



ATRIAL FIBRILLATION 2012



MINISTRY OF HEALTH
MALAYSIA



CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

STATEMENT OF INTENT

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

This guideline was issued in 2011 and will be reviewed in 2016 or sooner if new evidence becomes available

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Electronic version available on the following website:

<http://www.malaysianheart.org>

<http://www.moh.gov.my>

<http://www.acadmed.org.my>

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION



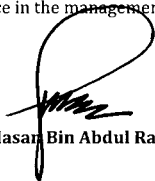
Foreword By The Director General Of Health Malaysia

Atrial fibrillation (AF) as the most common sustained cardiac arrhythmia is associated with an increased morbidity and mortality. AF has a slightly lower incidence and prevalence in Asian populations than in western populations, but the associated relative risk of stroke and mortality is similar. As such, AF has become accepted as a common and rapidly growing clinical problem and disease entity.

It is therefore timely that this Clinical Practice Guideline (CPG) for Atrial Fibrillation has been developed. This CPG was developed as a collaborative effort between the National Heart Association of Malaysia, Academy of Medicine Malaysia and the Ministry of Health Malaysia.

It incorporates a wealth of evidence, recommendations and information on the management of AF in order to aid clinicians address some important clinical issues encountered in their practice. I hope that this CPG will be able to address the unmet clinical needs in the prevention and treatment of AF, as well as promote the optimum management of patients with AF. However, the publication of this CPG alone will be insufficient to achieve success in the management of patients with AF unless there is clear commitment from the medical fraternity to ensure its implementation. It is hoped that this CPG will be used by all who manage AF.

I would like to commend the expert panel who took the time and effort to produce this CPG, which will enable health care practitioners translate knowledge into routine clinical practice in the management of AF.

A handwritten signature in black ink, consisting of a large, stylized initial 'H' followed by several smaller, cursive letters.

Dato' Sri Dr Hasan Bin Abdul Rahman

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

FOREWORD BY PRESIDENT OF NATIONAL HEART ASSOCIATION OF MALAYSIA (NHAM)

THE PUBLICATION of the Clinical Practice Guidelines for Atrial Fibrillation marked a milestone in the evolution of clinical practice guidelines and the delivery of care in cardiology. Specifically, these guidelines assist physicians in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of AF. **Clinical Issues eg: AF assessment, best treatment strategy for acute AF & reduce risk of adverse outcomes from AF, best long term treatment strategy, management of AF in specific special groups have been addressed in the CPG.**

In a broader sense, these guidelines emphasized that AF is a worldwide public health problem with increasing incidence and prevalence, high cost, and poor outcomes. Importantly, this AF CPG has provided the framework for a public health approach to improve the quality of care and outcomes of all individuals with AF. This is a major paradigm shift from the focus on AF treatment and care that has dominated the practice to **IMPORTANT STRATEGIES eg: risk stratification, appropriate antithrombotic therapy, safety consideration of antiarrhythmic agents emphasized in rhythm strategy.**

This latest version has undergone extensive revision in response to comments during the public review. While considerable effort has gone into their preparation over the past 2 years, and every attention has been paid to their detail and scientific rigor, no set of guidelines, no matter how well developed, achieves its purpose unless it is implemented and translated into clinical practice. Implementation is an integral component of the process and accounts for the success of the guidelines. The Work Group is now developing implementation tools essential to the success of this AF CPG.

In a voluntary and multidisciplinary undertaking of this magnitude, many individuals make contributions to the final product now in your hands. It is impossible to acknowledge them individually here, but to each and every one of them we extend our sincerest appreciation, especially to the members of the Writing Panel, an effort subsequently reinforced by the review of these final guidelines by the external reviewers. Thank you one and all for Making Lives Better for patients with AF throughout Malaysia. A special debt of gratitude is due to the members of the Work Group, their chair, Dr Ahmad Nizar. It is their commitment and dedication that has made it all possible.

Professor Dr. Sim Kui Hian *FNHAM*
NHAM President

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ABOUT THE GUIDELINE

GUIDELINE DEVELOPMENT PROCESS

This is the first Clinical Practice Guideline (CPG) for Atrial Fibrillation (AF). A committee was appointed by the National Heart Association of Malaysia (NHAM), Ministry of Health (MOH) and the Academy of Medicine Malaysia (AMM) to draw up this CPG. It comprises of sixteen members including cardiologists, a neurologist, a haematologist, a cardiac surgeon, an obstetrician, a gynaecologist, general physicians, an intensivist, a family medicine specialist and an emergency medicine specialist from the government, private sector and the public universities.

Objectives

This CPG is intended to assist health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of AF.

Rigour of Development

Evidence was obtained by systematic review of current medical literature on Atrial Fibrillation using the usual search engines – Guidelines International Network (G-I-N), Pubmed/Medline, Cochrane Database of Systemic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE), Journal full text via OVID search engine, International Health Technology Assessment websites (refer to Appendix A for Search Terms). In addition, the reference lists of all retrieved articles were searched to identify relevant studies. Search was limited to literature published in English. All searches were officially conducted between 15 January 2010 and 10 December 2011. We suggest that future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG secretariat.

Reference was also made to other guidelines on Atrial Fibrillation, Guidelines for the Management of Atrial Fibrillation published by The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) 2010, The National Institute for Health and Clinical Excellence Atrial Fibrillation Guideline 2006, Evidence-based Best Practice Guideline of New Zealand on Atrial Fibrillation 2005 and the ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation 2006 were also studied. These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior being used as references.

Forty-three clinical questions were developed and divided into eight major sections and members of the development panel were assigned individual questions within these subtopics (refer to Appendix B for Clinical Questions). The group members met a total 18 times throughout the development of the guideline. All retrieved literature were appraised by at least two members and subsequently presented for discussion during development group meetings.

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All statements and recommendations formulated were agreed collectively by members of the Development Panel. Where the evidence was insufficient the recommendations were derived by consensus of the Panel. These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

On completion, the draft guidelines was sent for review by external reviewers. It was posted on the Ministry of Health of Malaysia official website for comment and feedback from any interested parties. These guidelines had also been presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council, Ministry of Health of Malaysia for review and approval.

The level of recommendation and the grading of evidence used in this guideline were adapted from the American Heart Association and the European Society of Cardiology (AHA/ESC) and outlined on page xi. In the text, this is written in black and boxed on the left hand margin.

Sources of Funding

Sanofi Aventis (M) Sdn. Bhd. supported the development of the CPG on Management of Atrial Fibrillation financially. However, the views of the funding body have not influenced the content of the guideline.

Disclosure statement

The development panel members had completed disclosure forms. None held shares in pharmaceutical firms or acted as consultants to such firms. (Details are available upon request from the CPG Secretariat)

Clinical Issues Addressed

1. How do you assess a patient suspected of having atrial fibrillation?
2. What is the best strategy to treat patients with atrial fibrillation in the acute setting?
3. What is the best strategy to reduce the risk of adverse outcomes from atrial fibrillation?
4. What is the best long-term management strategy?
5. How to manage atrial fibrillation in specific special groups?

Target Group

This CPG is directed at all healthcare providers treating patients with AF – allied professionals, family and general physicians, medical officers, emergency physicians, intensivists and cardiologists.

Target Population

It is developed to assist clinical decision making for all adults and pregnant women with AF.

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Period of Validity of the Guidelines

This guideline needs to be revised at least every 5 years to keep abreast with recent developments and knowledge.

Implementation of the Guidelines

To ensure successful implementation of this CPG we suggest:

1. Constant checks and feedback on whether the guideline is relevant.
2. Identify implementation leaders

Identification of multiple leaders to share the implementation work and ensure seamless care. These leaders are likely to be prominent figures who will champion the guideline and inspire others.

3. Identify an implementation group

Support from medical associations such as the Private Medical Practitioners Society (PMPS), Society of Pacing and Electrophysiology (SOPACE) and Malaysian Medical Association (MMA) will help dissemination of the guidelines.

4. Carrying out a baseline assessment

This involves comparing current practice with the recommendations. The audit criteria will help this baseline assessment.

5. Developing an action plan

The baseline assessment will have identified which recommendations are not currently being carried out. These recommendations could be put into an action plan.

6. Key areas for implementation

We have identified several goals for implementation based on the key priorities for implementation identified in the guideline

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

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CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

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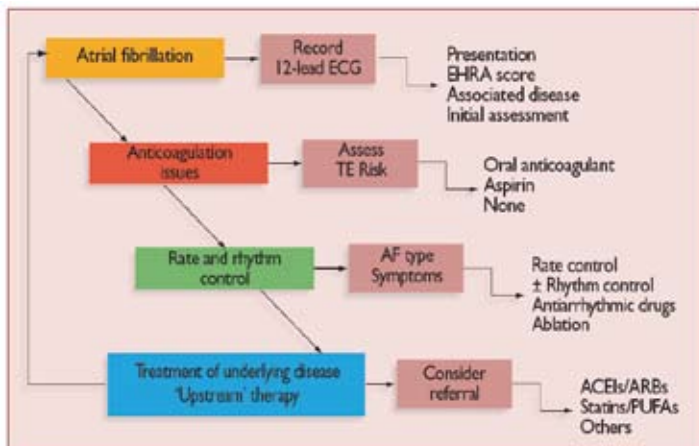
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SUMMARY

KEY MESSAGES

- 1 An electrocardiogram (ECG) should be performed in all patients, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected.
- 2 The stroke risk stratification algorithms, CHADS₂ and CHA₂DS₂-VASc, should be used in patients with AF to assess their risk of stroke and thrombo-embolism, while the HAS-BLED score should be used to assess their risk of bleeding.
- 3 Antithrombotic therapy should be based upon the absolute risks of stroke/ thrombo-embolism and bleeding, and the relative risk and benefit for a given patient.
- 4 When choosing either an initial rate-control or rhythm-control strategy, the indications for each option should not be regarded as mutually exclusive and the potential advantages and disadvantages of each strategy should be explained to patients before agreeing which to adopt. Any comorbidities that might indicate one approach rather than the other should be taken into account. Irrespective of whether a rate-control or a rhythm-control strategy is adopted in patients with persistent or paroxysmal AF, appropriate antithrombotic therapy should be used.
- 5 When choosing an antiarrhythmic agent for rhythm control strategy, safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic agent.
- 6 In patients with permanent AF, who need treatment for rate control, beta-blockers or rate-limiting calcium antagonists should be the preferred initial monotherapy in all patients while digoxin should only be considered as monotherapy in predominantly sedentary patients.

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The management cascade for patients with AF. ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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Grading System

The format used for Classification of Recommendations and Level of Evidence was adapted from the American Heart Association and the European Society of Cardiology.

GRADES OF RECOMMENDATIONS AND LEVELS OF EVIDENCE

GRADES OF RECOMMENDATION	
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective.
II	Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure/therapy.
II-a	Weight of evidence/opinion is in favor of its usefulness/efficacy.
II-b	Usefulness/efficacy is less well established by evidence/opinion
III	Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.
LEVELS OF EVIDENCE	
A	Data derived from multiple randomised clinical trials or meta analyses
B	Data derived from a single randomised clinical trial or large non randomised studies
C	Only consensus of opinions of experts, case studies or standard of care

Adapted from the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC)

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1 INTRODUCTION

1.1 DEFINITION

Atrial fibrillation (AF) is an atrial tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. The surface ECG is characterized by 'absolutely' irregular RR intervals and the absence of any distinct P waves. The P waves are replaced by fibrillary (F) waves.

Atrial Flutter (AFI) in the typical form is characterized by a saw-tooth pattern of regular atrial activation called flutter (F) waves on the ECG. AFI commonly occurs with 2:1 AV block, resulting in a regular or irregular ventricular rate of 120 to 160 beats per minute (most characteristically about 150 beats per minute).

1.2 TYPES OF ATRIAL FIBRILLATION

Clinically, five types of AF are recognized based on the presentation and the duration of the episode. These categories are set out below. (See Table 1 and Figure 2)

Table 1. Classification of AF subtypes

Terminology	Clinical Features	Pattern
Initial event (first detected episode)	Symptomatic Asymptomatic Onset unknown	May or may not recur
Paroxysmal	Spontaneous termination <7 days and most often < 48 hours	Recurrent
Persistent	Not self terminating Lasting >7 days or requiring cardioversion for termination	Recurrent
Long standing persistent	AF that has lasted for ≥ 1 year when it is decided to adopt a rhythm control strategy	Recurrent
Permanent	Not terminated Terminated but relapsed No cardioversion attempt	Established

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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The term 'lone AF' applies to young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension. These patients have a favourable prognosis with respect to thromboembolism and mortality.

'Silent AF' being asymptomatic is detected by an opportunistic ECG or may present as an AF-related complication such as ischemic stroke.

This classification is useful for clinical management of AF patients (Figure 1), especially when AF-related symptoms are also considered.

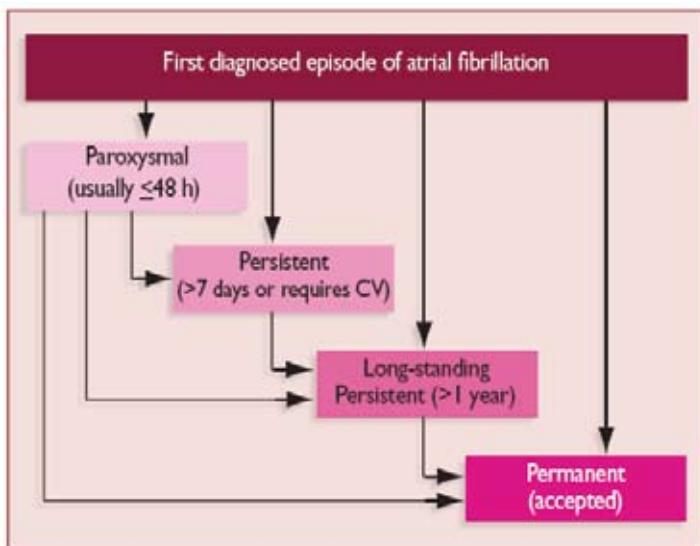


Figure 1: Different types of AF. AF = atrial fibrillation; CV = cardioversion. The arrhythmia tends to progress from paroxysmal (self-terminating, usually ≤48 h) to persistent [non-self-terminating or requiring cardioversion (CV)], long-standing persistent (lasting longer than 1 year) and eventually to permanent (accepted) AF. First-onset AF may be the first of recurrent attacks or already be deemed permanent.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

1.3 AF NATURAL TIME COURSE

AF is a naturally progressive disease except for a small proportion of patients (2-3%), who are free of AF-promoting conditions (see section 2.1.1, page 5), may remain in paroxysmal AF over several decades.¹ AF progresses from short rare episodes, to longer and more frequent attacks (See Figure 2). With time, often years, many patients will develop sustained forms of AF. Paroxysm of AF episodes also occurs in cluster and "AF burden" can vary markedly over months or years.²

Asymptomatic AF is common even in symptomatic patients, irrespective of whether the initial presentation was persistent or paroxysmal. This has important implications for strategies aimed at preventing AF-related complications.

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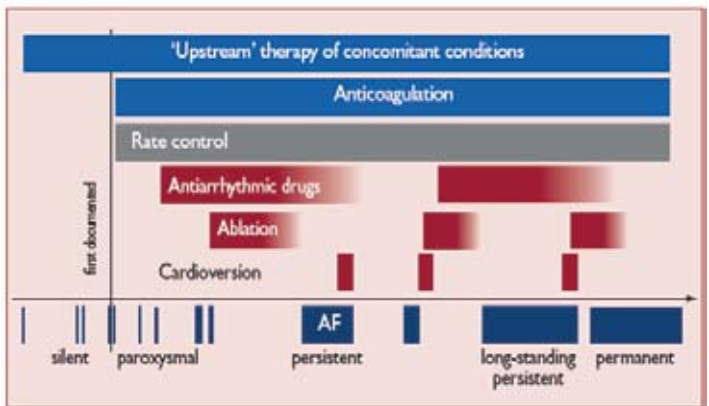


Figure 2 : 'Natural' time course of AF. AF = atrial fibrillation. The dark blue boxes show a typical sequence of periods in AF against a background of sinus rhythm, and illustrate the progression of AF from silent and undiagnosed to paroxysmal and chronic forms, at times symptomatic. The upper bars indicate therapeutic measures that could be pursued. Light blue boxes indicate therapies that have proven effects on 'hard outcomes' in AF, such as stroke or acute heart failure. Red boxes indicate therapies that are currently used for symptom relief, but may in the future contribute to reduction of AF-related complications. Rate control (grey box) is valuable for symptom relief and may improve cardiovascular outcomes.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

1.4 EPIDEMIOLOGY AND PROGNOSIS

AF is the commonest sustained cardiac arrhythmia. Information on AF in Malaysia is scarce. Hospital practice data may give a biased view of the clinical epidemiology of AF, since only one-third of patients with AF may actually have been admitted to hospital.

Data from predominantly western populations suggest the estimated prevalence of AF is 0.4% to 1% in the general population. The prevalence of AF doubles with each decade of age, from 0.5% at age 50-59 years to almost 9% at age 80-89 years.³⁻⁴

The mortality rate of patients with AF is about double that of patients in sinus rhythm.^{2,5}

AF is associated with a prothrombotic state, intra-atrial stasis, structural heart disease or blood vessel abnormalities and abnormal platelets haemostasis, leading to a predisposition to thrombus formation. This prothrombotic state leads to stroke and thromboembolism in AF (See Table 1, Page 1). Only antithrombotic therapy has been shown to reduce AF-related deaths.⁶

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Table 2: Clinical events (outcomes) affected by AF

Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke.
3. Hospitalizations	Hospitalizations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercise capacity	Wide variation, from no effect to major reduction. AF can cause marked distress through palpitations and other AF-related symptoms.
5. Left ventricular function	Wide variation, from no change to tachycardiomyopathy with acute heart failure.

AF = atrial fibrillation.

Outcomes are listed in hierarchical order modified from a suggestion put forward in a recent consensus document.² The prevention of these outcomes is the main therapeutic goal in AF patients.

Stroke in AF is often severe and results in long-term disability or death. Approximately 20% of stroke is due to AF and undiagnosed 'silent AF' is a likely cause of some 'cryptogenic' strokes.^{2,7} Paroxysmal AF carries the same stroke risk as permanent or persistent AF.⁸

AF also account for one-third of all admissions for cardiac arrhythmias. Acute Coronary Syndrome (ACS), aggravation of heart failure, thrombo-embolic complications, and acute arrhythmia management are the main causes.

Quality of life and exercise capacity are degraded in patients with AF.⁹ This may be related to impaired left ventricular (LV) function that accompanies the irregular, fast ventricular rate, loss of atrial contractile function and increased end-diastolic LV filling pressure.

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2. PATHOPHYSIOLOGY

Understanding the pathophysiology of atrial fibrillation (AF) requires integration of information from clinical, histological, electrophysiological and echocardiographic sources. There is no single cause or mechanism that results in AF, and it may present in a multitude of ways.

2.1 CLINICAL ASPECTS

There are many risk factors for developing AF. In the Framingham study the development of AF was associated with increasing age, diabetes, hypertension and valve disease. It is also commonly associated with, and complicated by HF and strokes.

2.1.1 CAUSES AND ASSOCIATED CONDITIONS

AF is often associated with co-existing medical conditions. The underlying conditions and factors predisposing patients to AF are listed in Table 3.

Table 3: Common cardiac and non-cardiac risk factors of AF.

Elevated Atrial Pressure
Systemic Hypertension
Pulmonary Hypertension
Myocardial disease (cardiomyopathy with systolic and/or diastolic dysfunction)
Mitral or tricuspid valve disease
Aortic or pulmonary valve disease
Intracardiac tumours
Sleep apnoea
Atrial ischemia
Coronary artery disease
Inflammatory or infiltrative atrial disease
Myocarditis or pericarditis
Amyloidosis
Age-induced atrial fibrosis
Primary or metastatic cancer in/or adjacent to the atrial wall
Drugs
Alcohol
Caffeine
Endocrine disorders
Hyperthyroidism
Phaeochromocytoma
Changes in autonomic tone
Increased sympathetic tone
Increased parasympathetic tone
Postoperative
Cardiothoracic surgery
Oesophageal surgery
Neurogenic
Subarchnoid haemorrhage
Haemorrhagic stroke
Ischemic stroke
Idiopathic
Lone AF
Familial AF
Other
Congenital heart disease
Chronic renal disease
Obesity

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Some of the conditions predisposing to AF may be reversible such as acute infections, alcohol excess, surgery, pericarditis, myocarditis, pulmonary pathology and thyrotoxicosis. Therefore, long-term therapy of AF may not be indicated once the reversible causes have been addressed. When AF is associated with other supraventricular arrhythmias, treatment of the primary arrhythmia reduces or eliminates the recurrence of AF.

Approximately 30 – 40% of cases of paroxysmal AF and 20 – 25% of persistent AF occur in young patients without demonstrable underlying disease. These cases are often referred to as 'lone AF'.

3 INITIAL MANAGEMENT

3.1 CLINICAL HISTORY, PHYSICAL EXAMINATION AND INVESTIGATIONS

The acute management of AF patients should concentrate on

- Relief of symptoms

- Assessment of AF-associated risk

- Determination of the European Heart Rhythm Association (EHRA) score (Table 5, page 7)

- Estimation of stroke risk (see Section 6.1, page 26)

- Search for conditions that predispose to AF (see Section 2.1.1, page 5) and

- Search for complications of the arrhythmia (see Section 1.4, page 3)

With the above in mind, a thorough medical history should be obtained from the patient with suspected or known AF (see Table 4).

Table 4: Relevant questions to be put to a patient with suspected or known AF

Does the heart rhythm during the episode feel regular or irregular?
Is there any precipitating factor such as exercise, emotion, or alcohol intake?
Are symptoms during the episodes moderate or severe—the severity may be expressed using the EHRA score , ³ which is similar to the CCS-SAF score. ⁴¹
Are the episodes frequent or infrequent, and are they long or short lasting?
Is there a history of concomitant disease such as hypertension, coronary heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, stroke, diabetes, or chronic pulmonary disease?
Is there an alcohol abuse habit?
Is there a family history of AF?

AF = atrial fibrillation; CCS-SAF = Canadian Cardiovascular Society Severity in Atrial Fibrillation; EHRA = European Heart Rhythm Association.

