



# Guidelines for the management of atrial fibrillation

## The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA)<sup>†</sup>

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

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**Keywords**

Atrial fibrillation • European Society of Cardiology • Guidelines • Anticoagulation • Rate control  
• Rhythm control • Upstream therapy • Pulmonary vein isolation • Left atrial ablation

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|  |      | ACTIVE . . . . .  | Atrial fibrillation Clopidogrel Trial with Irbesar-<br>tan for prevention of Vascular Events                                     |
|  |      | ADONIS . . . . .  | American–Australian–African trial with Drone-<br>darONE In atrial fibrillation or flutter for the<br>maintenance of Sinus rhythm |

|  |   |            |   |
|--|---|------------|---|
| AF-CHF                                 | Atrial Fibrillation and Congestive Heart Failure  | EAPCI      | European Association of Percutaneous Cardiovascular Interventions   |
| AFFIRM                                 | Atrial Fibrillation Follow-up Investigation of Rhythm Management  | EHRA       | European Heart Rhythm Association   |
| ANDROMEDA                              | ANtiarrhythmic trial with DRonedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrease  | ECG        | electrocardiogram   |
| AP                                     | accessory pathway   | EMA        | European Medicines Agency   |
| APAF                                   | Ablation for Paroxysmal Atrial Fibrillation study   | EURIDIS    | EUropean trial In atrial fibrillation or flutter patients receiving Dronedaron for the maintenance of Sinus rhythm  |
| ARB                                    | angiotensin receptor blocker  | GISSI-AF   | Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Atrial Fibrillation   |
| ARMYDA                                 | Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery  | GPI        | glycoprotein inhibitor  |
| ATHENA                                 | A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter                       | GRACE      | Global Registry of Acute Coronary Events  |
| ATRIA                                  | AnTicoagulation and Risk factors In Atrial fibrillation   | HAS-BLED   | hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly (1 point each) |
| AVRO                                   | A Phase III prospective, randomized, double-blind, Active-controlled, multicentre, superiority study of Vernakalant injection vs. amiodarone in subjects with Recent Onset atrial fibrillation  | HOPE       | Heart Outcomes Prevention Evaluation  |
| AVERROES                               | Apixaban VERSus acetylsalicylic acid to pRevent strOkES   | HOT CAFE   | How to Treat Chronic Atrial Fibrillation  |
| BAFTA                                  | Birmingham Atrial Fibrillation Treatment of the Aged  | HR         | hazard ratio  |
| b.i.d.                                 | bis in die (twice daily)  | HT         | hypertension  |
| bpm                                    | beats per minute  | INR        | international normalized ratio  |
| CABG                                   | coronary artery bypass graft  | i.v.       | intravenous   |
| CACAF                                  | Catheter Ablation for the Cure of Atrial Fibrillation study   | J-RHYTHM   | Japanese Rhythm Management Trial for Atrial Fibrillation  |
| CFAE                                   | complex fractionated atrial electrogram   | LA         | left atrial   |
| CHA <sub>2</sub> DS <sub>2</sub> -VASc | cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)  | LAA        | left atrial appendage   |
| CHADS <sub>2</sub>                     | cardiac failure, hypertension, age, diabetes, stroke (doubled)  | LIFE       | Losartan Intervention For Endpoint reduction in hypertension  |
| CHARISMA                               | Clopidogrel for High Athero-thrombotic Risk and Ischemic Stabilisation, Management, and Avoidance   | LMWH       | low molecular weight heparin  |
| CHARM                                  | Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity  | LoE        | level of evidence   |
| CI                                     | confidence interval   | LV         | left ventricular  |
| COPD                                   | chronic obstructive pulmonary disease   | LVEF       | left ventricular ejection fraction  |
| CPG                                    | clinical practice guidelines  | o.d.       | omni die (every day)  |
| CRT                                    | cardiac resynchronization therapy   | OAC        | oral anticoagulant  |
| CT                                     | computed tomography   | OR         | odds ratio  |
| CV                                     | cardioversion   | MRI        | magnetic resonance imaging  |
| DAFNE                                  | Dronedaron Atrial FibrillatioN study after Electrical cardioversion   | NYHA       | New York Heart Association  |
| DCC                                    | direct current cardioversion  | PAD        | peripheral artery disease   |
| DIONYSOS                               | Randomized Double blind trlal to evaluate efficacy and safety of drOnedaron [400 mg b.i.d.] versus amiodarone [600 mg q.d. for 28 daYS, then 200 mg qd thereafter] for at least 6 mOnths for the maintenance of Sinus rhythm in patients with atrial fibrillation | PCI        | percutaneous intervention   |
|  |   | PIAF       | Pharmacological Intervention in Atrial Fibrillation   |
|  |   | PPI        | proton pump inhibitor   |
|  |   | PROTECT-AF | System for Embolic PROTECTion in patients with Atrial Fibrillation  |
|  |   | PUFA       | polyunsaturated fatty acid  |
|  |   | PV         | pulmonary vein  |
|  |   | PVI        | pulmonary vein isolation  |
|  |   | RACE       | RAte Control versus Electrical cardioversion for persistent atrial fibrillation   |
|  |   | RACE II    | RAte Control Efficacy in permanent atrial fibrillation  |
|  |   | RAAFT      | Radiofrequency Ablation Atrial Fibrillation Trial   |
|  |   | RE-LY      | Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate  |
|  |   | RIKS-HIA   | Register of Information and Knowledge about Swedish Heart Intensive care Admissions   |
|  |   | RR         | relative risk   |

|           |  |
|-----------|--|
| SAFE-T    | Sotalol, Amiodarone, atrial Fibrillation Efficacy Trial  |
| SAFE      | Screening for AF in the Elderly  |
| SCD       | sudden cardiac death   |
| SPAF      | Stroke Prevention in Atrial Fibrillation   |
| STAF      | Strategies of Treatment of Atrial Fibrillation   |
| STEMI     | ST segment elevation myocardial infarction   |
| STOP-AF   | Sustained Treatment Of Paroxysmal Atrial Fibrillation  |
| TIA       | transient ischaemic attack   |
| t.i.d.    | ter in die (three times daily)   |
| TIMI      | Thrombolysis In Myocardial Infarction  |
| TOE       | transoesophageal echocardiogram  |
| TRANSCEND | Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease |
| UFH       | unfractionated heparin   |
| VALUE     | Valsartan Antihypertensive Long-term Use Evaluation  |
| VKA       | vitamin K antagonist   |
| WASPO     | Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF                         |

## 1. Preamble

Guidelines summarize and evaluate all currently available evidence on a particular issue with the aim of assisting physicians in selecting the best management strategy for an individual patient suffering from a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines are no substitutes for textbooks. The legal implications of medical guidelines have been discussed previously.

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. Because of the impact on clinical practice, quality criteria for development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC Web Site (<http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx>).

In brief, experts in the field are selected and undertake a comprehensive review of the published evidence for management and/or prevention of a given condition. A critical evaluation of diagnostic and therapeutic procedures is performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger societies are included, where data exist. The level of evidence and the strength of recommendation of particular treatment options are weighed and graded according to pre-defined scales, as outlined in *Tables 1 and 2*.

The experts of the writing panels have provided disclosure statements of all relationships they may have that might be perceived as real or potential sources of conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. Any changes in conflict of interest that arise during the writing period must be notified to the ESC. The Task Force report received its entire financial support from the

**Table 1** Classes of recommendations

| Classes of recommendations | Definition  |
|----------------------------|---|
| <b>Class I</b>             | <b>Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.</b>                        |
| <b>Class II</b>            | <b>Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.</b>         |
| <i>Class IIa</i>           | <i>Weight of evidence/opinion is in favour of usefulness/efficacy.</i>  |
| <i>Class IIb</i>           | <i>Usefulness/efficacy is less well established by evidence/opinion.</i>  |
| <b>Class III</b>           | <b>Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.</b> |

**Table 2** Levels of evidence

|                            |   |
|----------------------------|---|
| <b>Level of evidence A</b> | <b>Data derived from multiple randomized clinical trials or meta-analyses.</b>                      |
| <b>Level of evidence B</b> | <b>Data derived from a single randomized clinical trial or large non-randomized studies.</b>        |
| <b>Level of evidence C</b> | <b>Consensus of opinion of the experts and/or small studies, retrospective studies, registries.</b> |

ESC and was developed without any involvement of the pharmaceutical, device, or surgical industry.

The ESC Committee for Practice Guidelines (CPG) supervises and coordinates the preparation of new Guidelines produced by Task Forces, expert groups, or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines or statements. Once the document has been finalized and approved by all the experts involved in the Task Force, it is submitted to outside specialists for review. The document is revised, finally approved by the CPG, and subsequently published.

After publication, dissemination of the message is of paramount importance. Pocket-sized versions and personal digital assistant-downloadable versions are useful at the point of care. Some surveys have shown that the intended users are sometimes unaware of the existence of guidelines, or simply do not translate them into practice. Thus, implementation programmes for new guidelines form an important component of knowledge dissemination. Meetings are organized by the ESC, and directed towards its member National Societies and key opinion leaders in Europe. Implementation meetings can also be undertaken at national

levels, once the guidelines have been endorsed by the ESC member societies, and translated into the national language. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Thus, the task of writing Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. The loop between clinical research, writing of guidelines, and implementing them into clinical practice can then only be completed if surveys and registries are performed to verify that real-life daily practice is in keeping with what is recommended in the guidelines. Such surveys and registries also make it possible to evaluate the impact of implementation of the guidelines on patient outcomes. Guidelines and recommendations should help the physicians to make decisions in their daily practice; however, the ultimate judgement regarding the care of an individual patient must be made by the physician in charge of their care.

## 2. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages. It is now 4 years since the last AF guideline was published, and a new version is now needed.

AF confers a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia. Ischaemic strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. In consequence, the risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold. There has been much research into stroke prevention, which has influenced this guideline.

In the majority of patients there appears to be an inexorable progression of AF to persistent or permanent forms, associated with further development of the disease that may underlie the arrhythmia. Some advance has been made in the understanding of the dynamic development of AF from its preclinical state as an 'arrhythmia-in-waiting' to its final expression as an irreversible and end-stage cardiac arrhythmia associated with serious adverse cardiovascular events. Much recent therapeutic effort with 'upstream therapies' has been expended to slow or halt the progression of AF due to underlying cardiovascular disease and to AF itself. Limited success has been achieved and is recognized in this guideline.

