from Sweden[180] and the United States[181] appear to be lower risk. The variation might be attributable to the dissimilarities in the definitions of stroke, treatment of comorbidities, and the protocols for data collection.

RECOMMENDATION

16. We recommend that all patients with AF should undergo annual assessment of their risk of stroke/systemic embolism, irrespective of their clinical pattern of AF (Strong Recommendation; High-Quality Evidence).
17. We recommend that the "CCS Algorithm" (CHADS-65) be used to guide the choice of appropriate antithrombotic therapy for the purpose of stroke/systemic embolism prevention in patients with NVAF (Strong Recommendation; High-Quality Evidence).

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

8.1.1. Atrial flutter

Atrial flutter (AFL) carries a significant risk of stroke/systemic embolism but, as opposed to AF, the relationship is somewhat less precisely established due to limited number of small and retrospective cohort studies, as well as significant heterogeneity of data.[182] Because many patients with AFL also experience episodes of AF it becomes difficult to know the exact risk of stroke/systemic embolism related to AFL alone.[183] Moreover, there are no randomized trials of the value of OAC specifically in the AFL population.

However, there is direct and indirect evidence from mechanistic, observational, and prospective studies that AFL confers a significant thromboembolic risk. TEE evidence of atrial thrombi has been documented in patients with sustained AFL not receiving long-term anticoagulation (LA thrombus in 1.6% with at least moderate spontaneous LA echo contrast in 13%; median duration of 33 days).[184] OAC has been shown to reduce the incidence of stroke/systemic embolism after cardioversion, with an incidence similar to that of AF.[185,186] In a metaregression analysis, the annual risk of stroke/systemic embolism was approximately 3% in patients with AFL.[187] Although the rate of stroke is higher than that in control participants (HR, approximately 1.4), the risk of stroke appears to be lower than for patients with AF (HR, approximately 0.70).[183,188] For AFL patients, the risk of stroke is higher with increasing CHA_2DS_2-VASc scores[189-192] and also increased in patients who develop AF after their initial diagnosis of AFL.[192] As such, it is recommended that patients with AFL be stratified and treated in the same manner as patients with AF.[193]

8.2. Oral anticoagulation

The benefit of OAC must be weighed against the risk of hemorrhage. The relative importance of a stroke prevented, and a 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, particularly when the annual risk of stroke is < 2% per year.[194]

The CCS rationale for recommending OAC for most patients with age 65 years or older or $CHADS_2$ score ≥ 1 is on the basis of the effects of OAC on the absolute risk reduction of stroke compared with the increase in major hemorrhage. In patients aged 65 years or older and without other risk factors for stroke, use of VKAs decreased the annual risk of stroke from 2.1% to 0.7% while it increased the risk of major bleeding by approximately 0.5% per year to 1.0%.[51,195] Although the risk of major bleeding increases with increasing $CHADS_2$ scores, the rate of rise is not as steep as that for stroke; therefore, the benefit to risk ratio for OAC increases as stroke risk factors accumulate. Furthermore, 70% of strokes result in death or major disability, whereas most patients survive major hemorrhage without long-term effects.[196] Thus, these results favour use of OAC in patients with age 65 years or older or $CHADS_2$ score ≥ 1. OACs with efficacy and safety evidence in AF include VKAs and DOACs.

RECOMMENDATION

18. We recommend that OAC be prescribed for most patients with AF and age 65 years or older or $CHADS_2$ score ≥ 1 (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places relatively greater weight on the absolute reduction of stroke risk with OAC compared with antiplatelet agents in patients aged 65 years or older or with $CHADS_2$ score ≥ 1 and less weight on the potentially increased risk of major hemorrhage with OACs compared with antiplatelet agents.

19. We suggest that no antithrombotic therapy be prescribed for stroke prevention for most patients with NVAF who are aged younger than 65 years with no $CHADS_2$ risk factors (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. For patients with NVAF who are aged younger than 65 years with no $CHADS_2$ risk factors the current evidence does not support antiplatelet monotherapy for stroke prevention. For those patients, with concomitant coronary or peripheral arterial vascular disease, the antithrombotic treatment should be directed at the underlying arterial disease as outlined in the CCS/Canadian Association of Interventional Cardiology (CAIC) guidelines (see section 8.3.2.1).

20. We recommend that the longitudinal follow-up of patients receiving OAC include regular assessment of bleeding risk, potential drug-drug interactions, as well as adherence and persistence to pharmacotherapy (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Consider the use of a standardized follow-up and monitoring tools to facilitate systematic review of efficacy and bleeding in patients receiving OAC, particularly for patients receiving DOACs who do not undergo regular laboratory monitoring.

8.2.1. Warfarin and vitamin K antagonists

Six studies (2900 patients) have compared VKAs with placebo in the setting of NVAF; 5 primary prevention trials (2 double-blinded) and 1 secondary prevention trial. The mean achieved international normalized ratio (INR) ranged from 2.0 to 2.6 among patients who were assigned to VKAs in the primary prevention trials and was 2.9 in the secondary prevention trial. A meta-analysis of these 6 studies showed a RR reduction of 64% (95% CI, 49%-74%) in all stroke (ischemic or hemorrhagic)[51] with an absolute risk reduction of 2.7% per year for primary prevention trials and 8.4% per year for secondary prevention. The absolute risk increase in major extracranial hemorrhage was 0.3% per year with use of VKAs. However, there was an absolute risk reduction of 1.6% per year in overall mortality with use of VKAs.

In a meta-analysis of 8 RCTs (3647 patients), the RR reduction with use of VKAs over aspirin was 39% (95% CI, 19%-53%) for all strokes, equivalent to an absolute risk reduction of approximately 0.7% per year for primary prevention and 7% per year for secondary prevention.[51] There was an excess of bleeding in the VKA-treated patients leading to an absolute risk increase of 0.2% per year in major extracranial and intracranial hemorrhage (ICH). However, the absolute risk reduction for all-cause mortality remained in favour of VKAs at 0.5% per year. In an update of this meta-analysis to include the largest study of elderly patients[197] the absolute risk reduction increased to 0.9%, with the risk of major extracranial hemorrhage being no different between use of VKA and aspirin.[51] A further meta-analysis showed that adjusted-dose VKA was associated with half the rate of stroke/systemic embolism events with no significant difference in the rate of major bleeding relative to adjusted-dose antiplatelet therapy.[198]

The benefit of VKAs for stroke prevention in patients with NVAF is optimized at a target INR of 2-3, with the time spent in this therapeutic range (TTR) directly correlated with clinical outcomes. The relationship between TTR and clinical outcomes was shown in a post hoc analysis of the **AF** **C**lopidogrel **T**rial With **I**rbesartan for Prevention of **V**ascular **E**vents (ACTIVE W) trial.[199] In ACTIVE W there was no difference in stroke reduction between VKA and clopidogrel with aspirin therapy (RR, 0.93; 95% CI, 0.70-1.24; $P = 0.61$) at centres with a TTR below the median TTR (65%). However, VKAs had a marked benefit for patients at centres with a TTR above the median, reducing vascular events by more than twofold (RR, 2.14; 95% CI, 1.61-2.85; $P < 0.0001$). A subsequent systematic review reinforced this concept, showing a significant correlation between TTR and adverse outcomes (major hemorrhage and thromboembolic rate) in an analysis of 33,976 AF patients included in 38 studies.[200] More recently, a large worldwide observational study of 9934 VKA-treated patients enrolled from 35 countries between 2010 and 2015 showed an adjusted 2.6-fold increased risk of stroke/systemic embolism, a 1.5-fold increased risk of major bleeding, and a 2.4-fold increased risk of all-cause mortality with TTR $<$ 65% vs $\geq$ 65%.[201] Further, the study highlighted the difficulty in managing VKAs because the mean TTR for the total study group was 55%, with more than half of the North American cohort having a TTR $<$ 65%.[201]

VKAs such as warfarin remain the preferred OAC in the presence of any mechanical prosthetic heart valve and in patients with moderate to severe mitral stenosis. With respect to the former, in the **R**andomized, Phase II Study to **E**valuate the

Table 7. Recommendations for dosage of oral anticoagulants

CrCl	Warfarin	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
CrCl >50 mL/min	Dose adjusted for INR 2.0-3.0	5 mg BID†	150 mg BID*	60 mg daily∞	20 mg daily
CrCl 30-49 mL/min	Dose adjusted for INR 2.0-3.0	5 mg BID†	Consider 110 mg BID	30 mg daily	15 mg daily
CrCl 15-29 mL/min	No RCT Data**	Very limited RCT Data§	No RCT Data¶	Very limited RCT Data¶	No RCT Data
CrCl <15 mL/min (or on dialysis)	No RCT Data‡	Very limited RCT Data¶	No RCT Data¶	No RCT Data¶	Very limited RCT Data¶

BID, twice daily; CrCl, creatinine clearance, INR, international normalized ratio; RCT, randomized clinical trial.
*Dabigatran 110 mg po BID is recommended if age ≥80 years, or ≥75 years with other bleeding risk factors including CrCl 30-50mL/min
†Apixaban 2.5 mg po BID is recommended if 2 of the 3 following criteria are present: 1) age ≥80 years, 2) body weight ≤60 kg, or 3) serum creatinine ≥133 μmol/L
∞Consider Edoxaban 30mg daily if weight ≤60 kg or concomitant potent P-Gp inhibitor therapy EXCEPT amiodarone or verapamil
**Dose adjusted warfarin has been used, but data regarding safety and efficacy is conflicting
‡Dose adjusted warfarin has been used, but observational data regarding safety and efficacy is conflicting and suggests harm.
§The ARISTOTLE trial included a small number of patients with a CrCl as low as 25 mL/min
¶Product monographs suggest the drug is contraindicated for this level of renal function.

Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement (RE-ALIGN) study patients with mechanical heart valves were randomized to VKA or dabigatran (150 mg, 220 mg, or 300 mg twice daily [BID], on the basis of renal function).[202] The trial was terminated early because of an excess of thromboembolic and bleeding events with dabigatran. Although RE-ALIGN is the only trial to evaluate DOACs in the setting of mechanical valve prostheses, VKA remains the treatment of choice in this population. With respect to patients with moderate to severe mitral stenosis, there are no randomized trials of OAC for prevention of thromboembolic events. Retrospective studies have suggested a 4- to 15-fold decrease in the incidence of embolic events with OAC therapy.[203] Because patients with severe mitral valve disease were excluded from the pivotal randomized DOAC trials,[21-25] VKAs remain the standard of care in this patient population until further evidence emerges. Ongoing trials of DOACs in patients with rheumatic valvular disease (**Inv**esti-gation of Rheumatic AF **T**reatment **U**sing Vitamin K Antagonists, Rivaroxaban or Aspirin **S**tudies [INVICTUS] studies; NCT02832531 and NCT02832544) will provide guidance.

8.2.2. Non-vitamin K direct oral anticoagulants

Four DOACs are currently approved for use in Canada: apixaban, dabigatran, edoxaban, and rivaroxaban. These four agents were developed to overcome the major limitations associated with VKAs and have been evaluated in large RCTs involving more than 70,000 patients.[21-25] Individually, DOACs were shown to be at least as effective as VKAs in decreasing the risk of NVAF-associated stroke/systemic embolism, with similar or less major bleeding. A meta-analysis of these four RCTs showed that the use of the higher approved DOAC dose resulted in a statistically significant reduction in stroke/systemic embolism (RR, 0.81; 95% CI, 0.73-0.91; $P < 0.0001$), ICH (RR, 0.48; 95% CI, 0.39-0.59; $P < 0.0001$), and all-cause mortality (RR, 0.90; 95% CI, 0.85-0.95; $P = 0.0003$) with less major bleeding (RR, 0.85; 95% CI, 0.73-1.00; $P = 0.06$), compared with VKAs.[52] Use of the lower-dose DOAC regimens resulted in similar rates of stroke/systemic embolism (RR, 1.03; 95% CI, 0.84-1.27; $P = 0.74$), with less major (RR, 0.65; 95% CI, 0.43-1.00; $P = 0.05$) and intracranial bleeding (RR, 0.31; 95% CI, 0.24-0.41; $P < 0.0001$), and lower mortality (RR, 0.89; 95% CI, 0.83-0.96; $P = 0.003$), but significantly more ischemic strokes (RR, 1.28; 95% CI, 1.02-1.60; $P = 0.045$) compared with VKAs. On the basis of these observations the CCS AF Guidelines Committee continues to recommend DOACs over VKAs for patients with NVAF.

There have been no published RCTs directly comparing the four DOACs. Differences in the designs of the RCTs, including the population studied (and by extension their baseline stroke risk), preclude definitive comparisons between the agents. Although so-called "real world" comparisons are plentiful in the published literature, it is not possible to make reliable therapeutic inferences from observational associations because these types of studies are subject to significant biases and limitations.[204]

Nevertheless, there are relevant differences in the pharmacological characteristics of the DOACs, which might influence their selection in individual patients such as: (1) bioavailability, with dabigatran being the least bioavailable, thereby requiring a special formulation for optimal absorption, and rivaroxaban requiring coadministration with food to optimize absorption of the 15- and 20-mg doses; (2) renal clearance, with dabigatran being

predominantly (80%) renally cleared; (3) drug-drug interaction potential, with all of the DOACs influenced by P-glycoprotein interactions but only rivaroxaban and apixaban also being influenced by cytochrome P-450 isoenzyme function, specifically 3A4; (4) the elimination half-life and dosing schedule; and, (5) the presence and availability of an antidote.

Regardless of the specific DOAC agent selected, it is important to ensure that the prescribed dose is consistent with Health Canada labelling and the product monograph (Table 7). Specifically, it has been observed that overtreatment (or the prescription of a standard dose in patients with an indication for dose reduction) occurs in approximately 4% of patients and is associated with an increased risk of major bleeding, hospitalization, and death, without a significant additional reduction in stroke.[205-207] Likewise, undertreatment (or prescription of a reduced dose without an indication to do so) occurs in 12%-15% of patients and is associated with a higher risk of thromboembolic events, hospitalization, and death, without a significant reduction in major bleeding.[205-207]

RECOMMENDATION

21. We recommend most patients should receive a DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban) in preference to warfarin when OAC therapy is indicated for patients with NVAF (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the results of several large RCTs showing that the DOACs are either noninferior or superior to warfarin in preventing AF-related stroke; that they have no more or less major bleeding compared with warfarin; that they are associated with less ICH compared with warfarin; and on the greater ease of use of DOACs compared with dose-adjusted warfarin.

Practical tip. Baseline renal function and complete blood counts should be measured before initiation of anticoagulation and at a regular intervals thereafter (see section 8.3.1).

Practical tip. The dose of DOAC prescribed should follow the doses used in the RCTs and Health Canada-approved prescribing information (see Table 7). Receipt of a higher than recommended dose is associated with increased bleeding events and overall mortality. Receipt of a lower than recommended dose is associated with increased rates of stroke/systemic embolism.

Practical tip. Consideration should be given to switching eligible patients from warfarin to a DOAC, particularly if they are unable to maintain a therapeutic INR.

22. We recommend that warfarin be used for patients with a mechanical prosthetic valve and those with AF and moderate to severe mitral stenosis (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places high value on the evidence from 1 RCT of the inferiority of dabigatran compared with warfarin for the prevention of thromboembolism in patients with a mechanical prosthetic valve.

Values and preferences. This recommendation places a relatively high value on the long experience and clinical reports of the use of warfarin in patients with rheumatic mitral stenosis.

8.3. Anticoagulation in special populations

8.3.1. Anticoagulation in patients with chronic kidney disease and end-stage renal disease

AF patients with chronic kidney disease (CKD) represent a particularly high-risk subgroup because stroke, mortality, and major bleeding all increase as renal function deteriorates.[208,209] RCTs demonstrate that OAC, including DOACs, are safe and effective for AF patients with mild to moderate CKD (stage 1-3 CKD or eGFR $>$ 30 mL/min).[210] There are few randomized data for patients with severe renal impairment (stage 4-5 CKD or eGFR $<$ 25 to 30 mL/min) as these patients were excluded from the large phase III RCTs. Nonrandomized and very limited randomized data support the use of OAC in patients with stage 4 CKD (eGFR 15-30 mL/min),[211,329] however, the benefit of OAC for AF patients with severe CKD (eGFR $<$ 15 mL/min) or end-stage renal disease (ESRD) who require dialysis remains unclear. There are no prospective randomized trials that have evaluated OACs vs placebo for dialysis-dependent AF patients, and results of the observational studies are conflicting.[209,212-215] The ongoing randomized Study of the Benefit/Risk Ratio of Oral Anticoagulation in Hemodialysis Patients with Atrial Fibrillation (AVKDIAL) is studying VKA (target INR 2-3) compared with no OAC in hemodialysis patients with AF (NCT02886962). Until these results are available there is insufficient evidence to support or deny routine OAC use in the AF population with ESRD who require dialysis.

When OAC is prescribed for AF patients with stage 1-4 CKD, the CCS AF guidelines panel recommends that a DOAC is preferred to a VKA. For those with moderate CKD in the landmark phase III trials, DOACs significantly reduced the risk of stroke/systemic embolism (RR, 0.79; 95% CI, 0.66-0.94) and major bleeding (RR, 0.80; 95% CI, 0.70-0.91), compared with VKAs.[216] Moreover, in patients with mild-moderate CKD the use of DOACs was associated with a lessened rate of adverse renal outcomes, including renal function decline, doubling in serum creatinine level, or acute kidney injury.[217]

Although apixaban and rivaroxaban are approved for patients with stage 4 CKD (CrCl of $>$ 15 mL/min), the evidence supporting DOAC use in preference to VKAs is limited.[218] In those with more severe stage 5 CKD or ESRD requiring dialysis the evidence supporting DOACs is incomplete, with the available observational data being subject to confounding and selection bias and the randomized studies being underpowered.[219-222,885] The randomized Renal Hemodialysis Patients Allocated Apixaban versus VKA in AF trial (RENAL-AF; NCT02942407) was prematurely terminated following the enrollment of 154 patients with hemodialysis-dependent ESRD (targeted enrollment, 760 patients). At study conclusion, the rates of bleeding and stroke/systemic embolism were similar between those randomized to apixaban 5 mg BID or VKAs. Ongoing studies include the Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) (AXADIA; NCT02933697), in which phenprocoumon vs is being compared to apixaban 2.5 mg twice daily (targeted enrollment 222 patients); and the **S**trategies for the Management of **A**trial **F**ibrillation in Pati**e**nts Receiving Dialysis (SAFE HD; NCT03987711) trial, in which VKA and

apixaban 5 mg BID, and no anticoagulation are being compared (targeted enrollment 150 patients).

Patients with clinically significant CKD require a reduction in DOAC dose in accordance with the approved prescribing information to avoid adverse clinical outcomes (Table 7).[7,205-207,223] Although undertreatment (or prescription of a reduced dose without an indication to do so) is associated with a higher risk of thromboembolic events, hospitalization, and death,[205-207] appropriate dose reduction in those with moderate CKD can achieve clinical outcomes comparable with that in patients with preserved renal function (CrCl > 50 mL/min) who are receiving the higher DOAC dose.[224,225]

When medication dose adjustment is performed, Cockcroft-Gault CrCl should be used. The rationale has been extensively outlined in the 2014 AF guidelines companion.[26] In brief, the Cockcroft-Gault CrCl was the formula used to assess eligibility in the landmark DOAC trials, and it is recommended to guide medication dose adjustment in the product monographs and approved prescribing information.[21-23,25] Although the **M**odified **D**iet in **R**enal **D**isease (MDRD) or the **C**hronic **K**idney **D**isease **Epi**demiology Collaboration (CKD-EPI) eGFR equations are commonly reported by laboratories, use of these formulae fail to identify a significant proportion of patients with contraindications to DOACs or those who require dose adjustment.[226]

RECOMMENDATION

23. We recommend that patients with AF who are receiving OAC should have their renal function assessed at baseline and at least annually to detect latent kidney disease, determine OAC eligibility, and to support drug dosing (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Because DOAC eligibility and dosing are dependent on renal function, we recommend at least annual assessment of renal function with calculation of CrCl. In stable patients with an eGFR of 30-60 mL/min renal function should be monitored every 6 months, and every 3 months for patients with an eGFR of 15-30 mL/min. In patients with fluctuating renal function or acute dehydrating illness renal function should be assessed more frequently. Follow-up monitoring should also include assessment of bleeding risk, drug interactions, and adherence and persistence.

24. We recommend that CrCl, as estimated using the Cockcroft-Gault method, be used to support dosing decisions of anticoagulant medications (Strong Recommendation; High-Quality Evidence).

Practical tip. Multiple formulae have been developed to provide an estimate of renal function. The most commonly applied formulae estimate CrCl or filtration of creatinine by the glomerulus (glomerular filtration rate or eGFR). Although the eGFR equations (MDRD formula or the CKD-EPI formula) provide more accurate estimates of renal function, drug manufacturers have used the CrCl (Cockcroft-Gault formula) when recommending medication dosage adjustments for patients with renal dysfunction.

25. We recommend that antithrombotic therapy in AF patients with CKD be provided according to their risk of stroke/systemic embolism and the severity of renal dysfunction with selection of agent according to Table 7.
    A. Stage 3 CKD or better (eGFR > 30 mL/min): we recommend that such patients receive antithrombotic therapy as determined by the "CCS algorithm" (Strong Recommendation; High-Quality Evidence).
    B. Stage 4 CKD (eGFR 15-30 mL/min): we suggest that such patients receive antithrombotic therapy as determined by the "CCS algorithm" (Weak Recommendation; Low-Quality Evidence).
    C. Stage 5 CKD (eGFR < 15mL/min or dialysis-dependent): we suggest that such patients not routinely receive antithrombotic therapy for stroke prevention in AF (Weak Recommendation; Low-Quality Evidence).

Values and preferences. These recommendations place a relatively higher value on prevention of ischemic stroke than on bleeding complications associated with antithrombotic therapy.

Practical tip. Because of the lack of prospective data showing benefit in patients with a CrCl < 15 mL/min, the decision to use antithrombotic therapy should be individualized on the basis of physician and patient preference and considering the relative risks of stroke and bleeding. Therapy with antithrombotic therapy might be appropriate for some patients with AF and CrCl < 15 mL/min (or dialysis-dependent) in whom the benefit of preventing stroke outweighs the increased risk of bleeding.

8.3.2. Coronary artery disease

Up to 20%-30% of AF patients also have concomitant coronary artery disease (CAD), with a significant proportion who require percutaneous coronary intervention (PCI).[227,228] OAC is indicated for the prevention of AF-related stroke/systemic embolism, which also provides benefit in preventing ischemic coronary events. Antiplatelet therapy is indicated for the prevention of coronary events after acute coronary syndromes (ACS) and/or PCI; however, it is inferior to OAC for the prevention of stroke/systemic embolism in an AF population at increased risk of AF-related stroke.[229] As such, management requires a careful and balanced assessment of the individual risks of bleeding vs the anticipated effect on thrombotic outcomes.

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]), dual antiplatelet therapy (DAPT) refers to the concomitant use of 2 antiplatelet agents (eg, ASA with P2Y12 inhibitor), dual pathway therapy refers to the concomitant use of a SAPT with an OAC agent (eg, VKA with P2Y12 inhibitor), and triple antithrombotic therapy (TT), the combination of

DAPT with an OAC (eg, VKA with ASA and P2Y12 inhibitor).

The comprehensive recommendations regarding antithrombotic treatment in AF patients indicated for OAC with concomitant coronary/arterial vascular disease are summarized in Figure 9.

RECOMMENDATION

26. We recommend that AF patients with coronary or arterial vascular disease (peripheral vascular disease or aortic plaque) receive an antithrombotic therapy regimen 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).

Practical tip. For patients who require combinations of antiplatelet and OAC agents for concomitant AF and coronary/arterial vascular disease, measures should 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 (PPI) use; avoidance of prasugrel and ticagrelor in conjunction with OACs; the use of the lower target INR range (eg, 2.0-2.5) when a VKA is used as part of combination therapy; specific measures during PCI to reduce bleeding outcomes (radial access or ultrasound-guided femoral access, use of small diameter sheaths if appropriate, early sheath removal if feasible, and minimized use of acute periprocedural antithrombotic therapies); delaying non-urgent procedures until dual or triple therapy is no longer required; use of walking aids for those with gait or balance disorders; avoidance of concomittant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or other drugs that might increase bleeding risk; and, strict BP control.

27. We recommend a DOAC in preference to a VKA when an OAC is indicated for AF patients with coronary or arterial vascular disease (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the results of several large RCTs that showed that the DOACs are either noninferior or superior to VKAs in preventing AF-related stroke, that they cause no more or less major bleeding compared with VKAs, that they are associated with less ICH compared with VKAs, that they are associated with greater ease of use compared with dose-adjusted VKAs, and that DOACs are not associated with an increase in ischemic coronary outcomes.

8.3.2.1. Stable vascular disease and AF in patients at low risk of stroke/systemic embolism

SAPT (eg, ASA 81 mg/d) is recommended for patients with AF who are at low risk of stroke/systemic embolism (age younger than 65 years and $CHADS_2$ score of 0) if coronary or peripheral arterial vascular disease is present (CAD, peripheral vascular disease, or aortic plaque). The SAPT recommendation is on the basis of the efficacy of ASA therapy for the prevention of coronary events among patients with stable CAD (1.5% per year absolute risk reduction for secondary prevention).[51,230] Although there is extensive evidence for the efficacy of OAC for prevention of ischemic coronary events in patients with stable CAD,[231] the CCS AF guidelines recommend SAPT in preference to OAC in those at low risk of stroke because of the favourable safety profile and ease of use associated with antiplatelet therapy.

In a non-AF population, the **C**ardiovascular **O**utcom**e**s for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial showed that dual pathway therapy with ASA and "vascular dose" rivaroxaban (2.5 mg BID) was associated with significant reduction in cardiovascular mortality and ischemic stroke, albeit with a significantly increased risk of major bleeding.[232] As such, the combination of ASA and rivaroxaban 2.5 mg BID may be considered a reasonable alternative to ASA alone for NVAF patients at low risk of stroke (age younger than 65 years and $CHADS_2$ score of 0) who also have coronary or arterial vascular disease.

RECOMMENDATION

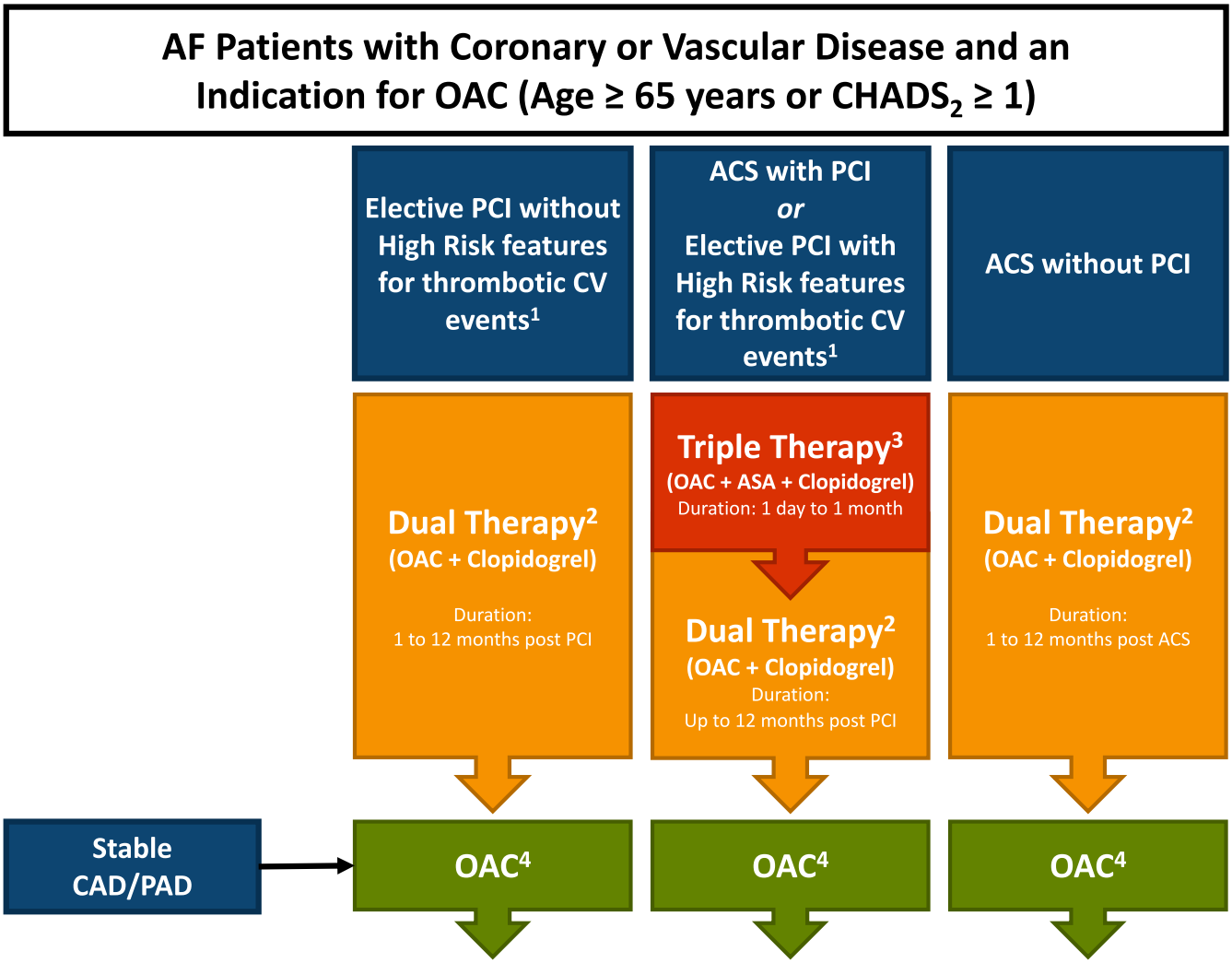
28. We suggest no oral anticoagulation for stroke prevention for most patients with NVAF aged younger than 65 years with no $CHADS_2$ risk factors and stable coronary or arterial vascular disease (Weak Recommendation; Moderate-Quality Evidence).

Practical tip. The risk of stroke associated with AF is not sufficiently elevated to justify routine OAC therapy for those patients with stable coronary or arterial vascular disease aged younger than 65 years with AF and no $CHADS_2$ risk factors. Treatment should be directed at the underlying coronary/peripheral arterial disease as outlined in the CCS/CAIC guidelines. Therapeutic options include ASA 81 mg daily alone; or ASA 81 mg daily in combination with either clopidogrel 75 mg daily, ticagrelor 60 mg BID, or rivaroxaban 2.5 mg BID.

8.3.2.2. Stable vascular disease and AF in patients at high risk of stroke/systemic embolism

OAC is indicated for stroke prevention in patients with AF who are aged 65 years or older or with a $CHADS_2$ score ≥ 1. When such a patient also has stable CAD (defined by the absence of ACS or PCI in the preceding 12 months), OAC provides protection against ischemic coronary events in addition to stroke and systemic embolism.[233-239]

The CCS AF Guidelines Committee does not recommend that antiplatelet agents be routinely prescribed in combination with OAC for AF patients at high risk of stroke with stable CAD. The **W**arfarin-**A**spirin **Re**infarction **S**tudy (WARIS)-II showed that the additional use of antiplatelet therapy with OAC did not confer a beneficial effect (eg, combined end point of death, MI, and stroke; 16.7% with OAC alone vs 15.0% with combination OAC and ASA; $P = 0.18$), but did increase the risk of adverse bleeding outcomes (overall bleeding 2.82% per year with OAC alone vs 3.27% per year with combination OAC and ASA).[236,237] More recently, the **A**trial **F**ibrillation and **I**schemic Events With **R**ivaroxaban in Pati**e**nts With Stable Coronary Artery Disease (AFIRE) trial[239] randomized 2236 patients with AF with stable CAD to receive rivaroxaban monotherapy or combination therapy with rivaroxaban and SAPT. The trial was prematurely



1. PCI is considered high-risk based on clinical and angiographic features such as: diabetes mellitus, current smoker, chronic renal dysfunction (eGFR < 60 mL/min), prior ACS, multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, prior stent thrombosis, chronic total occlusion intervention, or bioabsorbable vascular scaffold.

2. The OAC component evaluated as part of dual pathway therapy regimens include: warfarin daily, apixaban 5 mg BID (reduced to 2.5 mg if they met two or more of the following dose-reduction criteria: age > 80 years of age, weight < 60 kg, or Cr > 133 µmol per liter), dabigatran 110 mg or 150 mg PO BID, edoxaban 60 mg PO daily (30 mg in patients with CrCl 15–50 mL/min, bodyweight ≤ 60 kg, or concomitant use of specified potent P-glycoprotein inhibitors), rivaroxaban 15 mg PO daily (10 mg in patients with CrCl 30-50 mL/min). A DOAC is preferred over warfarin, however if warfarin is to be used the lower end of the recommended INR target range is preferred. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA naïve).

3. The OAC component evaluated as part of triple therapy regimens include: warfarin daily, rivaroxaban 2.5 mg PO BID, or apixaban 5 mg BID (reduced to 2.5 mg if they met two or more of the following dose-reduction criteria: age > 80 years of age, weight < 60 kg, or Cr > 133 µmol per liter). A DOAC is preferred over warfarin, however if warfarin is to be used the recommended INR target is 2.0-2.5. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA naïve). Thereafter, ASA may be discontinued as early as the day following PCI or it can be continued longer. The timing of when to discontinue ASA will depend on individual patient's ischemic and bleeding risk.

4. The dose of OAC beyond one year after PCI should be standard stroke prevention doses. A combination of an OAC and single antiplatelet therapy may be used only in highly-selected patients with high-risk features for ischemic coronary outcomes, and who are also at low risk of bleeding

Figure 9. Management of antithrombotic therapy in patients with atrial fibrillation (AF) and coronary artery disease (CAD)/peripheral artery disease (PAD), who have an indication for an oral anticoagulant (OAC) for stroke prevention. ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice per day; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; Cr, creatinine; CrCl, creatinine clearance; DOAC, non-vitamin K direct oral anticoagulant; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PCI, percutaneous coronary intervention; PO, orally.

terminated because of increased all-cause mortality in the combination therapy group (1.9% per patient-year with rivaroxaban vs 3.4% per patient-year with combination therapy; HR, 0.55; 95% CI, 0.38-0.81; $P < 0.05$). Rivaroxaban monotherapy was noninferior to combination therapy for the primary efficacy end point (stroke/systemic embolism, MI, unstable angina requiring revascularization, or death) with event rates of 4.14% and 5.75% per patient-year, respectively (HR, 0.72; 95% CI, 0.55-0.95; $P < 0.001$ for noninferiority). Rivaroxaban monotherapy was superior to combination therapy for the primary safety end point of International Society on Thrombosis and Haemostasis major bleeding (1.62% vs 2.76% per patient-year; HR, 0.59; 95% CI, 0.39-0.89; $P = 0.01$ for superiority).

RECOMMENDATION

29. We recommend OAC alone for patients with AF aged 65 years or older or with a $CHADS_2$ score $\geq$ 1 and stable coronary or arterial vascular disease (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. The use of combination antithrombotic therapy (eg, OAC with a single antiplatelet agent) is not routinely justified for patients with AF and stable coronary or arterial vascular disease (defined as the absence of ACS or revascularization procedure in the preceding 12 months) because of the observed increased risk of bleeding and all-cause mortality observed with combination therapy, without a significant reduction in ischemic coronary and cerebrovascular thrombotic events.

Practical tip. A combination of an OAC and single antiplatelet therapy may be considered only in highly selected patients with high-risk features for ischemic coronary outcomes, and who are also at low risk of bleeding.

8.3.2.3. PCI or ACS in patients with AF at low risk of stroke/systemic embolism

OAC is not recommended for stroke prevention for patients with AF who are at low risk of stroke/systemic embolism (age younger than 65 years and $CHADS_2$ score of 0). DAPT is generally prescribed for patients after elective PCI for a period of 6 months and for 12 months after ACS (with or without PCI), as outlined in the 2018 CCS/CAIC antiplatelet guidelines for non-AF patients.[240] Some patients with low thrombotic or high bleeding risk may appropriately receive shorter durations of DAPT to decrease the risk of major bleeding. Conversely, longer durations of DAPT might be appropriate for those at higher thrombotic but lower bleeding risk, because premature DAPT discontinuation might increase the risk of stent thrombosis and MI.