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The EHRA symptom score (see Table 5) provides a simple clinical tool for assessing symptoms during AF. The score only considers symptoms that are attributable to AF and reverse or reduce upon restoration of sinus rhythm or with effective rate control.

Table 5 : EHRA score of AF-related symptoms

Classification of AF-related symptoms (EHRA score)	
EHRA class	Explanation
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

3.1.1 DETECTION

Those with undiagnosed AF can receive treatment sooner if an opportunistic case finding is undertaken. Routine palpation of the radial pulse (not less than 20 seconds) during screening of blood pressure will be a good opportunity to pick up undiagnosed atrial fibrillation.

In patients presenting with any of the following:

- breathlessness/dyspnoea,
- palpitations,
- syncope/dizziness,
- chest discomfort or stroke/TIA,

manual pulse palpation should be performed to assess for the presence of an irregular pulse that may indicate AF.

3.1.1.1 ELECTROCARDIOGRAM

The diagnosis of AF requires confirmation by ECG, sometimes in the form of bedside telemetry, ambulatory Holter recordings and event loop recordings.^{2, 10}

If AF is present at the time of recording, a standard 12-lead ECG is sufficient to confirm the diagnosis. In paroxysmal AF, 7-days Holter ECG recording or daily and symptom-activated event recordings may document the arrhythmia in 70% of AF patients.²

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The search for AF should be intensified; including prolonged monitoring, when patients

- Are highly symptomatic (EHRA III & IV)
- Present with recurrent syncope and
- After a cryptogenic stroke.^{11, 12}

In stroke survivors, a step-wise addition of five daily short-term ECGs, one 24 h Holter ECG, and another 7-day Holter ECG will each increase the detection rate of AF by a similar extent.¹¹

3.2 DIAGNOSTIC EVALUATION

The initial diagnostic work-up is driven by the initial presentation.

The time of onset of AF should be established to define the type of AF (Figure 2).

Patients with AF and signs of acute heart failure require urgent rate control and often cardioversion. An urgent transthoracic echocardiogram (TTE) should be performed in haemodynamically-compromised patients to assess LV and valvular function and right ventricular pressure. If AF duration is >48 h or there is doubt about its duration, transesophageal echocardiogram (TOE) should be used to rule out intracardiac thrombus prior to cardioversion.¹³

Patients with stroke or TIA require immediate stroke diagnosis, usually via emergency computed tomography (CT).

Patients should be assessed for risk of stroke. Most patients with acute AF will require anticoagulation unless they are at low risk of thromboembolic complications (no stroke risk factors) and no cardioversion is necessary (e.g. AF terminates within 24 – 48 h).

After the initial management of symptoms and complications, underlying causes of AF should be sought. A TTE is useful to detect ventricular, valvular, and atrial disease as well as rare congenital heart disease. Thyroid function tests, a full blood count, a serum creatinine measurement and analysis for proteinuria, measurement of blood pressure, and a test for diabetes mellitus are useful. A serum test for hepatic function may be considered in selected patients. A stress test is reasonable in patients with signs or risk factors for coronary artery disease. Patients with persistent signs of LV dysfunction and/or signs of myocardial ischemia are candidates for coronary angiography

Table 6 lists the clinical evaluation that may be necessary in patients with AF.

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Table 6 : Clinical Evaluation in Patients With AF

Minimum evaluation

1. *Electrocardiogram, to identify*

- Rhythm (verify AF)
- LV hypertrophy
- P-wave duration and morphology or fibrillatory waves
- Preexcitation
- Bundle-branch block
- Prior MI
- Other atrial arrhythmias
- To measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy

2. *Transthoracic echocardiogram, to identify*

- Valvular heart disease
- LA and RA size
- LV size and function
- Peak RV pressure (pulmonary hypertension)
- LV hypertrophy
- LA thrombus (low sensitivity)
- Pericardial disease

3. *Blood tests of thyroid, renal, and hepatic function*

- For a first episode of AF, when the ventricular rate is difficult to control

Additional testing

One or several tests may be necessary.

1. *Six-minute walk test*

- If the adequacy of rate control is in question

2. *Exercise testing*

- If the adequacy of rate control is in question (permanent AF)
- To reproduce exercise-induced AF
- To exclude ischemia before treatment of selected patients with a type IC antiarrhythmic drug

3. *Holter monitoring or event recording*

- If diagnosis of the type of arrhythmia is in question
- As a means of evaluating rate control

4. *Transesophageal echocardiography*

- To identify LA thrombus (in the LA appendage)
- To guide cardioversion

5. *Electrophysiological study*

- To clarify the mechanism of wide-QRS-complex tachycardia
- To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
- To seek sites for curative ablation or AV conduction block/modification

6. *Chest radiograph, to evaluate*

- Lung parenchyma, when clinical findings suggest an abnormality
- Pulmonary vasculature, when clinical findings suggest an abnormality

Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs (see Appendix D). **AF** = atrial fibrillation; **AV** = atrioventricular; **LA** = left atrial; **LV** = left ventricular; **MI** = myocardial infarction; **RA** = right atrial; **RV** = right ventricular.

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3.3 ECHOCARDIOGRAPHY

TTE should be performed in patients with AF:

- For whom a baseline echocardiogram is important for long-term management.
- For whom a rhythm-control strategy that includes cardioversion (electrical or pharmacological) is being considered.
- In whom there is a high risk or a suspicion of underlying structural/functional heart disease (such as heart failure or heart murmur) that influences their subsequent management (for example, choice of antiarrhythmic drug)
- In whom refinement of clinical risk stratification for antithrombotic therapy is needed.

In patients with AF who require anticoagulation therapy based on relevant clinical criteria, TTE need not be routinely performed.

TOE should be performed in patients with AF:

- Where TTE is technically difficult and/or of questionable quality and where there is a need to exclude cardiac abnormalities
- For whom TOE-guided cardioversion is being considered. (See section 6.4.5, page 38)

3.4 CLINICAL FOLLOW-UP

The specialist caring for the AF patient should not only perform the baseline assessment and institute the appropriate treatment, but also suggest a structured plan for follow-up.

Important considerations during follow-up of the AF patient are listed below:

- Has the risk profile changed (e.g. new diabetes or hypertension), especially with regard to the indication for anticoagulation?
- Is anticoagulation now necessary—have new risk factors developed, or has the need for anticoagulation passed, e.g. postcardioversion in a patient with low thrombo-embolic risk?
- Have the patient's symptoms improved on therapy; if not, should other therapy be considered?
- Are there signs of proarrhythmia or risk of proarrhythmia; if so, should the dose of an antiarrhythmic drug be reduced or a change made to another therapy?
- Has paroxysmal AF progressed to a persistent/permanent form, in spite of antiarrhythmic drugs; in such a case, should another therapy be considered?
- Is the rate control approach working properly; has the target for heart rate at rest and during exercise been reached?

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Keypoints

- IB** The diagnosis of AF requires documentation by ECG.^{2,10}
- IB** In patients with suspected AF, an attempt to record an ECG should be made when symptoms suggestive of AF occur.^{2,14}
- IB** A simple symptom score (EHRA class) is recommended to quantify AF-related symptoms.^{2,15}
- IC** All patients with AF should undergo a thorough physical examination, and a cardiac- and arrhythmia-related history should be taken.
- IB** In patients with severe symptoms, documented or suspected heart disease, or risk factors, an echocardiogram is recommended.^{2,16,17}
- IC** In patients treated with antiarrhythmic drugs, a 12-lead ECG should be recorded at regular intervals during follow-up.
- IIaB** In patients with suspected symptomatic AF, additional ECG monitoring should be considered in order to document the arrhythmia.^{2,18}
- IIaB** Additional ECG monitoring should be considered for detection of 'silent' AF in patients who may have sustained an AF-related complication.^{2,19}
- IIaC** In patients with AF treated with rate control, Holter ECG monitoring should be considered for assessment of rate control or bradycardia.
- IIaC** In young active patients with AF treated with rate control, exercise testing should be considered in order to assess ventricular rate control.
- IIaC** In patients with documented or suspected AF, an echocardiogram should be considered.
- IIaC** Patients with symptomatic AF or AF-related complications should be considered for referral to a cardiologist.
- IIaC** A structured follow-up plan prepared by a specialist is useful for follow-up by a general or primary care physician.
- IIbB** In patients treated with rhythm control, repeated ECG monitoring may be considered to assess the efficacy of treatment.^{2,20,21}
- IIbC** Most patients with AF may benefit from specialist follow-up at regular intervals.

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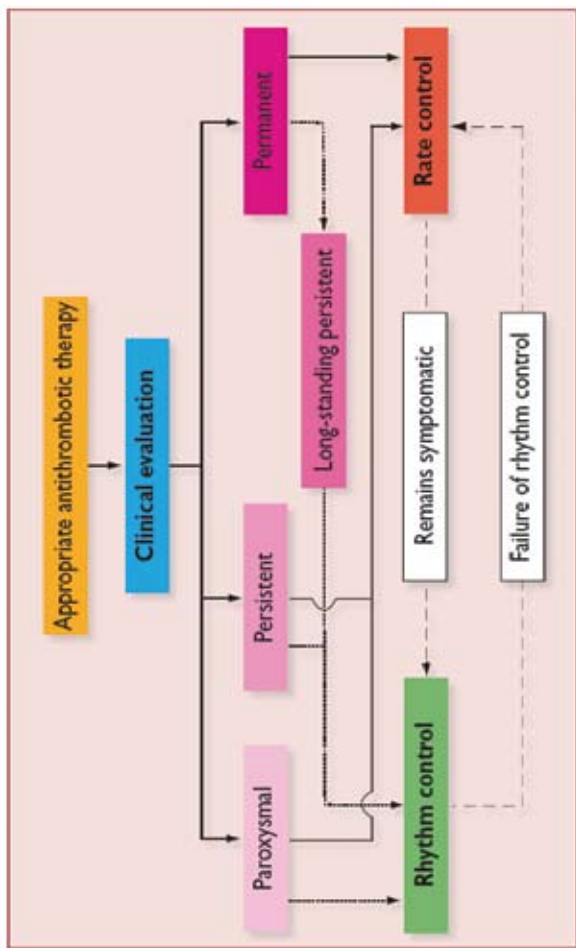


Figure 3: Choice of rate and rhythm control strategies. Rate control is needed for most patients with AF unless the heart rate during AF is naturally slow. Rhythm control may be added to rate control if the patient is symptomatic despite adequate rate control, or if a rhythm control strategy is selected because of factors such as the degree of symptoms, younger age, or higher activity levels. Permanent AF is managed by rate control unless it is deemed possible to restore sinus rhythm when the AF category is re-designated as 'long-standing persistent'. Paroxysmal AF is more often managed with a rhythm control strategy, especially if it is symptomatic and there is little or no associated underlying heart disease. Solid lines indicate the first-line management strategy. Dashed lines represent fall-back objectives and dotted lines indicate alternative approaches which may be used in selected patients.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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4. MANAGEMENT PRINCIPLES

4.1 GENERAL PRINCIPLES

In patients with AF or AFI, the aims of treatment involve the following five objectives.

- I Relief of symptoms, such as palpitations, dizziness, fatigue and dyspnoea, is paramount to the patient.
- II. The prevention of serious complications, such as thromboembolism (particularly ischaemic stroke) and heart failure, is equally important.
- III. Optimal management of concomitant cardiovascular disease.
- IV. Rate control.
- V. Correction of rhythm disturbance.

These goals are not mutually exclusive and may be pursued simultaneously. The initial strategy may differ from the long-term therapeutic goal.

A fundamental question to be answered for every patient with AF or AFI is whether to obtain and maintain sinus rhythm by pharmacological or nonpharmacological means (a rhythm-control strategy), or whether to aim primarily to control heart rate rather than the rhythm (a rate-control strategy).

For patients with symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control while the long-term goal is to restore sinus rhythm.

If rate control offers inadequate symptomatic relief, restoration of sinus rhythm becomes a clear long-term goal. When cardioversion is contemplated and the duration of AF is unknown or exceeds 48 h, anticoagulation will be necessary.

Early cardioversion may be necessary if AF causes hypotension or worsening heart failure. In contrast, amelioration of symptoms by rate control in older patients may steer the clinician away from attempts to restore sinus rhythm. In some circumstances, when the initiating pathophysiology of AF is reversible, as for instance in the setting of thyrotoxicosis or after cardiac surgery, no long-term therapy may be necessary.

Regardless of the approach, the need for anticoagulation is based on stroke risk and not on whether sinus rhythm is maintained.

For rate and rhythm control, drugs remain the first choice. Radiofrequency ablation may be considered in symptomatic AF and in lone AF to avoid long-term drug therapy. In selected individuals undergoing cardiac surgery, surgical maze procedure may be a therapeutic option.

4.2 THROMBOEMBOLIC PROPHYLAXIS

Antithrombotic therapy must be considered in all patients with AF. Strategies that may reduce thromboembolic risk include the following treatments:

- Anticoagulants such as Vitamin K Antagonist,
- Antiplatelet agents, such as aspirin and clopidogrel
- Intravenous (IV) heparin or low molecular weight heparin (LMWH)
- Left atrial appendage (LAA) occlusion, either surgically or percutaneously.

The decision regarding the method of reduction in the risk of stroke, should take into account both the person's risk of thromboembolism and their risk of bleeding. It is important to remember that vitamin K antagonist such as Warfarin is very effective and reduces the risk of stroke overall by two thirds. (For details see Section 6, page 26)

4.3. HEART RATE CONTROL VERSUS RHYTHM CONTROL

Rate control involves the use of chronotropic drugs or electrophysiological or surgical interventions to reduce the rapid heart rate (ventricular rate) often found in patients with AF. Although the atria continue to fibrillate with this strategy, it is nonetheless thought to be an effective treatment as it improves symptoms and reduces the risk of associated morbidity. However, the persistence of the arrhythmia continues the risk of stroke and thromboembolic events occurring. Administering antithrombotic drugs reduces this risk. (See Figure 3, page 12)

Rhythm control involves the use of electrical or pharmacological cardioversion or electrophysiological or surgical interventions to convert the arrhythmia associated with AF to normal sinus rhythm. Patients who have been successfully cardioverted are generally administered antiarrhythmic drugs for the long term to help prevent the recurrence of AF. The rhythm control strategies also require the appropriate administration of antithrombotic therapy to reduce the risk of stroke and thromboembolic events occurring.

Randomized trials comparing outcomes of rhythm versus rate control strategies in patients with AF are summarized in Table 7 and 8.²²⁻²⁸

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Table 7: General characteristics of rhythm control and rate control trials in patients with AF

Trial	Ref	Patients (n)	Mean age (years)	Mean follow-up (years)	Inclusion criteria	Primary outcome parameter	Patients reaching primary outcome (n)		P
							Rate control	Rhythm control	
PIAF (2000)	22	252	61.0	1.0	Persistent AF (7–360 days)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.32
AFFIRM (2002)	23	4060	69.7	3.5	Paroxysmal AF or persistent AF, age >65 years, or risk of stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
RACE (2002)	24	522	68.0	2.3	Persistent AF or flutter for <1 years and 1–2 cardioversions over 2 years and oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thrombo-embolic events, severe adverse effects of antiarrhythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF (2003)	25	200	66.0	1.6	Persistent AF (>4 weeks and <2 years), LA size >45 mm, CHF NYHA II–IV, LVEF <45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0%)	9/100 (9.0%)	0.99
HOTCAFE (2004)	26	205	60.8	1.7	First clinically overt persistent AF (>7 days and <2 years), age 50–75 years	Composite: death, thrombo-embolic events; intracranial/major haemorrhage	1/101 (1.0%)	4/104 (3.9%)	> 0.71
AF-CHF (2008)	27	1376	66	3.1	LVEF <35%, symptoms of CHF, history of AF (>6 h or DCC <last 6 months)	Cardiovascular death	175/1376 (25%)	182/1376 (27%)	0.59
J-RHYTHM (2009)	28	823	64.7	1.6	Paroxysmal AF	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, or physical/psychological disability	89/405 (22.0%)	64/418 (15.3%)	0.012

AF = atrial fibrillation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF = congestive heart failure; CPR = cardiopulmonary resuscitation; DCC = direct current cardioversion; HOT CAFE = How to Treat Chronic Atrial Fibrillation; J-RHYTHM = Japanese Rhythm Management Trial for Atrial Fibrillation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = Rate Control versus Electrical Cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

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Table 8: Comparison of adverse outcomes in rhythm control and rate control trials in patients with AF

Trial	Ref	Death from all causes (in rate/rhythm)	Deaths from cardiovascular causes	Deaths from non- cardiovascular causes	Stroke	Thrombo-embolic events	Bleeding
PIAF (2000)	22	4	1/1	1 ^a	ND	ND	ND
AFFIRM (2002)	23	666 (310/356)	167/164	113/165	77/80	ND	107/96
RACE (2002)	24	36	18/18	ND	ND	14/21	12/9
STAF (2003)	25	12 (8/4)	8/3	0/1	1/5	ND	8/1
HOT CAFÉ (2004)	26	4 (1/3)	0/2	1/1	0/3	ND	5/8
AF-CHF (2008)	27	228/217	175/182	53/35	11/9	ND	ND

^aTotal number of patients not reported.
AF = atrial fibrillation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; HOT CAFÉ = HOw to Treat Chronic Atrial Fibrillation; ND = not determined; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = RATE Control versus Electrical cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

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The consistent finding in all five studies was that rhythm control offered no survival advantage and, in most cases, had little effect on morbidity and quality of life. However, it should be emphasised that these conclusions are not necessarily applicable to all groups of patients. The five recent studies enrolled mostly older patients with additional risk factors for stroke, many of whom also had heart failure. Younger patients with normal hearts and primarily paroxysmal atrial fibrillation (PAF) were not well represented. Importantly, in a predefined subgroup of AFFIRM participants aged less than 65 years, hazard ratios for death showed a paradoxical trend towards superiority of the rhythm-control strategy.

The initial therapy after onset of AF should always include adequate antithrombotic treatment and control of the ventricular rate. If the ultimate goal is restoration and maintenance of sinus rhythm, rate control medication should be continued throughout follow-up, unless continuous sinus rhythm is present. The goal is to control the ventricular rate adequately whenever recurrent AF occurs.

The decision to add rhythm control therapy to the management of AF requires an individual decision and should therefore be discussed at the beginning of AF management. Before choosing rate control alone as a long-term strategy, the clinician should consider how permanent AF is likely to affect the individual patient in the future and how successful rhythm control is expected to be (Figure 3, page 12). Symptoms related to AF are an important determinant in making the decision to opt for rate or rhythm control (e.g. globally assessed by the EHRA score, Table 5, page 7), in addition to factors that may influence the success of rhythm control. The latter include a long history of AF, older age, more severe associated cardiovascular diseases, other associated medical conditions, and enlarged LA size.

A rate-control strategy should be the preferred initial option in the following patients with persistent AF:

- Over 65 years old
- With coronary artery disease and/or left ventricular dysfunction
- With contraindications to antiarrhythmic drugs
- Unsuitable for cardioversion*

A rhythm-control strategy should be the preferred initial option in the following patients with persistent AF:

- Those who are symptomatic
- Younger patients
- Those presenting for the first time with lone AF
- Those with AF secondary to a treated/corrected precipitant

Keypoints

- | | |
|------|--|
| IA | Rate control should be the initial approach in elderly patients with AF and minor symptoms (EHRA class 1). ^{23,24,27} |
| IB | Rhythm control is recommended in patients with symptomatic (EHRA class ≥ 2) AF despite adequate rate control. ^{2,21,29,30,31} |
| IA | Rate control should be continued throughout a rhythm control approach to ensure adequate control of the ventricular rate during recurrences of AF. ²³ |
| IIaC | Rhythm control as an initial approach should be considered in young symptomatic patients in whom catheter ablation treatment has not been ruled out. |

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IIac

Rhythm control should be considered in patients with AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyperthyroidism).

IIaB

Rhythm control in patients with AF and AF-related heart failure should be considered for improvement of symptoms.^{29,30,32}

5. MANAGEMENT – ACUTE-ONSET AF

5.1 ACUTE AF IN HEMODYNAMICALLY UNSTABLE PATIENTS

The majority of patients who present with AF are hemodynamically stable but there is a small group of patients who are significantly compromised by the onset of AF. These patients require immediate hospitalization and urgent intervention to prevent further deterioration.

Those considered in this group are;³³

- Those with a ventricular rate greater than 150 bpm
- With ongoing chest pains, or
- Critical perfusion.

In these circumstances, the concerns regarding intervention in the absence of anticoagulation and echocardiography are counterbalanced by the need for urgent treatment.

5.1.1 ACUTE RATE CONTROL

It is important to understand that in these circumstances the slow onset of digoxin makes it inappropriate for use in this situation. Patients whose AF is associated with thyrotoxicosis will not respond to any measures until the underlying thyroid disease is first treated. Patients with accessory pathway such as the Wolff-Parkinson-White (WPW) syndrome are particularly at risk following the onset of AF because they can present with very rapid ventricular rates (greater than 200 bpm) and may need specific management.

When patients present with unacceptably high ventricular rate the primary aim is one of rate control.

AF with slow ventricular rates may respond to atropine (0.5 – 2 mg i.v.), but many patients with symptomatic bradyarrhythmia may require either urgent placement of a temporary pacemaker lead in the right ventricle and/or cardioversion.

Acute initiation of rate control therapy should usually be followed by a long-term rate control strategy; details of drugs and doses are given in Section 7 on page 66.

Keypoints

IA

In the acute setting in the absence of pre-excitation, i.v. administration of β -blockers or non-dihydropyridine calcium channel antagonists is recommended to slow the ventricular response to AF, exercising caution in patients with hypotension or heart failure.³⁴

IB

In the acute setting, i.v. administration of amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the setting of hypotension.³⁵

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IC

In pre-excitation, preferred drugs are class I antiarrhythmic drugs (See Appendix D) or amiodarone.

IIIC

When pre-excited AF is present, β -blockers, non-dihydropyridine calcium channel antagonists, digoxin, and adenosine are contraindicated.