Clinical frustration has been fuelled by numerous clinical trials that have demonstrated that the strategic aim of maintaining sinus rhythm has no demonstrable value when compared with the *laissez-faire* approach of leaving AF unchecked apart from restriction of the ventricular rate. No advantage from strict rate control has been established. These sobering findings are clearly at odds with the severe complications associated with AF in surveys and epidemiological studies. However, new antiarrhythmic approaches may offer added value and have stimulated additions to these guidelines.

The problem of early recognition of AF is greatly aggravated by the often 'silent' nature of the rhythm disturbance. In about one-third of patients with this arrhythmia, the patient is not aware of so-called 'asymptomatic AF'. Much earlier detection of the arrhythmia might allow the timely introduction of therapies to protect the patient, not only from the consequences of the arrhythmia, but also from progression of AF from an easily treated condition to an utterly refractory problem. Monitoring and screening as advocated in this guideline may help to do this.

Non-pharmacological interventions to control the occurrence of AF or to limit its expression have been eagerly and substantially developed in the past decade. Ablation techniques, usually done percutaneously using a catheter, have proved successful in the treatment of AF, particularly by reducing the symptomatic burden associated with the arrhythmia, to such an extent that a 'cure' may be achieved in some patients. The new guidelines recognize these advances. When applied in concert with major new drug developments such as novel antithrombotic agents and emerging safer antiarrhythmic drugs, these therapeutic options should help to improve outcomes in AF patients.

The expanding and diversifying possibilities and restraints of medical care within Europe make it difficult to formulate guidelines that are valid throughout Europe. There are differences in the availability of therapies, delivery of care, and patient characteristics in Europe and in other parts of the world. Therefore, these European guidelines, though based largely on globally acquired data, are likely to require some modifications when applied to multiple healthcare settings.

### 2.1 Epidemiology

AF affects 1–2% of the population, and this figure is likely to increase in the next 50 years.<sup>1–2</sup> In acute stroke patients, systematic electrocardiographic (ECG) monitoring would identify AF in 1 in 20 subjects, a far greater number than would have been detected by standard 12-lead ECG recordings. AF may long remain undiagnosed (silent AF),<sup>3</sup> and many patients with AF will never present to hospital.<sup>4</sup> Hence, the 'true' prevalence of AF is probably closer to 2% of the population.<sup>3</sup>

The prevalence of AF increases with age, from <0.5% at 40–50 years, to 5–15% at 80 years.<sup>1–2,5–7</sup> Men are more often affected than women. The lifetime risk of developing AF is ~25% in those who have reached the age of 40.<sup>8</sup> The prevalence and incidence of AF in non-Caucasian populations is less well studied. The incidence of AF appears to be increasing (13% in the past two decades).

#### 2.1.1 Atrial fibrillation-related cardiovascular events ('outcomes')

AF is associated with increased rates of death, stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity, and left ventricular (LV) dysfunction (Table 3).

**Death** rates are doubled by AF, independently of other known predictors of mortality.<sup>3,9</sup> Only antithrombotic therapy has been shown to reduce AF-related deaths.<sup>10</sup>



**Table 3 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.<sup>3</sup> 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 every fifth stroke is due to AF; furthermore, undiagnosed 'silent AF' is a likely cause of some 'cryptogenic' strokes.<sup>3,11</sup> Paroxysmal AF carries the same stroke risk as permanent or persistent AF.<sup>12</sup>

**Hospitalizations** due to AF 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.

**Cognitive dysfunction**, including vascular dementia, may be related to AF. Small observational studies suggest that asymptomatic embolic events may contribute to cognitive dysfunction in AF patients in the absence of an overt stroke.<sup>11</sup>

**Quality of life and exercise capacity** are impaired in patients with AF. Patients with AF have a significantly poorer quality of life compared with healthy controls, the general population, or patients with coronary heart disease in sinus rhythm.<sup>13</sup>

**Left ventricular (LV) function** is often impaired by the irregular, fast ventricular rate and by loss of atrial contractile function and increased end-diastolic LV filling pressure. Both rate control and maintenance of sinus rhythm can improve LV function in AF patients.

### 2.1.2 Cardiovascular and other conditions associated with atrial fibrillation

AF is associated with a variety of cardiovascular conditions.<sup>14,15</sup> Concomitant medical conditions have an additive effect on the perpetuation of AF by promoting a substrate that maintains AF (see Section 2.2). Conditions associated with AF are also markers for global cardiovascular risk and/or cardiac damage rather than simply causative factors.

**Ageing** increases the risk of developing AF, possibly through age-dependent loss and isolation of atrial myocardium and associated conduction disturbances (see Section 2.2).

**Hypertension** is a risk factor for incident (first diagnosed) AF and for AF-related complications such as stroke and systemic thrombo-embolism.

**Symptomatic heart failure** [New York Heart Association (NYHA) classes II–IV] is found in 30% of AF patients,<sup>14,15</sup> and AF is found in up to 30–40% of heart failure patients, depending on the underlying cause and severity of heart failure. Heart failure can be both a consequence of AF (e.g. tachycardiomyopathy or decompensation in acute onset AF) and a cause of the arrhythmia due to increased atrial pressure and volume overload, secondary valvular dysfunction, or chronic neurohumoral stimulation.

**Tachycardiomyopathy** should be suspected when LV dysfunction is found in patients with a fast ventricular rate but no signs of structural heart disease. It is confirmed by normalization or improvement of LV function when good AF rate control or reversion to sinus rhythm is achieved.

**Valvular heart diseases** are found in ~30% of AF patients.<sup>14,15</sup> AF caused by left atrial (LA) distension is an early manifestation of mitral stenosis and/or regurgitation. AF occurs in later stages of aortic valve disease. While 'rheumatic AF' was a frequent finding in the past, it is now relatively rare in Europe.

**Cardiomyopathies**, including primary electrical cardiac diseases,<sup>16</sup> carry an increased risk for AF, especially in young patients. Relatively rare cardiomyopathies are found in 10% of AF patients.<sup>14,15</sup> A small proportion of patients with 'lone' AF carry known mutations for 'electrical' cardiomyopathies.

**Atrial septal defect** is associated with AF in 10–15% of patients in older surveys. This association has important clinical implications for the antithrombotic management of patients with previous stroke or transient ischaemic attack (TIA) and an atrial septal defect.

**Other congenital heart defects** at risk of AF include patients with single ventricles, after Mustard operation for transposition of the great arteries, or after Fontan surgery.

**Coronary artery disease** is present in ≥20% of the AF population.<sup>14,15</sup> Whether uncomplicated coronary artery disease *per se* (atrial ischaemia) predisposes to AF and how AF interacts with coronary perfusion<sup>17</sup> are uncertain.

Overt **thyroid dysfunction** can be the sole cause of AF and may predispose to AF-related complications. In recent surveys, hyperthyroidism or hypothyroidism was found to be relatively uncommon in AF populations,<sup>14,15</sup> but subclinical thyroid dysfunction may contribute to AF.

**Obesity** is found in 25% of AF patients,<sup>15</sup> and the mean body mass index was 27.5 kg/m<sup>2</sup> in a large, German AF registry (equivalent to moderately obese).

**Diabetes mellitus** requiring medical treatment is found in 20% of AF patients, and may contribute to atrial damage.

**Chronic obstructive pulmonary disease (COPD)** is found in 10–15% of AF patients, and is possibly more a marker for cardiovascular risk in general than a specific predisposing factor for AF.

**Sleep apnoea**, especially in association with hypertension, diabetes mellitus, and structural heart disease, may be a pathophysiological factor for AF because of apnoea-induced increases in atrial pressure and size, or autonomic changes.

**Chronic renal disease** is present in 10–15% of AF patients. Renal failure may increase the risk of AF-related cardiovascular complications, although controlled data are sparse.

## 2.2 Mechanisms of atrial fibrillation

### 2.2.1 Atrial factors

#### *Pathophysiological changes preceding atrial fibrillation*

Any kind of structural heart disease may trigger a slow but progressive process of structural remodelling in both the ventricles and the atria. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts and enhanced connective tissue deposition and fibrosis are the hallmarks of this process. Structural remodelling results in electrical dissociation between muscle bundles and local conduction heterogeneities facilitating the initiation and perpetuation of AF. This electroanatomical substrate permits multiple small re-entrant circuits that can stabilize the arrhythmia. Structural abnormalities reported in patients with AF are summarized in *Table 4*.

#### *Pathophysiological changes as a consequence of atrial fibrillation*

After the onset of AF, changes of atrial electrophysiological properties, mechanical function, and atrial ultrastructure occur with different time courses and with different pathophysiological consequences.<sup>18</sup> Shortening of the atrial effective refractory period within the first days of AF has been documented in humans.<sup>19</sup> The electrical remodelling process contributes to the increasing stability of AF during the first days after its onset. The main cellular mechanisms underlying the shortening of the refractory period are down-regulation of the L-type  $\text{Ca}^{2+}$  inward current and up-regulation of inward rectifier  $\text{K}^{+}$  currents. Recovery of

normal atrial refractoriness occurs within a few days after restoration of sinus rhythm.

Perturbation of atrial contractile function also occurs within days of AF. The main cellular mechanisms of atrial contractile dysfunction are down-regulation of the  $\text{Ca}^{2+}$  inward current, impaired release of  $\text{Ca}^{2+}$  from intracellular  $\text{Ca}^{2+}$  stores, and alterations of myofibrillar energetics.

In patients with 'lone' AF, fibrosis and inflammatory changes have been documented.<sup>20</sup>

### 2.2.2 Electrophysiological mechanisms

The initiation and perpetuation of a tachyarrhythmia requires both triggers for its onset and a substrate for its maintenance. These mechanisms are not mutually exclusive and are likely to co-exist at various times.

#### *Focal mechanisms*

Focal mechanisms potentially contributing to the initiation and perpetuation of AF have attracted much attention.<sup>21</sup> Cellular mechanisms of focal activity might involve both triggered activity and re-entry. Because of shorter refractory periods as well as abrupt changes in myocyte fibre orientation, the pulmonary veins (PVs) have a stronger potential to initiate and perpetuate atrial tachyarrhythmias.

Ablation of sites with a high dominant frequency, mostly located at or close to the junction between the PVs and the left atrium, results in progressive prolongation of the AF cycle length and conversion to sinus rhythm in patients with paroxysmal AF, while in persistent AF, sites with a high dominant frequency are spread throughout the entire atria, and ablation or conversion to sinus rhythm is more difficult.