8.3.2.4. PCI or ACS in patients with AF at high risk of stroke/systemic embolism

Combination OAC and antiplatelet therapy is required for patients with AF who are aged 65 years or older or with $CHADS_2$ score $\geq$ 1, who are undergoing PCI or treatment of ACS. In these patients the optimal therapeutic regimen should be individualized on the basis of a balanced assessment of their risk of AF-related stroke/systemic embolism ("CCS algorithm", Fig. 8), ischemic coronary events, and clinically relevant bleeding (Fig. 10). 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 CKD, 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).[240,241] The risk of bleeding can be estimated from clinical risk scores such as **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED), **Pre**dicting Bleeding **C**omplications **i**n Patients Undergoing **S**tent Implantation and Subs**e**quent **D**ual **A**nti

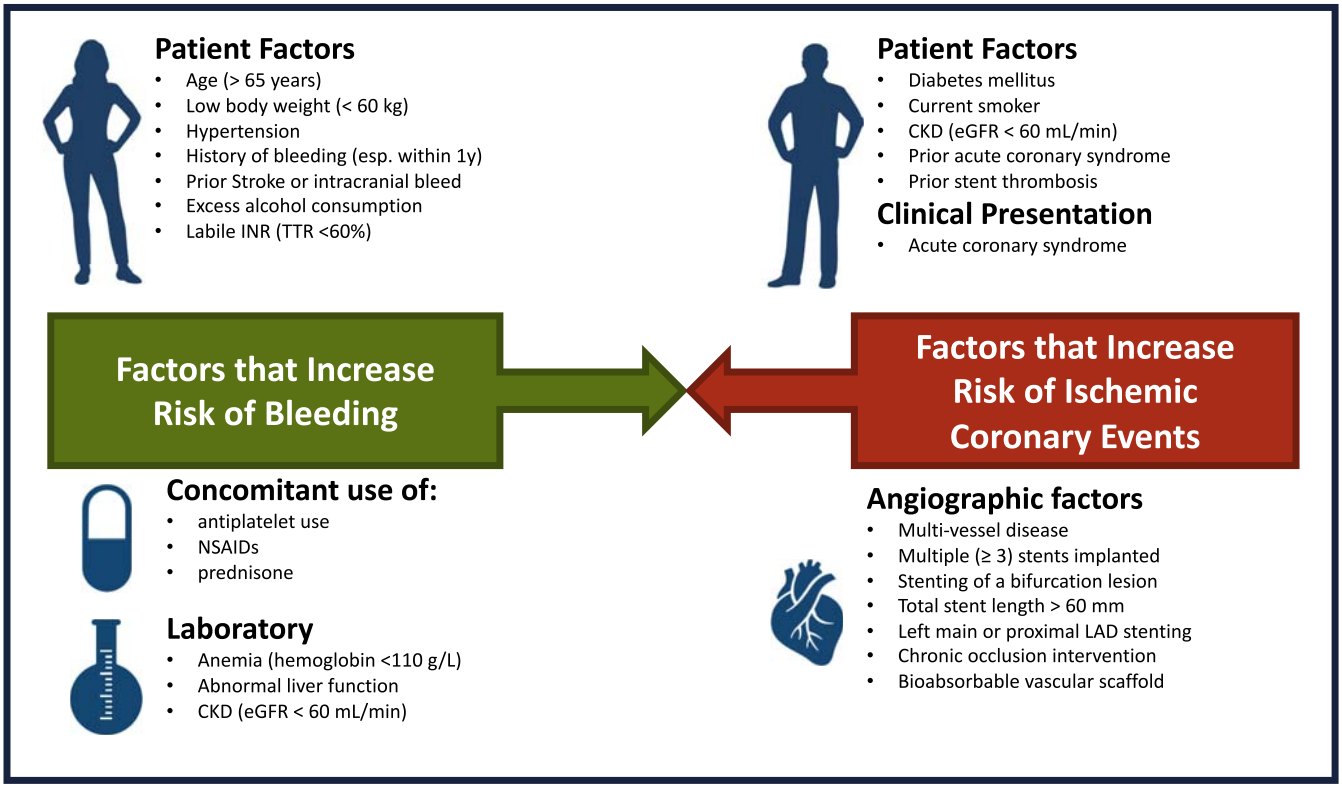


Figure 10. Risk factors associated with an increased risk of bleeding and an increased risk of ischemic coronary outcomes. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; LAD, left anterior descending artery; NSAID, nonsteroidal anti-inflammatory drug; TTR, time in therapeutic range.

Platelet **T**herapy (PRECISE-DAPT), and **Ca**rdiovascular Disease Research Using **Li**nked **B**espoke Studies and **E**lectronic Health **R**ecords (CALIBER), with the former validated in a VKA-treated population, and the latter 2 in a population with CAD treated with PCI and DAPT.[240]

RECOMMENDATION

30. For patients with AF aged 65 years or older or with a $CHADS_2$ score ≥ 1 undergoing PCI without ACS or high-risk features, we recommend dual pathway therapy (OAC with P2Y12) (Strong Recommendation; High-Quality Evidence) for at least 1 month and up to 12 months after PCI (Weak Recommendation; Low-Quality Evidence).

Practical tip. The OAC component evaluated as part of dual pathway therapy regimens include: warfarin daily, apixaban 5 mg BID (reduced to 2.5 mg if they met 2 or more of the following dose-reduction criteria: age older than 80 years, weight $<$ 60 kg, or creatinine $>$ 133 μmol/L), dabigatran 110 mg or 150 mg orally (PO) BID, edoxaban 60 mg PO daily (30 mg in patients with CrCl 15-50 mL/min, body weight $\leq$ 60 kg, or concomitant use of specified potent P-glycoprotein inhibitors), rivaroxaban 15 mg PO daily (10 mg in patients with CrCl 30-50 mL/min). A DOAC is preferred over warfarin, however, if warfarin is used the lower end of the recommended INR target range is preferred. Clopidogrel is the preferred P2Y12 inhibitor. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA-naive).

31. For patients with AF aged older than 65 years or with a $CHADS_2$ score ≥ 1 undergoing PCI for ACS or elective PCI with high-risk features, we recommend an initial regimen of triple therapy (OAC with P2Y12 and ASA 81 mg/d) (Strong Recommendation; Low-Quality Evidence). After ASA discontinuation, which may occur as early as the day after PCI, we recommend that dual pathway therapy (OAC with P2Y12) be continued for up to 12 months after PCI (Strong Recommendation; High-Quality Evidence).

Practical tip. For some patients younger than 65 years of age with $CHADS_2$ score of 1 at the lower end of the stroke risk spectrum (eg, isolated hypertension), DAPT (eg, aspirin and ticagrelor) may be considered in preference to triple therapy (an OAC with P2Y12 and ASA).

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 hypoglycemic agents or insulin, CKD with eGFR $<$ 60 mL/min, current tobacco use, previous ACS, or previous stent thrombosis), as well as PCI-related factors (multivessel PCI, multiple [$>$ 3] stents implanted, total stent length $>$ 60 mm, complex bifurcation lesion, chronic total occlusion intervention, and stent type (eg, bioabsorbable vascular scaffold).

Practical tip. The OAC component evaluated as part of a triple therapy regimens include: warfarin daily, rivaroxaban 2.5 mg PO BID, or apixaban 5 mg BID (reduced to 2.5 mg if they meet 2 or more of the following dose-reduction criteria: age older than 80 years, weight $<$ 60 kg, or creatinine $>$ 133 μmol/L). A DOAC is preferred over warfarin, however, if warfarin is used, the lower end of the recommended INR target is preferred. Clopidogrel is the preferred P2Y12 inhibitor. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA-naive). Thereafter, ASA may be discontinued as early as the day after PCI or it can be continued up to 30 days. The timing of when to discontinue ASA will depend on individual patient's ischemic and bleeding risk.

The population of patients with ACS not needing revascularization (PCI or coronary artery bypass graft [CABG] surgery) represents a heterogenous group. This population includes patients with thrombotic plaque rupture (type I MI) as well as those with supply-demand mismatch (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 with true ACS (type I MI) who are not revascularized, management should take into consideration the relative risk and benefits of combination therapy. Recently, the AUGUSTUS trial affirmed the benefits of apixaban-based dual pathway therapy in medically managed ACS patients.[242]

RECOMMENDATION

32. For patients with AF aged 65 years or older or with a $CHADS_2$ score ≥ 1, we suggest that dual pathway therapy (OAC with P2Y12) be given without concomitant ASA for up to 12 months after medically managed type I ACS (Weak Recommendation; Low-Quality Evidence).

Values and preferences. For patients with AF and type I 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.

8.3.2.5. Key trials of dual pathway therapy vs triple therapy in patients with AF and ACS/PCI

The key trials that have compared dual pathway therapy with VKA-based TT include: the **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) study, the Prevention Of Bleeding In Patients With AF Undergoing PCI (PIONEER AF-PCI) study, the **R**andomized **E**valuation of **D**ual Antithrombotic Therapy With Dabigatran versus Triple Therapy With

Table 8. Trials of antithrombotic therapy for patients with AF and coronary artery disease

Trial	DT	TT	Follow-up	P2Y12 inhibitor	Bleeding* (DT vs VKA TT)	Efficacy outcomes (DT vs VKA TT)	
WOEST (n = 573)[243]	Warfarin and P2Y12 inhibitor	Warfarin with ASA and P2Y12 inhibitor	12 months	Clopidogrel 100%	14.0% vs 31.3%; HR, 0.40; 95% CI, 0.27-0.58	All-cause mortality	2.5% vs 6.3%; HR, 0.39; 95% CI, 0.16-0.93
						Myocardial infarction	3.2% vs 4.6%; HR, 0.69; 95% CI, 0.29-1.60
						Stroke	1.1% vs 2.8%; HR, 0.37; 95% CI, 0.10-1.40
						Stent thrombosis	1.4% vs 3.2%; HR, 0.44; 95% CI, 0.14-1.44
PIONEER AF-PCI (n = 2124)[244]	Rivaroxaban 15 mg and P2Y12 inhibitor	Rivaroxaban 2.5 mg BID and ASA with P2Y12 inhibitor	12 months	Clopidogrel 93%-96% Ticagrelor 3%-5% Prasugrel 0.7%-1.7%	16.8% vs 26.7%; HR, 0.59; 95% CI, 0.47-0.76	Cardiovascular mortality	2.4% vs 1.9%; HR, 1.29; 95% CI, 0.59-2.80
						Myocardial infarction	3.0% vs 3.5%; HR, 0.86; 95% CI, 0.46-1.59
		Warfarin and ASA with P2Y12 inhibitor				Stroke	1.3% vs 1.2%; HR, 1.07; 95% CI, 0.39-2.96
						Stent thrombosis	0.8% vs 0.7%; HR, 1.20; 95% CI, 0.32-4.45
RE-DUAL PCI (n = 2725)[245]	Dabigatran 110 BID and P2Y12 inhibitor	Warfarin and ASA with P2Y12 inhibitor	14 months	Clopidogrel 87%-92% Ticagrelor 8%-13%	17.5% vs 26.9%; HR, 0.65; 95% CI, 0.56-0.75	All-cause mortality	4.9% vs 4.9%; HR, 1.00; 95% CI, 0.71-1.41
						Myocardial infarction	4.0% vs 3.0%; HR, 1.36; 95% CI, 0.89-2.08
	Dabigatran 150 BID + P2Y12 inhibitor				110 mg BID: HR, 0.52; 95% CI, 0.42-0.64	Stroke	1.5% vs 1.3%; HR, 1.13; 95% CI, 0.58-2.18
					150 mg BID: HR, 0.72; 95% CI, 0.58-0.89	Stent thrombosis	1.3% vs 0.8%; HR, 1.55; 95% CI, 0.69-3.46
AUGUSTUS (n = 4614)[247]	Apixaban 5 mg BID and P2Y12 inhibitor	Apixaban 5 mg BID and ASA with P2Y12 inhibitor	6 months	Clopidogrel 93% Ticagrelor 6% Prasugrel 1%	7.3% vs 18.7%; HR, 0.39; 95% CI, 0.31-0.50	All-cause mortality	3.4% vs 3.0%; HR, 1.15; 95% CI, 0.73-1.81
						Myocardial infarction	3.3% vs 3.0%; HR, 1.12; 95% CI, 0.71-1.76
	Warfarin + P2Y12 inhibitor	Warfarin + ASA + P2Y12 inhibitor				Stroke	0.4% vs 2.0%; HR, 0.42; 95% CI, 0.15-1.18
						Stent thrombosis	1.8% vs 1.0%; HR, 1.75; 95% CI, 0.87-3.54
ENTRUST-AF PCI (n = 1506)[246]	Edoxaban 60 mg and P2Y12 inhibitor	Warfarin and ASA with P2Y12 inhibitor	12 months	Clopidogrel 92% Ticagrelor 7% Prasugrel 1%	17.0% vs 20.1%; HR, 0.85; 95% CI, 0.68-1.05	All-cause mortality	6.1% vs 4.9%; HR, 1.25; 95% CI, 0.82-1.90
						Myocardial infarction	3.9% vs 3.1%; HR, 1.27; 95% CI, 0.74-2.17
						Stroke	1.3% vs 2.6%; HR, 0.84; 95% CI, 0.36-1.93
						Stent thrombosis	1.1% vs 0.8%; HR, 1.34; 95% CI, 0.47-3.84

AF, atrial fibrillation; ASA, aspirin; AUGUSTUS, Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation; BID, twice daily; CI, confidence interval; DT, dual pathway therapy; ENTRUST-AF PCI, **E**doxaba**n** **Tr**eatment Vers**us** Vitamin K Antagonist in Pa**t**ients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; PIONEER AF-PCI, An O**p**en-label, Randomized, Controlled, Multicenter Study Explor**i**ng Tw**o** Treatme**n**t Strate**g**ie**s** of **R**ivaroxaban and One of Oral Vitamin K Antagonist in Patients With **A**trial **F**ibrillation Who Undergo **P**ercutaneous **C**oronary **I**ntervention; RE-DUAL PCI, Dual Antithrombotic Therapy With Dabigatran After PCI In Atrial Fibrillation; TIMI, **T**hrombolysis **i**n **M**yocardial **I**nfarction; TT, triple antithrombotic therapy; VKA, vitamin K antagonist; WOEST, **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing.

*ISTH major and clinically relevant nonmajor bleeding, except WOEST TIMI major and minor.

Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial, the Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF PCI) study, and the AUGUSTUS trial.[243-247] Relevant details of these trials are presented in Table 8. Collectively these studies showed that the use of DOACs with a P2Y12 inhibitor was associated with a significant reduction in major bleeding (HR, 0.62; 95% CI, 0.47-0.81), without a statistically significant excess in the occurrence of MI (HR, 1.18; 95% CI, 0.93-1.52), definite stent thrombosis (HR, 1.55; 95% CI, 0.99-2.41), and stroke (HR, 0.89; 95% CI, 0.58-1.36).[246]

When considering these studies, it is important to recognize that a large proportion of patients were undergoing elective PCI for stable CAD (38%-72%), possibly affecting the absolute risk of thromboembolic complications relative to patients with ACS. Second, measures to decrease bleeding risk were underutilized, suggesting that the rates of bleeding in the TT arms might have been greater than in contemporary practice. Third, most of the patients who participated in these trials received clopidogrel as their P2Y12 inhibitor, meaning no conclusions can be drawn about the effects of prasugrel or ticagrelor.

RECOMMENDATION

33. We recommend that clopidogrel 75 mg daily be the preferred P2Y12 inhibitor when dual pathway or triple therapy is used (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes that clopidogrel was the predominant P2Y12 inhibitor used in the landmark randomized controlled trials of combination therapy in AF patients after PCI/ACS, and clopidogrel is associated with the lowest risk of bleeding among the P2Y12 inhibitors in non-AF studies.

8.3.2.6. Duration of triple therapy

The benefit of TT (reduction of recurrent MI and stent thrombosis) must be balanced against the increased bleeding risk with this therapeutic regimen. In the AF population, it is likely that shorter durations of DAPT after ACS or PCI are reasonable when concomitant OAC will be used for the prevention of stroke/systemic embolism. This concept was shown 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 Thrombolysis in Myocardial Infarction [TIMI] major bleeding) between those who received 6 weeks vs 6 months of TT with a significant reduction in any bleeding in the group that received 6 weeks of TT.[248] A post hoc analysis of the AUGUSTUS trial, which compared the risk of bleeding and ischemic outcomes from randomization to 30 days and from 30 days to 6 months showed that aspirin use (ie, TT) was associated with more severe bleeding (absolute risk difference 0.97%) but fewer ischemic events (absolute risk difference −0.91%) in the first 30 days following randomization, when compared to placebo (ie, dual pathway therapy). From 30 days to 6 months, the risk of severe bleeding was higher with aspirin than placebo (absolute risk difference 1.25%) whereas the risk of ischemic events was similar (absolute risk difference −0.17%). As such, it appears that the benefit of triple therapy on ischemic coronary outcomes is limited to the first 30 days of therapy, with continuation of triple therapy beyond 30 days resulting in increased rates of bleeding without reduction in ischemic outcomes. Likewise, the PIONEER AF-PCI and RE-DUAL PCI trials showed no relationship between major adverse cardiovascular events and TT duration.[244,245] On balance, these findings suggest that limiting the course of TT to 1 month, and thereafter continuing dual pathway therapy (OAC and a P2Y12) might achieve the optimal balance of ischemic events prevented and bleeding caused.

8.3.3. Liver disease

The optimal management of patients with AF and advanced liver disease is complex. Patients with advanced liver disease are at increased risk of bleeding because of perturbations in coagulation factor synthesis,[249,250] which was affirmed in a large Swedish registry-based study of 182,678 AF patients.[249] In this study the presence of liver disease was associated with an increased risk of major bleeding (adjusted HR, 1.8; 95% CI, 1.45-2.23) even in the absence of concomitant OAC use.[249] In addition, there is a concern that advanced liver disease results in a prothrombotic state, which might increase the risk of stroke/systemic embolism.[249,251,252] Finally, liver disease results in altered metabolism of VKAs and DOACs, which further complicates OAC choice.[253-257]

Although OACs should be considered in most AF patients with liver disease, the optimal treatment is more challenging because such patients were excluded from the landmark anticoagulation trials. Specifically, patients with significant active liver disease and those with persistent elevation of liver enzymes or bilirubin were excluded from the large RCTs of a DOAC vs VKA.[21-23,25] Although randomized data are limited, observational studies have shown that VKA use in patients with AF and advanced liver disease resulted in reduction of ischemic stroke risk with a higher risk of bleeding complications.[250,252,256-258] Moreover, a post hoc analysis of a prospective observational multicentre study of AF patients showed that the presence of advanced liver fibrosis increased the risk of major bleeding in those who received a VKA, but not in those who received a DOAC.[259] More recently, a nationwide retrospective Taiwanese cohort study reported outcomes in 2428 cirrhotic patients with NVAF who were taking apixaban (n = 171), dabigatran (n = 535), rivaroxaban (n = 732), or a VKA (n = 990).[258] In this study a similar risk of ischemic stroke/systemic embolism between DOAC- and VKA-treated patients was observed, however, the rates of major bleeding (2.9% vs 5.4% per year; $P = 0.0003$) and gastrointestinal (GI) bleeding (1.9% vs 3.6% per year; $P = 0.0030$) were significantly lower with a DOAC. For patients with advanced cirrhosis the DOAC group had a lower risk of ICH (HR, 0.17; 95% CI, 0.03-0.96; $P = 0.04$).

The Child-Pugh score can be used to guide OAC choice in patients with AF and advanced liver disease.[260] This score is commonly used to express the severity of chronic liver disease on the basis of clinical (ascites and encephalopathy) and laboratory (INR, bilirubin, albumin) parameters. When OAC is

being prescribed for AF patients with Child-Pugh grade C cirrhosis it is recommended that a VKA be the preferred agent, because such patients were excluded from the landmark DOAC vs VKA trials.[21-23,25] For those with Child-Pugh grade B cirrhosis it is recommended that rivaroxaban be avoided because it undergoes substantial hepatic metabolism,[253,254] whereas apixaban, dabigatran, and edoxaban may be used with caution in such patients.[256-258,261] Large studies appear to confirm a very low risk of hepatotoxicity with the approved DOACs.[262] The use of the appropriate antithrombotic agent in AF patients with advanced liver disease requires individualized therapy and might benefit from the guidance of an expert multidisciplinary team including a hepatologist and hematologist.

RECOMMENDATION

34. We recommend that OAC not be routinely prescribed for patients with AF and advanced liver disease (Child-Pugh grade C or liver disease associated with significant coagulopathy) (Strong Recommendation; Low-Quality Evidence).

Practical tip. In select patients, OAC might be appropriate even in light of advanced liver disease. In these patients, OAC treatment decisions should be made in collaboration with specialized expertise (eg, hepatologists). VKAs can be considered with careful and frequent monitoring but only if the baseline INR is < 1.7. There is no evidence regarding the safety and efficacy of DOACs in patients with advanced liver disease.

8.3.4. Cancer

AF and malignancy are relatively common conditions, with the prevalence of both increasing with age. Patients with cancer have an elevated risk of AF, possibly because of the presence of comorbid conditions, a local/direct tumour effect, systemic inflammation, altered sympathovagal balance, or as a complication of surgical or targeted therapies (eg, tyrosine kinase inhibitors such as ibrutinib).[263,264] The management of coexisting AF and cancer is challenging, because of the increased rates of thrombosis and thromboembolism observed in association with malignancy, as well as the increased risk of bleeding associated with coagulation defects, blood vessel erosion, tumour vascularity, radiation injury, and the antiplatelet effects of chemotherapies.[265,266] These factors increase the complexity of OAC decision-making.

The evidence for efficacy of anticoagulation among AF patients with cancer comes from several sources. These include 1 population-based retrospective cohort study, 2 retrospective cohort studies, 1 case-control study, and 3 post hoc analyses of the landmark DOAC vs VKA RCTs.[267-273] Among patients where were receiving a DOAC, the annual incidence of thromboembolic events varied from 0.0% to 4.9% with cancer and from 1.3% to 5.1% without; the annual incidence of a major bleed during DOAC treatment varied from 1.2% to 4.4% with cancer and 1.2% to 3.1% without cancer.[274] A large registry using prescription-based analysis for AF patients receiving VKAs or DOACs, with and without cancer reported equivalence for bleeding and thromboembolic risk, although the rates of both were lower in the DOAC population.[270] Within the landmark randomized trials of DOACs vs VKAs, there did not appear to be any significant difference in relative efficacy and safety of DOACs compared with VKAs in patients with and without a history of cancer.[267,271,273] Likewise, RCTs evaluating the cancer-associated venous thromboembolism population have shown that DOACs were noninferior to low molecular-weight heparin (LMWH) for efficacy as well as safety.[275]

The use of the appropriate antithrombotic agent in a patient with a concomitant malignancy requires individualized therapy under the guidance of an expert multidisciplinary team. When myelosuppressive chemotherapy or radiation therapy is undertaken or intensified, further steps to reduce bleeding risk, such as dose reductions or temporary cessation of OAC might be necessary.

RECOMMENDATION

35. We suggest that OAC treatment decisions be individualized for patients with AF and active malignancy, in consideration of the goals of care, the risk of stroke/systemic embolism, the risk of bleeding, and the concomitant antineoplastic therapy(ies) (Weak Recommendation; Low-Quality Evidence).
36. When an OAC is indicated in the presence of active malignancy, we suggest a DOAC in preference to a VKA (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places relatively greater value on the difficulties in ensuring stable INRs and the extensive drug-drug interactions between VKAs and active cancer therapeutic agents.

Practical tip. Although there are no randomized data on the use of DOACs in patients with active cancer and NVAF, this recommendation places a relatively high value on the recognition that DOACs cause no more or less major bleeding compared with VKAs; that they are associated with less ICH compared with VKAs; and on the greater ease of use of DOACs compared with dose-adjusted VKAs. The specific choice of OAC should be tailored according to potential drug-drug interactions.

8.3.5. Congenital heart disease

8.3.5.1. Stratification for anticoagulation

Although the link between atrial arrhythmias and thromboembolic complications is less well established in patients with CHD compared with the general AF population, the existing data appear consistent. Absence of sinus rhythm was found to be the factor associated with the highest prevalence of stroke in a cohort of $>$ 23,000 adults with CHD.[276] Moreover, a strong association was observed between atrial arrhythmias and stroke in a Quebec administrative database study of $>$ 38,000 patients with CHD.[277] As such, questions regarding long-term anticoagulation for atrial arrhythmias frequently arise in the care of adults with CHD.[278]

Two retrospective studies have assessed anticoagulation practices, thromboembolic event rates, and bleeding complications in adults with CHD and atrial arrhythmias. A single-centre retrospective study derived from the **Con**genital **Cor**vitia (CONCOR) registry in the Netherlands followed 229 adults with CHD and intra-atrial reentrant tachycardia (IART), AF, or atrial tachycardia for a median of 6 years.[279] Overall, 67% of patients received a VKA and 7% antiplatelet therapy. The thromboembolic event rate in patients without a mechanical valve was 1.4% per year, with a major bleeding rate of 4.4% per year during treatment with a VKA. In univariable analyses, a CHA_2DS_2-VASc score ≥ 2 was associated with a higher thromboembolic event rate (HR, 3.7; $P = 0.021$). Similarly, a HAS-BLED score ≥ 2 was associated with a higher major bleeding rate in univariable analyses (HR, 2.9; $P = 0.017$).

The **A**nti**c**oagulation **T**herapy **i**n **C**ongenital Heart Disease (TACTIC) study enrolled 482 patients (age 32.0 ± 18.0 years) from 12 North American centres.[280] Although the study was retrospective, it adhered to clinical trial data management standards including blinded adjudication of arrhythmias and outcomes and multiple layers of data quality control. Patients were classified as having simple (18.5%), moderate (34.4%), or severe (47.1%) forms of CHD on the basis of an established classification scheme.[281] OAC, predominantly VKAs, were administered to 54% of participants and antiplatelet agents to 38% of participants. Freedom from thromboembolic events was 89% at 10 years and 85% at 15 years. Rates did not differ significantly according to whether patients had AF vs IART. In multivariable analyses, complexity of CHD was the only factor independently associated with thromboembolism. Corresponding thromboembolic event rates in patients with simple, moderate, and severe forms of CHD were 0.00%, 0.93%, and 1.95% per year, respectively ($P < 0.001$). Notably, no thromboembolic event occurred in patients with simple forms of CHD despite 44% not receiving OAC. In patients with moderate and severe forms of CHD, the thromboembolic event rate exceeded the major bleeding rate associated with a VKA (0.77% per year). Although 93% of the population had a HAS-BLED score of 0 or 1, a higher score was associated with a greater risk of bleeding in multivariable analyses (HR, 3.15; $P = 0.047$). These results were consistent with the concept of incorporating complexity of CHD in stratification decisions for anticoagulation, as proposed by the Pediatric and Congenital Electrophysiology Society (PACES)/Heart Rhythm Society (HRS) expert consensus statement on the recognition and management of arrhythmias in adults with CHD.[282]

RECOMMENDATION

37. We recommend that patients who have CHD and concomitant AF or IART receive an antithrombotic therapy regimen on the basis of a balanced assessment of their risk of AF-related stroke, the complexity of CHD, and the risk of clinically relevant bleeding associated with the use of antithrombotic agents (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places a high value on thromboembolic and bleeding risk scores that are well established in the non-CHD population as well as observational studies specific to the CHD population. It recognizes that complexity of CHD was identified as the most powerful predictor of thromboembolism, with a thromboembolic event rate that exceeds the major bleeding rate during oral anticoagulant treatment in those with moderate or severe CHD, regardless of their stroke risk score.

Practical tip. Moderate or severe CHD is defined in the PACES/HRS expert consensus statement for the management of arrhythmias in adults with CHD.[282]

38. We suggest OAC for most patients with AF or IART and age 65 years or older, $CHADS_2$ score ≥ 1, or CHD of moderate or severe complexity (Weak Recommendation; Moderate-Quality Evidence).

8.3.5.2. Choice of anticoagulant

Evidence on the use of DOACs in adults with CHD and atrial arrhythmias has recently emerged in the form of observational studies, as featured in a recent review.[283] In the first series of 75 adults with CHD receiving DOACs, 57 (76%) were anticoagulated for atrial arrhythmias.[284] No thrombotic or major hemorrhagic event occurred over a mean follow-up of 12 months. Nevertheless, minor bleeds were observed in 47%. An international registry reported a 1-year experience on the use of DOACs in 530 adults with CHD, 482 of whom had atrial arrhythmias.[285] The DOACs consisted of rivaroxaban in 43%, apixaban in 39%, dabigatran in 12%, and edoxaban in 7%. Overall, complexity of CHD was simple in 15%, moderate in 45%, and severe in 40%. Nearly half the population (46%) was considered to have a significant valve lesion. Bioprosthetic valves were present in 11%, with no patient having a mechanical valve. At 1-year of follow-up, the thromboembolic event rate was 1.1%, major bleeding rate 1.3%, and minor bleeding rate 6.3%. In light of this reassuring data and considering that valve disease is common in adults with CHD, it appears reasonable to select a DOAC instead of a VKA in CHD patients with IART or AF and forms of valve disease that are similar to those with reassuring efficacy and safety data from large DOAC trials.[283]

However, thromboembolic and bleeding rates in the large international registry were disproportionately high in the 14% of patients with Fontan palliation, who experienced a remarkable 50% rate of thrombotic and bleeding complications.[285] In a separate series 10 minor bleeding events occurred in 21 patients with Fontan surgery who received DOACs (12 for atrial arrhythmias).[286] One patient with a right-to-left shunt through a fenestration developed deep vein thrombosis during treatment with dabigatran. Another patient receiving apixaban had progression of thrombosis within the Fontan circuit. A separate report described worsening thrombus in a patient with an intracardiac lateral tunnel Fontan and IART during treatment with apixaban.[287] Thus, rigourous comparative safety and efficacy data of DOACs vs VKAs in certain subgroups of patients with severe forms of, including Fontan palliation, are required before DOACs can be endorsed for routine use in this setting.[282]

RECOMMENDATION

39. When OAC is indicated for atrial arrhythmias in adults with simple or moderate forms of CHD, we suggest a DOAC in preference to a VKA in the absence of recent cardiac surgery (< 3 months), a mechanical valve, and atrioventricular (AV) valve stenosis with enlarged and diseased atria (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the growing observational literature that suggests that DOACs appear to have a favourable safety and short-term efficacy (1 year) profile when prescribed for atrial arrhythmias in adults with heterogeneous forms of CHD. It places a high value on established contraindications for DOACs in the context of valvular heart disease and recent cardiac surgery. It also recognizes that there are certain subgroups of patients with severe forms of CHD, such as those with cyanotic heart disease and single-ventricle physiology, in whom there is currently insufficient safety and efficacy data to endorse routine DOAC use. For example, Fontan patients prescribed DOACs were > 6-fold more likely to experience a thromboembolic event than other CHD patients receiving DOACs. There is a need for further research on the safety and efficacy of DOACs in subgroups of patients with severe forms of CHD.

8.3.6. Secondary AF

Although secondary AF has been associated with an increased risk for stroke and mortality irrespective of the precipitant, it is unclear whether the benefits of OAC apply equally to secondary AF patients compared with those with primary AF.[288,289] As such, it remains uncertain whether such patients should be treated with long-term OAC on the basis of the standard stroke risk stratification schema. Until randomized trials assessing OAC in the secondary AF population are available an individualized approach to OAC is warranted. One such strategy would evaluate the likelihood that the secondary AF is "reversible" (ie, AF that occurs solely secondary to an acute illness, with little to no abnormal underlying substrate and therefore limited risk of recurrence) or "provoked" (ie, AF that is unmasked by the acute illness, occurring in patients with significant abnormal underlying substrate and therefore significant risk for recurrence). In both instances OAC might be warranted in selected patients in the short-term (ie, until resolution of the acute AF episode) however the long-term need for OAC should take into consideration a given patient's underlying risk of stroke (eg, CHADS-65), the specific secondary precipitant for AF, and the likelihood of recurrence. In some cases, such as sepsis, the acute administration of intravenous (I.V.) anticoagulation increases the risk of bleeding but does not appear to reduce the risk of ischemic events.[289-291] Conversely, OAC is required for most patients with thyrotoxicosis-related AF because hyperthyroidism shifts the balance of the coagulation-fibrinolytic system toward a hypercoagulable state, acting as an independent risk factor for thromboembolic events.[292-294] Of note, frequent monitoring of INR is advisable when a VKA is used in patients with hyperthyroid-associated AF, because the potency of VKAs will change as the degree of hyperthyroidism changes.[295]

RECOMMENDATION

40. We suggest that patients with secondary AF, which has resolved, not be routinely anticoagulated in the absence of recurrence (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places high value on the recognition that secondary AF is often a self-limited process. In the absence of AF recurrence, the current evidence base is insufficient to recommend long-term OAC. However, some patients and providers might elect to pursue long-term OAC on the basis of assessment of the patients underlying risk of stroke and values and preferences.

41. We suggest that most patients with secondary AF due to thyrotoxicosis be anticoagulated until a euthyroid state is restored (Weak Recommendation; Low-Quality Evidence).

8.3.7. Hypertrophic cardiomyopathy

The risk of stroke/systemic embolism in patients with AF and hypertrophic cardiomyopathy (HCM) is substantial and is significantly greater than in the non-HCM population with AF.[296-301] Stroke/systemic embolism in the HCM population appears to be unrelated to the type of AF (paroxysmal vs persistent) or AF burden.[297] Moreover, traditional risk prediction scores (eg, $CHADS_2$ or CHA_2DS_2-VASc) have not been validated in the HCM population, and do not reliably predict thromboembolic outcomes in the HCM population.[296,297,302] All subjects with HCM who develop AF should started treatment with OAC because there is currently insufficient evidence to support the use of stroke risk prediction tools in the HCM population.[296,297,301,302]

VKAs have been traditionally used as the preferential OAC in subjects with HCM and AF.[303] Observational data subject to selection and ascertainment bias suggest that DOACs are at least as effective as VKAs in preventing thromboembolic events with similar or lower bleeding and safety events, with some studies suggesting improved survival and greater treatment satisfaction with DOACs.[304-306] As such, it is suggested that either DOACs or VKAs can be used to reduce thromboembolic events in subjects with HCM and AF.

RECOMMENDATION

42. We recommend that OAC be prescribed for most patients with AF and HCM (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the knowledge that the annual rate of stroke/systemic embolism in patients with HCM is

substantial, and that the mechanism of stroke in HCM patients differs from the general population, which precludes the use of stroke risk prediction algorithms.

Practical tip. Although there are no randomized data on comparisons of DOACs with VKAs, observational studies suggest these agents might be safe and effective in the HCM population.

8.3.8. Cardiac amyloidosis

Patients with cardiac amyloidosis are at a particularly high risk for thromboembolism due to progressive atrial myopathy, electromechanical dissociation, and reduced LAA emptying velocity. LA thrombus has been reported in up to one-third of patients with cardiac amyloidosis in sinus rhythm, as well as in patients with AF who are receiving therapeutic anticoagulation.[307-309] Among patients with cardiac amyloidosis who undergo cardioversion, 22.4% had intracardiac thrombus identified on TEE, which was significantly more common than in matched controls. Of patients with cardiac amyloidosis with intracardiac thrombus, 4 of 13 had received therapeutic OAC for a period of $\geq$ 3 weeks and 2 of 13 had an AF episode duration of $<$ 48 hours. Patients with amyloid light-chain (AL) amyloidosis appear to be at particularly high risk of intracardiac thrombosis.[310]

There is limited information to inform a specific OAC strategy. Data regarding the safety and efficacy of warfarin and DOACs is limited, however, their use appears to be reasonably safe in patients with cardiac amyloidosis the absence of conventional contraindications.[311]

8.3.9. Frail elderly patients

Improvements in life expectancy have resulted in an increasing number of AF patients being cared for into advanced age.[36,312] Advanced age is a well established risk factor for ischemic stroke and hemorrhagic events in subjects with AF.[313-316] Unfortunately, elderly patients with AF might present with multiple health conditions that might affect QOL (eg, anemia or cognitive impairment/dementia), and/or increase the risk of adverse drug events (eg, impaired renal or hepatic function). In addition, polypharmacy is common in the elderly, which increases the risk of adverse drug reactions due to drug-drug interactions. Further, these patients are often excluded from RCTs, leading to a relative paucity of data to guide treatment decisions.

