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National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018

David B. Brieger

University of Sydney, Concord Hospital

John Amerena

University Hospital Geelong

John R. Attia

University of Newcastle

Beata Bajorek

University of Technology Sydney, Royal North Shore Hospital, beata.bajorek@uts.edu.au

Kim H. Chan

University of Sydney, Royal Prince Alfred Hospital

See next page for additional authors

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National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018

Abstract

In 2015, the National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) undertook a survey of emerging issues in cardiovascular disease. The goal was to prioritise clinical conditions that would benefit from locally developed contemporary guidelines. Individual diseases were evaluated according to burden of disease, the existence of treatment gaps, an evolving therapeutic landscape, evidence of inequity and the existence of local treatment guidelines. Atrial fibrillation (AF) scored highly in each of these categories. Specifically, AF was recognised as a burdensome condition with increasing prevalence, where large numbers of patients are not treated with anticoagulation, despite the clear benefit of this therapy in stroke prevention. Other factors relevant to AF were:

- the relatively recent availability of non-vitamin K oral anticoagulants (NOACs), with a rapidly evolving evidence base guiding their use;
- variation and uncertainty about best practice use of antiarrhythmic drugs
- increasing availability of AF ablative procedures;
- an increasing prevalence of AF in older people and Aboriginal and Torres Strait Islander peoples.

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Authors

David B. Brieger, John Amerena, John R. Attia, Beata Bajorek, Kim H. Chan, Cia Connell, S Ben Freedman, Caleb Ferguson, Tanya Hall, Haris Haqqani, Jeroen Hendriks, Charlotte Hespe, Joseph Hung, Jonathan Kalman, Prashanthan Sanders, John M. Worthington, Tristan Yan, and Nicholas Arnold Zwar

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NHFA CSANZ Atrial Fibrillation Guideline Working Group:¹

David Brieger, MBBS, PhD, FCSANZ^{a,b*},
John Amerena, MBBS, FRACP, FCSANZ^c, **John Attia, MD, PhD, FRACP^d,**
Beata Bajorek, BPharm, PhD^e, **Kim H. Chan, MBBS, PhD, FRACP^{f,g},**
Cia Connell, BPharm, GCP PharmPrac, MCLinPharm^h,
Ben Freedman, MBBS, PhD, FRACP^{i,j}, **Caleb Ferguson, RN, PhD^k,**
Tanya Hall^l, **Haris Haqqani, MBBS, PhD, FRACP^m,**
Jeroen Hendriks, MSc, PhD^s, **Charlotte Hesse, MBBS, DCH, FRACGP^p,**
Joseph Hung, MBBS, FRACP, FCSANZ^q, **Jonathan M. Kalman, MBBS, PhD^r,**
Prashanthan Sanders, MBBS, PhD, FRACP^s,
John Worthington, MBBS, BSc(Med), FRACP^t,
Tristan D. Yan, MD, MS, PhD^u, **Nicholas Zwar, MBBS, MPH, PhD^v**

^aDepartment of Cardiology, Concord Hospital, Sydney, Australia^bUniversity of Sydney, Sydney, Australia^cGeelong Cardiology Research Unit, University Hospital Geelong, Geelong, Australia^dUniversity of Newcastle, Hunter Medical Research Institute, University of Newcastle, Newcastle, Australia^eGraduate School of Health, University of Technology Sydney & Department of Pharmacy, Royal North Shore Hospital, Australia^fRoyal Prince Alfred Hospital, Sydney, Australia^gSydney Medical School, The University of Sydney, Sydney, Australia^hThe National Heart Foundation of Australia, Melbourne, AustraliaⁱSydney Medical School, The University of Sydney, Sydney, Australia^jHeart Research Institute, Charles Perkins Centre, University of Sydney, Sydney, Australia^kWestern Sydney University, Western Sydney Local Health District, Blacktown Clinical and Research School, Blacktown Hospital, Sydney, Australia^lHearts4Heart, Melbourne, Australia^mUniversity of Queensland, Department of Cardiology, Prince Charles Hospital, Brisbane, AustraliaⁿDepartment of Cardiology, Royal Adelaide Hospital, Adelaide, Australia^oCentre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia^pGeneral Practice and Primary Care Research, School of Medicine, The University of Notre Dame Australia, Sydney, Australia^qMedical School, Sir Charles Gairdner Hospital Unit, University of Western Australia, Perth, Australia^rUniversity of Melbourne, Director of Heart Rhythm Services, Royal Melbourne Hospital, Melbourne, Australia^sCentre for Heart Rhythm Disorders (CHRD), South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia^tRPA Comprehensive Stroke Service, Royal Prince Alfred Hospital, Sydney, Australia^uRoyal Prince Alfred Hospital, Sydney, Australia^vGraduate Medicine, University of Wollongong, Wollongong, Australia

1. Rationale for These Guidelines

In 2015, the National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) undertook a survey of emerging issues in cardiovascular disease. The goal was to prioritise clinical conditions that would benefit from locally developed contemporary guidelines. Individual diseases were evaluated according to burden of disease, the existence of treatment gaps, an evolving therapeutic landscape, evidence of inequity and the existence of local treatment guidelines. Atrial fibrillation (AF) scored highly in each of these categories. Specifically, AF was recognised as a burdensome condition with increasing prevalence, where large numbers of patients are not

treated with anticoagulation, despite the clear benefit of this therapy in stroke prevention. Other factors relevant to AF were:

- the relatively recent availability of non-vitamin K oral anticoagulants (NOACs), with a rapidly evolving evidence base guiding their use;
- variation and uncertainty about best practice use of anti-arrhythmic drugs
- increasing availability of AF ablation procedures;
- an increasing prevalence of AF in older people and Aboriginal and Torres Strait Islander peoples.

International guidelines on the diagnosis and management of AF are available [1,2], but these often differ from each

*Corresponding author. Email: briegster@gmail.com

¹ The AF writing group would like to specifically acknowledge Associate Professor Huyen Tran MBBS (Hons) Master Clin Epi FRACP FRCPA. The "National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018" have been jointly developed by the Heart Foundation and the Cardiac Society of Australia and New Zealand. The Heart Foundation and the Cardiac Society of Australia and New Zealand are grateful for the contributions of all persons and entities involved in the development of the Guideline.

other with regards to individual recommendations, and no such guidelines had been developed specific to the Australian population. Therefore, NHFA and CSANZ resolved to produce Australian guidelines for AF.

These clinical guidelines have been developed to assist Australian practitioners in the management of adult patients with AF. They are intended to be used by practising clinicians across all disciplines caring for such patients. Some of the core recommendations of this document have been informed by existing international guidelines,

including the 2016 European Society of Cardiology *Guidelines for the management of atrial fibrillation* [1], which were developed in collaboration with the European Association for Cardio-Thoracic Surgery, and the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society *Guideline for the management of patients with atrial fibrillation* [2]. However, these Australian guidelines provide a focus on local practice and include some updated recommendations reflecting more recent evidence generation.

2. Key Recommendations

Recommendation	GRADE quality of evidence	GRADE strength of recommendation
Screening and prevention—screening for silent atrial fibrillation (AF)		
Opportunistic point-of-care screening in the clinic or community should be conducted in people aged 65 years or more.	Moderate	Strong
Screening for asymptomatic AF in patients with pacemakers and implanted devices		
Pacemakers and defibrillators should be interrogated regularly for atrial high-rate episodes (AHREs), and should be confirmed by atrial electrocardiogram (EGM) to be AF.	Moderate	Strong
Screening for AF in patients with embolic stroke of uncertain source (ESUS)		
For patients with ESUS, longer term ECG monitoring (external or implantable) should be used.	Moderate	Strong
Diagnostic work up		
A 12-lead electrocardiogram (ECG) is recommended for all patients with AF.	Low	Strong
A transthoracic echocardiogram should be performed in all patients with newly diagnosed AF.	Low	Strong
A thyroid stimulating hormone (TSH) test should be undertaken in patients with newly diagnosed AF but should be delayed in acutely ill patients.	Moderate	Strong
Detection and management of risk factors and concomitant diseases		
Intercurrent risk factors and comorbidities—including hypertension, diabetes, heart failure, valvular heart disease and alcohol excess—should be identified and their management considered an important component of treatment in patients with AF.	Low	Strong
Intensive management of weight—to a target of greater than or equal to 10% body weight loss, aiming for a body mass index (BMI) below 27—and concomitant management of associated cardiovascular risk factors to target levels should be performed in overweight and obese individuals with AF.	Moderate	Strong
Screening (by polysomnography) and management of sleep apnoea is recommended in individuals with recurrent symptomatic AF.	Moderate	Strong
Exercise that improves aerobic capacity is recommended in individuals with symptomatic AF, to reduce the AF burden.	Moderate	Strong
Arrhythmia management—rhythm control versus rate control		
A rhythm-control or a rate-control strategy should be selected, documented and communicated for all AF patients, and this strategy should be reviewed regularly.	Low	Strong

(continued).

Recommendation	GRADE quality of evidence	GRADE strength of recommendation
Arrhythmia management—acute rate control		
Beta adrenoceptor antagonists or non-dihydropyridine calcium channel antagonists are recommended for acute control of the ventricular rate in haemodynamically stable patients, although caution is needed if given intravenously.	Low	Strong
Amiodarone is recommended for acute control of the ventricular rate in highly symptomatic AF patients, or in those with known left ventricular systolic dysfunction, who are not unstable enough to require immediate electrical cardioversion.	Low	Strong
Digoxin may be considered to aid in acute control of ventricular rate either as add-on therapy to beta adrenoceptor antagonists or non-dihydropyridine calcium channel antagonists, or as stand alone therapy if these agents and amiodarone are contraindicated.	Low	Weak
Arrhythmia management—long-term rate control		
Beta adrenoceptor antagonists, digoxin and non-dihydropyridine calcium channel antagonists should be the first-line agents used for long-term control of the ventricular rate.	Moderate	Strong
Digoxin can be considered for control of the ventricular rate in patients with suboptimal rate control on, or with contraindications to, first-line agents.	Low	Weak
When digoxin is used, serum concentration should be monitored, with the goal of maintaining levels of <1.2 ng/mL.	Moderate	Strong
Calcium channel antagonists should be avoided in patients with left ventricular systolic dysfunction (ejection fraction <40%).	Low	Strong
Amiodarone should not be administered as a first-line agent for chronic rate control, given its toxicity profile.	Low	Strong
Membrane-active antiarrhythmic agents (e.g. sotalol or flecainide) should not be used in patients managed with a rate-control strategy.	Low	Strong
Documentation of the adequacy of ventricular rate control (<110 beats per minute [bpm]) at rest and with moderate exertion should be performed at regular intervals in asymptomatic patients without heart failure.	Moderate	Strong
Regular clinical surveillance for emergent cardiomyopathy or overt heart failure should be performed during long-term follow-up because heart failure may develop even in the presence of apparently adequate ventricular rate control.	Low	Strong
If pharmacological rate control fails, catheter ablation of the AV node should be considered after a permanent pacing device has been implanted.	Moderate	Strong
Arrhythmia management—acute rhythm control		
Electrical cardioversion should be performed urgently in haemodynamically unstable patients with AF.	Low	Strong
Electrical cardioversion can be considered—either as a first-line option or when pharmacological rhythm control fails—in haemodynamically stable patients, after consideration of thromboembolic risk	Low	Strong
Flecainide can be considered for rapid conversion to sinus rhythm, either intravenously or orally, in patients without left ventricular systolic dysfunction, moderate left ventricular hypertrophy, or coronary artery disease, after consideration of thromboembolic risk.	Moderate	Strong
AV nodal blocking medication is recommended for patients treated with flecainide.	Low	Strong

(continued).		
Recommendation	GRADE quality of evidence	GRADE strength of recommendation
Amiodarone administered intravenously may be considered for delayed conversion to sinus rhythm in patients with structural heart disease, including patients with heart failure and coronary artery disease.	Moderate	Strong
Arrhythmia management—long-term rhythm control		
Flecainide can be considered in the maintenance of sinus rhythm in patients without left ventricular systolic dysfunction, moderate left ventricular hypertrophy or coronary artery disease.	High	Strong
AV nodal blocking medication is recommended for patients treated with flecainide.	Low	Strong
Amiodarone can be considered for maintenance of sinus rhythm as a second-line agent or as a first-line agent in patients with left ventricular systolic dysfunction, moderate left ventricular hypertrophy or coronary artery disease.	High	Strong
Sotalol may be considered for maintenance of sinus rhythm but requires close monitoring of QT interval.	High	Strong
Beta adrenoceptor antagonists may be considered for the maintenance of sinus rhythm.	Moderate	Weak
Arrhythmia management—percutaneous catheter AF ablation		
Catheter ablation should be considered for symptomatic paroxysmal or persistent AF refractory or intolerant to at least one Class I or III antiarrhythmic medication.	High	Strong
Catheter ablation can be considered for symptomatic paroxysmal or persistent AF before initiation of antiarrhythmic therapy.	Moderate	Strong
Catheter ablation can be considered for symptomatic paroxysmal or persistent AF in selected patients with heart failure with reduced ejection fraction.	Moderate	Strong
Arrhythmia management—surgical management of AF in the context of concomitant cardiac surgery		
Surgical ablation of AF to restore sinus rhythm in the context of concomitant cardiac surgery may be considered for patients with symptomatic paroxysmal, persistent or long-standing persistent AF.	Moderate	Strong
Arrhythmia management—stand-alone surgical or hybrid management of AF		
Stand-alone surgical or hybrid ablation of AF can be considered for patients with symptomatic paroxysmal, persistent or long-standing persistent AF that is refractory, or intolerant to at least one Class I or III antiarrhythmic medication, or where there has been failed percutaneous ablation, or where the likelihood of successful percutaneous ablation is considered low.	Low	Weak
Stroke prevention—predicting stroke risk		
The CHA ₂ DS ₂ -VA score—the sexless CHA ₂ DS ₂ -VASc score—is recommended for predicting stroke risk in AF.	Moderate	Strong
The CHA ₂ DS ₂ -VA score should be re-evaluated yearly in low-risk patients who are not anticoagulated.	Low	Strong
Stroke prevention—prediction and minimisation of bleeding risk		
Reversible bleeding factors should be identified and corrected in AF patients for whom anticoagulation is indicated.	Low	Strong
Stroke prevention—anticoagulation		
Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients with non-valvular AF (N-VAF) whose CHA ₂ DS ₂ -VA score is 2 or more, unless there are contraindications to anticoagulation.	High	Strong

(continued).		
Recommendation	GRADE quality of evidence	GRADE strength of recommendation
Oral anticoagulation therapy to prevent stroke and systemic embolism should be considered in patients with N-VAF whose CHA ₂ DS ₂ -VA score is 1.	Moderate	Strong
Oral anticoagulation therapy to prevent thromboembolism and systemic embolism is not recommended in patients with N-VAF whose CHA ₂ DS ₂ -VA score is 0.	Moderate	Weak
In asymptomatic patients with atrial lead pacemakers, anticoagulation should be considered in device-detected and EGM-confirmed AF of 24 hours or more in patients with a CHA ₂ DS ₂ -VA score of 2 or more.	Moderate	Strong
When oral anticoagulation is initiated in a patient with N-VAF, a non-vitamin K oral anticoagulant (NOAC)—apixaban, dabigatran or rivaroxaban—is recommended in preference to warfarin.	Moderate	Strong
Warfarin is recommended and NOACs should not be used in patients with valvular AF (mechanical heart valves or moderate to severe mitral stenosis).	Moderate	Strong
Antiplatelet therapy is not recommended for stroke prevention in N-VAF patients, regardless of stroke risk.	Moderate	Strong
Point-of-care international normalised ratio (INR) measurement is recommended in the primary care management of patients receiving warfarin.	Moderate	Strong
Stroke prevention—management of bleeding		
Symptomatic treatment with fluid replacement or blood transfusion should be initiated for all patients with moderate to severe bleeding while treatment of the cause is addressed	Low	Strong
Factor replacement therapy with prothrombin complex concentrates (PCCs) can be considered for patients taking warfarin or specific factor Xa inhibitors with life threatening bleeding or those requiring emergency surgery.	Low	Weak
Idarucizumab is recommended for patients taking dabigatran who experience life-threatening bleeding or require emergency surgery.	Low	Strong
Anticoagulant therapy should be recommenced after bleeding has been addressed and when the stroke risk is believed to exceed the risk of further bleeding.	Low	Strong
Stroke prevention—combining oral anticoagulants (OAC) and antiplatelet agent		
Careful assessment of the bleeding and ischaemic risks (i.e. stroke, new or recurrent cardiac ischaemia or infarction, and stent thrombosis) should be undertaken for patients with AF who have a long-term requirement for anticoagulation for stroke prevention and require dual antiplatelet therapy (DAPT) after acute coronary syndrome (ACS) or stent implantation (or both).	Low	Strong
Duration of triple therapy (aspirin, P2Y ₁₂ inhibitor and OAC) should be as short as possible to minimise bleeding, while ensuring coverage of the initial period of high risk of stent thrombosis and/or recurrent coronary ischaemia.	Moderate	Strong
Where DAPT is required in combination with OAC, low-dose aspirin (100 mg) and clopidogrel (75 mg) are recommended.	Low	Strong
Ticagrelor and prasugrel are not recommended in this situation.		
Where OAC is used for AF, discontinuation of antiplatelet therapy should be considered 12 months after stent implantation, ACS, or both, with continuation of OAC alone.	Low	Weak
Anticoagulation in special situations—chronic kidney disease (CKD)		
The decision to use anticoagulants in patients with AF and severe CKD (creatinine clearance [CrCl] <30 mL/min) should be individualised because there are no prospective data showing benefit in this population.	Low	Strong

(continued).		
Recommendation	GRADE quality of evidence	GRADE strength of recommendation
Warfarin should be used if an AF patient with severe CKD requires anticoagulant therapy.	Low	Strong
Anticoagulation in special situations—bridging in anticoagulated patients requiring surgical procedures		
Bridging with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is not necessary for warfarin treated patients at low to moderate risk of stroke undergoing planned surgical intervention.	Moderate	Strong
Bridging with LMWH or UFH is not recommended for NOAC-treated patients.	Low	Strong
Bridging with LMWH or UFH is indicated for patients at very high risk of stroke (e.g. warfarin-treated patients with mitral mechanical prosthetic heart valves) undergoing planned surgical intervention.	Moderate	Strong
Anticoagulation in special situations—cardioversion		
Anticoagulation is recommended at the time of electrical or pharmacological cardioversion, and for at least four weeks post-procedurally.	Low	Strong
Anticoagulation for three weeks or a transoesophageal echocardiogram (to document absence of left atrial [LA] thrombus) is recommended before cardioversion in patients with more than 48 hours or an uncertain duration of AF.	Low	Strong
Anticoagulation in special situations—catheter ablation		
Uninterrupted oral anticoagulation is recommended for patients undergoing catheter ablation.	Moderate	Strong
Stroke prevention—left atrial appendage (LAA) occlusion and exclusion		
LAA occlusion may be considered for stroke prevention in patients with N-VAF at moderate to high risk of stroke and with contraindications to oral anticoagulation therapy.	Low	Strong
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.	Moderate	Strong
Secondary stroke prevention		
Early initiation of anticoagulants in the first few days after an ischaemic stroke is not recommended because of the risk of haemorrhage or haemorrhagic transformation of infarction.	High	Strong
For ischaemic stroke patients, the decision to begin OAC can be delayed for two weeks but should be made before discharge.	Very low	Weak
Early commencement of anticoagulants may be considered after transient ischaemic attack (TIA) or in mild stroke where the risk of haemorrhage is determined to be low.	Low	Weak
Integrated management		
An integrated care approach is recommended; such an approach aims to provide patient-centred comprehensive treatment delivered by a multidisciplinary team.	High	Strong
Targeted patient education is recommended throughout the continuum of AF management.	High	Strong
Shared decision-making should consider patients' beliefs, values and preferences, with a goal of empowering patients to undertake self-management.	Moderate	Strong
Treatment goals should be developed in partnership with patients, and communicated with all members of the multidisciplinary team.	Low	Strong

(continued).

Recommendation	GRADE quality of evidence	GRADE strength of recommendation
eHealth tools and resources should be used by patients and health professionals, to support the integrated management of AF.	High	Strong
All patients prescribed pharmacotherapy for the management of AF, including core rhythm control and anticoagulation therapies, should have their treatment adherence and persistence regularly monitored and supported using accessible and patient-centred strategies.	Low	Strong

ACS: acute coronary syndrome, AF: atrial fibrillation, AHRE: atrial high rate episode, AV: atrioventricular, BMI: body mass index, bpm: beats per minute, CKD: chronic kidney disease, CrCl: creatinine clearance, DAPT: dual antiplatelet therapy, ECG: electrocardiogram, EGM: atrial electrocardiogram, GRADE: Grading of Recommendations Assessment: Development and Evaluation, INR: international normalised ratio, LAA: left atrial appendage, LMWH: low-molecular-weight heparin, NOAC: non-vitamin K oral anticoagulant, N-VAF: non-valvular AF, OAC: oral anticoagulant, PCC: prothrombin complex concentrate, TIA: transient ischaemic attack, TSH: thyroid stimulating hormone, UFH: unfractionated heparin.

3. Preamble

3.1. Epidemiology of Atrial Fibrillation

AF is the most common recurrent arrhythmia faced in clinical practice, and it causes substantial morbidity and mortality [3–5]. Current estimates of AF prevalence in developed countries such as Australia range from 2% to 4%, and there is a steep gradient with increasing age [4,6]. However, true prevalence is underestimated because subclinical AF is frequent [7]. This can be a challenge for treating clinicians, because adverse consequences of AF (e.g., a stroke) may occur before AF is diagnosed. Apart from age, the prevalence of AF is influenced by risk factors and comorbidities such as hypertension, heart failure, coronary artery disease, valvular heart disease, obesity, diabetes, and chronic kidney disease (CKD) [4,6]. It is not surprising that Aboriginal and Torres Strait Islander peoples have a higher incidence of AF and subsequent mortality attributable to their greater burden of cardiovascular disease [8]. In Australia, prevalent AF cases in people aged 55 years or more are projected to double over the next two decades as a result of an ageing population and improved survival from contributory diseases [9]. Future prevalence of AF will also be affected by better detection of AF and by a changing pattern of risk factors such as obesity.

AF is independently associated with an increased long-term risk of stroke, heart failure and all-cause death [3–5], and often leads to an impaired quality of life [10]. The risk of dying from stroke can largely be mitigated by oral anticoagulants (OACs), but all-cause mortality and deaths from complications such as heart failure remain high, despite guideline-adherent treatment [3,6]. The concomitant diseases that contribute most to all-cause mortality are not thromboembolic [3], indicating the need for a comprehensive care approach to reduce overall mortality in AF-affected patients [11].

From a public health perspective, AF imposes a large and growing burden on healthcare resources, with hospitalisations being the major cost driver [12]. Between 10% and 30%

of patients with AF are admitted to hospital each year for cardiovascular and non-cardiovascular causes [13]. A study showed that the total number of AF hospitalisations in Australia was increasing by 6% per year over a 15-year period, which was greater than that for other cardiovascular conditions [14]. Hence, the societal and healthcare costs of AF will continue to escalate unless AF and its risk factors and complications are prevented and treated effectively.

3.2. The Process of Developing the 2018 Atrial Fibrillation Guidelines

These clinical guidelines for the management of AF seek to provide guidance regarding the clinical care of patients with AF. This is the first Australian guideline on this topic.