#### *The multiple wavelet hypothesis*

According to the multiple wavelet hypothesis, AF is perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. Fibrillation wavefronts continuously undergo wavefront–waveback interactions, resulting in wavebreak and the generation of new wavefronts, while block, collision, and fusion of wavefronts tend to reduce their number. As long as the number of wavefronts does not decline below a critical level, the multiple wavelets will sustain the arrhythmia. While in most patients with paroxysmal AF localized sources of the arrhythmia can be identified, such attempts are often not successful in patients with persistent or permanent AF.

### 2.2.3 Genetic predisposition

AF has a familial component, especially AF of early onset.<sup>22</sup> During the past years, numerous inherited cardiac syndromes associated with AF have been identified. Both short and long QT syndromes and Brugada syndrome are associated with supraventricular arrhythmias, often including AF.<sup>23</sup> AF also frequently occurs in a variety of inherited conditions, including hypertrophic cardiomyopathy, a familial form of ventricular pre-excitation, and abnormal LV hypertrophy associated with mutations in the *PRKAG* gene. Other familial forms of AF are associated with mutations in the gene coding for atrial natriuretic peptide,<sup>24</sup> loss-of-function

**Table 4** Structural abnormalities associated with AF

|  |
|--|
| <b>Extracellular matrix alterations</b>                          |
| Interstitial and replacement fibrosis                            |
| Inflammatory changes   |
| Amyloid deposit  |
| <b>Myocyte alterations</b>                                       |
| Apoptosis  |
| Necrosis   |
| Hypertrophy  |
| Dedifferentiation  |
| Gap junction redistribution                                      |
| Intracellular substrate accumulation (haemocromatosis, glycogen) |
| <b>Microvascular changes</b>                                     |
| <b>Endocardial remodelling (endomyocardial fibrosis)</b>         |

AF = atrial fibrillation.

mutations in the cardiac sodium channel gene *SCN5A*,<sup>25</sup> or gain of function in a cardiac potassium channel.<sup>26</sup> Furthermore, several genetic loci close to the *PITX2* and *ZFHX3* genes associate with AF and cardioembolic stroke in population-wide studies.<sup>27</sup> The pathophysiological role of other genetic defects in the initiation and perpetuation of AF is currently unknown.<sup>23</sup>

### 2.2.4 Clinical correlates

#### Atrioventricular conduction

In patients with AF and a normal conduction system [in the absence of accessory pathways (APs) or His–Purkinje dysfunction], the atrioventricular node functions as a frequency filter preventing excessive ventricular rates. The main mechanisms limiting atrioventricular conduction are intrinsic refractoriness of the atrioventricular node and concealed conduction. Electrical impulses reaching the atrioventricular node may not be conducted to the ventricles, but may alter atrioventricular node refractoriness, slowing or blocking subsequent atrial beats.

Fluctuations in sympathetic and parasympathetic tone result in variability of the ventricular rate during the diurnal cycle or during exercise. The high variability of the ventricular rate is often a therapeutic challenge. Digitalis, which slows down the ventricular rate by an increase in parasympathetic tone, is effective for controlling heart rate at rest, but to a lesser extent during exercise.  $\beta$ -Blockers and non-dihydropyridine calcium channel antagonists reduce the ventricular rate during both rest and exercise.

In patients with pre-excitation syndromes, fast and potentially life-threatening ventricular rates may occur. In patients with AF and pre-excitation syndromes, administration of compounds that slow atrioventricular nodal conduction without prolonging atrial/AP refractory periods (e.g. verapamil, diltiazem, and digitalis) can accelerate conduction via the AP.

#### Haemodynamic changes

Factors affecting haemodynamic function in patients with AF involve loss of coordinated atrial contraction, high ventricular rates, irregularity of the ventricular response, and decrease in myocardial blood flow, as well as long-term alterations such as atrial and ventricular cardiomyopathy.

Acute loss of coordinated atrial mechanical function after the onset of AF reduces cardiac output by 5–15%. This effect is more pronounced in patients with reduced ventricular compliance in whom atrial contraction contributes significantly to ventricular filling. High ventricular rates limit ventricular filling due to the short diastolic interval. Rate-related interventricular or intraventricular conduction delay may lead to dyssynchrony of the left ventricle and reduce cardiac output further.

In addition, irregularity of the ventricular rate can reduce cardiac output. Because of force–interval relationships, fluctuations of the RR intervals cause a large variability in the strengths of subsequent heart beats, often resulting in pulse deficit.

Persistent elevation of ventricular rates above 120–130 bpm may produce ventricular tachycardiomyopathy.<sup>28</sup> Reduction of the heart rate may restore normal ventricular function and prevent further dilatation and damage to the atria.

#### Thrombo-embolism

Risk of stroke and systemic embolism in patients with AF is linked to a number of underlying pathophysiological mechanisms.<sup>29</sup> ‘Flow abnormalities’ in AF are evidenced by stasis within the left atrium, with reduced left atrial appendage (LAA) flow velocities, and visualized as spontaneous echo-contrast on transoesophageal echocardiography (TOE). ‘Endocardial abnormalities’ include progressive atrial dilatation, endocardial denudation, and oedematous/fibroelastic infiltration of the extracellular matrix. The LAA is the dominant source of embolism (>90%) in non-valvular AF.<sup>29</sup> ‘Abnormalities of blood constituents’ are well described in AF and include haemostatic and platelet activation, as well as inflammation and growth factor abnormalities.<sup>29</sup>

## 3. Detection, ‘natural’ history, and acute management

### 3.1 Definition

AF is defined as a cardiac arrhythmia with the following characteristics:

- (1) The surface ECG shows ‘absolutely’ irregular RR intervals (AF is therefore sometimes known as *arrhythmia absoluta*), i.e. RR intervals that do not follow a repetitive pattern.
- (2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
- (3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm).

#### Differential diagnosis

Several supraventricular arrhythmias, most notably atrial tachycardias and atrial flutter, but also rare forms of frequent atrial ectopy or even dual antegrade atrioventricular nodal conduction, may present with rapid irregular RR intervals and mimic AF. Most atrial tachycardias and flutters show longer atrial cycle lengths  $\geq 200$  ms. Patients on antiarrhythmic drugs may have slower atrial cycle lengths during AF.

An ECG recording during the arrhythmia is usually needed to differentiate the common diagnosis of AF from other rare supraventricular rhythms with irregular RR intervals, or the common occurrence of ventricular extrasystoles. Any episode of suspected AF should be recorded by a 12-lead ECG of sufficient duration and quality to evaluate atrial activity. Occasionally, when the ventricular rate is fast, atrioventricular nodal blockade during the Valsalva manoeuvre, carotid massage, or intravenous (i.v.) adenosine administration<sup>30</sup> can help to unmask atrial activity.

### 3.2 Detection

An irregular pulse should always raise the suspicion of AF, but an ECG recording is necessary to diagnose AF. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered as AF.<sup>3,31</sup> The heart rate in AF can be calculated from a standard 12-lead ECG by multiplying the number of



RR intervals on the 10 s strip (recorded at 25 mm/s) by six. The risk of AF-related complications is not different between short AF episodes and sustained forms of the arrhythmia.<sup>12</sup> It is therefore important to detect paroxysmal AF in order to prevent AF-related complications (e.g. stroke). However, short 'atrial high-rate episodes', e.g. detected by pacemakers, defibrillators, or other implanted devices, may not be associated with thrombo-embolic complications unless their duration exceeds several hours (see Section 3.4).

AF may manifest initially as an ischaemic stroke or TIA, and it is reasonable to assume that most patients experience asymptomatic, often self-terminating, arrhythmia episodes before AF is first diagnosed. The rate of AF recurrence is 10% in the first year after the initial diagnosis, and ~5% per annum thereafter. Co-morbidities and age significantly accelerate both the progression of AF and the development of complications.<sup>3,23</sup>

### 3.3 'Natural' time course

AF progresses from short, rare episodes, to longer and more frequent attacks. Over time (years), many patients will develop sustained forms of AF (Figure 1). Only a small proportion of patients without AF-promoting conditions (see Section 2.1.2) will remain in paroxysmal AF over several decades (2–3% of AF patients).<sup>32</sup> The distribution of paroxysmal AF recurrences is not random, but clustered.<sup>3</sup> 'AF burden' can vary markedly over months or even years in individual patients.<sup>3</sup> Asymptomatic AF is common even in symptomatic patients, irrespective of whether the initial presentation was persistent or paroxysmal. This has important implications for (dis)continuation of therapies aimed at preventing AF-related complications.

### 3.4 Electrocardiogram techniques to diagnose and monitor atrial fibrillation

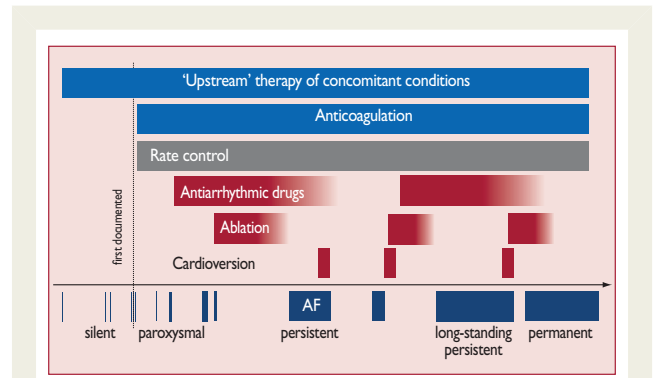
The intensity and duration of monitoring should be determined by the clinical need to establish the diagnosis, and should be driven mainly by the clinical impact of AF detection. More intense AF recording is usually necessary in clinical trials than in clinical practice.<sup>3,33</sup>

#### Patients with suspected but undiagnosed atrial fibrillation

In patients with suspected AF, a 12-lead ECG is recommended as the first step to establish the diagnosis. Clinical symptoms such as palpitations or dyspnoea should trigger ECG monitoring to demonstrate AF, or to correlate symptoms with the underlying rhythm. There are only limited data comparing the value of different monitoring strategies.<sup>3,34–37</sup> More intense and prolonged monitoring is justified in highly symptomatic patients [European Heart Rhythm Association IV (EHRA IV)—see Section 3.6], patients with recurrent syncope, and patients with a potential indication for anticoagulation (especially after cryptogenic stroke).<sup>34,38</sup> In selected patients, implantation of a leadless AF monitoring device may be considered to establish the diagnosis.<sup>39</sup>

#### Patients with known atrial fibrillation

Indications for AF monitoring in patients with previously diagnosed AF differ compared with undiagnosed patients. When arrhythmia- or therapy-related symptoms are suspected, monitoring using



**Figure 1** '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.

Holter recordings or external event recorders should be considered. In patients with rhythm or rate control treatment and without further arrhythmia- or therapy-related symptoms, a 12-lead ECG should be recorded at regular intervals. In patients receiving antiarrhythmic drug therapy, the frequency of 12-lead ECG recording depends on the type of antiarrhythmic drug treatment, the potential side effects, complications, and risks of proarrhythmia.