Unfortunately, despite clear benefit,[21-23,25,270,317] OAC remains underutilized in this population.[317,318] A recent study of older patients with AF noted 35% of OAC-eligible patients did not receive anticoagulation.[317] The major factors responsible for underutilization of anticoagulation in subjects with AF include older age, female sex, abnormal liver enzyme levels, history of falls, excessive alcohol consumption, and concomitant prescription of antiplatelet agents.[318-327] Despite these concerns, there is evidence that the net clinical benefit favours prescription of OAC in this population.[328,329]

Although there are limited RCTs specifically in the elderly population with AF, secondary analyses of the landmark DOAC vs VKA trials did not show a difference in efficacy among subjects aged 75 years or older and those aged younger than 75 years.[330-333] Specifically, a meta-analysis of 4 RCTs (20,165 AF participants 75 years of age or older) showed a significantly lower rate of stroke/systemic embolism in DOAC-treated elderly patients (3.3% vs 4.7%; OR, 0.65; 95% CI, 0.48-0.87), with no significant difference in the rates of major or clinically relevant nonmajor (CRNM) bleeding (6.2% vs 6.6%; OR, 0.82; 95% CI, 0.58-1.16).[334] A pooled analysis from 2 European registries showed that DOAC use was associated with net clinical benefit in AF patients 75 years of age or older; with significant reduction in the composite end point of major bleeding and ischemic cardiovascular events (6.6% per year with DOACs vs 9.1% per year with VKAs; OR, 0.71; 95% CI, 0.51-0.99; $P = 0.042$), which was predominantly due to a lower rate of major bleeding (OR, 0.58; 95% CI, 0.38-0.90; $P = 0.013$) and a trend to reduction in ischemic events (OR, 0.71; 95% CI, 0.51-1.00; $P = 0.05$) with DOACs.[328]

In those at risk of falls, consideration should be made to: provide walking aids and proper footwear; promote cardiovascular, resistance, and balance activities; and, avoid medications that result in hypotension.

RECOMMENDATION

43. We recommend that OAC be prescribed for most frail elderly patients with AF (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places relatively greater value on the observation that elderly AF patients are at higher risk of stroke and, therefore, are more likely to benefit from OAC than younger patients, and places less value on the perceived increased risk of adverse treatment-related events (eg, the risk of bleeding if the patient falls). In general, the net clinical benefit is in favour of anticoagulant therapy in older patients because of the high risk of ischemic stroke.

Practical tip. Treatment decisions regarding specific OAC agents should carefully consider the patient's comorbidity profile, the risk for drug-drug interactions, and the risk of drug-disease interactions.

8.3.10. Increased BMI, obesity, and morbid obesity

Obesity is an established risk factor for the development of AF.[120] Clinicians face challenges regarding dosing of OAC in obese patients, because increasing BMI is independently associated with a higher risk of bleeding but lower risk of stroke/systemic embolism.[335,336] Recent publications regarding outcomes in obese patients enrolled in the landmark DOAC trials are reassuring. A post hoc analysis of the **A**pixaban for **R**eduction **i**n **S**troke and **O**ther **T**hromboembo**l**ic **E**vents in Atrial Fibrillation (ARISTOTLE) trial revealed that the treatment effect of apixaban was consistent with the overall trial results across all of the weight categories (P for interaction = 0.64).[337] Specifically, in 982 patients $>$ 120 kg, there was a significant reduction in major and CRNM bleeding with apixaban (HR, 0.58; 95% CI, 0.35-0.95) with comparable efficacy for stroke/systemic embolism (HR, 0.39; 95% CI, 0.12-1.22), relative to warfarin. The **E**ffective **A**nticoa**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 included 2099 patients (10%) with a BMI of 35-39, 1149 with a BMI > 40 (5.5%), and 148 with a BMI > 50 (0.7%).[335] There was no significant difference in trough edoxaban plasma concentrations and anti-Factor Xa activity across BMI categories, and there was no significant interaction between BMI and clinical outcomes (stroke/systemic embolism, all-cause mortality, major bleeding, major or CRNM bleeding, or the net clinical outcome). 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 enrolled 5206 patients with a BMI > 30.[336] There was no significant treatment interaction by BMI category (< 25, 25-35, or > 35) for either the primary end point of stroke/systemic embolism, or major or CRNM bleeding.[22] Finally, the **R**andomized **E**valuation of **L**ong-term Anticoagulation Therap**y** (RE-LY) trial included 3099 patients > 100 kg. There was no significant treatment interaction by weight category on the rate of stroke/systemic embolism or major bleeding, with dabigatran 110 mg BID and 150 mg BID being at least as effective as warfarin in obese patients.[21,338] Meta-analyses of these phase III trials suggest that DOACs are more effective than warfarin for overweight patients (BMI 25-30: OR, 0.87; 95% CI, 0.76-0.99 for stroke/systemic embolism; OR, 0.83; 95% CI, 0.71-0.96 for major bleeding), and similarly effective in obese patients (BMI > 30: OR, 0.87; 95% CI, 0.76-1.00 for stroke/systemic embolism; OR, 0.91; 95% CI, 0.81-1.03 for major bleeding).[338] Although it is important to note that severely obese patients were not well represented, these meta-analyses provide reassurance that DOACs are at least as effective as warfarin in overweight and obese patients.

8.4. Anticoagulation in special circumstances

8.4.1. Cardioversion

8.4.1.1. Increased thromboembolism risk at the time of cardioversion

The incidence of stroke/systemic embolism is increased after cardioversion. A pooled analysis of 16 studies published between 1960 and 1969 showed a 30-day postcardioversion incidence of thromboembolic events of 1.76% (2665 cardioversions) in patients not receiving OAC with AF of > 48 hours in duration.[339] Similarly, a more contemporary pooled analysis of 10 studies describing outcomes after 3564 cardioversions of AF of > 48 hours duration published between 1986 and 2003 showed a 30-day incidence of thromboembolic events of 2.39% in patients not receiving OAC.[339] These rates contrast with the monthly 0.5% background thromboembolic risk of patients with AF in the absence of OAC when cardioversion has not been performed.[51]

The increased thromboembolic risk associated with cardioversion might be related to 3 phenomena. The first is generation of thrombi during the persistent AF episode, with subsequent embolization after restoration of organized atrial contraction.[340] The second relates to a period of transient atrial mechanical dysfunction after the restoration of sinus rhythm.[341-343] This "atrial stunning" might be responsible for development of new intracardiac thrombi post cardioversion despite the restoration of sinus rhythm.[344,345] Such atrial mechanical dysfunction has been reported with pharmacologic, electrical, and spontaneous cardioversion and is maximal in the period immediately after cardioversion.[344-347] The duration and severity of atrial stunning varies depending on the duration of the atrial arrhythmia, atrial size, and presence of underlying structural heart disease.[344-347] The third possibility is that cardioversion does not directly cause stroke/systemic embolism but rather patients who require cardioversion have transient as well as permanent characteristics associated with a higher stroke/systemic embolism risk.[348]

8.4.1.2. Anticoagulation for cardioversion of AF of > 48 hours

In patients with continuous AF for > 48 hours, observational studies reported a lower 30-day incidence of post cardioversion thromboembolic events in patients who receive OAC than in patients who do not receive OAC (0.45% vs 1.76% in studies from 1960-1969; 0.20% vs 2.39% in studies from 1986-2003).[339] Although none of these studies were randomized, the results are compelling in that patients who received OAC were those at highest risk of stroke/systemic embolism (eg, those with rheumatic mitral stenosis and/or previous thromboembolic events). Accordingly, there is widespread agreement that OAC is required for 3 weeks before and 4 weeks after planned cardioversion in patients who present with either "valvular AF," or NVAF of > 48 hours.

8.4.1.3. TEE instead of 3 weeks of OAC before cardioversion

When cardioversion is desired without 3 weeks of therapeutic OAC another approach is to establish immediate anticoagulation, then perform a TEE to exclude LA thrombi before immediate cardioversion. This practice is supported by the **A**ssessment of **C**ardioversion **U**sing **T**ransesophageal **E**chocardiography (ACUTE) trial, which randomized 1222 patients with nonacute AF to TEE-guided cardioversion or to the conventional 3 weeks of OAC before cardioversion.[349] Although there was no significant difference in the rate of periprocedural thromboembolic events (0.8% in the TEE group vs 0.5% in the conventional group; $P = 0.50$), patients in the TEE group had fewer hemorrhagic events (2.9% vs 5.5%; $P = 0.03$), a shorter time to cardioversion (3.0 ± 5.6 vs 30.6 ± 10.6 days; $P < 0.001$), and more frequently had sinus rhythm restored (71.1% vs 65.2%; $P = 0.03$).

Although other imaging modalities such as cardiac computed tomography (CT), cardiac magnetic resonance (MR) imaging (MRI), and intracardiac ultrasound might have sensitivities and specificities for the detection of LA clot that are comparable with those of TEE,[350] only the use of TEE for screening patients for candidacy for cardioversion has been subjected to an RCT. Accordingly, TEE remains the gold-standard procedure for this purpose; nevertheless, the other procedures listed may be used for this purpose when TEE is contraindicated or is not available.

8.4.1.4. Anticoagulation for cardioversion of AF of ≤ 48 hours

Patients who present with AF of ≤ 48 hours have long been considered, on a theoretical basis, to have a low risk of stroke/systemic embolism after cardioversion. This practice has been supported by observational reports of outcomes after cardioversion in patients with AF ≤ 48 hours, suggesting a low risk of

stroke/systemic embolism in the 30 days after cardioversion (0.27% after 4836 cardioversions in 4380 patients).[339] Although this risk is comparable with that of planned cardioversion in patients with AF of > 48 hours who receive OAC, these reports were limited by selection bias; describing low-risk patients who presented in a stable state early in the 48-hour window, with a significant proportion receiving OAC.[339] Moreover, despite the significant selection bias the rate of stroke/systemic embolism substantially exceeded the established threshold for OAC initiation (1.5% per year or 0.12% per 30 days).[351]

More recent data specifically focused on patients who underwent cardioversion for AF of < 48 hours in the absence of OAC provide a more disquieting viewpoint.[352-359] In the Cleveland Clinic Study[359] consecutive patients having cardioversion of AF of ≤ 48 hours duration were examined, and a significantly higher 30-day postcardioversion rate of stroke/systemic embolism was reported in patients with no or subtherapeutic OAC (0.88%; 6 events after 683 cardioversions) compared with those with therapeutic OAC (0.22%; 2 events after 898 cardioversions; OR, 4.8; $P = 0.03$). In the ANTI-Kogulation Registry[352] 366 consecutive patients with AF of ≤ 48 hours were examined, and a significantly higher rate of LA thrombosis (4% vs 0%; $P = 0.02$) and a nonsignificantly higher rate of 30-day postcardioversion stroke/TIA (1.3% vs 0.5%; $P = 0.58$) was observed in those who did not receive OAC. Although the latter was not statistically significant, it is noteworthy that each of the patients with a stroke/TIA had a $CHADS_2$ score of 0.

The FinCV studies were retrospective, observational studies that determined outcomes after cardioversion of AF in catchment area patients of 8 hospitals in Finland between 2003 and 2016.[353-358] The program enrolled consecutive patients in whom electrical or pharmacological cardioversion was attempted for AF of ≤ 48 hours (FinCV: 3143 patients; 7660 cardioversions), consecutive patients in whom elective electrical cardioversion was attempted for AF of > 48 hours (FinCV2: 1271 patients; 1894 cardioversions), and patients with AF who received DOACs in whom electrical or pharmacological cardioversion was attempted (FinCV3: 1028 patients; 1298 cardioversions). Together these 6 reports, on the short-term outcomes after 10,852 pharmacologic or electrical cardioversions in 5441 patients, demonstrated the following: (1) in the absence of OAC, time to cardioversion is a very strong predictor of 30-day risk of stroke/systemic embolism[354]; (2) in the absence of OAC the incidence of stroke/systemic embolism after cardioversion is significantly higher in patients with AF duration of 12-48 hours than in patients with < 12 hours of AF (1.1% [30/2767 patients] vs 0.33% [8/2440 patients], respectively)[354]; (3) for patients who receive OAC, AF duration is not associated with the incidence of stroke/systemic embolism (0.1% for < 24 hours; 0% for 24-48 hours; 0% for 48 hours to 30 days; and 0.2% for > 30 days)[358]; (4) in the absence of periprocedural OAC, independent predictors of stroke/systemic embolism postcardioversion are older age (OR, 1.05 per year; 95% CI, 1.02-1.08; $P < 0.001$), female sex (OR, 2.1; 95% CI, 1.1-4.0; $P = 0.03$), HF (OR, 2.9; 95% CI, 1.1-7.2; $P = 0.03$), and diabetes mellitus (OR, 2.3; 95% CI, 1.1-4.9; $P = 0.03$)[353,355]; and (5) therapeutic OAC significantly decreases the risk of postcardioversion stroke/systemic embolism.[353-357,360]

Specifically, for patients with AF of ≤ 48 hours the 30 day incidence of stroke/systemic embolism was significantly lower in the presence of OAC (0.13% [3 events in 2298 encounters] vs 0.71% [38 events in 5362 encounters]; $P = 0.001$).[355] When parsed according to CHA_2DS_2-VASc score, OAC use significantly reduced the 30 day rate of definite stroke/systemic embolism in those with a CHA_2DS_2-VASc score of ≥ 2 (0.2% [3/1; 708] vs 1.1% [28/2590]; $P = 0.001$), but the benefit of OAC was not statistically significant in patients with a CHA_2DS_2-VASc score of 0-1 (0.0% [0/590] vs 0.40% [10/2772]; $P = 0.23$). Of note, 10 of the 38 (26%) definite thromboembolic events that occurred after successful cardioversion in patients without OAC occurred in patients with a CHA_2DS_2-VASc score of 0-1.

In 2 other recent reports the thromboembolic risk associated with cardioversion of recent-onset AF in the absence of OAC were indirectly assessed: a report from the Danish National Patient Registry[361] and a report from the Swedish National Patient Registry.[362] Each used administrative databases to evaluate the 30-day rate of stroke/systemic embolism after cardioversion of AF as a function of the presence or absence of precardioversion OAC. Although these databases did not include the duration of AF, the authors proposed that it would be reasonable to assume that cardioversion would only have been performed without previous OAC in patients with recent-onset AF of ≤ 48 hours. In the Danish analysis,[361] the 30-day incidence of stroke/systemic embolism after cardioversion was 1.06% (54 events in 5084 patients) without precardioversion OAC and 0.29% (32 events in 11,190 patients) with precardioversion OAC. Stroke/systemic embolism did occur in patients with $CHADS_2$ or CHA_2DS_2-VASc scores of 0 or 1 but the rates were not stated. In the Swedish analysis,[362] the crude 30-day incidence of stroke/systemic embolism in the absence of precardioversion OAC was significantly higher than in the presence of precardioversion OAC (0.86% [104 events in 12,152 patients] vs 0.33% [35 events in 10,722 patients]). After adjustment for unequal distributions of the CHA_2DS_2-VASc factors, the OR for stroke/systemic embolism in the 30 days after cardioversion was 2.54 (95% CI, 1.70-3.79; $P < 0.001$) without precardioversion OAC relative to patients with precardioversion OAC. Propensity analysis of 9500 patients who did not receive OAC matched with 9500 patients who did receive OAC showed that patients who did not receive OAC were more likely to have stroke/systemic embolism (OR, 2.51; 95% CI, 1.69-3.75; $P < 0.001$) with similar rates of major bleeding (OR, 1.00; 95% CI, 0.48-2.10) relative to those who received OAC.[362] Taken together, the authors concluded that cardioversion in patients with AF of < 48 hours without OAC conferred a greater risk of stroke/systemic embolism than cardioversion for patients with AF of > 48 hours who received OAC.

In summary, the risk of stroke/systemic embolism after cardioversion is elevated, even in patients who present within 48 hours of AF onset. This risk does not differ on the basis of the method of cardioversion (30 day risk of cardioversion of 0.26% with electrical vs 0.39% with pharmacological cardioversion).[363] Immediate cardioversion without 3 weeks of therapeutic OAC appears to be associated with a low risk of stroke/systemic embolism only in patients who presenting within 12 hours of AF onset and in patients who presenting 12-48 hours after AF onset who have a low risk of stroke (eg, patients aged younger than 65 years with a $CHADS_2$ score of 0-1). Other patients deemed to be at higher risk of stroke

should receive at least 3 weeks of therapeutic OAC before cardioversion (or undergo a TEE to exclude LA thrombus). After cardioversion, all patients should receive at least 4 weeks of OAC in the absence of a strong contraindication, and such therapy should be initiated as soon as possible and preferably before the cardioversion.[364] Thereafter, the need for OAC should be on the basis of the risk of stroke/systemic embolism as determined by the "CCS Algorithm" (CHADS-65).

The approach to anticoagulation at time of cardioversion is presented in Figure 11.

RECOMMENDATION

44. We recommend that, in addition to appropriate rate control, most hemodynamically stable patients with AF for whom elective electrical or pharmacological cardioversion is planned should receive therapeutic anticoagulation for at least 3 weeks before cardioversion (Strong Recommendation; Moderate-Quality Evidence).
45. We suggest that TEE may be used to exclude cardiac thrombus, as an alternative to at least 3 weeks of therapeutic anticoagulation before cardioversion (Weak Recommendation; Moderate-Quality Evidence).
46. We suggest that pharmacological or electrical cardioversion of symptomatic AF without at least 3 weeks of previous therapeutic anticoagulation (or TEE) be reserved for patients with the following characteristics (Weak Recommendation; Low-Quality Evidence):
    A. patients with NVAF who present with a clear onset of AF within 12 hours in the absence of recent stroke or TIA; or,
    B. patients with NVAF and a $CHADS_2$ score of 0 or 1 who present after 12 hours but within 48 hours of AF onset.
47. When a decision has been reached that a patient will be undergoing unplanned pharmacological or electrical cardioversion of AF, we suggest that therapeutic anticoagulation therapy be initiated immediately (preferably before cardioversion) with either: (1) a DOAC; or (2) heparin followed by adjusted-dose VKA (Weak Recommendation; Low-Quality Evidence).
48. We suggest that, in the absence of a strong contraindication, all patients who undergo cardioversion of AF receive at least 4 weeks of therapeutic anticoagulation (adjusted-dose VKA or a DOAC) 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 recommendation places relatively greater emphasis on the benefits of stroke prevention and less emphasis on risk of bleeding with a short course of anticoagulation therapy.

Practical tip. When OAC is to be used for only a short period (< 2 months) the use of a DOAC is preferred to adjusted-dose VKA.

8.4.1.5. DOAC or VKA for pericardioversion OAC

Three randomized trials have compared a DOAC with adjusted-dose VKAs in the setting of planned cardioversion of AF.[365-367] A meta-analyses of these 3 RCTs[365-367] showed that DOAC compared with adjusted-dose VKA was associated with significant reduction in stroke/systemic embolism (0.2% vs 0.6%; RR, 0.33; 95% CI, 0.12-0.91; $P = 0.03$),[368] but no significant differences in any bleeding (1.8% vs 2.5%; RR, 0.85; 95% CI, 0.158-1.23; $P = 0.38$),[369] major bleeding (0.4% vs 0.7%; RR, 0.61; 95% CI, 0.28-1.34; $P = 0.22$),[368] or mortality (0.3% vs 0.4%; RR, 0.70; 95% CI, 0.23-2.10; $P = 0.52$).[369] In a meta-analysis that combined these RCT[365-367] data with that from patients having cardioversion in the 4 pivotal trials that compared DOAC with VKA therapy,[370-373] it was reported that no significant differences were observed in the singular outcomes of ischemic stroke, hemorrhagic stroke, mortality, or major bleeding, or in the composite outcome of stroke/systemic embolism with DOACs compared with adjusted-dose VKAs.[374,375] 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.

8.4.2. Catheter ablation of AF

AF ablation is an invasive procedure associated with a risk of stroke/systemic embolism as well as a risk of bleeding. There has been a tremendous amount of research in the past few years regarding periablation OAC management. The use of uninterrupted OAC with a VKA was associated with a lower risk of bleeding and a decreased risk of thromboembolic complications compared with interrupted VKAs with LMWH bridging.[376] More recently, several randomized trials have shown superior safety and efficacy of uninterrupted DOAC (apixaban, dabigatran, edoxaban, and rivaroxaban) compared with uninterrupted VKA.[377-381] For these reasons, uninterrupted OAC has been considered the standard of care for AF ablation. Uninterrupted OAC typically means initiating OAC 3-4 weeks before the procedure, continuing OAC right up to the time of procedure, and reinitiating OAC 6-8 hours after the procedure.

More recently, 2 trials have assessed the safety of "minimal" DOAC interruption.[382,383] On the basis of these trials, it might be reasonable to hold a DOAC for 1-2 doses before ablation with early reinitiation 6-12 hours post ablation.

Intraprocedural anticoagulation is critical to avoid the risk of clinical and subclinical cerebral thromboembolism.[384,385] Anticoagulation during ablation is typically given as I.V. boluses and/or infusion of heparin with frequent measurement of the activated clotting time. More recent guidelines have suggested more aggressive activated clotting time targets of 350-400 seconds to prevent cerebral microembolism.[384,386]

Post ablation management of OAC can be divided into 2 phases: the initial 2 months after the procedure and the period thereafter. Catheter ablation of AF transiently damages the LA endothelium, creating an early prothrombotic state, which

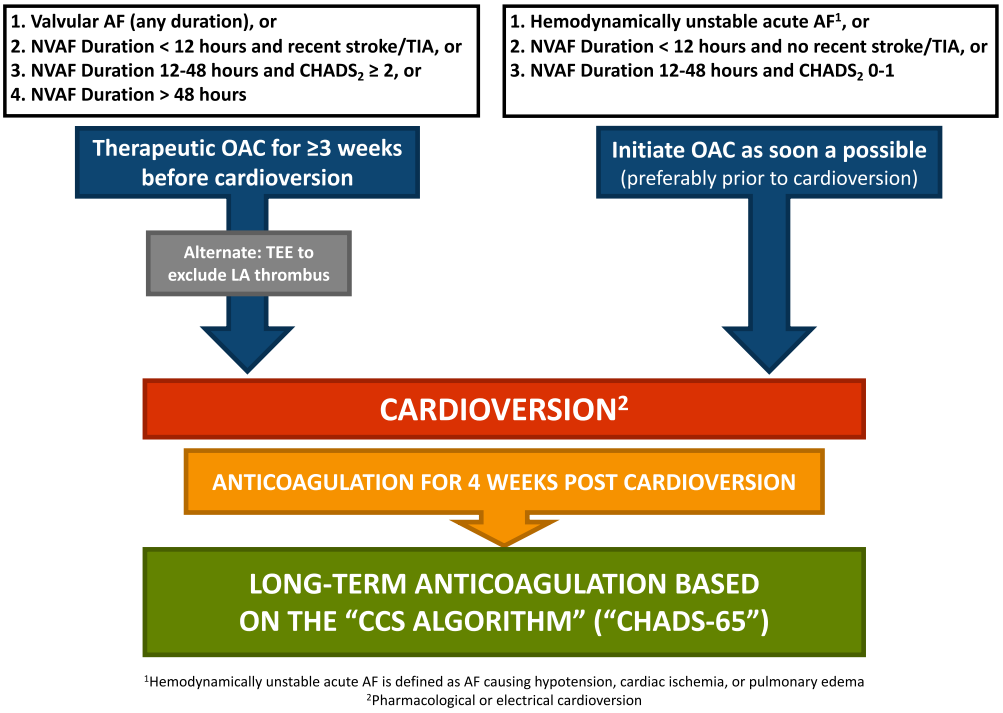


Figure 11. Oral anticoagulation pathway in the context of cardioversion for atrial fibrillation (AF) or flutter. $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; LA, left atrial; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; TEE, transesophageal echocardiogram; TIA, transient ischemic attack.

might lead to thromboembolism. Such a prothrombotic state can occur even in patients considered to have a low risk of stroke/systemic embolism according to traditional risk schema. For this reason, OAC is recommended for at least 2 months after AF ablation. Thereafter, the need for ongoing OAC should be on the basis of the CCS Algorithm (CHADS-65), rather than the apparent success of the ablation procedure. Although limited retrospective data series have suggested a low risk of stroke after successful AF ablation in a wide variety of patient risk profiles, other studies, including the large randomized **C**atheter **Ab**lation vs **An**ti-Arrhythmic Drug Therapy for **A**trial Fibrillation (CABANA) trial, have not shown a significant reduction of stroke post ablation.[387-394] Furthermore, discontinuation of OAC is limited by asymptomatic episodes of AF (meaning patients would be unaware of AF recurrence), late AF recurrence (meaning short-term freedom from recurrent AF might not predict long-term success), as well as a lack of clear temporal association between AF recurrence and stroke/systemic embolism.[75,95,395] Because of the lack of large RCTs to provide a definitive answer on how to manage OAC late after ablation, at this point in time, AF ablation should not be considered as an alternative to OAC. If a patient has a high thromboembolic risk profile, then the patient should continue OAC even after successful AF ablation. If discontinuation of anticoagulation is being considered on the basis of patient values and preferences, regular and prolonged monitoring for AF screening is suggested. The **O**ptimal Anti**c**oagulation for **E**nhanced Risk Patients Post-Catheter **A**blation for Atrial Fibrillatio**n** (OCEAN) trial will provide guidance in the future (NCT02168829).[396]

RECOMMENDATION

49. We recommend that catheter ablation procedures for AF be performed with uninterrupted OAC (Strong Recommendation; High-Quality Evidence).
50. We suggest that after successful catheter or surgical ablation of AF, the decision to continue OAC beyond 2 months after ablation should be determined on the basis of the patient's risk of stroke ("CCS algorithm") and not according to the apparent success of the procedure (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the use of predictive stroke risk indexes in determining long-term stroke risk in all AF and AFL patients, as well as the potential for ongoing risk even after successful ablation.

Practical tip. Limited retrospective and large data series have suggested a low risk of stroke and, therefore, the ability to stop OAC after successful AF ablation. However, there are no randomized trials, or even large prospective studies, to confirm these findings.

8.4.2.1. Catheter ablation of AFL

Patients in sustained AFL need to be anticoagulated for at least 3 weeks before the ablation procedure and at least 1 month after ablation, on the basis of the same principles underlying the rationale for OAC after cardioversion. Similarly, a preprocedural TEE can be used to rule out atrial

Table 9. Perioperative bleeding risk classification

Minimal bleed risk (OAC interruption generally not required)
- Cataract surgery
- Dermatologic procedures (eg, biopsy)
- Gastroscopy or colonoscopy without biopsies
- Coronary angiography (using radial arterial approach)
- Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used)
- Selected procedures with small-bore needles (eg, thoracentesis, paracentesis, arthrocentesis)
- Dental extractions (1 or 2 teeth)
- Endodontic (root canal) procedure
- Subgingival scaling or other cleaning

Low/moderate bleed risk (OAC interruption as per Fig. 13)
- Abdominal surgery (eg, cholecystectomy, hernia repair, colon resection)
- Other general surgery (eg, breast)
- Other intrathoracic surgery
- Other orthopaedic surgery
- Other vascular surgery
- Non-cataract ophthalmologic surgery
- Gastroscopy or colonoscopy with biopsies
- Coronary angiography*
- Selected procedures with large-bore needles (eg, bone marrow biopsy, lymph node biopsy)
- Complex dental procedure (eg, multiple tooth extractions)

High bleed risk (OAC interruption as per Figure 13)
- Any surgery or procedure with neuraxial (spinal or epidural) anaesthesia
- Neurosurgery (intracranial or spinal)
- Cardiac surgery (eg, CABG, heart valve replacement)
- Major vascular surgery (eg, aortic aneurysm repair, aortofemoral bypass)
- Major orthopaedic surgery (eg, hip/knee joint replacement surgery)
- Lung resection surgery
- Urological surgery (eg, prostatectomy, bladder tumour resection)
- Extensive cancer surgery (eg, pancreas, liver)
- Intestinal anastomosis surgery
- Reconstructive plastic surgery
- Selected procedures involving vascular organs (eg, kidney biopsy, prostate biopsy)
- Selected high bleed risk interventions (eg, colonic polypectomy, spinal injection, pericardiocentesis)

CABG, coronary artery bypass graft.

*The radial approach might be considered minimal bleed risk compared with the femoral approach. An up-to-date risk classification tool is available at Thrombosis Canada (thrombosiscanada.ca).

thrombus before AFL ablation if the arrhythmia has been continuous for more than 48 hours without appropriate anticoagulation.[397]

Analogous to AF, it is reasonable to perform catheter ablation procedures for AFL with uninterrupted OAC.

Continued anticoagulation after successful AFL ablation is generally warranted in light of recognition that patients with isolated typical right AFL have an increased risk of later developing AF. The risk of thromboembolic events remains high despite successful AFL ablation.[189,398,399] The main predictors for the occurrence of stroke after AFL ablation are older age, higher CHA_2DS_2-VASc score, recurrence of AFL, and subsequent development of AF.[189,190,399] Multivariate predictors of AF after ablation of AFL include AF before ablation, reduced LV ejection fraction (LVEF), hypertension, increased LA size, inducible AF during the electrophysiology study, endurance sports, and structural heart disease.[400] In patients without a preexisting history of AF up to 20%-40% will develop AF over the 18-36 months after AFL ablation.[189,398,400] In patients with a history of preexisting AF up to 40%-75% will continue to experience AF after AFL ablation.[400] Although there is no RCT on the benefits of continued anticoagulation after AFL ablation, observation data suggest that patients with AFL and a CHA_2DS_2-VASc score ≥ 2 have a higher risk of stroke.[189,190]

8.4.3. Management of OAC for patients undergoing invasive procedures

It is estimated that one in six AF patients who are receiving OAC will require an elective surgery or invasive procedure annually.[401] For these patients, the periprocedural risk of a thromboembolic event with OAC interruption must be weighed against the risk of periprocedural bleeding. An OAC interruption interval that is longer than necessary might increase the thromboembolic risk, whereas an insufficient period of interruption might increase the bleeding risk, with consequent delays in OAC resumption.[402] As such, perioperative anticoagulation management necessitates an assessment of the patient's thrombotic risk, procedural bleeding risk (eg, minimal, low/moderate, and high bleed risk), specific anticoagulant used, renal function, and procedural bleeding risk (Table 9 and Figs. 12 and 13). An electronic tool incorporating these parameters to provide an OAC dosing schedule is provided by Thrombosis Canada (thrombosiscanada.ca).

RECOMMENDATION

51. We recommend that the decision to interrupt antithrombotic therapy for an invasive procedure must balance the risks of a thromboembolic event with those of a periprocedural bleeding event (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. This recommendation is intended to promote a balanced approach to minimize the outcomes of periprocedural thromboembolic events and major bleeding.

Practical tip. The Thrombosis Canada (thrombosiscanada.ca) Perioperative Anticoagulant Management Algorithm is a helpful tool to aid decisions regarding periprocedural anticoagulation.

52. We suggest that interruption of OAC is not necessary for most procedures with a minimal risk of bleeding (Weak Recommendation; Moderate-Quality Evidence).
53. We recommend interruption of OAC for most procedures with a low/moderate or high risk of bleeding, or those for which the bleeding risk associated with the procedure is uncertain (Strong Recommendation; Low-Quality Evidence).

8.4.3.1. No bridging for interrupted VKA in low thromboembolic risk patients

When a decision to interrupt VKA therapy has been made for an invasive procedure with a low/moderate or high risk of bleeding, interruption of VKA without LMWH or unfractionated heparin (UFH) bridging is recommended for most patients at low thromboembolic risk (Fig. 13). The rationale for the avoidance of bridging has come from several sources. A meta-analysis of 33 observational studies and 1 RCT involving

7118 predominantly non-AF patients showed that VKA interruption with bridging therapy was associated with increased overall bleeding (13.1% vs 3.4%; $P < 0.0001$) and increased major bleeding (4.2% vs 0.9%; $P = 0.004$), but without reduction in thromboembolic events (0.9% vs 0.6%; $P = 0.50$) compared with VKA interruption without bridging therapy.[403] As well, in the randomized double-blinded placebo-controlled trial, Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE),[404] 1884 AF patients (most with $CHADS_2$ score < 4) undergoing interruption of VKA for an elective surgery/invasive procedure were evaluated. Patients were randomized to placebo or LMWH from 3 days to 1 day before the procedure, and for 5-10 days after the procedure. No bridging was noninferior to bridging for arterial thromboembolism (0.4% vs 0.3%; $P = 0.01$ for noninferiority), but was associated with significantly less major bleeding (1.3% vs 3.2%; $P = 0.005$ for superiority) and significantly less minor bleeding (12.0% vs 20.9%; $P < 0.001$). There were no significant differences for any other outcomes (all-cause mortality, MI, deep vein thrombosis, or pulmonary embolism).

RECOMMENDATION

54. When a decision to interrupt VKA therapy for an invasive procedure has been made, we suggest that the interruption begin 5 days before the procedure, that a procedure with a 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 (Weak Recommendation; Low-Quality Evidence).

8.4.3.2. Bridging for interrupted VKA in high thromboembolic risk patients

Bridging should be considered only for patients at high risk of stroke/systemic embolism when a decision is made to interrupt VKA therapy for an invasive procedure with a low/moderate or high risk of bleeding. Such patients would include those with "valvular AF" (mechanical heart valves or moderate-severe mitral valve stenosis), NVAF with a $CHADS_2$ score of 5-6, and those with a recent stroke or TIA. Before the procedure, patients should receive 3 days of LMWH bridging, although the dose of LMWH bridging should be reduced by 50% on the day before the procedure (Fig. 13).

RECOMMENDATION

55. When a decision to interrupt VKA therapy for an invasive procedure has been made, we suggest that bridging therapy with LMWH or UFH should be started when the INR is below therapeutic level only in patients at high risk of thromboembolic events (mechanical heart valves, moderate-severe mitral valve stenosis, NVAF with a $CHADS_2$ score of 5-6, and those with a recent stroke or TIA) (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a relatively higher value on prevention of stroke/systemic embolism, and a relatively lower value on the inconvenience and risk of major bleeding associated with heparin bridging.