Table 9 : Intravenous pharmacological agents for acute control of ventricular rate in AF/AFL

Drug	Commonly used loading dose (IV)	Onset of action	Commonly-used maintenance dose (IV)	Adverse effects	Limitations	Commonly-used oral maintenance dose for long-term rate control
Beta-blockers						
Esmolol (very short-acting)	0.5 mg/kg over 1 min	5 min	0.05 to 0.2 mg/kg/min infusion	Hypotension, heart block, bradycardia, asthma, heart failure	Negative inotropic effect	Oral preparation not available
Metoprolol					In people with heart failure, lower doses may be advisable. Negative inotropic effect	23.75 to 200 mg/day (divided doses)
Propranolol	0.15mg/kg over 5 min	5 min	N/A			80 to 240 mg/day (divided doses)
Calcium channel blockers						
Diltiazem				Hypotension, heart block, heart failure	In people with heart failure, lower doses may be advisable. Negative inotropic effect	120 to 360 mg/day (once daily long-acting)
Verapamil	0.075 to 0.15 mg/kg over 2 min	3 to 5 min	N/A			120 to 360 mg/day (divided doses or once daily long-acting)
Other						
Digoxin	0.25 to 1.0 mg	2 hr	0.125 to 0.25 mg/day	Digoxin toxicity, heart block, bradycardia	N/A	0.0625 to 0.375 mg/day (individualise dosage)
Amiodarone	5 mg/kg over 20 min	Variable (10 min to 4 hours)	50 mg/hour infusion	Hypotension, back pain, heart block, phlebitis	N/A	100 to 200 mg/day

Note: Administration of beta-blockers together with IV verapamil is contraindicated.

N/A = not available

Adapted from: Fuster V, Ryden LE, Asinger RW, *et al.*¹³⁴

5.1.2 PHARMACOLOGICAL CARADIOVERSION

In the presence of other cardiac abnormalities (e.g. hypertensive heart disease, valvular heart disease), onset of AF with acceptable ventricular rates may still compromise cardiac function. While rate control is unlikely to bring about clinical improvement in these circumstances, there is a need for the restoration of sinus rhythm.

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Pharmacological cardioversion of AF may be initiated by a bolus administration of an antiarrhythmic drug. Although the conversion rate with antiarrhythmic drugs is lower than with direct current cardioversion (DCCV), it does not require conscious sedation or anesthesia, and may facilitate the choice of antiarrhythmic drug therapy to prevent recurrent AF.

Most patients who undergo pharmacological cardioversion require continuous medical supervision and ECG monitoring during the drug infusion and for a period afterwards (usually about half the drug elimination half-life) to detect proarrhythmic events such as ventricular proarrhythmia, sinus node arrest, or atrioventricular block.

Several agents are available for pharmacological cardioversion (see Table 10 on page 20).

Table 10: Drug and doses for pharmacological conversion of (recent-onset) AF

Drug	Dose	Follow-up dose	Risk
Amiodarone	5 mg/kg i.v over 1h	50mg/kg	Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecainide	200-300 mg p.o	N/A	Not suitable for patients with marked structural heart disease, may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Propafenone	450-600 mg p.o		Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.

In clinical practice, amiodarone is the most common agent used in the management of patients presenting in AF with haemodynamic compromise, as it appears to have a hybrid effect of rapid reduction in ventricular rate in most patients with a proportion of these reverting to sinus rhythm over a longer period.

Adapted with modification from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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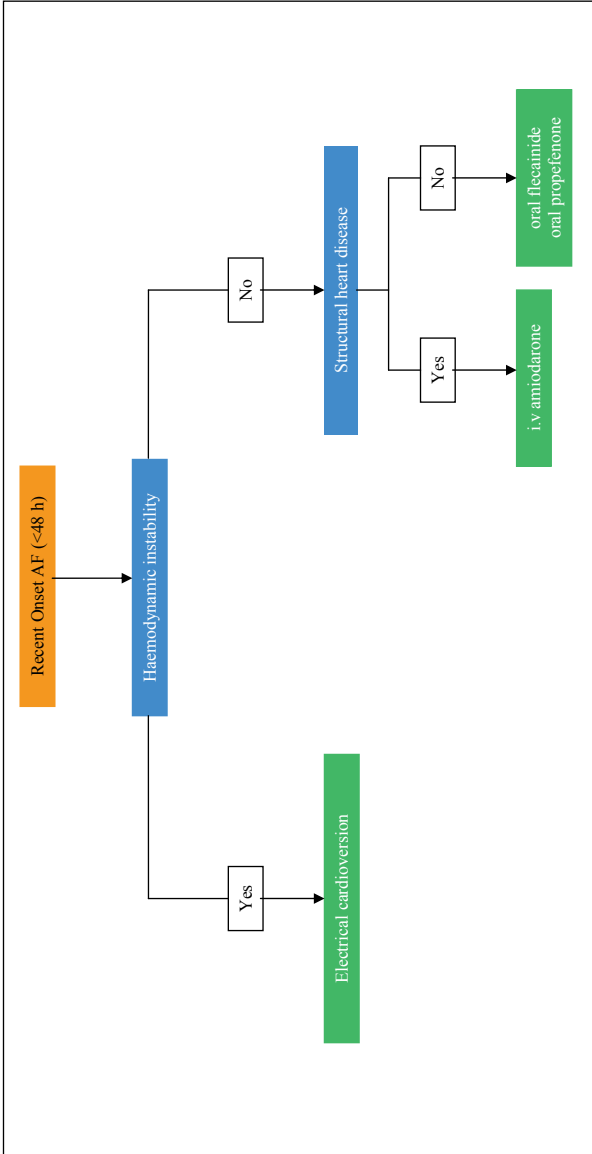


Figure 4 Direct current conversion and pharmacological cardioversion of recent-onset AF in patients considered for pharmacological cardioversion. AF= atrial fibrillation

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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In suitable patients with recent-onset AF (generally <48 hours duration), a trial of pharmacological cardioversion to sinus rhythm can be offered with flecainide or propafenone (when there is little or no underlying structural heart disease) or i.v amiodarone (when there is structural disease) (Figure 4, page 21). The anticipated conversion rate is $\geq 50\%$ within ~15 – 120 min.

Keypoints

- | | |
|--------|--|
| IA | When pharmacological cardioversion is preferred and there is no structural heart disease, oral flecainide or propafenone is recommended for cardioversion of recent-onset AF. ³⁶⁻³⁸ |
| IA | In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended. ³⁹⁻⁴¹ |
| IIIABC | Digoxin (Level of Evidence A), verapamil, sotalol, metoprolol (Level of Evidence B), other β -blocking agents (Level of Evidence C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended. |
| IC | In patients with a life-threatening deterioration in haemodynamic stability following the onset of AF, emergency electrical cardioversion should be performed, irrespective of the duration of the AF. |

5.1.2.1 Pill-in-the-pocket approach

The pill-in-the-pocket approach⁴² refers to outpatient administration of oral flecainide (200 to 300 mg) or propafenone (450 to 600 mg) to **carefully selected patients whose initial therapy in hospital was effective and well tolerated.**

Keypoints

- | | |
|------|---|
| IIaB | This approach could be considered in appropriately selected patients who have infrequent but prolonged symptoms of paroxysmal AF (PAF).

There is an uncommon probability of AF reverting to AFL with this approach and before antiarrhythmic medication is initiated, a beta-blocker, diltiazem or verapamil should be given to prevent rapid AV conduction.

Patients with the conditions below are contraindicated for such an approach: <ul style="list-style-type: none">• Those aged more than 75 years,• Those with AF duration greater than 7 days,• NYHA Class III to IV or signs of heart failure on examination,• AF with a mean ventricular rate less than 70 bpm,• Previous myocardial infarction or angina,• Valvular heart disease,• Cardiomyopathy,• Bundle branch block,• Known sick sinus syndrome,• Low serum potassium,• Or renal or hepatic insufficiency. |
|------|---|

With such an approach emergency room visits and hospitalization could markedly be reduced.

- | | |
|------|--|
| IIaB | In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment. ⁴² |
|------|--|

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5.1.3 DIRECT CURRENT CARADIOVERSION

DCCV is an effective method of converting AF to sinus rhythm. Successful DCCV is usually defined as termination of AF, documented as the presence of two or more consecutive P waves after shock delivery.

5.1.3.1 Procedure

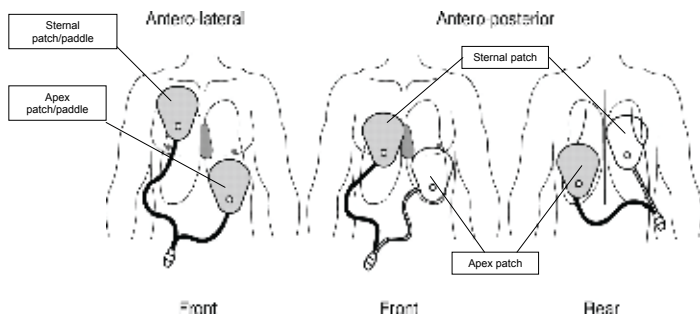
Unless adequate anticoagulation has been documented for 4 weeks or AF is <48 h from a definite onset, a TOE should be performed to rule out atrial thrombi (see Figure 9, page 39).

A pacing catheter or external pacing pads may be needed if asystole or bradycardia occurs.

Evidence favours the use of biphasic external defibrillators because of their lower energy requirements and greater efficacy compared with monophasic defibrillators. Trials have demonstrated a significant increase in the first shock success rate of DCCV for AF when biphasic waveforms were used.

Currently, two conventional positions are commonly used for electrode placement (see Figure 5). Several studies have shown that anteroposterior electrode placement is more effective than anterolateral placement.⁴³ If initial shocks are unsuccessful for terminating the arrhythmia, the electrodes should be repositioned and cardioversion repeated.

Figure 5: Patch/paddle placement for DCCV

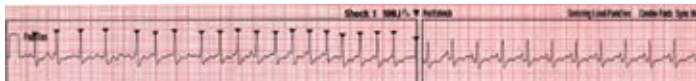


The recommended initial energy for synchronised cardioversion (see figure 6) is:

- 200J or greater with monophasic waveform
- 100J or greater with biphasic waveform
- 10-50J biphasic waveform for AFL

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Figure 6 : ECG strip showing synchronized cardioversion



Outpatient/day care DCCV can be undertaken in patients who are haemodynamically stable and do not have severe underlying heart disease. At least 3 h of ECG and haemodynamic monitoring are needed after the procedure, before the patient is allowed to leave the hospital.

Internal cardioversion may be helpful in special situations, e.g. when a patient undergoes invasive procedures and cardioversion catheters can be placed without further vascular access and when implanted defibrillation devices are present.

5.1.3.2 Complications

The risks and complications of cardioversion are associated primarily with

- Thrombo-embolic events,
- Post-cardioversion arrhythmias, and
- The risks of general anaesthesia.

The procedure is associated with 1 – 2% risk of thromboembolism, which can be reduced by adequate anticoagulation in the weeks prior to cardioversion or by exclusion of left atrium thrombi before the procedure. Skin burns are a common complication. In patients with sinus node dysfunction, especially in elderly patients with structural heart disease, prolonged sinus arrest without an adequate escape rhythm may occur. Dangerous arrhythmias, such as ventricular tachycardia and fibrillation, may arise in the presence of hypokalaemia, digitalis intoxication, or improper synchronization. The patient may become hypoxic or hypoventilate from sedation, but hypotension and pulmonary oedema are rare.

5.1.3.3 Cardioversion in patients with implanted pacemakers and defibrillators

The electrode paddle should be at least 8 cm from the pacemaker battery, and the antero-posterior paddle positioning is recommended. Biphasic shocks are preferred because they require less energy for AF termination. In pacemaker-dependent patients, an increase in pacing threshold should be anticipated. In the absence of a pacemaker programmer, a pacing magnet may be placed over the pacemaker generator pocket to provide temporary pacing support. These patients should be monitored carefully. After cardioversion, the device should be interrogated and evaluated to ensure normal function.

5.1.3.4 Recurrence after cardioversion

Recurrences after DCCV can be divided into three phases:

- (1) Immediate recurrences, which occur within the first few minutes after DCCV.
- (2) Early recurrences, which occur during the first 5 days after DCCV.

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(3) Late recurrence, which occur thereafter.

Factors that predispose to AF recurrence are age, AF duration before cardioversion, number of previous recurrences, an increased LA size or reduced LA function, and the presence of coronary heart disease or pulmonary or mitral valve disease. Atrial ectopic beats with a long – short sequence, faster heart rates, and variations in atrial conduction increase the risk of AF recurrence.

Pre-treatment with antiarrhythmic drugs such as amiodarone, sotalol, flecainide, and propafenone increases the likelihood of restoration of sinus rhythm.⁴⁴⁻⁴⁶

Some highly symptomatic patients in whom AF occurs infrequently (e.g. once or twice a year) strongly prefer to undergo repeated cardioversions as a long-term rhythm control strategy, rather than opting for rate control or other rhythm control modalities which they may find uncomfortable.

Keypoints

- IC** Immediate DCCV is recommended when a rapid ventricular rate does not respond promptly to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, angina, or heart failure.
- IB** Immediate DCCV is recommended for patients with AF involving pre-excitation when rapid tachycardia or haemodynamic instability is present.⁴⁷
- IIaB** Elective DCCV should be considered in order to initiate a long-term rhythm control management strategy for patients with AF.^{41,43,48}
- IIaB** Pre-treatment with amiodarone, flecainide, propafenone or sotalol should be considered to enhance success of DCCV and prevent recurrent AF.⁴⁴⁻⁴⁶
- IIbC** Repeated DCCV may be considered in highly symptomatic patients refractory to other therapy.
- IIbC** Pre-treatment with β -blockers, diltiazem or verapamil may be considered for rate control, although the efficacy of these agents in enhancing success of DCCV or preventing early recurrence of AF is uncertain.
- IIIC** DCCV is contraindicated in patients with digitalis toxicity.

5.1.3 Antithrombotic therapy for acute-onset AF

Please go to section 6, page 26.

6. MANAGEMENT - PREVENTION OF THROMBOEMBOLISM

6.1 RISK STRATIFICATION FOR STROKE

Assessment of thromboembolic risk or risk stratification allows the clinician to consider anticoagulant treatment for those people who are at an increased risk of stroke.

Two recent systematic reviews have addressed the evidence base for stroke risk factors in AF,^{49,50} and concluded that prior stroke/TIA/thrombo-embolism, age, hypertension, diabetes, and structural heart disease are important risk factors. The presence of moderate to severe LV systolic dysfunction TTE is the only independent echocardiographic risk factor for stroke on multivariable analysis. On TOE, the presence of LA thrombus, complex aortic plaques, spontaneous echo-contrast and low LAA velocities are independent predictors of stroke and thrombo-embolism.

Patients with paroxysmal AF should be regarded as having a stroke risk similar to those with persistent or permanent AF, in the presence of risk factors.

Patients aged less than 60 years, with 'lone AF', i.e. no clinical history or physical evidence of cardiovascular disease, carry a very low cumulative stroke risk, estimated to be 1.3% over 15 years.

The various stroke clinical risk factors has led to publication of various stroke schemes.^{51,52} The simplest risk assessment scheme is the CHADS₂ score and as shown in Table 11, has good stroke correlation. The CHADS₂ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index evolved from the AF Investigators and Stroke Prevention in Atrial Fibrillation (SPAF) Investigators criteria, and is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure.⁵¹

The CHADS₂ stroke risk stratification scheme should be used as an initial, rapid, and easy-to-remember means of assessing stroke risk. In patients with a CHADS₂ score ≥ 2 , chronic OAC therapy with a VKA is recommended in a dose-adjusted approach to achieve an international normalized ratio (INR) target of 2.5 (range, 2.0 – 3.0), unless contraindicated.^{6,52}

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Table 11: CHADS₂ score and stroke rate

CHADS ₂ Score	Patients (n=1733)	Adjusted stroke rate (%/year) ^a (95% confidence interval)
0	120	1.9 (1.2-3.0)
1	463	2.8 (2.0-3.8)
2	523	4.0 (3.1-5.1)
3	337	5.9 (4.6-7.3)
4	220	8.5 (6.3-11.1)
5	65	12.5 (8.2-17.5)
6	5	18.2 (10.5-27.4)

^aThe adjusted stroke rate was derived from the multivariable analysis assuming no aspirin usage; these stroke rates are based on data from a cohort of hospitalized AF patients, published in 2001, with low numbers in those with a CHADS₂ score of 5 and 6 to allow an accurate judgement of the risk in these patients. Given that stroke rates are declining overall, actual stroke rates in contemporary non-hospitalized cohorts may also vary from these estimates. Adapted from Gage F et al.⁵¹ AF = atrial fibrillation; CHADS₂ = cardiac failure, hypertension, age, diabetes, stroke (doubled).

A comparison of the 12 published risk-stratification⁴⁹ schemes to predict stroke in patients with non-valvular AF found that most had very modest predictive value for stroke and the proportion of patients assigned to individual risk categories varied widely across the schemes. The CHADS₂ score categorized most subjects as 'moderate risk'. The choice of antithrombotic (anticoagulants or antiplatelets) for the 'moderate risk' group was at best uncertain.

Several published analyses^{49,50,53-55} have found even patients at 'moderate risk' (currently defined as CHADS₂ score =1, i.e. one risk factor) still derive significant benefit from OAC over aspirin use, often with low rates of major haemorrhage. Importantly, prescription of an antiplatelet agent was not associated with a lower risk of adverse events.

Also, the CHADS₂ score does not include many stroke risk factors, and other 'stroke risk modifiers' need to be considered in a comprehensive stroke risk assessment (see Table 11, page 27).

Rather than the use of the 'low', 'moderate', and 'high' risk characterization that only showed a modest predictive value, this guideline has adopted and recognize that risk is a continuum. A risk factor-based approach for a more detailed stroke risk assessment is encouraged for recommending the use of antithrombotic therapy.

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The risk factor-based approach for patients with non-valvular AF have been given an acronym, CHA₂DS₂VASc and the schema is based on two groups of risk factors:

- **Major risk factors** - prior history of stroke, TIA or thromboembolism and/or age 75 or older
- **Clinically relevant 'non-major' risk factors** - hypertension, heart failure (EF ≤ 40%), diabetes, age 65–74 years, female gender, and vascular disease (myocardial infarction, complex aortic plaques and PAD).

The risk may be calculated based on a point system in which 2 points are allocated for each '**Major risk factors**'; and 1 point each is assigned for '**Clinically relevant 'non major' risk factors**' (see Table 11 on page 27).

6.2 STRATEGIES FOR THROMBOEMBOLIC PROPHYLAXIS

The CHADS₂ stroke risk stratification scheme should be used as a simple initial (and easily remembered) means of assessing stroke risk, particularly suited to primary care doctors and non-specialists.

In patients with a CHADS₂ score of ≥2, chronic OAC therapy, e.g. with a VKA, is recommended in a dose adjusted to achieve an INR value in the range of 2.0 – 3.0, unless contraindicated.

In patients with a CHADS₂ score of 0 – 1, or where a more detailed stroke risk assessment is indicated, it is recommended to use a more comprehensive risk factor-based approach incorporating other risk factors for thrombo-embolism (see Table 12 and Figure 7).⁵⁶⁻⁵⁸

In all cases where OAC is considered, a discussion of the pros and cons with the patient, and an evaluation of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and patient preferences are necessary. In some patients, for example, women aged less than 65 years with no other risk factors (i.e. a CHA₂DS₂VASc score of 1) aspirin rather than OAC therapy may be considered.

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Table 12. CHA₂DS₂-VAS_c Score, stroke rate and approach to thromboprophylaxis in patients with AF

a) Risk Factors for Stroke and thrombo embolism in non-valvular AF		
Major' risk factors	Clinically relevant non-major' risk factors	
Previous stroke, TIA or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g, LV EF ≤ 40%) Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease ^a	
b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA ₂ DS ₂ -VAS _c (Note: maximum score is 9 since age may contribute 0,1 or 2 points)		
Risk factor	Score	
Congestive heart failure/LV dysfunction	1	
Hypertension	1	
Age ≥ 75	2	
Diabetes mellitus	1	
Stroke/TIA/thrombo-embolism	2	
Vascular disease	1	
Age 65-74	1	
Sex category (i.e, female sex)	1	
Maximum score	9	
c) Adjusted stroke rate according to CHA ₂ DS ₂ -VAS _c score		
CHA ₂ DS ₂ -VAS _c score	Patients (n=7329)	Adjusted stroke rate (%/year) ^b
0	1	0%
1	422	1.30%
2	1230	2.20%
3	1730	3.20%
4	1718	4.00%
5	1159	6.70%
6	679	9.80%
7	294	9.60%
8	82	6.70%
9	14	15.20%
Approach to thromboprophylaxis in patients with AF		
Risk category	CHA ₂ DS ₂ -VAS _c score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major risk factors	≥2	OAC ^c
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin
No risk factors	0	Either aspirin 75-325mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin

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See text for definitions.

^aPrior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

^bBased on Lip et al.54

AF=atrial fibrillation; EF =ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV=left ventricular; TIA=transient ischaemic attack.

CHA₂DS₂-VAS_c=cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR=international normalized ratio; OAC=oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

^cOAC, such as a VKA, adjusted to an intensity range of INR 2.0–3.0 (target 2.5). New OAC drugs, which may be viable alternatives to a VKA, may ultimately be considered. For example, should both doses of dabigatran etexilate receive regulatory approval for stroke prevention in AF, the recommendations for thromboprophylaxis could evolve as follows considering stroke and bleeding risk stratification:

(a) Where oral anticoagulation is appropriate therapy, dabigatran may be considered, as an alternative to adjusted dose VKA therapy. (i) If a patient is at low risk of bleeding (e.g. HAS-BLED score of 0–2; see Table 14 for HAS-BLED score definition), dabigatran 150 mg b.i.d. may be considered, in view of the improved efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and similar rates of major bleeding events, when compared with warfarin); and (ii) If a patient has a measurable risk of bleeding (e.g. HAS-BLED score of ≥3), dabigatran etexilate 110 mg b.i.d. may be considered, in view of a similar efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and of major bleeding compared with VKA). (b) In patients with one 'clinically relevant non-major' stroke risk factor, dabigatran 110 mg b.i.d. may be considered, in view of a similar efficacy with VKA in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and (probably) aspirin. (c) Patients with no stroke risk factors (e.g. CHA₂DS₂-VAS_c = 0) are clearly at so low risk, either aspirin 75–325 mg daily or no antithrombotic therapy is recommended. Where possible, no antithrombotic therapy should be considered for such patients, rather than aspirin, given the limited data on the benefits of aspirin in this patient group (i.e., lone AF) and the potential for adverse effects, especially bleeding.