#### Tools for non-continuous ECG monitoring

Available non-continuous ECG methods include scheduled or symptom-activated standard ECGs, Holter (24 h to 7 days) monitoring and transtelephonic recordings, patient- and automatically activated devices, and external loop recorders. If AF is present at the time of recording, use of the standard 12-lead ECG is sufficient to confirm the diagnosis. In paroxysmal AF, prolonged non-continuous recording will facilitate AF detection. It has been estimated that 7 day Holter ECG recording or daily and symptom-activated event recordings may document the arrhythmia in ~70% of AF patients, and that their negative predictive value for the absence of AF is between 30 and 50%.<sup>3</sup> 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.<sup>34</sup>

#### Tools for continuous ECG monitoring

Implantable devices capable of intracardiac atrial electrogram recording such as dual-chamber pacemakers and defibrillators can detect AF appropriately, particularly when an arrhythmia duration  $\geq 5$  min is used as a cut-off value. Longer atrial high-rate episodes (e.g.  $>5.5$  h) may be associated with thrombo-embolic

events.<sup>35,36</sup> Leadless implantable loop recorders provide continuous AF monitoring over a 2 year period with automatic AF detection based on RR interval analysis. Preliminary clinical data indicate good sensitivity but less specificity for AF detection.<sup>40</sup> No data exist on the implementation of such devices in the clinical routine of AF monitoring.

### 3.5 Types of atrial fibrillation

Clinically, it is reasonable to distinguish five types of AF based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (Figure 2).

- (1) Every patient who presents with AF for the first time is considered a patient with **first diagnosed AF**, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
- (2) **Paroxysmal AF** is self-terminating, usually within 48 h. Although AF paroxysms may continue for up to 7 days, the 48 h time point is clinically important—after this the likelihood of spontaneous conversion is low and anticoagulation must be considered (see Section 4.1).
- (3) **Persistent AF** is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC).
- (4) **Long-standing persistent AF** has lasted for  $\geq 1$  year when it is decided to adopt a rhythm control strategy.
- (5) **Permanent AF** is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control

strategy be adopted, the arrhythmia is redesignated as ‘long-standing persistent AF’.

This classification is useful for clinical management of AF patients (Figure 2), especially when AF-related symptoms are also considered. Many therapeutic decisions require careful consideration of additional individual factors and co-morbidities.

**Silent AF** (asymptomatic) may manifest as an AF-related complication (ischaemic stroke or tachycardiomyopathy) or may be diagnosed by an opportunistic ECG. Silent AF may present as any of the temporal forms of AF.

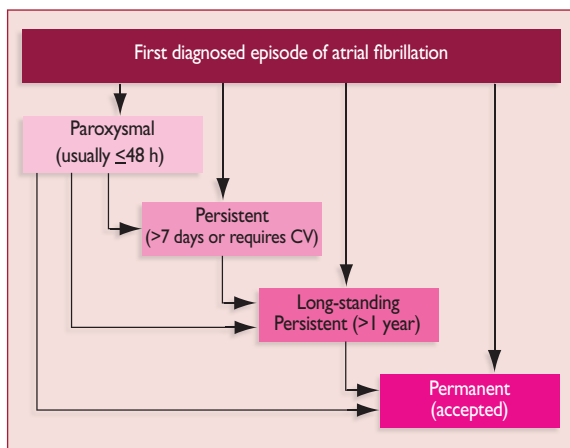
### 3.6 Initial management

A thorough medical history should be obtained from the patient with suspected or known AF (Table 5). The acute management of AF patients should concentrate on relief of symptoms and assessment of AF-associated risk. Clinical evaluation should include determination of the EHRA score (Table 6<sup>3</sup>), estimation of stroke risk (see Section 4.1), and search for conditions that predispose to AF (see Section 2.1.2) and for complications of the arrhythmia (see Section 2.1.1). The 12-lead ECG should be

**Table 5** 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 <b>EHRA score</b> , <sup>3</sup> which is similar to the CCS-SAF score. <sup>41</sup>                            |
| 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.



**Figure 2** 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.

**Table 6** 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.

inspected for signs of structural heart disease (e.g. acute or remote myocardial infarction, LV hypertrophy, bundle branch block or ventricular pre-excitation, signs of cardiomyopathy, or ischaemia).

### Diagnostic evaluation

A recently suggested symptom score (EHRA score,<sup>3</sup> Table 6) provides a simple clinical tool for assessing symptoms during AF. A very similar scale has been validated by the Canadian Cardiovascular Society.<sup>41</sup> The EHRA score only considers symptoms that are attributable to AF and reverse or reduce upon restoration of sinus rhythm or with effective rate control.

The initial diagnostic work-up is driven by the initial presentation. The **time of onset of the arrhythmia episode** should be established to define the type of AF (Figure 2). Most patients with AF <48 h in duration can be cardioverted (see Section 4.1.7) on low molecular weight heparin (LMWH) without risk for stroke. If AF duration is >48 h or there is doubt about its duration, **TOE** may be used to rule out intracardiac thrombus prior to cardioversion,<sup>42</sup> although it can be difficult in patients in acute distress and may not be available in emergency settings. The transthoracic echocardiogram can provide useful information to guide clinical decision making, but cannot exclude thrombus in the LAA.

Patients with AF and **signs of acute heart failure** require urgent rate control and often cardioversion. An urgent echocardiogram should be performed in haemodynamically compromised patients to assess LV and valvular function and right ventricular pressure.

Patients with **stroke or TIA** require immediate stroke diagnosis, usually via emergency computed tomography (CT) and adequate cerebral revascularization.

Patients should be assessed for risk of stroke. Most patients with acute AF will require anticoagulation unless they are at low risk of thrombo-embolic 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. An *echocardiogram* is useful to detect ventricular, valvular, and atrial disease as well as rare congenital heart disease. *Thyroid function tests* (usually measurement of serum thyroid-stimulating hormone), a full *blood count*, a serum *creatinine* measurement and analysis for *proteinuria*, measurement of *blood pressure*, and a test for *diabetes mellitus* (usually a fasting glucose measurement) 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 ischaemia are candidates for *coronary angiography*.

## 3.7 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. post-cardioversion 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?

At follow-up visits, a 12-ECG should be recorded to document the rhythm and rate, and to investigate disease progression. For those on antiarrhythmic drug therapy it is important to assess potential proarrhythmic ECG precursors such as lengthening of PR, QRS, or QT intervals, non-sustained ventricular tachycardia, or pauses. If any worsening of symptoms occurs, repeated blood tests, long-term ECG recordings and a repeat echocardiogram should be considered.

The patient should be fully informed about the pros and cons of the different treatment options, whether it is anticoagulation, rate control drugs, antiarrhythmic drugs, or interventional therapy. It is also appropriate to inform the patient with 'lone' or idiopathic AF about the good prognosis, once cardiovascular disease has been excluded.

## 4. Management

Management of AF patients is aimed at reducing symptoms and at preventing severe complications associated with AF. These therapeutic goals need to be pursued in parallel, especially upon the initial presentation of newly detected AF. Prevention of AF-related complications relies on antithrombotic therapy, control of ventricular rate, and adequate therapy of concomitant cardiac diseases. These therapies may already alleviate symptoms, but symptom relief may require additional rhythm control therapy by cardioversion, antiarrhythmic drug therapy, or ablation therapy (Figure 3).

### 4.1 Antithrombotic management

Cohort data as well as the non-warfarin arms of clinical trials have identified clinical and echocardiographic risk factors that can be related to an increased risk of stroke in AF.<sup>47,48</sup> These risk factors are limited to those documented in these studies, whilst many other potential risk factors were not systematically documented.

Two recent systematic reviews have addressed the evidence base for stroke risk factors in AF,<sup>47,48</sup> 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 on two-dimensional transthoracic echocardiography is the only independent echocardiographic risk factor for stroke on multivariable analysis. On TOE, the presence of LA thrombus relative risk (RR) 2.5;  $P = 0.04$ , complex aortic plaques (RR 2.1;  $P < 0.001$ ), spontaneous

**Recommendations for diagnosis and initial management**

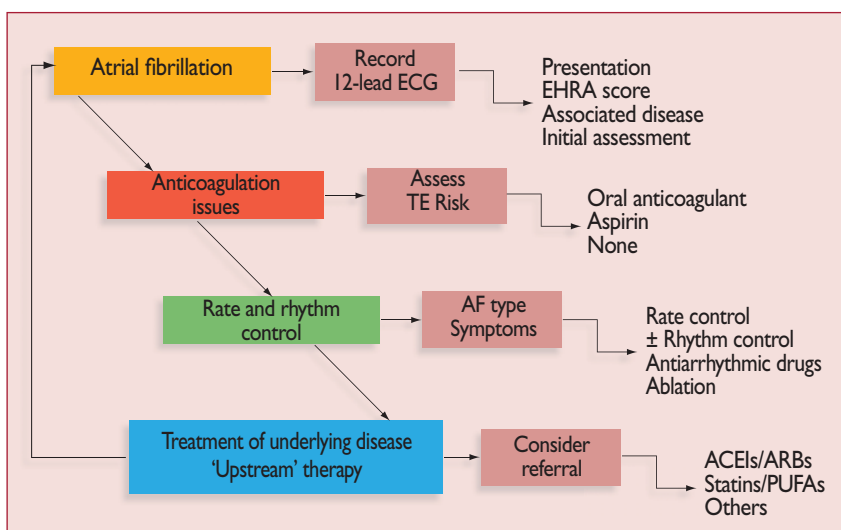
| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| The diagnosis of AF requires documentation by ECG.   | I                  | B                  | 3, 31             |
| In patients with suspected AF, an attempt to record an ECG should be made when symptoms suggestive of AF occur.                                | I                  | B                  | 3, 43             |
| A simple symptom score (EHRA score) is recommended to quantify AF-related symptoms.  | I                  | B                  | 3, 41             |
| All patients with AF should undergo a thorough physical examination, and a cardiac- and arrhythmia-related history should be taken.            | I                  | C                  |                   |
| In patients with severe symptoms, documented or suspected heart disease, or risk factors, an echocardiogram is recommended.                    | I                  | B                  | 3, 23, 44         |
| In patients treated with antiarrhythmic drugs, a 12-lead ECG should be recorded at regular intervals during follow-up.                         | I                  | C                  |                   |
| In patients with suspected symptomatic AF, additional ECG monitoring should be considered in order to document the arrhythmia.                 | IIa                | B                  | 3, 33             |
| Additional ECG monitoring should be considered for detection of 'silent' AF in patients who may have sustained an AF-related complication.     | IIa                | B                  | 3, 34             |
| In patients with AF treated with rate control, Holter ECG monitoring should be considered for assessment of rate control or bradycardia.       | IIa                | C                  |                   |
| In young active patients with AF treated with rate control, exercise testing should be considered in order to assess ventricular rate control. | IIa                | C                  |                   |
| In patients with documented or suspected AF, an echocardiogram should be considered.   | IIa                | C                  |                   |
| Patients with symptomatic AF or AF-related complications should be considered for referral to a cardiologist.                                  | IIa                | C                  |                   |
| A structured follow-up plan prepared by a specialist is useful for follow-up by a general or primary care physician.                           | IIa                | C                  |                   |
| In patients treated with rhythm control, repeated ECG monitoring may be considered to assess the efficacy of treatment.                        | IIb                | B                  | 3, 45, 46         |
| Most patients with AF may benefit from specialist follow-up at regular intervals.  | IIb                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