In late 2016, a partnership was formed between the NHFA and the Cardiac Society of Australia and New Zealand (CSANZ) to develop the guidelines, with the NHFA as the lead organisation. Clinical committees of both organisations were approached for advice regarding the content (scope) and development process for the guideline.

Acting on advice from the NHFA internal clinical advisory committees, members were approached to be in the working group, according to expertise.

Based on the determined scope, guideline writing groups were established to cover the following topics: screening and prevention, arrhythmia management, and stroke prevention. For each writing group, a primary writer was appointed by group consensus, on the basis of expertise and previous experience in guideline development. The other members of the writing groups comprised members with recognised expertise, from stakeholder groups, and the clinical community, and included a consumer representative. The writing groups met on several occasions to discuss the content of the guideline during the development process.

A reference group was established comprising appointed representatives of key stakeholder organisations with national relevance in the provision of AF care in Australia. The key roles of the group were to review and provide input into the scope of the guidelines and the questions being

submitted for literature review, draft guideline content and recommendations, and facilitate implementation of the guidelines.

The working group generated clinical questions to form the basis of external literature searches in consultation with the clinical expert committees of NHFA and CSANZ. Questions for external literature searches were prioritised according to uniqueness to Australia, and to areas not covered in recent European guidelines [1,15]. These questions were reviewed and refined by the reference group, and by clinical expert committees from NHFA and CSANZ. Appendix 1 lists the questions proposed for the literature review.

The literature reviewer was appointed through an open tender process in May 2017. The external literature review was started in the second half of 2017 and completed in December 2017. The evidence summaries generated by the reviewer were reviewed and signed off by the working group, and relevant content for the guideline was based on these evidence summaries. At the same time, the writing group members reviewed evidence and drafted content for the topics (in the agreed scope) in addition to those sent for external literature searches.

In February 2018, the reference group was consulted on the first full draft of the guideline. A public consultation period of 21 days was conducted in April 2018. Final approval by the clinical committees and the Boards of the NHFA and CSANZ and submission for journal publication was undertaken in June 2018.

3.2.1. Conflicts of Interest Process

Conflicts of interest were considered within a framework of both the relationship (direct or indirect) of the participating individual to any third party with interest in the topic under consideration within the guideline development process, and the nature (financial and non-financial) of the potential conflict. All members of the working groups and reference group were asked to declare all potential conflicts of interest and these declarations were updated every 6 months and at each meeting. All conflicts of interest were managed by the working group chair or primary writer. A summary of the conflicts of interest and responses will be provided in the online appendix at the time of publication, and a full description of the governance process for the development of this guideline will be available on the NHFA website.

3.2.2. Development of Recommendations

In addition to reviews of published trials and systematic reviews, guideline content was informed by other international clinical guidelines and local clinical expertise. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to evaluate the strength of recommendations. The first step in this process involved an evaluation of the quality of the evidence supporting the recommendation. If guided by randomised clinical trials (RCTs), the quality of evidence was initially estimated as high; if guided by observational or lower-quality evidence, the quality was estimated as low. Following this, estimates were refined through detailed evaluation of

the quality of the evidence. Factors that lowered quality included risk of bias, heterogeneity, or inconsistency between studies, indirectness, imprecision, and publication bias. Factors that increased quality included large magnitude of effect, all plausible residual confounding worked to reduce the demonstrated effect and dose–response gradient. The final evaluation of the quality of evidence supporting each recommendation is reported in these guidelines. Following this evaluation, the strength of recommendation for or against an intervention was provided. This was determined by considering the quality of evidence, balance between benefits and harms, uncertainty or variability in patient values and preferences, and resource considerations. The strength of the recommendation was graded as either ‘weak’ or ‘strong’. This methodology is increasingly being used by guideline developers in Australia and worldwide.

Each of the final recommendations was reviewed and refined by the writing groups and the reference group, with final review and endorsement by the whole working group. The definition of consensus was more than 80% agreement of all members of the working group.

The ‘Rationale’ section under each recommendation provides a brief summary of the key evidence underpinning the recommendation. Economic implications or other relevant system factors are discussed in the ‘Resources and other considerations’ sections, where appropriate.

For topics where there is a limited evidence base, but where the writing group felt there were important practical factors to be considered, comments are included in the ‘Practice advice’ sections of the guideline. Where medication recommendations are provided in this guideline, clinicians are advised to refer to additional resources such as the *Australian Medicines Handbook* for relevant doses, contraindications, precautions, drug interactions, and adverse effects.

4. Screening and Prevention

4.1. Pathophysiology and Genetic Factors

4.1.1. Risk Factors and Atrial Fibrillation

Several conditions have been shown to result in AF, by causing structural alteration of the myocardium, which creates the electrophysiological milieu for the maintenance of AF. In the preclinical setting this has resulted in an increase in interstitial fibrosis, alteration of gap-junctional proteins, altered tissue refractoriness, conduction slowing, and increase in the heterogeneity of conduction [16–19]. Interestingly, a chronic obesity ovine model indicated that epicardial fat infiltration of the adjacent atrial myocardium may form a unique substrate in obesity [20], and studies of sleep apnoea have highlighted the potentially dynamic nature of this substrate [21]. Clinical studies have also confirmed these findings with areas of low voltage (presumably indicative of loss of atrial myocardium), slowed and heterogenous conduction with regions of complex and fractionated electrograms demonstrated in mitral stenosis [22], heart failure [23],

hypertension [24], congenital heart disease (atrial septal defects) [25,26], sinus node disease [27], and obesity [28]. These changes have also been observed in the atria of individuals with no identifiable risks for AF, considered to be 'lone AF', suggesting the presence of either unrecognised or undertreated insult that continues to damage the atrial myocardium [29]. Newer risk factors are likely to emerge that contribute to the burden of AF in the community [30]. Risk factors for AF are not only important determinants of the development of AF, but also contribute to the associated risks, particularly that of stroke.

4.1.2. Genetic Predisposition

Underlying the potential for these conditions to result in atrial remodelling is the likelihood of a genetic predisposition. Increasingly, the contribution of a genetic predisposition is recognised. This should be considered as two entities: channelopathies that are associated with a greater risk of AF and genes that are more frequently seen in individuals with AF, particularly when there is a strong family history. These entities are discussed below.

Channelopathies

The channelopathies that are known to result in ventricular arrhythmias are associated with an increased risk of AF, presumably because the atrial myocardium carries the same abnormalities. They include the long or short QT and Brugada syndromes. The incidence of early onset AF (aged <50 years) is about 2% with genetically proven long QT syndrome (LQTS), which is significantly higher than the expected incidence of AF in this age group in the absence of LQTS (<0.1%) [31]. AF is the most common atrial arrhythmia in Brugada syndrome, with a reported incidence of 6%–53% [32,33]. The SCN5A gene, which is one of the common mutations responsible for Brugada syndrome, is also a common mutation detected in familial AF. Often, these are young patients who present with isolated AF, and the treating clinician needs to be alert to the potential for harbouring an underlying channelopathy.

Recognition of these conditions is particularly important in the choice of antiarrhythmic drugs for these individuals. Sotalol may unmask LQTS with the potential for pro-arrhythmia. Flecainide potentially unmasks the Brugada syndrome, with the risk of arrhythmia or presenting with sinus arrest in the context of associated SCN5A gene defects. We strongly recommend scrutiny of the family history and ECG in all patients, but particularly in the young, with targeted investigations as appropriate.

Familial Atrial Fibrillation

Families with a high prevalence of AF have been observed and reported in the literature since the 1950s [34,35]. From a large national registry with more than 90 million person-years follow-up, and close to 10,000 patients with lone AF, the incident risk ratios for lone AF given an affected first-degree or second-degree relative were 3.48 and 1.64, respectively [36]. The risk of AF was even higher in the younger members (aged <40 years) of the families of the patients with lone AF [36]. The Framingham Heart Study showed a 26.8% prevalence of familial AF,

and the prevalence of premature familial AF in the young participants was 7.9% [37]. Even after adjusting for modifiable risk factors for AF (i.e. sleep apnoea and obesity) the familial tendency of AF remains a relatively significant attributable risk of AF [38]. Linkage analysis studies have implicated mutations in potassium (KCNQ) and sodium (SCN5A) channels for familial AF [39,40]. Unlike linkage analysis, genome-wide studies have allowed testing of variants in genes or genetic regions previously not suspected in AF pathogenesis. The most significantly associated variant associated with AF is the paired-like homeodomain 2 transcription factor (PITX2) on chromosome 4q25 locus [41]. It is becoming apparent that these variants may also be important determinants of treatment outcomes [42,43].

4.1.3. Electrophysiological Mechanisms of Atrial Fibrillation

The development of AF depends on the critical interaction of various triggers with the atrial substrate for AF [44]. These triggers are increasingly recognised as coming from within the venous structures appended to the atria. Less frequently, they have been described from other atrial sources. Much less is known about the mechanisms that maintain AF. These mechanisms have included theories of the multiple wavelet re-entry, focal drivers or rotors, and endo-epicardial re-entry. The contribution of each of these mechanisms, and the ability to identify them in the clinical setting, continues to be an important area of investigation.

4.2. Definition of Non-valvular Atrial Fibrillation

This guideline encompasses both N-VAF and valvular AF. N-VAF refers to AF in the absence of moderate to severe mitral stenosis or mechanical heart valve [45].

4.3. Classification

In many patients, AF progresses from short paroxysmal episodes to more frequent and persistent attacks, and then often to permanent AF. However, progression can be mitigated by aggressive targeting of modifiable cardiovascular risk factors [46]. Four main clinical patterns of AF have been described, based on duration and termination of AF episodes (see Table 1) [15].

While classifying patterns of AF has some clinical value, it is often inaccurate and underestimates the temporal persistence of AF captured by continuous ECG monitoring [47]. Furthermore, the independent role of these AF patterns for distinguishing the response to therapies, such as antiarrhythmic drugs, and for prediction of stroke risk and survival is uncertain [48].

4.4. Diagnosis and Timely Detection

The diagnosis of atrial fibrillation requires rhythm documentation using an ECG showing absolutely irregular RR intervals and no discernible distinct P waves. By accepted convention, an episode lasting at least 30 seconds is diagnostic.

Table 1 Patterns of atrial fibrillation^a.

Paroxysmal AF	Episodes that terminate spontaneously or are cardioverted within 7 days; may recur with variable frequency.
Persistent AF	Episodes of continuous AF that last >7 days and do not self-terminate, including episodes that are cardioverted after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	Applies when a decision has been made jointly by the physician and patient to accept the presence of AF and stop further attempts to restore or maintain sinus rhythm. This represents clinical acceptance rather than an inherent pathophysiological attribute of AF and, should a rhythm-control strategy be adopted, the arrhythmia should be re-classified as 'long-standing persistent AF'.

AF, atrial fibrillation.

^aKirchhof P, et al. 2016. *Eur Heart J* 2016; 37 (38): 2893–2962. By permission of OUP on behalf of the ESC. This table is not included under the Creative Commons license of this publication. © ESC 2016. All rights reserved. For permissions email journals.permissions@oup.com [15].

4.4.1. Screening for Silent Atrial Fibrillation

Recommendation: Opportunistic point-of-care screening in the clinic or community should be conducted in people aged 65 years or more.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: There is strong epidemiological evidence that previously unknown AF is associated with about 10% of all ischaemic strokes [49,50]. Evidence from systematic reviews indicates that 1.4% of patients in community or practice situations aged 65 years or more will have unknown asymptomatic AF on single time point screening of pulse ECG [7]. Screening using patient-activated handheld ECG devices twice daily over 2 weeks in those aged 75 or 76 years found 3% with unknown AF [51]. Most of those found with unknown AF by screening will be at high enough risk of stroke score to justify treatment with an OAC based on net clinical benefit. Thus, AF meets the justification for screening, which is to find patients with unknown asymptomatic AF at high-enough risk of stroke to result in a reduction in stroke burden from combined screening and treatment [50].

The actual risk of stroke and death in people with screen-detected AF is unknown, and determination of this risk would require an unethical natural history study withholding treatment. The closest approximation of risk is patients with AF detected incidentally in the absence of symptoms [50]. Several cohort studies have shown that such patients are at similar if not greater risk than patients with a symptomatic presentation [52–57]. In one of these cohort studies [54,58], the effect of anticoagulant versus no anticoagulant treatment was similar to that seen in the meta-analysis of controlled studies of anticoagulants in AF. Several cost-effectiveness simulations [50,59–68], based on screening study data, have suggested that screening for AF is cost effective for both increasing quality-adjusted life years (QALYs) and reducing stroke. Additionally, opportunistic case finding (opportunistic screening) was found to be more cost effective than systematic screening in an RCT [60,61].

Benefits and harms: The benefits (stroke prevention or reduction of death) and harms (major bleeding) of anticoagulant treatment in screen-detected AF have been assumed to

be the same as for symptomatic AF. The potential harms of screening include anxiety over a false diagnosis (which can be minimised by screening using a handheld ECG with immediate diagnosis), and an anticipated anxiety over the diagnosis of AF in a person who previously had no illness. The potential harms of not screening are strokes that may occur because the condition is not diagnosed before stroke. One large randomised outcome study of population systematic screening is due to report in August 2018 and may resolve some of these questions [51].

Resources and other considerations: Opportunistic case finding for AF should be recommended as standard practice for patients aged 65 years or more, given the likely favourable risk to benefit ratio of treating screen-detected AF; the consistent finding of cost-effectiveness of health economic analyses (including one using Australian costs) [63]; and the rate, ease, and low cost of detection of AF by opportunistic screening in the clinic demonstrable in Australian studies. If twice-daily, 30-second, patient-initiated ECG rhythm recordings are found to be effective for stroke prevention, this may be a preferred option for both systematic and opportunistic screening.

Practice advice: Opportunistic annual screening for AF in general practice in patients aged 65 years or more is easily accomplished by pulse palpation, followed by an ECG (if irregular), or by an ECG rhythm strip using a handheld ECG. This screening can be incorporated into standard consultations or undertaken by practice nurses during chronic care consultations or immunisations. Devices that provide a medical-quality ECG trace are preferred to pulse-taking or pulse-based devices (i.e. photoplethysmography and blood pressure oscillometry) for screening, because an ECG is required to confirm the diagnosis.

4.4.2. Screening for Asymptomatic Atrial Fibrillation in Patients with Pacemakers and Implanted Devices

Recommendation: Pacemakers and defibrillators should be interrogated regularly for AHREs, and should be confirmed by EGM to be AF.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: Implanted pacemakers, defibrillators and other cardiac implanted electrical devices (CIEDs) with atrial leads allow continuous monitoring of atrial rhythm and identification of patients with AHREs. Implanted loop recorders (also known as implanted cardiac monitors [ICMs]) allow continuous examination of cardiac rhythm and produce a single-lead ECG. AHREs or AF on ICMs are usually defined as lasting longer than 5 or 6 minutes. Not all automated AHRE detection in CIEDs or automated AF detection in ICMs represent AF. The stroke risk in these patients seems lower than the stroke risk in patients with clinically diagnosed AF [69,70]. There is considerable debate about the cut-off for duration of episode or AF daily burden required before the risk is sufficient to justify anticoagulation [69–73], with some recommending anticoagulation for a daily burden of more than 5.5 hours, or a single episode lasting more than 24 hours, in those with stroke risk scores equivalent to the threshold for anticoagulation of patients with clinical AF. There is an increasing consensus that episodes of more than 24 hours denote a greater burden of AF and may justify anticoagulation in at-risk patients [74,75], though even this threshold is not excluded from the Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes (NOAH-AFNET 6) trial [76], indicating some equipoise. There is considerable uncertainty about the prognosis and anticoagulant requirement for episodes or AHREs with daily AHREs burden between 5.5 and 24 hours. Further data will be available when the

ongoing randomised studies NOAH-AFNET 6 [76] and Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-detected sub-clinical Atrial Fibrillation (ARTESiA) [77] are completed. Recommendations for anti-coagulation in this guideline are provided and discussed in Figure 1 and in Section 6.3.

Detection of AHREs on devices indicates a high risk of subsequent development of clinical AF [69,70]. Patients with pacemakers should be routinely interrogated for AHRE and, if AHRE is detected, further assessment of stroke risk factors and surveillance for development of clinical AF should be performed [78]. It is uncertain what ECG surveillance should be used, other than continued surveillance and interrogation of implanted devices, or whether device telemetry with remote monitoring is worthwhile [79].

Practice advice: For CIEDs with an atrial electrode, the electrograms must be examined to ensure that an AHRE actually represents AF and not another arrhythmia or artefact. For ICMs, the output trace is essentially a single-lead ECG rhythm strip, which needs to be examined to verify that the arrhythmia is actually AF.

4.4.3. Screening for Atrial Fibrillation in Patients with Embolic Stroke of Uncertain Source

Recommendation: For patients with ESUS, longer term ECG monitoring (external or implantable) should be used. (GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

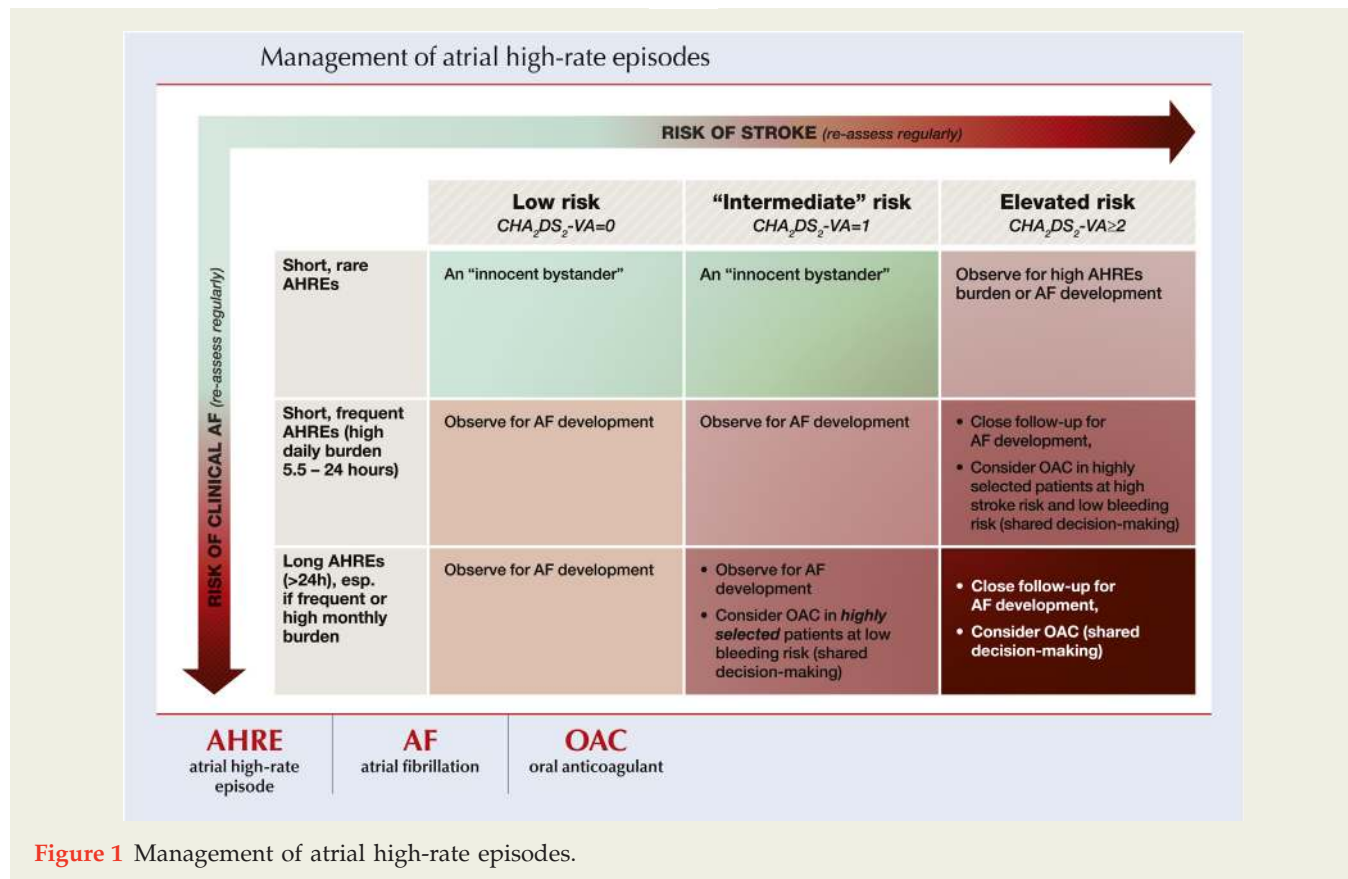


Figure 1 Management of atrial high-rate episodes.

Rationale: The detection of unrecognised paroxysmal AF in patients with presumed embolic stroke presenting in sinus rhythm with no history of AF may be important to reduce the risk of recurrent stroke. Twenty-four-hour Holter monitoring has been commonly used and is readily available, but a substantial proportion of patients with paroxysmal AF are not detected using this approach [80,81]. External rhythm recording devices can be worn for up to 30 days, but data from implanted devices show that a substantial proportion of AF occurs beyond the first 30 days following an event. Implantable loop recorders can provide up to 3 years of continuous monitoring. Whilst there is some question about the relevance of AF detected many months after the stroke to the aetiology of the original event, late-detected AF does remain a significant risk factor for subsequent stroke.

ESUS describes a subgroup of patients at theoretically higher risk of silent paroxysmal AF and comprises a non-lacunar infarct in the absence of significant proximal cerebral vessel disease, no evidence of thrombus on an echocardiogram, and no AF following at least 24 hours of ECG monitoring. Whether empiric anticoagulation of these patients improves outcomes compared to standard care is being evaluated in ongoing randomised trials, one of which (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source—NAVIGATE ESUS) was recently prematurely halted for futility. However, there is clear evidence that a longer duration of monitoring is associated with higher frequency of AF detection in patients with embolic stroke of uncertain source [80,81]. When AF is detected and anticoagulation is commenced, the benefits for stroke prevention in patients with previous stroke are well-established (see Section 6.3.6).

Benefits and harms: The randomised Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke (CRYSTAL AF) reported a significantly higher rate of AF detection using the ILR compared with standard of care at 6 months (hazard ratio [HR] = 6.4 (95% confidence interval [CI]: 1.9–21.7), 12 months (HR = 7.3 (95% CI: 2.6–20.8)), and 36 months (HR = 8.8 (95% CI: 3.5–22.2)). Of those detected with AF, 23/29 of cases (79%) were asymptomatic over 12 months [82]. The risk of an adverse event associated with ILR implantation is low.

Practical advice: This section aligns with recommendations in the Stroke Foundation *Clinical Guidelines for Stroke Management*. Further details on management of this patient cohort can be found in their online resource [83].

4.5. Diagnostic Work up

Recommendation: A 12-lead ECG is recommended for all patients with AF.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: All patients with newly diagnosed AF require a complete medical history and evaluation, focusing on the following domains:

- haemodynamic stability or severe symptoms;
- presence of precipitating factors (e.g., sepsis, recent surgery, thyrotoxicosis, electrolyte imbalance) and underlying cardiovascular conditions;
- stroke risk and need for anticoagulation (see Section 6);
- heart rate and need for rate control (see Sections 5.1 and 5.2);
- symptom assessment and decision for rhythm control (see Section 5.3).