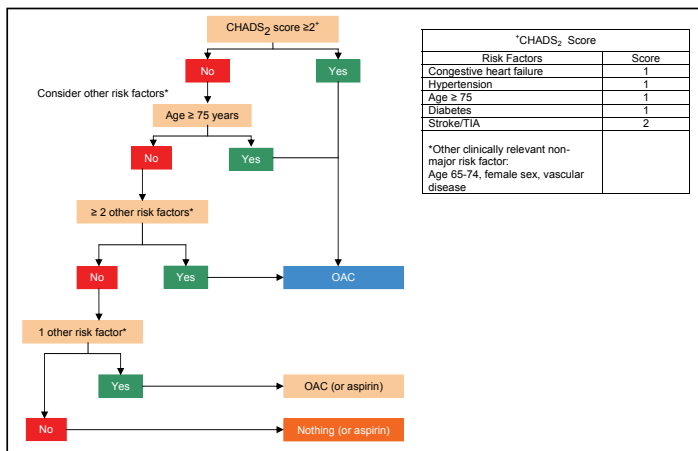


Figure 7 Clinical flowchart for the use of oral anticoagulant for stroke prevention in AF. AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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6.3 ANTITHROMBOTIC THERAPY

6.3.1 ANTICOAGULATION WITH VITAMIN K ANTAGONISTS

There were 6 large randomized trials, both primary and secondary prevention, that provided an extensive and robust evidence base for VKA therapy in AF.

In a meta-analysis⁵⁵ adjusted-dose VKA (international normalized ratio [INR] 2-3) showed a significant 64% risk reduction of stroke and 26% risk reduction of all cause mortality in patients with non valvular AF.^{53,59-63}

Risk of intracranial hemorrhage was small (0.3-1.8%).^{53,59-63} When VKA is given to elderly patients with atrial fibrillation, hypertension must be managed aggressively.

Keypoints

IC Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.

IIaA The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent).^{49,50}

IA Antithrombotic therapy to prevent thrombo-embolism is recommended for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications).^{49,50,64}

IA It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/ thrombo-embolism and bleeding, and the relative risk and benefit for a given patient.^{49,50,51}

IA The CHADS₂ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF.⁵¹

IA For the patients with a CHADS₂ score of ≥ 2 , chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0–3.0 (target 2.5), unless contraindicated.^{49,50,55}

IA For a more detailed or comprehensive stroke risk assessment in AF (e.g. with CHADS₂ scores 0–1), a risk factor-based approach is recommended, considering 'major' and 'clinically relevant non-major' stroke risk factors.⁵³

IA Patients with 1 'major' or > 2 'clinically relevant non-major' risk factors are high risk, and OAC therapy is recommended, unless contraindicated.⁵³

Patients with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as:

IA i. VKA therapy⁵³ or

IB ii. aspirin 75–325 mg daily⁵⁰

IB Patients with no risk factors are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors) and the use of either aspirin 75–325 mg daily or no antithrombotic therapy is recommended.⁵³

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IIaA

Most patients with one 'clinically relevant non-major' risk factor should be considered for OAC therapy (e.g. with a VKA) rather than aspirin, based upon an assessment of the risk of bleeding complications, the ability to safely sustain adjusted chronic anticoagulation, and patient preferences.^{49,50}

IA

Anticoagulation with VKA is also recommended for patients with more than 1 moderate risk factor (female gender, age between 65-74, hypertension, diabetes mellitus, vascular disease, HF, or impaired LV systolic function [ejection fraction 35% or less or fractional shortening less than 25%]).^{3,4,65}

6.3.2 OPTIMAL INTERNATIONAL NORMALIZED RATIO

The level of anticoagulation is expressed as the INR and is derived from the ratio between the actual prothrombin time and that of a standardized control serum.

Keypoints

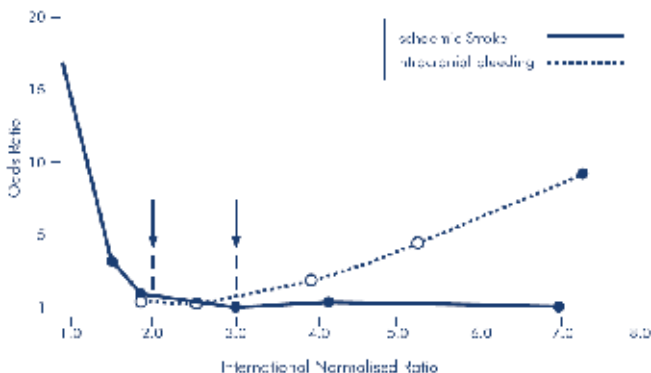
IA

For patients with non-valvular AF, it is recommended that the target intensity of anticoagulation with a VKA should to maintain an INR range of 2.0-3.0 (target 2.5)^{49,50,64}

IB

For patients with AF who have mechanical heart valves, it is recommended that the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve.^{64,66}

Figure 8: Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to intensity of anticoagulation in randomised trials of antithrombotic therapy for people with atrial fibrillation.



Reproduced with permission from Ann Intern Med. Hylek E, Singer D. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897-902.

IA

A target INR of 2.5 (target range of 2.0 to 3.0) is safe for primary prevention in older patients more than 75 years, unless contraindicated.⁶⁷

The major bleeding rate for 5 randomized clinical trials was 1.2% per year. In 2

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time-dependent INR analyses of anticoagulation in elderly AF cohorts, intracranial bleed increased with INR values over 3.5 to 4.0, and there was no

increment with values between 2.0 and 3.0 compared with lower INR levels. (See Figure 6, page 24)

For guide of using VKA in daily practice please refer to Appendix C, page 74.

6.3.2.1 Point-of-care testing and self-monitoring of anticoagulation

Self-monitoring may be considered if preferred by a patient who is both physically and cognitively able to perform the self-monitoring test, and, if not, a designated carer could help. Appropriate training by a competent healthcare professional is important, and the patient should remain in contact with a named clinician.

These point-of-care devices may also be useful in remote places and allow patients easy access to testing. Point-of-care devices also require adequate quality assurance and calibration.

6.3.3 ANTICOAGULATION WITH DIRECT THROMBIN INHIBITORS

Dabigatran etexilate is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a potent, direct, competitive inhibitor of thrombin. It does not require regular monitoring and has a serum half-life of 12 to 17 hours.

The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) was a randomized trial comparing two fixed doses of dabigatran, given in a blinded manner, with open-label use of VKA in patients with atrial fibrillation.⁵⁸ Dabigatran 110 mg b.i.d. was non-inferior to VKA for the prevention of stroke and systemic embolism with lower rates of major bleeding, whilst dabigatran 150 mg b.i.d. was associated with lower rates of stroke and systemic embolism with similar rates of major haemorrhage, compared with VKA.

Keypoints

IB Where oral anticoagulation is appropriate therapy for patients with non-valvular AF, dabigatran may be considered, as an alternative to adjusted dose VKA therapy.

There is currently no evidence to support the use of dabigatran for AF associated with valve disease, prosthetic valve, in pregnancy and chronic renal failure.

IB Patients with AF who are indicated for OAC but are unwilling to go on VKA because of the inconvenience, chronic oral anticoagulant therapy with dabigatran 150 mg twice daily may be considered, unless contraindicated.

IC Where patients are at a higher risk of bleeding (HAS-BLED ≥ 3), dabigatran 110 mg twice daily may be considered, unless contraindicated.

There was however an increase in the rate of gastrointestinal bleeding with the higher dose of dabigatran, despite an overall lower rates of bleeding at other sites.

IA Antithrombotic agent should be chosen based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient.

6.3.4 INVESTIGATIONAL AGENTS

Several new anticoagulant drugs—broadly in two classes, another oral direct thrombin inhibitors (e.g. AZD0837) and the oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban, YM150, etc.)—are being developed for stroke prevention in AF.

6.3.5 ANTIPLATELET AGENT ASPIRIN

Aspirin has been perceived to be safer than VKA in AF patients, but recent trials have shown that VKA are substantially more effective than aspirin for stroke prevention, with no difference in major bleeding event rates between VKA and aspirin treated patients.^{55,68}

In seven primary prevention trials, treatment with aspirin was associated with a non-significant 19% reduction in the incidence of stroke. There was an absolute risk reduction of 0.8% per year for primary prevention trials and 2.5% per year for secondary prevention by using aspirin. When data from all comparisons of antiplatelet agents and placebo or control groups were included in the meta-analysis, antiplatelet therapy reduced stroke by 22%.⁵⁵

The magnitude of stroke reduction from aspirin vs. placebo in the meta-analysis is broadly similar to that seen when aspirin is given to vascular disease subjects. Given that AF commonly co-exists with vascular disease, the modest benefit seen for aspirin in AF is likely to be related to its effects on vascular disease.

In the Japan Atrial Fibrillation Stroke Trial,⁶⁹ patients with lone AF were randomized to an aspirin group (aspirin at 150 – 200 mg/day) or a placebo control group. The primary outcomes of cardiovascular death and non fatal stroke or TIA was 3.1% per year in the aspirin group and was worse than those in the control group, 2.4% per year, and treatment with aspirin caused a non-significant increased risk of major bleeding (1.6%) compared with control (0.4%).

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study also showed that VKA (target INR 2 – 3) was superior to aspirin 75 mg daily in reducing the primary endpoint of fatal or disabling stroke, intracranial hemorrhage, or thromboembolism by 52%, with no difference in the risk of major hemorrhage between VKA and aspirin.⁶⁸

6.3.6 ASPIRIN AND CLOPIDOGREL COMBINATION

In patients with non valvular AF, adjusted dose VKA was found to be superior to the combination of clopidogrel (75mg daily) plus aspirin (75-100 mg daily) for the prevention of first occurrence of stroke, non-CNS systemic embolism, myocardial infarction and vascular death.⁵⁶

However, clopidogrel (75mg daily) plus aspirin (75-100 mg daily) conferred a relative risk reduction of 11% compared to aspirin.⁵⁷

There was an increased risk of major bleeding in patients receiving clopidogrel plus aspirin compared to patients receiving aspirin alone and was broadly similar to that seen with VKA.⁵⁷

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Keypoints

IaB

Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.⁵⁷

IbC

In some patients with one 'clinically relevant non-major' risk factor, e.g., female patients aged <65 years with no other risk factors, aspirin may be considered rather than OAC therapy.

6.4 ANTICOAGULATION IN SPECIAL CIRCUMSTANCES

6.4.1 PERIOPERATIVE ANTICOAGULATION

Patients with AF who are anticoagulated will require temporary interruption of VKA treatment before surgery or an invasive procedure. Many surgeons require an INR less than 1.5 or even INR normalization before undertaking surgery. The risk of clinically significant bleeding, even among outpatients undergoing minor procedures, should be weighed against the risk of stroke and thrombo-embolism in an individual patient before the administration of bridging anticoagulant therapy. (see Appendix C.1.9, page 80)

If the VKA used is warfarin, which has a half-life of 36 – 42 h, treatment should be interrupted for about 5 days before surgery (corresponding approximately to five half-lives of warfarin),

Examples of procedures with a low risk of bleeding,

• Dental Surgery – Restorative Surgery and Extractions

- Anticoagulation can be continued with an INR of less than 3.0 and appropriate topical haemostatic measures should be used. There is no need to discontinue warfarin.

• Minor Non-Invasive Surgery (e.g., dilation and curettage [D & C])

- Transient adjustment of the INR to below 1.5 for the perioperative period is required.

In cases of major surgery, consideration should be given to the risk of thromboembolism. (see CHA₂DS₂VAS_C scoring on page 29)

• Major Surgery (Interruption of Anticoagulation Required)

- In most people without mechanical prosthetic heart valves, anticoagulation can be safely discontinued temporarily, without the need for heparin cover. The decision is made on the basis of the risk of thrombosis.

Keypoints

IaC

In patients with AF who do not have mechanical prosthetic heart valves or those who are not at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures that carry a risk of bleeding, the interruption of OAC (with sub therapeutic anticoagulation for up to 48 h) should be considered, without substituting heparin as 'bridging' anticoagulation therapy. (see Appendix C.1.9 on page 80).

IaC

In patients with a mechanical prosthetic heart valve or AF at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures,

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'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin during the temporary interruption of OAC therapy should be considered.

IIaB Following surgical procedures, resumption of OAC therapy should be considered at the 'usual' maintenance dose (without a loading dose) on the evening of (or the next morning after) surgery, assuming there is adequate haemostasis.

IIbC When surgical procedures require interruption of OAC therapy for longer than 48h in high-risk patients, unfractionated heparin or subcutaneous LMWH may be considered.

6.4.2 ACUTE STROKE

Keypoints

IIaC In all patients with AF who have had an acute stroke, any uncontrolled hypertension should be appropriately managed before antithrombotic therapy is started.

IIaC Patients with AF and an acute stroke should have imaging done to exclude cerebral haemorrhage. In the presence of cerebral infarction, the decision on the timing of anticoagulation should be weighed between the risk of haemorrhagic transformation and the risk of recurrent thromboembolism.

- In the absence of haemorrhage, anticoagulation may start 2 weeks after stroke.
- In the presence of a large infarct, anticoagulation may be delayed after 2 weeks.
- In the presence of haemorrhage, anticoagulation should be withheld until an appropriate time.

IIaC Patients with AF and a recent TIA should have imaging done to exclude cerebral haemorrhage.

- In the absence of a haemorrhage, anticoagulation should be started as soon as possible.

IIbC In patients with AF who sustain ischaemic stroke or systemic embolism during treatment with usual intensity anticoagulation with VKA (INR 2.0–3.0), raising the intensity of the anticoagulation to a maximum target INR of 3.0–3.5 may be considered, rather than adding an antiplatelet agent.

6.4.3 Anticoagulant and Antiplatelet Therapy Use in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

There is a lack of published evidence on what is the optimal management strategy in anticoagulated patients with nonvalvular atrial fibrillation (AF) who undergo percutaneous coronary intervention (PCI) and, hence, need antiplatelet therapy.

Based on consensus, the post-PCI strategy should be tailored to the individual patient and their risk of thromboembolism and stent thrombosis weighed against their risk of bleeding while receiving triple therapy (see Table 13)

Keypoints

IIaC Following elective PCI in patients with AF with stable coronary artery disease, BMS should be considered, and drug-eluting stents avoided or strictly limited to those clinical and/or anatomical situations (e.g. long lesions, small vessels, diabetes, etc.), where a significant benefit is expected when compared with BMS.

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IaC

Following elective PCI, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term, followed by more long-term therapy (up to 1 year) with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily).

IaC

Following elective PCI, clopidogrel should be considered in combination with VKA plus aspirin for a minimum of 1 month after implantation of a BMS, but longer with a drug-eluting stent (at least 3 months for a sirolimus-eluting stent and at least 6 months for a paclitaxel-eluting stent); following which VKA and clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily).

6.4.4 NON-ST ELEVATION MYOCARDIAL INFARCTION

In patients with non-ST elevation myocardial infarction, dual antiplatelet therapy with aspirin plus clopidogrel is recommended, but in AF patients at moderate to high risk of stroke, OAC should also be given.

In the acute setting, patients are often given aspirin, clopidogrel, UFH, or LMWH (e.g. enoxaparin) or bivalirudin and/or a glycoprotein IIb/IIIa inhibitor (GPI). Drug-eluting stents should be limited to clinical situations, as described above (see Table 13). An uninterrupted strategy of OAC is preferred, and radial access should be used as the first choice.

For medium to long-term management, triple therapy (VKA, aspirin, and clopidogrel) should be used in the initial period (3 – 6 months), or for longer in selected patients at low bleeding risk. In patients with a high risk of cardiovascular thrombotic complications [e.g. high Global Registry of Acute Coronary Events (GRACE) or TIMI risk score], long-term therapy with VKA may be combined with clopidogrel 75 mg daily (or, alternatively, aspirin 75 – 100 mg daily).

Table 13: Antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0-2)	Elective	Bare-metal	1 month: triple therapy of VKA (INR 2.0-2.5) + aspirin 75-100mg/day +clopidogrel 75 mg/day Lifelong: VKA (INR 2.0-3.0) alone
	Elective	Drug-eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0-2.5) + aspirin 75-100mg/day +clopidogrel 75 mg/day Up to 12 th month: combination of VKA (INR 2.0-2.5) + clopidogrel 75/dayb (or aspirin 100m/day) Lifelong: VKA (INR 2.0-3.0) alone
	ACS	Bare-metal/drug-eluting	6 months: triple therapy of VKA (INR 2.0-2.5) + aspirin 75-100mg/day +clopidogrel 75 mg/day Up to 12 th month: combination of VKA (INR 2.0-2.5) + clopidogrel 75/dayb (or aspirin 100m/day) Lifelong: VKA (INR 2.0-3.0) alone
High (e.g. HAS-BLED score >3)	Elective	Bare-metalc	2-4 weeks: triple therapy of VKA (INR 2.0-2.5) + aspirin 75-100mg/day +clopidogrel 75 mg/day Lifelong: VKA (INR 2.0-3.0) alone
	ACS	Bare-metalc	4 weeks: triple therapy of VKA (INR 2.0-2.5) + aspirin 75-100mg/day +clopidogrel 75 mg/day (or aspirin 100m/day) Lifelong: VKA (INR 2.0-3.0) alone

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ACS = acute coronary syndrome; AF = atrial fibrillation; INR = international normalized ratio; VKA = vitamin K antagonist.

Gastric protection with a proton pump inhibitor (PPI) should be considered where necessary.

^aSirolimus, everolimus, and tacrolimus.

^bCombination of VKA (INR 2.0–3.0)+aspirin \leq 100 mg/day (with PPI, if indicated) may be considered as an alternative.

^cDrug-eluting stents should be avoided as far as possible, but, if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary.

Adapted from Lip et al.⁵⁴

Keypoints

IaC

Following an ACS with or without PCI in patients with AF, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term (3–6 months), or longer in selected patients at low bleeding risk, followed by long-term therapy with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily).

IaC

In anticoagulated patients at very high risk of thrombo-embolism, uninterrupted therapy with VKA as the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3).

IbC

When VKA is given in combination with clopidogrel or low-dose aspirin, careful regulation of the anticoagulation dose intensity may be considered, with an INR range of 2.0–2.5.

IbC

Following revascularization surgery in patients with AF, VKA plus a single antiplatelet drug may be considered in the initial 12 months, but this strategy has not been evaluated thoroughly and is associated with an increased risk of bleeding.

IbC

In patients with stable vascular disease (e.g. >1 year, with no acute events), VKA monotherapy may be considered, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event.

6.4.5 CARIOVERSION

Conversion of AF to sinus rhythm results in transient mechanical dysfunction of the LA and LAA⁷⁰ ("stunning"), which can occur after spontaneous, pharmacological,^{48,71} or electrical^{71,73} conversion of AF. Thrombus may form during the period of stunning and is expelled after the return of mechanical function, explaining the clustering of thromboembolic events during the first 10 d after cardioversion.^{74,75} Recovery of mechanical function may be delayed, depending partially on the duration of AF before conversion.^{76,46,87}

The risk of thromboembolism after cardioversion is between 1% and 5%^{77,78} and is reduced when anticoagulation (INR 2.0 to 3.0) is given for 4 wk before and after conversion^{79,80} (see Figure 9).

Keypoints

IB

For patients with AF or AFL of 48-h duration or longer, or when the duration of AF or AFL is unknown, anticoagulation (INR 2.0 to 3.0) is recommended for at least 4 weeks prior to and 4 weeks after cardioversion, regardless of the method used to restore sinus rhythm.⁶⁴

IC

For patients with AF requiring immediate/emergency cardioversion because of haemodynamic instability, heparin (i.v. UFH bolus followed by infusion, or weight-adjusted therapeutic dose LMWH) is recommended.

IB

After immediate/emergency cardioversion in patients with AF of 48 hour duration or longer, or when the duration of AF is unknown, OAC therapy is recommended for at least 4 weeks, similar to patients undergoing elective cardioversion.⁶⁴

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IIbC

For patients with AF duration that is clearly <48 h and no thrombo-embolic risk factors, i.v. heparin or weight-adjusted therapeutic dose LMWH may be considered peri-cardioversion, without the need for post-cardioversion oral anticoagulation.

It is important to stress that in following cardioversion of all patients at high risk of AF recurrence or with stroke risk factors, consideration should be given towards long-term anticoagulation, as thromboembolism may occur during asymptomatic recurrence of AF.

IB

For patients with AF <48 h and at high risk of stroke, i.v. heparin or weight-adjusted therapeutic dose LMWH is recommended peri-cardioversion, followed by OAC therapy with a VKA (INR 2.0–3.0) long term.^{49,55,64}

IB

In patients at high risk of stroke, OAC therapy with a VKA (INR 2.0–3.0) is recommended to be continued long-term.^{49,55,64}

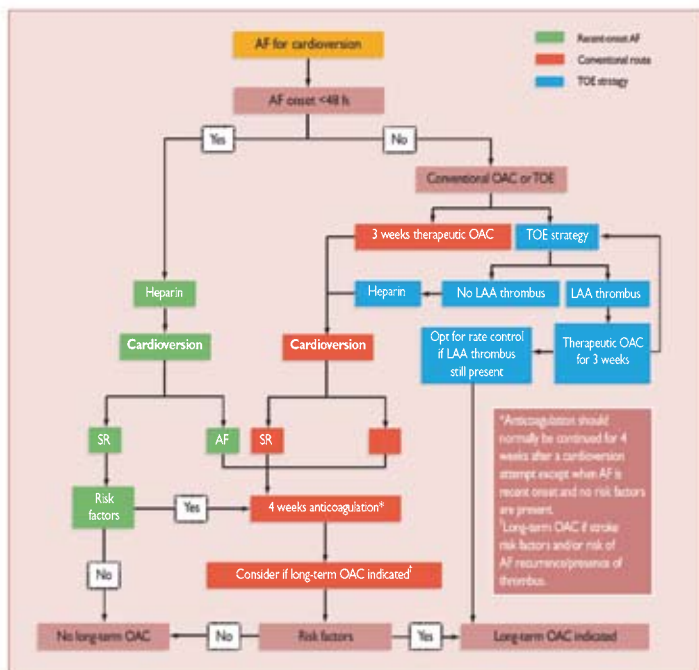


Figure 9: Cardioversion of haemodynamically stable AF, the role of TOE-guided cardioversion, and subsequent anticoagulation strategy. AF = atrial fibrillation; DCC = direct current cardioversion; LA = left atrium; LAA = left atrial appendage; OAC = oral anticoagulant; SR = sinus rhythm; TOE = transoesophageal echocardiography.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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IB As an alternative to anticoagulation prior to cardioversion of AF or AFL, it is reasonable to perform TOE in search of thrombus.¹³

IIaB • For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation.