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



**Figure 3** 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.

echo-contrast (RR 3.7;  $P < 0.001$ ), and low LAA velocities ( $\leq 20$  cm/s; RR 1.7;  $P < 0.01$ ) 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  $< 60$  years, with 'lone AF', i.e. no clinical history or echocardiographic evidence of cardiovascular disease, carry a very low cumulative stroke risk, estimated to be 1.3% over 15 years. The probability of stroke in young patients with lone AF appears to increase with advancing age or development of hypertension, emphasizing the importance of re-assessment of risk factors for stroke over time.

### Caveats and inconsistencies

In some series, concomitant aspirin use may have influenced thrombo-embolic event rates. Of note, stroke rates are generally declining. In addition, anticoagulation monitoring is improving for those taking vitamin K antagonists (VKAs), and new oral anticoagulant (OAC) drugs that may not need monitoring are on the horizon.

Also, definitions and categorization of risk factors have been inconsistent over time. For example, age as a risk factor is not a 'yes/no' phenomenon, and stroke risk in AF starts to rise from age  $> 65$ , although it is clear that AF patients aged  $\geq 75$  years (even with no other associated risk factors) have a significant stroke risk and derive benefit from VKA over aspirin.<sup>47,48</sup> As patients with AF get older, the relative efficacy of antiplatelet therapy to prevent ischaemic stroke decreases, whereas it does not change for VKAs. Thus, the absolute benefit of VKAs for stroke prevention increases as AF patients get older. This is supported by other 'real-world' data.

In the older trials, hypertension was often defined as untreated blood pressure  $> 160/95$  mmHg or the use of antihypertensive drugs. Well-controlled blood pressure may represent a low risk of stroke and thrombo-embolism. In addition, a clinical diagnosis of heart failure was not a consistent risk factor for stroke in the systematic reviews mentioned above; indeed, a label of 'heart failure' may not necessarily reflect systolic LV impairment. Whilst the risk of thrombo-embolism with moderate to severe systolic impairment is clear, the risk of thrombo-embolism with heart failure and preserved ejection fraction is less defined.<sup>44,47,48</sup>

The presence of atherosclerotic vascular disease may contribute to stroke risk. An increased risk of stroke and thrombo-embolism with previous myocardial infarction is present in most (but not all) studies,<sup>49</sup> but a diagnosis of 'angina' *per se* is unreliable, as many such patients do not have coronary heart disease. Also, AF confers a poor prognosis in patients with peripheral artery disease (PAD), and the presence of complex aortic plaque on the descending aorta on TOE is an independent risk factor for stroke and thrombo-embolism.

Female sex results in an adjusted RR of 1.6 [95% confidence interval (CI) 1.3–1.9] for thrombo-embolism. Gender analyses from population studies, cohort studies, trial cohorts, and surveys also suggest higher thrombo-embolism rates in female subjects.

**Table 7 CHADS<sub>2</sub> score and stroke rate**

| CHADS <sub>2</sub> score | Patients (n=1733) | Adjusted stroke rate (%/year) <sup>a</sup> (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)   |

<sup>a</sup>The 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 CHADS<sub>2</sub> 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 BF *et al.*<sup>50</sup>  
AF = atrial fibrillation; CHADS<sub>2</sub> = cardiac failure, hypertension, age, diabetes, stroke (doubled).

A recent analysis suggested that proteinuria increased the risk of thrombo-embolism by 54% (RR 1.54; 95% CI 1.29–1.85), with higher stroke risk at an estimated glomerular filtration rate of  $< 45$  mL/min. Thus, chronic kidney disease may increase the risk of thrombo-embolism in AF, although such patients are also at increased mortality and bleeding risk and have not been studied in prospective clinical trials.

Patients with thyrotoxicosis are at risk of developing AF, but stroke risk may be more related to the presence of associated clinical stroke risk factors. Other conditions such as hypertrophic cardiomyopathy and amyloidosis may be risk factors for stroke, but have not been studied or included in clinical trials of thromboprophylaxis.

#### 4.1.1 Risk stratification for stroke and thrombo-embolism

The identification of various stroke clinical risk factors has led to the publication of various stroke risk schemes. Most have (artificially) categorized stroke risk into 'high', 'moderate', and 'low' risk strata. The simplest risk assessment scheme is the CHADS<sub>2</sub> score, as shown in Table 7. The CHADS<sub>2</sub> [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.<sup>50</sup>

Thus, the CHADS<sub>2</sub> stroke risk stratification scheme should be used as an initial, rapid, and easy-to-remember means of assessing stroke risk. In patients with a CHADS<sub>2</sub> score  $\geq 2$ , 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. Such a practice appears to translate to better outcomes in AF patients in routine care.<sup>10,51</sup>

As shown in Table 7, there is a clear relationship between CHADS<sub>2</sub> score and stroke rate.<sup>50</sup> The original validation of this scheme classified a CHADS<sub>2</sub> score of 0 as low risk, 1–2 as moderate risk, and >2 as high risk.

The Stroke in AF Working Group performed a comparison of 12 published risk-stratification schemes to predict stroke in patients with non-valvular AF, and concluded that there were substantial, clinically relevant differences among published schemes designed to stratify stroke risk in patients with AF. Most had very modest predictive value for stroke (c-statistics—as a measure of the predictive value—of ~0.6); also, the proportion of patients assigned to individual risk categories varied widely across the schemes. The CHADS<sub>2</sub> score categorized most subjects as ‘moderate risk’ and had a c-statistic of 0.58 to predict stroke in the whole cohort.

In the present guidelines, we have tried to de-emphasize the use of the ‘low’, ‘moderate’, and ‘high’ risk categorizations, given the poor predictive value of such artificial categories, and recognize that risk is a continuum. Thus, we encourage a risk factor-based approach for more detailed stroke risk assessment, recommending the use of antithrombotic therapy on the basis of the presence (or absence) of stroke risk factors.

Support for this approach comes from various published analyses, where even patients at ‘moderate risk’ (currently defined as CHADS<sub>2</sub> 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 CHADS<sub>2</sub> score does not include many stroke risk factors, and other ‘stroke risk modifiers’ need to be considered in a comprehensive stroke risk assessment (Table 8).

**‘Major’ risk factors** (previously referred to as ‘high’ risk factors) are prior stroke or TIA, or thrombo-embolism, and older age ( $\geq 75$  years). The presence of some types of valvular heart disease (mitral stenosis or prosthetic heart valves) would also categorize such ‘valvular’ AF patients as ‘high risk’.

**‘Clinically relevant non-major’ risk factors** (previously referred to as ‘moderate’ risk factors) are heart failure [especially moderate to severe systolic LV dysfunction, defined arbitrarily as left ventricular ejection fraction (LVEF)  $\leq 40\%$ ], hypertension, or diabetes. Other ‘clinically relevant non-major’ risk factors (previously referred to as ‘less validated risk factors’) include female sex, age 65–74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and PAD). Note that risk factors are cumulative, and the simultaneous presence of two or more ‘clinically relevant non-major’ risk factors would justify a stroke risk that is high enough to require anticoagulation.

This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, **CHA<sub>2</sub>DS<sub>2</sub>-VASc** [congestive heart failure, hypertension, age  $\geq 75$  (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)].<sup>52</sup> This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age  $\geq 75$ ; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease

**Table 8** CHA<sub>2</sub>DS<sub>2</sub>-VASc score and stroke rate

| <b>(a) Risk factors for stroke and thrombo-embolism in non-valvular AF</b>  |  |  |
|---|--|--|
| <b>‘Major’ risk factors</b>   | <b>‘Clinically relevant non-major’ risk factors</b>  |  |
| Previous stroke, TIA, or systemic embolism<br>Age $\geq 75$ years   | Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF $\leq 40\%$ )<br>Hypertension - Diabetes mellitus<br>Female sex - Age 65–74 years<br>Vascular disease <sup>a</sup> |  |
| <b>(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA<sub>2</sub>DS<sub>2</sub>-VASc</b><br>(Note: maximum score is 9 since age may contribute 0, 1, or 2 points) |  |  |
| <b>Risk factor</b>  | <b>Score</b>   |  |
| Congestive heart failure/LV dysfunction   | 1  |  |
| Hypertension  | 1  |  |
| Age $\geq 75$   | 2  |  |
| Diabetes mellitus   | 1  |  |
| Stroke/TIA/thrombo-embolism   | 2  |  |
| Vascular disease <sup>a</sup>   | 1  |  |
| Age 65–74   | 1  |  |
| Sex category (i.e. female sex)  | 1  |  |
| <b>Maximum score</b>  | <b>9</b>   |  |
| <b>(c) Adjusted stroke rate according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>   |  |  |
| <b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>   | <b>Patients (n=7329)</b>   | <b>Adjusted stroke rate (%/year)<sup>b</sup></b> |
| 0   | 1  | 0%   |
| 1   | 422  | 1.3%   |
| 2   | 1230   | 2.2%   |
| 3   | 1730   | 3.2%   |
| 4   | 1718   | 4.0%   |
| 5   | 1159   | 6.7%   |
| 6   | 679  | 9.8%   |
| 7   | 294  | 9.6%   |
| 8   | 82   | 6.7%   |
| 9   | 14   | 15.2%  |

See text for definitions.