A 12-lead ECG not only establishes the diagnosis of AF, it also provides evidence of conduction defects, ischaemia, and signs of structural heart disease.

Initial blood tests should include full blood count, electrolytes, and renal function, as well as tests of thyroid function (see Section 4.5.1). Transthoracic echocardiography is also recommended (see Section 4.5.2).

4.5.1. The Role of Electrolyte Assessment in Newly Diagnosed Atrial Fibrillation

A strong recommendation has traditionally been made for the assessment of electrolytes, despite the lack of high-quality data from randomised trials. This is because of a general view that the benefits of the assessment outweigh the risks, and because of the physiological role of electrolytes in electrical and mechanical actions of the body.

A diagnostic work up should include serum electrolytes, including potassium, sodium, magnesium, and calcium, which play a significant physiological role in the regulation of the electrical and mechanical action of the heart. Any abnormal concentration of these ions may result in muscle contraction disorders, cardiac arrhythmias, and drug interactions.

Acute presentations of AF may also require normalisation of fluid balance and management of heart failure, which in turn requires measurement of electrolytes for safe administration of therapy.

4.5.2. Role of Echocardiography in Newly Diagnosed Atrial Fibrillation

Recommendation: A transthoracic echocardiogram should be performed in all patients with newly diagnosed AF.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: A transthoracic echocardiogram can assist patient management by identifying valvular heart disease, and quantifying left ventricle (LV) function and atrial size. Transthoracic echocardiogram will yield data on some key parameters:

- mitral stenosis and regurgitation—both of these conditions can lead to increased atrial size and hence AF; mitral stenosis can also increase thromboembolic risk, and NOACs are contraindicated in patients with moderate or severe mitral stenosis;
- LA size and volume [84]—LA volume may be a stronger predictor than LA size for predicting AF and stroke risk [85];
- LV—moderate to severe LV systolic dysfunction leads to a 2.5-fold increase in the risk of thromboembolism [86];

reversible LV dysfunction may develop in patients with uncontrolled AF (see Section 5.2).

Transoesophageal echocardiography (TOE) can be considered when findings might affect patient management,

primarily where electrical or pharmacological cardioversion is indicated and the presence of thrombus may affect timing (see Figure 2).

Resources and other considerations: No studies have been found to indicate the yield or cost-effectiveness of this

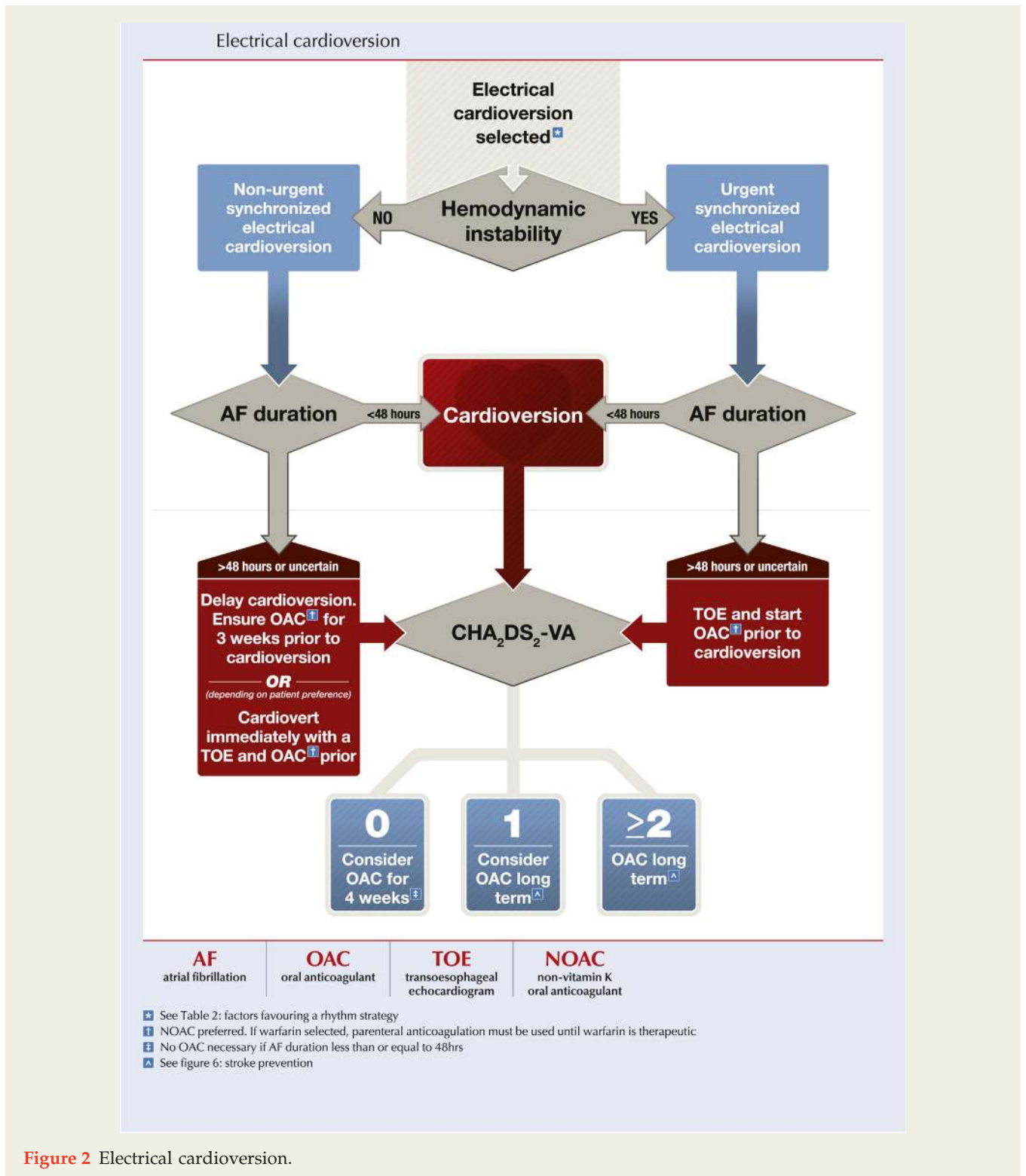


Figure 2 Electrical cardioversion.

investigation in Australian populations. In rural centres where echocardiography may be limited, referral to a regional centre is warranted.

4.5.3. Role of Thyroid Function Testing in Newly Diagnosed Atrial Fibrillation

Recommendation: A TSH test should be undertaken in patients with newly diagnosed AF but should be delayed in acutely ill patients.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: AF is traditionally associated with hyperthyroidism, but overt thyroid disease appears to be rare in people presenting with AF, and yield of testing is low [87]. Making a diagnosis of overt thyroid disease is also complicated by the fact that any acute illness affects thyroid indices, and most abnormal indices in hospital return to normal when repeated after the resolution of the acute illness [88]. Hence, this screening should be reserved for stable outpatients.

Subclinical hyperthyroidism due to various pathologies (e.g., thyroid adenomas, multinodular goitre, Grave's disease, or thyroiditis) needs to be treated to avoid longer-term sequelae of subclinical hyperthyroidism. Such sequelae include low bone mineral density, heart failure, angina, and progression to overt hyperthyroidism. It is unknown whether treating subclinical hyperthyroidism prevents incident AF.

4.5.4. Detection and Management of Risk Factors and Concomitant Diseases

Recommendation: Intercurrent risk factors and comorbidities—including hypertension, diabetes, heart failure, valvular heart disease and alcohol excess—should be identified and their management considered an important component of treatment in patients with AF.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Intensive management of weight—to a target of greater than or equal to 10% body weight loss, aiming for a BMI below 27—and concomitant management of associated cardiovascular risk factors to target levels should be performed in overweight and obese individuals with AF.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Screening (by polysomnography) and management of sleep apnoea is recommended in individuals with recurrent symptomatic AF.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Exercise that improves aerobic capacity is recommended in individuals with symptomatic AF, to reduce the AF burden.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: Cardiovascular risk factors are recognised contributors to the development of AF [89]. Several of these risk factors are well established; they include hypertension,

diabetes mellitus, and alcohol excess. In addition, several cardiovascular conditions are associated with the development of AF, including coronary artery disease, heart failure, valvular disease, and sinus node disease.

The more risk factors that an individual has, the greater the likelihood that a person will develop AF and more persistent AF [90,91]. Cardiovascular risk factors are also an important determinant of recurrence of AF when using a rhythm-control strategy [92–97].

More recently, studies have presented data on the treatment of these risk factors in reducing the symptom burden and increasing the likelihood of maintaining sinus rhythm in patients with established AF [98–101]. This has led to the concept that risk factor management represents the 'fourth pillar' in AF management [15,89].

Management of Concomitant Disease in AF

Treating underlying disease state has been observed to reduce incident AF, particularly in cohorts with heart failure [102,103]. However, these conditions can also exacerbate the risk of complications associated with AF; hence, their management is an important part of the management of individuals with AF. The impact of management of these conditions on AF itself has not been evaluated.

Treating Risk Factors in Isolation

Observational studies suggest that treating individual risk factors may affect the maintenance of sinus rhythm in individuals with AF. For example, an increasing amount of data suggests that treatment of sleep apnoea improves the maintenance of sinus rhythm in rhythm-control strategies [94,95]. However, data from RCTs are lacking.

Short-term randomised studies demonstrate some improvements in reducing AF symptom burden. This has been observed in a small randomised study that evaluated the role of exercise intervention [104].

There are data that suggest that treatment of hypertension has a role in the primary prevention of AF [102]. However, regarding secondary prevention, the Substrate Modification with Aggressive Blood Pressure Control (SMAC-AF) study showed that aggressive management of hypertension in isolation peri-ablation did not alter the maintenance of sinus rhythm [105]. This experience highlights the limited value of treating isolated risk factors in a disease such as AF, which has multiple contributors in a given individual [106].

Detection and Management of Newer Risk Factors

With the burden of AF increasing at rates greater than those predicted by known risk factors, there has been interest in several newer risk factors [107], including obesity, sleep apnoea, physical inactivity and prehypertension [30,108–111]. These risk factors have now been demonstrated to result in change to the atrial myocardium and remodelling that favours the development and maintenance of AF [18–20,24,112–114]. Several studies have characterised the atrial substrate for arrhythmia in these conditions, and reported similar findings to those seen with the various cardiac risk factors [16,22,23,27].

Comprehensive and Aggressive Risk Factor Management

A study has demonstrated that physician-led intervention of

weight and risk factor management in overweight and obese patients led to a marked reduction in AF symptom burden, and AF episode frequency and duration, and to an improvement in quality of life in patients with paroxysmal AF [98]. The response is graded—the greater the weight loss, the more the likelihood that the sinus rhythm will be maintained [100]. Similar findings have been reported for physical activity levels [101]. In addition, in patients undergoing catheter ablation, aggressive management of risk factors has been associated with a significantly greater chance of remaining in sinus rhythm [99].

Practice advice: The aggressive risk factor management treatment targets used in the above studies included:

- weight loss of at least 10% or final BMI less than 27 kg/m², with avoidance of weight fluctuation. Target BMI or weight in people aged over 75 years is unknown;
- exercise to improve aerobic capacity for up to 210 minutes/week;
- blood pressure of less than or equal to 130/80 mm Hg at rest, and less than or equal to 200/100 mm Hg on exercise;
- maximal compliance with continuous positive airway pressure (CPAP) therapy if the apnoea–hypopnea index was equal to or greater than 15/hour;
- an HbA1c of less than or equal to 6.5%;
- lipid targets per overall cardiovascular risk profile;
- smoking cessation;
- limitation of alcohol consumption to less than or equal to three standard drinks per week [46,115].

5. Arrhythmia Management

Recommendation: A rhythm-control or a rate-control strategy should be selected, documented and communicated for all AF patients, and this strategy should be reviewed regularly.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

5.1. Acute Rate Control

Recommendation: Beta adrenoceptor antagonists or non-dihydropyridine calcium channel antagonists are recommended for acute control of the ventricular rate in haemodynamically stable patients, although caution is needed if given intravenously.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Amiodarone is recommended for acute control of the ventricular rate in highly symptomatic AF patients, or in those with known left ventricular systolic dysfunction, who are not unstable enough to require immediate electrical cardioversion.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Digoxin may be considered to aid in acute control of ventricular rate either as add-on therapy to beta adrenoceptor antagonists or non-dihydropyridine

calcium channel antagonists, or as stand-alone therapy if these agents and amiodarone are contraindicated.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Weak.)

Rationale: Significant symptoms can result from acute episodes of new onset AF, and from breakthrough rapid episodes in those with an established diagnosis of AF. Less commonly, in the acute setting, haemodynamic compromise may also result from such episodes. When severe and life-threatening, the latter situation calls for immediate electrical cardioversion (see Table 2 and Figure 2). In any less-serious circumstance, particularly while thromboembolic risk assessment and management are being instituted, urgent rate control is the most effective option for alleviating symptoms. Secondary causes of rapid ventricular response—including sepsis, pulmonary embolism, and thyrotoxicosis—must be excluded.

Effective options for immediate rate control include beta adrenoceptor antagonists and non-dihydropyridine calcium antagonists [116] (see Figure 3). Oral administration of these agents may be sufficient in many situations, but this will be associated with a longer time to onset of effect. A more rapid onset of action may be seen with careful administration of intravenous aliquots of metoprolol or esmolol. The only intravenous rate-control calcium antagonist available in Australia is verapamil, but it must be used with extreme caution because of its strong negatively inotropic effect.

Digoxin may be considered in addition to the above agents, but it has a delayed onset of action, may have a weak effect in terms of rate control, and has a narrow therapeutic index. Digoxin monotherapy may not result in effective rate control [117].

In patients with marginal haemodynamic reserve, established heart failure, or other significant structural heart disease, amiodarone may be the most effective (and only) rate-control option. The initial mode of activity of amiodarone is through both Class II and Class IV effects, and this results in early effective slowing of atrioventricular (AV) conduction [118]. Intravenous loading is usually preferred in the acute situation; however, oral bioavailability is excellent and oral loading may also be rapidly effective in some instances.

Table 2 Factors favouring a strategy of rhythm control over rate control.

Patient preference
Highly symptomatic or physically active patients
Difficulty in achieving adequate rate control
LV dysfunction (mortality benefit)
Paroxysmal or early persistent AF
Absence of severe atrial enlargement
Acute AF

AF: atrial fibrillation, LV: left ventricle.

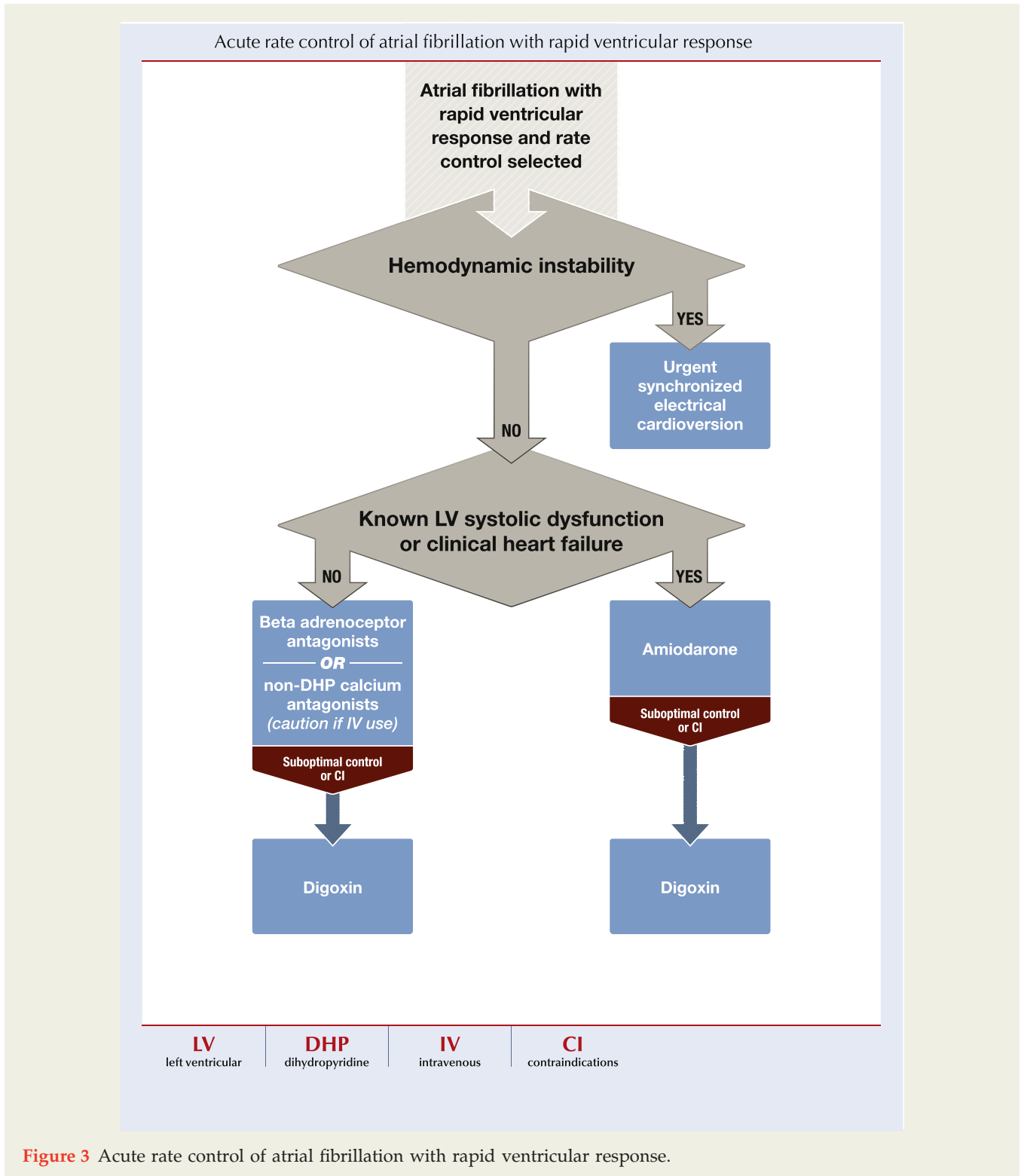


Figure 3 Acute rate control of atrial fibrillation with rapid ventricular response.

Practice advice: If intravenous loading with amiodarone is undertaken, chemical phlebitis can occur, necessitating high-quality and preferably central venous access.

5.2. Long-term Rate Control

Recommendation: Beta adrenoceptor antagonists or non-dihydropyridine calcium channel antagonists should be

the first-line agents used for long-term control of the ventricular rate.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Digoxin can be considered for control of the ventricular rate in patients with suboptimal rate control on, or with contraindications to, first-line agents.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Weak.)

Recommendation: When digoxin is used, serum concentration should be monitored, with the goal of maintaining levels of <1.2 ng/mL.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Calcium channel antagonists should be avoided in patients with left ventricular systolic dysfunction (ejection fraction <40%).

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Amiodarone should not be administered as a first-line agent for chronic rate control, given its toxicity profile.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Membrane-active antiarrhythmic agents (e.g., sotalol or flecainide) should not be used in patients managed with a rate-control strategy.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Documentation of the adequacy of ventricular rate control at (<110 bpm) at rest and with moderate exertion should be performed at regular intervals in asymptomatic patients without heart failure.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Regular clinical surveillance for emergent cardiomyopathy or overt heart failure should be performed during long-term follow-up because heart failure may develop even in the presence of apparently adequate ventricular rate control.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: There are few RCTs to guide treatment decisions in AF rate control, and most recommendations are based on observational data or expert consensus.

Clinical trials comparing rate-control and rhythm-control strategies for managing AF with and without heart failure were completed more than 10 years ago, and they failed to demonstrate an improvement in prognosis with pharmacological rhythm control [119–124]. Large-scale RCTs comparing rate control with contemporary (particularly non-pharmacological) rhythm-control strategies are lacking.

One randomised trial—Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II (RACE II)—compared a lenient rate-control target (<110 bpm resting ventricular rate) to a strict rate target (<80 bpm resting and <110 bpm during moderate exertion) in 614 patients with permanent AF [125]. No difference in the primary composite outcome was found, and there was no benefit on symptoms with a strict rate-control strategy. However, two-thirds of patients were asymptomatic at enrolment, and the lenient rate-control group had an actual mean resting rate during the study of 85 bpm, only 10 bpm faster than the strict rate-control group.

A ventricular rate-control strategy is implemented by the use of beta adrenoceptor antagonists, diltiazem or verapamil, alone or in combination [126] (see Figure 4). Digoxin should not generally be used alone because of its slow onset of action in the acute situation and its weak effect in chronic rate control, particularly during exertion [127]. However, digoxin can be useful as a second-line agent or in combination with beta blockers or calcium antagonists. There are conflicting data on the association between all-cause mortality and digoxin use in AF, with or without concomitant heart failure, although this signal has generally not been seen in RCTs [128]. In a recent observational analysis of patients anticoagulated for atrial fibrillation, digoxin use was not associated with an increase in mortality; however among patients taking digoxin the risk of death was independently related to serum digoxin concentration and was highest in patients with concentrations ≥ 1.2 ng/mL [129]. Verapamil and diltiazem should not be used in the presence of left ventricular systolic dysfunction because of their negative inotropic effect. Amiodarone should be considered a last-line option for chronic pharmacological rate control, given its toxicity profile. Membrane-active rhythm-control agents (e.g., flecainide or sotalol) should not be used or continued in patients being started on or transitioned to a rate-control strategy. This is because the potential proarrhythmic side effects of these agents cannot be justified when no active pursuit of sinus rhythm is being made.