IIaB • Thereafter, continuation of oral anticoagulation (INR 2.0 to 3.0) is reasonable for at least 4 weeks, as for elective cardioversion.

IIaB • For patients in whom thrombus is identified, oral anticoagulation (INR 2.0 to 3.0) is reasonable for at least 4 weeks before and 4 weeks after restoration of sinus rhythm, and longer anticoagulation may be appropriate after apparently successful cardioversion, because the risk of thromboembolism often remains elevated in such cases.

IC For patients undergoing a TOE-guided strategy in whom thrombus is identified, VKA (INR 2.0–3.0) is recommended for at least 4 weeks, followed by a repeat TOE to ensure thrombus resolution.

IIaC If thrombus resolution is evident on repeat TOE, cardioversion should be performed, and OAC should be considered for 4 weeks or lifelong (if risk factors are present).

IIbC If thrombus remains on repeat TOE, an alternative strategy (e.g. rate control) may be considered.

This strategy may be useful to allow early cardioversion of patients with AF > 48 hours or where a minimal period of anticoagulation is preferred.

6.5 NON-PHARMACOLOGICAL METHODS TO PREVENT STROKE

The left atrial appendage (LAA) is considered the main site of atrial thrombogenesis and thus, occlusion of the LAA orifice may reduce the development of atrial thrombi and stroke in patients with AF

The PROTECT AF trial⁸¹ randomized 707 eligible patients to percutaneous closure of the LAA using a WATCHMAN device and subsequent discontinuation of warfarin (intervention, n = 463), or to VKA treatment (INR range 2 – 3; control, n = 244). The primary efficacy event rate (a composite endpoint of stroke, cardiovascular death, and systemic embolism) of the WATCHMAN device was considered non-inferior to that of VKA. There was a higher rate of adverse safety events in the intervention group than in the control group, due mainly to periprocedural complications.

6.6 RISK OF LONG-TERM ANTICOAGULATION

6.6.1. ASSESSMENT OF RISK OF BLEEDING

An assessment of bleeding risk should be part of the clinical assessment of patients before starting anticoagulation therapy.

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In order to provide adequate thromboprophylaxis with minimal risk of bleeding, current clinical practice aims for a target INR of between 2.0 and 3.0; INRs of more than 3.0 are associated with increases in bleeding and INRs of less than 2.0 are associated with increases in stroke risk.

The annual risks of intracranial haemorrhage increased from 0.1% in control to 0.3% in VKA groups, which represents an excess of two intracranial bleeds per annum per 1,000 patients treated.

Even low-dose aspirin increases the risk of major haemorrhage by two-fold, especially in the setting of uncontrolled hypertension.

Controlling and monitoring of hypertension and other associated co morbidities is extremely important in minimizing the risk of bleeding in patients on prophylactic OAC.

The fear of falls may be overstated, as a patient may need to fall 300 times per year for the risk of intracranial haemorrhage to outweigh the benefit of OAC in stroke prevention.

While these factors are often cited as reasons for non-prescription of VKA in the elderly, the absolute benefit is likely to be greatest in this same group in view of their high risk.⁶⁸

6.6.2 RISK SCORE FOR BLEEDING

The bleeding risk score **HAS-BLED** was formulated by incorporating risk factors from a derivation cohort of a large population database of the prospective Euro Heart Survey on AF.⁸² The clinical characteristic comprising the HAS-BLED bleeding risk score is shown in Table 14.

It is reasonable to use the HAS-BLED score to assess bleeding risk in AF patients, whereby a score of ≥ 3 indicates 'high risk', and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin.

A schema such as HAS-BLED is a user-friendly method of predicting bleeding risk and is easy to remember.

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Table 14 : Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic ^a	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRS	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

^a 'Hypertension' is defined as systolic blood pressure ≥ 160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 μ mol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin ≥ 2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase ≥ 3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR = international normalized ratio.

Adapted from Pisters et al.⁸²

Keypoints

IIaA Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly.^{68,82,83}

IIaB The HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly] should be considered as a calculation to assess bleeding risk, whereby a score of ≥ 3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin.⁸²

7 MANAGEMENT – LONGTERM RATE CONTROL

7.1 PHARMACOLOGICAL RATE CONTROL

Criteria for rate control vary with patient age but usually involve achieving ventricular rates

- 60 - 80 beats per minute at rest and
- 90 – 115 beats per minute during moderate exercise.²³

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However, maintaining lenient control of heart rate (a resting rate of less than 100 beats per minute) is easier to achieve and is comparable to strict control (a resting heart rate of 80 beats per minute and a heart rate during moderate exercise of less than 110 beats per minute) on long-term composite outcomes.⁸⁴ For patients without severe symptoms due to high ventricular rate, a lenient rate control therapy approach is reasonable (See Figure 10).

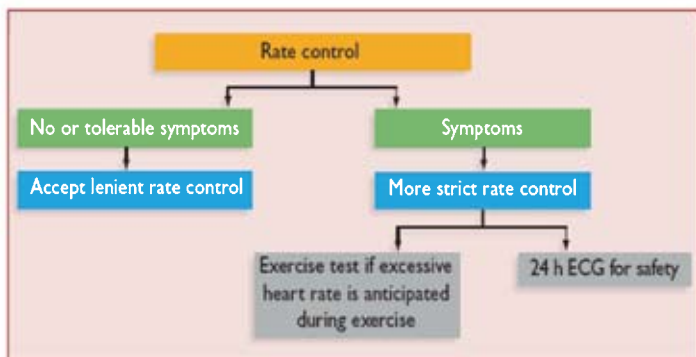


Figure 10: Optimal level of heart rate control.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

Drugs commonly used are β -blockers, non-dihydropyridine calcium channel antagonists, and digitalis. Acute treatment is described in Section 5.1.1.

Combinations of drugs may be necessary. Dronedaronone may also effectively reduce heart rate during AF recurrences. Amiodarone may be suitable for some patients with otherwise refractory rate control. The combination of a β -blocker and digitalis may be beneficial in patients with heart failure.

When a strict rate control policy is adopted (resting heart rate < 80 bpm and a target heart rate of <110 bpm during moderate exercise) a 24 h Holter monitor should be performed to assess pauses and bradycardia.

Selection of the most effective and appropriate rate-control agent, or combination of agents, is vital. Table 15 lists rate-control treatments in order of preference, taking into account other conditions that may be present. Figure 11, page 47 provides an algorithm on how to make the drug choice and Table 16 list the drugs and their doses for rate control.

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Table 15: Choice of a rate-control agent

Co morbidity	First-line	Second-line	Less effective or desirable
No heart disease	Beta-blockers* OR Non-dihydropyridine Calcium channel blockers†		Digoxin‡ (can be first-line in people unlikely to be active)
Hypertension	Beta-blockers* OR Non-dihydropyridine Calcium channel blockers†		Digoxin‡
Ischaemic heart disease	Beta-blockers*	First line agent plus Non-dihydropyridine Calcium-channel blockers† OR Digoxin‡	Ablation + pacing
Congestive heart failure	Digoxin in overt heart failure Carvedilol or bisoprolol or metoprolol in stable heart failure	Beta-blockers* (excluding carvedilol, bisoprolol and metoprolol) OR Diltiazem	Amiodarone Ablation and pacing should be considered
Chronic obstructive pulmonary disease	Non-dihydropyridine Calcium channel blockers†	First line agent plus beta-blockers (if there is no reversible bronchospasm.	Digoxin‡

* excluding sotalol

† diltiazem or verapamil

‡ as monotherapy (can be used in combination with other rate-control agents)

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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Table 16: Oral pharmacological agents for rate control in people with atrial fibrillation/atrial flutter

Drug	Oral loading dose	Onset of action	Commonly used oral maintenance doses	Adverse effects	Comments
Beta-blockers					
Atenolol	N/A	2 to 3 hr	25 to 50 mg	Hypotension, heart block, bradycardia, asthma, heart failure	In people with heart failure, lower doses may be advisable (negative inotropic effect)
Carvedilol	N/A	60 to 90 min	6.25 to 25 mg bd		
Metoprolol	N/A	4 to 6 hr	23.75 to 200 mg/day*		
Nadolol	N/A	3 to 4 hr	20 to 80 mg/day		
Propranolol	N/A	60 to 90 min	80 to 240 mg/day		
Calcium channel blockers					
Diltiazem	N/A	1 to 4 hr	120 to 360 mg/day	Hypotension, heart block, heart failure	In people with heart failure, lower doses may be advisable
Verapamil	N/A	1 to 2 hr	120 to 360 mg/day	Hypotension, heart block, heart failure, digoxin interaction	In people with heart failure, lower doses may be advisable (negative inotropic effect)
Other					
Digoxin	0.5 to 1.0 mg	2 hr	0.0625 to 0.375 mg/day	Digoxin toxicity, heart block, bradycardia	First-line therapy only for people unlikely to be active (eg, older people or infirm) and for people with heart failure. Less effective in hyperadrenergic states
Amiodarone	400 to 800 mg/day for 1 week	1 to 3 wk	200 mg/day	Photosensitivity and other skin reactions, pulmonary toxicity, polyneuropathy, gastrointestinal upset, bradycardia, hepatic toxicity, thyroid dysfunction, torsades de pointes (rare)	Although there is fairly good evidence of efficacy, this is an agent of last resort in this indication, due to its long-term toxicity

N/A = Not applicable

Adapted from: Fuster V, Ryden LE, Asinger RW, *et al.*¹³⁴

Keypoints

IB

Rate control using pharmacological agents (β -blockers, non-dihydropyridine calcium channel antagonists, digitalis, or a combination thereof) is recommended in patients with paroxysmal, persistent, or permanent AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia.³⁴

IC

In patients who experience symptoms related to AF during activity, the adequacy of heart rate control should be assessed during exercise, adjusting pharmacological treatment as necessary to keep the rate in the physiological range.

IC

In pre-excitation AF, or in patients with a history of AF, preferred drugs for rate control are propafenone or amiodarone

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IIbB

It is reasonable to initiate treatment with a lenient rate control protocol aimed at a resting heart rate <110 bpm.⁸⁴

IIbB

It is reasonable to adopt a stricter rate control strategy when symptoms persist or tachycardiomyopathy occurs, despite lenient rate control: resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm. After achieving the strict heart rate target, a 24 h Holter monitor is recommended to assess safety.⁸⁴

IIaC

Digoxin is indicated in patients with heart failure and LV dysfunction, and in sedentary (inactive) patients.

IIbC

Rate control may be achieved by administration of oral amiodarone when other measures are unsuccessful or contraindicated.

IIIB

Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.⁸⁸

IB

Intravenous administration of amiodarone is recommended to control the heart rate in patients with AF and HF who do not have an accessory pathway.

IIaC

Intravenous amiodarone can be useful to control the heart rate in patients with AF when other measures are unsuccessful or contraindicated.³⁵

7.1.2 Combination therapy

Combination of drugs may be required to control heart rate. Care should be taken to avoid severe bradycardia. The combination of digoxin and β -blocker appears more effective than the combination of digoxin with a CCB.⁸⁹

Keypoint

IIaB

A combination of digoxin and either a β -blocker, diltiazem, or verapamil is reasonable to control the heart rate both at rest and during exercise in patients with AF.

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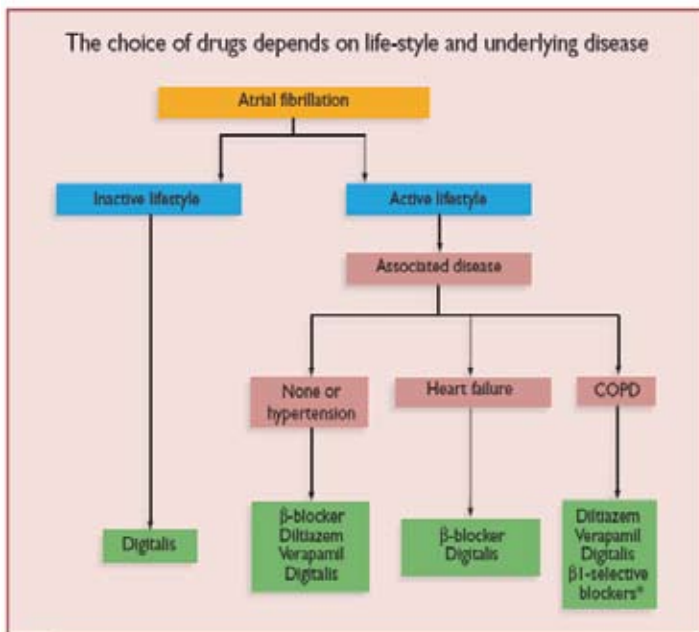


Figure 11 : Rate control. COPD = chronic obstructive pulmonary disease. *Small doses of β_1 -selective blockers may be used in COPD if rate control is not adequate with non-dihydropyridine calcium channel antagonists and digoxin. Amiodarone is also used for rate control in patients who do not respond to glycosides, β -blockers or non-dihydropyridine calcium antagonists. Dronedarone may also be used for rate control in patient with recurrent episodes of atrial fibrillation.

Adapted from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

7.2 NON-PHARMACOLOGICAL RATE CONTROL

7.2.1 AV NODAL ABLATION AND PACING

AV nodal ablation in conjunction with permanent pacemaker implantation provides highly effective control of the heart rate and improves symptoms, quality of life, exercise capacity, ventricular function and healthcare utilization in selected patients with AF.^{90,100}

Ablation of the atrioventricular node is a palliative but irreversible procedure and is therefore reasonable in patients in whom pharmacological rate control, including combination of drugs, has failed or rhythm control with drugs and/or LA ablation has failed.

When the rate of ventricular response to AF cannot be controlled with pharmacological agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in conjunction with permanent pacemaker implantation.

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It is suggested that programming the pacemaker initially for the 1st month post-ablation to a higher nominal rate (90 beat per minutes) will reduce the risk of sudden cardiac death.

Keypoints

- IIaB** Ablation of the AV node to control heart rate should be considered when the rate cannot be controlled with pharmacological agents and when AF cannot be prevented by antiarrhythmic therapy or is associated with intolerable side effects, and direct catheter-based or surgical ablation of AF is not indicated, has failed, or is rejected.^{90,100}
- IIaB** Ablation of the AV node should be considered for patients with permanent AF and an indication for CRT (NYHA functional class III or ambulatory class IV symptoms despite optimal medical therapy, LVEF <35%, QRS width >130 ms).¹⁰¹⁻¹⁰⁴
- IIaC** Ablation of the AV node should be considered for CRT non-responders in whom AF prevents effective biventricular stimulation and amiodarone is ineffective or contraindicated.
- IIaC** In patients with any type of AF and severely depressed LV function (LVEF <35%) and severe heart failure symptoms (NYHA III or IV), biventricular stimulation should be considered after AV node ablation.
- IIbC** Ablation of the AV node to control heart rate may be considered when tachycardia-mediated cardiomyopathy is suspected and the rate cannot be controlled with pharmacological agents, and direct ablation of AF is not indicated, has failed, or is rejected.
- IIbC** Ablation of the AV node with consecutive implantation of a CRT device may be considered in patients with permanent AF, LVEF <35%, and NYHA functional class I or II symptoms on optimal medical therapy to control heart rate when pharmacological therapy is insufficient or associated with side effects.
- IIbC** In patients with any type of AF, moderately depressed LV function (LVEF <45%) and mild heart failure symptoms (NYHA II), implantation of a CRT pacemaker may be considered after AV node ablation.
- IIbC** In patients with paroxysmal AF and normal LV function, implantation of a dual-chamber (DDDR) pacemaker with mode-switch function may be considered after AV node ablation.
- IIbC** In patients with persistent or permanent AF and normal LV function, implantation of a single-chamber (VVIR) pacemaker may be considered after AV node ablation.
- IIIC** Catheter ablation of the AV node should not be attempted without a prior trial of medication, or catheter ablation for AF, to control the AF and/or ventricular rate in patients with AF.

8 MANAGEMENT – LONGTERM RHYTHM CONTROL

The term 'rhythm control' encompasses the processes of conversion of atrial fibrillation (AF) or atrial flutter (AFI) to normal sinus rhythm, as well as the maintenance of sinus rhythm.

Maintenance of sinus rhythm may also be referred to as prevention of AF/AFI relapse or recurrence, and may be achieved by pharmacological or nonpharmacological means, or both (hybrid therapy).

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

In the absence of spontaneous reversion, cardioversion is chosen as part of the rhythm-control strategy.

The following are the guiding principles of antiarrhythmic drug therapy to maintain sinus rhythm in AF:

- (1) Treatment is motivated by attempts to reduce AF-related symptoms.
- (2) Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest.
- (3) Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate recurrence of AF.
- (4) If one antiarrhythmic drug 'fails', a clinically acceptable response may be achieved with another agent.
- (5) Drug-induced proarrhythmia or extra-cardiac side effects are frequent.
- (6) Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic agent

8.1 EFFICACY OF ANTIARRHYTHMIC DRUGS IN PREVENTING RECURRENT ATRIAL FIBRILLATION

In a recent meta-analysis of 44 randomized controlled trials comparing antiarrhythmic drugs against control,¹⁰⁵ the antiarrhythmic drugs significantly reduced the rate of recurrent AF. Overall, the likelihood of maintaining sinus rhythm is approximately doubled by the use of antiarrhythmic drugs.¹⁰⁶ Amiodarone was superior to class I agents and sotalol.

The number of patients needed to treat for 1 year was 2 – 9. Withdrawal due to side effects was frequent (1 in 9 – 27 patients), and all drugs except amiodarone and propafenone increased the incidence of proarrhythmia.¹⁰⁵ The number of patients needed to harm was 17 – 119. Most of the trials included in the analysis enrolled relatively healthy patients without severe concomitant cardiac disease. Although mortality was low in all studies (0 – 4.4%), rapidly dissociating sodium channel blockers (disopyramide phosphate, quinidine sulfate) were associated with increased mortality.

8.2 CHOICE OF ANTIARRHYTHMIC DRUGS

Antiarrhythmic therapy for recurrent AF is recommended on the basis of choosing safer, although possibly less efficacious, medication before resorting to more effective but less safe therapy. Upon initiation of antiarrhythmic therapy, regular ECG monitoring is recommended (see Table 16. page 45).

8.2.1 PATIENTS WITH LONE ATRIAL FIBRILLATION

In patients with no or minimal heart disease, β -blockers represent a logical first attempt to prevent recurrent AF when the arrhythmia is clearly related to mental or physical stress (adrenergic AF). Flecainide, propafenone, sotalol, or dronedarone is usually prescribed as second line agents (Figure 12, page 50).^{107,108}

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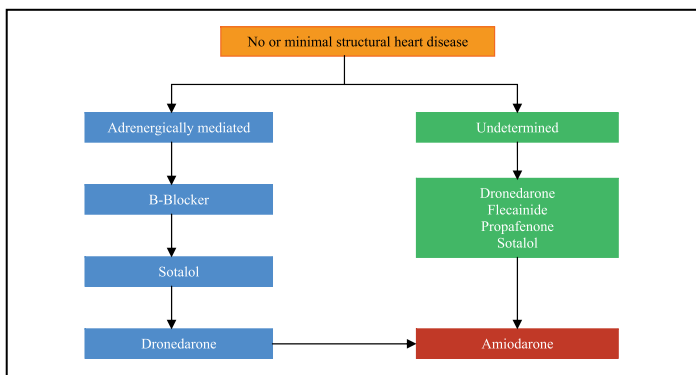
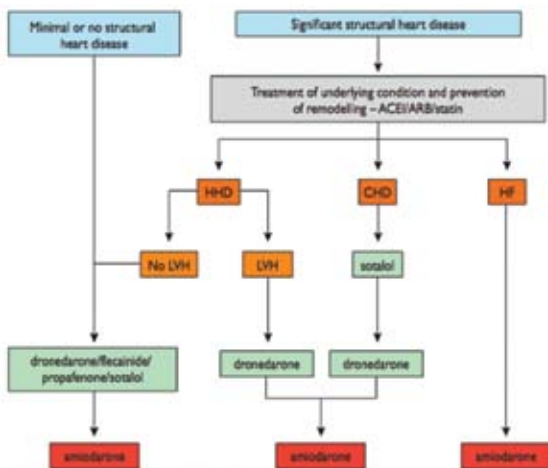


Figure 12. Choice of antiarrhythmic medication for the patient with AF and no or minimal structural heart disease. Medication may be initially based on the pattern of arrhythmia onset. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Adapted with modification from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

8.2.2 PATIENTS WITH UNDERLYING HEART DISEASE

Cardiovascular disease has conventionally been divided into a variety of pathophysiological substrates: hypertrophy, ischaemia, and congestive heart failure (Figure 13). For each of these it has been recommended that specific drugs be avoided.



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy; NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Figure 13. Choice of antiarrhythmic drug according to underlying pathology. ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CAD = coronary artery disease; CHF=congestive heart failure; HT=hypertension; LVH =left ventricular hypertrophy; NYHA=New York Heart Association; unstable=cardiac decompensation within the prior 4 weeks. Antiarrhythmic agents are listed in alphabetical order within each treatment box. ? = evidence for 'upstream' therapy for prevention of atrial remodelling still remains controversial.

Adapted with modification from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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Individual drugs and their main disadvantages are listed in Table 17.

Amiodarone is the most efficacious antiarrhythmic drug for the prevention of recurrent AF. However, several meta-analyses^{105,109-111} have failed to identify a beneficial effect of amiodarone on cardiovascular outcomes. In view of the better safety and potential outcome benefit, dronedarone may be preferable as the first antiarrhythmic option, at least in patients with symptomatic AF and underlying cardiovascular disease. Should dronedarone fail to control symptoms, amiodarone might then be necessary.