<sup>a</sup>Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

<sup>b</sup>Based on Lip *et al.*<sup>53</sup>

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.

(myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex (Table 8). Thus, this acronym extends the CHADS<sub>2</sub> scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate (see Section 4.1.1).

### 4.1.2 Antithrombotic therapy

Numerous clinical trials have provided an extensive evidence base for the use of antithrombotic therapy in AF.

#### 4.1.2.1 Anticoagulation therapy with vitamin K antagonist vs. control

Five large randomized trials published between 1989 and 1992 evaluated VKA mainly for the primary prevention of thrombo-embolism in patients with non-valvular AF. A sixth trial focused on secondary prevention among patients who had survived non-disabling stroke or TIA.

In a meta-analysis, the RR reduction with VKA was highly significant and amounted to 64%, corresponding to an absolute annual risk reduction in all strokes of 2.7%.<sup>54</sup> When only ischaemic strokes were considered, adjusted-dose VKA use was associated with a 67% RR reduction. This reduction was similar for both primary and secondary prevention and for both disabling and non-disabling strokes. Of note, many strokes occurring in the VKA-treated patients occurred when patients were not taking therapy or were subtherapeutically anticoagulated. All-cause mortality was significantly reduced (26%) by adjusted-dose VKA vs. control. The risk of intracranial haemorrhage was small.

Four of these trials were placebo controlled; of the two that were double blind with regard to anticoagulation, one was stopped early because of external evidence that OAC with VKA was superior to placebo, and the other included no female subjects. In three of the trials, VKA dosing was regulated according to the prothrombin time ratio, while two trials used INR target ranges of 2.5–4.0 and 2.0–3.0.

Supported by the results of the trials cited above, VKA treatment should be considered for patients with AF with  $\geq 1$  stroke risk factor(s) provided there are no contraindications, especially with careful assessment of the risk–benefit ratio and an appreciation of the patient's values and preferences.

#### 4.1.2.2 Antiplatelet therapy vs. control

Eight independent randomized controlled studies, together including 4876 patients, have explored the prophylactic effects of antiplatelet therapy, most commonly aspirin compared with placebo, on the risk of thrombo-embolism in patients with AF.<sup>54</sup>

When aspirin alone was compared with placebo or no treatment in seven trials, treatment with aspirin was associated with a non-significant 19% (95% CI –1% to –35%) 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.<sup>54</sup> Aspirin was also associated with a 13% (95% CI –18% to –36%) reduction in disabling strokes and a 29% (95% CI –6% to –53%) reduction in non-disabling strokes. When only strokes classified as ischaemic were considered, aspirin resulted in a 21% (95% CI –1% to –38%) reduction in strokes. 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% (95% CI 6–35).

The dose of aspirin differed markedly between the studies, ranging from 50 to 1300 mg daily, and there was no significant heterogeneity between the results of the individual trials. Much of the beneficial effect of aspirin was driven by the results of one single positive trial, SPAF-I, which suggested a 42% stroke risk reduction

with aspirin 325 mg vs. placebo. In this trial, there was internal heterogeneity, with inconsistencies for the aspirin effect between the results for the warfarin-eligible (RR reduction 94%) and warfarin-ineligible (RR reduction 8%) arms of the trial. Also, aspirin had less effect in people older than 75 years and did not prevent severe or recurrent strokes. The SPAF-I trial was also stopped early and its result may be exaggerated. Pharmacologically, near-complete platelet inhibition is achieved with aspirin 75 mg. Furthermore, low-dose aspirin (<100 mg) is safer than higher doses (such as 300 mg), given that bleeding rates with higher doses of aspirin are significant. Thus, if aspirin is used, it is reasonable to use doses in the lower end of the allowed range (75–100 mg daily).

The magnitude of stroke reduction from aspirin vs. placebo in the meta-analysis (19%) 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. More recent cardiovascular primary prevention trials in non-AF cohorts have not shown a significant benefit from aspirin in reducing risk of cardiovascular events.

In the Japan Atrial Fibrillation Stroke Trial,<sup>55</sup> patients with lone AF were randomized to an aspirin group (aspirin at 150–200 mg/day) or a control group without antiplatelet or anticoagulant therapy. The primary outcomes (3.1% per year) in the aspirin group were 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%).

#### 4.1.2.3 Anticoagulation therapy with vitamin K antagonist vs. antiplatelet therapy

Direct comparison between the effects of VKA and aspirin has been undertaken in nine studies, demonstrating that VKA were significantly superior, with an RR reduction of 39%.

The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that VKA (target INR 2–3) was superior to aspirin 75 mg daily in reducing the primary endpoint of fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism by 52%, with no difference in the risk of major haemorrhage between warfarin and aspirin.<sup>56</sup> This is consistent with the small Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trial, in which there were significantly more adverse events with aspirin (33%) than with warfarin (6%,  $P = 0.002$ ), including serious bleeding. When the trials conducted prior to BAFTA were considered, the risk for intracranial haemorrhage was doubled with adjusted-dose warfarin compared with aspirin, although the absolute risk increase was small (0.2% per year).<sup>54</sup>

#### 4.1.2.4 Other antithrombotic drug regimens

In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events–Warfarin arm (ACTIVE W) trial, anticoagulation therapy was superior to the combination of clopidogrel plus aspirin (RR reduction 40%; 95% CI 18–56), with no difference in bleeding events between treatment arms.<sup>57</sup> The Aspirin arm (ACTIVE A) trial found that major vascular events were reduced in patients receiving aspirin–clopidogrel, compared with aspirin

monotherapy (RR 0.89; 95% CI 0.81–0.98;  $P = 0.01$ ), primarily due to a 28% relative reduction in the rate of stroke with combination therapy.<sup>58</sup> Major bleeding was significantly increased (2.0% per year vs. 1.3% per year; RR 1.57; 95% CI 1.29–1.92;  $P < 0.001$ ), broadly similar to that seen with VKA therapy. Of note, 50% of patients entered the trial due to ‘physician’s perception of being unsuitable for VKA therapy’ and 23% had a risk factor for bleeding at trial entry. Thus, aspirin plus clopidogrel therapy could perhaps be considered as an interim measure where VKA therapy is unsuitable, but not as an alternative to VKA in patients at high bleeding risk.

Other antiplatelet agents such as indobufen and triflusal have been investigated in AF, with the suggestion of some benefit, but more data are required. Combinations of VKA (INR 2.0–3.0) with antiplatelet therapy have been studied, but no beneficial effect on ischaemic stroke or vascular events were seen, while more bleeding was evident. Thus, in patients with AF who sustain an ischaemic stroke despite adjusted dose VKA (INR 2.0–3.0), raising the intensity of anticoagulation to a higher INR range of 3.0–3.5 may be considered, rather than adding an antiplatelet agent, given that an appreciable risk in major bleeding only starts at INRs  $> 3.5$ .

#### 4.1.2.5 Investigational agents

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

In the Randomized Evaluation of Long-term anticoagulant therapy with dabigatran etexilate (RE-LY) study,<sup>59</sup> 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.<sup>59</sup> The Apixaban VERSus acetylsalicylic acid to pRevent strOkES (AVERROES) study was stopped early due to clear evidence of a reduction in stroke and systemic embolism with apixaban 5 mg b.i.d. compared with aspirin 81–324 mg once daily in patients intolerant of or unsuitable for VKA, with an acceptable safety profile.

### 4.1.3 Current recommendations for antithrombotic therapy

Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thrombo-embolism, rather than on an artificial division into high, moderate, or low risk categories.

The CHADS<sub>2</sub> stroke risk stratification scheme (see Section 4.1.1) 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 CHADS<sub>2</sub> score of  $\geq 2$ , 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 CHADS<sub>2</sub> 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 (Table 9 and Figure 4). This risk factor-based approach can also be expressed as a point-based scoring system, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>52</sup> (see Table 8 for definition). Many contemporary clinical trials of stroke prevention in AF have included some of these additional risk factors as part of their inclusion criteria.<sup>57–59</sup>

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  $< 65$  years with no other risk factors

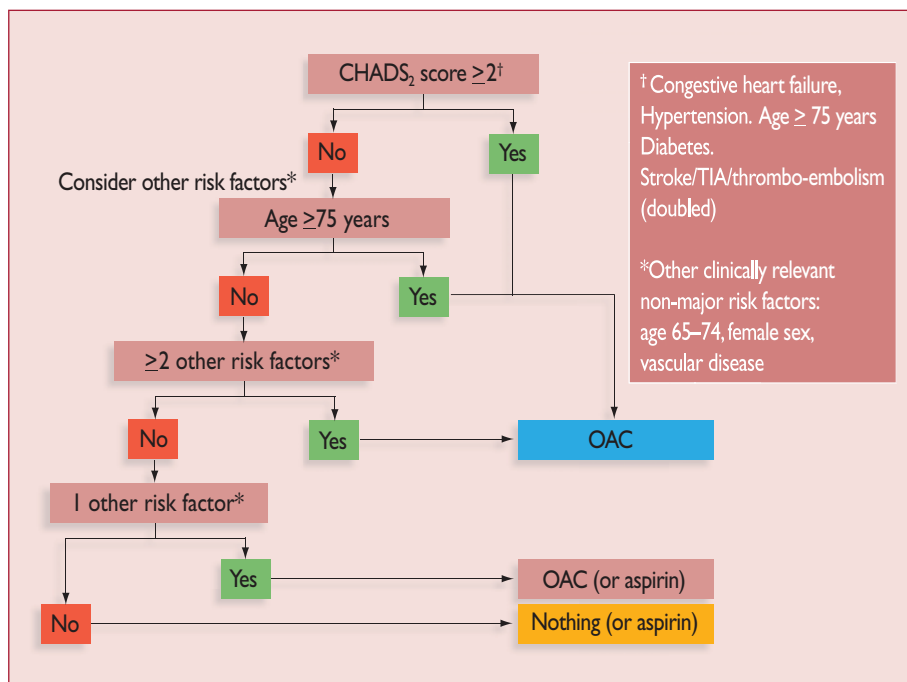
**Table 9 Approach to thromboprophylaxis in patients with AF**

| Risk category  | CHA <sub>2</sub> DS <sub>2</sub> -VASc score | Recommended antithrombotic therapy   |
|--|--|--|
| One ‘major’ risk factor or $\geq 2$ ‘clinically relevant non-major’ risk factors | $\geq 2$                                     | OAC <sup>a</sup>   |
| One ‘clinically relevant non-major’ risk factor                                  | 1  | Either OAC <sup>a</sup> or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.                                |
| No risk factors  | 0  | Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin. |

AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = cardiac failure, hypertension, age  $\geq 75$  (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).