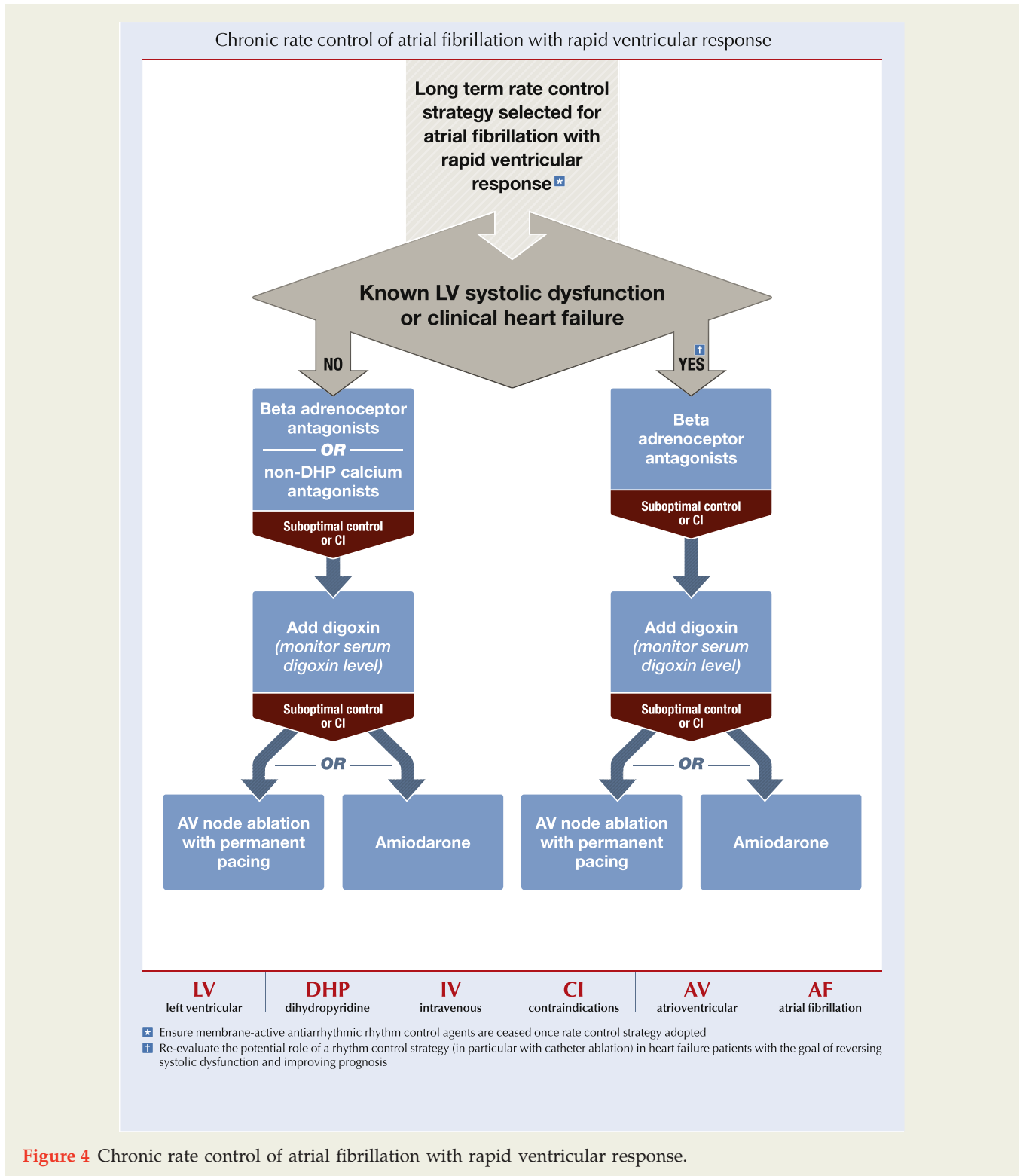
Practice advice: A rate-control strategy may be used in preference to rhythm-control in patients with minimal symptoms or in those in whom attempts at maintaining sinus rhythm are likely to be futile. Patients who have not responded to a rhythm-control strategy may be managed with rate control. In general, a rate-control strategy is not useful for patients with symptomatic paroxysmal AF episodes; also, it should not be used in pregnancy or in the special situation of pre-excited AF.

A growing amount of data demonstrates that apparently adequate rate control may be associated with suboptimal symptom control, and with attendant or progressive ventricular systolic dysfunction. Hence, it is important that AF patients being managed with a rate-control strategy are kept under regular and close surveillance for any suggestion of clinical decompensation, and for the potential development of AF-related cardiomyopathy. Patients developing symptoms or signs of left ventricular dysfunction should be referred for cardiology review and considered for echocardiography. However, there is no role for routine screening echocardiography for detection of subclinical left ventricular dysfunction in patients with atrial fibrillation.

Recommendation: If pharmacological rate control fails, catheter ablation of the AV node should be considered after a permanent pacing device has been implanted.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: Several small RCTs (all with <250 patients) have compared medical rate control and catheter ablation of the AV node in AF patients with heart failure. Despite limited



sample size and significant heterogeneity, there was a consistent tendency to AV node ablation patients having improvements in symptomatic outcome, VO₂ max, 6-minute walk distance, heart failure admissions, ejection fraction, and mortality (where assessed) [130–133].

For patients who fail medical rate control and for whom AF ablation is not deemed appropriate, permanent pacemaker

implantation followed by catheter ablation of the AV node offers a permanent solution to the problem of rapid ventricular response in AF [134–136] (see Figure 4). One multicentre prospective study, the Ablate and Pace Trial, showed significant improvements in quality of life and left ventricular systolic function in a group of 156 medically refractory patients [135,136]. There is no indication of impaired long-

term survival with AV node ablation compared with pharmacological rate control [137].

Practice advice: When planning AV node ablation, the optimal choice of pacemaker type and pacing configuration is still unclear. The limited data available from randomised trials suggests an advantage for biventricular pacing in improving functional capacity and preserving ejection fraction compared with right ventricular pacing.

5.3. Rhythm Control

5.3.1. Acute Rhythm Control

Recommendation: Electrical cardioversion should be performed urgently in haemodynamically unstable patients with AF.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Electrical cardioversion can be considered—either as a first-line option or when pharmacological rhythm control fails—in haemodynamically stable patients, after consideration of thromboembolic risk.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Flecainide can be considered for rapid conversion to sinus rhythm, either intravenously or orally, in patients without left ventricular systolic dysfunction, moderate left ventricular hypertrophy or coronary artery disease, after consideration of thromboembolic risk.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: AV nodal blocking medication is recommended for patients treated with flecainide.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Amiodarone administered intravenously may be considered for delayed conversion to sinus rhythm in patients with structural heart disease, including patients with heart failure and coronary artery disease.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: Patients with haemodynamic instability require urgent electrical cardioversion (see Table 2 and Figure 2). In haemodynamically stable patients, acute rhythm rather than rate control can be considered if symptoms are unacceptable or in patients experiencing their first episode of AF. There is a high spontaneous reversion rate to sinus rhythm for new-onset AF within 48 hours, so while pharmacological cardioversion can be considered, a ‘wait and watch’ approach with rate control may be reasonable in a mildly symptomatic patient.

Flecainide or amiodarone are the recommended drugs for pharmacologic cardioversion. The evidence for flecainide for acute (rapid) conversion to sinus rhythm is based on several RCTs of modest size and one meta-analysis [138–142]. The evidence for amiodarone for acute (delayed) conversion to sinus rhythm involves more RCTs including one meta-analysis [142–145]. Compared with amiodarone, flecainide results in earlier and more effective conversion to sinus rhythm [138,142].

The evidence for sotalol in acute conversion to sinus rhythm is limited. Some data suggest similar but low efficacy of oral sotalol compared with amiodarone (27% at 28 days); other data suggest that sotalol has lower efficacy than flecainide and amiodarone [146–149]. In view of this uncertainty, these guidelines do not recommend the use of sotalol for the acute reversion to sinus rhythm.

Electrical cardioversion may be required to facilitate restoration of sinus rhythm in stable patients if pharmacotherapy fails or is not tolerated. Pre-treatment with AADs can improve the efficacy of electrical cardioversion. The choice of AAD is discussed below (Section 5.3.2).

Benefits and harms: There is some variation in reported efficacy of AADs for cardioversion. Success rates for flecainide range from 55% to 85%, and for amiodarone from 35% to 90% [150]. One meta-analysis comparing Class IC agents (including flecainide) to amiodarone suggested that the former were more than twice as likely to revert patients within the first 3–5 hours (50% vs 22%) [142].

Practice advice: Electrical cardioversion may be less desirable in the older patient due to the need for general anaesthetic, and the increased risks of cognitive change and delirium in this population. Outpatient oral flecainide for acute reversion (the ‘pill-in-pocket’ approach) should be used in conjunction with an AV nodal block agent (taken at least 30 minutes prior) to avoid 1:1 conduction of atrial flutter.

In patients with an AF duration of more than 48 hours or of unknown duration, acute rhythm control should generally not be attempted unless LA thrombus is excluded with TOE.

5.3.2. Long-term Rhythm Control

Recommendation: Flecainide can be considered in the maintenance of sinus rhythm in patients without left ventricular systolic dysfunction, moderate left ventricular hypertrophy, or coronary artery disease.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: AV nodal blocking medication is recommended for patients treated with flecainide.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Amiodarone can be considered for maintenance of sinus rhythm as a second-line agent or as a first-line agent in patients with left ventricular systolic dysfunction, moderate left ventricular hypertrophy, or coronary artery disease.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: Sotalol may be considered for maintenance of sinus rhythm but requires close monitoring of QT interval.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: Beta adrenoceptor antagonists may be considered for the maintenance of sinus rhythm.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Weak.)

Rationale: The decision to aim for rhythm (instead of rate) control requires discussion between the patient and the treating physician. Factors favouring rhythm over rate control include patients who are younger, more physically active and highly symptomatic; those with paroxysmal or early persistent AF; and those with LV dysfunction; no severe LA enlargement; and those in whom adequate control of the ventricular rate is difficult to achieve (see Table 2) [150].

On average, AAD therapy reduces the risk of AF recurrence by 50% compared with placebo. There is currently no published randomised study suggesting that rhythm control is associated with decreased stroke risk and mortality. The results of the Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial addressing this question were recently presented and are discussed below (see Section 5.3.3). A second study in this area, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, Atrial Fibrillation Network (EAST-AFNET-4) is awaited.

The choice of AAD therapy depends on the patient's comorbidities (e.g., presence of structural heart disease, coronary artery disease, or renal dysfunction) and preferences, and requires a discussion of the risks and benefits with the patient (see Figure 5).

Several RCTs [149,151,152] and meta-analyses support the superior efficacy of amiodarone over other AADs or placebo in maintenance of sinus rhythm [153,154]. However, amiodarone is associated with potential long-term toxicities, and therefore should not be a first-line treatment choice in patients suitable for other drug(s).

A limited number of prospective observational studies, RCTs, and meta-analyses support the efficacy of flecainide in maintenance of sinus rhythm [153,155,156]. Flecainide should be used in conjunction with an AV nodal block agent to avoid 1:1 conduction of atrial flutter, and should not be used in patients with LV systolic dysfunction, moderate LV hypertrophy, or coronary artery disease.

A number of RCTs and meta-analyses support the modest efficacy of sotalol in maintenance of sinus rhythm [149,151,157,158]. It is less effective than alternatives and torsades de pointes occurs in about 2% of patients [159]. A recent Cochrane review [153] suggests increased mortality with sotalol. Close monitoring of the QT interval is therefore required, particularly in older people, women and those with impaired renal function [160].

Two small placebo-controlled studies with persistent AF have found a lower risk of recurrence after cardioversion with sustained release metoprolol [161,162] and one study suggested comparable efficacy between beta blockers (metoprolol and atenolol) and sotalol [163]. However, beta blockers are generally regarded as less effective than AAD in the maintenance of sinus rhythm [1,2,153].

Class Ia AADs (quinidine and disopyramide) appear more effective than placebo in maintenance of sinus rhythm; however, meta-analyses of RCTs similarly suggest increased mortality associated with these drugs [153,164], and hence they are not recommended for the maintenance of sinus rhythm. The only exceptions to this are for disopyramide

in specific situations; it may have a role in some cases of vagally mediated AF and in patients with hypertrophic obstructive cardiomyopathy [165,166].

Benefits and harms: In a comprehensive Cochrane review, pooled recurrence rates of AF at 12 months were 69%–84% in controls not receiving antiarrhythmic treatment but were reduced to 43%–67% in patients treated with AADs. The corresponding average numbers needed to treat for 1 year to avoid one recurrence of AF were three with amiodarone, four with flecainide, eight with sotalol, and nine with metoprolol [153]. Proarrhythmia was observed less frequently. The number needed to treat, to harm with one proarrhythmic event, was 38 with both flecainide and sotalol. Amiodarone and metoprolol were not associated with proarrhythmia. The number needed to treat with sotalol to cause one excess death was 169, but 95% CIs were wide (60–2067) [153].

Practice advice: Adjunctive lifestyle modification and strict cardiovascular risk factor control should not be overlooked in rhythm control management of AF (see Section 4.5.4) [98,100].

5.3.3. Percutaneous Catheter Atrial Fibrillation Ablation Recommendation: Catheter ablation should be considered for symptomatic paroxysmal or persistent AF refractory or intolerant to at least one Class I or III antiarrhythmic medication.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: Catheter ablation can be considered for symptomatic paroxysmal or persistent AF before initiation of antiarrhythmic therapy.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Catheter ablation can be considered for symptomatic paroxysmal or persistent AF in selected patients with heart failure with reduced ejection fraction.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: These recommendations and commentary are complementary to and update those provided in the NHFA consensus statement on catheter ablation as a therapy for AF [167].

AF ablation is an effective procedure for appropriately selected patients with symptomatic AF. It is applicable to patients who have failed or are intolerant to AADs, or for some patients who decline AAD treatment (see Figure 5). Patients frequently report a dramatic improvement in quality of life with AF ablation. Multiple RCTs have demonstrated higher rates of sinus rhythm maintenance compared with AADs [168].

Recent evidence demonstrates that the procedure may have a mortality benefit in patients with heart failure [133]. Ongoing studies are evaluating the potential for stroke risk reduction and reduction in mortality in patients with AF. The results of one of these trials, Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA), was recently presented [169]. In this study 2204 AF patients tolerant of at least two AADs and with one risk factor for stroke were randomised to catheter ablation or drug therapy.

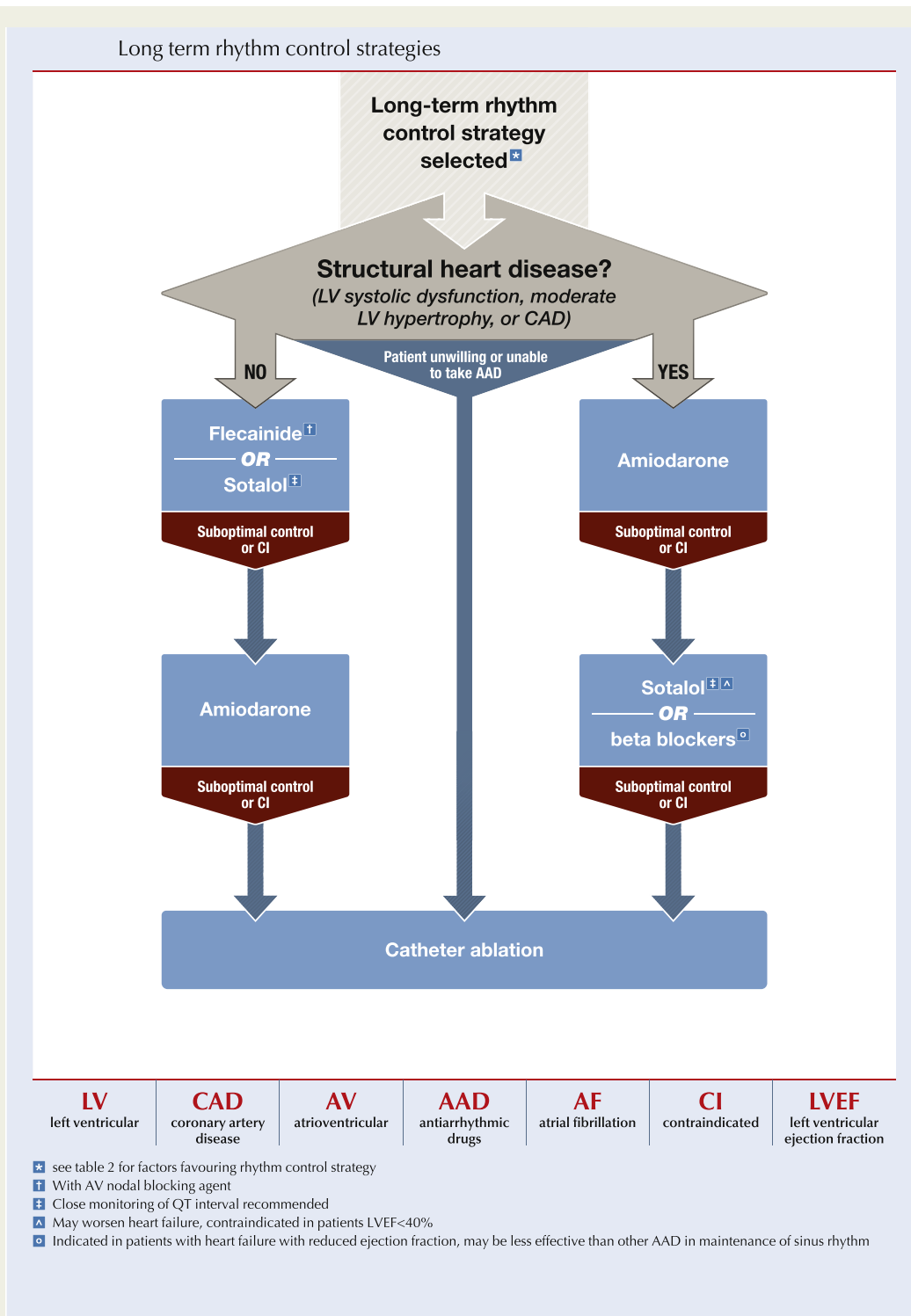


Figure 5 Long term rhythm control strategies.

The primary outcome of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years was not significantly different between ablation versus drug therapy. There was a significant reduction in AF burden and improvement in quality of life with ablation. Publication of CABANA is awaited. In the discussion with the patient it is important to emphasise that 20%–30% of ablation patients will require a

second procedure within the first 12 months. Published major complication rates range from 1% to 7%, with rates being lower for experienced centres and operators.

Certain patient characteristics can be used to define patients in whom a lower success rate or a higher complication rate is likely. These characteristics include the presence of concomitant heart disease, obesity, sleep apnoea, LA size,

patient age and frailty, as well as the duration of time the patient has been in continuous AF. Although these factors do not constitute contraindications to the procedure, each should be considered when discussing the risks and benefits of AF ablation with a patient.

In patients at increased risk of stroke, anticoagulation should be continued indefinitely, even following a successful procedure (see Section 6.3.4.5).

AF ablation may be considered in selected asymptomatic patients after a clear discussion of risks and benefits.

Benefits and harms: A meta-analysis of eight RCTs (844 patients), with follow-up ranging from 6 to 12 months, reported freedom from recurrent AF rates of 76.8% in patients in the ablation group and 23.4% in patients receiving an AAD. The rate of major complications in the ablation group was 6.2% [170].

Practice advice: International guidelines recommend that this procedure be performed only in centres with onsite cardiac surgery. Furthermore, there is observational evidence that outcomes are better when experienced operators are performing the procedure in high-volume centres. Operators with fewer than 25 procedures annually and hospital volumes of fewer than 50 procedures annually have been significantly associated with adverse outcomes [171]. Published complication rates from experienced Australian institutions have been about 1% [172].

Early in the course of their AF journey, some patients might have only infrequent episodes for many years, or could have AF that is responsive to well-tolerated AAD therapy. In patients with recently diagnosed AF, ablation can be deferred until the natural history in that individual patient is declared.

5.3.4. Surgical Management of Atrial Fibrillation in the Context of Concomitant Cardiac Surgery

Recommendation: Surgical ablation of AF to restore sinus rhythm in the context of concomitant cardiac surgery may be considered for patients with symptomatic paroxysmal, persistent, or long-standing persistent AF.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: The presence of AF in patients undergoing aortic valve replacement (AVR) or coronary artery bypass grafting (CABG) (i.e. non-atriotomy cardiac procedures) or mitral valve surgery (i.e. atriotomy cardiac procedure) has been shown in multiple studies to be associated with increased rates of early and late morbidity and mortality [173,174].

Most of the studies comparing CABG with concomitant surgical ablation of AF with CABG alone showed benefit in terms of reduction in AF recurrence, and no significant difference in morbidity or mortality [174–177]. One important consideration relating to the harms of concomitant surgical ablation and CABG is the increased cardiopulmonary bypass time that is required for this concomitant procedure [178].

The problem in interpreting the data from the literature surrounding this topic is that most studies group non-atriotomy cardiac procedures (i.e. CABG and AVR), making it difficult to apply the results to a selected procedure group.

The literature also reports different ablative sources (e.g., radiofrequency and cryoablation) and different surgical techniques (e.g., epicardial versus endocardial ablation). Some studies have also noted that duration of AF and LA size are important predictors of ablation failure [177,179].

Benefits and harms: Surgical ablation for AF in the context of concomitant CABG has been shown to produce AF-free rates of greater than 85% at 18-month follow-up, compared with AF-free rates of below 50% in the CABG-only groups at the same endpoint [174,176,177,180–182].

Resources and other considerations: Surgical management of AF is only available for patients at centres with a specialist cardiothoracic service.

Practice advice: Patients should be considered on an individual basis in a multidisciplinary team meeting that includes both the treating cardiologist and cardiothoracic surgeon and aims to determine the best management plan for each patient. Surgical expertise and training in these surgical ablation procedures are of key importance to optimise patient outcomes. Surgeons should ensure that they undergo recognised surgical ablation courses to understand the fundamentals of the procedure, and that they are adequately proctored at the commencement of their program. In patients at increased risk of stroke, anticoagulation should be continued indefinitely, even following a successful procedure (see Section 6).

5.3.5. Stand-alone Surgical and Hybrid Management of Atrial Fibrillation

Recommendation: Stand-alone surgical or hybrid ablation of AF can be considered for patients with symptomatic paroxysmal, persistent or long-standing persistent AF that is refractory, or intolerant to at least one Class I or III antiarrhythmic medication, or where there has been failed percutaneous ablation, or where the likelihood of successful percutaneous ablation is considered low.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Weak.)

Rationale: The surgical management of AF was first reported in the literature by Cox and his colleagues, who described their ‘Cox-Maze procedure’, which showed excellent results in terminating AF [183]. Since then, several modifications to the original procedure have been made; however, the procedure is time consuming, technically challenging, and invasive, and requires cardiopulmonary bypass. Therefore, research has focused on newer procedures that are minimally invasive and use thoracoscopic guidance and an energy source (either radiofrequency or cryoablation) to create epicardial lesions, the aim being to provide evidence for a safer and less invasive surgical procedure for the stand-alone management of AF [184,185]. A recent focus of research has been a hybrid procedure that combines both a surgical epicardial ablation procedure and a catheter endocardial procedure (either staged or simultaneously) to achieve better outcomes for patients.

The body of literature surrounding the stand-alone surgical management of AF mostly comprises observational studies with varied cohort sizes, and the results must be interpreted cautiously.

Benefits and harms: A review of the above literature revealed that the surgical management of AF produces AF-free rates of 82% with AADs and 65% without AADs at mean follow-up of 28.6 months (± 16.6). Estimates of the complication rates associated with these procedures revealed the risk of death as 0.5%, conversion to sternotomy 1.1%, bleeding 2.1%, stroke or TIA 0.8%, permanent pacemaker insertion 1.6% and phrenic nerve injury 1.1%.

Resources and other considerations: Surgical management of AF is only available for patients at centres with a cardiothoracic service; therefore, it might not be a feasible treatment option for patients living in rural or remote areas.

Practice advice: Patients should be considered on an individual basis in a multidisciplinary team meeting that includes both the treating electrophysiologist and cardiothoracic surgeon, with the aim of determining the best management plan for each patient. Surgical expertise and training in these newer minimally invasive epicardial procedures are of key importance to optimise patient outcomes.

5.4. Arrhythmia Management in Special Situations

5.4.1. Arrhythmia Management—Atrial Flutter

RCT data comparing rate and rhythm control strategies in individuals with atrial flutter are sparse. Within the subgroup of patients with atrial flutter that were included in the Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) trial, there was no significant difference in outcomes between the rate-control and rhythm-control groups with respect to the primary endpoint [120]. Options for rhythm control in atrial flutter include electrical cardioversion, cavotricuspid isthmus (CTI) ablation (for typical atrial flutter) or AAD therapy. Observational studies have shown that electrical cardioversion can facilitate acute rhythm control in more than 90% of cases [186–188]. For sustained rhythm control, small RCTs have found CTI ablation to be significantly better than AADs for preventing atrial flutter recurrence. Atrial flutter recurrence rates of 6.4%–8.7% were reported in patients treated with CTI ablation compared with 50%–52.9% in patients receiving AADs [189,190]. A meta-analysis of studies that performed CTI ablation with large-tip or irrigated catheters and employed bidirectional isthmus block as the procedural endpoint reported a mean atrial flutter recurrence rate of 6.7% and a complication rate of 2.7% (most of which were vascular complications) [191]. Despite the efficacy of CTI ablation in curing atrial flutter, 51.3% of patients with pre-existing AF will experience AF recurrence post-CTI ablation, and 26.2% of patients with no previous history of AF will develop new AF if followed up for at least 2 years [192]. Unfortunately, no large studies have compared CTI ablation to AAD and incorporated atrial arrhythmia recurrence as an endpoint.