Dronedarone can be used safely in patients with ACS, chronic stable angina, hypertensive heart disease. Dronedarone should only be used in maintaining sinus rhythm and in whose normal heart rhythm has been restored. Dronedarone should not be used in patients with heart failure.¹¹²

8.2.2.1 Patients with left ventricular hypertrophy

In patients with LV hypertrophy, sotalol is thought to be associated with an increased incidence of proarrhythmia. Flecainide and propafenone may be used, but there is some concern about proarrhythmic risk, especially in patients with marked hypertrophy (LV wall thickness >1.4 cm according to previous guidelines), and associated coronary artery disease.

Since dronedarone was demonstrated to be safe and well tolerated in a large study including patients with hypertension and possible LV hypertrophy, it is an option for this population, although definitive data do not exist. Amiodarone should be considered when symptomatic AF recurrences continue to impact on the quality of life of these patients.

8.2.2.2 Patients with coronary artery disease

Patients who have coronary artery disease should not receive flecainide¹⁶³ or propafenone. Sotalol or dronedarone should be administered as first-line therapy. Dronedarone may be preferred based on its safety profile. Amiodarone is considered as the drug of last resort in this population due to its extra-cardiac side effect profile.

8.2.2.3 Patients with heart failure

Amiodarone is the only agents available in Malaysia that can be safely administered in patients with heart failure.

Dronedarone is contraindicated in patients with all classes of heart failure.¹¹² In such patients, amiodarone should be used.

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:

Keypoints

- IA • amiodarone^{21,105,113}
- IA • dronedarone^{85,86}
- IA • flecainide^{105,114}
- IA • propafenone^{105,113}
- IA • d,l-sotalol^{21,48,105}
- IA/C Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy), or dronedarone (Level of Evidence A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (Level of Evidence C).^{21,105,110,113}
- IB In patients with severe heart failure, NYHA class III and IV or recently unstable (decompensation within the prior month) NYHA class II, amiodarone should be the drug of choice.¹¹⁵
- IA In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.^{85,86,105,113-115}
- IC β -Blockers are recommended for prevention of adrenergic AF.
- IIaC If one antiarrhythmic drug fails to reduce the recurrence of AF to a clinically acceptable level, the use of another antiarrhythmic drug should be considered.
- IIaB Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.^{85,86}
- IIaC β -blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF.
- IIIB Dronedarone is not recommended for treatment of permanent AF and all classes of heart failure.
- IIIC Antiarrhythmic drug therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning permanent pacemaker.

8.3 NONPHARMACOLOGICAL THERAPY

There is a variety of alternative non-pharmacological therapies for the prevention and control of AF.

8.3.1 LEFT ATRIAL CATHETER ABLATION

Catheter ablation of AF particularly circumferential pulmonary vein ablation (isolation) in the left atrium represents a promising and evolving therapy for selected patients resistant to pharmacological therapy.

Ablation is indicated in highly symptomatic, paroxysmal or persistent AF, despite optimal medical therapy and in patients with minimal or moderate structural heart disease.

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A recent meta-analysis found a 77% success rate for catheter ablation strategies vs. 52% for antiarrhythmic medication.¹¹⁷ Similar results have been reported in other meta-analyses,¹¹⁸⁻¹²⁰ one of which showed that PV isolation for paroxysmal or persistent AF was associated with markedly increased odds of freedom from AF at 1 year.¹¹⁹

Ablation may particularly benefit younger patients with lone AF who are frequently symptomatic and for whom long-term antiarrhythmic poses higher risk and lifestyle cost.

For patients with either persistent AF or long-standing persistent AF, and no or minimal organic heart disease, the treatment strategies and the benefit – risk ratio of catheter ablation are less well established. Extensive and frequently repeated ablation procedures may be necessary in these patients, and it seems reasonable to recommend that they should be refractory to antiarrhythmic drug treatment before ablation is considered (See Figure 14).

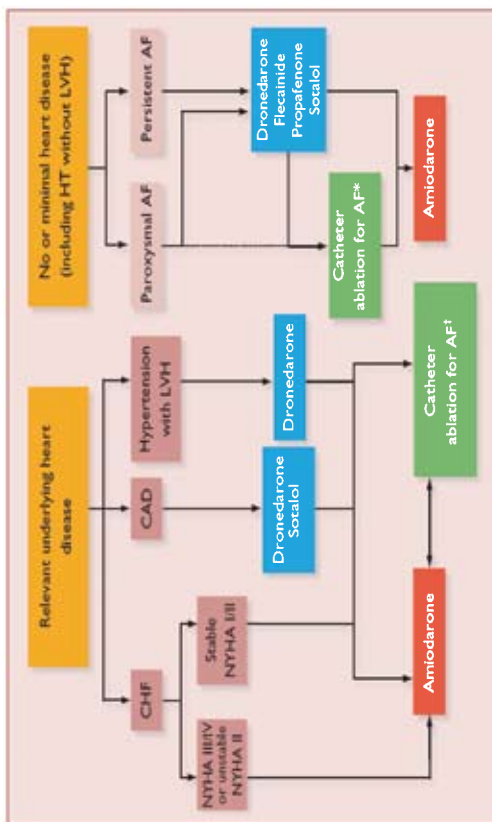


Figure 14. Choice between ablation and antiarrhythmic drug therapy for patients with and without structural heart disease. Proposed integration of antiarrhythmic drug and catheter ablation for AF in patients with relevant underlying heart disease and for those with no or minimal heart disease, including hypertension (HT) without left ventricular hypertrophy (LVH). More extensive LA ablation may be needed; usually PVI is appropriate. AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; HT = hypertension; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; PVI = pulmonary vein isolation. Antiarrhythmic agents are listed in alphabetical order within each treatment box. Please note that left atrium (LA) ablation as first-line therapy (dashed line) is a Class IIB recommendation for patients with paroxysmal AF and no or minimal heart disease, who remain highly symptomatic, despite rate control, and who reject antiarrhythmic drug therapy.

Adapted with modification from the ESC Guidelines for the Management of Atrial Fibrillation (2010 Version) (European heart Journal 2010; doi:10.1093/eurheartj/ehq278)

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For symptomatic paroxysmal and persistent AF in patients with relevant organic heart disease, antiarrhythmic drug treatment is recommended before catheter ablation. In such patients, successful ablation is more difficult to achieve. Major symptoms should be associated with the arrhythmia to justify the procedure. Ablation of persistent and long-standing persistent AF is associated with variable but encouraging success rates, but very often requires several attempts.

Keypoints

- IB** Ablation of common atrial flutter is recommended as part of an AF ablation procedure if documented prior to the ablation procedure or occurring during the AF ablation.¹⁸
- IIaA** Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication.^{31,117,122-125}
- IIaB** Ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option.¹⁸
- IIaC** In patients post-ablation, LMWH or i.v. UFH should be considered as 'bridging therapy' prior to resumption of systemic OAC, which should be continued for a minimum of 3 months. Thereafter, the individual stroke risk factors of the patient should be considered when determining if OAC therapy should be continued.
- IIaB** Continuation of OAC therapy post-ablation is recommended in patients with 1 'major' ('definitive') or >2 'clinically relevant non-major' risk factors (i.e. CHA₂DS₂-VASc score >2).¹²⁶
- IIbC** Catheter ablation of AF may be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs.
- IIbB** Catheter ablation of AF in patients with heart failure may be considered when antiarrhythmic medication, including amiodarone, fails to control symptoms.^{29,30}
- IIbB** Catheter ablation of AF may be considered prior to antiarrhythmic drug therapy in symptomatic patients despite adequate rate control with paroxysmal symptomatic AF and no significant underlying heart disease.¹¹⁷

8.3.2 SURGICAL ABLATION

The major indication for surgical ablation of AF is the presence of both AF and the requirement for cardiac surgery for structural heart disease.^{120,127,128} Stand-alone surgery for AF should be considered for symptomatic AF patients who prefer a surgical approach, have failed one or more attempts at catheter ablation, or who are not candidates for catheter ablation.

Keypoints

- IIaA** Surgical ablation of AF should be considered in patients with symptomatic AF undergoing cardiac surgery.^{120,127,128}
- IIbC** Surgical ablation of AF may be performed in patients with asymptomatic AF undergoing cardiac surgery if feasible with minimal risk.
- IIbC** Minimally invasive surgical ablation of AF without concomitant cardiac surgery is feasible and may be performed in patients with symptomatic AF after failure of catheter ablation.

8.3.3 SUPPRESSION OF AF THROUGH PACING

Several studies have examined the role of atrial pacing to prevent recurrent paroxysmal AF. In patients with symptomatic bradycardia, the risk of AF is lower with atrial than with ventricular pacing.¹²⁹ In patients with sinus node dysfunction and normal AV conduction, data from several randomized trials support atrial or dual-chamber rather than ventricular pacing for prevention of AF.¹³⁰⁻¹³³ Patients with paroxysmal AF and symptomatic bradycardia should be referred for electrophysiological review for consideration of atrial based pacing.

Keypoint

IaB

When ventricular pacing with dual-chamber devices is unavoidable because of concomitant disease of the AV conduction system, the evidence is less clear that atrial-based pacing is superior. Although atrial-based pacing is associated with a lower burden of AF and stroke risk compared to ventricular-based pacing in patients requiring pacemakers for bradyarrhythmias, the value of pacing as a primary therapy for prevention of recurrent AF has not been proven.

8.4 UPSTREAM THERAPY

Upstream therapy is a term used that relates to prevention or delaying of myocardial remodelling associated with hypertension, heart failure, or inflammation (e.g. after cardiac surgery) and therefore may deter the development of new AF (primary prevention) or, once established, its rate of recurrence or progression to permanent AF (secondary prevention).¹³⁵

Treatments with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone antagonists, statins, and omega-3 polyunsaturated fatty acids (PUFAs) are usually referred to as 'upstream' therapies for AF.

8.4.1 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

Primary prevention

In patients with **congestive cardiac failure**, several meta-analyses have shown a significant 30 – 48% reduction in risk of AF associated with ACEI and ARB therapies.¹³⁶⁻¹⁴⁰

While in patients with **hypertension**, in meta-analyses, the overall trend was in favour of ACEI- or ARB-based therapy, but only one meta-analysis has shown a statistically significant 25% reduction in RR of incident AF.¹³⁸

Keypoints

IaA

ACEIs and ARBs should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.¹³⁶⁻¹⁴⁰

IaB

ACEIs and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with left ventricular hypertrophy.^{138,141,142}

IIIC

Upstream therapies with ACEIs, ARBs, and statins are not recommended for primary prevention of AF in patients without cardiovascular disease.

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

Secondary prevention

Several relatively small prospective randomized controlled trials have demonstrated that therapy with ACEI/ARB conferred an additional benefit on risk of recurrent **AF after cardioversion** when co-administered with antiarrhythmic drug therapy, usually amiodarone, compared with an antiarrhythmic drug alone.^{143,144} Meta-analyses driven by these studies have reported a significant 45 – 50% reduction in RR of recurrent AF.¹³⁶⁻¹³⁹ Conversely, a double-blind, placebo-controlled study failed to demonstrate any benefit of therapy with candesartan for promotion of sinus rhythm after cardioversion in patients who did not receive antiarrhythmic drug therapy.¹⁴⁵

Evidence to support the use of ACEI/ARB in patients with paroxysmal or persistent AF who are not undergoing electrical cardioversion remains controversial.

Keypoints

IIbB

Pre-treatment with ACEIs and ARBs may be considered in patients with recurrent AF and receiving antiarrhythmic drug therapy.^{136-138,143,144}

IIbB

ARBs or ACEIs may be useful for prevention of recurrent paroxysmal AF or in patients with persistent AF undergoing electrical cardioversion in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g. hypertension).^{136,146,147}

8.4.3 STATINS

For **post-operative AF**, a recent systematic review,¹⁴⁸ have reported a lower incidence of new onset AF favouring statins. Some studies, particularly in patients with LV dysfunction and **heart failure**, have shown a 20 – 50% reduction in the incidence of new-onset AF.¹⁴⁹

Keypoints

IIaB

Statins should be considered for prevention of new-onset AF after coronary artery bypass grafting, isolated or in combination with valvular interventions.^{148,150}

IIbB

Statins may be considered for prevention of new-onset AF in patients with underlying heart disease, particularly heart failure.^{151,152}

8.4.4 POLYUNSATURATED FATTY ACIDS AND ALDOSTERONE ANTAGONIST

At present, there is no robust evidence to make any recommendation for the use of PUFAs or aldosterone antagonist for primary or secondary prevention of AF.

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

9 MANAGEMENT – SPECIAL POPULATIONS

9.1 POST-OPERATIVE AF

Although AF may occur after noncardiac surgery, the incidence of atrial arrhythmias including AF after open-heart surgery is between 20% and 50%. Post-operative AF usually occurs within 5 d of open-heart surgery, with a peak incidence on the second day. The arrhythmia is usually self-correcting, and sinus rhythm resumes in more than 90% of patients by 6 to 8 wk after surgery.

A systematic review of 58 studies in 8565 patients has shown that interventions to prevent and/or treat post-operative AF with β -blockers, sotalol, or amiodarone and, less convincingly, atrial pacing, are favoured with respect to outcome.¹⁵³

9.1.1 PREVENTION OF POST-OPERATIVE ATRIAL FIBRILLATION

β -Blocker therapy is most effective when provided both before and after cardiac surgery compared with only before or after surgery.¹⁵³⁻¹⁵⁵ Withdrawal of β -blockers is a significant risk factor for the development of post-operative AF and should be avoided. Treatment should be started at least 1 week before surgery with a β -blocker without intrinsic sympathomimetic activity.

Prophylactic **amiodarone** decreased the incidence of post-operative AF¹⁵⁶. The beneficial effect of amiodarone has been consistently demonstrated in a systematic review.¹⁵³ The adverse effects of perioperative prophylactic i.v. amiodarone include an increased probability of post-operative bradycardia and hypotension.¹⁵³

Sotalol has been reported to reduce the incidence of post-operative AF by 64% compared with placebo.¹⁵³ However, the use of sotalol places patients at risk of bradycardia and torsade de pointes, especially those with electrolyte disturbances, and its use in post-operative AF is limited.

Meta-analyses demonstrated that **corticosteroid** therapy was associated with a 26 – 45% reduction in post-operative AF and shorter hospital stay.¹⁵⁷ However, the potential adverse effects on glucose metabolism, wound healing, and infection, make their use for prevention of AF as controversial.

One meta-analysis of eight trials has shown that prophylactic **atrial pacing** reduced the incidence of post-operative AF regardless of the atrial pacing site or pacing algorithm used.¹⁵³

9.1.2 TREATMENT OF POST-OPERATIVE ATRIAL FIBRILLATION

In haemodynamically stable patients, the majority will convert spontaneously to sinus rhythm within 24 h. Initial management includes correction of predisposing factors (such as pain management, haemodynamic optimization, weaning of i.v. inotropes, correcting electrolytes and metabolic abnormalities, and addressing anaemia or hypoxia) where possible.¹⁵⁸

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

In the highly symptomatic patient or when rate control is difficult to achieve, cardioversion may be performed. DCCV is 95% successful but pharmacological cardioversion is more commonly used. Amiodarone was shown to be more effective than placebo in converting post-operative AF to sinus rhythm.

Short-acting β -blockers (e.g. esmolol) are particularly useful when haemodynamic instability is a concern. Other atrioventricular nodal blocking agents, such as non-dihydropyridine calcium channel antagonists, can be used as alternatives, but digoxin is less effective when adrenergic tone is high. The agents used for rate control of AF following cardiac surgery are listed in Table 15.

A number of studies have shown an increased risk of stroke in patients after cardiac surgery. Anticoagulation with heparin or VKA is appropriate when AF persists longer than 48 h.¹⁵⁹ Standard precautions regarding anticoagulation pericardioversion should be used (see Section 4.3).

Keypoints

- IA Oral β -blockers are recommended to prevent post-operative AF for patients undergoing cardiac surgery in the absence of contraindications.^{153,154}
- IB If used, β -blockers (or other oral antiarrhythmic drugs for AF management) are recommended to be continued until the day of surgery.^{154,155}
- IC Restoration of sinus rhythm by DCCV is recommended in patients who develop post-operative AF and are haemodynamically unstable.
- IB Ventricular rate control is recommended in patients with AF without haemodynamic instability.¹⁵⁵
- IIaA Pre-operative administration of amiodarone should be considered as prophylactic therapy for patients at high risk for post-operative AF.^{153,154,160}
- IIaA Unless contraindicated, antithrombotic/anticoagulation medication for post-operative AF should be considered when the duration of AF is >48 hours.¹⁵⁹
- IIaB If sinus rhythm is restored successfully, duration of anticoagulation should be for a minimum of 4 weeks but more prolonged in the presence of stroke risk factors.¹⁵⁹
- IIaC Antiarrhythmic medications should be considered for recurrent or refractory postoperative AF in an attempt to maintain sinus rhythm.
- IIbA Sotalol may be considered for prevention of AF after cardiac surgery, but is associated with risk of proarrhythmia.¹⁵³
- IIbA Batrial pacing may be considered for prevention of AF after cardiac surgery.¹⁵³
- IIbB Corticosteroids may be considered in order to reduce the incidence of AF after cardiac surgery, but are associated with risk.¹⁵⁷

Atrial flutter is less common than AF after cardiac surgery,¹⁶¹ but pharmacological therapy is similar. Prevention of postoperative atrial flutter is as difficult as prevention of AF, but atrial overdrive pacing is generally useful for termination of atrial flutter when epicardial electrodes are in place.

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

9.2 ACUTE CORONARY SYNDROME

AF occurs with an incidence between 2 to 21% in patients with ACS¹⁶² and is more commonly associated with ACS in older patients and those with higher heart rate and LV dysfunction.¹⁶²

AF is associated with increased in-hospital mortality in the setting of ACS. Stroke rates are also increased in patients with ACS and AF.

Specific recommendations for management of patients with AF in the setting of ACS are based primarily on consensus, because no adequate trials have tested alternative strategies.

Keypoints

- IC** Direct-current cardioversion is recommended for patients with severe hemodynamic compromise or intractable ischemia, or when adequate rate control cannot be achieved with pharmacological agents in patients with ACS and AF.
- IC** Intravenous beta blockers and nondihydropyridine calcium antagonists are recommended to slow a rapid ventricular response to AF in patients with ACS who do not have LV dysfunction, bronchospasm, or AV block.
- IC** Intravenous amiodarone is recommended to slow a rapid ventricular response to AF and improve LV function in patients with ACS.
- IaC** Intravenous administration of non-dihydropyridine calcium antagonists (verapamil, diltiazem) should be considered to slow a rapid ventricular response to AF in patients with ACS and no clinical signs of heart failure.
- IbC** Intravenous administration of digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with heart failure.
- IIIB** Administration of flecainide or propafenone is not recommended in patients with AF in the setting of ACS.¹⁶³

9.3 WOLFF-PARKINSON-WHITE (WPW) PRE-EXCITATION SYNDROMES

Since accessory pathways (AP) lack the decremental conduction properties of the AV node, patients with overt pre-excitation and AF are at risk of rapid conduction across the AP, resulting in fast ventricular rates and possible sudden cardiac death (SCD) because of degeneration into ventricular fibrillation. This makes AF in this patient cohort a potentially life-threatening arrhythmia. For information relating to acute and long-term pharmacological rate control in patients with an AP, see Section 5.1.1, page 18.

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

9.3.1 SUDDEN DEATH AND RISK STRATIFICATION

The incidence of SCD in patients with the Wolff – Parkinson – White syndrome has ranged from 0.15 to 0.39% over 3- to 22-year follow-up.

The markers of increased risk are:

- Shortest pre-excited RR interval <250 ms during spontaneous or induced AF.
- A history of symptomatic tachycardia.
- The presence of multiple APs.
- Ebstein's anomaly.

Since the efficacy of catheter ablation of APs is 95%, this is the management of choice for patients with evidence pre-excitation and AF.¹⁶ Patients who have survived SCD in the presence of an overt AP should have urgent AP ablation. Successful catheter ablation in those patients eliminates the risk for SCD.

Patients with overt pre-excitation and high risk of AF, or patients with high-risk professions such as public transport vehicle drivers, pilots, or competitive athletes should be considered for ablation.

The indication for catheter ablation of an overt AP in an asymptomatic patient is still controversial (especially in children).¹⁶⁵ Most patients with asymptomatic pre-excitation have a good prognosis; SCD is rarely the first manifestation of the disease.

The positive predictive value of invasive electrophysiological testing is considered to be too low to justify routine use in asymptomatic patients. Catheter ablation of an asymptomatic overt AP should remain a case-by-case decision with detailed counseling of the patient (and family) about the natural course and the risk of SCD versus the risk of an ablation procedure.

Keypoints

- | | |
|------|--|
| IA | Catheter ablation of an overt AP in patients with AF is recommended to prevent SCD. ¹⁶⁴ |
| IC | Immediate referral to an experienced ablation centre for catheter ablation is recommended for patients who survived SCD and have evidence of overt AP conduction. |
| IB | Catheter ablation is recommended for patients with high-risk professions (e.g. pilots, public transport drivers) and overt but asymptomatic AP conduction on the surface ECG. ¹⁶⁴ |
| IB | Catheter ablation is recommended in patients at high risk of developing AF in the presence of an overt but asymptomatic AP on the surface ECG. ¹⁶⁶ |
| IIaB | Asymptomatic patients with evidence of an overt AP should be considered for catheter ablation of the AP only after a full explanation and careful counseling. ¹⁶⁶ |

9.4 HYPERTHYROIDISM

AF occurs in 10% to 25% of patients with hyperthyroidism, more commonly in men and elderly patients.

CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF ATRIAL FIBRILLATION

Treatment is directed primarily toward restoring a euthyroid state, which is usually associated with a spontaneous reversion to sinus rhythm.

Antiarrhythmic drugs and direct-current cardioversion are generally unsuccessful while the thyrotoxicosis persists.

The occurrence of hyperthyroidism following treatment with amiodarone is often encountered in clinical practice. There are two types of amiodarone-induced hyperthyroidism:

- Type I, where there is an excess iodide-induced production of T4 and T3
- Type II, where there is a destructive thyroiditis with a transient excess release of T4 and T3, and, later, reduced thyroid function.

Although amiodarone may be continued when hypothyroidism has been successfully treated with replacement therapy, it is necessary to discontinue amiodarone if hyperthyroidism develops. Thyrotoxicosis may also occur after cessation of amiodarone therapy.