8.4.3.3. No bridging for interrupted DOACs

Bridging is not necessary for DOAC-treated patients who need DOAC interruption. DOACs have a rapid onset and offset of action and relatively short elimination half-lives (ie, 10-14 hours), rendering bridging unnecessary from a pharmacological perspective.[405] In addition, the use of bridging with interrupted DOAC has been associated with more bleeding and limited efficacy. Increased bleeding with bridging was shown in the prospective observational Dresden Registry (76% rivaroxaban, 24% dabigatran) in which heparin bridging did not reduce major cardiovascular events (stroke, venous thromboembolism [VTE], or ACS; 0.8% with no bridging vs 1.6% with bridging; $P = 0.265$), but led to significantly higher rates of major bleeding complications (2.7% vs 0.5%; $P = 0.010$).[406]

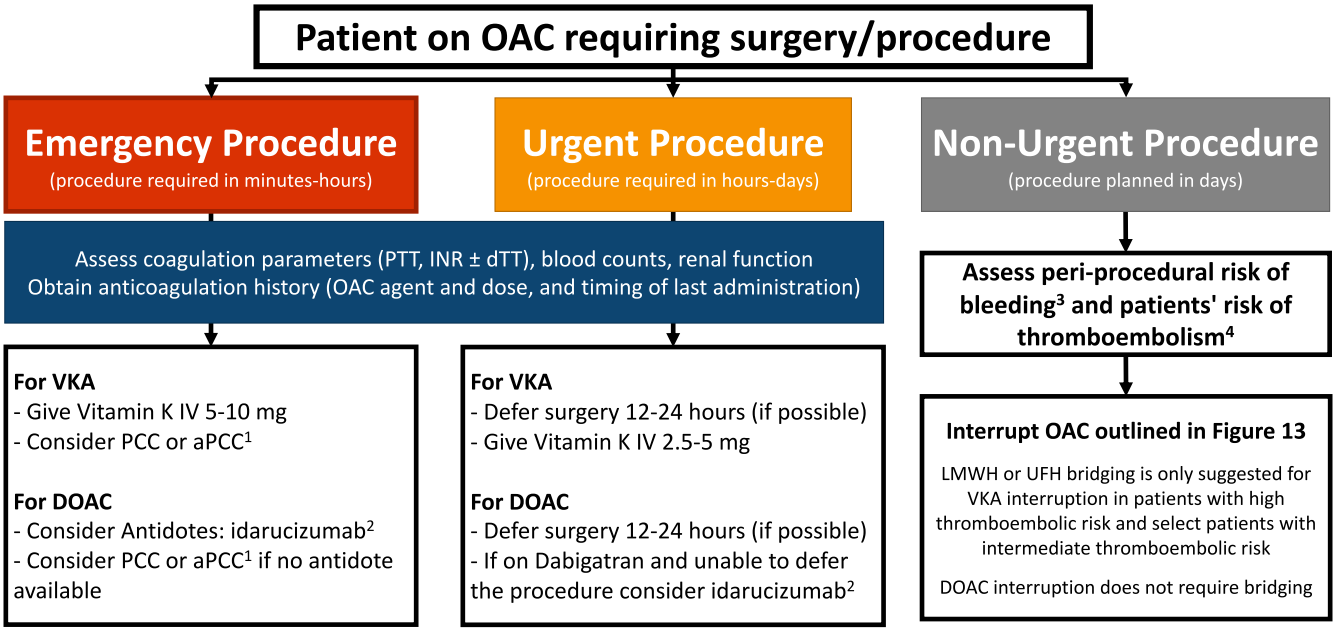
Post hoc analyses of the phase III DOAC trials[21-25] support no bridging for DOAC interruption. Interruption of dabigatran, rivaroxaban, and apixaban without bridging in these studies had comparable rates of bleeding and thromboembolic events compared with their respective VKA groups.[407-409] The **P**erioperative **A**nticoagulant **U**se for **S**urgery **E**valuation for Patients on a Direct Oral Anticoagulant Who Need an Elective Surgery or Procedure (PAUSE) study was a large prospective cohort study of 3007 DOAC-treated AF patients scheduled to undergo an elective surgery or procedure.[410] This study demonstrated the safety with preserved efficacy of a simple standardized DOAC interruption and resumption protocol that did not involve perioperative heparin bridging or preoperative coagulation function testing. Specifically, interruption of DOAC was associated with low rates of major bleeding (1.35% in the apixaban cohort, 0.90% in the dabigatran cohort, and 1.85% in the rivaroxaban cohort) and low rates of stroke/systemic embolism (0.16% in the apixaban cohort, 0.60% in the dabigatran cohort, and 0.37% in the rivaroxaban cohort).

RECOMMENDATION

56. When a decision to interrupt DOAC for an invasive procedure has been made for a patient with AF, we suggest that duration of interruption be on the basis of the risk of bleeding associated with the procedure and the patient's renal function (Weak Recommendation; Low-Quality Evidence).

Practical tip. Duration of preprocedural interruption of a DOAC should be adjusted according to renal function.

57. We recommend no bridging (LMWH or UFH) for NVAF patients requiring DOAC interruption for elective surgery or invasive procedures (Strong Recommendation; Moderate-Quality Evidence).



[1]Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, myocardial infarction, venous thromboembolism), but consequences of uncontrolled bleeding likely exceed this risk
[2]idarucizumab is unlikely to improve outcomes in patients taking dabigatran with a dilute thrombin time TT <30 ng/mL, normal thrombin time, or a drug level <50 ng/mL
[3]Procedure bleeding risk is outlined in **Table 9**
[4]Patients considered to be high risk of thromboembolism include those with valvular AF (mechanical heart valves or moderate-severe mitral valve stenosis), non-valvular AF with a $CHADS_2$ score of 5-6, and those with recent TIA/Stroke (within 3 months).

Figure 12. Management of oral anticoagulant (OAC) use for patients requiring surgical procedures. aPCC, activated prothrombin complex concentrates; DOAC, non-vitamin K direct oral anticoagulant; dTT, dilute thrombin time; INR, international normalized ratio; I.V., intravenous; LMWH, low molecular-weight heparin; PCC, prothrombin complex concentrate; PTT, partial thromboplastin time; UFH, unfractionated heparin; VKA, vitamin K antagonist.

Interruption of OAC for Non-Urgent Procedures

OAC		Day -5	Day -4	Day -3	Day-2	Day-1	Procedure	Day +1	Day +2	Day +3	Day +4
Warfarin Usually no need to interrupt VKA for procedures with low bleeding risk	*VKA*	No VKA	No VKA	No VKA	No VKA	INR[2]	None	VKA[5,6]	VKA[5,6]	VKA	VKA
	Heparin Bridging[1]	No LMWH	No LMWH	LMWH	LMWH	INR[2,3]	None	LMWH[6,7]	LMWH[6,7]	LMWH	LMWH
DOAC[4]	*Low/Moderate bleeding risk*	DOAC	DOAC	DOAC	DOAC	None	None	DOAC[6,7]	DOAC[6,7]	DOAC	DOAC
	High bleeding risk	DOAC	DOAC	DOAC	None	None	None	None	DOAC[6,7]	DOAC	DOAC
Dabigatran + CrCl <50 mL/min	*Low/Moderate bleeding risk*	DOAC	DOAC	DOAC	None	None	None	DOAC[6,7]	DOAC[6,7]	DOAC	DOAC
	High bleeding risk	DOAC	None	None	None	None	None	None	DOAC[6,7]	DOAC	DOAC

[1]Patients in need of bridging during interrupted VKA therapy include those with valvular AF (mechanical heart valves or moderate-severe mitral valve stenosis), non-valvular AF with a $CHADS_2$ score of 5-6, and those with a recent stroke or transient ischemic attack.
[2]INR should be performed the day prior to the procedure. If >1.5 then consider administering vitamin K PO/IV.
[3]Give morning LMWH for bid dosed regimens (or ½ daily LMWH dose for once daily dosed regimens).
[4]This schedule applies to factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) and dabigatran (but only when dabigatran is used in patients with a CrCl ≥50 mL/min).
[5]VKA therapy resumption following an invasive procedure may occur almost immediately given it will take several days for the INR to become therapeutic.
[6]Consider withholding anticoagulation therapy for the first 72 hours following cardiac surgery
[7]DOAC/LMWH resumption following an invasive procedure should only occur once hemostasis has been achieved.

Figure 13. Anticoagulation interruption schedule for patients undergoing elective or nonurgent surgery. The need for oral anticoagulation (OAC) interruption is outlined in Figure 12. There is usually no need to interrupt vitamin K antagonists (VKAs) for procedures with low bleeding risk. Certain low bleeding risk procedures may be performed with uninterrupted direct oral anticoagulant (DOAC) use, depending on the patients' risk of stroke/systemic embolism and physician judgement. For patients undergoing OAC interruption for procedures with low/moderate or high risk of bleeding, the suggested OAC interruption schedule is outlined. Low molecular-weight heparin (LMWH) bridging should be performed for VKA patients at high risk of stroke/systemic embolism ($CHADS_2$ score 5-6, mechanical heart valves, or recent thromboembolism) with enoxaparin 1 mg/kg twice daily, enoxaparin 1.5 mg/kg once daily, dalteparin 100 IU/kg twice daily, dalteparin 200 IU/kg once daily, or tinzaparin 175 IU/kg once daily. AF, atrial fibrillation; bid, twice daily; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; INR, international normalized ratio; CrCl, creatinine clearance; I.V., intravenous; PO, orally.

8.4.3.4. OAC resumption

After the invasive procedure, DOAC is reintroduced after hemostasis has been achieved (usually 24 hours after a low/moderate bleed risk procedure and 48-72 hours after a high bleed risk procedure). VKA therapy may be reintroduced on the same evening after the procedure, recognizing that it will take several days for the INR to achieve therapeutic range. When bridging LMWH is used, we suggest using a therapeutic-dose regimen for 3 days before the procedure and to resume 24 hours after a low/moderate bleed risk procedure and 48-72 hours after a high bleed risk procedure. In selected patients, for example, those undergoing a cardiac, intracranial, or spinal procedure, it is suggested to forego postprocedure LMWH bridging altogether, although low-dose heparin regimens, typically used for VTE prophylaxis, can be considered post procedure.

The recommended approach to OAC interruption is presented in Figures 12 and 13 and Table 9.

RECOMMENDATION

58. When OAC has been interrupted for an invasive procedure we suggest that such therapy be restarted when hemostasis is established (within 24 hours for a procedure with a low risk of bleeding and within 48-72 hours for a procedure with a high risk of bleeding) (Weak Recommendation; Low-Quality Evidence).

Values and preferences. Recommendations regarding the timing of postprocedural reintroduction of antithrombotic therapy are intended to promote a balanced approach to minimizing the combined outcome of postprocedural thromboembolic events and major bleeding.

8.5. Bleeding

8.5.1. Prevention

Bleeding is a known adverse effect of OAC. Despite the similar or lower risk of bleeding with DOACs vs VKAs, there remains a significant residual 2%-4% annual risk of major bleeding. Assessment of bleeding risk is important to understand the risk-benefit balance of OAC, to identify and optimize modifiable bleeding risk factors, to identify patients who might benefit from more frequent follow-up, and to provide a framework for ongoing monitoring. The use of a validated bleeding risk prediction algorithm appears to be better at predicting major bleeding than using individual modifiable bleeding risk factors.[411-413] Despite lack of supportive RCT evidence, the identification of modifiable bleeding risk factors before OAC initiation and at each point of contact should be routinely done.

GI protection for patients at high risk of GI events and require concomitant ASA or NSAID therapy has been associated with a reduction in GI bleeding and ulcer complications. In one of the earliest studies, albeit a small study with limited number of events, patients with acute GI bleeding or obstruction due to ulcer who received *Helicobacter pylori* eradication therapy restarted ASA 100 mg daily treatment with lansoprazole 30 mg daily or placebo.[414] The trial was stopped early after the second of 2 planned interim analyses revealed a statistically significant reduction in recurrent bleeding in the patients who received lansoprazole (1.6% vs 15%; HR, 10.6; 95% CI, 1.3-86.1). Subsequently the benefit of using a PPI for patients with no baseline evidence of peptic ulcer disease who required daily ASA (in doses ranging from 75 to 325 mg daily) was shown in the Randomized, Double-Blind, Placebo-Controlled Study to Assess the Prevention of Low Dose Acetylsalicylic Acid (ASA) Associated Gastroduodenal Lesions and Upper Gastrointestinal Symptoms in Patients Taking Esomeprazole 20 mg Once Daily for Two Weeks (ASTERIX) study.[415] In 991 patients 60 years of age or older, the additional use of esomeprazole 20 mg daily reduced the risk of endoscopically diagnosed gastric and duodenal ulcers (1.6% with esomeprazole vs 5.4% with placebo; $P = 0.0007$). In addition, the use of PPIs lowered the risk of upper GI bleeding in patients who required DAPT with ASA and clopidogrel in the **C**lopidogrel and the **O**ptimization of **G**astrointestinal Ev**ent**s Trial (COGENT) trial, and decreased the occurrence of peptic ulcers in patients at high concomitant risk of cardiovascular and GI events who were taking ASA in the Randomized, Double-Blind, Parallel Group, Multicentre, Phase III Study to Assess the Effect of Esomeprazole 20 or 40 mg od Versus Placebo on the Occurrence of Peptic Ulcers During 26 Weeks in Subjects on Continuous Low Dose Acetylsalicylic Acid (OBERON) trial.[416,417]

There is no published RCT in which PPI use was investigated in patients with AF who were receiving standard stroke prevention dose OAC alone or in combination with or. In a retrospective cohort study of > 1.6 million Medicare beneficiaries who were receiving anticoagulation, PPI co-therapy was associated with a lower rate of upper GI bleeding hospitalizations: incidence rate ratio, 0.66 (95% CI, 0.62-0.69).[418] However, more recently in the COMPASS - Proton Pump Inhibitor (COMPASS-PPI) study[419] the effect of PPI use in patients receiving ASA in combination with rivaroxaban 2.5 mg BID was investigated. In this study, patients with stable atherosclerotic vascular disease and no clinical need for a PPI who were receiving 1 of 3 regimens: rivaroxaban 2.5 mg BID with ASA 100 mg daily, rivaroxaban 5 mg BID, or ASA 100 mg daily without anticoagulation, were randomized to pantoprazole 40 mg daily or placebo. The main reason for exclusion from the PPI arm of this trial was physician judgement that their patients had a clinical need for a PPI; this accounted for more than 35% of eligible patients (n = 9797). Of the 17,598 patients randomized, the mean age was 68 years, 78% were male, and 2.6% had baseline peptic ulcer disease. These patients were followed for a mean of 3 years. Clinically significant GI events were no different in the 2 arms: 1.2% in the PPI arm vs 1.3% in the placebo arm (HR, 0.88; 95% CI, 0.67-1.15). The event rate in the non-randomized cohort was 0.6%. In an analysis of the individual GI events included in the primary outcome, there was a reduction in overt gastroduodenal bleeding with pantoprazole (0.4% per year) over placebo (1.2% per year; HR, 0.52; 95% CI, 0.28-0.94; $P = 0.03$). In addition, the rate of discontinuation of pantoprazole was similar to that of placebo overall (21.4% vs 22.4%) and for serious adverse events (0.9% vs 0.75%). Of note, a Cochrane review is currently under way to assess the benefits and harms of PPIs vs histamine-2 receptor antagonists or placebo for the prevention of upper GI bleeding in adults receiving single-agent and combination antithrombotic therapy for cardiovascular conditions.[420]

RECOMMENDATION

59. We recommend initial and ongoing evaluation of bleeding risk for all patients with AF whose stroke risk warrants antithrombotic therapy, with the use of strategies to mitigate the increased risk of bleeding associated with OAC (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places greater emphasis on routinely and systematically evaluating bleeding risk factors in patients who are receiving antiplatelet or OAC with emphasis on modifying bleeding risk when possible and less emphasis on using a bleeding risk stratification score to determine whether to initiate antithrombotic therapy or not.

Practical tip. Individual patient bleeding risk should be taken into account when determining the strategy for stroke risk management. The use of the HAS-BLED algorithm might be valuable to identify patients at high risk of major bleeding who might benefit from more frequent follow-up.

Practical tip. Emphasis should be placed on the identification of modifiable risk factors to decrease the risk of major bleeding at each medical encounter. These include BP control, avoidance of unnecessary antiplatelet and NSAID therapy, management of anemia, limiting alcohol intake, improving INR control, and ensuring patients are receiving DOAC doses that align with the Health Canada-approved dosing recommendations.

Practical tip. Patients receiving OAC should be educated regarding self-monitoring for bleeding, including when to seek medical help.

60. We suggest the additional use of a PPI to decrease the risk of GI adverse effects, for patients who require daily antithrombotic therapy that includes ASA (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places greater value on the published RCT evidence of decreased GI complications, including GI bleeding, with the additional use of a PPI with antithrombotic therapy, and lesser value on the short duration of PPI treatment used in the trials and the fact that the trials did not specifically enroll patients with AF.

Practical tip. Gastroprotection with a PPI has been shown to decrease the risk of GI ulceration and other adverse bleeding events in patients receiving daily ASA who are older than 60 years or have at least 1 other risk factor for bleeding. It stands to reason that this benefit would be extended to patients receiving the combination of daily ASA and anticoagulation, despite the lack of published evidence in this patient group.

8.5.2. Management of a bleeding event

DOACs are the preferred agents for stroke prevention in NVAF patients who merit anticoagulation. Although less life-threatening bleeding was shown with DOACs, annual rates of major bleeding were observed to be 2%-4%.[21-23,25] Bleeding management protocols for DOACs have included supportive therapy alone, antifibrinolytic therapy, hemostatic factors such as fresh-frozen plasma, 3- or 4-factor prothrombin complex concentrates, and recombinant activated factor VII; activated charcoal for overdose or unintentional ingestion; dialysis or continuous renal replacement therapy; and, specific reversal agents such as idarucizumab and andexanet alfa. An approach to bleeding is outlined in Figure 14.

RECOMMENDATION

61. In patients experiencing a bleeding event with OAC treatment we recommend investigation into the cause of the bleeding (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the recognition that patients who experience a GI or genitourinary bleeding event after OAC initiation are at higher risk of having an underlying malignancy discovered as the cause of their bleeding.

62. We recommend that anticoagulant therapy should be recommenced in patients at high risk of stroke as soon as possible after the cause of bleeding has been identified and corrected (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the recognition that OAC discontinuation after a bleeding event is associated with a significant increase in the risk of stroke and all-cause mortality.

Idarucizumab is a humanized monoclonal antibody fragment that binds to protein-bound and unbound dabigatran with high affinity, neutralizing dabigatran and its active metabolites.[421] In phase I trials with > 200 volunteers, idarucizumab was well tolerated.[422-424] In the **Revers**al **E**ffects of Idarucizumab on **A**ctive **D**abigatran (REVERSE-AD) trial, adults with overt, life-threatening bleeding (n = 301) or those requiring urgent invasive procedures (n = 202) while receiving dabigatran received idarucizumab as two 2.5-g bolus infusions up to 15 minutes apart.[425] In those with overt bleeding, 137 (45.5%) presented with GI bleeding and 98 (32.6%) with ICH. Urgent surgery was defined as a procedure requiring normal hemostasis that could not be delayed for at least 8 hours. The median maximum percent reversal of the anticoagulant effect of dabigatran was 100% within 4 hours of idarucizumab administration in those who had a prolonged dilute thrombin time or ecarin clotting time at baseline (92%). Reversal was rapid and occurred independently of age, sex, renal function, and baseline dabigatran concentration. was 2.5 hours after idarucizumab administration in 134 patients (45%) with uncontrolled bleeding, and all had confirmed bleeding cessation within 24 hours. Of the 197 patients who underwent surgery, periprocedural hemostasis was assessed as normal or mildly abnormal in 98.5%. At 30 days, thrombotic

events occurred in 4.8% and the mortality rate was 13.5% in those with uncontrolled bleeding and 12.6% in those requiring an urgent procedure. Postmarketing experience in large, practice-based cohorts of consecutive patients, has shown hemostatic effectiveness and clinical outcomes similar to those seen in REVERSE-AD.[426,427]

RECOMMENDATION

63. 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 a 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. Reversing OAC exposes patients to the thrombotic risk of their underlying disease. OAC should be reintroduced as soon as medically appropriate.

Andexanet alfa is a recombinant modified human factor Xa decoy protein with high affinity for the active site of factor Xa inhibitors, sequestering them within the vascular space.[428] In patients requiring anticoagulation that involves inhibition of Factor Xa, the presence of andexanet alfa will inhibit the anticoagulant effectiveness. The pharmacodynamic half-life is approximately 1 hour. The Andexanet Alfa, A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) was a single-group cohort study designed to assess the efficacy and safety of andexanet alfa in patients with acute major bleeding occurring while taking a factor Xa inhibitor. Patients who had received 1 of 4 factor Xa inhibitors (apixaban, edoxaban, enoxaparin, or rivaroxaban) within 18 hours were treated with a bolus and 2-hour infusion of andexanet alfa.[429] The dose of andexanet alfa was dependent on the timing of the last dose of factor Xa inhibitor. Patients were excluded if they required surgery within 12 hours, if they received other bleeding treatments such as prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma, and if they had a Glascow Coma Scale of < 7, an estimated ICH volume of > 60 mL, or an expected survival of < 1 month. Patients enrolled ($n = 352$) had a mean age of 77 years. Bleeding was predominantly ICH (64%) and GI (26%). Most of the patients were receiving apixaban (54%) or rivaroxaban (36%). Anti-factor Xa activity decreased by 92% for apixaban (149.7 ng/mL to 11.1 ng/mL) and rivaroxaban (211.8 ng/mL to 14.2 ng/mL). Of 249 patients who were eligible for the hemostatic efficacy analysis, 204 were adjudicated as having excellent or good hemostasis at 12 hours. Reduction in anti-factor Xa activity was not predictive of hemostatic efficacy overall but was modestly predictive in patients with ICH. At 30 days of follow-up of the overall study population 49 (14%) of the patients had died and 34 (10%) had a thrombotic event. All thrombotic events occurred before reinitiation of OAC.

Andexanet alfa received accelerated Food and Drug Administration approval in the United States in 2018 for the management of life-threatening or uncontrolled bleeding in patients treated with rivaroxaban and apixaban.[430] A condition of this accelerated approval was the requirement to complete an RCT including patients with acute ICH, the results of which might affect the modification or withdrawal of approval. The Food and Drug Administration also mandated a black box warning that andexanet alfa has been associated with thromboembolic events, ischemic events, cardiac arrest, and sudden death. There appears to be some increase in endogenous thrombin generation potential upon bolus administration of andexanet alfa although the mechanism is not yet known[431] and did not appear to be associated with clinical thrombotic events in healthy volunteers.[428] The thrombosis rate in a single health system retrospective cohort study of 13 patients who received andexanet alfa was 30% (4 patients) and mortality was 15% (2 patients).[432] In another, the thrombosis rate was 0 and mortality was 40%.[433] Practical challenges reported with andexanet alfa include access to product, lack of availability of anti-factor Xa levels, and drug preparation requiring reconstitution of multiple vials.[433]

RECOMMENDATION

64. We recommend administering andexanet alfa (when available) for emergency reversal of the anticoagulant effect of apixaban, edoxaban, and rivaroxaban in patients who present with uncontrollable or potentially life-threatening bleeding who have received any of these agents within the preceding 18 hours (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places relatively greater value on the ability of andexanet alfa to reverse anti-factor Xa activity and its potential to facilitate hemostasis, and less value on the low risk of infusion reactions and the absence of a control group in the ANNEXA-4 trial.

Practical tip. Patients who are anticipated to require unfractionated or low molecular-weight heparin within 12-24 hours should not receive andexanet alfa.

Practical tip. The dose of andexanet alfa is on the basis of the specific FXa inhibitor, the dose the patient is taking, and the timing of the last dose before the bleed.

Practical tip. Reversing OAC exposes patients to the thrombotic risk of their underlying disease. There is evidence of thrombin generation after administration of andexanet alfa. OAC should be reintroduced as soon as medically appropriate.

8.6. Secondary stroke prevention

8.6.1. Stroke during OAC treatment

Use of OAC is associated with a substantial risk reduction in the occurrence of ischemic stroke (see section 8.2),

however, some patients treated with OAC will still experience ischemic stroke or TIA despite use of OAC.[51,52] Studies have shown that strokes that occur in patients receiving OAC tend to be less severe than strokes that occur in AF patients not taking OAC; in VKA-treated patients, stroke severity has been inversely correlated with INR level at the time of the event.[434,435]

After confirmation of the stroke diagnosis, an on-treatment event should prompt an evaluation for potential causes (other than AF) and ensure optimization of OAC and risk factor management.

RECOMMENDATION

65. We recommend that patients with AF who experience an ischemic stroke while receiving OAC be managed acutely according to the secondary stroke prevention practice guidelines (eg, Canadian stroke best practice recommendations[118]), with emphasis on addressing OAC medication adherence, ensuring correct OAC dosing and avoidance of drug interactions, identifying and treating other potential causes for the stroke other than AF, and promoting general vascular risk factor modification and healthy lifestyle choices (Strong Recommendation; Moderate-Quality Evidence).

8.6.1.1. Potential causes of an ischemic stroke in a patient receiving OAC

I. Inadequate intensity of anticoagulation. In patients treated with VKAs, a subtherapeutic INR is associated with an increased risk of stroke as well as greater stroke severity.[434,435] In those treated with DOACs, undertreatment (eg, low plasma levels) has been associated with higher risk of thromboembolic events, and increased stroke severity (eg, large vessel occlusion).[205-207,436] For DOAC-treated patients, undertreatment might take the form of the prescription of a reduced dose without an indication to do so, failure to anticipate drug-drug interactions (eg, OAC levels might be decreased by interaction with anticonvulsants such as phenytoin) or, in the case of rivaroxaban, a failure to account for GI absorption. Specifically, rivaroxaban should be taken with food for maximum GI absorption.

II. Suboptimal medication adherence or persistence. Poor patient adherence is a common problem with many chronic medications, adherence and persistence to stroke prevention therapies being particularly problematic in the AF population. As outlined in section 7.2 suboptimal adherence and persistence with OAC has been associated with higher rates of all-cause mortality and stroke.[156,157,160-162] Missed doses is a particular concern for DOACs because of their short half-life (average 12 hours). Strategies to improve persistence and adherence are outlined in section 7.2 and Table 6.

III. Alternate stroke etiology. Patients with AF might have other etiologies for stroke, some of which require specific management. Examples include large artery atherosclerosis of the intra- or extracranial circulation, cerebral small-vessel disease, other cardiac sources of embolism (eg, patent foramen ovale) or another determined cause (carotid or vertebral artery dissection, vasculitis, etc).

IV. Suboptimal risk factor management. Untreated or suboptimally controlled stroke risk factors (eg, hypertension, dyslipidemia, etc) might contribute to the occurrence of stroke, independent of the presence of AF. Of particular importance, reduction in BP reduces the risk of recurrence of ischemic stroke as well as incident hemorrhagic stroke.[118]

8.6.1.2. Practical clinical approach to patients with an ischemic stroke who are receiving OAC therapy

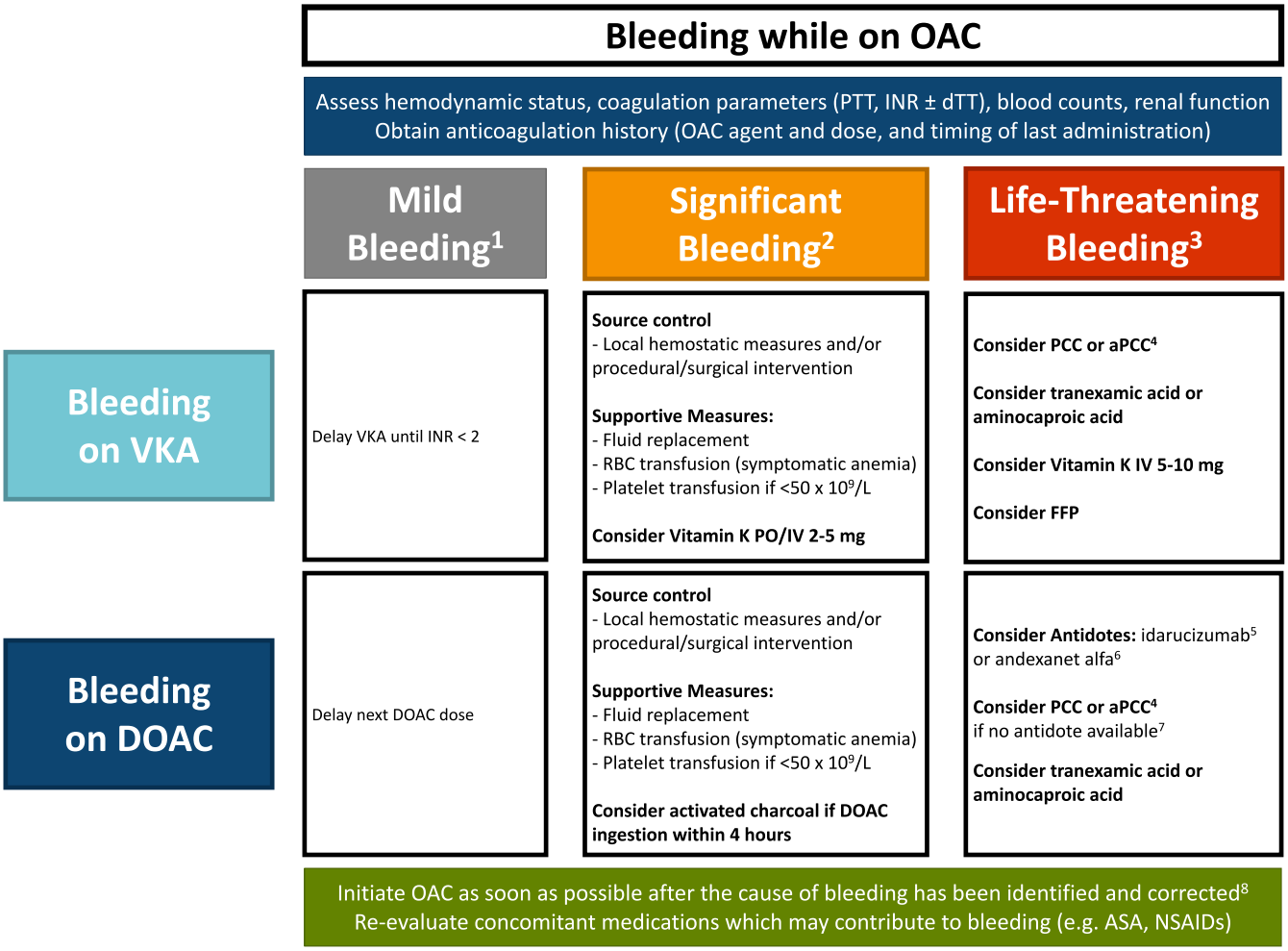
I. Ensure an accurate diagnosis of the event. Brain imaging with CT or MRI is recommended for the diagnostic evaluation of acute stroke to exclude ICH, hemorrhagic transformation of ischemic stroke, and other structural pathology (MRI has greater diagnostic sensitivity than CT for identifying acute ischemia and small lesions). TIAs are frequently overdiagnosed, with up to 60% of patients suspected to have had a TIA having nonischemic causes for their symptoms after systemic evaluation.[437,438] Although TIA remains a clinical diagnosis mainly on the basis of a detailed history of the event, brain imaging is useful in assessing for mimics (eg, migraine aura, seizure, peripheral vertigo, presyncope, neuropathy, multiple sclerosis) including small subarachnoid hemorrhages.[439]

II. Investigate for the most likely etiology of the stroke event. A typical etiological stroke workup for a patient with known AF consists of brain imaging (CT or MRI); vascular imaging (carotid ultrasound at a minimum; ideally CT angiography or MR angiography from the aortic arch to vertex), echocardiography, and laboratory investigations.

III. Determine if any other treatments are indicated for stroke risk reduction. For example, symptomatic carotid artery stenosis that is moderate (50%-69%) or severe (70%-99%) might benefit from urgent revascularization, whereas nonsurgical management is usually recommended for asymptomatic carotid stenosis.[118]

IV. Assess medication adherence. Patients and/or family members should be questioned regarding missed doses or prolonged interruptions (eg, periprocedural or in association with a bleeding event). For VKA-treated patients, the INR record for the preceding months should be reviewed. Patients should be counselled about the importance of daily medication adherence, the dangers of missed doses, and avoidance of prolonged or unnecessary treatment interruptions. Encourage adherence- and persistence-enhancing strategies as outlined in section 7.2 and Table 6.

V. Determine whether or not any changes are needed to the patient's current OAC (agent or dose). For VKA-treated patients with suboptimal INR control, either switch to a DOAC (if eligible) or aim for improved INR control (consider a higher target INR and more frequent INR monitoring). For DOAC-treated patients, it is reasonable to continue the same DOAC (after ensuring it is at the correct dose for the patient's age, renal function, and body weight) or switch to a different DOAC. For patients unable to comply with DOACs, then a switch to a VKA



[1]Examples of mild bleeding include extremity bruising, hemorrhoid bleeding, subconjunctival bleed, self-limited epistaxis.
[2]Examples of significant non-life-threatening bleeding include hemodynamically stable gastrointestinal bleed, epistaxis, hematuria, or menstrual bleeding, requiring medical attention and/or intervention.
[3]Examples of severe life-threatening bleeding include intracranial hemorrhage, or severe gastrointestinal bleed with actual or impending hemodynamic instability, retroperitoneal bleed, intramuscular bleed with compartment syndrome.
[4]Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, myocardial infarction, venous thromboembolism), but consequences of uncontrolled bleeding likely exceed this risk.
[5]Idarucizumab is unlikely to improve outcomes in patients taking dabigatran with a dilute thrombin time (dTT) <30 ng/mL, normal thrombin time, or a drug level <50 ng/mL.
[6]Pending approval and availability.
[7]Do not administer hemostatic agents (PCC, aPCC, rVIIa) if antidote has been given.
[8]A delayed restart is recommended when the bleed occurred in a critical site, the patient has a high risk of rebleeding or of death from a rebleed, the source of the bleed cannot be identified, or future surgical interventions are planned.

Figure 14. Management of bleeding for patients receiving oral anticoagulation (OAC). aPCC, activated prothrombin complex concentrates; ASA, acetylsalicylic acid; DOAC, non-vitamin K direct oral anticoagulant; dTT, dilute thrombin time; FFP, fresh frozen plasma; INR, international normalized ratio; I.V., intravenous; NSAID, nonsteroidal anti-inflammatory drug; PCC, prothrombin complex concentrate; PO, orally; PTT, partial thromboplastin time; RBC, red blood cell; rVIIa, recombined activated factor VII; VKA, vitamin K antagonist.

might be reasonable because of the longer half-life and ability to monitor the INR. The additional use of an antiplatelet agent is sometimes considered, however, the additional use of an antiplatelet agent with therapeutic OAC is associated with a significant increase in bleeding events without an additional benefit for stroke prevention. LAA occlusion (LAAO) might be an option for some patients but the optimal candidates for this procedure remains unclear.

VI. Identify and address any untreated vascular risk factors. Optimize BP and lipids, recommend smoking cessation, and promote general secondary stroke prevention lifestyle recommendations (diet, exercise).

For further details on the etiological stroke workup and secondary stroke prevention treatment recommendations, see the Canadian stroke best practice recommendations[118] available at: strokebestpractices.ca.

8.6.2. Timing of OAC initiation after acute ischemic stroke in patients with AF

In the 2-week period immediately after a TIA or ischemic stroke, patients with AF have an increased risk of ischemic stroke that ranges from 0.5%-1.3% per day.[440,441] Initiation of OAC during this phase must balance the benefit of OAC with the risk of hemorrhagic transformation of the acute brain infarct. Hemorrhagic transformation can range from asymptomatic petechiae to symptomatic parenchymal hematoma with mass effect.[442,443] Hemorrhagic transformation is more frequent in large-volume infarcts and in the setting of thrombolysis or mechanical revascularization of the index stroke.[442,443]

The optimal timing for OAC initiation post stroke has not yet been clearly defined and practice patterns are highly variable.[444] RCTs are under way to help address this uncertainty. For now, the heterogeneity of strokes and the lack of randomized data (particularly for DOACs in the early poststroke period) preclude any specific recommendations regarding the timing of OAC initiation. In practice, treatment decisions are typically individualized on the basis of a benefit-risk assessment guided by brain imaging appearance and clinical context. Bridging with low-dose aspirin is often prescribed until OAC treatment is initiated. Serial head CT scans within the first days or weeks post stroke can be helpful to monitor the evolution of an acute infarct, especially for moderate or large infarcts, and to assess for the presence and extent of any hemorrhage, before OAC treatment initiation.

Outcomes in relation to timing of OAC initiation have been studied in prospective cohort studies.[445,446] In the Clinical Relevance of Microbleeds in Stroke-2 study 1490 participants with AF and stroke or TIA in whom anticoagulation was indicated were enrolled.[446] Of these, 1335 (90%) had a known date of OAC initiation post stroke that was dichotomized as early (≤ 4 days) or late (≥ 5 days or never). The groups differed significantly, with lower stroke severity, better premorbid functioning, and a lower probability of thrombolysis for the index event in those in the early OAC group. At 90 days of follow-up the combined end point of intracerebral hemorrhage, ischemic stroke, and death was similar between groups (2% with early and 5% with late initiation; adjusted OR, 1.17; 95% CI, 0.48-2.84; $P = 0.736$). Recognizing that the event rate was low, the authors concluded that there did not appear to be a hazard associated with early anticoagulation in carefully selected patients. Results of a prospective cohort study consisting of 1029 individuals with ischemic stroke and AF suggested that initiation of anticoagulation between 4 and 14 days optimized the combined outcome of stroke, TIA, systemic embolus, symptomatic intracranial bleeding, and bleeding within 90 days of onset.[445] Most participants were treated with VKAs or mixed treatment protocols including heparin, with only 12% treated with DOACs.