5.4.2. Arrhythmia Management in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular condition; it has an estimated prevalence of 0.2%–0.5% [193]. AF in turn is the most common

sustained arrhythmia in HCM patients, with a prevalence of nearly one in four and an annual incidence of 3% [194]. The development of AF in HCM patients is associated with an increased risk of stroke, impaired quality of life, increased hospitalisation, and higher mortality [195–199].

Data regarding rate versus rhythm control in AF patients with HCM are limited. However, the symptomatic and prognostic impact of AF on HCM patients—particularly in the presence of rapid ventricular rates or left ventricular outflow tract (LVOT) obstruction—makes the restoration of sinus rhythm the recommended strategy [195,200]. Haemodynamically unstable patients or those with severe symptoms require urgent cardioversion. Beta blockers and non-dihydropyridine calcium channel blockers are reasonable agents to use for rate control, given their established safety and efficacy profiles, as well as the desired negative inotropic effect, which can ameliorate the haemodynamic consequences of AF [201,202]. In contrast, digoxin is contraindicated when there is LVOT obstruction [200]. Disopyramide, a Class Ia AAD, is often used to treat LVOT obstruction in combination with a rate-limiting medication (because it can increase AV nodal conduction), but its use to treat AF is not established [165,200].

Amiodarone (a Class III AAD) has long been used for the treatment of AF in HCM patients [203–206], but its toxicity limits its long-term use, and it has similar efficacy to other AADs [198]. Sotalol has been shown to be successful in suppressing atrial arrhythmias [207–209], but careful monitoring is required because of its proarrhythmic, QT-prolonging effect [200]. A retrospective study of 4248 HCM patients showed that the protective effect of beta blockers, non-dihydropyridine calcium channel blockers, and disopyramide in preventing AF recurrence is limited to two to three years [198]. Class IC antiarrhythmics such as flecainide should be avoided due to their proarrhythmic effects [200].

Multiple small studies have shown catheter ablation for AF to be a reasonable and safe option to maintain sinus rhythm and improve symptoms in HCM patients [210]. A systematic review of 14 observational studies reported freedom from atrial arrhythmia following catheter ablation in 51.8% of patients, with a median follow-up of 1.8 years after a median of 1.4 procedures [211] (see Section 5.3.3).

5.4.3. Arrhythmia Management for Post-operative Atrial Fibrillation

Postoperative AF is well-documented, with an incidence of 8%–50%, depending on the type and site of the surgery [212–215]. AF is responsible for increasing the postoperative hospital length of stay and is an independent predictor of mortality [3,216]. Although several observational studies have suggested a survival benefit following restoration of the sinus rhythm following cardiovascular surgery [213,215,217], the most recent RCT that studied the effectiveness and safety of rate control versus rhythm control after cardiothoracic surgery showed equal duration of hospital stay and complications [218]. Postoperative AF management remains controversial, and evidence to support rhythm control versus rate control in this population of patients is lacking.

5.4.4. Arrhythmia Management in Grown-up Patients with Congenital Heart Disease

The occurrence of atrial arrhythmia, including AF, in grown-up patients with congenital heart disease (GUCH) increases with age, complexity of congenital heart disease (CHD), and the timing and number of surgical interventions undertaken. Overall, atrial arrhythmias are usually seen late after surgical repair of CHD, occurring in 25%–40% of GUCH patients. The atrial arrhythmias are poorly tolerated and are associated with heart failure, thromboembolism, syncope, and sudden death [219–222].

Class IC and III agents are effective in treating atrial arrhythmias. Amiodarone is more effective and is recommended in the presence of ventricular dysfunction [222]. However, long-term treatment carries a high risk of side effects in this relatively young population. Radiofrequency ablation should be considered for symptomatic GUCH patients with atrial arrhythmias or drug-refractory AF [223–225]. Atrial arrhythmias may also be the first manifestation of failing or obstructed atriopulmonary anastomosis circuits. Operative conversion to total cavopulmonary artery connection with arrhythmia surgery in selected patients improves heart failure and reduces recurrent arrhythmias [226].

5.4.5. Arrhythmia Management in Athletes

An increasing amount of data shows an excess of AF among athletes, particularly those engaged in endurance sports. Recent estimates from large-cohort studies show a 20%–30% increased risk among athletes [227], although previous estimates from case–control studies had suggested a five-fold increase in risk. The mechanisms contributing to AF in athletes are unclear, although they are probably due to an increase in parasympathetic tone coupled with the development of an arrhythmogenic substrate [228].

Although few studies have assessed treatment strategies among athletes, rhythm control is often the preferred approach because it has less impact on exercise performance, and because rate control can be difficult due to the baseline level of bradycardia observed in this population. Several small studies have compared catheter ablation outcomes between athletes and non-athletes, showing comparable freedom from AF [229,230]. Rate control may be appropriate, although its impact on exercise tolerance should be considered.

6. Stroke Prevention

6.1. Prediction of Stroke Risk

Recommendation: The CHA₂DS₂-VA score—the sexless CHA₂DS₂-VASc score—is recommended for predicting stroke risk in AF.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: The CHA₂DS₂-VA score should be re-evaluated yearly in low-risk patients who are not anticoagulated.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: Development of the CHADS₂ score using simple clinical markers allowed some prediction for risk of stroke among patients with non-valvular AF, although the predictive capacity was modest. Other scores have produced minor improvements, especially in the low-risk group, and comparisons between different scores (e.g., CHA₂DS₂-VASc, ATRIA, and ORBIT) do not show major differences in predicting high risk of stroke. A systematic review has provided the strength of the stroke risk factors used in the CHA₂DS₂-VASc score [231].

Of the available scores the CHA₂DS₂-VASc score is simple to use, widely known, and accepted in clinical practice. The female sex category component of the score (Sc) adds the most predictive value in the presence of multiple additional risk factors. Female sex alone or in the presence of one additional risk factor does not confer sufficient or consistent increased risk [232–234]. Most guidelines have adopted the cumbersome practice of selecting different CHA₂DS₂-VASc thresholds for males and females when recommending anticoagulation. To avoid this practice, we recommend a sexless CHA₂DS₂-VASc score (i.e. removing female sex), abbreviated as CHA₂DS₂-VA score in these guidelines, and we provide one consistent recommendation for both sexes (see Table 3).

Resources and other considerations: The addition of biomarkers (e.g., troponin, B-type natriuretic peptide [BNP] [235], transthoracic and transoesophageal echo measurements) to existing scores improves overall predictive capacity. However, these algorithms have not been evaluated in sufficient numbers of low-risk patients on no therapy to demonstrate their value in reliably differentiating those with truly low risk who do not require anticoagulation from those with low to intermediate risk who do require anticoagulation. Moreover, biomarker use adds measurement and biological variability, and additional steps, which increase complexity relative to the simple bedside clinical score risk estimation. Some ongoing studies will address whether biomarkers will allow adequate risk discrimination in patients at low to intermediate predicted risk to permit a greater number of patients to safely be managed without lifelong anticoagulants.

Practice advice: The definitions of the letters in the acronym CHA₂DS₂-VA are shown in Table 3. Stroke risk factors may change over time due to ageing or development of new comorbidities. Hence, annual review of low-risk patients is recommended to ensure that risk is adequately characterised to guide OAC therapy.

6.2. Prediction and Minimisation of Bleeding Risk

Recommendation: Reversible bleeding factors should be identified and corrected in AF patients for whom anticoagulation is indicated.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

6.2.1. Prediction of Bleeding Risk

The risk of bleeding with warfarin is 1.3% per year in patients with an INR of 2.0–3.0 [236], but estimates vary widely,

Table 3 Definitions and points in the CHA₂DS₂-VA score.

Score	Points	Definition
C	1	Congestive heart failure—recent signs, symptoms or admission for decompensated heart failure; this includes both HFrEF and HFpEF, or moderately to severely reduced systolic left ventricular function, whether or not there is a history of heart failure
H	1	History of Hypertension, whether or not BP is currently elevated
A ₂	2	Age ≥75 years
D	1	Diabetes
S ₂	2	History of prior Stroke or TIA or systemic thromboembolism
V	1	Vascular disease, defined as prior myocardial infarction or peripheral arterial disease or complex aortic atheroma or plaque on imaging (if performed)
A	1	Age 65–74 years

AF, atrial fibrillation; BP, blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; TIA, transient ischaemic attack.

depending on the population studied and the quality of INR control for warfarin.

NOACs have either a comparable or a slightly reduced major bleeding risk relative to warfarin, with the difference being more pronounced in centres with lower time in therapeutic range for warfarin, a greater incidence of gastrointestinal (GI) bleeding and a significantly reduced risk of intracranial haemorrhage [237]. Bleeding risk can be estimated by a variety of clinical scores—for example, HEMORR₂HAGES [238], HAS-BLED [239], ATRIA [240], ORBIT [241], and GARFIELD [242]—and by ABC (age, biomarkers, clinical history) bleeding risk score [243] incorporating biomarkers. C statistics for predicting major bleeds are modest at best (~0.6), and adding biomarkers provides only minimal improvement. Higher CHADS₂ and CHA₂DS₂-VASc scores also predict major bleeding, which indicates that patients at high risk of stroke are also at higher risk of major bleeding, but the specialised bleeding risk scores are better predictors [244]. The net clinical benefit almost always favours stroke prevention over major bleeding, so bleeding risk scores should not be used to avoid anticoagulation in patients with AF. Higher scores might be used to alert the clinician to a greater need to attend to any modifiable bleeding risk factors.

6.2.2. Minimisation of Bleeding Risk

Treating reversible bleeding risk factors such as hypertension, falls and peptic ulceration should be prioritised to minimise the bleeding rate in patients on anticoagulants (see Table 4). The risk associated with recurrent falls may be reduced by falls prevention programs. In people with recurrent falls despite efforts to decrease risk of falling, a more detailed discussion may need to be had on the risks associated with continuing anticoagulation versus the risks associated with stopping anticoagulation. The difficulty for clinicians and patients is that there is no high-quality evidence to help guide this discussion.

In secondary prevention after cerebrovascular events, the risk of intracranial haemorrhage (ICH) can be reduced from 2% to 1% through reduction in blood pressure (BP) [245]. Reintroduction of anticoagulants after both spontaneous and traumatic ICH on warfarin reduces ischaemic stroke or systemic embolus and mortality [246]. Patients who have had unprovoked (spontaneous) ICH should have a specialist assessment of their bleeding risk on an OAC.

The presence of congophilic angiopathy, also known as cerebral amyloid angiopathy (CAA) and cerebral microbleeds on magnetic resonance imaging (MRI) are markers for heightened ICH rates on anticoagulants. Symptomatic ICH, related to CAA, is a relative contraindication to anticoagulation, although this may be considered in individual patients 4–6 weeks following lobar haemorrhage.

Asymptomatic CAA on MRI sequences, without ICH, is highly prevalent, being 16% in older patients [247], and is not a contraindication to anticoagulation.

Most significant bleeds before anticoagulation and after anticoagulation occur from the GI tract (GIT). Causes of prior upper GIT bleeding in cardiovascular prevention, such as peptic ulceration, are usually preventable [248] and are not a contraindication. Dabigatran 150 mg and rivaroxaban 20 mg were associated with increased GI bleeding relative to warfarin in RCTs. Other agents or doses should be preferentially used in patients with prior GI bleeding. Untreatable or difficult to prevent causes of lower GIT bleeding (e.g., recurrent bleeding from angiodysplasia) may be a contraindication to anticoagulation.

Practice advice: Major bleeding can be reduced through high-quality INR control on warfarin [249], and appropriate selection of NOAC dosage according to age and renal function [248,250].

Recurrent falls are associated with increased mortality in AF patients but not increased ICH, although these data come from a Markov modelling analysis that has been criticised for

Table 4 Bleeding risk factors.

Modifiable bleeding risk factors	Comment
Hypertension (SBP >160)	Blood pressure control reduces the potential risk of bleeding
Labile INR (TTR <60%)	Consider changing to a NOAC
Concomitant medications including antiplatelet agents and NSAIDs	Minimise duration of double or triple therapy in patients with coronary disease and AF
Excess alcohol (>8 drinks per week)	
Potentially modifiable bleeding risk factors	Correct these factors where possible
Anaemia	
Impaired renal function	Monitor, especially in situations when renal function may be affected
Impaired liver function	
Frailty and falls	Walking aids, footwear, aged care home review
Non-modifiable bleeding risk factors	
Advanced age	Stroke risk outweighs bleeding risk
History of major bleeding	
Previous stroke	Risk of recurrent stroke outweighs risk of bleeding
Dialysis-dependent kidney disease	The role of anticoagulation (warfarin only indicated) in this population is controversial
Cirrhotic liver disease	Contraindication to NOACs (these patients are excluded from trials); consider advice from hepatologist
Malignancy	Individualise decisions about anticoagulation based on risk and benefit
Genetic or racial variation	Subgroup analyses from the NOAC versus warfarin RCTs suggest that, when warfarin is used, Asian patients are at higher risk of major bleeding and ICH than non-Asians; standard-dose NOACs appear to be as effective in Asians as non-Asians [419] ICH risk is high in Aboriginal and Torres Strait Islander patients on anticoagulation [252] Pay careful attention to blood pressure control in these populations

AF: atrial fibrillation, ICH: intracranial haemorrhage, INR: international normalised ratio, NOAC: non-vitamin K oral anticoagulant, NSAID: nonsteroidal antiinflammatory drug, RCT: randomised controlled trial, SBP: systolic blood pressure, TTR: time in therapeutic range.

Kirchhof P, et al. 2016. *Eur Heart J* 2016; 37 (38): 2893–2962. By permission of OUP on behalf of the ESC. This table is not included under the Creative Commons license of this publication. © ESC 2016. All rights reserved. For permissions email journals.permissions@oup.com [1].

assuming no pre-existing comorbidities in the patient population. Under certain circumstances (e.g., frail people and older people, see Section 6.3.4.2), a high bleeding score should prompt a discussion between physician and patient in which the facts and physician's opinion are presented, allowing the patient or carer to make an informed decision.

In Australia, high ICH rates have been observed in those born in Oceania (other than Australia) and in northeast and southeast Asia [251]. In Aboriginal people, the risk of ICH has been reported as markedly increased (up to six-fold) (see Section 6.3.4.3) [252].

6.3. Stroke Prevention with Anticoagulation

Recommendation: Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients

with N-VAF whose CHA₂DS₂-VA score is 2 or more, unless there are contraindications to anticoagulation.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: Oral anticoagulation therapy to prevent stroke and systemic embolism should be considered in patients with N-VAF whose CHA₂DS₂-VA score is 1.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Oral anticoagulation therapy to prevent thromboembolism and systemic embolism is not recommended in patients with N-VAF whose CHA₂DS₂-VA score is 0.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Weak.)

Recommendation: In asymptomatic patients with atrial lead pacemakers, anticoagulation should be considered in device-detected and EGM-confirmed AF of 24 hours or more in patients with a CHA₂DS₂-VA score of 2 or more. (GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: When oral anticoagulation is initiated in a patient with N-VAF, an NOAC—apixaban, dabigatran, or rivaroxaban—is recommended in preference to warfarin.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Warfarin is recommended and NOACs should not be used in patients with valvular AF (mechanical heart valves or moderate to severe mitral stenosis).

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Antiplatelet therapy is not recommended for stroke prevention in N-VAF patients, regardless of stroke risk.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: The guiding principle for use of the CHA₂DS₂-VA score is to define truly low-risk patients for whom stroke risk is too low to justify the risk of major bleeding from anticoagulant therapy. Thus, the score is not used to provide an arbitrary allocation to low, medium, or high stroke risk, nor to concentrate on high risk, but rather to define low risk; that is, a CHA₂DS₂-VA score of 0. For a CHA₂DS₂-VA score of 2 or more, the benefits of reduced stroke and reduced mortality from anticoagulation certainly outweigh the risk of major haemorrhage, and an OAC is recommended. At a CHA₂DS₂-VA score of 1, the risk–benefit equation is more balanced, so other factors require greater consideration in the decision on anticoagulation (see Figure 6).

Asymptomatic patients with AF detected on opportunistic screening are regarded as having a comparable risk to symptomatic patients; thus, recommendations for anticoagulation apply (see Section 4.4.2 Figure 1).

Patients with atrial flutter have a slightly lower stroke risk than patients with atrial fibrillation, but the risk still exists [253]. Furthermore, many of these patients have episodes of atrial fibrillation so the same recommendations for anticoagulation apply.

The stroke risk for patients with implantable devices and incidentally detected AF appears to be lower than in the general AF population, and there are less data to guide the threshold AF burden upon which to recommend anticoagulation (see Section 4.4.2 Figure 1). However, because of the high rate of progression to clinical episodes and the greater burden, patients with a CHA₂DS₂-VA score of 2 should have close follow-up with consideration of OAC when an episode lasts for more than 24 hours. There are insufficient data to provide recommendations for patients with lower burdens of implanted-device-detected AF, regardless of CHA₂DS₂-VA score.

Anticoagulation with warfarin reduces the risk of embolic stroke by 70% and of mortality by 29% when used in patients with N-VAF. However, warfarin is difficult to use in clinical practice because of multiple food and drug interactions, and the need for frequent monitoring to keep the anticoagulation within the therapeutic range [2,254]. As with all forms of antithrombotic or anticoagulant therapy, bleeding is increased with warfarin, but ICH is greatly increased compared with other agents [255–257].

The evidence for stroke prevention with aspirin is weak [255,258], and it is not as benign as many think, with data suggesting that bleeding rates were similar to apixaban in patients with N-VAF who were deemed ineligible for anticoagulation with warfarin [259]. Aspirin together with clopidogrel reduced stroke by 28% when compared with aspirin alone, but at the expense of a 57% increase in major bleeding. The combination antiplatelet therapy was 44% less effective than warfarin in stroke prevention, with comparable incidence of major bleeding [260].

There are strong data to show that the NOACs (dabigatran, rivaroxaban, and apixaban, also known as ‘direct-acting oral anticoagulants’ or ‘DOACs’; see Table 5) are as good as or better than warfarin in reducing stroke and systemic embolism, and that bleeding rates are less or similar to warfarin, depending on the agent chosen and the dose used. ICH is significantly reduced with all agents compared with warfarin, independent of the dose used, and pooled data suggest there is a mortality benefit over warfarin. NOACs have minimal drug and food interactions, and do not need haematological monitoring, so are much easier for the patient and physician to use [237,261–263].

These data form the basis for the strong recommendation that NOACs are preferred over warfarin for stroke prevention in N-VAF if the patient is eligible [15].

Benefits and harms: The NOACs have overall better or similar efficacy and safety when used in patients with N-VAF for stroke prevention compared with warfarin, but the absolute risk reductions are relatively small, so the number needed to treat to prevent stroke, and to reduce ICH and mortality is in the hundreds relative to warfarin [237].

Resources and other considerations: The NOACs are considerably more expensive than warfarin, but cost–benefit analyses, admittedly in countries where medical costs are higher [264,265], have shown that NOACs are cost effective compared with warfarin using conventional measures. There are no Australian data on this, but the Pharmaceutical Benefits Advisory Committee has funded these drugs, and is satisfied that they provide good value for money in an Australian context.

Australia is a large country, and medical resources and the ability to monitor INRs are often scarce in remote communities. In such communities, NOACs have the capacity to greatly improve the health of patients with N-VAF and risk factors for stroke, because monitoring is not required and patients who were previously considered poor candidates for anticoagulation with warfarin due to these constraints can be treated with proven alternative therapy.

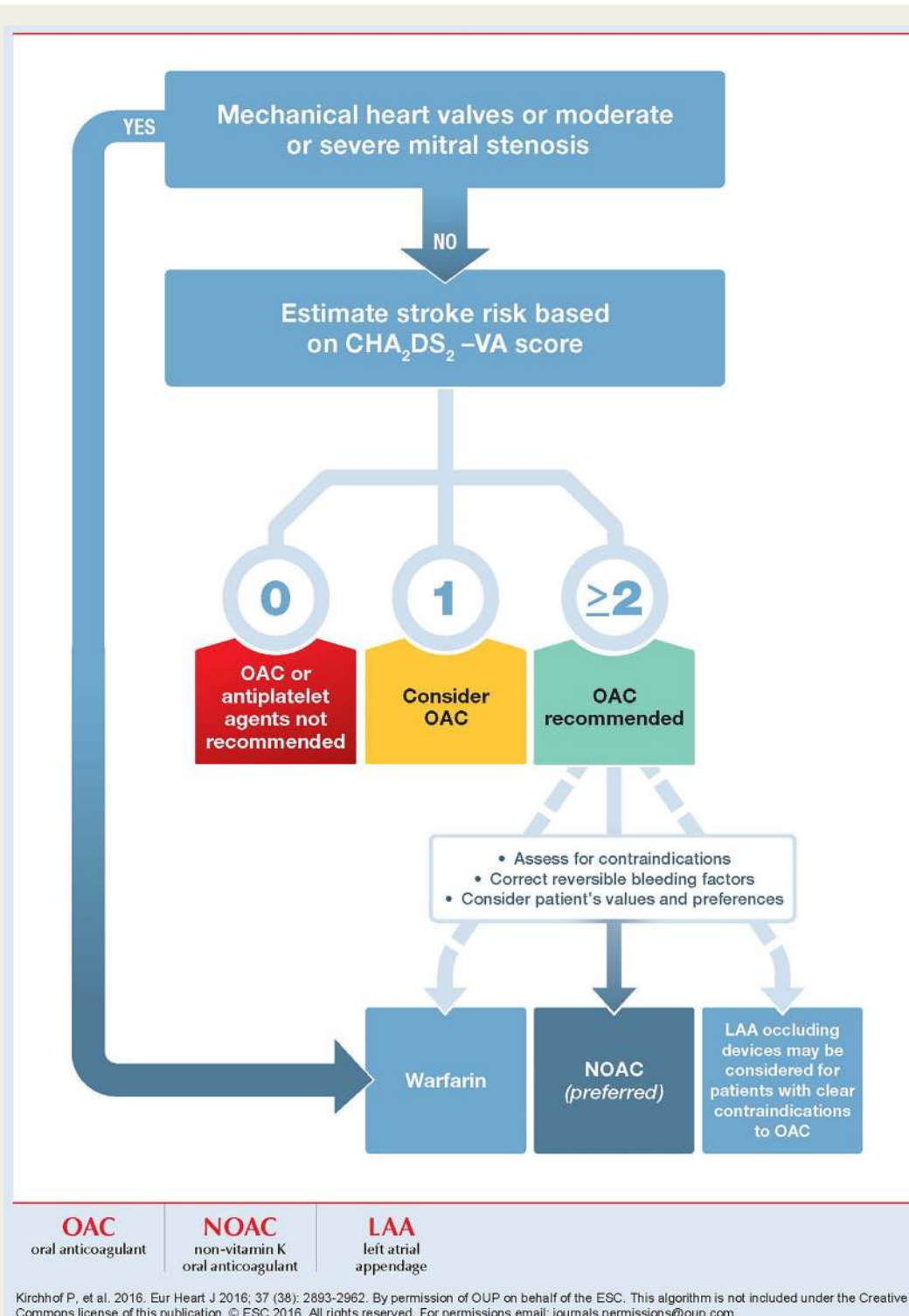


Figure 6 Stroke prevention in atrial fibrillation.