Keypoints

- IC In patients with active thyroid disease, antithrombotic therapy is recommended based on the presence of other stroke risk factors.
- IC Administration of a β -blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.
- IC When a β -blocker cannot be used, administration of a non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis.
- IC If a rhythm control strategy is desirable, it is necessary to normalize thyroid function prior to cardioversion, as otherwise the risk of relapse remains high.
- IC Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.

9.5. PREGNANCY

AF is rare during pregnancy and usually has an identifiable underlying cause, such as:

- Mitral stenosis,¹⁶⁷
- congenital heart disease,¹⁶⁸ or
- hyperthyroidism.¹⁶⁹

A rapid ventricular response to AF can have serious hemodynamic consequences for both the mother and the foetus. In a pregnant woman who develops AF, diagnosis and treatment of the underlying condition causing the arrhythmia are the first priorities.

Keypoints

- IC Digoxin, a beta blocker, or non-dihydropyridine calcium channel antagonist is recommended to control the ventricular rate in pregnant patients.¹⁷⁰⁻¹⁷²
- Propranolol and metoprolol would be the beta-blockers of choice, while atenolol is contraindicated. Atenolol given in the first trimester, but not later, has been associated with foetal growth retardation. Use of beta-blockers in the first trimester is to be preferably avoided.

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All currently available antiarrhythmic drugs have the potential to cross the placenta and enter breast milk and should therefore be avoided if possible.

Quinidine,¹⁷¹ sotalol,¹⁷³ and flecainide¹⁷³ have all been used successfully for pharmacological cardioversion during pregnancy, however, in relatively small numbers of cases.

IIBc

Quinidine (has the longest record of safety in pregnancy) or procainamide may be considered for pharmacological cardioversion in hemodynamically stable patients who develop AF during pregnancy.^{171,174}

IC

DCCV can be performed safely at all stages of pregnancy, and is recommended in patients who are haemodynamically unstable due to AF, and whenever the risk of ongoing AF is considered high, for the mother or for the foetus. Foetal monitoring should be done during and following the DCCV.

The role of anticoagulation to prevent systemic arterial embolism has not been systematically studied in pregnant patients with AF, but the arrhythmia is frequently associated with conditions that carry a high risk of thromboembolism, including congenital or valvular heart disease.

IC

Protection against thromboembolism is recommended throughout pregnancy for patients with AF except those at low thromboembolic risk. The choice of anticoagulant or aspirin should be chosen according to the stage of pregnancy.

Consideration should be given to avoiding warfarin because it crosses the placental barrier and is associated with teratogenic embryopathy in the first trimester and with foetal haemorrhage in the later stages of pregnancy.¹⁷²⁻¹⁷⁹

Heparin is the preferred anticoagulant because it does not cross the placenta.

IB

Subcutaneous administration of LMWH in weight-adjusted therapeutic doses is recommended during the first trimester and the last month of pregnancy. Alternatively, UFH may be given, to prolong the activated partial thromboplastin time to 1.5 times the control.¹⁸⁰

IIBc

During the second trimester, consider oral anticoagulation for pregnant women with AF at high thromboembolic risk.¹⁸⁰

The following are guiding principles for the use of drugs in pregnancy:

- Frequent monitoring with ECG and drug levels is recommended to reduce the risk of toxicity.
- If possible, start after 8 weeks of pregnancy or as late as possible.
- Use lowest effective dose.
- Low dose combination therapy preferable to higher dose single drug therapy.
- Use older agents with longest tract record.

9.6 HYPERTROPHIC CARDIOMYOPATHY

Patients with hypertrophic cardiomyopathy (HCM) are at greater risk of developing AF compared with the general population, and around 20 – 25% develop AF with an annual incidence of 2%.

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AF is the major determinant of hemodynamic deterioration in patients with HCM and symptoms can be ameliorated by restoration of sinus rhythm.

Amiodarone may be the most effective agent for reducing the occurrence of paroxysmal AF and for preventing recurrence.

In chronic AF, rate control can usually be achieved with β -blockers and verapamil. AV nodal ablation with permanent ventricular pacing (to promote late septal activation) may be helpful in selected patients.

Unless contraindicated, OAC therapy should be administered to patients with HCM and paroxysmal, persistent, or permanent AF.

Outcomes after AF ablation in patients with HCM are favourable, but not as successful as in unselected populations. LA ablation is significantly better in paroxysmal AF than in persistent AF. In addition, patients with marked atrial enlargement and severe diastolic dysfunction are at high risk of recurrence.

The small series of surgical ablation (Maze-III procedure) in combination with myomectomy when LV outflow tract obstruction was present, for AF in patients with HCM showed no increase in operative mortality and a high proportion of patients remained in sinus rhythm over a mean follow-up of 15 months.¹⁸¹ Despite conflicting data, there seems to be an overall beneficial effect of myomectomy in reducing the burden of AF in HCM patients.

Keypoints

- IB** Restoration of sinus rhythm by DCCV or pharmacological cardioversion is recommended in patients with HCM presenting with recent-onset AF.¹⁸²
- IB** OAC therapy (INR 2.0–3.0) is recommended in patients with HCM who develop AF unless contraindicated.¹⁸²
- IIaC** Amiodarone should be considered in order to achieve rhythm control and to maintain sinus rhythm in patients with HCM.
- IIaC** Catheter ablation of AF should be considered in patients with symptomatic AF refractory to pharmacological control.
- IIaC** Ablation procedures (with concomitant septal myomectomy if indicated) may be considered in patients with HCM and refractory AF.

9.7 PULMONARY DISEASES

Supraventricular arrhythmias, including AF, are common in patients with COPD and have adverse prognostic implications in patients with acute exacerbations of COPD.

Keypoints

- IC** For patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease, treatment of the underlying lung disease and correction of hypoxemia and acidosis are the primary therapeutic measures.
- IIIC** Theophylline and beta-adrenergic agonist agents are not recommended in patients with bronchospastic lung disease who develop AF.
- IIIC** Beta-blockers, sotalol, propafenone, and adenosine are contraindicated in patients with bronchospasm.

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IC

Diltiazem or verapamil is recommended to control the ventricular rate in patients with obstructive pulmonary disease who develop AF with or without digoxin.

IIaC

β -1 selective blockers (e.g. bisoprolol) in small doses should be considered as an alternative for ventricular rate control.

Cardioversion may be ineffective against AF unless respiratory decompensation has been corrected.

IC

Direct-current cardioversion should be attempted in patients with pulmonary disease who become hemodynamically unstable as a consequence of AF.

In patients refractory to drug therapy, AV nodal ablation and ventricular pacing may be necessary to control the ventricular rate.

In patients with AF and pulmonary disease, the general recommendations for antithrombotic therapy apply.

9.8 HEART FAILURE

AF is a strong and independent risk factor for the development of heart failure, and both conditions frequently co-exist.^{17,183} The onset of AF in a patient with heart failure often leads to symptomatic deterioration, predisposes to episodes of worsening heart failure, increases the risk of thrombo-embolic episodes, and worsens long-term outcome.

In the initial approach to heart failure patients with AF, the following issues need to be considered:¹⁷

- Potential precipitating factors and secondary causes should be identified and if possible corrected.
- Background heart failure treatment should be optimized.

When ventricular rate control is required in patients with heart failure and AF, β -blockers are preferred over digitalis glycosides due to their rate-controlling effect during exertion rather than only at rest. A combination of digoxin and a β -blocker may be more effective than a single drug for heart-rate control at rest. Therapy with β -blockers alone or in combination with digoxin was associated with lower mortality rates compared with treatment with digoxin alone.¹⁸⁴

β -Blockers have favourable effects on mortality and morbidity in patients with systolic heart failure. A recent meta-analysis also showed a 27% reduction in the incidence of new-onset AF in patients with systolic heart failure treated with β -blockers.¹⁸⁵

Although diltiazem effectively controls excessive heart rate during exercise, it adversely suppresses myocardial contraction and increases the risk of heart failure. For patients with heart failure and preserved ejection fraction, these drugs used in combination with digoxin appear to be more effective in controlling heart rate over 24 h and during exercise than digoxin or non-dihydropyridine calcium channel antagonist monotherapy.

The rhythm control strategy has not been shown to be superior to rate control in heart failure patients with AF.²⁷ Catheter-based LA ablation procedures in heart failure patients may lead to improvement in LV function, exercise tolerance, and quality of life in selected patients (see Section 8.3.1).^{29,30}

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The prevention of thrombo-embolism is covered in Section 6, but the presence of heart failure due to systolic dysfunction is itself a risk factor for stroke and thrombo-embolism, and OAC therapy is generally indicated when AF is present.

The use of aspirin is not recommended due to the increased risk of bleeding in combination with OAC therapy and some evidence that aspirin may increase the risk of hospitalizations for heart failure.

Keypoints

- IC** DCCV is recommended when a rapid ventricular rate does not respond to pharmacological measures in patients with AF and ongoing myocardial ischaemia, symptomatic hypotension, or symptoms of pulmonary congestion.
- IC** In patients with AF and severe (NYHA class III or IV) or recent (<4 weeks) unstable heart failure, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone.
- IIaB** Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF, or to facilitate electrical cardioversion of AF.^{21,39,45,186}
- IIaC** In patients with AF and stable heart failure (NYHA class I, II) dronedarone should be considered to reduce cardiovascular hospitalizations.
- IIbB** For patients with heart failure and symptomatic persistent AF despite adequate rate control, electrical cardioversion and rhythm control may be considered.^{27,29,30,32,187}
- IIbB** Catheter ablation (pulmonary vein isolation) may be considered in heart failure patients with refractory symptomatic AF.^{29,30}

9.9 ATHLETES

In population-based studies, the intensity of physical activity showed a U-shaped relationship with incident AF, which may indicate that the positive antiarrhythmic effects of physical activity are partially negated when exercise is too strenuous.^{188,189} AF is 2 – 10 times more prevalent in active or former competitive athletes and those performing intense recreational endurance sports.^{190,191} The reasons for this association are probably both functional (increased sympathetic activity, volume load during exercise, vagotonia at rest) and structural (atrial hypertrophy and dilatation).

Rate control is difficult to achieve in athletes. β -blockers are not well tolerated and may even be prohibited in some competitive sports, and digoxin or non-dihydropyridine calcium antagonists will not be potent enough to slow heart rate during exertional AF.

When the heart rate during AF is acceptable at maximal physical performance for a given athlete without signs of haemodynamic impairment (dizziness, syncope, sudden fatigue), competitive sports activity can be resumed.

Caution is necessary when using flecainide and propafenone as monotherapy in athletes with AF.¹⁹² These drugs may lead to atrial flutter, with 1 to 1 conduction to the ventricles during high sympathetic tone. Therefore, ablation of the flutter circuit may be needed in athletes with documented atrial flutter. Continuation of drug therapy for AF will often be required despite successful ablation ('hybrid therapy').

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In some athletes with paroxysmal AF, flecainide or propafenone can be used for acute conversion (the 'pill-in-the-pocket' approach; see Section 5.1.2.1).⁴² These patients should refrain from sports as long as the atrial arrhythmia persists and until one to two half-lives of the antiarrhythmic drug have elapsed.

Non-pharmacological options such as catheter ablation can be considered.¹⁹³

Anticoagulation may be necessary depending on the presence of risk factors for thrombo-embolic events (see Section 6.1). However, anticoagulation cannot be used in individuals participating in sporting activities with a risk of bodily collision.

Keypoints

- IIaC** When a 'pill-in-the-pocket' approach with sodium channel blockers is used, sport cessation should be considered for as long as the arrhythmia persists, and until 1–2 half-lives of the antiarrhythmic drug used have elapsed.
- IIaC** Isthmus ablation should be considered in competitive or leisure-time athletes with documented atrial flutter, especially when therapy with flecainide or propafenone is intended.
- IIaC** Where appropriate, AF ablation should be considered to prevent recurrent AF in athletes.
- IIIC** When a specific cause for AF is identified in an athlete (such as hyperthyroidism), it is not recommended to continue participation in competitive or leisure time sports until correction of the cause.
- IIIC** It is not recommended to allow physical sports activity when symptoms due to haemodynamic impairment (such as dizziness) are present.

9.10 VALVULAR HEART DISEASE

AF frequently accompanies valvular heart disease. LA distension is an early manifestation of progressive mitral valve disease, and the presence of paroxysmal or permanent AF is an accepted indication for early percutaneous or surgical mitral intervention.⁶⁶ AF is also frequently seen in later stages of aortic valve disease when LV dilatation and elevated end-diastolic pressure exert secondary effects on LA function.

Management of AF follows conventional recommendations in the setting of valvular heart disease, although a rate control strategy is usually adopted because of the low likelihood of maintaining sinus rhythm in the long term.

Principal concerns surround the high risk of thrombo-embolism in subjects with valvular heart disease, and a low threshold for anticoagulation is recommended (See Section 6.1).

Keypoints

- IC** OAC therapy (INR 2.0–3.0) is indicated in patients with mitral stenosis and AF (paroxysmal, persistent, or permanent).
- IC** OAC therapy (INR 2.0–3.0) is recommended in patients with AF and clinically significant mitral regurgitation.

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IaC

Percutaneous mitral balloon valvotomy should be considered for asymptomatic patients with moderate or severe mitral stenosis and suitable valve anatomy who have new-onset AF in the absence of LA thrombus.

IaC

Early mitral valve surgery should be considered in severe mitral regurgitation, preserved LV function, and new-onset AF, even in the absence of symptoms, particularly when valve repair is feasible.

10. REFERRALS

10.1 Acute hospitalisation/referral

This is required for patients with:

- AF/AFL with haemodynamic compromise, acute dyspnoea, acute heart failure, chest pain, ischaemia, near syncope, hypotension
- AF/AFL with rapid uncontrolled heart rate, e.g., over 140 bpm at rest
- AF/AFL with acute systemic illness requiring acute management
- first/new onset of AF/AFL symptoms, no contraindications to cardioversion, with the possibility of cardioversion within 48 hours of onset.

10.2 Outpatient specialist physician/cardiologist

Outpatient specialist referral is recommended for those who:

- Need further investigation/echocardiography
- Have suspected structural heart disease (e.g., hypertensive, valvular, ischaemic)
- Are to be considered for cardioversion
- Are highly symptomatic, requiring 'maintenance of sinus rhythm' antiarrhythmic therapy
- Are having difficulty with pharmacological rate control
- Require a second opinion of the risk/benefit ratio of anticoagulation
- Are having syncopal attacks.

10.3 Cardiac electrophysiologist (heart-rhythm specialist)

Tertiary referral is recommended for patients who have:

- AF with WPW syndrome (pre-excited AF)
- Highly-symptomatic AF unresponsive to first-line antiarrhythmic treatment
- Uncontrolled ventricular rate with maximally tolerated atrioventricular-blocking therapy
- Recurrent AFL (including mixed AFL and AF where AFL is the dominant arrhythmia)
- Tachycardia-bradycardia syndrome (sinus node dysfunction)
- Suspicion or documentation of a regular tachycardia triggering AF (e.g., SVT).

10.4 No referral

Referral is not needed for patients who have rate-controlled AF with mild or occasional symptoms, for whom echocardiography is not required (e.g., previously obtained), and for whom the decision regarding stroke prevention management is clear cut.

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11. AUDIT & EVALUATION

The Table below lists the audit criteria identified to evaluate the impact of the implementation of the six key priority areas detailed above on clinical practice and health outcomes.

Criterion	Exception	Definition of terms
All people presenting to primary or secondary care with a history of hypertension, heart failure, diabetes or stroke and noted to have an irregular pulse to be offered an ECG and any new diagnosis of AF recorded.	None.	Percentage of patient records with a new diagnosis of AF made following an ECG made on the basis of detection of an irregular pulse.
All patients should be assessed for risk of stroke/ thromboembolism and given thromboprophylaxis according to the stroke risk stratification algorithms and have this assessment and any antithrombotic therapy recorded.	Haemodynamically unstable patients or those in whom assessment is impossible or inappropriate.	Percentage of patient records with a documentation of risk assessment and thromboprophylaxis consistent with the stroke risk stratification algorithm.
All patients should be assessed for risk of bleeding and according to the bleeding risk stratification algorithms and have this assessment recorded.	Haemodynamically unstable patients or those in whom assessment is impossible or inappropriate.	Percentage of patient records with a documentation of risk assessment for bleeding consistent with the bleeding risk stratification algorithm.
All AF patients in whom a rate-control or rhythm-control strategy is initiated to have their involvement in choosing a treatment strategy recorded.	Postoperative or haemodynamically unstable patients, or those otherwise not able to engage in a decision-making process.	Percentage of patient records with a documentation of involvement of the patient in the decision- making process.
All patients who are prescribed digoxin as initial monotherapy for	None.	Percentage of patient records with a prescription of digoxin for

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<p>rate control to have the reason for this prescription recorded where it is not obvious (e.g. sedentary patient, presence of contraindication to alternative agents).</p>		<p>initial rate-control monotherapy where the reason for digoxin prescription is:</p> <ul style="list-style-type: none"> • Sedentary patient • Presence of contraindications to beta-blockers or rate-limiting calcium Antagonists • Other reasons.
<p>All patients who are prescribed amiodarone as long-term therapy for rhythm control to have the reason for this prescription recorded where it is not obvious (e.g. failure of other agents to control rhythm, presence of contraindication to alternative agents).</p>	<p>None.</p>	<p>Percentage of patient records with a prescription of amiodarone for long-term rhythm-control therapy where the reason for amiodarone prescription is:</p> <ul style="list-style-type: none"> • Presence of contraindications to beta-blockers, dronedarone, flecainide or propafenone • Other reasons.

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APPENDIX A

Search Terms

Scope of search

A literature search was conducted for guidelines, systematic reviews and randomized controlled trials on the primary care management of Atrial fibrillation, with additional searches in the following areas:

- Outpatient therapy
- Rhythm versus rate control
- Anti-arrhythmics for cardioversion
- Drugs for rate control
- Anticoagulation versus antiplatelet drugs to prevent thromboembolism
- Stroke risk versus bleeding risk
- Invasive or emerging therapies
- Referral criteria

Search dates

January 2010 –December 2011

Key search terms

Various combinations of searches were carried out. The terms listed below are the core search terms that were used for Medline and these were adapted for other databases.

- exp Atrial Fibrillation/, atrial fibrillation.tw
- exp Diagnosis/, exp Diagnosis, Differential/, exp Electrocardiography/, exp Echocardiography/, exp Radiography, Thoracic/, exp Thyroid Function Tests/, exp Hematologic Tests/, blood test\$.tw
- exp atrial flutter.tw
- Outpatients/
- Ambulatory Care/
- (outpatient or out-patient).tw.
- exp Platelet Aggregation Inhibitors/, exp Aspirin/, exp Warfarin/
- exp thromboembolism/
- exp anticoagulants/
- \$thromb\$.ti,ab.
- anticoagul\$.tw.
- exp Blood Coagulation/de, dt, pc [Drug Effects, Drug Therapy, Prevention & Contro
- exp Platelet Aggregation Inhibitors/
- Aspirin/
- aspirin.tw.
- exp Anti-Arrhythmia Agents/, exp Calcium Channel Blockers/, exp Verapamil/, exp Diltiazem/, exp Nifedipine/
- exp Adrenergic beta-Antagonists/, exp Atenolol/, exp Bisoprolol/, exp Metoprolol/, exp Acebutolol/, exp Nadolol/, exp Oxprenolol/, exp Propranolol/

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- exp Digoxin/, exp Amiodarone/
- cardioversion/
- defibrillation/
- (countershock\$ or (counter adj shock\$)).tw. cardioconver\$.tw.
- (electr\$ adj3 (cardiover\$ or conver\$ or countershock)).tw. rhythm control.tw.
- (electrover\$ or (electric\$ adj3 defibrillat\$)).tw
- (antiarrhythm\$ or anti-arrhythm\$).tw.
- (pharmacol\$ adj3 (cardiover\$ or conver\$ or cardioconver\$)).tw.
- exp heart rate/
- (heart or cardiac or ventricular) adj3 rate).tw.
- (rate adj3 (control\$ or reduc\$ or normal\$)).tw.
- (chronotrop\$ adj3 therapy).tw.
- Digoxin/
- Verapamil/
- Diltiazem/
- (beta\$ adj block\$).tw.
- exp Beta Adrenergic Receptor Blocking Agent/
- Amiodarone/
- Clonidine/
- (ventricular adj5 pac\$).
- exp thromboembolism/
- exp anticoagulants/
- \$thromb\$.ti,ab.
- anticoagul\$.tw.
- exp Blood Coagulation/de, dt, pc [Drug Effects, Drug Therapy, Prevention & Control
- exp Platelet Aggregation Inhibitors/
- Aspirin/
- aspirin.tw.
- exp Stroke/
- exp Hemorrhage/
- (heart or ventricular) adj3 rate).tw.
- *Heart Rate/de [Drug Effects]
- rate control.tw.
- (Cox or Maze).tw.
- (internal adj3 (defibrill\$ or cardiover\$)).tw.
- (radio\$ or microwave\$).tw.
- (cryotherm\$ or cryoablat\$).tw.
- laser\$.tw.
- (atrial adj3 pac\$).tw.
- (dual adj3 pac\$).tw.
- (implant\$ adj3 pacemaker\$).tw.
- (AV nod\$ adj3 ablat\$).tw.
- (implant\$ adj3 defibrill\$).tw.
- (surg\$ or catheter\$) adj3 ablat\$).tw.
- surgery/ or thoracic surgery/
- defibrillators, implantable/ or implants, experimental/
- exp Pulmonary Veins/ pulmonary vein\$.tw
- exp Catheter Ablation/ or radiofrequency ablation.tw
- exp Catheter Ablation or radiofrequency catheter ablation.tw

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APPENDIX B

Clinical questions

A. Introduction

1. What is the best way to classify atrial fibrillation?
2. What is the epidemiological characteristic of atrial fibrillation?

B. Initial management

1. What are the frequencies of the presenting symptoms?
2. In patients with suspected AF based on an irregular pulse, how accurate is an ECG in diagnosing AF?
3. Should echocardiography be performed to identify underlying structural heart disease?
4. In patients with suspected intermittent AF, how effective is ambulatory ECG compared to an event ECG in diagnosing AF?
5. Which patients with AF would benefit from referral to specialist?