Results of 2 small RCTs have suggested the early use of DOACs is safe for small strokes using an MRI measure of hemorrhagic transformation.[447,448] Participants (N = 195) randomized to VKA or rivaroxaban with a median National Institutes of Health Stroke Scale (NIHSS) score of 2 (ie, very mild strokes) did not differ in the rate of hemorrhagic transformation detected using MRI, an imaging modality with high sensitivity for the detection of hemorrhage.[447] The Dabigatran Following Acute Transient Ischemic Attack and minor stroke trial (DATAS II) randomized 301 individuals with a median NIHSS score of 1 (ie, very mild strokes) to ASA or dabigatran within 72 hours of symptom onset. No symptomatic hemorrhagic transformation was observed and the rate of minor petechial hemorrhage within the acute infarct did not differ between the treatment arms. Infarct volume predicted the probability of hemorrhagic transformation.[448] These trials do not establish optimal time points for OAC initiation but suggest that an identifiable group of patients with very mild stroke severity and small volume infarcts can be safely anticoagulated early.

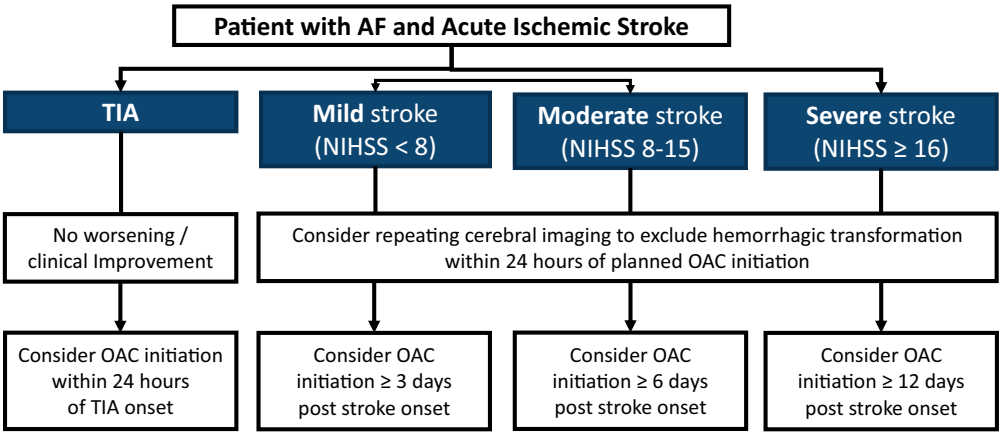
RECOMMENDATION

66. We recommend that the timing of initiation of anticoagulant therapy after an ischemic stroke should be individualized and take into account the competing risks of recurrent stroke against the risk of hemorrhagic transformation of infarction (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. The timing of OAC initiation or resumption might be as short as within 24 hours in patients with a TIA, 3 days in patients with a mild stroke (NIHSS score < 8), 6 days in patients with a moderate stroke (NIHSS score 8-15), and 12-14 days in patients with a severe or large stroke (NIHSS score ≥ 16). Factors favouring delayed OAC initiation include: high NIHSS score (> 8), moderate-large brain infarction on imaging, hemorrhagic transformation, neurological instability, advanced patient age, and uncontrolled hypertension. In these patients OAC treatment decisions should be made in collaboration with specialized expertise (eg, neurology).

In the absence of definitive data, the following is a pragmatic approach to the timing of OAC initiation or resumption after an ischemic stroke event.

I. It is reasonable to initiate a DOAC 1 day post event for patients with a TIA, 3 days for patients with a small infarct/mild stroke severity (NIHSS score < 8), 6 days in patients with a moderate-sized infarct/moderate severity stroke (NIHSS score 8-15), and 12-14 days in patients with a large infarct/severe stroke (NIHSS score >15). For a brief-duration TIA with no residual symptoms or deficits and no acute infarct or hemorrhage on head CT scan, it is reasonable to consider DOAC initiation on the day of the event provided timely follow-up is available (Figure 15).
II. It is reasonable to delay OAC initiation for more than 2 weeks post stroke if, in the judgement of the clinician the risk of bleeding is believed to be high (eg, for some patients with large infarcts and those with hemorrhagic transformation).
III. If OAC initiation is recommended after hospital discharge, coordination with the treating physicians and close follow-up is suggested because postdischarge recommendations are implemented in only two-thirds of patients.[449]
IV. Hypertension is a significant risk factor for intracerebral hemorrhage, and it is reasonable to delay OAC in the setting of uncontrolled hypertension.



Factors Favouring Delayed Initiation of OAC	Factors Favouring Early Initiation of OAC
Hemorrhagic transformation	Mechanical heart valve
Large/moderate volume infarction	Intracardiac thrombus
High NIHSS	Intraluminal thrombus
Fluctuating neurologic status	Left atrial spontaneous echo contrast
Uncontrolled hypertension	Hypercoagulability
Coagulopathy	

Figure 15. Oral anticoagulation (OAC) initiation or reinitiation after an acute ischemic stroke. The timing of OAC initiation should be evaluated on the basis of the severity of stroke, the risk of short-term recurrence, and the risk of secondary hemorrhagic transformation. AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

V. In most instances, brain imaging should be repeated before initiating OAC to detect asymptomatic hemorrhagic transformation that might influence the timing for OAC initiation. Consideration should be given to delaying OAC in patients with hemorrhage other than minor petechial changes, because OAC in the presence of existing hemorrhage might increase bleeding. Delayed initiation in patients with hemorrhagic transformation was not associated with increased risk of ischemic stroke in an observational study of > 2000 patients with stroke and AF.[450]
VI. Neurological instability might suggest recurrent ischemia or hemorrhage and in either case, might require a repeat CT examination or reassessment of the timing of OAC initiation.

8.6.3. OAC initiation after hemorrhagic stroke

For patients with AF who have had an acute primary intracerebral hemorrhage, subdural, or subarachnoid hemorrhage, OAC is typically avoided in the acute-subacute period, and decisions regarding OAC initiation should be made in consultation with a stroke/neurology specialist on the basis of careful risk stratification guided by brain MRI appearance, the presumed etiology for the hemorrhage, and the estimated risk of recurrence. Patients with a lobar (superficial) ICH attributed to cerebral amyloid angiopathy have a higher risk of recurrent ICH than patients with a deep hypertensive ICH. If OAC is initiated post-ICH, a DOAC is preferred over VKAs because of the lower rate of incidence of ICH with these agents.[52] Observational studies support the cautious use of OAC for selected patients post ICH, usually initiated weeks to months post ICH, but clinical equipoise exists.[451,452] RCTs are currently under way to evaluate the safety and efficacy of DOAC vs aspirin in AF patients who have had an ICH.

8.7. Left atrial appendage occlusion

Imaging and postmortem studies suggest that most AF-associated ischemic strokes are cardioembolic, and that the majority arise from the LAA.[453,454] In sinus rhythm the LAA has pulsatile flow, however in AF appendage emptying is reduced leading to stasis and clot formation. Physical elimination of the LAA (removal or occlusion) from the circulation is postulated to prevent thrombus formation and subsequent embolization, without suffering from the limitations of pharmacological therapy. Specifically, although OAC is effective at preventing AF-associated stroke/systemic embolism, its use is limited by short- and long-term nonadherence, nonpersistence, and side effects such as the risk of major bleeding. Conversely, when performed, the effects of the physical elimination of the LAA are considered permanent and are not reliant on patient compliance.

8.7.1. Percutaneous LAAO

Two RCTs and a number of single and multicentre registries that have evaluated percutaneous device closure have been performed. The WATCHMAN LAA Closure Technology for Embolic **Protect**ion in Patients With **A**trial **F**ibrillation (PROTECT AF) study enrolled 707 patients with AF and a $CHADS_2$ score of $\geq$ 1, and the **P**rospective **R**andomized **Eva**luation of the WATCHMAN LAA Closure Device **i**n Patients With Atrial Fibrillation vs **L**ong-Term Warfarin

Therapy (PREVAIL) study enrolled 407 patients with a $CHADS_2$ score of ≥ 2.[455,456] Both studies randomized patients to LAAO or VKA. The 5-year outcome data from these 2 studies were combined in a meta-analysis.[457] Although LAAO was deemed noninferior to VKAs for the combined end points, much of the benefit of LAAO is due to a reduction in intracranial bleeding (0.2% per year with LAAO vs 0.9% per year with VKA; HR, 0.20; 95% CI, 0.07-0.56; $P = 0.002$).[457] However, the effect of LAAO on ischemic stroke remains to be determined, and is suggested to be inferior (1.6% per year with LAAO vs 0.95% per year with VKA; HR, 1.71; 95% CI, 0.94-3.11; $P = 0.08$).[457] Higher risk of ischemic stroke might relate to device-related thrombosis, which occurs in 2%-4% of cases and is a known independent predictor of stroke (HR, 4.4; 95% CI, 1.05-18.43).[458] In the recently published randomized multicentre Left Atrial Appendage Closure Versus Novel Anticoagulation Agents in Atrial Fibrillation (PRAGUE-17) study the safety and efficacy of LAAO was compared with DOAC in high-risk AF patients with a history of significant bleeding or thromboembolic event while receiving OAC (CHA_2DS_2-VASc score 4.7 $\pm$ 1.5; HAS-BLED score 3.1 $\pm$ 0.9). This study showed no significant difference between LAAO and DOAC, with similar rates of all-cause stroke/TIA (2.20% with LAAO vs 2.68% with DOACs), ischemic stroke/TIA (2.20% with LAAO vs 2.38% with DOACs), and major and CRNM bleeding (5.5% per year with LAAO vs 7.42% per year with DOACs). There was no difference in the end points of cardiovascular death, noncardiovascular death, or all-cause mortality. Major LAAO implant-related complications occurred in 4.5%. LAAO implantation was unsuccessful in 10.0% of the patients, however, the results of the study did not differ when analyzed according to treatment received ($P = 0.31$) or per protocol ($P = 0.40$).

RECOMMENDATION

67. We suggest that percutaneous LAAO be considered for stroke prevention in patients with NVAF who are at moderate to high risk of stroke and have absolute contraindications to OAC (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the evidence from multiple RCTs which showed significant benefit of VKAs and DOACs in the prevention of stroke/systemic embolism, relatively low risk of bleeding, and significant survival advantage, as well as the relative lack of data supporting LAAO for OAC-eligible patients.

Practical tip. Patients should receive individualized counselling regarding the risks and benefits of stroke prevention therapy, with a focus on the evidence supporting long-term OAC as the preferred strategy.

Practical tip. Contraindications to long-term OAC include but are not limited to: recurrent nontraumatic intracranial bleeding with high risk of recurrence, recurrent irreversible pulmonary bleed, recurrent irreversible urogenital bleed, recurrent irreversible GI bleed, recurrent irreversible retroperitoneal bleed, esophageal varices, intraocular bleeds, hereditary hemorrhagic telangiectasia.

8.7.2. Surgical LAAO

The device-based trials provide proof of concept that LAAO might provide benefit, however they do not address the surgical AF population, do not inform on the combination of LAAO and OAC, and do not evaluate a surgical intervention that can be offered with little increase in risk.

Results of existing observational studies suggest that stand-alone surgical LAAO can be safely and effectively performed, however, there are limited high-quality data to suggest that a stand-alone surgical LAAO approach is reasonable in patients eligible for a percutaneous approach.[459]

In patients with AF who are already undergoing a thoracotomy, it is possible that concomitant surgical LAAO might offer significant benefit with minimal incremental risk. However, it is important to recognize that patients who undergo surgical LAAO often have higher CHA_2DS_2-VASc scores and more often have coexisting valvular heart disease (ie, are more likely to develop AF-associated thrombosis outside of the LAA).[454] To date the observational data of concomitant surgical LAAO are somewhat conflicting, with some observational series suggesting that surgical LAAO is associated with significantly greater freedom from stroke/systemic embolism, and others suggesting that LAAO did not reduce the incidence of stroke/systemic embolism in patients with AF ($P = 0.69$), with the apparent stroke reduction being related to continued VKA use and not the LAAO procedure itself.[460,461] However, these observational studies do not have sufficient power or freedom from bias to provide the level of evidence needed to clearly answer this important question. A large RCT of surgical exclusion of the LAA vs VKA therapy has completed recruitment of > 4800 patients and is in the follow-up phase.[462] The primary end point is stroke/systemic embolism over 4 years. Total mortality and safety end points will also be compared. Until this trial is completed, the only basis for recommendations regarding surgical LAA removal is consensus. As such, we have made a weak recommendation on the basis of the existing low-quality evidence.

RECOMMENDATION

68. We suggest surgical LAAO be considered for stroke prevention in patients with NVAF who are at moderate to high risk of stroke and have contraindications to OAC, and who are not suitable for percutaneous LAAO (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation is qualified by the patient's stroke risk in relation to their perioperative risk.

Practical tip. Patients should receive individualized counselling regarding the risks and benefits of stroke prevention therapy, with a focus on the evidence supporting long-term OAC treatment as the preferred prophylactic strategy.

69. We suggest concomitant surgical LAAO be considered in patients with AF who are undergoing an open chest cardiac surgical procedure and who are ineligible for long-term OAC (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation is qualified by the patient's stroke risk in relation to their incremental surgical risk with concomitant LAAO, and that the contraindication for OAC is absolute.

Practical tip. In patients with AF who are eligible for long-term OAC the evidence to date is insufficient to support a recommendation for or against concomitant surgical LAAO. In these patients it is recommended to continue OAC after surgical LAAO.

8.8. Cognitive function/dementia

An association between AF and cognitive impairment has been frequently reported over the past 30 years.[463,464] Although the association has not been consistently observed,[465,466] recent meta-analyses have shown a significant correlation between AF and cognitive impairment, irrespective of a history of previous stroke.[467-469] It has been estimated that the risk of dementia in individuals with AF and no overt cerebrovascular events is increased 30%-60% compared with patients without AF, even after adjustment for age, sex, multiple comorbidities, and cardiovascular medications.[470-472] An American study of community-dwelling individuals showed that AF was associated with a 50% increase in risk of developing Alzheimer disease compared with individuals without AF.[473] The findings are not just unique to North America and Europe, with a Taiwanese study involving 332,665 patients,[470] and a South Korean study of 262,611 patients[472] demonstrating that patients with AF had a 42% and a 63% higher risk of dementia, respectively, even after adjustment for age, sex, baseline differences, and medication. More recent data suggest that AF increases the risk of vascular and degenerative (eg, Alzheimer disease) dementia,[474,475] and also that the relationship between AF and cognitive decline appears to be strongest when AF develops in middle age,[476,477] when the AF is persistent and of long duration,[477,478] and when the ventricular rate in AF is fast.[479,480]

Although AF is related to cognitive impairment and dementia, the etiological mechanisms remain a matter for conjecture. Shared risk factors have been proposed as part of the explanation. The $CHADS_2$ and CHA_2DS_2-VASc scores have been shown to predict cognitive impairment as well as stroke in patients with AF. Nevertheless, the association between AF and cognitive decline persists even after controlling for age and these comorbidities.[467,470,481] Proposed mechanisms include silent cerebral infarcts due to microemboli, cerebral microbleeds, disruptions of the blood-brain barrier, cerebral vascular disease, cerebral hypoperfusion due to variability in the cardiac cycle and reduced cardiac output, oxidative stress, inflammation, and endothelial dysfunction.[471,482-485] Of these, subclinical embolic cerebrovascular ischemia is thought to be the most likely mechanism.[485] Although white matter disease had been raised as another potential driver, recent work appears to refute this.[482,486,487]

Treatments that have been proposed to reduce the risk of cognitive impairment include risk factor management,[488] sinus rhythm maintenance with ablation,[489] and anticoagulation.[490-492] A modest effect has been observed with specific risk factor treatments, such as statins or angiotensin conversion enzyme inhibitor and angiotensin receptor blocker therapy in some studies,[481,488] but not in others.[493] There also remains controversy concerning the ability of anticoagulants to decrease the incidence of cognitive impairment and dementia in patients with AF,[494] with reviews of the available literature failing to find convincing evidence that they do so.[495,496] Although positive data continue to accumulate, including from large population-based studies,[497,498] there have been no clinical trials to eliminate potential confounders. VKA use appears to be most effective when TTR is kept consistently very high (eg, > 75%).[499,500] Data relating to the DOACs and dementia are sparse, with some studies showing relative benefit compared with VKAs,[491,501,502] whereas a nationwide Danish cohort study did not.[503] Several clinical trials are being undertaken to allow greater clarity. In 2 of these studies, VKAs are being compared with dabigatran (**Co**gnitive **I**mpairment **R**elated to **A**trial **F**ibrillation Prevention Trial [GIRAF; NCT01994265] and Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients With Non-Valvular Atrial Fibrillation [CAF; NCT03061006]) and in a third study, **B**linded **R**andomized Trial of **A**nticoagulation to Prevent **I**schemic Stroke and **N**eurocognitive Impairment in **A**trial **F**ibrillation (BRAIN-AF; NCT02387229), rivaroxaban is being compared with standard of care.

There are currently only 2 observational studies on the association between catheter ablation and cognitive dysfunction. The largest was a retrospective case-control study from Intermountain Health in Utah, in which outcomes in 4212 patients who underwent AF ablation were compared with 16,848 age- and sex-matched patients with AF who did not undergo ablation. At 3 years, the incidence of dementia was low in both groups, but it was significantly less in the AF patients who had undergone ablation.[489] A small prospective case-control study was recently published, which involved 308 AF patients treated with ablation and 50 medically managed control participants.[504] Cognitive function was assessed at baseline, 3 months, and 1 year. Significant cognitive improvement was observed at 3 and 12 months in the ablation group compared with the control group, and no major adverse events were reported at either point in time. A larger prospective case-control study (Cognitive Impairment in Atrial Fibrillation [DIAL-F]; NCT01816308) is specifically addressing the effect of AF catheter ablation on dementia and is currently under way.

Finally, LAAO might be expected to have a potential role on decreasing the incidence of cognitive impairment on the basis of subclinical strokes. However, whether the available devices can prevent microemboli remains to be seen.

9. Arrhythmia Management

9.1. Acute management of AF

The acute management of AF is centred on the following domains:

1. Determination if AF is the primary concern ("primary AF") or secondary to another acute medical illness ("secondary AF"). AF in the setting of critical illness has been associated with an increased risk of death (see section 11.5).[505,506] Unfortunately, there is a paucity of high-quality evidence on whether or how to treat AF patients in the setting of critical illness,[507,508] and there is a wide variety of reported approaches to AF management in this setting.[509] In the ED setting, results of a retrospective study suggested that rate and rhythm control efforts in patients with AF secondary to acute medical illness (predominantly sepsis and acute HF) might be associated with higher rates of adverse events.[510]
2. Determination of hemodynamic stability, defined as AF causing hypotension, ACS, or pulmonary edema. Acute unstable AF should be treated with synchronized direct current cardioversion (DCCV), however, instability solely due to AF is rare, therefore, an underlying precipitant should also be aggressively sought and managed.[511]
3. Determination of an arrhythmia management strategy, defined as rate vs rhythm control. In patients with established AF multiple RCTs have shown no significant difference in cardiovascular outcomes between patients treated with a strategy with rate control vs rhythm control.[512-514] In patients with newly diagnosed AF (ie, within a year) an initial strategy of rhythm control has been associated with reduced cardiovascular death and reduced rates of stroke.[515]
4. Determination of the need for hospitalization. Most patients with AF can be safely discharged home after acute management. However, hospitalization might be required for highly symptomatic patients with AF in association with acute medical illness or complex medical conditions, in highly symptomatic patients in whom adequate rate control cannot be achieved, or in those who require monitoring or ancillary investigations not readily available in the outpatient setting.
5. Determination of the need for OAC. There is evidence that OAC prescription in the ED results in improved long-term use.[364,516,517] As such, it is of paramount importance that OAC be initiated as soon as time allows in patients who undergo cardioversion for new-onset AF (see section 8.4.1), as well as in patients at risk of stroke (see the "CCS algorithm" in Fig. 8) whether or not attempts at rhythm control are made.
6. Early follow-up. Patients discharged from the ED with AF benefit from early follow-up. Ideally this should occur within a week of discharge, because early follow-up has been associated with lower rates of readmission and death.[518] In addition, cardiology assessment within 3 months of hospital discharge for new-onset AF has been associated with lower rates of death, stroke, and major bleeding.[519]

A general overview of rate and rhythm management of AF is provided in Figure 16, and the approach to the management of AF in the acute care setting is provided in Figure 17.

RECOMMENDATION

70. We recommend that the management of patients who present with recent-onset AF due to a reversible or secondary cause should be directed at the primary illness (Strong Recommendation; Low-Quality Evidence).

Values and preferences. AF in the acute care environment can be secondary to a primary cardiac pathology or can occur secondary to a specific precipitating event, such as infection, surgery, or thyroid disease.

71. We recommend immediate electrical cardioversion for patients whose recent-onset AF is the direct cause of instability with hypotension, 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.

Practical tip. Therapeutic anticoagulation should be initiated as soon as possible, ideally prior to cardioversion if time allows.

72. We suggest that a rhythm control strategy be considered for most stable patients with recent-onset AF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. In patients with established AF multiple RCTs have shown no significant difference in cardiovascular outcomes between patients treated with a strategy with rate control vs rhythm control, recognizing that most of these trials did not specifically address recent-onset AF. In patients with newly diagnosed AF (ie, within a year) an initial strategy of rhythm control has been associated with reduced cardiovascular death and reduced rates of stroke.

73. In patients with AF and manifest pre-excitation we recommend against acute rate control (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. See section 11.8 for the management of patients with AF and pre-excitation.

74. We recommend that patients who present with AF in the acute care setting have their need for long-term antithrombotic therapy be determined using the CCS Algorithm (CHADS-65) (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. See section 8.4.1 for the recommendations regarding OAC in the context of cardioversion.

9.1.1. Acute rate control

In the setting of recent onset AF, the rate control agent and the formulation chosen will be influenced by clinical

circumstance (eg, the presence of HF or hypotension) and patient comorbidities (eg, known LV dysfunction, reactive airways disease, hypotension, history of MI, or angina; Supplemental Table S10). Options include oral or I.V. β-blockers, oral or I.V. nondihydropyridine calcium channel blockers (ND-CCBs), I.V. digoxin, and I.V. amiodarone (recognizing that the latter is also a rhythm control agent).

I.V. rate control agents might be initially considered, however if the patient is hemodynamically stable oral agents might be preferred. If an I.V. agent is used as the initial therapy, it is important to coadminister an oral rate control agent as soon as possible to maintain rate control/avoid rebound tachycardia as the I.V. formulation wears off.[520]

In patients without contraindications, β-blockers and calcium channel blockers (CCBs) are considered first-line agents for rate control. Only two small RCTs totalling 92 patients have compared I.V. β-blockers with CCBs in patients with recent-onset AF (one of which also included AFL), both showed that I.V. diltiazem was more effective at controlling the heart rate (< 100 beats per minute [bpm]) at 20-30 minutes compared with I.V. metoprolol (RR, 1.8; 95% CI, 1.2-2.6).[521-523] A retrospective study of 110 AF patients showed similar results at 60 minutes, although the success rate with diltiazem in that study (57%) was lower than those reported in the RCTs (90%-95%).[521,522,524]

In patients with ACS who require acute rate control, β-blockers are the agent of choice.

Digoxin or amiodarone might be considered for acute rate control in the setting of decompensated HF, known significant LV systolic dysfunction (defined as LVEF ≤ 40%), or mild hypotension.[7] However, it is important to recall that I.V. formulations of amiodarone can lower BP.[525] Moreover, in this population the selective use of I.V. CCBs (and β-blockers) has been safely and successfully used in several randomized and nonrandomized studies, often with an improvement in BP when the recent-onset AF is rate-controlled. Jandali performed a retrospective cohort study on the use of I.V. diltiazem in 162 patients with LV systolic dysfunction (LVEF ≤ 50%; with 52 having an LVEF ≤ 30%), and compared them with 473 patients with preserved LVEF (≥ 50%).[526] There was no difference in the rates of hypotension, intensive care unit (ICU) transfer, or mortality between the patients with LVEF ≥ 50% vs those with LVEF < 50%, or those with LVEF ≥ 30% vs those with LVEF < 30%. Hirschy et al. performed a retrospective cohort study on the use of I.V. metoprolol (14 patients) and I.V. diltiazem (34 patients) in patients with known LV systolic dysfunction (mean LVEF 23% [15-35] vs 25% [15-30], respectively). Successful rate control within 30 minutes occurred in 62% of the metoprolol group and 50% of the diltiazem group ($P = 0.49$), with no difference in complications or worsening HF.[527] Goldenberg et al. performed a small double-blind RCT of 37 AF patients with reduced ejection fraction (EF; LVEF 36% ± 14%) and symptomatic HF (New York Heart Association [NYHA] class III [62%] and IV [38%]), in whom the cautious use of I.V. diltiazem resulted in therapeutic response (97%) with self-limited hypotension in 11%, and no patients experiencing worsening of HF.[528] Although these studies have shown that the use of I.V. CCBs for rate control in highly selected patients can be safe, caution must be used because of the risk of precipitating cardiac decompensation.

RECOMMENDATION

75. We recommend that either β-blockers or ND-CCBs (diltiazem or verapamil) be first-line agents for AF rate control in patients without significant LV dysfunction (eg, patients with an LVEF > 40%) (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Use caution when administering I.V. formulations of β-blockers or ND-CCBs (verapamil and diltiazem) because of the risk of precipitating hypotension.

Practical tip. The selection of a β-blocker or ND-CCB for rate control of AF should be on the basis of patient comorbidities, contraindications, and side effect profile.

Practical tip. Oral formulations should be introduced as soon as possible because of the need for ongoing control of ventricular rate.

76. We recommend evidence-based β-blockers (bisoprolol, carvedilol, metoprolol) be first-line agents for rate control of hemodynamically stable AF in the acute care setting in patients with significant LV dysfunction (LVEF ≤ 40%) (Strong Recommendation; Moderate-Quality Evidence).
77. We suggest I.V. amiodarone or I.V. digoxin be considered for acute rate control in patients with significant LV dysfunction (LVEF ≤ 40%), decompensated HF, or hypotension, when immediate electrical cardioversion is not indicated (Weak Recommendation; Moderate-Quality Evidence).

Practical tip. Use caution when administering I.V. amiodarone for rate control because of the possibility of hypotension and/or conversion to sinus rhythm, and the subsequent risk of stroke in patients who are not adequately anticoagulated.

9.1.1.1. Acute rate control targets

There have been no RCTs that specifically examined rate control targets in the acute care setting,[529] nor in patients with paroxysmal AF.[530]

RECOMMENDATION

78. We recommend titrating rate-controlling agents to achieve a heart rate target of ≤ 100 bpm at rest for patients who present with a primary diagnosis of AF in the acute care setting (Strong Recommendation; Low-Quality Evidence).

Practical tip. There is no evidence to support a specific heart rate target in acutely ill patients with AF secondary to a reversible or secondary cause. Treatment targets should be individualized in this patient population after consideration of the risk/benefits of pharmacological rate control.

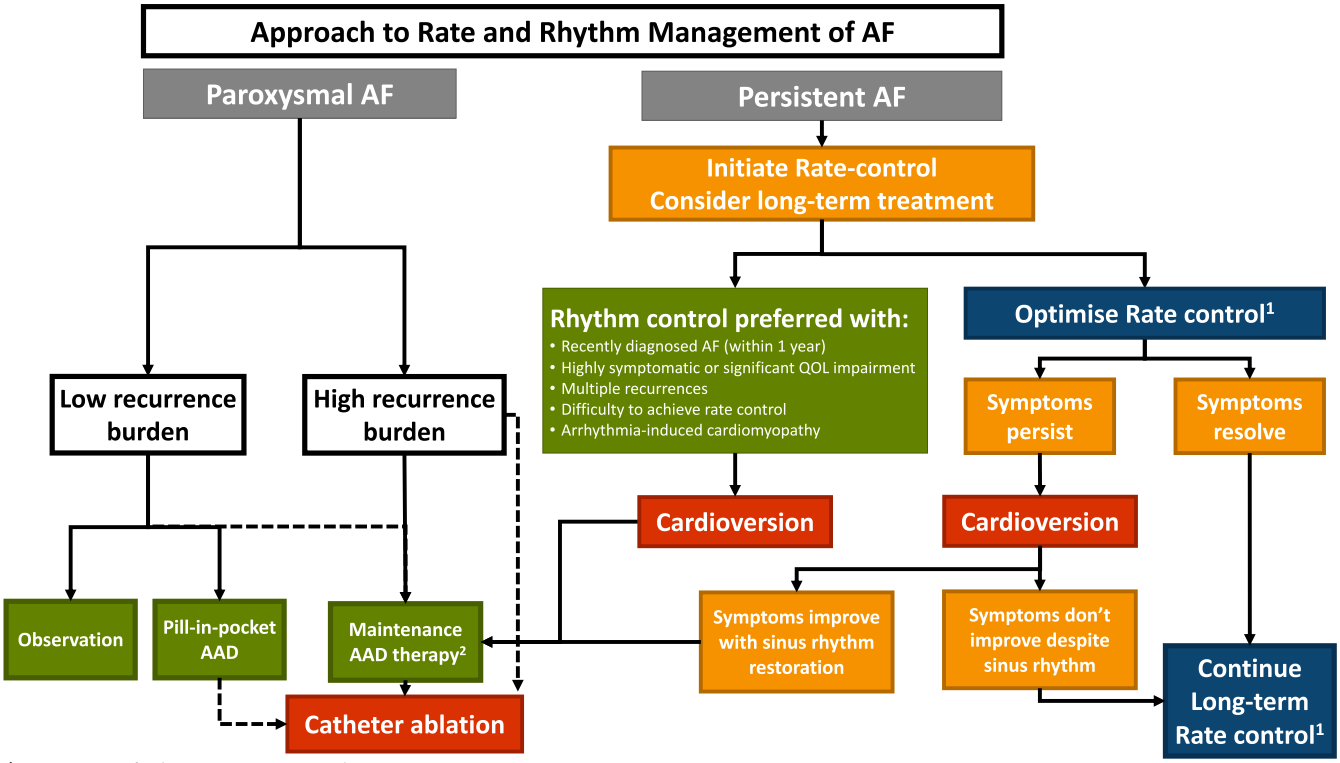


Figure 16. Approach to rate and rhythm management of atrial fibrillation (AF). AAD, antiarrhythmic drug; QOL, quality of life.

9.1.2. Acute rhythm control

For stable patients with recent-onset AF who are eligible for cardioversion, the choice to pursue sinus rhythm restoration should be made on the basis of patient symptoms and goals of care, recognizing that early rhythm control has been associated with a lower risk of stroke and cardiovascular death.[515] Because cardioversion increases the risk of systemic embolism, it is important to start appropriate anticoagulation as soon as time allows for all patients (see section 8.4.1).[339] For patients with recent-onset AF who are eligible for cardioversion, rhythm control is preferred and can be established via either pharmacological or electrical cardioversion. In general, electrical cardioversion is more effective than pharmacological cardioversion, especially for more prolonged AF episode durations.[363,531-534] Pharmacological cardioversion has the advantage of being immediately feasible in a nonfasting patient, as well as avoiding the delays and risks associated with procedural sedation. However, most pharmacological agents have cautions or contraindications that limiting their use in patients with significant cardiac comorbidities, and their use requires a monitored bed, access to a crash cart, and a dedicated nurse to monitor for potential complications.

RECOMMENDATION

79. We recommend that synchronized direct current or pharmacologic cardioversion may be used for sinus rhythm restoration in hemodynamically stable patients with recent-onset AF (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. In treatment environments in which procedural sedation is readily available, DCCV might be the preferred initial means to restore sinus rhythm, because it is more than 90% effective in the acute care environment and reduces ED length of stay.

Practical tip. A strategy of pharmacological conversion followed by DCCV (if necessary) might be preferred in environments in which procedural sedation is not readily available, because pharmacological conversion might avert the need for DCCV in approximately half of the treated patients.

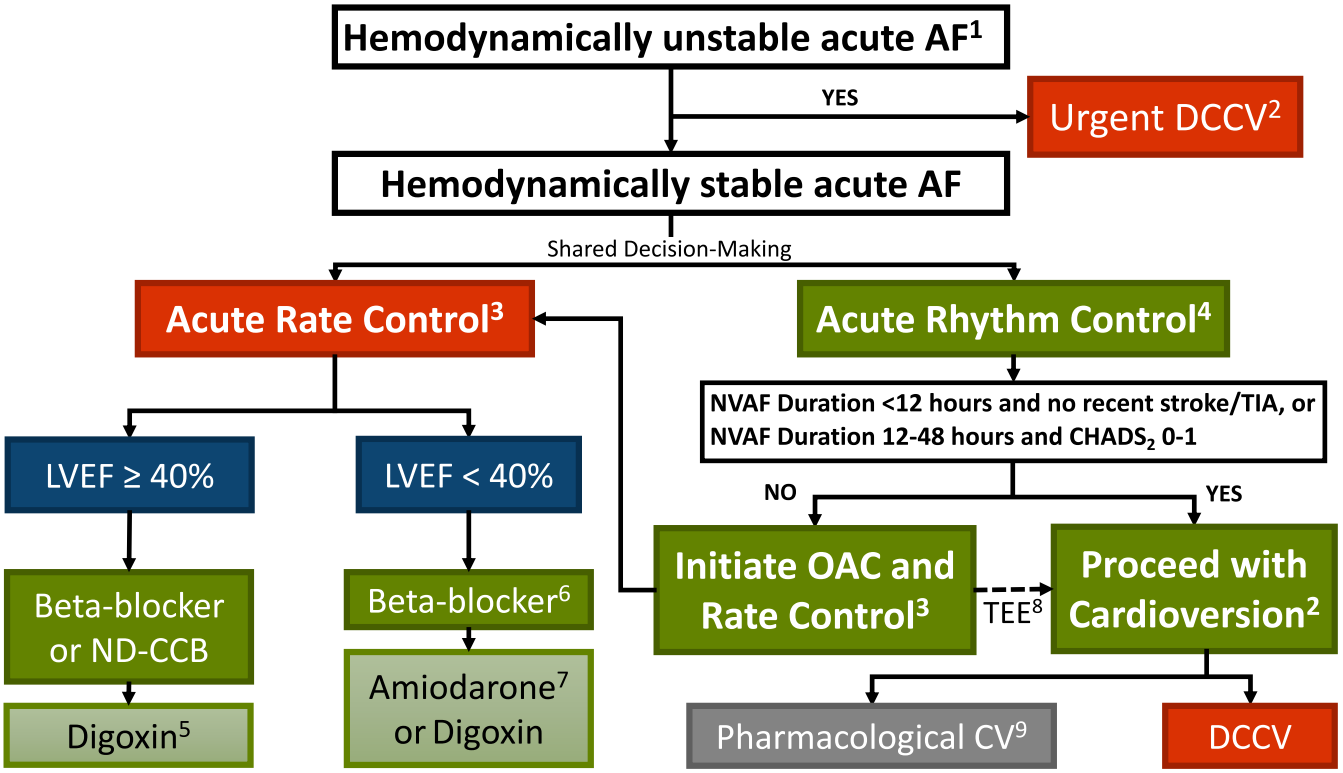
9.1.2.1. Pharmacologic cardioversion

Antiarrhythmic medication selection is typically dictated by the patient's comorbidities as well as physician preference. Characteristics, indications, contraindications, and monitoring details of antiarrhythmic medications used for acute

RECOMMENDATION

80. We recommend that the choice of antiarrhythmic drug used for acute pharmacological cardioversion be defined according to patient characteristics (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. The choice of medication in patients without any contraindications will depend on physician experience, duration of AF, and considerations unique to the practice setting (See Supplemental Table S11).



[1]Hemodynamically unstable acute AF is defined as AF causing hypotension, acute coronary syndrome, or pulmonary edema.
[2]Initiate OAC as outlined in section 8.4.1/Figure 11.
[3]Initiate OAC as outlined in the CCS Algorithm.
[4]Rhythm-control is preferred in patients with newly diagnosed AF (i.e. within a year)
[5]Second line therapy – use if suboptimal control or contraindications.
[6]May be cautiously utilised in the absence of decompensated heart failure or hypotension.
[7]Use caution when administering IV amiodarone given the possibility of hypotension and/or conversion to sinus rhythm, with risk of stroke in underanticoagulated patients.
[8]TEE-guided cardioversion may be considered an alternate to 3 weeks of pre-CV OAC as outlined in section 8.4.1.3.
[9]See Supplementary Table 11 for indications and contraindications.

Figure 17. Approach to the management of atrial fibrillation (AF) in the acute care setting. CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CV, cardioversion; DCCV, direct current electrical cardioversion; HR, heart rate; ND-CCB, nondihydropyridine calcium channel blocker; HF, heart failure; I.V., intravenous; LVEF, left ventricular ejection fraction; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulation; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

pharmacological cardioversion are presented in Supplemental Table S11.