<sup>a</sup>OAC, 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 10 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  $\geq 3$ ), 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. CHA<sub>2</sub>DS<sub>2</sub>-VASc = 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 4** Clinical flowchart for the use of oral anticoagulation for stroke prevention in AF. AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack. A full description of the CHADS<sub>2</sub> can be found on page 13.

(i.e. a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1) may consider aspirin rather than OAC therapy.

**4.1.4 Risk of bleeding**

An assessment of bleeding risk should be part of the patient assessment before starting anticoagulation. Despite anticoagulation of more elderly patients with AF, rates of intracerebral haemorrhage are considerably lower than in the past, typically between 0.1 and 0.6% in contemporary reports. This may reflect lower anticoagulation intensity, more careful dose regulation, or better control of hypertension. Intracranial bleeding increases with INR values >3.5–4.0, and there is no increment in bleeding risk with INR values between 2.0 and 3.0 compared with lower INR levels.

Various bleeding risk scores have been validated for bleeding risk in anticoagulated patients, but all have different modalities in evaluating bleeding risks and categorization into low-, moderate-, and high-risk strata, usually for major bleeding risk. It is reasonable to assume that the major bleeding risk with aspirin is similar to that with VKA, especially in elderly individuals.<sup>56</sup> 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.

Using a ‘real-world’ cohort of 3978 European subjects with AF from the EuroHeart Survey, a new simple bleeding risk score, **HAS-BLED** (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly), has been derived (Table 10).<sup>60</sup> It would seem reasonable to use the HAS-BLED score to assess bleeding risk in AF patients, whereby a score of ≥3 indicates

**Table 10** Clinical characteristics comprising the HAS-BLED bleeding risk score

| Letter | Clinical characteristic <sup>a</sup>             | 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 |

<sup>a</sup>‘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 μmol/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.<sup>60</sup>

‘high risk’, and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin.



#### 4.1.5 Optimal international normalized ratio

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

Based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0–3.0 is the likely optimal range for prevention of stroke and systemic embolism in patients with non-valvular AF.

One of the many problems with anticoagulation with VKA is the high interindividual and intraindividual variation in INRs. VKAs also have significant drug, food, and alcohol interactions. On average, patients may stay within the intended INR range of 2.0–3.0 for 60–65% of the time in controlled clinical trials, but many 'real-life' studies suggest that this figure may be <50%. Indeed, having patients below the therapeutic range for <60% of the time may completely offset the benefit of VKA.

Whilst a lower target INR range (1.8–2.5) has been proposed for the elderly, this is not based on any large trial evidence base. Cohort studies suggest a 2-fold increase in stroke risk at INR 1.5–2.0 and, therefore, an INR <2.0 is not recommended.

The maintenance, safety, and effectiveness of INR within range can be influenced by the pharmacogenetics of VKA therapy, particularly the cytochrome P450 2C9 gene (*CYP2C9*) and the vitamin K epoxide reductase complex 1 gene (*VKORC1*). *CYP2C9* and *VKORC1* genotypes can influence warfarin dose requirements, whilst *CYP2C9* variant genotypes are associated with bleeding events. Systematic genotyping is not usually required, being unlikely to be cost-effective for typical patients with non-valvular AF, but it may be cost-effective in patients at high risk for haemorrhage who are starting VKA therapy.

##### *Near-patient 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. Self-monitoring devices also require adequate quality assurance and calibration.

#### 4.1.6 Special situations

##### 4.1.6.1 Paroxysmal atrial fibrillation

The stroke and thrombo-embolic risk in paroxysmal AF is less well defined, and such patients have represented the minority (usually <30%) in clinical trials of thromboprophylaxis. Stroke risk in paroxysmal AF is not different from that in persistent or permanent AF,<sup>12</sup> and is dependent upon the presence of stroke risk factors (see Section 4.1.1). Therefore, patients with paroxysmal AF should receive OAC according to their risk score.

##### 4.1.6.2 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 <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.

If the VKA used is warfarin, which has a half-life of 36–42 h, treatment should be interrupted ~5 days before surgery (corresponding approximately to five half-lives of warfarin), to allow the INR to fall appropriately. If the VKA is phenprocoumon, treatment should be interrupted 10 days before surgery, based on the half-life of phenprocoumon of 96–140 h. It would be reasonable to undertake surgical or diagnostic procedures that carry a risk of bleeding in the presence of subtherapeutic anticoagulation for up to 48 h, without substituting heparin, given the low risk of thrombo-embolism in this period. VKA should be resumed at the 'usual' maintenance dose (without a loading dose) on the evening of (or the morning after) surgery, assuming there is adequate haemostasis. If there is a need for surgery or a procedure where the INR is still elevated (>1.5), the administration of low-dose oral vitamin K (1–2 mg) to normalize the INR may be considered.

In patients with a mechanical heart valve or AF at high risk for thrombo-embolism, management can be problematic. Such patients should be considered for 'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin (UFH) during the temporary interruption of VKA therapy.

##### 4.1.6.3 Stable vascular disease

Many anticoagulated AF patients have stable coronary or carotid artery disease and/or PAD, and common practice is to treat such patients with VKA plus one antiplatelet drug, usually aspirin. Adding aspirin to VKA does not reduce the risk of stroke or vascular events (including myocardial infarction), but substantially increases bleeding events.

##### 4.1.6.4 Acute coronary syndrome and/or percutaneous coronary intervention

Current guidelines for ACS and/or percutaneous coronary intervention (PCI) recommend the use of aspirin–clopidogrel combination therapy after ACS, and a stent (4 weeks for a bare-metal stent, 6–12 months for a drug-eluting stent). VKA non-treatment is associated with an increase in mortality and major adverse cardiac events, with no significant difference in bleeding rates between VKA-treated and non-treated patients. The prevalence of major bleeding with triple therapy (VKA, aspirin, and clopidogrel) is 2.6–4.6% at 30 days, which increases to 7.4–10.3% at 12 months. Thus triple therapy seems to have an acceptable risk–benefit ratio provided it is kept short (e.g. 4 weeks) and the bleeding risk is low.

A systematic review and consensus document published by the ESC Working Group on Thrombosis, endorsed by the EHRA and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), suggests that drug-eluting stents should be avoided and triple therapy (VKA, aspirin, and clopidogrel) used in the short term, followed by longer therapy with VKA plus a single antiplatelet drug (either clopidogrel or aspirin) (Table 11).<sup>61</sup> In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding year), VKA monotherapy should be used, and concomitant antiplatelet therapy should not be prescribed. Published data support the use of VKA for secondary prevention in patients with coronary artery disease, and VKA is at least as effective as aspirin.



**Table 11 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                  | <u>1 month</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day<br><u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day <sup>b</sup><br>(or aspirin 100 mg/day)<br><u>Lifelong</u> : VKA (INR 2.0–3.0) alone  |
|   | Elective         | Drug-eluting                | <u>3 (-olimus<sup>a</sup> group) to 6 (paclitaxel) months</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day<br><u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day <sup>b</sup><br>(or aspirin 100 mg/day)<br><u>Lifelong</u> : VKA (INR 2.0–3.0) alone |
|   | ACS              | Bare-metal/<br>drug-eluting | <u>6 months</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day<br><u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day <sup>b</sup><br>(or aspirin 100 mg/day)<br><u>Lifelong</u> : VKA (INR 2.0–3.0) alone   |
| High (e.g. HAS-BLED score ≥3)                 | Elective         | Bare-metal <sup>c</sup>     | <u>2–4 weeks</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day<br><u>Lifelong</u> : VKA (INR 2.0–3.0) alone  |
|   | ACS              | Bare-metal <sup>c</sup>     | <u>4 weeks</u> : triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day<br><u>Up to 12th month</u> : combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day <sup>b</sup><br>(or aspirin 100 mg/day)<br><u>Lifelong</u> : VKA (INR 2.0–3.0) alone  |

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.

<sup>a</sup>Sirolimus, everolimus, and tacrolimus.

<sup>b</sup>Combination of VKA (INR 2.0–3.0)+aspirin ≤100 mg/day (with PPI, if indicated) may be considered as an alternative.

<sup>c</sup>Drug-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.<sup>61</sup>

4.1.6.5 Elective percutaneous coronary intervention

In elective PCI, drug-eluting stents should be limited to clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc., where a significant benefit is expected compared with bare-metal stents, and triple therapy (VKA, aspirin, and clopidogrel) should be used for 4 weeks. Following PCI with bare-metal stents, patients with AF and stable coronary artery disease should receive long-term therapy (12 months) with OAC plus clopidogrel 75 mg daily or, alternatively, aspirin 75–100 mg daily, plus gastric protection with proton pump inhibitors (PPIs), H2-receptor antagonists, or antacids depending on the bleeding and thrombotic risks of the individual patient. Triple therapy (VKA, aspirin, and clopidogrel) should be administered for a minimum of 1 month after implantation of a bare-metal stent, but for much longer with a drug-eluting stent [≥3 months for an ‘-olimus’ (sirolimus, everolimus, tacrolimus) type 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, plus gastric protection with either PPIs, H2-receptor antagonists, or antacids may be continued.

When anticoagulated AF patients are at moderate to high risk of thrombo-embolism, an uninterrupted anticoagulation strategy can

be preferred during PCI, and radial access should be used as the first choice even during therapeutic anticoagulation (INR 2–3).

4.1.6.6 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 11). 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, plus gastric protection) for 12 months.