C. Management principles

1. In which patients with persistent AF does rate control result in improved mortality/morbidity/quality of life over rhythm control?
2. In which patients with persistent AF does rhythm control result in improved mortality/morbidity/quality of life over rate control?

D. Acute-onset AF

1. In haemodynamically unstable patients presenting with acute AF, what is the best treatment strategy?
2. In which patients should pill-in-the-pocket therapy be recommended?
3. Does electrical cardioversion versus pharmacological cardioversion affect rates of thromboembolism, quality of life, success rates?
4. In patients with persistent AF, is amiodarone better than a) flecainide or b) propafenone for use in cardioversion?
5. In patients with persistent AF is amiodarone better than sotalol for use in cardioversion?
6. What is the safety and efficacy of the adjunctive administration of antiarrhythmic drugs for use in electrical cardioversion in comparison to electrical cardioversion without adjunctive antiarrhythmic drugs?
7. Is a conventional anticoagulation strategy for elective cardioversion as effective as a transoesophageal echocardiogram plus anticoagulation?

E. Prevention of thromboembolism

1. In patients with AF, what are the risk factors associated with stroke/TIA and thromboembolism?
2. What is the efficacy of anticoagulation therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f)

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asymptomatic AF?

3. What is the efficacy of anticoagulation therapy versus antiplatelet therapy for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?
4. What is the efficacy of antiplatelet therapy versus placebo for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?
5. What is the efficacy of vitamin K antagonist versus novel anticoagulant for stroke prevention in: a) paroxysmal AF b) permanent AF c) peri/post cardioversion to sinus rhythm d) acute/post-op AF e) peri/post stroke f) asymptomatic AF?
6. What is the role of point-of-care testing and self-monitoring of anticoagulation.
7. How best to institute anticoagulant and antiplatelet therapy in patients with AF undergoing percutaneous coronary intervention and non-ST elevation myocardial infarction
8. In patients with AF what are the risks of long-term oral anticoagulation therapy?
9. In patients with AF and vitamin K antagonist, what are the risk factors associated with bleeding?

F. Long-term rate control

1. In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists compared with digoxin in rate control?
2. In patients with permanent AF, what is the efficacy of beta-blockers compared with digoxin in rate control?
3. In patients with permanent AF, what is the efficacy of beta-blockers compared with rate-limiting calcium antagonists in rate control?
4. In patients with permanent AF, what is the efficacy of rate-limiting calcium antagonists in combination with digoxin compared with rate-limiting calcium antagonists monotherapy in rate control?
5. In patients with permanent AF, what is the efficacy of beta-blockers in combination with digoxin compared with beta-blocker monotherapy in rate control?
6. In patients with permanent AF, what is the efficacy of AV node ablation with permanent pacemaker therapy in rate control?

G. Long-term rhythm control

1. In patients with paroxysmal AF, is flecainide/propafenone better than beta-blockers in reducing the frequency of paroxysms?
2. In patients with paroxysmal AF, is amiodarone or sotalol better than beta-blockers in reducing the frequency of paroxysms?
3. In patients with paroxysmal AF, is flecainide/propafenone better than amiodarone or sotalol in reducing the frequency of paroxysms?

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4. In patients with AF, is flecainide or propafenone better than beta-blockers in maintaining sinus rhythm post cardioversion?
5. In patients with AF, is amiodarone or sotalol better than beta-blockers in maintaining sinus rhythm post cardioversion?
6. In patients with AF, is flecainide/propafenone better than amiodarone or sotalol in maintaining sinus rhythm post cardioversion?
7. Which antiarrhythmic agents should be chosen to maintain sinus rhythm for patients with normal hearts?
8. Which antiarrhythmic agents should be chosen to maintain sinus rhythm for patients with structural heart disease?
9. What is the efficacy of left atrial catheter ablation and surgical ablation therapy for rhythm control in patients with a) paroxysmal AF b) persistent AF?
10. What is the efficacy of cardiac pacing therapy for rhythm control in patients with paroxysmal AF?

H. Referrals

1. Which patients with AF benefit from referral to specialist services for assessment and management?
2. Which patients with AF benefit from referral to specialist services for non-pharmacological treatment or electrophysiological studies?

APPENDIX C

C. WARFARIN IN PRACTICE

Barriers that may prevent people accessing medication and INR testing include:

- Financial barriers (including the ability to take time off work)
- Travel difficulties
- Lack of access to a telephone
- Fear or dislike of regular blood tests
- Difficulties with general practitioner monitoring.

Possible solutions include the following:

- Financial assistance from relevant agencies
- Provision of transport (e.g., shuttle service, taxi chits)
- Domiciliary testing, either at home or the work place
- Testing people in groups at a public health centre using a point-of-care monitor

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C.1 INITIATION OF WARFARIN THERAPY

Loading doses are not recommended because they may increase the risk of bleeding

Initiation of warfarin should be 5 mg daily in most patients (usually achieves INR ≥ 2 in 4-5 days)

A starting dose < 5 mg should be considered for patients >65 yrs, liver disease, malnourished, severe heart failure, or concomitant drugs affecting warfarin metabolism.

If overlapping LMWH or heparin with warfarin, overlap for at least 5 days. Discontinue LMWH or heparin when INR is therapeutic on two consecutive measurements 24 hr apart.

C.1.2 Frequency of INR Monitoring:

Check baseline INR prior to ordering warfarin

Check INR daily (AM lab) until therapeutic for two consecutive days then two-three times weekly during initiation

C.1.2.1 Standard

Traditionally patients come into the clinic (or the hospital) to have venous blood drawn for routine laboratory INR determination.

C.1.2.2 Point of Care

Finger tip capillary blood can be used with small, light weight and portable instruments. The clinical trials result have compared favorably with traditional INR determination.

Use in anticoagulation clinic.

Home use or Patient Self Test (PST)

- Need good quality control for point of care INR measurement.
 - Patient selection is essential.
 - Patients must have long-term indication for anticoagulation therapy.
 - Patients must be willing and able to perform self-management.
 - Patients must be willing to record results accurately and attend clinics regularly for quality assurance.
 - Patients must demonstrate competence in using the instrument and interpreting the results.
 - Patients must not have shown previous noncompliance in terms of clinic attendance or medication management.
- Can increase INR testing frequency and decrease complications associated with oral anticoagulation therapy.

C.1.3 Therapeutic INR Ranges:

AF alone: INR 2 – 3

Prosthetic Heart Valve: INR 2.5 – 3.5

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C.1.4 Average Daily Dose

There are differences among various ethnic groups

About 4-5 mg/day or 28-35 mg/week for caucasian for target INR of 2.5 (2.0-3.0)

About 3-4 mg/day or 21-28 mg/week for Pacific-Asian (exclude caucasian in this region). This dose will be less if target INR is recommended at <2.0.

C.1.5 Factors Effecting the Daily Dose

- Age (For caucasian)
 - <35 yr ----- 8.1 mg/day.
 - 35-49 yr --- 6.4 mg/day.
 - 50-59 yr --- 5.1 mg/day.
 - 60-69 yr --- 4.2 mg/day.
 - >70 yr ----- 3.6 mg/day.
- Genetic. Hereditary warfarin sensitive and resistance.
- Medicine noncompliance.
- Drugs interaction, including herbal medicine.
- Concurrent illness, fever, diarrhea, post op major surgery (i.e.. heart valve replacement), malignancy, lupus anticoagulants.
- Impaired liver function, CHF with liver congestion.
- Food effect, vitamin K intake, alcohol.
- Hyperthyroidism, renal disease.
- During heparin and direct thrombin inhibitors treatment.

C.1.6 Warfarin Initiation

Day 1

(If there is an active or acute thromboembolic condition, warfarin should be started along with heparin, unless there is a contraindication or patient cannot take medicine orally. Following warfarin initiation, heparin should be continued until INR reaches therapeutic level for 2 days).

5 mg (2.5-7.5). This dose is a good choice since it is known that average daily dose is close to 5 mg. Using higher dose than necessary may lead to bleeding complication due to rapidly and severely reduce factor VII. It may deplete protein C too quick, and theoretically can cause hypercoagulable state. The 5 mg size tablet is recommended for both inpatient and outpatient use, making inpatient to outpatient transition more convenient. It is the most commonly used size tablet by the majority of anticoagulation clinics today.

The higher dose warfarin initiation has also been tested successfully by using normogram. It may be considered in patient who may need shorter period of time to reach therapeutic INR. It should be done as inpatient. INR have to be done frequently enough to prevent over anticoagulation and bleeding complication

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Use lower dose (2.5 mg).

- >80 yr.
- Concurrent illness.
- On interaction drug.
- S/P major surgery, i.e. heart valve surgery.
- Chronic malnourished.
- Impaired liver function, liver congestion. □

Use higher dose (7.5-10.0 mg).

- Young healthy subject.
- In the first two days.

Day 2

A. If INR <1.5, continue the same dose.

B. If INR >1.5, give lower dose (2.5 mg or none)

Day 3

For #A. of Day 2

- If INR <1.5, suggests a higher than average maintenance dose of 5 mg/day or 35 mg/week will be needed. Give higher dose than 5 mg. i.e.7.5 mg for now.
- If INR 1.5-2.0, suggests an average maintenance dose close to 5 mg/day or close to 35 mg/week will be needed, and continue 5 mg for now.
- If INR >2.0, suggests a lower than average maintenance dose of 5 mg/day or 35 mg/week will be needed. Give less than 5 mg, i.e.2.5 mg or none for now.

For #B. of Day 2

- If INR 1.5-2.0, suggests daily dose will be close to or less than 5 mg/day or close to 35 mg/week or less. May give 5 mg or less for now.
- If INR >2.0, suggests daily dose will be lower than 5 mg/day or less than 35 mg/week. May give 2.5 mg or none for now.

Day 4

If there is no need for heparin therapy, the patient may have been discharged by now, and warfarin initiation is continued as an outpatient.

- INR 2 times a week until INR is in target range twice in a row, then INR 1 time weekly until INR is in target range twice in a row, then INR 1 time in 2 week until INR is in target range twice in a row, then enter the patient in to maintenance schedule (usually INR every 4 weeks).
- Patients during an acute illness, or post operative of major surgeries may be more sensitive to warfarin than when they become more stable.

Out patient (See also "Day 4" above)

- Obtain baseline INR
- Start with 5 mg daily. See more detail for dose variation in "Inpatient guideline"
- Check INR 2 times a week, or more often if necessary, during the first week or so. Adjust warfarin dose and timing for INR check as outline in "Inpatient" guidelines.

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C.1.7 Ethnic Difference for Chinese-Asian or Pacific-Asian (exclude caucasian in this region)

- Average daily dose of Warfarin for Pacific-Asian (exclude caucasian in this region) or Chinese-Asian is about 3 mg. Weekly dose is about 21-28 mg, or lower if "target INR" for various diagnoses are about 0.4-0.5 lower than those of Caucasian-American-European level.
- "Target INR" for or Pacific-Asian (exclude caucasian in this region) or Chinese-Asian should be lower than those of Caucasian-American-European. The suggest level for nonvalvular atrial fibrillation is 1.6-2.6, to achieve less combine thromboembolic and major bleeding events. (Need more database for confirmation)
- Difference in polymorphism of CYP 2C9 and VKORC1 which will influence Warfarin dosage

Warfarin Initiation Table for average daily dose of 5 mg and 3 mg further

DAY	INR	DOSE	
		INPATIENT (Usually with daily INR)	OUTPATIENT
1	Normal	5.0 mg (2.5 or 7.5-10.0 mg in patients listed in the text)	5.0 mg (2.5 or 7.5-10.0 mg in patients listed in the text)
2	< 1.5	5.0 mg	5.0 mg
	> 1.5	0.0 - 2.5 mg	0.0 - 2.5 mg
3	< 1.5	5.0 - 10 mg	5.0 - 10 mg
	1.5 - 1.9	2.5 - 5.0 mg	2.5 - 5.0 mg
	2.0 - 3.0	0.0 - 2.5 mg	0.0 - 2.5 mg
	> 3.0	0.0 mg	0.0 mg
			INR should be measured today. If INR is not measured, may use the same dose as day 2, and should not > 5 mg
4	< 1.5	10.0 mg	10.0 mg
	1.5 - 1.9	5.0 - 7.5 mg	5.0 - 7.5 mg
	2.0 - 3.0	0.0 - 5.0 mg	0.0 - 5.0 mg
	> 3.0	0.0 mg	0.0 mg
			INR measurement should be done, if INR on day 3 is < 1.5 or > 3.0
5	< 1.5	10.0 - mg	10.0 - mg
	1.5 - 1.9	7.5 - 10.0 mg	7.5 - 10.0 mg
	2.0 - 3.0	0.0 - 5.0 mg	0.0 - 5.0 mg
	> 3.0	0.0 mg	0.0 mg
			INR measurement should be done, if INR on day 4 is < 1.5 or > 3.0
	< 1.5	7.5 - 12.5 mg	7.5 - 12.5 mg
	1.5 - 1.9	5.0 - 10.0 mg	5.0 - 10.0 mg
	2.0 - 3.0	0.0 - 7.5 mg	0.0 - 7.5 mg
	> 3.0	0.0 mg	0.0 mg
			INR measurement should be done, if INR on day 5 is < 1.5 or > 3.0

Note: Frequent INR measurement during warfarin initiation helps prevent bleeding from over anticoagulation and helps reaching target INR sooner.

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DAY	INR	DOSE	
		INPATIENT (Usually with daily INR)	OUTPATIENT
1	Normal	3.0 mg (1.5 or 3.0-6.0 mg in patients listed in the text)	3.0 mg (1.5 or 3.0-6.0 mg in patients listed in the text)
2	< 1.3	3.0 mg	3.0 mg
	> 1.3	0.0 - 1.5 mg	0.0 - 1.5 mg
3	< 1.3	3.0 - 6 mg	3.0 - 6 mg
	1.3 - 1.6	1.5 - 3.0 mg	1.5 - 3.0 mg
4	1.6 - 2.6	0.0 - 1.5 mg	0.0 - 1.5 mg
	> 2.6	0.0 mg	0.0 mg
5	< 1.3	4.5 - 6.0 mg	4.5 - 6.0 mg
	1.3 - 1.6	3.0 - 4.5 mg	3.0 - 4.5 mg
6	1.6 - 2.6	1.5 - 3.0 mg	0.0 - 3.0 mg
	> 2.6	0.0 mg	0.0 mg
7	< 1.3	6.0 - 7.5 mg	6.0 - 7.5 mg
	1.3 - 1.6	3.0 - 4.5 mg	3.0 - 4.5 mg
8	1.6 - 2.6	1.5 - 3.0 mg	1.5 - 3.0 mg
	> 2.6	0.0 mg	0.0 mg
9	< 1.3	6.0 - 7.5 mg	6.0 - 7.5 mg
	1.3 - 1.6	4.5 - 6.0 mg	4.5 - 6.0 mg
10	1.6 - 2.6	1.5 - 3.0 mg	1.5 - 3.0 mg
	> 2.6	0.0 mg	0.0 mg
Note: Frequent INR measurement during warfarin initiation helps prevent bleeding from over anticoagulation and helps reaching target INR sooner.			

C.1.8 Dose Adjustments for Warfarin Maintenance Therapy (Target INR 2.0-3.0)

INR	Dose Adjustments
<1.5	Increase weekly dose by 20%
1.5-1.9	Increase weekly dose by 10%
2.0-3.0	No change
3.1-3.9	No change; if persistent decrease weekly dose by 10-20%
4.0-5.0	Omit 1 dose; decrease weekly dose by 10-20%
>5.0	See recommendations for managing elevated INR When resume decrease weekly dose 20-50%

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C.1.8.1 Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving Warfarin:

Condition	Recommendation
INR above therapeutic range but < 5; no significant bleeding	Lower the dose or omit a dose and resume with lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR \geq 5 but < 9; no significant bleeding	Omit next one or two doses, monitor INR more frequently, and resume with lower dose when INR therapeutic. If risk of bleeding, omit the next dose and give vitamin K 1-2.5 mg PO.
INR \geq 9; no significant bleeding	Hold warfarin and give Vitamin K 2.5-5 mg orally; expect substantial INR reduction in 24-48hr. Monitor INR more frequently and repeat vitamin K if necessary. Resume warfarin at an adjusted dose when INR therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin and give vitamin K 10 mg slow IV infusion, supplemented with FFP, prothrombin complex concentrate or rVIIa, depending on urgency of situation. Vitamin K can be repeated q12hr
Life threatening bleeding	Hold warfarin and give FFP, prothrombin complex concentrate, or rVIIa supplemented with vitamin K 10 mg slow IV infusion. Repeat, if necessary, depending on INR.

C.1.9 Interruption of Warfarin Therapy for Surgery

Condition	Recommendations
Low risk of thromboembolism	Stop warfarin 5 days before surgery allowing INR to return to near normal. Bridge therapy with low dose LMWH or no bridging.
Moderate risk of thromboembolism	Stop warfarin 5 days before surgery allowing INR to fall, start bridge therapy with therapeutic dose LMWH 2-3 days prior to surgery (or when INR is sub-therapeutic). Administer last dose of LMWH 24 hrs before surgery.
High risk of thromboembolism	Stop warfarin 5 days before surgery allowing INR to fall, start bridge therapy with therapeutic dose LMWH 2-3 days prior to surgery (or when INR is sub-therapeutic). Administer last dose of LMWH 24hrs before surgery.
Low risk of bleeding	Lower warfarin dose and operate at an INR of 1.3-1.5; the dose may be lowered 4-5 days before surgery; warfarin can be restarted post-op, supplement with LMWH if necessary.
Urgent surgical or other invasive procedure (within 12 hours)	For immediate reversal give FFP, prothrombin complex concentrate in addition to vitamin K 2.5-5 mg po or by slow IV infusion.

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Urgent surgical or other invasive procedure (within 18-24 hours)	If surgery is urgent but can be delayed for 18-24 hrs give vitamin K 2.5- 5 mg po or by slow IV infusion. If INR is still high, additional vitamin K 1-2 mg po can be given.
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Low risk: VTE: Single VTE occurred >12 months ago and no other risk factors, AF: (CHADS2 score 0-2) without a history of stroke or other risk factors, Mech heart valve: bileaflet aortic valve without AF and no other risk factors for stroke.

Moderate risk: VTE: VTE within 3-12 months, non-severe thrombophilic conditions, recurrent VTE, active cancer, AF: (CHADS2 score 3 or 4), Mech heart valve: bileaflet aortic valve and one of the following: AF, prior stroke or TIA, HTN, DM, CHF, age >75 yr.

High risk: VTE: recent (within 3mo) VTE, severe thrombophilia, AF:(CHADS2 score 5 or 6), recent (within 3 months) stroke or TIA, rheumatic valvular heart disease,

Mech heart valve: any mitral valve prosthesis, older aortic valve prosthesis (caged-ball or tilting disc), recent (within 6 months) stroke or TIA

- Resume warfarin therapy 12-24 hrs after surgery and when there is adequate hemostasis.
- Resume bridge therapy:
 - Minor surgery or other invasive procedure and receiving therapeutic dose LMWH: Resume 24 hrs after the procedure when there is adequate hemostasis
 - Major surgery or high bleeding risk surgery/procedure where post-op therapeutic dose LMWH is planned: delay initiation of therapeutic dose LMWH for 48-72 hours after surgery when hemostasis is secured or administering low dose LMWH after surgery when hemostasis is secured or completely avoiding LMWH after surgery.

APPENDIX D

Vaughn Williams Classification of Antiarrhythmic Drugs

Type IA

Disopyramide
Procainamide
Quinidine

Type IB

Lignocaine
Mexilitine

Type IC

Flecainide
Propafenone

Type II

Beta blockers (e.g. propranolol)

Type III

Amiodarone
Dronedarone
Bretylium
Dofetilide
Ibutilide
Sotalol

Type IV

Nondihydropyridine calcium channel antagonist (verapamil and diltiazem)

Table includes compounds introduced after publication of the original classification.

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GLOSSARY

ACEI	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AF	Atrial fibrillation
AFI	Atrial Flutter
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AP	Accessory Pathway
AV	Atrioventricular
ARB	Angiotensin Receptor Blocker
BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged
bpm	Beats per minute
CCB	Calcium Channel Blocker
CAD	Coronary Artery Disease
CCS-SAF	Canadian Cardiovascular Society Severity in Atrial Fibrillation
CHA ₂ DS ₂ VASc	Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus and Stroke, Vascular Disease
CHADS ₂	Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus and Stroke
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CPR	Cardiopulmonary Resuscitation
CRT	Cardiac Resynchronisation Therapy
CT	Computed tomography
CV	Cardioversion
CYP	Cytochrome P
DCCV	Direct Current Cardioversion
DM	Diabetes Mellitus
EAPCI	European Association of Percutaneous Cardiovascular Interventions
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
GPI	Glycoprotein IIb/IIIa Inhibitor
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HOT CAFÉ	HOw to Treat Chronic Atrial Fibrillation
HTN	Hypertension
ICD	Implantable Cardioverter Defibrillator

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INR	International Normalised Ratio
IV	Intravenous
J-RHYTHM	Japanese Rhythm Management Trial for Atrial Fibrillation
LA	Left atrium
LAA	Left atrial appendage
LMWH	Low molecular weight heparin
LoE	Level of Evidence
LV	Left ventricle
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
N/A	Not available
ND	Not Determined
NYHA	New York Heart Association
OAC	Oral Anticoagulant
PAD	Peripheral Artery Disease
PAF	Paroxysmal atrial fibrillation
PCI	Percutaneous Intervention
PIAF	Pharmacological Intervention in Atrial Fibrillation
PUFA	Polyunsaturated fatty acids
PVI	Pulmonary Vein Isolation
RACE	RAte Control versus Electrical CardioversionFor Persistent Atrial Fibrillation
RE-LY	Randomised Evaluation of Long-Term Anticoagulation Therapy
SCD	Sudden Cardiac Death
SR	Sinus Rhythm
STAF	Strategies of Treatment of Atrial Fibrillation
TE	Thromboembolism
TE risk	Thrombo-embolic risk
TIA	Transient ischemic attack
TOE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram
UFH	Unfractionated Heparin
VHD	Valvular Heart Disease
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism Prophylaxis
WPW	Wolff-Parkinson-White Syndrome

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