Practice advice: There are some clinically significant differences between the NOACs that need to be considered when prescribing these drugs (see Table 5).

Full anticoagulation is achieved within 1–2 hours of dosing for all agents due to their rapid onset of action [262,263,266]. Similarly, they also have a rapid offset of action compared

with warfarin, so that within 24 hours of taking the last dose, minimal anticoagulant effect remains. Missed doses are problematic due to the rapid offset of action, which could potentially increase risk of stroke due to periods of non-anticoagulation. This is less of an issue with warfarin, which has a much longer half-life.

Table 5 Non-Vitamin K oral anticoagulants for prevention of emboli in atrial fibrillation—dose adjustments in Australia.

NOAC	Full dose	Dose reduction	Indications for dose reductions
Apixaban	5 mg bd	2.5 mg bd	At least two of the following: <ul style="list-style-type: none"> • aged 80 years or more • weight 60 kg or less • serum creatinine 133 $\mu\text{mol/L}$ or more
Rivaroxaban	20 mg daily	15 mg daily	CrCl 30–49 mL/min and/or combination with DAPT ^b
Dabigatran	150 mg bd	110 mg bd	Aged 75 years or more and/or CrCl 30–50 mL/min and/or increased risk of major bleeding (e.g., combination with DAPT ^a)

bd, twice daily; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; NOAC, non-vitamin K oral anticoagulant.

^aIf DAPT is required with anticoagulation and another indication(s) for dose reduction, consider using single antiplatelet therapy.

^bIn patients receiving rivaroxaban who require antiplatelet therapy following stenting, consider early de-escalation to SAPT + OAC [297].

The NOACs are all renally excreted, with dabigatran being most dependent on renal excretion, and rivaroxaban and apixaban less so. Thus, in the presence of renal dysfunction, a longer treatment discontinuation period is required with dabigatran than with the other agents to allow coagulation status to return to normal. Dabigatran and rivaroxaban should be taken with meals to reduce the risk of dyspepsia and improve absorption, respectively.

The relationship between the INR and activated partial thromboplastin time (APTT) and drug levels is nonlinear; thus, it is not helpful in determining the extent of anticoagulation. These tests, however, can be used to assess medication adherence, because levels are usually elevated when the patient has taken the drug. Similarly, these tests can be useful in patients requiring urgent surgery or treatment for bleeding, because normal levels of these parameters would suggest that very little active drug is present.

In patients with stable INR control on warfarin, it is reasonable to consider changing to a NOAC on the basis of the consistent decrease in ICH with all doses of the NOACs compared with warfarin. Patient wishes need to be considered in this context (see Section 7.2); for example, the absence of the need for haematological monitoring and the ability to have a more liberal diet may influence some patients, whereas others may prefer the reassurance offered by a therapeutic INR taken on a regular basis.

6.3.1. Optimising Anticoagulation

For warfarin, optimal therapeutic outcomes are achieved within a narrow therapeutic index; therefore, treatment is carefully dosed according to a specified target INR range. To facilitate these dosage adjustments, regular INR

measurement is needed for the duration of the warfarin therapy. There are various approaches to achieving this, including:

- general practitioner (GP) led management;
- anticoagulation clinic;
- pathology service-led care (with validated computerised dosing algorithms);
- point-of-care testing (including patient self-management).

Although point-of-care INR testing is becoming more common in Australian practice, for most patients the process of INR measurement and dosage adjustment is still undertaken collaboratively by the GP and local pathology service. Typically, the patient's GP (prescriber) refers the patient to a local pathology service for blood tests. INR test results are reported back to the GP (typically electronically) for their review; INR results that are out of range are communicated back to the patient by either the GP or the pathology service, alerting the patient to the need for a dosage adjustment (as prescribed by the GP).

In Australia, anticoagulation clinics providing specialised anticoagulation monitoring and management are offered in some outpatient departments of major hospitals, and may be led by clinicians or other health professionals (e.g., nurses, pharmacists). Internationally, compared with usual care, anticoagulation clinics have been shown to result in better patient treatment satisfaction [267], as well as better quality of anticoagulation control, lower rates of bleeding and thromboembolic events, and lower healthcare costs [268].

In rural Australian settings, coordinated anticoagulation management services—incorporating patient education, point-of-care INR testing, patient self-care models, protocols

and use of specially trained personnel (e.g., nurse, dietician and pharmacist)—have been shown to increase time spent in therapeutic range and to reduce complications related to anticoagulation [269].

Published algorithms and guidelines are available to assist dosage adjustments during the initiation and maintenance of warfarin therapy, including response to over-anticoagulation (cardiovascular therapeutic guidelines [270]).

6.3.1.1. Point-of-care International Normalised Ratio Measurements for Patients Receiving Warfarin.

Recommendation: Point-of-care INR measurement is recommended in the primary care management of patients receiving warfarin.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: Point-of-care devices using finger-prick capillary blood sampling have enabled convenient and efficient measurement of anticoagulation control in the practice setting or the patient's home. In addition, the mobility of point-of-care testing enables multidisciplinary management of patients and improves continuity of care. In Australia, practitioner-led point-of-care INR testing for the management of patients with AF has been trialled in general practices [271,272], outpatient clinics [273], aged-care facilities [274], and community pharmacies [275,276], as well as in conjunction with home-based medicine review services led by accredited pharmacists [277], across metropolitan or urban, [271,273,274,277–279], rural [271,272,276,277], and remote [271,277] settings. Collectively, Australian studies have shown that point-of-care INR measurement is associated with improved INR control (i.e. proportion of INR results within therapeutic range and time in therapeutic range); a significant decrease in adverse clinical events, including thrombosis, and minor and major haemorrhagic events; and significantly increased persistence with warfarin therapy.

Resources and other considerations: In general, point-of-care devices (and consumables such as testing strips) are currently relatively expensive to purchase (in the absence of Medicare rebates). Overall, they are generally cost effective in terms of optimising related health outcomes [280]; however, this depends on the overall model of care in which the devices are used [281]. Patients may be able to claim certain costs against their own private health insurance. Some practices (e.g., medical centres and community pharmacies) may offer point-of-care testing on a fee-for-service basis (including package or subscription-based plans). Some local health districts support the use of point-of-care INR testing, particularly within hospital-to-home or post-discharge liaison or follow-up services.

Practice advice: Current point-of-care measurement of coagulation parameters (e.g., INR) applies only to those using warfarin therapy. Specific point-of-care coagulation tests for the NOACs are not available. Only INR measurement devices that are approved by Australia's Therapeutic Goods Administration (TGA) and those that have been demonstrated to be accurate and precise should be used for point-of-care testing, with appropriate procedures in place for

quality control and quality assurance, addressing device operation, device calibration, and responding to aberrant results [282,283]. All device users (health professionals, patients, and carers) must be adequately trained in use of the device. Hence, not all settings will be suitable for point-of-care testing, particularly among self-monitoring patients (e.g., those with poor cognition or comprehension skills, or poor manual dexterity).

Although generally comparable [284,285], point-of-care coagulometers are less consistent and tend to slightly overestimate the INR when measurements are above the therapeutic range (INR > 3.5) [286,287]. These devices may also underestimate INR when measurements are below the therapeutic range (i.e. INR ≤ 1.9) [288,289]. Measurements may also be inaccurate in certain patients (e.g., severe anaemia, antiphospholipid syndrome). Therefore, point-of-care testing is most useful for the ongoing management of patients who are generally stable and/or in acute situations where a timely result is needed to guide patient management.

A range of guidelines and online or eHealth resources are available to help guide both practitioners and patients in point-of-care INR testing. They include computer decision support software that can link INR results and automatically recommend the patient's next dose of warfarin.

6.3.2. Management of Bleeding

Recommendation: Symptomatic treatment with fluid replacement or blood transfusion should be initiated for all patients with moderate to severe bleeding while treatment of the cause is addressed.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Factor replacement therapy with PCCs can be considered for patients taking warfarin or specific factor Xa inhibitors with life-threatening bleeding or those requiring emergency surgery.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Weak.)

Recommendation: Idarucizumab is recommended for patients taking dabigatran who experience life-threatening bleeding or require emergency surgery.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Anticoagulant therapy should be recommenced after bleeding has been addressed and when the stroke risk is believed to exceed the risk of further bleeding.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: General principles in the management of patients bleeding while receiving anticoagulation have been described in a consensus document developed by the Thrombosis & Haemostasis society of Australia and New Zealand (THANZ, previously known as Australian Society of Thrombosis and Haemostasis) [290]. These principles are drug discontinuation, baseline laboratory assessment (APTT, prothrombin time [PT] and thromboplastin time [TT], drug

levels and creatinine), general supportive care measures, activated charcoal if patients present within four hours of the last oral dose of NOAC and administration of a haemostatic agent (see Figure 7).

Vitamin K can reverse the anticoagulant action of warfarin but has delayed onset of activity. Prothrombin factor

concentrates (PCCs) were developed for the reversal of warfarin; in Australia three-factor PCC (Prothrombinex-VF, CSL, Melbourne) can be used for this purpose [291].

A second PCC, factor eight inhibitor bypassing activity (FEIBA) has been evaluated for the prevention of life threatening bleeding in patients on NOACs in laboratory and

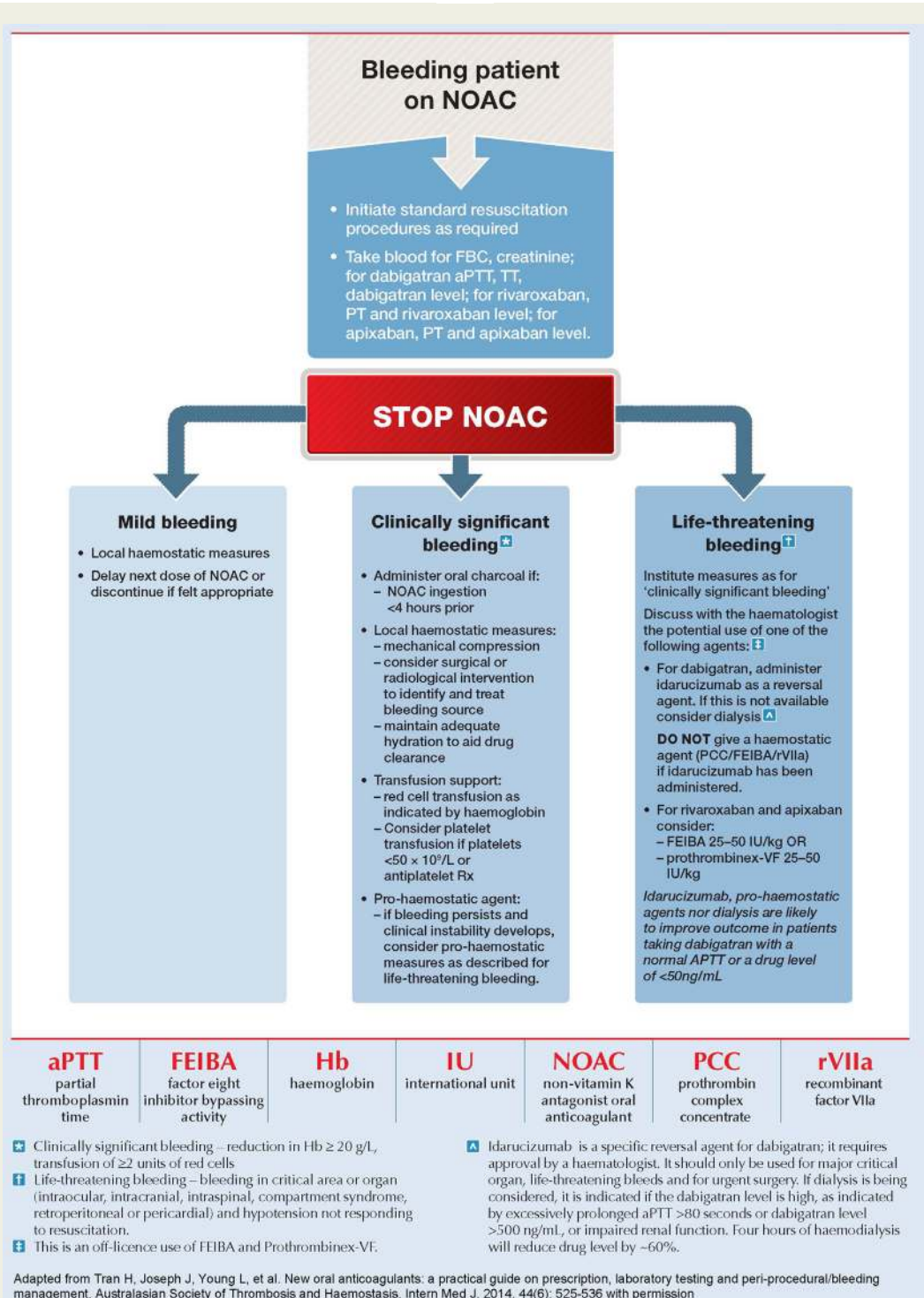


Figure 7 Management of bleeding for non-vitamin K antagonist oral anticoagulant treated patients.

animal studies. FEIBA appears to have a more consistent impact on haemostatic changes associated with the NOACs than other agents, but clinical data are limited.

FEIBA is not used for patients on warfarin and the efficacy of three-factor PCC on reversing bleeding due to the NOACs has not been evaluated [290,292].

Idarucizumab is a humanised specific monoclonal antibody fragment that binds dabigatran with high affinity. It was shown to rapidly and completely inhibit the anticoagulant activity of dabigatran in more than 90% of critically ill patients who suffered uncontrolled bleeding or required emergency surgery [293]. It has become available in most hospitals in Australia and New Zealand since the publication of the THANZ recommendations, and it should be considered in patients meeting the criteria above. It does not reverse the activity of any other anticoagulant drug.

The resumption of OAC following interruption of treatment because of GI bleeding is associated with decreased mortality and no increase in bleeding, provided that the drug is reintroduced 1 week following control of bleeding [294]. In the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study of idarucizumab, thrombotic events occurred within 6 days after administration of the reversing agent when anticoagulation was not reinitiated [293]. The above recommendation to commence OAC within 1 week is based on consensus opinion [295].

Practice advice: If major/life-threatening bleeding occurs, the anticoagulant effects of warfarin can be reversed rapidly with prothrombin factor concentrate, and more slowly with administration of vitamin K. Similarly, if major/life threatening bleeding occurs during treatment with a factor Xa inhibitor (rivaroxaban or apixaban), supportive measures and FEIBA can be considered (see Figure 7), because the specific reversal agent for these agents (andexanet) is not yet approved for use in Australia.

For patients with major bleeding requiring a haemostatic agent, the choice of specific agent depends on drug availability and the experience of the centre, and should therefore be made in consultation with a local haematologist.

6.3.3. Combining Anticoagulants and Antiplatelet Agents

Recommendation: Careful assessment of the bleeding and ischaemic risks (i.e. stroke, new or recurrent cardiac ischaemia or infarction, and stent thrombosis) should be undertaken for patients with AF who have a long-term requirement for anticoagulation for stroke prevention and require dual antiplatelet therapy (DAPT) after acute coronary syndrome (ACS) or stent implantation (or both).

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Duration of triple therapy (aspirin, P2Y₁₂ inhibitor and OAC) should be as short as possible to minimise bleeding, while ensuring coverage of the initial period of high risk of stent thrombosis and/or recurrent coronary ischaemia.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Where DAPT is required in combination with OAC, low-dose aspirin (100 mg) and clopidogrel (75 mg) are recommended. Ticagrelor and prasugrel are not recommended in this situation.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Where OAC is used for AF, discontinuation of antiplatelet therapy should be considered 12 months after stent implantation, ACS, or both, with continuation of OAC alone.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Weak.)

Rationale: Recent guidelines based predominantly on consensus opinion have supported the use of combined anticoagulant and DAPT in patients who require OAC for stroke prevention, and DAPT following ACS or stent implantation, or both. To minimise the risk of bleeding and maintain effectiveness, it is recommended that the INR be kept between 2.0 and 2.5 in patients on warfarin, and that the doses of NOAC evaluated in the appropriate clinical trials be used (see Table 5). Low-dose aspirin (100 mg) should be used, and clopidogrel is favoured over ticagrelor or prasugrel as the second antiplatelet (see Figure 8). With regards to down-titrating antiplatelet therapy, several trials published in this area inform practice [296–298]. The What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial showed that clopidogrel and warfarin caused less bleeding than triple therapy in patients undergoing stenting, and that there was less recurrent ischaemia and mortality with this strategy, although many of these patients did not have AF [296]. The Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) trial with rivaroxaban [297] and the Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran Versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial with dabigatran [298] looked exclusively at patients who had N-VAF and required OAC for stroke prevention, but also required antiplatelet therapy after stenting. Single antiplatelet therapy (SAPT)—predominantly clopidogrel, but some use of ticagrelor and prasugrel—and the NOAC (with specific dosing regimens: dabigatran 150 mg or 110 mg bd, rivaroxaban 15 mg daily) was shown to cause significantly less bleeding than triple therapy, with no increase in ischaemic events, but none of these trials was sufficiently powered to definitely prove this. Also, these results were attained with dual therapy starting several days after percutaneous coronary intervention in both the PIONEER and RE-DUAL studies, irrespective of the type of stent used. No recommendation regarding the use of SAPT with apixaban can be made until the completion of

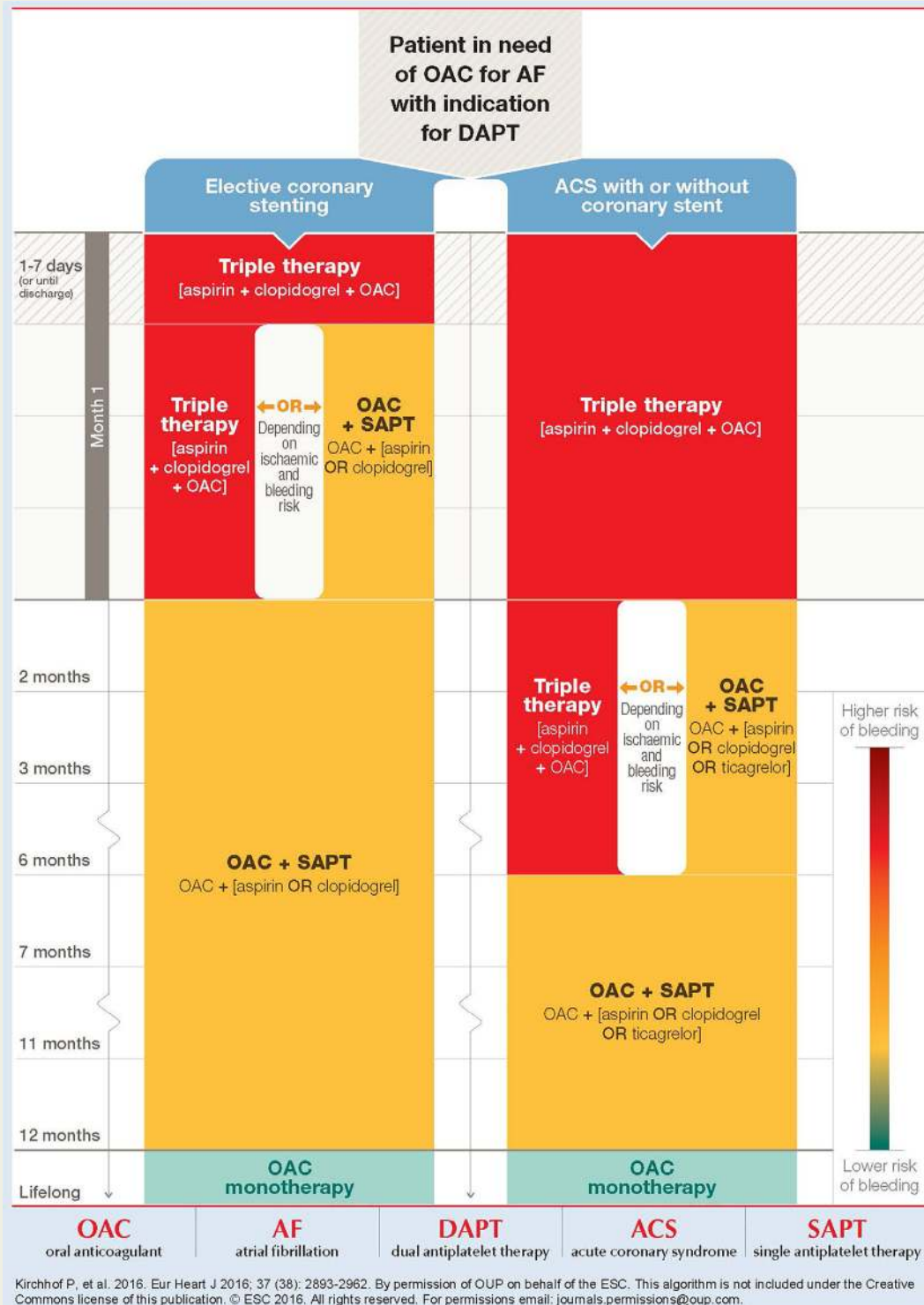


Figure 8 Combining anticoagulants and antiplatelet agents.

the Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention (AUGUSTUS) trial, which will directly address the issue.

In a Danish nationwide study of AF patients with stable coronary artery disease, the addition of antiplatelet

therapy to warfarin was found to be associated with an increased risk of bleeding but no reduction in ischaemic risk [299]. Thus, consideration should be given to stopping antiplatelet therapy in anticoagulated patients 12 months following an ACS or stent implantation [299,300] (see Figure 8).

Benefits and harms: When patients need to be treated with OAC and DAPT there is always trade-off between preventing new or recurrent ischaemic events and bleeding. The balance between these factors varies between individuals, in that stent and lesion characteristics, location, patient comorbidities, and concomitant medication can all influence the risk vs. benefit equation [295]. In general, the duration of triple therapy should be as short as possible, to reduce the substantial risk of bleeding with this combination [15,301].

Practice advice: Patients who require long-term OAC for stroke prevention in N-VAF but also require shorter-term DAPT are difficult to manage; however, based on recent studies [296–298] some practical advice can be provided. Clopidogrel is the recommended second antiplatelet agent [15,301], and using it with a NOAC [15] is generally preferred to warfarin. The decision on duration of triple therapy depends on the individual patient characteristics, balancing the risk of ischaemia and the risk of bleeding. Bleeding scores such as the HAS-BLED score [239], although not recommended when deciding whether or not to use an anticoagulant in a patient with AF at risk of stroke, may be of some value in determining high risk of bleeding in patients in whom irreversible factors are present and a shorter duration of triple therapy may be considered. Recommendations regarding optimal duration of therapy continue to evolve [302]. In patients following elective stenting with newer-generation drug-eluting stents, early cessation (within 1 week of stenting) of aspirin may be considered, with continuation of single antiplatelet and OAC. In patients following an ACS with or without stenting, a longer duration of triple therapy (1–6 months) may be preferred. Further guidance can be found in Figure 8.