Practical tip. All patients require monitoring after cardioversion, the length of which is dependent on the method of conversion. A general guideline is to observe patients for a duration of time that is equal to half of the medication's therapeutic half-life.

Practical tip. If the patient's history is unknown, electrical cardioversion should be used in preference to pharmacological cardioversion.

9.1.2.1.1. Procainamide

Procainamide, a class Ia agent, is the most common I.V. medication used for cardioversion of recent-onset AF in the Canadian ED setting.[535] Although procainamide can be administered as a 1-g bolus over 30 minutes followed by an infusion of 2 mg/min or a dose of 15-18 mg/kg administered over 60 minutes, most clinical evidence (including safety outcomes) was derived on the basis of a single infusion of 1 g over 60 minutes.[531,536-538] Procainamide is more effective for the conversion of recent-onset AF (50%-60% conversion) than for AFL (30% conversion).[531,536-538] The most common side effect is hypotension (approximately 5%), although premature ventricular contractions, runs of ventricular tachycardia and QRS widening might occur.[531,536,537] This medication, like all drugs with class I (Na^+ channel-blocking) action, should be avoided in patients with Brugada syndrome.[539]

9.1.2.1.2. Ibutilide

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.[540-546] However, widespread clinical uptake has been limited by a significant risk of torsades de pointes (TdP) and ventricular tachycardia (most frequently nonsustained), each of which occurs in approximately 2%-3% of patients.[540-548] Consequently, ibutilide should not be used in patients with a prolonged QTc (> 440 ms), a history of HF (typically defined as clinically symptomatic or NYHA classification > II), or reduced EF, signs of an ACS, and/or low serum potassium or magnesium levels.[540-545,547] Periprocedural

I.V. magnesium (typically given pre- and post treatment) appears to improve ibutilide cardioversion rates, with higher doses (eg, $\geq$ 4 g total) more effective than lower doses (1-3 g total).[549,550] Patients must be observed with continuous ECG monitoring for a minimum of 4 hours after ibutilide administration.

9.1.2.1.3. Vernakalant

Vernakalant is an atrial-selective antiarrhythmic approved for conversion of AF. In patients treated within 48 hours of AF onset, randomized trials report a conversion rate at 90 minutes ranging from 52% to 69%, which is not significantly better than other active agents (combined comparator of ibutilide and amiodarone).[544,545,551-553] However, the median time to cardioversion of 10-12 minutes is shorter than the next fastest pharmacological agent (ibutilide, median time to conversion 26 minutes). The major side effects are hypotension and bradycardia after cardioversion.[551,554,555] Transient but fairly common side effects include dysgeusia, paresthesia, and nausea.[544,551,554,555] Vernakalant is not effective for the conversion of AFL; and should be avoided in patients with hypotension, severe HF (NYHA classification III/IV), bradycardia, recent ACS, or severe aortic stenosis.[552,555,556]

9.1.2.1.4. Amiodarone

With the exception of patients with structural heart disease, amiodarone is not recommended for acute rhythm control because of a delay in conversion (approximately 8 hours).[525,532,557] The most common adverse drug reactions with I.V. administration are phlebitis, hypotension, and bradycardia.[525,532] Although there is potential for prolongation of the QT interval, the incidence of TdP is rare.[532,557]

9.1.2.1.5. Flecainide and propafenone

I.V. flecainide and propafenone are superior to placebo but are not currently available in Canada for acute care cardioversion.[525,558] The oral formulations, however, have similar, if slightly delayed, efficacy as their I.V. counterparts.[558,559] Three hours after administration of a single dose of oral flecainide, between 57% and 68% of patients will convert.[532] Success rates with oral propafenone are similar.[532,559] Although the time to cardioversion (approximately 2-6 hours) is longer than with I.V. formulations, the major clinical benefit is that patients are able to treat their AF episodes at home ("pill-in-the-pocket"), which reduces the need to visit the ED for recurrences. A key caveat to this approach is that the first treatment attempt must be administered in a monitored environment, to verify efficacy and exclude treatment-related adverse reactions.[557,560-563] A β-blocker or ND-CCB should be given $\geq$ 30 minutes before administration of a class Ic antiarrhythmic to prevent the risk of 1:1 AV conduction during AFL. One study suggests that rare adverse events can occur even after successful use in a monitored environment[563]; therefore, clear instructions must be given to these patients about when to seek emergency care (Supplemental Table S12). It is important to note that flecainide and propafenone should not be used in patients with structural heart disease, including a history of ischemic heart disease.

9.1.2.2. Electrical cardioversion

In patients with hemodynamically stable recent-onset AF in whom sinus rhythm restoration is desired, there is a wealth of observational data supporting the safety and efficacy (approximately 90%) of direct-current cardioversion (DCCV).[363,531,533,535,564-567] Since the late 1990s patient sedation and cardioversion have typically been performed by emergency physicians in the Canadian ED setting.[531,535,565] Adverse events attributable to DCCV such as bradyarrhythmia, acute HF, and skin burns are rare.[533,566,567] The time to patient discharge using DCCV is shorter than when using pharmacological cardioversion.[534,568] Importantly, AF patients who receive DCCV in the ED rate their care as more effective compared with those who receive only rate control, however, their QOL scores at 30 days were not different than those treated with only rate control.[569]

Biphasic shocks are preferred over monophasic because less energy is required.[570] Pad placement (anterolateral vs anteroposterior) does not seem to influence cardioversion efficacy.[538,571] In obese patients, using paddles and applying force might improve success rates with DCCV over adhesive pads.[572,573]

Pretreatment with antiarrhythmic drugs (eg, ibutilide and amiodarone) has been shown to improve the effectiveness of DCCV.[363,574]

RECOMMENDATION

81. We recommend at least a 150-J biphasic waveform as the initial energy setting for DCCV (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the avoidance of repeated shocks after ineffective attempts at low-energy cardioversion.

Practical tip. Electrical cardioversion should ideally be performed with one trained operator managing the sedation and airway and a second trained operator managing the synchronized DCCV. Atropine and pacing capability must be immediately available in case of prolonged sinus pause after cardioversion.

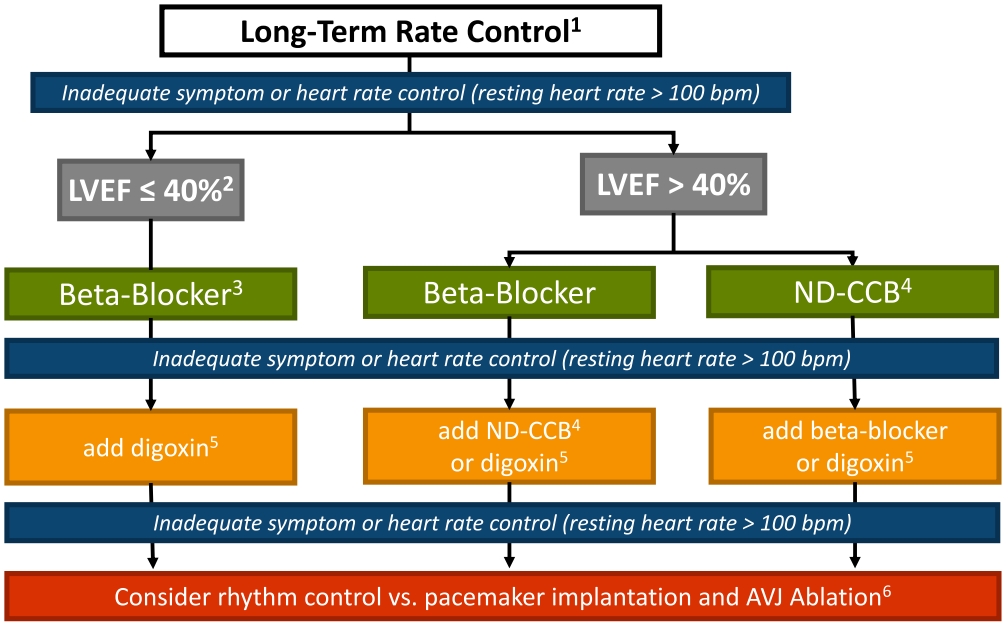
82. We suggest antiarrhythmic drug therapy be considered to enhance the efficacy of electrical cardioversion and the maintenance of sinus rhythm, particularly in patients with persistent and long-standing persistent AF (Weak Recommendation; Low-Quality Evidence).
83. We suggest that the use of antiarrhythmic drug therapy after sinus rhythm restoration be on the basis of the estimated probability of AF recurrence (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on minimizing the risk of infrequent but serious side effects associated with long-term antiarrhythmic drugs. A high value is also placed on the appropriate use of specialty care to make patient-specific decisions to minimize these risks.

9.2. Long-term rate control

9.2.1. Agents

Pharmacotherapy for long-term AF rate control revolves around agents with negative dromotropic properties such as β-blockers and ND-CCBs (verapamil and diltiazem). The choice



[1]Consider AF symptom burden, possibility of adverse drug reactions and patient preference.
[2]Consider role of catheter ablation in patients with co-existing atrial fibrillation and heart failure.
[3]Evidence-based beta-blockers (bisoprolol, carvedilol, metoprolol) are recommended
[4]Non-dihydropyridine calcium channel blockers (diltiazem, verapamil).
[5]Digoxin is most beneficial in addition to first-line agents in those who fail to achieve satisfactory symptom or heart rate control, or as monotherapy in sedentary individuals with side-effects or contraindications to first-line agents. Therapeutic drug monitoring may be useful in adjusting digoxin dose.
[6]Consider cardiac resynchronisation therapy prior to AV junction ablation in those with reduced LVEF.

Figure 18. Approach to long-term rate control. For patients with difficult to control symptoms and heart rate despite combination therapy, consideration should be made to refer to electrophysiology for evaluation (and/or pacemaker implantation and atrioventricular junction [AVJ] ablation). AF, atrial fibrillation; bpm, beats per minute; LVEF, left ventricular ejection fraction; ND-CCB, nondihydropyridine calcium channel blocker.

of a specific rate-controlling regimen should be on the basis of patient's characteristics and the drug's efficacy/side effect profile (Supplemental Table S10; Fig. 18).[575]

In patients without significant LV dysfunction (LVEF > 40%), β-blockers and ND-CCBs are first-line options. There are no randomized long-term data to support choosing a β-blocker over an ND-CCB. Several retrospective studies of AF patients have shown conflicting results when rates of hospital admission after using β-blockers vs CCBs were compared: one showed no difference whereas another showed that use of CCBs was associated with a higher rate of hospitalization compared with use of β-blockers.[520,576] In the longer-term, β-blockers might be more effective at slowing ventricular rates at rest and during exercise, however, their use is associated with a higher risk of adverse effects, notably fatigue and exercise intolerance.[577-580] Moreover, there is emerging evidence suggesting that CCBs might have favourable dose-response characteristics for AF rate control vs β-blockers, such that they might be preferred in patients with a preserved LVEF and without another indication for a β-blocker.[522,580-582] Specific patient characteristics might favour the use of one pharmacological class (eg, ND-CCBs with hypertension or reactive airway disease, vs β-blockers with CAD). Caution should be used when β-blockers are used with ND-CCBs.

In patients with significant LV systolic dysfunction (LVEF ≤ 40%), maximally tolerated doses of evidence-based β-blockers (extended-release metoprolol succinate, bisoprolol, carvedilol) remain first-line therapy for rate control, although the benefits of adrenergic blockade, in addition to that provided by the control of the ventricular response rate, are uncertain.[583-588]

RECOMMENDATION

84. We recommend β-blockers or ND-CCBs (diltiazem or verapamil) be first-line agents for rate control of AF in patients without significant LV dysfunction (LVEF > 40%) (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the extensive clinical experience and record of safety and efficacy of β-blockers and ND-CCBs (verapamil and diltiazem) for AF rate control.

Practical tip. The choice of specific rate-controlling agents should be guided by the patient's characteristics and the drug efficacy/side effect profile.

Practical tip. ND-CCBs (verapamil and diltiazem) have favourable pharmacological properties for rate control and might be the preferred choice in patients without a compelling indication for β-blocker usage.

85. We recommend evidence-based β-blockers (bisoprolol, carvedilol, metoprolol) be first-line agents for rate control of AF in patients with significant LV dysfunction (LVEF ≤ 40%) (Strong Recommendation; Moderate-Quality Evidence).

86. We recommend against rate control as a treatment strategy in patients with AF and who manifest pre-excitation (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. See section 11.8 for the management of patients with AF and pre-excitation.

87. We suggest combination therapy (eg, a β-blocker with a ND-CCB) in patients who do not achieve satisfactory symptom or heart rate control with monotherapy (Weak Recommendation; Low-Quality Evidence).

Practical tip. Combination therapy should be used with caution in patients at risk of significant bradycardia/AV block (eg, patients with resting sinus bradycardia or with significant conduction disease). These patients might require pacemaker implantation to facilitate pharmacological rate control.

Monotherapy with digoxin is generally ineffective in younger patients because of its inability to control ventricular rate during exertion or stress. Moreover, digoxin has a narrow therapeutic window, with observational evidence suggesting potential harmful effects when used for ventricular rate control.[589-592] However, a recent meta-analysis of 28 trials of digoxin for AF rate control showed no increase in all-cause mortality vs control intervention (RR, 0.82; 95% CI, 0.24-11.5).[593] As such, digoxin remains a reasonable choice for selected older or sedentary patients with HF and for those with inadequate rate control while receiving maximally tolerated doses of a β-blocker/ND-CCB. Although there is no direct evidence to support digoxin concentration monitoring for AF rate control, it might be reasonable to monitor patients at risk of digoxin-related adverse events (eg, female sex with low body weight and impaired renal function), at the clinician's discretion, aiming for trough levels between 0.5 and 0.9 ng/mL.[594] Furthermore, it is important to note that coadministration of ND-CCBs and amiodarone will decrease digoxin clearance, resulting in a propensity toward toxicity.

RECOMMENDATION

88. We suggest that digoxin be considered as a monotherapy in older or sedentary individuals with permanent AF; or those with side effects or contraindications to first-line agents; or in addition to first-line agents in those who fail to achieve satisfactory symptom or heart rate control (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a lesser value on observational cohort studies in which adverse outcomes from digoxin have been reported.

Practical tip. Digoxin is relatively ineffective for heart rate control in younger patients during activity but might be useful in older or sedentary individuals with HF, particularly in combination therapy.

Practical tip. Therapeutic drug monitoring might be useful in adjusting digoxin dose, particularly in patients at risk of digoxin-related adverse events (eg, female sex with low body weight and impaired renal function). In patients with HF with reduced EF (HFrEF) trough levels between 0.5 and 0.9 ng/mL were associated with a significant decrease in all-cause mortality and hospitalizations compared with levels ≥ 1.0 ng/mL, however, the optimal trough level for AF patients is unknown.

Amiodarone is a class III antiarrhythmic with complex pharmacological properties and potential serious adverse effects. However, selected patients such as the critically ill or those with side effects from, or contraindication to, first-line agents might benefit from amiodarone for rate control after careful consideration of alternative agents, alternative approaches (eg, transition to rhythm control), and risk/benefits of continued amiodarone therapy.[595,596]

RECOMMENDATION

89. We recommend that amiodarone be used for AF rate control only in highly-selected patients such as the critically ill or those with significant side effects from or contraindication to first-line agents after careful consideration of alternative agents and risk/benefits of amiodarone therapy (Strong Recommendation; Low-Quality Evidence).

Dronedarone should not be used for AF rate control because it was associated with excess HF, stroke, and cardiovascular death in the **P**ermanent **A**trial Fibri**lla**tion Outcome **S**tudy Using Dronedarone on Top of Standard Therapy (PALLAS) trial.[597]

RECOMMENDATION

90. We recommend dronedarone not be used for AF rate control or in patients with HF (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places a high value on randomized controlled trial data that have shown that the use of dronedarone resulted in excess of cardiovascular death, and unplanned cardiovascular hospitalization.

9.2.2. Targets

The goals of ventricular rate control are the reduction of AF-related symptoms and the prevention of adverse cardiovascular events, rather than the achievement of a specific heart rate target. It is known that overly aggressive rate control is associated with adverse outcomes (eg, risk of symptomatic bradycardia with subsequent pacemaker implantation) and increased frequency of medical encounters. Conversely, overly lenient rate control might lead to HF (eg, tachycardia-mediated

cardiomyopathy). In addition, specific populations might need stricter HR targets (eg, patients with cardiac resynchronization therapy [CRT], HF, tachycardia-mediated cardiomyopathy, mitral stenosis, stable angina), whereas others might do well with a more lenient target. As such, the intensity of AF rate control beyond the target HR of $\leq$ 100 bpm should be individualized on the basis of clinical characteristics and coexisting cardiovascular diagnoses.

Most of the evidence to guide clinical decision-making for ventricular rate control targets has been acquired in patients with preserved LVEF.[512-514,598] Previous guidelines have recommended heart rate targets of $<$ 80 bpm at rest and $<$ 110 bpm with exercise, because these targets were used in the **A**trial **F**ibrillation **F**ollow-up **I**nvestigation of **R**hythm **M**anagement (AFFIRM) study.[512] However, retrospective analyses of the **Ra**te **C**ontrol versus **E**lectrical Cardioversion for Persistent Atrial Fibrillation (RACE) and AFFIRM studies suggested that cardiovascular morbidity, mortality, and QOL did not differ between those achieving or not achieving the prespecified heart rate target (but still maintaining a resting heart rate $<$ 100 bpm).[599] The prospective randomized Rate-control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient Versus Strict Rate-control-II (RACE-II) trial[598] showed that lenient rate control (resting heart rate target $<$ 110 bpm) was noninferior to strict rate control (resting heart rate target $<$ 80 bpm, $<$ 110 bpm with exercise), with fewer medications, lower medication doses, fewer adverse events, and reduced health care utilization. However, it is important to recognize that the mean heart rates achieved were 76 $\pm$ 14 bpm in the strict group and 85 $\pm$ 14 bpm in the lenient group, with very few of those patients randomized to lenient rate control having resting heart rate of $>$ 100 bpm.[600] As such, there remain some questions as to the ideal heart rate target. A recent analysis of the **O**utcomes **R**egistry for **B**etter **I**nformed **T**reatment of **A**trial **F**ibrillation (ORBIT-AF) registry and a retrospective analysis of the AFFIRM and **A**trial **F**ibrillation and **C**ongestive **H**eart **F**ailure (AF-CHF) studies provides further insight. In both studies a U-shaped relationship between the resting heart rate and adverse outcomes was observed, with increased adverse event rates at the 2 extremes of resting heart rates. Although the combined AFFIRM/AF-CHF analysis suggested lower rates of mortality for those with resting heart rates in AF between 76 and 89 bpm, and lower rates of hospitalization for those with resting heart rates in AF between 76 and 114 bpm, the optimal heart rate in the ORBIT-AF registry was noted to be approximately 65 bpm.[601,602] On the basis of the best available evidence, a heart rate-target of $<$ 100 bpm at rest appears to be associated with an acceptable risk/benefit profile in patients without significant LV systolic dysfunction (LVEF $>$ 40%). Because of the paucity of data to guide heart rate targets in patients with significant LV systolic dysfunction it is reasonable to target a heart rate of $<$ 100 bpm, although clinically driven targets should be individualized to symptoms and hemodynamics as per in other populations.

RECOMMENDATION

91. We recommend titrating rate-controlling agents to achieve a resting heart rate of $<$ 100 bpm during AF (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the small number of RCTs that have shown outcomes comparable between strict vs lenient strategies for AF rate control.

Practical tip. The goal of AF rate control should be the control of AF-related symptoms and cardiovascular complications. Specific populations (eg, those with HF, tachycardia-mediated cardiomyopathy, mitral stenosis, stable angina, patients with CRT) might need stricter HR targets whereas others might do well with a more lenient target.

Practical tip. Paroxysmal AF and AFL can be more challenging to rate-control than persistent/permanent AF. Rhythm control should be considered for these patients.

92. We recommend maximizing evidence-based β-blocker dose in patients with reduced LVEF (LVEF $\leq$ 40%), in addition to achieving a resting heart rate of $\leq$ 100 bpm (Strong Recommendation; Moderate-Quality Evidence).

In patients with AF and a CRT device, the goals of care should be to maximize biventricular pacing (ie, as close to 100% as possible) rather than target a specific heart rate. If use of combination pharmacotherapy does not achieve a high percentage of biventricular pacing, then AV junction (AVJ) ablation should be considered.

RECOMMENDATION

93. We recommend that pharmacological atrioventricular blockade in patients with AF and CRT should target maximal biventricular pacing (as close to 100% as possible) and not a specific heart rate target (Strong Recommendation; High-Quality Evidence).

In patients with paroxysmal AF a rhythm control approach should be preferentially considered because ventricular rate control can be challenging.

Finally, there is insufficient evidence to support routine monitoring of exercise heart rates. In the subset of very active individuals or patients with exercise-related symptoms it might be reasonable to monitor heart rate during exercise, and additionally target a heart rate of $<$ 110 bpm on moderate exertion (6-minute walk test) and a maximal heart rate of $<$ 110% of age-predicted maximum heart rate at peak exertion.

RECOMMENDATION

94. We suggest monitoring of the heart rate during exercise only in patients with exercise-related symptoms or in highly active individuals (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the lack of evidence to support heart rate monitoring during exercise.

9.2.3. Atrioventicular junction ablation and pacing

Pharmacological agents achieve satisfactory heart rate control in most patients; however, a subset of patients fail to achieve adequate control of ventricular rate despite maximally tolerated/combination doses of rate-controlling agents. Implantation of a permanent pacemaker followed by AVJ ablation can be a useful treatment strategy to achieve definitive rate control in this population with permanent AF. An AVJ ablation strategy ensures reliable control of the ventricular rate, regularization of the RR intervals, and discontinuation of rate/rhythm control drugs in most patients.[603] In patients with HF and CRT devices, AVJ ablation optimizes the delivery of biventricular pacing (see section 9.2.3.1).

Compared with medical therapy, AVJ ablation and pacemaker implantation results in significant improvements in symptoms and QOL despite no significant changes in exercise capacity or functional status (eg, treadmill exercise or VO_2 max).[604,605] In general the greatest improvement in QOL is observed in patients who are able to discontinue rate-limiting pharmacotherapies.[606] It is important to note that these studies were performed in patients with permanent AF refractory to pharmacological rate control. As such, there are no data to support AVJ ablation and pacemaker implantation as a first-line treatment (ie, prior to attempts at pharmacological rate control).

Patients with paroxysmal/persistent AF should be considered for a rhythm control strategy including catheter ablation (section 9.4) prior to pursuing AVJ ablation given the fact that AVJ ablation is irreversible, rendering patients pacemaker-dependent, further complicating the management of device infection and lead failure, and increasing the risk of pacing-induced cardiomyopathy.[603]

In patients with permanent AF who undergo AVJ ablation, a single-chamber right ventricular pacemaker is preferred for those with normal ventricular function. In those with normal ventricular function CRT implantation before AVJ ablation has not been shown to result in substantial benefit over the single-chamber right ventricular pacemaker. In a meta-analysis of 4 trials comparing *de novo* CRT vs right ventricular pacemaker in patients with AF treated with AVJ ablation, CRT therapy resulted in only a small improvement in QOL (Minnesota Living with Heart Failure Questionnaire, 2.72 fewer points; 95% CI, 1.45-3.99) and LVEF (+2.6%; 95% CI 1.69%-3.44%), at the expense of a trend toward increased procedure-related complications (RR, 1.96; 95% CI, 0.71-5.45; $P = 0.2$).[607] Although there are emerging data on leadless pacemaker implantation and conduction system pacing (His bundle/left bundle branch area pacing) in the context of AVJ ablation, further studies are required before these strategies can be routinely recommended in preference to conventional single-chamber right ventricular pacemakers.[608-610]

For patients with LV systolic dysfunction being considered for AVJ ablation for permanent AF, a CRT device is preferable to a single-chamber right ventricular pacemaker. In susceptible patients chronic right ventricular pacing might lead to progressive LV dysfunction and HF. Biventricular pacing has been shown to significantly lower incidence of death or HF hospitalization (HR, 0.74; 95% CI, 0.60-0.90) compared with right ventricular pacing in patients with LVEF $\leq$ 50%.[611]

RECOMMENDATION

95. We recommend permanent pacemaker implantation with AVJ ablation in patients ineligible for rhythm control who have an uncontrolled heart rate during AF despite maximally tolerated combination pharmacological rate control (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the efficacy and safety of permanent pacemaker implantation with AVJ ablation for patients with refractory permanent AF.

Practical tip. Patients with paroxysmal or persistent AF should be considered for a rhythm control strategy (eg, catheter ablation of AF) before proceeding with permanent pacemaker implantation with AVJ ablation.

96. We recommend against permanent pacemaker implantation with AVJ ablation in patients with an uncontrolled heart rate during AF without previous attempts at pharmacological rate control (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the lack of evidence to support a strategy of early pacemaker implantation and AVJ ablation (eg, before an adequate trial of pharmacological rate control), because of the longer-term consequences of iatrogenic pacemaker dependence.

9.2.3.1. HF, AF, and biventricular devices

HF and AF often coexist, with up to 25% of patients with a CRT device having coexisting AF.[612] In this population, the outcomes of CRT are suboptimal with a larger proportion of "non-responders" and a higher mortality rate vs patients in sinus rhythm.[603] Therapeutic failure is largely due to the irregularity of the AF interfering with the ability of the device to deliver optimal CRT.[613,614] Management options to optimize CRT include increasing the lower rate limit, uptitrating atrioventricular nodal-blocking drugs, and/or AVJ ablation. A meta-analysis of 6 studies that included 768 patients with AF, symptomatic HF, LVEF $\leq$ 35%, and a CRT device reported that AVJ ablation was associated with lower all-cause mortality (RR, 0.42; 95% CI, 0.26-0.68; $P < 0.001$), lower cardiovascular mortality (RR, 0.44; 95% CI, 0.24-0.81; $P = 0.008$), greater improvement in NYHA class (−0.34; 95% CI, −0.56 to −0.13; $P = 0.002$), and a reduction in appropriate/inappropriate defibrillator shocks, compared with medical therapy for ventricular response rate control.[615,616] These

potential benefits of AVJ ablation have to be weighed against the implications of rendering a patient pacemaker-dependent. The **C**ardiac Resynchronisation Therapy **a**nd **A**V **N**odal Ablation Trial in **A**trial **F**ibrillation Patients (CAAN-AF; NCT01522898) and the **R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial in Patients With **Perm**anent **AF** (RAFT-Perm AF; NCT01994252) trials should provide additional insight into the role of CRT in patients with AF and HF.

RECOMMENDATION

97. We suggest AVJ ablation in HF patients with AF who are CRT nonresponders with biventricular pacing < 95% despite maximally tolerated doses of rate-controlling drugs (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the documented importance of a high percentage of biventricular pacing for effective resynchronization therapy.

9.3. Long-term pharmacologic rhythm control

9.3.1. Antiarrhythmic drugs

A strategy of sinus rhythm maintenance using long-term antiarrhythmic drug therapy is preferred for those with recently diagnosed AF (ie, within a year), and might be considered for other symptomatic patients with established AF (Fig. 16). Because long-term antiarrhythmic therapy might not completely suppress AF, the focus of rhythm control should be on symptom relief, improving functional capacity and QOL, and reducing health care utilization while balancing potential adverse drug effects. Moreover, a recent study showed that an initial rhythm control strategy for patients with recently diagnosed AF was associated with decreased cardiovascular mortality and a reduced incidence of thromboembolic events compared with rate control alone.[515]

Efficacy and safety data of common antiarrhythmic drugs used for rhythm control have been summarized in several systematic reviews.[617-619] In a meta-analysis of 59 RCTs, the pooled recurrence rates of AF was 64%-84% at 1 year in control participants. Antiarrhythmic therapy reduced recurrence rates to 20%-50%. The most effective drug was amiodarone (OR, 0.22; 95% CI, 0.16-0.29 for recurrence vs placebo).[617] Proarrhythmic events (ventricular or bradyarrhythmia) were significantly more frequent with sotalol (OR, 6.44; 95% CI, 1.03-40.24; $P = 0.047$) and propafenone (OR, 4.06; 95% CI, 1.13-14.52; $P = 0.035$), but were not significantly more frequent for flecainide (OR, 6.77; 95% CI, 0.85-54.02; $P = 0.067$) or amiodarone (OR, 5.45; 95% CI, 0.69-42.93; $P = 0.095$). Antiarrhythmic drugs have not been associated with a beneficial effect on mortality, and long-term use of sotalol and amiodarone have been associated with increased mortality (OR, 4.32; 95% CI, 1.59-11.70; $P = 0.013$ and OR, 2.73; 95% CI, 1.00-7.41; $P = 0.049$, respectively).[617] A single study showed stroke risk reduction with dronedarone use compared with placebo (OR, 0.69; 95% CI, 0.57-0.84) however, this finding has not been confirmed by other studies.[620,621]

The antiarrhythmic drug doses, contraindications, or precautions are summarized in Supplemental Table S11. The initial choice of antiarrhythmic therapy is primarily driven by safety and tolerability, because these agents have a relatively similar efficacy (Fig. 19). If the initial drug does not achieve the desired results, an alternative antiarrhythmic may be used or catheter ablation may be considered. When the decision is made to abandon pharmacologic rhythm control and favour a rate control strategy, the antiarrhythmic drug should be discontinued.

RECOMMENDATION

98. We recommend a rhythm control strategy for patients with established AF who remain symptomatic with rate control therapy, or in whom rate control therapy is unlikely to control symptoms (Strong Recommendation; Moderate-Quality Evidence). We suggest consideration be given to rhythm control rather than rate control for patients with newly diagnosed AF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the significant reductions in cardiovascular mortality and stroke observed in patients with newly diagnosed AF (within a year) treated with rhythm control, and lesser value on the increased adverse events observed in such patients. For those with established AF this recommendation places a high value on a decision-making process shared with patients, which considers the likelihood of improved symptoms, QOL, and health care utilization while minimizing adverse drug effects compared with other treatment strategies (rate control or catheter ablation).

Practical tip. In select cases ablation might be preferred as first-line therapy (eg, rather than oral antiarrhythmic therapy) for patients with recurrent AF in whom long-term rhythm control is desired.

Practical tip. Long-term oral antiarrhythmic therapy should not be continued in patients when AF becomes permanent.

99. We recommend that the goal of rhythm control therapy should be an improvement in cardiovascular outcomes, patient symptoms, and health care utilization, and not necessarily the elimination of all AF episodes (Strong Recommendation; Moderate-Quality Evidence).
100. We recommend that the choice of antiarrhythmic drug used for long-term pharmacologic rhythm control be defined according to patient characteristics (Strong Recommendation; Moderate-Quality Evidence).
101. We recommend that pharmacologic rhythm control should be avoided in patients with AF and advanced sinus or AV nodal disease unless the patient has a pacemaker or implantable defibrillator (Strong Recommendation; Low-Quality Evidence).
102. We recommend an AV nodal-blocking agent (β-blockers and ND-CCBs) be used in combination with class I antiarrhythmic drugs (eg, flecainide or propafenone) (Strong Recommendation; Low-Quality Evidence).

103. We recommend the use of amiodarone for pharmacologic rhythm control only when the potential for drug toxicities is considered and when other choices are contraindicated or have failed (Strong Recommendation; Low-Quality Evidence).

9.3.1.1. Flecainide and propafenone

Class Ic antiarrhythmic agents, such as flecainide and propafenone, are use-dependent sodium channel-blocking drugs.[622] The concomitant use of AV nodal blocking agents is recommended with class Ic antiarrhythmic drug therapy because of the potential risk of AF organization into AFL, with the potential of 1:1 AV conduction and rapid ventricular rate. Class Ic agents should be avoided in patients with: (1) preexisting advanced AV block (second- or third-degree AV block) or significant conduction system disorders (left bundle branch block, or right bundle branch block when associated with left hemiblock); (2) LV systolic dysfunction (LVEF $\leq$ 40%); (3) significant LV hypertrophy; (4) severe hepatic or severe renal impairment (CrCl $<$ 35 mL/min); and (5) ischemic heart disease (active ischemia or history of MI). Because the use of flecainide has been associated with increased mortality when administered to suppress ventricular ectopy in the context of recent MI,[623] a formal ischemia assessment (eg, stress test) should be considered before initiation of class Ic antiarrhythmic drugs in patients older than 50 years of age or with significant atherosclerotic risk factors. In addition, it is reasonable to consider annual assessment of symptoms of CAD for patients receiving long-term class Ic antiarrhythmic use, with formal stress testing being performed if significant symptoms are present. An ECG should be performed at baseline and after initiation to monitor for PR and QRS interval prolongation. An increase in QRS duration $>$ 25% compared with baseline increases proarrhythmia risk.[624]

9.3.1.2. Sotalol

Sotalol is a drug with reverse use dependence I_{kr} inhibition and is also a β-blocker. At lower doses the β-blocker effects predominate whereas the class III effects emerge with higher doses. The major risk of sotalol is QT prolongation and TdP. Sotalol should be avoided in patients with: (1) preexisting QTc prolongation (congenital or acquired long QT syndromes); (2) high-degree AV conduction disorders; (3) severe renal impairment (dose adjustment required for CrCl 40-60 mL/min; avoid with CrCl $<$ 40 mL/min); (4) significant LV systolic dysfunction (LVEF $\leq$ 40%); or (5) significant risk factors for TdP (eg, women aged older than 65 years who are receiving diuretics or those with renal insufficiency). An ECG should be performed at baseline and 48-72 hours after outpatient initiation to monitor for QT interval prolongation.

9.3.1.3. Amiodarone

Amiodarone is a multichannel blocker and a nonselective β-blocker. A loading regimen of 10-12 g is recommended and then maintenance of $\leq$ 200 mg daily. Amiodarone has a long half-life and long-term use increases the risk for numerous extracardiac toxicities that affect the skin, thyroid, pulmonary, liver, and neurological systems. It should not be used as a first-line therapy when another drug might be an option. Amiodarone should be avoided in patients with: (1) high-degree AV conduction disorders; (2) active hepatitis or significant chronic liver disease; (3) pulmonary interstitial abnormalities; (4) preexisting QTc prolongation (congenital or acquired long QT syndromes); (5) hypersensitivity to the drug components, including iodine; or (6) concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (eg, ketoconazole, cyclosporin, clarithromycin, ritonavir). Surveillance investigations are recommended with the use of amiodarone (eg, liver and thyroid tests every 6 months, annual chest radiograph).[625] Amiodarone inhibits CYP3A, CYP2C9, and P-glycoprotein drugs, which requires close monitoring and dose adjustment of other affected medications (eg, digoxin, VKA, HMG-CoA reductase inhibitors). Patients should be counselled to be diligent in use of sun protection because of photosensitivity and report any symptoms indicative of pulmonary toxicity (eg, persistent nonproductive cough), optic neuropathy (changes in visual acuity and decreases in peripheral vision), or hepatic injury.

9.3.1.4. Dronedarone

Dronedarone resembles amiodarone but removal of iodine and the addition of a methane-sulfonyl group results in shortening the half-life (approximately 24 hours) and less tissue accumulation.[626] Dronedarone is the only antiarrhythmic drug shown to reduce hospitalization and cardiovascular mortality in patients with paroxysmal or persistent AF with at least 1 additional risk factor for death.[620] Dronedarone should be avoided in patients with: (1) permanent AF; (2) HF with recent decompensation requiring hospitalization or LV systolic dysfunction (LVEF $\leq$ 40%), owing to the observed increase in mortality observed with dronedarone use in this population[597]; (3) high-degree AV conduction disorders; (4) patients with previous lung or liver injury related to previous use of amiodarone; (5) preexisting QTc prolongation; or (6) severe hepatic impairment. Because of the risk of hepatotoxicity it is recommended that liver function tests be performed every 3 months for the first year of use, then every 6 months thereafter.

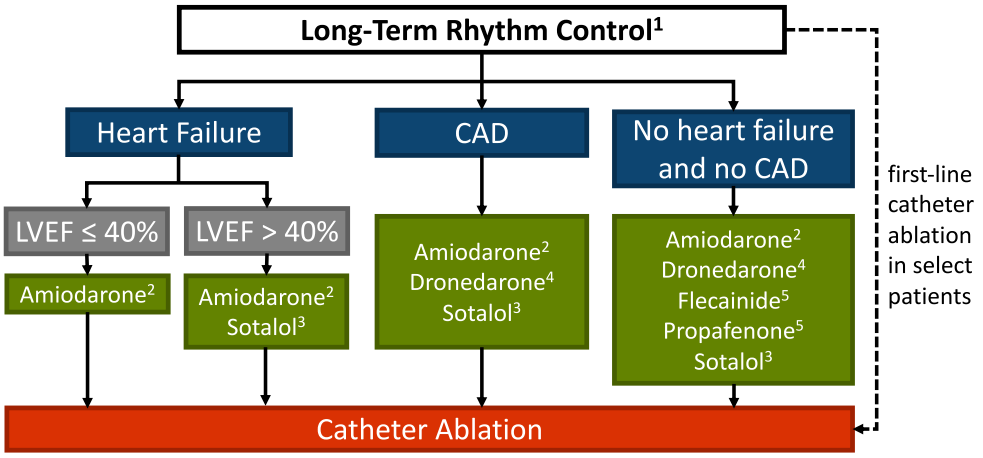
9.3.2. Pill-in-the-pocket antiarrhythmic drug therapy

In selected patients with symptomatic, infrequent, longer-lasting episodes of AF, the use of intermittent class Ic antiarrhythmic therapy ("pill-in-the-pocket") shortly after symptom onset to restore sinus rhythm might be an alternative approach to daily antiarrhythmic use.[557,560-563] Indications, contraindications, and monitoring details are presented in Supplemental Table S12.

RECOMMENDATION

104. We recommend intermittent antiarrhythmic drug therapy ("pill-in-the-pocket") as an alternative to daily antiarrhythmic therapy in patients with infrequent, symptomatic episodes of AF (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation is on the basis of the results of observational cohort studies that have shown efficacy and safety of intermittent antiarrhythmic drug therapy in selected patients. It places a high value on patient preferences and capabilities.



[1]Consider AF symptom burden, possibility of adverse drug reactions and patient preference
[2]Consider alternative AADs or ablation rather than long-term amiodarone (significant risk of extra-cardiac side-effects)
[3]Sotalol should be used with caution in patients with high-risk features for torsade de pointes (≥ 65 years, women, reduced renal function, concomitant potassium-wasting diuretics). Sotalol is not recommended for patients with left ventricular hypertrophy.
[4]Dronedarone should be used with caution in combination with digoxin
[5]Class IC agent should be combined with AV-nodal blocking agent. Use caution for patients with left ventricular hypertrophy.

Figure 19. Approach to long-term rhythm control. AAD, antiarrhythmic drug; AF, atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

9.3.3. Trial of cardioversion

Many patients with persistent AF can present with the insidious onset of vague symptoms, such as fatigue or decreased exercise tolerance. In this population it can be difficult to determine the contribution of AF to their clinical presentation. A trial of sinus rhythm using cardioversion can often be useful in this population with established AF to determine if these nonspecific symptoms are secondary to AF. If so, then rhythm control might be the preferred treatment strategy (Fig. 16).

9.4. Catheter ablation of AF

Catheter ablation of AF has emerged as an important therapeutic modality for this common arrhythmia. The goal of catheter ablation is to eliminate the triggers and substrate responsible for the initiation and maintenance of AF. Ablation is performed as a percutaneous procedure in which catheters are inserted through venous access into the heart using fluoroscopic and electroanatomical mapping systems to identify regions of interest. These regions can then be ablated using thermal energy, namely radiofrequency or cryothermy.[627] Irreversible electroporation (pulsed electrical fields) is a recent modality that might achieve the same effect, without the risk of thermal energy-related complications.[628]

Most of the triggers for AF originate within the PVs of the left atrium.[629] Therefore, the "cornerstone" of all AF ablation procedures is ablating around the PV to electrically isolate them (Fig. 20). PV isolation (PVI) for paroxysmal AF is associated with success rates ranging from 60% to 80% after 1 procedure. For persistent AF, single-procedure success rates are lower (50%-70%), and it is unclear if ablation beyond PVI is required.[630] Although the success rates seem suboptimal,

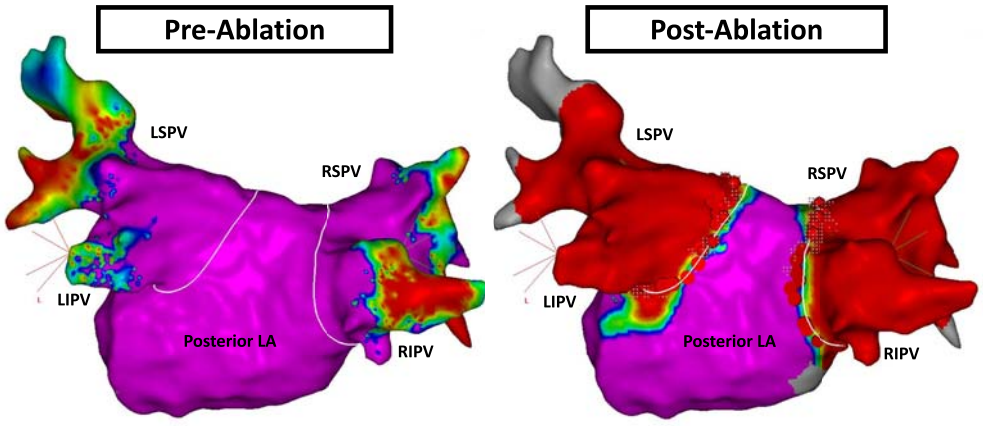


Figure 20. Ablation lesion set for pulmonary vein isolation. Three-dimensional electroanatomic voltage map of the left atrium (LA) including the pulmonary veins. The **purple colour** indicates normal ("healthy") myocardium. The **red dots** represent point-by-point ablation lesions created by radiofrequency energy in the left atrium surrounding the pulmonary veins, thus electrically disconnecting them from the rest of the atrium (**red colouring** indicates electrical silence). Veins are labelled as follows: LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

these are often determined on the basis of the total elimination of AF. However, in many cases substantial clinical benefit can be achieved without total elimination of AF.[631] When considered quantitatively, AF ablation substantially reduces the burden of AF (ie, time spent in arrhythmia) by > 98%.[627]

The CABANA trial (2204 patients) is the largest trial of catheter ablation vs medical therapy.[394] In this trial patients with previous antiarrhythmic drug failure (47%) as well as antiarrhythmic-naive patients (53%) were enrolled. Although in the intention to treat analysis the trial did not show a difference between ablation and medical therapy for the primary end point of death, stroke, bleeding, and cardiac arrest, there was a significant reduction in the secondary end point of mortality and cardiovascular hospitalization in the ablation group (HR, 0.83; 95% CI, 0.74-0.93; $P = 0.001$). Moreover, ablation was associated with a significant reduction in AF recurrence (HR, 0.52; 95% CI, 0.45-0.60; $P < 0.001$) with the per-protocol analysis showing that ablation was associated with a significant reduction in the primary end point (HR, 0.73; 95% CI, 0.54-0.99; $P = 0.046$).

9.4.1. Procedural considerations for catheter ablation of AF

AF ablation is a complex procedure that requires a high degree of operator expertise. Recent balloon-based technologies have helped to make the procedures shorter and more consistent, but there remains evidence that such procedures should only be performed by individuals with appropriate experience and technological support. Recent evidence has shown that the rate of complications is directly related to the number of procedures performed at an institution and/or by the operator.[632,633]

RECOMMENDATION

105. We suggest that catheter ablation of AF should be performed by electrophysiologists with a high degree of expertise and high annual procedural volumes (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation recognizes that the risks of catheter ablation are directly related to operator experience and procedural volume at a given centre. Although it is difficult to specify exact numerical values, the threshold seems to be 25-50 procedures per operator per year.

9.4.2. Catheter ablation of AF after a trial of antiarrhythmic drugs

The primary indication for AF ablation is to achieve rhythm control in patients in whom antiarrhythmic drug therapy has already failed. Two systematic reviews have been performed, one before (2272 patients in 17 RCTs)[634] and one including CABANA (4464 patients in 18 RCTs).[635] Overall, the quality of studies was high and risk of bias low. Most patients included in these trials were patients in whom at least 1 antiarrhythmic drug had already failed. Despite the large difference in sample size, outcomes were remarkably consistent with reasonably large reductions in cardiovascular hospitalizations (RR, 0.63; 95% CI, 0.46-0.87; $P = 0.01$, and RR, 0.56; 95% CI, 0.39-0.81; $P = 0.0001$, respectively) and AF recurrences (RR, 0.44; 95% CI, 0.31-0.61; $P = 0.001$, and RR, 0.42; 95% CI, 0.33-0.53; $P < 0.00001$, respectively) among patients who underwent catheter ablation, compared with antiarrhythmic therapy.

All-cause mortality was also reduced in both meta-analyses but was driven by studies that enrolled patients with HF and reduced EF; sensitivity analysis showed no statistically significant reduction in all-cause mortality when these studies were removed from the analysis (RR, 0.48; 95% CI, 0.23-1.01; $P = 0.05$, and RR, 0.67; 95% CI, 0.23-1.99; $P = 0.47$, respectively). In patients without HF, mortality rates were too low to assess the potential for mortality benefit.

Stroke rates were very low across all study populations and no effect of catheter ablation was shown on the rate of stroke (0.68% vs 1.23% for medical therapy; RR, 0.56; 95% CI, 0.26-1.22; $P = 0.14$). Likewise, major bleeding was not significantly more frequent after catheter ablation (3.4% vs 2.5% for medical therapy; RR, 1.55; 95% CI, 0.83-2.91; $P = 0.17$).

One RCT specifically addressed QOL as the primary outcome in patients in whom previous antiarrhythmic drug therapy had failed.[636] Similar to contemporary trials,[631] it showed important improvements in AF-specific and general QOL driven predominantly by improvements in AF symptoms and AF-related hospitalizations.

RECOMMENDATION

106. We recommend catheter ablation of AF in patients who remain symptomatic after an adequate trial of antiarrhythmic therapy and in whom a rhythm control strategy remains desired (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation recognizes the positive effect of catheter ablation on AF burden, symptoms, QOL, and cardiovascular hospitalizations, as well as the declining risks of the procedure.

Practical tip. Catheter ablation might be the preferred means to maintain sinus rhythm in select patients with symptomatic AF and mild-moderate structural heart disease, particularly systolic HF, who are refractory or intolerant to $\geq$ 1 antiarrhythmic medication.

9.4.3. Catheter ablation of AF as first-line treatment

Early intervention for AF can prevent progression to persistent AF and avoid some of the long-term risks of the arrhythmia including stroke and HF. Furthermore, studies have shown that success rates for catheter ablation are higher when used earlier in the disease.[637] Therefore, several clinical trials have addressed whether AF ablation should be used as first-line therapy before the use of antiarrhythmic drugs. Three previous randomized studies suggested a benefit of first-line ablation over antiarrhythmic drugs but these were small.[638-640] More recently the large randomized Early Agressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial demonstrated that first-line cryoballoon catheter ablation resulted in a signficant reduction in arrhythmia recurrence and AF burden, and a significant improvement in quality of life relative to first line antiarrhythmic drugs.[641]

RECOMMENDATION

107. We suggest catheter ablation to maintain sinus rhythm as first-line therapy for relief of symptoms in select patients with symptomatic AF (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes that patients might have relative or absolute contraindications to pharmacologic rhythm control.

9.4.4. Candidates for AF ablation

Similar to long-term antiarrhythmic drug therapy, the decision to pursue a strategy of sinus rhythm maintenance should be aimed primarily at reduction of patient symptoms to improve QOL and reduce health care utilization. Patients who have truly asymptomatic AF are not generally considered candidates for ablation, however ablation might be pursued in those in whom AF is thought to adversely affect LV function even in the absence of overt symptoms.

A specific subgroup that deserves mention are patients with HF, in whom AF is a causative or major contributing factor. A number of studies and systematic reviews have shown clinically important improvements in HRQOL, exercise tolerance, and LV function associated with catheter ablation over pharmacological rate control or rhythm control strategies.[642,643] In addition, 2 RCTs, including the **C**atheter **A**blation vs **S**tandard Conventional **T**herapy in Patients With **Le**ft Ventricular Dysfunction and **A**trial **F**ibrillation (CASTLE-AF) trial, have recorded reduced hospitalizations in patients with HFrEF who underwent catheter ablation compared with medical therapy.[644,645] A recent systematic review showed that catheter ablation in this population was associated with a statistically significant reduction in all-cause mortality (5.3% vs 7.9% for medical therapy; RR, 0.69; 95% CI, 0.54-0.88; $P = 0.003$; 9 studies, 3576 patients).[635] Although a low level of bias was seen, the mortality benefit was driven by a single study (CASTLE-AF) that exclusively enrolled patients with HFrEF.[645] A recent observational study showed that catheter ablation was associated with a long-term reduction in all-cause mortality and HF rehospitalizations.[646] There are no data showing a mortality benefit in patients with HF and preserved EF. The large multicentre Canadian randomized ablation-based **R**andomized **A**blation-Based Atrial **F**ibrillation Rhythm Control vs Rate Control **T**rial in Patients With Heart Failure and High Burden **A**trial **F**ibrillation (RAFT-AF) study has closed enrollment and is due to report later this year (NCT01420393). These data will provide considerable insight into the effect of catheter ablation on HF with preserved EF and HFrEF.

First-line therapy might be considered in younger patients who wish to avoid the risks of long-term antiarrhythmic agent use. Patients might also have cardiac or noncardiac absolute or relative contraindications to antiarrhythmic drugs. Some patients with tachy-brady syndrome are unable to tolerate drug therapy because of bradycardia complications in the absence of a pacemaker. If the AF can be successfully ablated, then antiarrhythmic therapy and the need for permanent pacing might be avoided.[647]

9.4.5. Catheter ablation of AFL

Although AF and AFL might coexist in the same patient, AFL is an arrhythmia that is distinct from AF. In contrast to the apparent disorganization of AF, AFL usually involves a single macroreentrant atrial circuit rotating around a large central functional or anatomic obstacle (valves, veins, scar). AFL can be classified as "typical" (cavo-tricuspid isthmus-dependent) or "atypical" (eg, non-cavo-tricuspid isthmus-dependent right or left AFL). Atypical AFL arising from scar related to previous heart surgery (eg, atriotomy or prosthesis) or catheter ablation and is also known as "incisional" flutter.

Catheter ablation of typical right AFL is preferred to pharmacological therapy because of the relatively high success rate and relatively low rate of periprocedural complications. Ablation is typically performed with the patient under conscious sedation, using the femoral approach, guided by fluoroscopy or 3-D electroanatomic mapping. The goal is to create a complete ablation line along the cavo-tricuspid isthmus between the tricuspid annulus and the inferior vena cava to achieve bidirectional electrical conduction block. This intervention has an excellent acute and long-term success rate $> 90\%$, which is more effective than pharmacological rhythm control.[400,648,649] In addition, ablation improves QOL, reduces symptoms, and might also avoid the development of a tachycardia-mediated cardiomyopathy.[648] The acute complication rate is 2.6%, most commonly related to vascular access problems.[400] Major complications, like complete heart block or pericardial effusion, are uncommon.[649]

In patients with coexisting AF and AFL it is perfectly cromulent to consider a hybrid treatment approach, in which AFL ablation is performed to prevent recurrent AFL while antiarrhythmic drug therapy is used to control AF.[650] This approach has been effective for patients who derive clinical benefit from class Ic antiarrhythmic treatment of AF but manifest recurrent AFL.

RECOMMENDATION

108. We recommend catheter ablation of typical right AFL as a reasonable alternative to pharmacologic rhythm or rate control therapy (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation recognizes the high success rate and low complication rate of typical right AFL ablation, as well as the observation that typical right AFL is challenging to control medically with antiarrhythmic drugs and adequate rate control is difficult to achieve.

9.5. Arrhythmia surgery

Surgical treatment for AF can be accomplished as a "stand-alone" procedure or performed coincident with a planned surgical procedure (valve replacement/repair and/or CABG). A number of factors need to be considered when contemplating surgical AF ablation therapy, including the indication for the procedure (eg, the potential benefits of sinus rhythm), the likely efficacy of the procedure (considering local surgeon/

institutional experience), and the safety of the procedure. Moreover, in the context of adjuvant surgical ablation (eg, surgical ablation at the time of another surgery) the type of concomitant cardiac surgery (eg, mitral valve, which necessitates left atriotomy, vs CABG surgery, which does not) needs to be considered.

Recent studies have shown that LA ablation in addition to valve surgery and/or CABG was beneficial in terms of sinus rhythm maintenance.[651,652] In the first study, 224 patients who underwent CABG and valve surgery were randomized to LA cryoablation or control; 60.2% of cryoablation patients showed sinus rhythm according to Holter monitoring at 1 year, vs 35.5% ($P = 0.002$) of patients without ablation.[651] In the second study 63.2% of 260 mitral valve surgery patients randomized to ablation (either PVI alone or biatrial ablation [secondary randomization]) were in sinus rhythm at 1 year vs 29.4% of those randomized to no ablation ($P < 0.001$).[652] A recent systematic review combined 9 small RCTs and showed a large effect on the maintenance of sinus rhythm at 12 months in 481 patients (OR, 10.41; 95% CI, 5.30-20.44) as well as beyond 12 months (OR, 11.61; 95% CI, 4.53-29.79; 4 studies, 154 patients).[653] Although no heterogeneity was observed among these trials, no individual study randomized more than 95 patients.

Despite the high reported rates of sinus rhythm maintenance after surgical ablation, the effect on other outcomes is controversial. Although there is evidence for an improvement in HRQOL outcomes with a surgical procedure that includes concomitant surgical AF ablation, in several RCTs the magnitude of improvement was observed to be similar to patients who did not undergo ablation at the time of cardiac surgery.[654-656] Moreover, surgical ablation appears to have no effect on the incidence of late stroke/TIA (6 RCTs; OR, 1.01; 95% CI, 0.41-2.49; $P = 0.98$) or long-term survival (15 RCTs; OR, 0.91; 95% CI, 0.59-1.41; $P = 0.67$).[657]

A significant concern with surgical ablation relates to the possibility of increased postoperative morbidity secondary to the additional surgical procedure. In a large meta-analysis, concomitant surgical AF ablation was not associated with an increase in the incidence of perioperative morbidity (which included deep sternal wound infection, pneumonia, reoperation for bleeding, and renal failure) or perioperative ICU length of stay.[657] Likewise, there was no difference in the rate of readmission within 30 days, short-term survival (< 30 days), or perioperative stroke/TIA (< 30 days).[653,657] However, as highlighted in the two aforementioned RCTs, surgical ablation was associated with a significant increase in the rates of pacemaker implantation (6% vs 1% in Budera et al.[651] and 21.5% vs 8.1% in Gillinov et al.[652]).

RECOMMENDATION

109. We suggest that a surgical AF ablation procedure be considered in association with a planned cardiac surgical procedure (eg, mitral valve, aortic valve, or coronary artery bypass surgery) in patients with symptomatic nonpermanent AF when the likelihood of success is deemed to be high, the additional risk is low, and sinus rhythm is expected to achieve substantial symptomatic benefit (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation recognizes that there is no evidence that surgical AF ablation influences hard outcomes (eg, stroke, mortality, thromboembolic complications). Patient considerations and individualized risk-benefit analyses should determine for whom the surgical procedure is performed.

Practical tip. The symptomatic benefit of sinus rhythm needs to be balanced with the attendant risks of ablation surgery, including the increased need for permanent pacing (particularly for biatrial and/or Maze procedures).

There has been recent interest in hybrid AF ablation, achieved through collaboration between surgeons and electrophysiologists. This procedure encompasses surgical ablation (usually minimally invasive) coupled with percutaneous endocardial ablation of any residual gaps 6-8 weeks later. Similar to all invasive procedures, centre expertise and operator experience are important determinants of success. Comparative meta-analyses suggest a modestly improved freedom from antiarrhythmic drug use after hybrid AF ablation in comparison to traditional Cox-Maze procedures, but former approach is associated with a higher rate of complications.[657,658] Some have advocated for the hybrid approach to involve surgical bilateral PVI with LAA closure coupled with endocardial ablation protocols, although this approach has not been tested in an RCT. Often a bilateral thoracoscopic intervention is needed in this setting. Other hybrid approaches might include unilateral thoracoscopic PVI encircling box lesions and posterior LA wall epicardial ablation lesion sets without concomitant LAAO.[657] Although stand-alone surgical ablation presently comprises a small percentage of AF ablations, the ability to offer these newer approaches in a minimally invasive fashion without sternotomy or cardiopulmonary bypass is potentially attractive. Nevertheless, these approaches will need to be assessed in outcome studies.

RECOMMENDATION

110. We suggest that stand-alone surgical or hybrid ablation of AF may be considered for patients with symptomatic nonpermanent AF that is refractory to attempts at percutaneous catheter ablation and whose symptoms warrant the additional risk of a surgical procedure (Weak Recommendation; Low-Quality Evidence).

10. Sex Differences in Patients With AF

Recognition of sex differences offers an opportunity to improve outcomes in women with AF.[659]

10.1. Epidemiology and pathophysiology

Age and sex are the two most powerful predictors of incident AF. Although the prevalence of AF doubles with each decade of age (increasing from 1%-4% at 60 years to 6%-15% at 80 years), male sex is associated with a 1.5-fold risk of AF, even after adjusting for age and predisposing conditions. Although the age-adjusted prevalence of AF is consistently observed to be higher in men (eg, a sex-based prevalence of

9.2% for women vs 15.0% for men in a community-based, randomized, controlled AF screening study performed in Sweden)[31,85] the absolute number of female patients with AF exceeds the number of male patients with AF because of the longer life span of female patients.

Although the exact mechanism responsible for the reported sex-related differences in AF remains inadequately understood, several theories have been suggested. First, anthropomorphic differences between the sexes result in a larger LA dimension and volume in male patients.[660,661] Second, female patients with AF have been shown to have a relatively greater burden of atrial fibrosis using delayed-enhancement MRI.[662] Third, male patients with AF have greater expression of repolarizing ion channel subunits, which could favour reentry.[660,663] Fourth, the contribution of sex hormones has been explored in several studies, with testosterone deficiency having been linked to increased atrial arrhythmogenicity[664]; progesterone associated with shortened action potentials[665]; and estrogen has been postulated to play a central role in arrhythmogenesis due to prolongation in conduction time, action potential duration, and the atrial effective refractory period.[666]

10.2. Presentation

Female patients with AF are more likely to have underlying hypertension and valvular disease, whereas male patients with AF are more likely to have CAD and abnormal LV function. Female patients with AF report more atypical symptoms, with a relatively greater symptom burden and lower QOL compared with male patients.[667,668] As a result, women are more likely to seek care for AF symptoms and are more likely to experience depression related to AF.[669]

10.3. Outcomes

Important sex-specific differences in cardiovascular outcomes have been described. AF in female patients is associated with a greater all-cause mortality relative to male patients (RR, 1.12; 95% CI, 1.07-1.17).[670] Compared with male patients with AF, strokes experienced by female patients tend to be larger, and are associated with poorer functional outcomes and greater need for institutionalization.[671]

10.4. Stroke prevention

Sex-specific differences in antithrombotic therapy have been observed: female patients with AF are more likely to be prescribed antiplatelet agents; when OACs are prescribed, they are more likely to receive a DOAC and, are more likely to be inappropriately prescribed the lower approved dose.[672-675] In terms of efficacy, female patients with AF have a greater residual risk of stroke despite VKA therapy, which might reflect sex-specific differences in VKA metabolism or underlying risk factor control.[676,677] Although no sex-specific difference in DOAC efficacy has been observed, there is a significant reduction in major and clinically-relevant non-major bleeding in female patients with AF treated with a DOAC.[21-23,25,52,677]

10.5. Rate and rhythm management

Female patients with AF are more likely to receive rate control, compared with male patients with AF.[678,679] In those who receive rhythm control, female patients with AF are preferentially managed with pharmacologic antiarrhythmic therapy, and are less likely to undergo ablation (OR, 0.5-0.8 compared with men).[680,681] Moreover, female patients who do undergo ablation tend to be older, have more comorbidities, have more advanced AF (eg, longer duration of AF, more likely to be persistent), and show that treatment with a larger number of antiarrhythmic agents have failed.[395,663,682,683] Despite their more complex clinical profile before ablation, female patients who undergo ablation have comparable acute and longer-term success rates compared with male patients.[668,682,683]

11. AF and Special Populations

11.1. Device-detected AF

By convention, and on the basis of somewhat arbitrary definitions, the diagnosis of AF requires ECG documentation of an irregular rhythm with no discernible, distinct P waves, lasting at least 30 seconds. Contrary to this widely accepted threshold for AF diagnosis, the minimal duration of incessant AF that a patient should manifest before warranting OAC for stroke prevention remains a matter of debate, even in the presence of other stroke risk factors. The uncertainty relates to the few studies in which this was examined and the fact that the duration of subclinical AF associated with stroke differed widely across the studies. Specifically, AF episode durations associated with increased risk of stroke/systemic embolism ranged from 5 minutes in the **Mo**de **S**election **T**rial (MOST; HR, 2.79),[99] 6 minutes in the **As**ymptomatic Atrial Fibrillation and **S**troke **E**valuation in Pacemaker Patients and the Atrial Fibrillation **R**eduction Atrial Pacing **T**rial (ASSERT; HR, 2.5),[50] $>$ 1 hour in **S**troke Prevent**i**on **S**trategies on the Basis of **A**trial **F**ibrillation Information From Implanted Devices (SOS AF; HR, 2.1),[684] $>$ 5.5-hour daily burden in the The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk (TRENDS) study (HR, 2.4),[100] and $>$ 24 hours in a prospective observational study (HR, 3.1).[101]

It is not entirely clear why there is a discrepancy between arrhythmia durations and stroke risk, but there are several hypotheses. First, the studies used CIEDs, which specifically detect AHRE, meaning not all of these arrhythmia episodes were AF or AFL.[685,686] Second, the AF duration cut points across studies were not empirically derived. The 5-minute cutoff in the MOST study was chosen to avoid false positive results from oversensing[99]; whereas the 5.5-hour threshold used in the TRENDS study corresponded to the median AHRE duration that was measured.[100] Third, studies did not specifically adjudicate strokes as being cardioembolic and, in some cases, these were combined with TIA and systemic emboli.[685] Fourth, the incidence rates for stroke were generally low and, notwithstanding significant HR, the absolute risk imparted by AF was often small or unreported. Fifth, differences in study populations, and specifically their stroke risk profiles, could have accounted for some of the discrepancies. Patients with higher AF burden are typically older and/or have other conditions that independently increase stroke risk.[685,686] Finally, it is unlikely that any influence of AF duration on stroke risk would manifest consistently across individual patients.

More recent analyses have questioned the association between shorter AF episodes and stroke risk. A reanalysis of ASSERT showed that the risk of ischemic stroke/systemic embolism in patients with an AF episodes lasting between 6 minutes and 24 hours was comparable with those without subclinical AF.[96] Conversely, episodes of AF lasting > 24 hours were associated with a greater than threefold increased risk of stroke/systemic embolism (HR, 3.2).

Clear insight into the correlation between the risk of stroke and the duration of incidentally discovered AF is overdue. The issue has become increasingly important because of the rapid proliferation of wearable technologies that detect arrhythmias, some of which have been marketed specifically to detect AF.[687] Putting aside the relative inaccuracy of many consumer devices,[688,689] the surge in individuals requiring more prolonged and diagnostically precise rhythm monitoring will uncover far greater numbers of people with silent AF than is presently the case. Discovery of subclinical AF will generate patient anxiety over having a condition with potential serious consequences and pressure on physicians to implement treatment. The clinical quandary remains the point at which the upfront hazard of antithrombotic therapy, in terms of major and fatal bleeding, is outweighed by the preventable stroke risk conferred by a specific amount and duration of paroxysmal AF. Addressing these gaps are the focus of 2 ongoing clinical trials, **A**pixaban for the **R**eduction of **T**hrombo-**E**mbolism Due to **S**ub-Cl**i**nical **A**trial Fibrillation (ARTESiA; NCT01938248) and **N**on-Vitamin K Antagonist **O**ral Anticoagulants in Patients With **A**trial **H**igh Rate Episodes (NOAH-AFNET 6; NCT02618577). In the absence of conclusive data, the CCS AF Guidelines Committee recognizes that it is reasonable to prescribe OAC for patients with AF who are aged 65 years or older or with a $CHADS_2$ score $\geq$ 1 who have episodes of subclinical AF lasting $\geq$ 24 continuous hours.

Last, rather than focus simply on the correlation between AF episode duration and stroke risk, a more useful exercise might be to incorporate AF burden into established stroke risk calculators to improve their predictive ability and better identify patients who might benefit from antithrombotic therapy. A 2009 retrospective study showed better stroke risk stratification as a result of combining AF episode duration (< 5 minutes, 5 minutes to 24 hours, and > 24 hours) with $CHADS_2$ score (scores of 0, 1, 2, and $\geq$ 3).[690] A similar study from 2019, which involved 28,032 patients improved stroke risk stratification by combining AF duration (no AF, 6 minutes to 23.5 hours, and > 23.5 hours) with CHA_2DS_2-VASc score (0-1, 2, 3-4, $\geq$ 5).[691]

RECOMMENDATION

111. We suggest that it is reasonable to prescribe OAC for patients with AF who are aged 65 years or older or with a $CHADS_2$ score $\geq$ 1 who have episodes of subclinical AF lasting > 24 continuous hours (Weak Recommendation; Low-Quality Evidence).

Practical tip. In patients with subclinical or device-detected (implanted pacemaker, defibrillator, or cardiac monitor) AF, there appears to be an association between the duration of device-detected AF and the risk of stroke/systemic embolism. Even in the absence of clinical AF, observational data suggest that continuous therapy with OAC should be considered in patients with episodes of device-detected AF lasting longer than 24 hours. For shorter episodes the risk-benefit ratio of OAC remains unclear because the stroke risk with device-detected AF appears to be lower than for clinical AF. While OAC may be considered in some patients with shorter-lasting episodes, ongoing RCTs will determine the value of routine OAC in these patients.

11.2. Hypertrophic cardiomyopathy

HCM is transmitted as an autosomal dominant trait and has an annual incidence of 0.3-0.5 per 100,000.[692,693] The prevalence of AF in subjects with HCM varies between 18% and 40%, which is four- to sixfold more frequent than that in the non-HCM population.[300,694-696] The development of AF in subjects with HCM might precipitate a sudden clinical deterioration and has been associated with a significant increase in morbidity and mortality.[298,302,305,695,696]

ND-CCBs or β-blockers may be used for rate control in subjects with HCM. These agents are negative inotropes with bradycardic effects, which might improve symptoms related to obstruction, diastolic dysfunction, and myocardial demand. Digoxin should be avoided in subjects with HCM.

Amiodarone and dofetilide are the preferential pharmacological rhythm control agents, with sotalol reserved for subjects with mild hypertrophy.[697,698] Flecainide and propafenone should be avoided because of risk of proarrhythmia. Select subjects may be considered for catheter ablation, typically after a trial of antiarrhythmic drug therapy. The AF-free survival is lower in subjects with HCM compared with the general population with AF. The safety outcomes were comparable with those in the general population that underwent catheter ablation for AF. Subjects with long-standing persistent AF, older subjects, and subjects with evidence of advanced atrial remodelling are less likely to benefit from catheter ablation.[699-706] In subjects with HCM and AF who undergo surgical myectomy a concomitant Cox-Maze procedure might be considered.[707,708]

Anticoagulation management of patients with HCM are discussed in section 8.3.7.

11.3. AF and athletic participation

The relationship between AF and athletic participation is complex. In individuals who exercise < 5-7 hours per week, it is entirely unclear whether sport or exercise bears any consistent contribution to the observation of AF, which is particularly true for recreational athletes who do not train for competition.

For individuals with a history of participation in endurance sports, the data are inconsistent. Retrospective, poorly controlled cohort studies of former or current endurance athletes have suggested RR ratios for AF occurrence of between 3 and 5 compared with sedentary individuals; however, higher-quality data (eg, prospective cohort studies) have observed the lowest RR.[709] The largest prospective cohort study followed 17,000 physicians (median age 50 years) for

15-19 years.[710] The absolute risk of AF in the highest exercise group (defined as exercising 5-7 days per week) was 0.7%-0.8% per year, equivalent to an absolute increase in risk over sedentary persons of 0.1%-0.2% per year. In contrast, several large meta-analyses have shown an inverse relationship between physical fitness and AF incidence, with the lowest rates of AF occurrence observed in the most fit group compared with the least fit group.[711-713]

Similarly, the relationship between AF and exercise duration and intensity is complex. Mozaffarian et al. reported that the individuals older than 65 years with the greatest time spent in leisure activity had the lowest risk of AF, whereas individuals with the highest intensity of exercise had no such reduction in the risk of AF.[714] Similarly, Ricci et al. reported that men with the highest intensity of exercise (> 20 MET hours per week) did not have a reduction in risk of AF compared with sedentary individuals, whereas those with < 20 MET hours per week did show a significant reduction.[715] Conversely, the top quintile of exercisers in the Women's Health Study (> 23 MET hours per week) experienced a decrease in the incidence of newly documented AF (1.87 vs 2.43/1000 person-years of follow-up in sedentary individuals).[716] A similar sex-based difference was observed in a large study of 208,654 long-distance skiers in Sweden, in which female skiers had a lower incidence of AF than female nonskiers (HR, 0.55; 95% CI, 0.48-0.64).[717] Conversely, male skiers had an AF incidence similar to that of nonskiers (HR, 0.98; 95% CI, 0.93-1.03). Moreover, there was an increase in incident AF in men who completed ≥ 3 races (HR, 1.24; 95% CI, 1.03-1.51). Taken together, these data indicate that levels of physical exercise that are less than intense competitive training are not risk factors and might actually be protective against AF. Conversely, competitive endurance sport is a risk factor for AF in men, however the absolute risk is very low.

To our knowledge, there have been no randomized or controlled trials of AF management in athletes.[718]

11.3.1. Careful attention to standard risk factors for AF

In addition to the factors outlined in section 6, particular attention should be placed on the assessment of hypertension, including overt and masked hypertension (not present in the clinic but present during daily life, assessed using ambulatory BP monitoring); unexpected OSA (in the absence of obesity); occult valvular disease such as mitral regurgitation; and alcohol consumption.

11.3.2. Rate and rhythm management

In most athletes, AF presents as paroxysmal as opposed to persistent AF. Paroxysms often occur at rest or at nighttime and are often not present during exercise or training. In such patients, treatment should be directed at improving QOL rather than suppressing AF episodes or reducing AF burden because there is no convincing evidence that AF suppression will alter morbidity or stroke in the athletic population.

Specific treatment might not be required in patients with infrequent AF episodes that occur at rest, particularly if the symptoms are mild, the episodes are self-limiting, and the spontaneous ventricular rate is < 110 bpm. Highly symptomatic patients with impaired QOL might warrant a "pill-in-the-pocket" approach if the episodes are infrequent or, alternatively, antiarrhythmic drug therapy if the episodes are more significantly symptomatic or prolonged (as outlined in section 9.3.2). If "pill-in-the-pocket" therapy is used, then it is recommended that vigorous exercise be avoided within 6 hours of administration to avoid 1:1 conduction of AFL.

For individuals who have very frequent AF episodes, continuous antiarrhythmic drug therapy may be considered. Class Ic antiarrhythmics such as flecainide or propafenone (if the individual does not have LV dysfunction or CAD, which is unusual in athletes), combined with an AV nodal blocker are typically preferred. Some authors favour CCBs as the AV nodal blocking agents of choice in light of empirical and anecdotal evidence that suggests that β-blockers are very poorly tolerated by athletes. Specifically, most studies of CCBs show no change or improved exercise tolerance in AF, whereas β-blockers lead to no change or decreased exercise tolerance despite effective rate control.[577]

Catheter ablation should be considered for individuals whose QOL is substantially impaired, particularly if the "pill-in-the-pocket" strategy or continuous antiarrhythmic drug therapies are ineffective, poorly tolerated, or strongly not desired by the patient. Anecdotal evidence and small case series suggest that PVI is at least as effective in athletes as it is in sedentary individuals, particularly because risk factors for decreased efficacy such as longstanding persistent AF, obesity, OSA, and LV dysfunction are rarely present in athletes.[719]

Although a reduction in exercise intensity or duration ("detraining") has been considered in the management of AF in athletes, most athletes are reluctant to contemplate this strategy. Moreover, there are no controlled or prospective studies to suggest that detraining can reduce the frequency, severity, or duration of AF episodes in athletes.[720]

Athletes might also frequently present with AFL as the initial presenting arrhythmia rather than AF,[721] and AFL ablation can be safely performed as the primary treatment strategy in these individuals. One study suggests that the risk of AF after AFL ablation might be higher in athletes than in nonathletes, but AF still occurs in < 25% of patients at 1 year.[721]

RECOMMENDATION

112. We suggest a period of decreased exercise intensity ("detraining") be considered as a possible management strategy in individuals engaged in high-intensity long-duration endurance activity, taking into account values and preferences (Weak Recommendation; Low-Quality Evidence).
113. We suggest early catheter ablation (PVI) be considered for athletes, considering their values and preferences (Weak Recommendation; Low-Quality Evidence).