One of the main concerns of triple therapy is the risk of GI bleeding. There are no studies evaluating the benefit of proton pump inhibitors in patients on combined antiplatelet and anticoagulant drugs. However, PPIs reduce GI bleeding in high-risk patients taking aspirin, and lower-risk patients taking both aspirin and clopidogrel [303,304]. The risk of GI bleeding in patients on triple therapy is therefore likely to be reduced by concomitant administration of proton pump inhibitors [303].

6.3.4. Anticoagulation in Special Situations

6.3.4.1. Anticoagulation in Patients with Atrial Fibrillation and Chronic Kidney Disease.

Recommendation: The decision to use anticoagulants in patients with AF and severe CKD (CrCl <30 mL/min) should be individualised because there are no prospective data showing benefit in this population.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Warfarin should be used if an AF patient with severe CKD requires anticoagulant therapy.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: CKD increases the risk of both stroke and bleeding in patients with AF [305]. Anticoagulation can be safely

used in patients with mild to moderate CKD (CrCl 30–60 mL/min), with a meta-analysis of the NOAC trials suggesting fewer ischaemic or bleeding events on NOACs than on warfarin [306]. Renal function should be regularly monitored in AF patients on NOACs to ensure appropriate dose adjustment (see Table 5).

There are no data from prospective randomised trials evaluating the use of warfarin in patients with severe renal impairment or those on dialysis (CrCl <30 mL/min). Also, observational studies are conflicting, with some suggesting benefit [307] and others harm [308]. Importantly, NOACs are contraindicated in this population.

Practice advice: In patients with compromised renal function (CrCl 30–50 mL/min) renal function needs to be assessed at least twice yearly, and more frequently if the patient becomes unwell. The Cockcroft–Gault formula should be used to calculate CrCl. Patients should be advised to seek medical attention if they develop concomitant illness that could further compromise renal function. The lack of data showing benefit of anticoagulation in AF patients with severe CKD or end-stage renal failure is not widely appreciated by practising clinicians. At present, the decision to anticoagulate these patients should be individualised with the knowledge that an estimate of benefits and harms cannot be provided.

6.3.4.2. Anticoagulation in the Older or Frail Patient.

Thromboembolic risk of stroke in N-VAF increases strongly with increasing age, with a risk ratio of 1.4 per decade in those aged more than 65 years [309]. However, clinicians are traditionally hesitant to prescribe anticoagulant therapy in older people (those aged more than 75 years) because of a perceived increased risk of adverse events, in particular bleeding if the patient falls (see Section 6.2.2) [310–312].

Patients with a high risk of falling do have increased risk of ICH; however, they also have a high risk of ischaemic stroke, and will benefit from anticoagulant therapy. Modelling has indicated that older people would have to fall almost 300 times a year for the risk of traumatic ICH among patients on warfarin to outweigh the benefits [313].

Data from registries indicate that the risk of bleeding increases less with increasing age than the risk of stroke. Thus, the net clinical benefit is in favour of treating older people and those aged more than 85 years [314].

It is common practice to adopt aspirin over OAC in older people because of a perceived lower bleeding risk. In the small Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial of patients with AF aged more than 75 years, warfarin resulted in a halving of the incidence of stroke relative to aspirin, whereas bleeding events were comparable [315]. The use of OACs in a general practice RCT has demonstrated safety and benefit in older people, including those aged more than 85 years [315].

Subgroup analyses of the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial

Fibrillation (ARISTOTLE) trials show that the superiority of rivaroxaban and apixaban over warfarin is maintained in older people [316,317]. Pharmacodynamic considerations suggest that rivaroxaban and apixaban are preferable to dabigatran in older people, due to decreasing renal function with age. Although data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study suggested dabigatran has acceptable safety and efficacy in the elderly when compared to warfarin [318,319], other cohort studies [320–322] suggest an increased GI bleeding risk. More research needs to be carried out to arrive at definite conclusions about preference of one NOAC over the other in this patient population. Dabigatran and rivaroxaban are contraindicated with a CrCl of less than 30 mL/min, whereas dose reductions are possible with apixaban down to a CrCl of 25 mL/min. Given the prevalence of polypharmacy in older people, these agents may also be preferable to warfarin; however, missed doses, more common with increasing numbers of medications, may be more detrimental with NOACs than with warfarin.

Practice advice: The combination of impaired hepatic, renal, cognitive function, high-risk medications, and polypharmacy make drug interactions and complications more likely. Furthermore, these patients are usually excluded from randomised trials and observational registries, so there are few data to guide decisions. An integrated management approach would be of particular value in this cohort (see Section 7).

6.3.4.3. Anticoagulation in Aboriginal and Torres Strait Islander peoples. There are many barriers to the optimal medical management of Aboriginal and Torres Strait Islander peoples with AF. The risk of all types of stroke is three-fold higher than in the broader population [323], and the ratio is higher in younger age groups. This is contributed to by the increased burden of AF in Aboriginal and Torres Strait Islander patients [8,324], resulting from high rates of rheumatic heart disease and other cardiovascular diseases, and the prevalence of other risk factors including obesity, diabetes, hypertension, and CKD.

Stroke risk calculators have not been specifically tested or adapted for Aboriginal and Torres Strait Islander peoples with non-rheumatic AF. Making the assumption that these calculators are applicable, one local audit suggested that Aboriginal and Torres Strait Islander patients at high risk of stroke are undertreated whereas low-risk patients are overtreated, in a similar fashion to the general population [325].

The need for regular monitoring of warfarin therapy provides additional challenges, particularly for the geographically isolated, and this can be eased by point-of-care testing, which is unfortunately not available in all communities.

There are limited data on the use of NOACs in this population, and the out-of-pocket costs of these drugs relative to warfarin may be real disincentives to their use. However, the lack of INR monitoring makes this an attractive treatment option, although clinical monitoring is still important when using NOACs.

Integrated care, with an emphasis on culturally appropriate healthcare workers to facilitate patient-centred decision-making, and coordinated outreach strategies that include provision of specialist clinics and echocardiographic services are currently inadequate because of shortfalls in the workforce and funding; hence, they remain aspirational objectives [326,327].

6.3.4.4. Bridging for Patients with Atrial Fibrillation Undergoing Surgical Procedures.

Recommendation: Bridging with LMWH or UFH is not necessary for warfarin treated patients at low to moderate risk of stroke undergoing planned surgical intervention.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Bridging with LMWH or UFH is not recommended for NOAC-treated patients.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Bridging with LMWH or UFH is indicated for patients at very high risk of stroke (e.g., warfarin-treated patients with mitral mechanical prosthetic heart valves) undergoing planned surgical intervention.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: It has traditionally been standard practice to stop warfarin 5 days before surgical procedures, and commence parenteral heparin once the INR has fallen to a subtherapeutic range while awaiting surgery (bridging). The Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial evaluated this strategy in AF patients receiving warfarin with at least one risk factor for stroke (but no recent stroke or TIA) undergoing non-cardiac surgical procedures [328]. The mean stroke risk score of this cohort was CHADS₂ of 2.3, equivalent to a CHA₂DS₂-VA ranging from 2 to 5. Bridging was associated with increased bleeding but no protection against stroke when compared to stopping warfarin without bridging anticoagulation. This finding was supported by a subsequent meta-analysis [329], and bridging is no longer recommended in this population of patients. Bridging for patients at higher risk of stroke (e.g., CHA₂DS₂-VA > 5) undergoing surgical procedures should be evaluated on a case-by-case basis.

Heparin bridging is not required in patients receiving NOACs because of the short half-lives of these therapies. Each of the large RCTs of these therapies has reported comparable bleeding and embolic events between warfarin and NOACs in patients undergoing surgical procedures in whom therapy was usually interrupted [330–332].

In general, the NOAC can be omitted for 24 hours in patients with normal renal function undergoing a low bleeding risk surgical procedure, and for 48–72 hours if renal function is impaired or the bleeding risk of the surgery is high.

For procedures in which haemostasis is immediate post-operatively, anticoagulation can be recommenced 6–8 hours following the procedure. More generally, NOACs can be

commenced 24 hours following low bleeding risk procedures or 48–72 hours for procedures with higher bleeding risk. It is recommended that the decision on timing of postoperative anticoagulation be made in conjunction with the involved proceduralist or surgeon.

Practice advice: Bridging is still recommended in patients with mitral mechanical valve replacements requiring warfarin cessation for surgical procedures. The BRIDGE trial included few patients at high embolic risk, and patients with strokes or TIA within the preceding 12 weeks were excluded [328], thus bridging may still be considered in these patients if receiving warfarin.

6.3.4.5. Anticoagulation for Patients Undergoing Invasive Coronary Procedures

About 20% of patients with AF will require some form of coronary intervention over time [333]. In general, non-urgent catheterisation should be delayed until anticoagulation status and renal function are known. Recommendations for periprocedural management of anticoagulation in these patients pertain to those who are on OAC at the time of their presentation; the recommendations are guided by consensus opinion [334]. Specific factors known to reduce bleeding complications should be implemented (radial access and use of small-diameter sheaths). Several case series have suggested that it is safe to continue warfarin through the angiographic procedure [335,336]. There are no randomised studies evaluating this, but extrapolation from the BRIDGE study suggests this to be reasonable practice.

Because of the shorter half-lives of the NOACs, these agents can be withheld 24 hours before the procedure in patients with normal renal function and 48–72 hours in those with impaired renal function, without bridging therapy. The NOAC can be recommenced at the scheduled time post-procedure. In stented or ACS patients requiring DAPT, doses of NOAC should be as recommended in Table 5

6.3.4.6. Anticoagulation for Cardioversion.

Recommendation: Anticoagulation is recommended at the time of electrical or pharmacological cardioversion, and for at least 4 weeks post-procedurally.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Recommendation: Anticoagulation for 3 weeks or a transoesophageal echocardiogram (to document absence of LA thrombus) is recommended before cardioversion in patients with more than 48 hours or an uncertain duration of AF.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: Clinical cardioversion of AF may be achieved by electrical or chemical means. The associated risk of thromboembolism (leading to stroke or systemic embolism) is high, both at the time of the cardioversion and for some weeks afterwards [337,338]. This risk is independent of the mode of arrhythmia termination, and is more strongly related to the duration of the preceding period of AF as well as to attendant risk factors. In a recent large series of patients who were not anticoagulated for cardioversion, those with heart failure and

diabetes had a very high (9.8%) thromboembolic risk within the 30-day period afterwards [337].

In those patients who have a likely duration of arrhythmia onset of more than 48 hours, or in those in whom the time of onset is uncertain, therapeutic anticoagulation for at least 3 weeks is required, to ensure the resolution of any attendant LA thrombus that may be present. Alternatively, TOE may be used to exclude the presence of LA thrombus [339]. LA thrombus most commonly forms within the LA appendage, often in the setting of poor LA appendage contractility caused by AF. The stasis caused by this reduced emptying of the appendage may result in spontaneous echocardiographic contrast being visible on TOE. The presence of spontaneous echocardiographic contrast is not a contraindication to cardioversion [340].

It must be stressed that a reassuring TOE documenting the absence of thrombus at the time of cardioversion does not obviate the need for anticoagulation in the post-procedural month, and potentially indefinitely following that, depending on thromboembolic risk factors. Recent data with NOACs indicate the ease, efficacy, and safety of use of these agents for cardioversion [341–343]. The rapid onset of full anticoagulation effect with these agents eliminates the requirement for bridging with heparin or LMWH until a therapeutic INR is achieved in those patients anticoagulated with warfarin.

Although data from RCTs are lacking, it is reasonable for patients with lone AF (without thromboembolic risk factors) and a known arrhythmia onset time within 48 hours prior, to undergo cardioversion without administering 1 month of periprocedural anticoagulation. However, determining the arrhythmia onset time may be difficult and imprecise in all but the youngest and most symptomatic paroxysmal AF patients. Patients with established, ambient AF may develop a sudden onset of symptoms when adrenergic factors lead to a precipitant onset of rapid ventricular response. Where there is any doubt, the periprocedural anticoagulation recommendations outlined above should be followed. See Figure 2 for more information.

6.3.4.7. Anticoagulation for Catheter Ablation Procedures. Recommendation: Uninterrupted oral anticoagulation is recommended for patients undergoing catheter ablation.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: Pulmonary vein isolation is associated with a risk of serious bleeding. Tamponade rates have been reported to be 1.3% internationally, although they are thought to be lower in Australian practice [344]. On the other hand, endocardial ablation constitutes a prothrombotic insult, so relatively high levels of anticoagulation are mandated during the procedure. There has been a shift towards performing ablation on uninterrupted anticoagulant therapy following the randomised Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE-AF) trial (n = 1584), which showed that warfarin discontinuation increased the incidence of periprocedural stroke and minor bleeding when compared with uninterrupted therapy [345].

Subsequently, two RCTs have compared uninterrupted NOAC with uninterrupted warfarin therapy in patients undergoing catheter ablation [346,347]. The small Study Exploring Two Treatment Strategies in Patients with Atrial Fibrillation Who Undergo Catheter Ablation Therapy (VENTURE-AF) (n = 250) compared rivaroxaban (20 mg once daily) against warfarin. It found low event rates in both arms and no difference in the incidence of embolic or ischaemic events between the two groups [347]. The Randomized Evaluation of Dabigatran Etxilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy (RE-CIRCUIT) trial (n = 704) reported significantly fewer bleeding events in patients randomised to dabigatran 150 mg bd than patients receiving warfarin, although again, the absolute number of events was small [346].

Practice advice: In addition to the body of data from RCTs supporting their use, it is recommended that uninterrupted warfarin or dabigatran be used preferentially as the OAC for patients undergoing catheter ablation because agents are available to rapidly reverse the anticoagulant action of both drugs. For patients taking apixaban or rivaroxaban, lack of a reversing agent dissuades many operators from performing the procedure on uninterrupted OAC. One frequently adopted strategy is minimally interrupted OAC (i.e. withhold one or two doses prior to the procedure). Although not evaluated in randomised trials, this practice appears to minimise the risk of bleeding without exposing the patient to prolonged risk of thrombosis [348].

6.3.4.8. Anticoagulation in Patients with Hypertrophic Cardiomyopathy

The mechanistic and clinical differences between the general population and HCM patients preclude the use of stroke risk scores [349]. Given the significantly increased risk of thromboembolic events (incidence of 3.8% annually [194]), anticoagulation is recommended in all HCM patients who develop AF [196,200,350]. Limited data exist for the use of NOACs, but observational studies suggest that their use can be safe and effective in HCM patients with AF [351,352].

6.3.4.9. Anticoagulation in Grown-up Patients with Congenital Heart Disease

GUCH with atrial arrhythmias have a higher risk of atrial thrombo-emboli and should be considered for oral anticoagulation [353]. In patients undergoing cardioversion, in particular cyanotic CHD, a TOE should be considered (see Section 6.3.4.6). There is lack of evidence for the NOACs in this population. Warfarin and LMWH are therefore the mainstay for long-term anticoagulation.

6.3.4.10. Anticoagulation in Athletes

Anticoagulation strategies, although rarely required due the typically low CHA₂DS₂-VA score among healthy athletes, should follow standard guidelines. However, additional consideration may be warranted for athletes participating in high-impact sports, where bleeding risk may be elevated.

6.3.4.11. Anticoagulation in Post-operative Atrial Fibrillation

Postoperative AF occurs in about 3% of patients undergoing non-cardiac surgery [354], and while most revert to sinus rhythm, the

occurrence of AF in this context is associated with an increased risk of stroke both within 30 days and in the long term [355]. In patients for whom AF persists for more than 48 hours, long-term anticoagulation practice should be the same as for those who have not had surgery [356].

Although AF is more common following cardiac surgery, occurring in up to 30% of patients, the majority have reverted to sinus rhythm by 6 weeks. Observational studies have suggested the long-term stroke risk is less than that observed for the N-VAF population, and comparable to patients who undergo CABG without developing AF [357]. This suggests that many of these patients may not require long-term anticoagulation.

6.3.5. Stroke Prevention with Left Atrial Appendage Occlusion and Exclusion

Recommendation: LAA occlusion may be considered for stroke prevention in patients with N-VAF at moderate to high risk of stroke and with contraindications to oral anticoagulation therapy.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

6.3.5.1. Percutaneous Left Atrial Appendage Occlusion.

There have been two randomised trials of percutaneous LAA occlusion compared with warfarin [358,359]. A meta-analysis of these two trials and their respective registries showed no difference in the incidence of stroke or systemic embolism, or in major bleeding between the two groups. There are no randomised trials comparing LAA occlusion to standard therapy in patients with contraindications to anticoagulation. Extrapolation from the RCTs of LAA occlusion compared with warfarin [358,359] have provided indirect evidence that LAA closure improved some clinical outcomes when compared with placebo [360]. These findings indicated that LAA closure reduced cardiovascular or unexpected death and all-cause stroke by a statistically significant amount.

With regards to acute procedural complications of LAA occlusion device implantation, among 1021 patients who were included in the EWOLUTION: Design of a Registry to Evaluate Real-world Clinical Outcomes in Patients with AF and High Stroke Risk-treated with the WATCHMAN Left Atrial Appendage Closure Technology register [361], 3.6% (95% CI: 2.5%–4.9%) of patients experienced a serious procedure or device adverse event within 30 days of the procedure. Event rates were comparable between those ineligible and those eligible for an OAC (2.2% and 3.8%, respectively, p = 0.129). However, a recent European survey detected complication rates considerably higher than this [362].

Resources and other considerations: Economic modelling in the Australian context has suggested that use of the LAA occlusion device in appropriate populations will result in an incremental cost-effectiveness ratio (ICER) of about \$28,000 per QALY, based on a plausible extrapolated incremental survival gain of 10 years or more. This is regarded as acceptably cost effective for the proposed high clinical need population [360].

Practice advice: Percutaneous LAA occlusion should be limited to patients at high risk of stroke in whom anticoagulation is contraindicated, see Figure 6.

6.3.5.2. Surgical Left Atrial Appendage Occlusion.

Recommendation: Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Rationale: A recent meta-analysis that collated the key pieces of evidence from the literature pertaining to LAA occlusion in cardiac surgery reported that the incidence of post-stroke was significantly reduced in the LAA occlusion group compared with the LAA preservation group (1.4% versus 4.1%; odds ratio [OR]: 0.48; 95% CI: 0.24–0.98; $p = 0.04$) [363]. However, a large observational study that followed almost 10,000 patients after having cardiac surgery (CABG or valve repair or replacement) was recently published. It presented results suggesting that LAA closure during routine cardiac surgery did not significantly influence the risk of stroke or long-term mortality [364].

Incomplete LAA occlusion can increase stroke risk; therefore, continued anticoagulation is recommended unless complete occlusion is confirmed, generally by TOE [365].

Practice advice: Various surgical methods can be used to occlude the LAA during cardiac surgery; e.g., sutures, staples, ligation, resection, and LAA clip devices. Any possible differences in safety and efficacy of the different surgical techniques are currently unknown. Therefore, surgeons should perform the LAA occlusion technique with which they have the most experience.

6.3.6. Secondary Stroke Prevention

Recommendation: Early initiation of anticoagulants in the first few days after an ischaemic stroke is not recommended because of the risk of haemorrhage or haemorrhagic transformation of infarction.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: For ischaemic stroke patients, the decision to begin OAC can be delayed for 2 weeks but should be made before discharge.

(GRADE quality of evidence: Very low; GRADE strength of recommendation: Weak.)

Recommendation: Early commencement of anticoagulants may be considered after TIA or in mild stroke where the risk of haemorrhage is determined to be low.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Weak.)

Rationale: For ischaemic stroke and TIA patients with paroxysmal or chronic AF, oral anticoagulation is recommended for long-term secondary prevention.

The large International Stroke Trial (IST) [366] and Chinese Acute Stroke Trial (CAST) [367] studies reported no clinical advantage to early commencement of heparin following ischaemic stroke. A reduction in recurrent ischaemic strokes was offset by increased haemorrhagic stroke, and heparin

was associated with an excess of transfused or fatal extracranial bleeds, especially at higher heparin doses. There was no advantage in death or dependence at 6 months. In a meta-analysis of early parenteral anticoagulants [368], there was non-significant reduction in recurrent stroke in 7–14 days, a significant increase in symptomatic intracranial bleeding, and a similar rate of death or disability compared with other treatments (aspirin or placebo).

The major NOAC trials have specifically delayed randomisation beyond the early post-stroke period. Nonetheless, based on the available data for parenteral drugs, beginning any anticoagulants (e.g., therapeutic heparin, fractionated heparin, warfarin, or NOAC) in the first days after stroke is likely to be associated with a small or insignificant reduction in recurrent stroke and a significant increase in symptomatic haemorrhage.

Practice advice: Care is required if commencement of anticoagulation is delayed to after discharge, to ensure timely follow-up for anticoagulation commencement.

Early commencement of anticoagulants should be considered following a TIA where the lack of tissue evidence of stroke is expected to lower the risk of intracranial bleeding. The Stroke Foundation additionally recommends that anticoagulation be commenced urgently after TIA, at 5–7 days after moderate stroke and at 10–14 days after severe stroke, acknowledging a lack of evidence for these recommendations and that timing of commencement of anticoagulation after stroke is complex and based on the perceived risk balance between haemorrhagic transformation of the infarct and recurrent embolic stroke [83]. The early recommencement of anticoagulants after ischaemic stroke may be guided by estimated risk of stroke recurrence, repeat imaging, and considering the consequences of haemorrhagic conversion in the posterior fossa.

For recommendations regarding screening for AF in patients with embolic stroke of uncertain source, see Section 4.4.3.

7. Integrated Management

Recommendation: An integrated care approach is recommended; such an approach aims to provide patient-centred comprehensive treatment delivered by a multidisciplinary team.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Rationale: The rapidly increasing prevalence of AF has placed a significant burden on healthcare use in Australia, challenging the delivery of health services, and resulting in care that is consequently more fragmented. There is a clear need for more integrated care to support the comprehensive treatment required, and to address the specific needs of people with AF.

Integrated care is defined as a collaborative, patient-centred approach to the provision of healthcare that focuses on improving patients' experiences, health outcomes, and quality of life, while creating efficiencies in the health system. It

requires access to, and coordination of, health services at all levels of care; seamless communication and transitioning of care across settings; effective use of available resources; use of expertise across all health disciplines; support for patient and carer engagement in their care; and application of evidence-based strategies. The goal is to provide effective, efficient, holistic, and comprehensive treatment that is tailored to the individual patient's values and preferences, focusing on those with chronic conditions and multi-morbidities, and recognising the multidimensional needs of this population. In the context of AF, there is a need to particularly focus on three fundamental aspects (see [Figure 9](#)):

- multidisciplinary teams, recognising the important roles of GPs, other medical specialists, nurses, Aboriginal and Torres Strait Islander health practitioners or workers, and allied health professionals;
- patient-centred care with a focus on patient education, self-management, shared decision-making and caregiver involvement;
- application of eHealth to support AF management.