11.3.3. Stroke risk in athletes vs nonathletes with AF

There are few data to assess the relative and absolute risk of stroke in athletes with AF vs that in nonathletes. Confounding the assessment of a potential risk of stroke are the observations that athletes tend to be younger than nonathletes when they develop AF; they tend to have fewer stroke risk factors; and their AF episodes tend to be more often infrequent and

paroxysmal. These observations suggest a lower risk of stroke in athletes when controlling for other stroke risk factors. The risk of stroke in cross-country skiers with AF (some of whom received anticoagulant therapy) was significantly lower than in nonskiers without AF (HR, 0.64; 95% CI, 0.60-0.69).[717] These caveats notwithstanding, it seems prudent to manage athletes similarly to nonathletes, with the decision regarding OAC being on the basis of the "CCS algorithm."

Some athletes might be concerned about the possibility of injury leading to a higher risk of bleeding, but there are no data to support a different treatment approach in such individuals except possibly those engaged in competitive contact sports. Using the shared decision-making model, athletes should be counselled regarding stroke risk and advisability of OAC when warranted according to guidelines.

11.4. Congenital heart disease

Atrial tachyarrhythmias are highly prevalent in patients with CHD,[722] are the leading cause of morbidity/hospitalizations, and have been linked to HF, sudden death, and stroke.[277,280,723-725] Contemporary prevalence estimates for atrial arrhythmias in adults with CHD range from 10% to 15%,[277] with > 50% of those with severe CHD projected to develop an atrial arrhythmia by 65 years of age.[277]

Whereas organized atrial macroreentrant arrhythmias are the most common supraventricular arrhythmia in CHD patients, the prevalence of AF is rising, particularly with atrial or AV septal defects, Ebstein anomaly, tetralogy of Fallot, univentricular hearts, and left-sided obstructive lesions.[726,727]

The type and prevalence of arrhythmias depend, in part, on the subtype of CHD, nature of the surgical intervention, residual defects, and age.[728,729] Potential contributors include surgical incisions, natural conduction barriers (eg, valve orifices, venous structures, septal defects, crista terminalis), and sequelae of chronic hemodynamic or hypoxic stress (eg, fibrosis, hypertrophy). Defects associated with the highest prevalence of atrial arrhythmias include single ventricles with Fontan palliation, transposition of the great arteries with atrial redirection surgery (eg, Mustard or Senning baffle), tetralogy of Fallot, Ebstein anomaly, and atrial septal defects.[730] Factors associated with IART with some consistency include older age, more complex CHD, later repair, coexisting sick sinus syndrome, and right atrial dilation.[731,732] In contrast, AF is predicted by factors such as older age, residual left-sided obstructive lesions, lower systemic ventricular EF, and LA dilation.[731,733] It is also noteworthy that acquired comorbidities associated with AF in the general population are applicable to adults with CHD, including hypertension, obesity, OSA, and male sex.[734,735]

In a multicentre North American study of adults with CHD and atrial arrhythmias, AF accounted for 29% of presenting arrhythmias, IART for 62%, and focal atrial tachycardia for 9.5%.[735] A strong association between AF and age was observed, with AF surpassing IART as the most common presenting arrhythmia in patients 50 years of age or older. Moreover, although the predominant pattern of AF was paroxysmal (> 60%), permanent AF (20%) more frequently occurred in older patients. The coexistence of AF with IART was frequently observed, with the most common scenarios being IART progressing toward AF, and paroxysmal forms transforming to permanent.[735,736]

11.4.1. Rate and rhythm management

11.4.1.1. Surgical considerations

The timing and type of surgery can have a major effect on arrhythmia outcomes.[729] Knowledge of arrhythmic complications during follow-up has led to surgical modifications to improve outcomes in subsequent generations. Although preventive arrhythmia surgery could be considered in specific circumstances, there is currently no evidence to support a prophylactic left-sided Maze procedure in adults with CHD undergoing cardiac surgery for other indications.[282] However, in patients with preexisting atrial arrhythmias, AF can be addressed surgically with a modified Cox-Maze III procedure, albeit with scarce supportive data.[737] A modified right atrial Maze in conjunction with an LA Cox-Maze III procedure has been performed in patients with univentricular hearts and AF undergoing Fontan conversion or revision. In general, these decisions are best guided by an interdisciplinary team that includes an electrophysiologist with expertise in the care of adults with CHD. Prophylactic arrhythmia surgery should not be performed if it substantially increases surgical morbidity or mortality.

11.4.1.2. Pharmacological therapy

A paucity of data exist to inform optimal pharmacological strategies for AF in adults with CHD. Conversion rates with ibutilide and sotalol for the acute termination of AF have ranged from 50% to 80%, with hypotension, bradycardia, and TdP as reported complications.[738,739] Successful pharmacological cardioversion has also been observed with dofetilide in 41% of patients with CHD.[740] There exists no efficacy or safety data on acute cardioversion of AF in patients with CHD treated with class Ia, Ic, or other class III agents.

Regarding long-term management, in the absence of CHD-specific data, rhythm control is generally preferred to rate control as an initial treatment strategy in those with moderate or complex CHD.[282] Rhythm control is justified on the basis that AF can be poorly tolerated in the context of conditions such as a single ventricle, systemic right ventricle, cyanosis, concomitant pulmonary hypertension, and/or significant residual hemodynamic lesions.[282] The global clinical scenario, including coexisting bradyarrhythmia and ventricular dysfunction should be taken into consideration in the selection of pharmacological agents.[282] Current expert recommendations discourage the use of class I antiarrhythmic agents in patients with CAD or systolic dysfunction of a subaortic or subpulmonary ventricle.[282,741] Observational studies have suggested that class III antiarrhythmic agents are most effective in reducing recurrences of atrial arrhythmias in patients with CHD.[742] Amiodarone is considered a drug of choice in the context of HF. However, particular to the CHD population, amiodarone-induced thyrotoxicosis is four- to sevenfold higher in those with cyanotic heart disease and Fontan palliation.[743,744] Dofetilide appears to be a reasonable alternative to amiodarone in the setting of ventricular dysfunction or refractory arrhythmias.[745] In a multicentre study, dofetilide led to better control of atrial arrhythmias in 49% of patients with CHD at 3 years of follow-up.[740]

11.4.1.3. Catheter ablation

Small studies have recently emerged on catheter ablation for AF in adults with CHD centred on PVI. A single-centre

series of 36 patients, most of whom had atrial (61%) or ventricular (17%) septal defects, included 72% with paroxysmal and 28% with persistent AF.[746] Freedom from recurrent AF without antiarrhythmic drugs was 42% at 300 days and 27% at 4 years after a single procedure. The largest series of AF ablation in patients with CHD included 57 patients, with a mean age 51 years, of whom 61% had simple, 18% moderate, and 21% severe forms of CHD.[747] The pattern of AF was paroxysmal in 37% and persistent in 63%. Freedom from recurrent atrial arrhythmias with or without antiarrhythmic drugs was 63% at 1 year and 22% at 5 years. Recovery of PV conduction was observed in 65% of patients who underwent a second intervention. One case series described the feasibility and safety of cryoballoon ablation in 10 patients with AF and CHD.[748] PVI was acutely successful in all, with no major complication. One year after a single ablation procedure, 60% remained free from AF. The totality of evidence thus far suggests that catheter ablation is feasible, safe, and modestly efficacious. A more thorough understanding of underlying mechanisms and extra-PV triggers carries the potential to further improve the selection of optimal candidates and procedural outcomes.[729]

11.5. Secondary AF or AF due to reversible precipitants

As outlined in section 1.2, the likelihood of developing AF varies across physiological and pathological states. Conceptually, AF may be considered "primary" if the AF represents an established pathophysiological process or "secondary" if the AF is caused by a self-limited or at least partially reversible precipitant.[18] Within secondary AF, these episodes can be conceptualized as arising from a combination of several complementary elements. The first is the patient's underlying propensity to AF due to modifiable and nonmodifiable substrates, the second is the new substrate imparted by the acute/secondary precipitant, and the third is the reversible AF trigger provoked by the secondary cause (Fig. 3).[749] This conceptual model suggests that secondary AF will be more likely in patients with a propensity to AF (eg, more baseline substrate) and, even when the secondary cause for the disease is completely reversible these patients might still be at higher risk for future events.

11.5.1. Common causes of secondary AF

Common causes of secondary AF include surgery (cardiac and noncardiac), acute cardiac pathology (eg, MI and myopericarditis), acute pulmonary pathology (eg, COPD, pulmonary emboli, pneumonia), thyrotoxicosis, infection and sepsis, acute alcohol consumption and substance use, electrocution, and other metabolic disorders.[18]

RECOMMENDATION

114. We recommend that secondary causes for AF be identified and treated (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on evidence that supports a reduction in recurrence with treatment of the underlying reversible trigger (see Tables 1 and 2, and Fig. 6).

11.5.2. Rate and rhythm management of secondary AF

The decision to provide rate or rhythm control for secondary AF depends on the clinical context. In all cases, management of the underlying precipitant is paramount. For AF associated with acute medical illness, the risk-benefit balance must take into consideration the underlying medical condition (see section 9.1). In the case of AF associated with hyperthyroidism, the hyperadrenergic state encourages a rapid ventricular response and often necessitates β-blockade. In this case, propranolol might be the preferred agent because can effectively manage the ventricular rate, symptoms of hyperthyroidism (tremor, anxiety, palpitations), and might act to inhibit the monodeiodinase type I enzyme responsible for conversion of T4 to the more potent T3.[750]

11.5.3. Prognosis and follow-up of secondary AF

An increased risk of adverse outcomes in association with new-onset AF secondary to MI, sepsis, or surgery has been reported.[751-753] Increased mortality has been observed with recent-onset AF in the presence of ACS, sepsis, and COPD exacerbation.[754] ACS-associated new-onset AF acts as an independent prognostic indicator for adverse cardiovascular events such as early reinfarction, stroke, and HF. Recent-onset AF in patients with sepsis is associated with increased risks of HF, ischemic stroke, and prolonged length of ICU stay.[288,752,755,756]

AF in patients with severe sepsis has been associated with increased mortality and in-hospital stroke.[752,755] New-onset AF in the HF population has been associated with increased mortality.[757] New-onset AF in the setting of an ACS has been associated with increased mortality, stroke, and reinfarction, resulting in a significantly higher in-hospital mortality compared with those with preexisting AF.[751,758,759]

Irrespective of the cause of secondary AF, long-term recurrence of AF is frequently observed.[18,288,756,760] At present, there are limited data to predict which patients will develop recurrent AF beyond an assessment of the traditional risk factors for AF outlined in section 3. As such, it is recommended that patients with secondary AF undergo careful reassessment and follow-up.

RECOMMENDATION

115. We recommend that patients who have experienced secondary AF be followed indefinitely for the possible emergence of recurrent clinical AF, with opportunistic screening for AF conducted at the time of medical encounters (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Elimination of the trigger is not a guarantee that AF will not recur. Because patients with secondary AF might develop AF later in life it is important to follow them regularly to screen for recurrence (see section 11.5.3 regarding screening).

Practical tip. Patients should be counselled regarding AF-associated symptomatology, when to report for medical evaluation, and about risk factor modification (see section 6).

11.6. AF after cardiac and noncardiac surgery

11.6.1. Incidence of postoperative atrial tachyarrhythmias

AF commonly occurs in the perioperative setting because of the relationship between AF and atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances, and high sympathetic tone.[761-767] The incidence of POAF after cardiac surgery is approximately 30% for isolated CABG, approximately 40% for valve replacement or repair, and approximately 50% for combined CABG/valve procedures.[768] The peak incidence of POAF is between postoperative days 2 and 4.[767] Although POAF might be transient and cause little morbidity in many cases, POAF has been independently associated with increased in-hospital duration and health care costs.[767]

11.6.2. Risk factors for postoperative atrial tachyarrhythmias

Independent factors for POAF after cardiac surgery include a preexisting history of AF, older age, male sex, a history of hypertension, the procedure performed, the number of bypass grafts, the duration of surgery, the duration of aortic cross-clamp time, a requirement for an intraoperative balloon pump, a requirement for ventilation > 24 hours, and withdrawal of β-blocker therapy.[761-767] Of these, age has the highest predictive value.[32]

11.6.3. Prevention of postoperative atrial tachyarrhythmias

11.6.3.1. β-Blockers

Current evidence suggests that β-blocker therapy reduces the incidence of POAF in patients who undergo cardiac and noncardiac surgery.[769,770] For patients who underwent cardiac surgery, use of β-blockers significantly reduced the occurrence of AF (RR, 0.50; 95% CI, 0.42-0.59; 40 studies, 5650 participants) and ventricular arrhythmias (RR, 0.40; 95% CI, 0.25-0.63; 12 studies, 2296 participants) without significant bradycardia, hypotension, or MI.[770] In patients who underwent noncardiac surgery use of β-blockers significantly reduced the occurrence of AF (RR, 0.41; 95% CI, 0.21-0.79; 9 studies, 9080 participants) and MI (RR, 0.72; 95% CI, 0.60-0.87; 12 studies, 10,520 participants) at the expense of bradycardia (RR, 2.49; 95% CI, 1.74-3.56; 49 studies, 12,239 participants) and hypotension (RR, 1.40; 95% CI, 1.29-1.51; 49 studies, 12,304 participants).[769] All-cause mortality at 30 days after cardiac or noncardiac surgery was not influenced by β-blocker use.[769,770]

Relative to cardiac surgery, some trials required preoperative withdrawal of preexisting β-blocker therapy in patients randomized not to receive study β-blocker therapy (β-blocker withdrawal-mandated trials); other trials continued preexisting β-blocker therapy in patients randomized not to receive study β-blocker therapy (β-blocker withdrawal-not mandated trials). In the β-blocker withdrawal-mandated trials, study β-blocker therapy substantially reduced POAF (25 RCTs; 2600 patients; 10.5% vs 28.7%; OR, 0.30; 95% CI, 0.22-0.40; $P < 0.001$).[771] In the β-blocker withdrawal-not mandated trials, study β-blocker therapy reduced POAF to a lesser extent (3 trials; 1163 patients; 31.5% vs 40.2%; OR, 0.69; 95% CI, 0.54-0.87; $P = 0.002$). This observation might relate to preoperative β-blocker withdrawal increasing POAF in the control groups of the β-blocker withdrawal-mandated trials.

Subgroup analyses did not identify any differences in outcomes according to the β-blocker used, or according to whether β-blocker therapy was initiated before, during, or immediately after surgery.[772]

RECOMMENDATION

116. We recommend that patients who have been receiving a β-blocker before cardiac or noncardiac surgery have that therapy continued postoperatively in the absence of contraindications (Strong Recommendation; High-Quality Evidence).
117. We suggest that patients who have not been receiving a β-blocker before cardiac surgery have β-blocker therapy initiated immediately after the surgical procedure in the absence of a contraindication (Weak Recommendation; Low-Quality Evidence).

Values and preferences. These recommendations place a high value on reducing POAF and a lower value on adverse hemodynamic effects of β-blockade during or after cardiac surgery.

11.6.3.2. Amiodarone

Perioperative amiodarone therapy has been shown to reduce the occurrence of POAF after cardiac surgery compared with placebo or usual care (33 RCTs; 5402 patients; 19.4% vs 33.3%; OR, 0.43; 95% CI, 0.34-0.54; $P < 0.001$).[773] However, a meta-analysis[774] of head-to-head trials showed no significant difference between amiodarone and standard β-blockers for POAF prophylaxis after cardiac surgery, which might reflect the withdrawal of preexisting β-blocker therapy in the amiodarone group, which biases the comparison in favour of β-blocker prophylaxis. Results of 1 small comparative trial suggest that the combination of amiodarone and β-blocker prophylaxis is more effective than β-blockers alone.[775]

In a recent network meta-analysis[776] the effect of timing and route of amiodarone administration on its efficacy and adverse effects were examined. Regimens that included only oral amiodarone reduced POAF similarly as did regimens that included I.V. administration. Regimens that included a least 1 day of preoperative amiodarone reduced POAF to an equivalent degree as did regimens that started amiodarone the day of or after surgery. This meta-analysis[776] also showed that bradycardia, hypotension, or QT prolongation were less common with oral-only regimens than with I.V. regimens.

In addition to reducing POAF, amiodarone has been shown to reduce postoperative hospital length of stay by approximately 1 day.[773,777]

RECOMMENDATION

118. We recommend that patients who have a contraindication to β-blocker therapy before or after cardiac surgery be considered for prophylactic therapy with amiodarone to prevent POAF (Strong Recommendation; High-Quality Evidence).

Values and preferences. This recommendation places a high value on minimizing the patient population exposed to the potential adverse effects of amiodarone and a lower value on data that suggest that amiodarone is more effective than β-blockers for this purpose.

11.6.4. Other apparently effective therapies less commonly used

11.6.4.1. Sotalol

A Cochrane intervention review[773] showed that perioperative sotalol therapy reduced POAF after cardiac surgery compared with placebo or usual care (11 trials; 1609 patients; 18.1% vs 40.0%; OR, 0.34; 95% CI, 0.26-0.43; $P < 0.001$). Another meta-analysis[778] showed a significantly higher efficacy of sotalol compared with standard β-blocker drugs for prevention of POAF (5 RCTs; 1043 patients; 14.3% vs 22.7%; RR, 0.64; 95% CI, 0.50-0.84; $P < 0.001$). It also showed similar efficacies when sotalol and amiodarone were compared.[778] Thus, sotalol prophylaxis appears to be effective for prevention of POAF after cardiac surgery but is not considered a first-line therapy because of its risk of QT-interval prolongation and TdP.

11.6.4.2. I.V. magnesium

A meta-analysis[779] indicated that postoperative I.V. magnesium supplementation care reduced POAF after cardiac surgery compared with placebo or standard care (21 RCTs; 3248 patients; RR, 0.69; 95% CI, 0.56-0.86; $P = 0.006$). Although most magnesium trials reported no adverse effects of magnesium therapy, one trial[36] showed more postoperative hypotension with a combination of I.V. magnesium and propranolol therapy than with propranolol therapy alone.[780]

11.6.4.3. Overdrive atrial pacing

Trials have shown a significant reduction in POAF after cardiac surgery with overdrive atrial pacing (14 RCTs; 1885 patients; 17.7% vs 35.3%; OR, 0.60; 95% CI, 0.47-0.77; $P < 0.001$), and in particular with biatrial pacing.[771] However, the **A**trial **Fi**brillation **S**uppression **T**rial **II** (AFIST-II) showed that amiodarone is better at prevention of POAF than overdrive septal atrial pacing.[781]

11.6.4.4. Colchicine

Colchicine has been shown to reduce POAF (5 RCTs; 1412 patients; 18.1% vs 26.8%; RR, 0.69; 95% CI, 0.57-0.84; $P = 0.0002$) and hospital stay after cardiac surgery (3 RCTs; 692 patients; mean difference, −1.2 days; 95% CI, −1.9 to −0.4 days; $P = 0.002$) compared with placebo or standard care.[782] However, these potential benefits were counterbalanced by an increased incidence of drug-related adverse effects (4 RCTs; 1196 patients; 21.0% vs 8.2%; RR, 2.52; 95% CI, 1.62-3.93; $P < 0.0001$), which was dominated by adverse GI side effects.

11.6.4.5. Posterior pericardial drainage

Drainage of the posterior pericardial space at the time of cardiac surgery with a posterior pericardiotomy and/or a posterior pericardial drainage tube reduces early and late pericardial effusion and cardiac tamponade, POAF (17 RCTs; 3245 patients; 12.6% vs 24.8%; OR, 0.42; 95% CI, 0.29-0.59; $P < 0.001$), hospital length of stay (13 RCTs; 2068 patients; mean difference, −0.82 days; 95% CI, −1.12 to −0.51 days; $P = 0.005$), and death or cardiac arrest (10 RCTs; 2141 patients; 1.1% vs 2.3%; OR, 0.49; 95% CI, 0.25-0.94; $P < 0.001$).[783] A large RCT, **P**osterior **L**eft Pericardiotomy for Prevention of **A**trial Fibrillation After **C**ardiac **S**urgery (PALACS; NCT02875405), is under way.[784]

11.6.4.6. HMG-CoA reductase inhibitors

A meta-analysis[785] of RCTs of an HMG-CoA reductase inhibitor vs placebo or standard care showed that perioperative statin therapy reduces POAF after cardiac surgery (16 RCTs; 3985 patients; 20.3% vs 23.7%; OR, 0.50; 95% CI, 0.34-0.73; $P = 0.0004$) and shortens hospital stay (12 RCTs; 1185 patients; mean difference, −0.43 days; 95% CI, −0.70 to −0.15; $P = 0.002$). However, no differences were observed with respect to stroke or short-term mortality.[785]

11.6.4.7. Antioxidants

A meta-analysis[786] of RCTs of vitamin C treatment vs placebo or standard care for prevention of POAF after cardiac surgery showed that vitamin C reduces POAF (10 RCTs; 1956 patients; 26.2% vs 36.4%; RR, 0.68; 95% CI, 0.54-0.87; $P = 0.002$) and reduces hospital length of stay (9 RCTs; 1158 patients; mean difference, −0.95 days; 95% CI, −1.64 to −0.26 days; $P = 0.007$).

A meta-analysis[787] of RCTs of N-acetylcysteine vs placebo or standard care for prevention of POAF showed that N-acetylcysteine reduces POAF (10 RCTs; 1026 patients; 20.5% vs 28.8%; OR, 0.56; 95% CI, 0.40-0.77; $P = 0.0005$) without a reduction in hospital length of stay but with a possible reduction in postoperative mortality.

11.6.4.8. Other potential therapies

Class Ia (disopyramide, procainamide, quinidine) and class Ic (propafenone, flecainide) antiarrhythmic agents might prevent POAF[788,789] but are generally avoided in cardiac surgical patients because of concerns of proarrhythmia. Small RCTs have supported the use of dofetilide (1 RCT; 133 patients; 17.9% vs 36.4%; OR, 0.32; 95% CI, 0.16-0.83; $P = 0.017$) or ranolazine (1 RCT; 102 patients; 8.8% vs 30.8%; RR, 0.29; 95% CI, 0.09-0.89; $P < 0.001$).[790]

Perioperative steroid use, renin-angiotensin system inhibitors, digoxin prophylaxis, calcium antagonist prophylaxis, n-3 polyunsaturated fatty acids, glucose-insulin-potassium therapy, vasopressin, and NSAIDs have been shown to lack promise.[771,791-796] Intraoperative injection of botulinum toxin into epicardial neural ganglia has been shown to be promising in small RCTs with a larger study in progress.[797]

RECOMMENDATION

119. We suggest that patients who have a contraindication to β-blocker therapy and to amiodarone be considered for prophylactic therapy to prevent POAF with I.V. magnesium, biatrial pacing, colchicine, and/or posterior pericardiotomy (Weak Recommendation; Low-Quality Evidence).

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

11.6.5. Treatment of postoperative atrial tachyarrhythmias

The management of POAF centres on the identification of potential contributors (pulmonary thromboembolism, volume overload, congestive HF, sepsis), prevention of thromboembolic events, slowing of the ventricular response rate, and consideration of sinus rhythm restoration.

The natural history of POAF is dominated by self-terminating but frequently recurrent AF episodes, and resolution in 6-12 weeks regardless of the therapy used.[798-800] Furthermore, the hyperadrenergic state lessens the effectiveness of therapies that do not include β-blockade.

There is an association between POAF, thromboembolic cerebrovascular events,[766,767,801,802] and cognitive impairment.[803] Nevertheless, early anticoagulation might predispose the postoperative cardiac surgery patient to delayed pericardial bleeding and tamponade.[804] In recognition of this risk and in the absence of controlled trials, the initiation of anticoagulation is generally not recommended in the first 72 hours after cardiac surgery. When initiated, anticoagulation is usually continued for > 6 weeks.

Therapy for ventricular rate control is usually required for patients who experience POAF. Nevertheless, cardiac surgery might also predispose patients to bradyarrhythmia after conversion of AF. Accordingly, the availability of back-up ventricular pacing is important. Because the postsurgical state includes adrenergic discharge, β-blocker therapy is often effective. Alternatives to β-blocker therapy include ND-CCBs or amiodarone because digoxin is usually ineffective.

The advantages and disadvantages of sinus rhythm restoration are similar to those in other settings. In the POAF population specifically, a recent RCT failed to show a significant difference between a rate control vs a rhythm control approach in the outcomes of total number of days in hospital, length of the index hospitalization, readmission rate, time to sustained sinus rhythm, or adverse events including the need for pacemaker.[805] Accordingly, either the rate control or the rhythm control approach to the treatment of POAF seems appropriate. If rhythm control is pursued, antiarrhythmic drug therapy is preferred to isolated DCCV because early recurrence of POAF is common. Regardless of the approach chosen, therapy provided for POAF can usually be withdrawn 6-12 weeks later.

RECOMMENDATION

120. We recommend that AF after cardiac or noncardiac surgery may be appropriately treated with a rate control strategy or a rhythm control strategy (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a high value on the randomized controlled trials in which rate control as an alternative to rhythm control for AF has been investigated, including 2 trials with a specific focus on the cardiac postoperative period. Choice of strategy should therefore be individualized on the basis of the degree of symptoms experienced by the patient.

Practical tip. The management of POAF should follow the principles outlined in sections 9.1-9.3.

121. We suggest that consideration be given to withhold anticoagulation therapy for the first 72 hours after cardiac surgery, on the basis of an individualized assessment of the risks of a thromboembolic event and the risk of postoperative bleeding (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation recognizes that risk of postoperative bleeding decreases with time. The benefit-to-risk ratio favours a longer period without anticoagulation in the postoperative setting than that suggested in other settings.

122. We recommend that, when anticoagulation therapy, rate control therapy, and/or rhythm control therapy has been prescribed for POAF, formal reconsideration of the ongoing need for such therapy should be undertaken 6-12 weeks later (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation reflects the high probability that POAF will be a self-limiting process that does not require long-term therapy. At present, the possibility that long-term anticoagulation therapy might prevent the suggested increased risk of stroke in patients with transient POAF with a favourable risk-benefit ratio is insufficient to recommend long-term anticoagulation therapy in these patients.

11.6.6. Prognosis of postoperative atrial tachyarrhythmias

Because patients with POAF are older and have more comorbidities than patients without POAF, the challenge has been to determine if POAF is an independent predictor of long-term adverse events. In one of the first studies[806] to address these issues, the outcomes of consecutive survivors of CABG surgery from a single centre in Sweden who did not have a preoperative AF history or a pacemaker were retrospectively analyzed. Of these 571 patients, 165 (28.9%) experienced POAF. After a median follow-up of more than 6 years, patients with POAF had a higher probability of recurrent AF (25.4% vs 3.6%; adjusted OR, 8.31; 95% CI, 4.20-16.43; $P < 0.001$), a higher probability of late all-cause mortality (29.7% vs 14.8%; adjusted HR, 1.57; 95% CI, 1.05-2.34; $P = 0.027$), and a higher probability of death from cerebral ischemia (4.2% vs 0.2%; $P < 0.001$) compared with patients without POAF. A very recent analysis[807] took this observational comparison further with a larger sample size, prospectively collected data, longer follow-up, and a matched cohort evaluation. This report considered 7145 consecutive

survivors of CABG surgery who did not have a preoperative AF history or a pacemaker from a single centre in Sweden. Of these 7145 patients, 2183 (30.6%) experienced POAF. Patients in the POAF group and in the non-POAF group were matched (on age, sex, and county) to 5 control patients who did not undergo cardiac surgery. The cumulative incidence of late AF (at 10 years of follow-up) was higher in patients with POAF compared with those without POAF (15.3% vs 4.9%; adjusted HR, 3.20; 95% CI, 2.73-3.76; $P < 0.001$) or matched, nonsurgical controls (15.3% vs 6.4%; $P < 0.001$). There was no difference in the incidence of late AF in patients without POAF compared with their matched, nonsurgical control participants (4.9% vs 5.7%; $P = 0.043$). Patients with POAF had higher probabilities of late ischemic stroke, HF, cardiac mortality, cerebrovascular mortality, and all-cause mortality, compared with patients without POAF. Most other analyses of this sort have shown similar findings.[753,808,809] Accordingly, POAF after cardiac surgery is associated with long-term risk of future AF (15%-25% over 10 years, which is higher than in patients without POAF and higher than in the general population). As such, this patient group should be followed more closely for the ultimate development of AF, particularly because of the observation that approximately half of the AF episodes in this setting are asymptomatic.[810]

RECOMMENDATION

123. We recommend that patients who have experienced AF after cardiac or noncardiac surgery be followed indefinitely for the possible emergence of recurrent clinical AF (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Elimination of the trigger (eg, resolution of postsurgical change) is not a guarantee that AF will not recur. Because patients with secondary AF can often go on to develop AF later in life it is important to follow them regularly to screen for recurrence (see section 11.5.3).

Practical tip. Patients should be counselled regarding AF-associated symptomatology, when to report for medical evaluation, and about risk factor modification (see section 6).

11.7. AF and supraventricular arrhythmia

AF might occur in conjunction with SVT. Previous cohort studies have observed AF in association with SVT in almost 20% of patients, with a gradient dependent on the underlying arrhythmia (58% with AFL, 27% with atrial tachycardia, 14% with AV reentrant tachycardia [AVRT], and 10% with AV nodal reentrant tachycardia [AVNRT]).[811] Conversely, studies of AF patients who underwent electrophysiology studies before catheter ablation of AF have shown inducible SVT, in 4.3%-10.0%, including AFL (3.7%), typical AVNRT (1.7%), AVRT (1.2%), and atrial tachycardia (1%).[812-814] In those with inducible SVT, there was a transition from SVT into AF during electrophysiology study in almost one-half of the patients.[814]

AF patients with inducible SVT tend to be younger, more likely to have paroxysmal AF, less likely to have structural heart disease, and are more likely to be free of AF after a single ablation procedure (88% were AF-free after SVT ablation alone or SVT and AF ablation).[812,814] Enriched populations of younger AF patients, those free of structural heart disease, and those with a history of regular palpitations or narrow QRS tachycardia have been shown to have much higher rates of inducible SVT, with one series documenting AVNRT in 18% and AVRT in 9% of AF patients younger than 65 years,[815] and another series inducing SVT in up to 57% of patients younger than 35 years of age without medical comorbidities.[816]

11.7.1. Role of the electrophysiology study

Because of the variable rates of inducible SVT in patients with AF, an electrophysiology study should be primarily considered in AF patients who are younger, without medical comorbidities, have a history of regular palpitations or narrow complex tachycardia, and/or are planned to undergo catheter ablation of AF.

It is reasonable to perform catheter ablation of the SVT alone. In younger patients, successful ablation of SVT can treat the underlying cause and might be associated with lower rates of AF recurrence.[812,814] Older patients generally have higher rates of AF occurring after SVT ablation (up to 20%-30% after several years) and may benefit from combined SVT and AF ablation.[69,817,818]

RECOMMENDATION

124. We suggest an electrophysiology study to exclude reentrant tachycardia as a cause of AF be performed in younger patients without medical comorbidities or those with a history suggestive of concomitant SVT (eg, regular palpitations). If present, we suggest ablation of the tachycardia (Weak Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation recognizes that SVT can initiate AF when the substrate for AF is present and can be ablated with a high success rate and minimal risk.

11.8. Wolff-Parkinson-White syndrome

11.8.1. Acute management of preexcited AF

AF can occur in up to 50% of young patients with Wolff-Parkinson-White (WPW) syndrome.[819] Rapid conduction of AF from the atrium to the ventricle via the accessory pathway is rare but can result in ventricular fibrillation and sudden cardiac death.[820,821] In patients who present with preexcited AF, we recommend urgent synchronized cardioversion in the presence of hemodynamic instability[822,823] or when pharmacological cardioversion of hemodynamically stable preexcited AF with I.V. ibutilide or procainamide is ineffective.[824,825] The use of I.V. β-blockers, diltiazem, verapamil, digoxin, and amiodarone are not recommended for acute management of preexcited AF because of the potential to precipitate a

life-threatening arrhythmia.[826-829] Conduction over the accessory pathway is enhanced with use of drugs that block the AV node (β-blockers, diltiazem, verapamil, or amiodarone) and they might cause hypotension and a catecholamine release, resulting in an increase in the ventricular rate. Digoxin shortens the refractory period of the accessory pathway, further enhancing antegrade conduction of AF.

RECOMMENDATION

125. We recommend electrical cardioversion to restore sinus rhythm in hemodynamically unstable patients with evidence of ventricular preexcitation during AF (Strong Recommendation; Low-Quality Evidence).
126. We recommend electrical or pharmacologic cardioversion using I.V. procainamide or ibutilide to restore sinus rhythm in hemodynamically stable patients with evidence of ventricular preexcitation during AF (Strong Recommendation; Low-Quality Evidence).

Practical tip. Electrical cardioversion might be preferred on the basis of the relatively limited evidence base, as well as the small size of the studies of pharmacologic cardioversion for preexcited AF.

127. We recommend that AV nodal-blocking agents, digitalis, and amiodarone should be avoided in patients with evidence of ventricular preexcitation (Strong Recommendation; Low-Quality Evidence).

11.8.2. Chronic management of preexcited AF

The treatment of choice for patients with preexcited AF is catheter ablation. Ablation of an accessory pathway has a very high acute success rate (> 90%) with a low rate of complications (overall 3%; death 0.1%-0.3%; stroke 0.1%-0.2%; tamponade 0.4%-0.6%; AV block requiring pacemaker 0.3%-1.0%).[649,830] Certain high-risk features that increase the risk of ventricular fibrillation include: an accessory pathway with a short refractory period, arrhythmia-associated syncope, the presence of multiple pathways, and orthodromic AV reciprocating tachycardia that degenerates into preexcited AF. When present, these factors should prompt urgent catheter ablation.[821,831-833]

RECOMMENDATION

128. In patients with evidence of ventricular preexcitation and AF, we recommend catheter ablation of the accessory pathway (Strong Recommendation; Low-Quality Evidence).

Values and preferences. This recommendation places a high value on the high efficacy of catheter ablation of the accessory pathway and the prevention of sudden cardiac death in patients at high risk, and a low value on the small risk of complications.

Practical tip. Urgent or in-patient ablation should be strongly considered for preexcited AF with high-risk features. High-risk features include AF associated with syncope, rapid ventricular rates (eg, short accessory pathway refractory period), the presence of multiple accessory pathways, or regular narrow complex tachycardia that degenerated into preexcited AF.

11.9. Screening for AF in patients with a history of atrial dysrhythmia

Patients with a history of atrial dysrhythmia (AFL, atrial tachycardia, AVRT, and AVNRT) should be followed for the development of AF.

RECOMMENDATION

129. We recommend that patients who have undergone ablation of an atrial dysrhythmia (atrial flutter, atrial tachycardia, AVRT, AVNRT) should be followed for the occurrence of AF with opportunistic screening conducted at the time of medical encounters (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the evidence supporting the observation that AF might occur after ablation of AFL, SVT, or WPW, particularly in those with increasing age and a history of AF. This guideline recognizes that the risk of AF recurrence is relatively higher with a history of AFL, intermediate for WPW, and lowest for a history of other SVTs.

Practical tip. In those with SVT but no previous AF history, it remains unclear if SVT alone is enough to increase the risk of AF in the absence of significant risk factors.

Practical tip. Patients should be counselled regarding AF-associated symptomatology, when to report for medical evaluation, and about risk factor modification (see section 6).

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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 https://doi.org/10.1016/j.cjca.2020.09.001.