These fundamental aspects drive the comprehensive treatment approach needed in the management of AF, which comprises a range of interventions targeting the arrhythmia itself, as well as risk factors and complications (see [Figure 9](#)). These interventions may be multimodal in nature, involving pharmacotherapy, specific procedures (invasive and non-invasive) and lifestyle strategies, delivered as part of acute or long-term management. Given the dynamic nature of AF, the interventions required in any individual patient may change over time, and therefore a core requirement of integrated care is coordination, including the need for regular review and risk assessment, with clear communication of the treatment goals and care plans to patients, carers, and all members of the healthcare team. Importantly, these must be delivered alongside interventions that support patient adherence to the treatment plan. Furthermore, there is a need to understand the specific and unique challenges of the target AF patient population in Australia, including Aboriginal and Torres Strait Islander peoples (Section [6.3.4.3](#)), those from non-English speaking backgrounds, those from lower socioeconomic groups, those from regional and remote communities, and older or frail patients (Section [6.3.4.2](#)).

To date, several structured and integrated approaches to AF care have been developed [[11](#)]. Integrated AF management in a European RCT increased the use of evidence-based care, and reduced by one-third the composite outcome of cardiovascular hospitalisation and cardiovascular death over a mean follow-up of 22 months (14.3% vs 20.8%; HR: 0.65; 95% CI: 0.45–0.93; $p = 0.017$) compared with usual care in a large tertiary care centre [[369](#)]. Moreover, integrated AF management appeared cost effective in that study [[370](#)]. However, an Australian RCT showed no significant difference in rates of unplanned admissions and death, although patients in the integrated care arm were alive and/or out of hospital for significantly more days [[371](#)]. Integrated AF care is likely to require different designs in different healthcare settings.

In the Australian context, there are existing opportunities and resources to support integrated care, including:

- access to multidisciplinary expertise (e.g., allied health services, nurse practitioners, accredited pharmacists) via Medicare-funded care plan referrals, multidisciplinary case conferences, medication management reviews, and health assessments for Aboriginal and Torres Strait Islander peoples and older persons;
- initiatives to support the adoption of eHealth in general practice (e.g., the Medicare-funded Practice Incentives Program eHealth incentive);
- online systems to facilitate safe, effective, and efficient communication between patients, clinicians, and health practitioners around the care plan and provision of care (e.g., the My Health Record and Healthcare Identifiers systems);
- collaboration with consumer groups and patient advocates for broader patient and community engagement, particularly around health promotion, education, liaison and peer support;
- local evidence-based guidelines to inform best practice;
- access to written and online information and resources for consumers (patients and carers).

7.1. Multidisciplinary Teams

Many of the components of care for individuals with AF require input from multidisciplinary healthcare professionals. A multidisciplinary care team has been defined as “a team comprising diverse health care professionals who communicate regularly about the care of a defined group of patients and participate in that care on a continuing basis” [[372](#)]. Effective team-based chronic illness programs for conditions such as AF often include the following strategies [[373](#)]:

- population-based care, which tries to ensure that effective interventions reach all the patients that need them;
- treatment planning, in which formal written plans help organise the work of teams and patients to navigate the health system;
- evidence-based clinical management;
- self-management support, which emphasises both skills and knowledge, and boosts motivation and confidence;
- more effective consultations, which are structured and have sufficient time allocated;
- sustained follow-up.

Key elements for building effective teams include defined goals; clinical and administrative systems; definitions of tasks and division of labour; education and training; and communication structures and processes [[374](#)].

There is some evidence that integrated and skilled AF healthcare teams may offer efficient methods of optimising care for individuals with AF in the outpatient setting [[369,371,375](#)]. Roles and responsibilities should be defined so that important investigations such as measuring thyroid function are not overlooked, and so that key management decisions (e.g., rate and rhythm control) are clearly

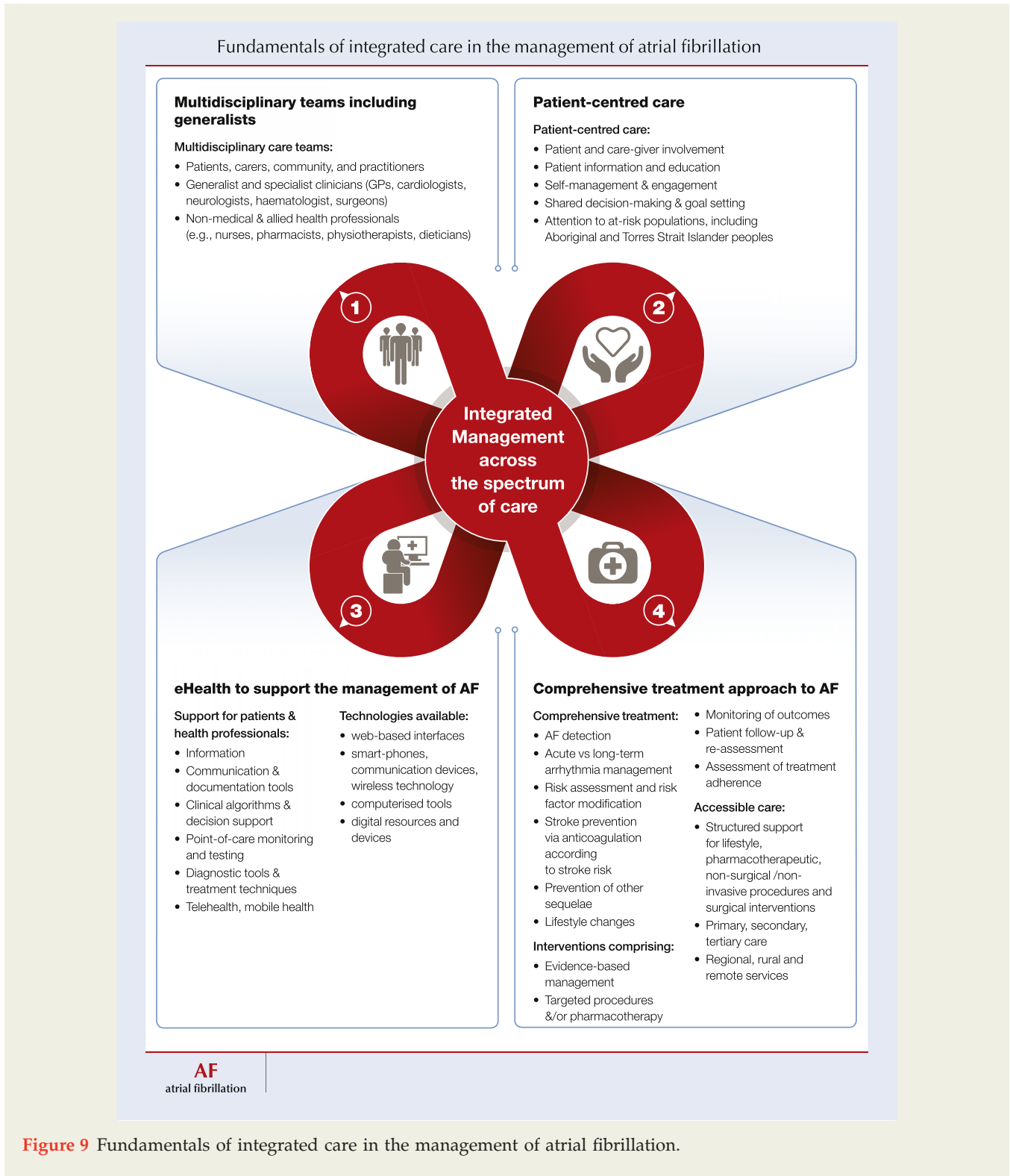


Figure 9 Fundamentals of integrated care in the management of atrial fibrillation.

communicated to the patient, their family and all members of the multidisciplinary team.

Given the high population prevalence of AF and the fact that it most often occurs in the context of multimorbidity, there is a need for widely available generalist health services—in particular, general practice—to have a major role in

the care of AF. General practice has a key role in screening, case finding, diagnosis, and management including medical specialist and allied health referrals and ongoing monitoring and follow-up.

Each health discipline offers a unique lens to optimising care for AF and each of the health disciplines actively

contributes to achieving comprehensive AF treatment. Importantly, each may have a role in leading the healthcare team or in care management in the outpatient setting.

Practice advice: Australia's health system provides some support for access to health services and treatments via the government-funded Medicare program (including the Pharmaceutical Benefits Scheme). Within this, there are increasing opportunities to provide comprehensive, multidisciplinary care tailored to individual AF patients; e.g., under the Chronic Disease GP Management Plans and Team Care Arrangements. Aboriginal and Torres Strait Islander patients require multidisciplinary care, which may need to be delivered outside the GP practice model, involving Aboriginal health workers, cardiac nurse coordinators, primary care practitioners, and family members all working together with specialists. Careful consideration and explanation is essential for optimal management, especially in remote areas.

7.2. Patient-centred Care

Recommendation: Targeted patient education is recommended throughout the continuum of AF management.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Recommendation: Shared decision-making should consider patients' beliefs, values, and preferences, with a goal of empowering patients to undertake self-management.

(GRADE quality of evidence: Moderate; GRADE strength of recommendation: Strong.)

Recommendation: Treatment goals should be developed in partnership with patients, and communicated with all members of the multidisciplinary team.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: A fundamental aspect of integrated care is to organise the care following a patient-centred approach. This includes active patient involvement and engagement in their care process, as well as comprehensive education to prepare patients for informed and shared decision-making and self-management of their condition. Care should be responsive to the preferences, values, and beliefs of the individual patient as well as based on the best available evidence [376]. An explanation of the patient's role and vital contribution to the care process may result in improved responsibility and the patient taking ownership and self-managing the condition [377].

To prepare patients to take on such roles, it is important to continuously provide education and instruction on the condition, symptoms, therapy and possible complications, and when to contact healthcare services in case of worsening symptoms or an emergency situation [378]. Autonomous and empowered patients are likely to participate in decision-making, which potentially improves the uptake of the therapy, on the basis of shared accountability [379]. However, educational background and cultural diversity should always be taken into account because these factors may influence this process significantly.

Practice advice: Besides a central role for patients, it is recommended to involve family and informal caregivers in

order to support patients in their self-management. For Aboriginal and Torres Strait Islander peoples, a patient-centred approach particularly requires cultural awareness, sensitivity, and safety, alongside engagement of family members and the wider community, to build respectful and sustained partnerships in care.

The role of community groups and patient advocates is important to ensuring patient involvement, particularly in terms of increasing public awareness about AF (including existing health services and resources), and engaging with policymakers to ensure that patients have access to treatments and services.

7.3. eHealth to Support Atrial Fibrillation Management

Recommendation: eHealth tools and resources should be used by patients and health professionals, to support the integrated management of AF.

(GRADE quality of evidence: High; GRADE strength of recommendation: Strong.)

Rationale: The term 'eHealth' refers to the use of electronic media (e.g., web-based interfaces) or other technology (e.g., computerised tools and digital resources) to support the provision of care to an individual.

eHealth can be used across all stages of the disease-management pathway, from screening and diagnosis, to decision-making around treatment selection, to ongoing therapeutic monitoring and management [380,381]. Furthermore, eHealth has enabled components of AF care to be offered in a wide range of practice settings, including community pharmacies, nurse-led clinics, and home-based services. In Australia, this technology may also support the implementation of outreach and telehealth services, providing access to care in regional settings and where many Aboriginal and Torres Strait Islander peoples reside.

Overall, the results from initial and pilot studies are encouraging in terms of increasing the detection of AF cases through mobile ECG devices [63,382–385]; optimising the use of antithrombotic therapy for stroke prevention in AF via computerised decision support [386–388]; improving the time in therapeutic range for patients using warfarin via point-of-care monitoring of anticoagulation; increasing adherence to cardiovascular pharmacotherapy via smartphone text messaging [389–391]; and increasing access to information for patients and their carers [392–395].

Practice advice: Given the cultural diversity in Australia, it is an issue that many eHealth interventions currently provide information and instructions only in English. Furthermore, since most AF patients are older adults, health professionals must first gauge their digital literacy before delivering eHealth interventions. Health professionals are also responsible for ensuring that they refer their patients to appropriate web-based resources [396] and smartphone applications [397], so that poor-quality or imbalanced information from potentially biased sources does not undermine patients' engagement in shared decision-making and adherence to medicines.

7.4. Medication Adherence and Persistence to Atrial Fibrillation Pharmacotherapy

Recommendation: All patients prescribed pharmacotherapy for the management of AF, including core rhythm control and anticoagulation therapies, should have their treatment adherence and persistence regularly monitored and supported using accessible and patient-centred strategies.

(GRADE quality of evidence: Low; GRADE strength of recommendation: Strong.)

Rationale: Following an increased focus on the management of AF, the use of specific pharmacotherapies appears to have increased in Australia. This is particularly true for the use of antithrombotics, following the availability of NOACs—and their cost-subsidisation under the Pharmaceutical Benefits Scheme—as alternatives to warfarin [398].

Although access to treatment options has assisted the initial decision to prescribe therapy, optimal treatment outcomes depend heavily on a patient's **adherence** (i.e. the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen [399]) and **persistence** (i.e. the duration of time from initiation to discontinuation of therapy [399]) with it. Poorer adherence and/or persistence to anticoagulant therapy (whether warfarin or NOAC) is associated with worse clinical outcomes [400], especially in those at higher risk of stroke (i.e. CHA₂DS₂-VASc score ≥ 2) [401]. Adherence to warfarin is reported to range from 32.3% [402] (using the medication possession ratio) to 67.7% [403], with persistence ranging from 44.8% [404] to 77.2% [405]. Data on adherence to NOACs are limited, but similar variations in adherence and persistence are reported [406,407]. The literature consistently reports that long-term persistence to any of the anticoagulants tends to decrease over time, which is of most concern in this population where the risk of stroke is likely to increase over time. Real-world persistence is lower than reported in clinical trials, with only a small proportion of discontinuations explained through switching to alternative anticoagulants [406]. Approximately one-third to half of patients discontinue therapy within 2–2.5 years of initiation [406,408]; 15% of patients fail to even collect their first repeat prescription for therapy [409]. Patients' perspectives must be incorporated into the decision-making process for anticoagulant selection to obtain optimum adherence and persistence [410].

Among the broader non-AF literature, meta-analyses have shown that medication adherence interventions can lead to significant, albeit modest, improvements in patient-centred outcomes. Medicines self-monitoring and self-management programs appear to be generally effective but may not be suitable for all patients. Interventions such as simplification of dosing regimens and interventions, pharmacist-led medicines management, care plans, and structured follow-up have also been shown to be beneficial. Unfortunately, the most effective interventions are usually complex (comprising

tailored ongoing support, cognitive behavioural therapy, motivational interviewing, education, or daily treatment support; which are delivered face-to-face, often via pharmacists) and may be difficult to implement in real-world practice [411]. More recent findings show the benefits of focusing on interventions on behavioural strategies (e.g., habit-based interventions), in preference to cognitive strategies targeting knowledge and beliefs [412]. Additionally, attention to the use of decision aids is needed, given that people exposed to decision aids tend to feel more knowledgeable, better informed, and clearer about preferences, translating to a more active role in decision-making, which is likely to promote treatment adherence [413].

Studies evaluating interventions to specifically improve adherence or persistence to AF pharmacotherapy are limited. Recent studies focus on improving adherence to anticoagulants via the use of electronic applications (see Section 7.3) (one study with additional pharmacist-led patient education), with mixed results. Earlier studies focused on educational and behavioural interventions, but did not generate enough evidence to determine their impact [414]. No recent studies have focused on promoting adherence to antiarrhythmic therapies.

There are training resources available to support health professionals in effectively and efficiently improving medication adherence [415]. A range of additional Australian resources may be obtained from the NHFA, the National Stroke Foundation, and the National Prescribing Service (NPS) MedicineWise.

In addition, many community pharmacies in Australia are accredited to provide appropriate support services, as funded under the Sixth Community Pharmacy Agreement between the Australian Government and the Pharmacy Guild of Australia:

- Home Medicines Review and Residential Medication Management Review;
- MedsCheck;
- Dose Administration Aid (DAA) service delivery;
- QUMAX (Quality use of medicines maximised for Aboriginal and Torres Strait Islander peoples).

8. Quality Indicators and Research Priorities

8.1. Quality Indicators

The development of quality indicators facilitates the monitoring of quality of care, which in turn accelerates the translation of evidence into practice. In Australia, the use of these measures is in its infancy in cardiovascular disease. A clinical care standard for ACS has been developed by the Australian Commission on Safety and Quality in Health Care, and is accompanied by suggested quality indicators to facilitate audit of adherence with this standard [416]. To date, no standard or indicators have been developed for AF in Australia. It is envisaged that these ACS indicators serve

as suggestions for those healthcare services and practices that wish to monitor the care of their patients with AF.

The development of these indicators followed two principles: adherence with each measure should improve care for patients with AF, and information on adherence with each measure can be readily obtained from the clinical record. The suggested quality indicators for AF (listed below) were generated following review of the recommendations in these guidelines and informed by those used internationally [417]. Further research is required to evaluate the impact of quality indicators in AF on patient outcomes. One Japanese study showed that adherence with United States defined performance measures derived from indicators was associated with improved quality of life in patients with AF [418]. Measures are divided into those to be used by hospitals and outpatient services treating patients with a new diagnosis of AF, and those to be used by those clinicians managing patients with chronic AF in the outpatient setting.

Suggested quality indicators for investigation and management of patients with a new diagnosis of AF are:

- echocardiogram performed;
- rate versus rhythm strategy documented;
- CHA₂DS₂-VA score documented;
- prescription of anticoagulation for patients with a CHA₂DS₂-VA score of more than 1;
- documented discussion and shared decision-making in patients with a CHA₂DS₂-VA score of more than 1 who are not anticoagulated.

Suggested quality indicators for the management of patients with chronic AF are:

- CHA₂DS₂-VA score is documented annually for low-risk patients who are not anticoagulated;
- monthly INR monitoring for patients on warfarin.

8.2. Research Priorities

Certain areas have been identified as priorities for future research in AF, either because they are felt to be important to augment the quality of evidence guiding existing recommendations, or because they will guide future recommendations. Some of these studies have been initiated and their results are anticipated at the time of writing. The areas are:

- further studies to understand the stroke risk of brief durations of AF detected following screening of asymptomatic patients;
- comparison of percutaneous catheter AF ablation and AAD on the outcomes of death, stroke, or systemic embolism in patients without heart failure;
- trials of anticoagulation compared with no anticoagulation in patients with implanted atrial sensing devices and AHREs of less than 24 hours (e.g., 5–24 hours);
- comparison of single antiplatelet therapy versus DAPT in anticoagulated AF patients with ACS and/or stenting powered for ischaemic outcomes of stroke, myocardial infarction, or cardiac death;

- studies of surgical LAA occlusion compared with no occlusion in patients with AF undergoing CABG powered for the outcomes of stroke and death;
- studies to address the predictive value of the CHA₂DS₂-VA score in Aboriginal and Torres Strait Islander patients;
- barriers to anticoagulation in Aboriginal and Torres Strait Islander patients;
- trials of anticoagulation in AF patients with severe CKD.

9. Disclaimer

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- The AF writing group would like to specifically acknowledge Associate Professor Huyen Tran MBBS (Hons) Master Clin Epi FRACP FRCPA.

11. Appendices

11.1. Appendix 1–Atrial Fibrillation Guideline 2017–2018: Prioritised Clinical Questions for External Literature Review

1. Do patients with CHA₂DS₂-VASc 1 benefit from long-term anticoagulation?
2. Does the addition of biomarkers (troponin, BNP, cystatin C, D-dimer, CRP and interleukin 6) to CHA₂DS₂-VASc improve the predictive ability of the score?
3. Does point-of-care INR measurement improve outcomes in Australian patients with atrial fibrillation receiving warfarin?
4. What is the persistence to risk factor control and what interventions have been shown to improve this?
5. What is the persistence and adherence to atrial fibrillation drugs (rhythm control and anticoagulants) and what interventions have been shown to improve this?

BNP, B-type natriuretic peptide; CRP, C-reactive protein; INR, international normalised ratio.

11.2. Appendix 2–Abbreviations and Acronyms

AAD	Antiarrhythmic drug
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHRE	Atrial high-rate episode
APTT	Activated partial thromboplastin time
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial
ARTESiA	Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-detected sub-clinical Atrial Fibrillation trial
AUGUSTUS trial	Apixaban Versus Vitamin K Antagonist in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention
AV	Atrioventricular
AVR	Aortic valve replacement
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BRIDGE	Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery trial
CAA	Cerebral amyloid angiopathy

CABANA	Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation
CABG	Coronary artery bypass graft
CAST	Chinese Acute Stroke Trial
CHD	Congenital heart disease
CI	Confidence interval
CIED	Cardiac implanted electrical device
CKD	Chronic kidney disease
COMPARE-AF	Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation
CPAP	Continuous positive airway pressure
CrCl	Creatinine clearance
CRYSTAL AF	Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke study
CSANZ	Cardiac Society of Australia and New Zealand
CTI	Cavotricuspid isthmus
DAPT	Dual antiplatelet therapy
EAST-AFNET-4	Early Treatment of Atrial Fibrillation for Stroke Prevention Trial, Atrial Fibrillation Network trial
ECG	Electrocardiogram
EGM	Atrial electrocardiogram
ESUS	Embollic stroke of uncertain source
EWOLUTION	Design of a Registry to Evaluate Real-world Clinical Outcomes in Patients with AF and High Stroke Risk-treated with the WATCHMAN Left Atrial Appendage Closure Technology register
FEIBA	Factor eight inhibitor bypassing activity
GI	Gastrointestinal
GIT	Gastrointestinal tract
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUCH	Grown-up patients with congenital heart disease
HCM	Hypertrophic cardiomyopathy
HR	Hazard ratio
ICH	Intracranial haemorrhage
ICM	Implanted cardiac monitor
INR	International normalised ratio
IST	International Stroke Trial
LA	Left atrial
LAA	Left atrial appendage
LMWH	Low molecular weight heparin
LQTS	Long QT syndrome
LV	Left ventricle
LVOT	Left ventricular outflow tract
MRI	Magnetic resonance imaging
NAVIGATE ESUS	Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source
NHFA	National Heart Foundation of Australia

NOAC	Non-vitamin K oral anticoagulant
NOAH-AFNET 6	Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes trial
N-VAF	Non-valvular atrial fibrillation
OAC	Oral anticoagulant
OR	Odds ratio
PCC	Prothrombin complex concentrate
PIONEER AF-PCI	Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention trial
PT	Prothrombin time
QALY	Quality-adjusted life year
RACE	Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation trial
RACE II	Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II trial
RCT	Randomised clinical trial
RE-CIRCUIT	Randomized Evaluation of Dabigatran Etexilate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy trial
RE-DUAL PCI	Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran Versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RE-VERSE AD	Reversal Effects of Idarucizumab on Active Dabigatran study
ROCKET AF	Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SAPT	Single antiplatelet therapy
THANZ	Thrombosis & Haemostasis Society of Australia and New Zealand
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiography
TSH	Thyroid stimulating hormone
TT	Thromboplastin time
UFH	Unfractionated heparin
WOEST	What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting trial
VENTURE-AF	Study Exploring Two Treatment Strategies in Patients with Atrial Fibrillation Who Undergo Catheter Ablation Therapy

11.3. Appendix 3—Online Register of Conflicts of Interest

Available at: <https://www.heartfoundation.org.au/for-professionals/clinical-information/atrial-fibrillation>

11.4. Appendix 4—Endorsing Organisations

The following organisations have endorsed these guidelines:



**Australian
College of
Nursing**



Australian College of
Rural & Remote Medicine
WORLD LEADERS IN RURAL PRACTICE

AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

CRANAplus
improving
remote health



Stroke
FOUNDATION

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