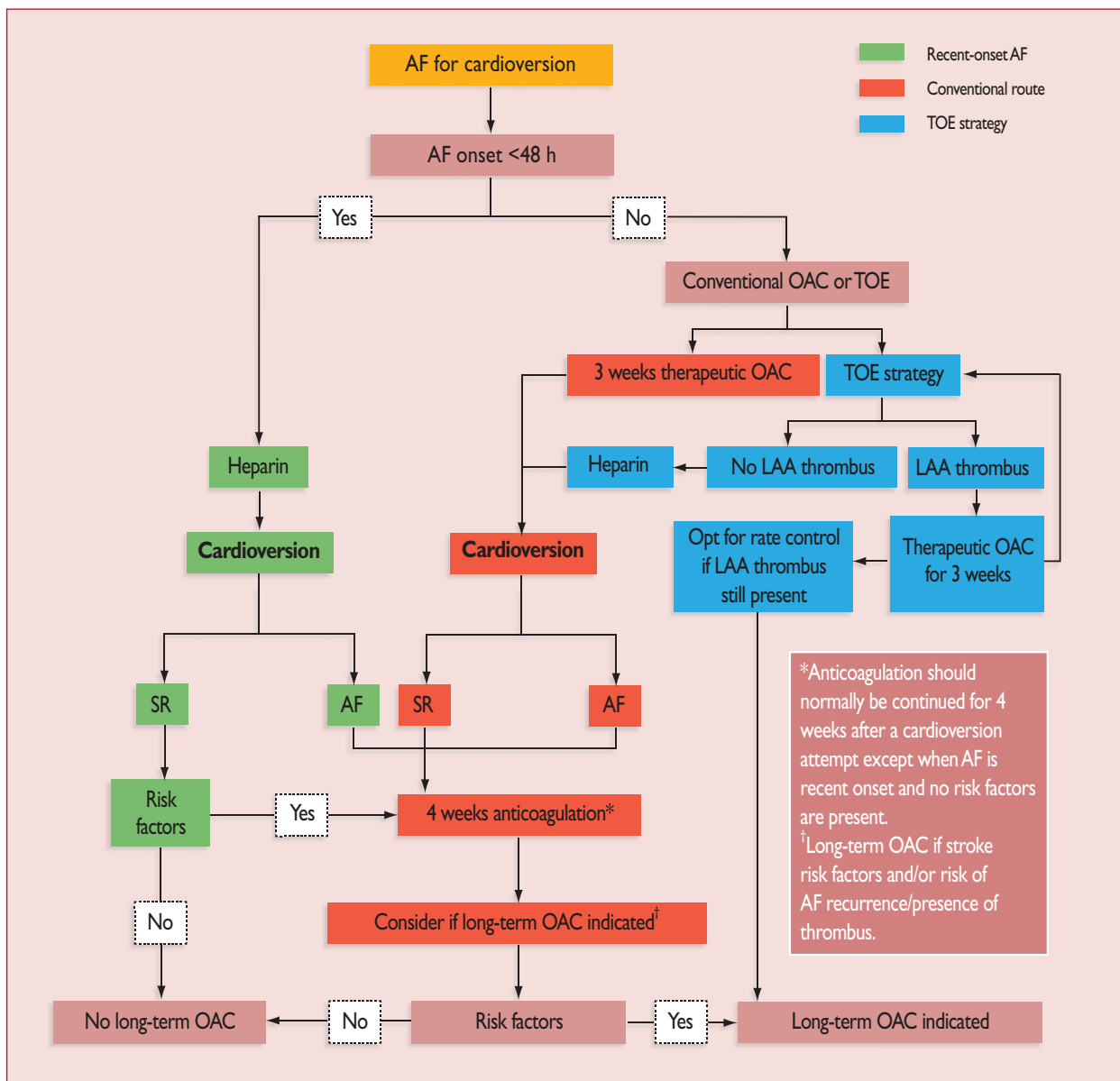
4.1.6.7 Acute ST segment elevation myocardial infarction with primary percutaneous intervention

Such patients are often given aspirin, clopidogrel, and heparin in the acute setting. When patients have a high thrombus load, bivalirudin or GPIs may be given as a 'bail-out' option. Mechanical thrombus removal (e.g. thrombus aspiration) is encouraged. Given the risk of bleeding with such a combination of antithrombotic therapies, GPIs or bivalirudin would not be considered if the INR is >2, except in a 'bail-out' option. For medium- to long-term management, triple therapy (VKA, aspirin, and clopidogrel) should be used in the initial period (for 3–6 months), or for longer in selected patients at low bleeding risk, followed by longer therapy

(up to 12 months) with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection).

4.1.6.8 Acute stroke

An acute stroke is a common first presentation of a patient with AF, given that the arrhythmia often develops asymptotically. There are limited trial data to guide their management, and there is concern that patients within the first 2 weeks after cardioembolic stroke are at greatest risk of recurrent stroke because of further thrombo-embolism. However, anticoagulation in the acute phase may result in intracranial haemorrhage or haemorrhagic transformation of the infarct.



**Figure 5** 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.

**Recommendations for prevention of thrombo-embolism**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| 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).   | I                  | A                  | 47, 48, 63        |
| 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.  | I                  | A                  | 47, 48, 50        |
| The CHADS <sub>2</sub> [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.   | I                  | A                  | 50                |
| • For the patients with a CHADS <sub>2</sub> 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.   | I                  | A                  | 47, 48, 54        |
| For a more detailed or comprehensive stroke risk assessment in AF (e.g. with CHADS <sub>2</sub> scores 0–1), a risk factor-based approach is recommended, considering 'major' and 'clinically relevant non-major' stroke risk factors <sup>3</sup> .  | I                  | A                  | 52                |
| • Patients with 1 'major' or ≥ 2 'clinically relevant non-major' risk factors are high risk, and OAC therapy (e.g. with a VKA, dose adjusted to achieve the target intensity INR of 2.0–3.0) is recommended, unless contraindicated.  | I                  | A                  | 52                |
| • Patients with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as:  | I                  | A/B                | 52                |
| i. OAC therapy (e.g. VKA), or   | I                  | A                  | 52                |
| ii. aspirin 75–325 mg daily   | I                  | B                  | 48                |
| • 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.  | I                  | B                  | 52                |
| 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.  | I                  | B                  | 63, 64            |
| Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.  | I                  | C                  |                   |
| The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent).   | IIa                | A                  | 47, 48            |
| 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.   | IIa                | A                  | 47, 48            |
| In patients with no risk factors who are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors), no antithrombotic therapy should be considered, rather than aspirin.  | IIa                | B                  | 47, 48            |
| 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.   | IIa                | B                  | 58                |
| 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.  | IIa                | A                  | 56, 60, 65        |
| 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. | IIa                | B                  | 60                |
| 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 subtherapeutic anticoagulation for up to 48 h) should be considered, without substituting heparin as 'bridging' anticoagulation therapy.                        | IIa                | C                  |                   |
| In patients with a mechanical prosthetic heart valve or AF at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures, 'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin during the temporary interruption of OAC therapy should be considered.  | IIa                | C                  |                   |
| 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.   | IIa                | B                  |                   |
| Re-evaluation at regular intervals of the benefits, risks, and need for antithrombotic therapy should be considered.  | IIa                | C                  |                   |
| In patients with AF presenting with acute stroke or TIA, management of uncontrolled hypertension should be considered before antithrombotic treatment is started, and cerebral imaging (computed tomography or magnetic resonance imaging) performed to exclude haemorrhage.  | IIa                | C                  |                   |
| In the absence of haemorrhage, OAC therapy should be considered ~2 weeks after stroke, but, in the presence of haemorrhage, anticoagulation should not be given.  | IIa                | C                  |                   |
| In the presence of a large cerebral infarction, delaying the initiation of anticoagulation should be considered, given the risk of haemorrhagic transformation.   | IIa                | C                  |                   |

Continued

## Continued

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| In patients with AF and an acute TIA, OAC therapy should be considered as soon as possible in the absence of cerebral infarction or haemorrhage.   | <b>IIa</b>         | <b>C</b>           |                   |
| 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.   | <b>IIb</b>         | <b>C</b>           |                   |
| When surgical procedures require interruption of OAC therapy for longer than 48 h in high-risk patients, unfractionated heparin or subcutaneous LMWH may be considered.  | <b>IIb</b>         | <b>C</b>           |                   |
| 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. | <b>IIb</b>         | <b>C</b>           |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

<sup>d</sup>Major risk factors are those associated with the highest risk for stroke patients with AF are prior thrombo-embolism (stroke, TIA, or systemic embolism), age  $\geq 75$  years and rheumatic mitral stenosis. 'Clinically relevant non-major' risk factors include hypertension, heart failure, or moderate to severe LV dysfunction (ejection fraction 40% or less), and diabetes mellitus. (Level of evidence A). Other 'clinically relevant non-major' risk factors include female sex, age 65–74 years, and vascular disease (myocardial infarction, complex aortic plaque, carotid disease, peripheral artery disease). This risk factor-based approach for non-valvular AF can also be expressed by an acronym, CHA<sub>2</sub>DS<sub>2</sub>-VASc, [cardiac failure, hypertension, age  $\geq 75$  years (doubled), diabetes, stroke (doubled) vascular disease, age 65–74, and sex category (female)]. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age  $\geq 75$ ; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, peripheral artery disease, complex aortic plaque), and female sex.

AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub> = cardiac failure, hypertension, age, diabetes, stroke (doubled); INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

## Recommendations for antithrombotic therapy in AF and ACS/PCI

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| 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.  | <b>IIa</b>         | <b>C</b>           |                   |
| 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, plus gastric protection with PPIs, H <sub>2</sub> antagonists, or antacids).  | <b>IIa</b>         | <b>C</b>           |                   |
| 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, plus gastric protection with either PPIs, H <sub>2</sub> antagonists, or antacids) should be considered, if required. | <b>IIa</b>         | <b>C</b>           |                   |
| 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, plus gastric protection with PPIs, H <sub>2</sub> antagonists, or antacids).  | <b>IIa</b>         | <b>C</b>           |                   |
| 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).  | <b>IIa</b>         | <b>C</b>           |                   |
| 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.  | <b>IIb</b>         | <b>C</b>           |                   |
| 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.  | <b>IIb</b>         | <b>C</b>           |                   |
| 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.  | <b>IIb</b>         | <b>C</b>           |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

ACS = acute coronary syndrome; AF = atrial fibrillation; BMS = bare-metal stent; INR = international normalized ratio; PCI = percutaneous intervention; PPIs = proton pump inhibitors; VKA = vitamin K antagonist.

**Recommendations for anticoagulation pericardioversion**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| For patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy (INR 2.0–3.0) is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).                                       | I                  | B                  | 63                |
| 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.   | I                  | C                  |                   |
| After immediate/emergency cardioversion in patients with AF of 48 h 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.  | I                  | B                  | 63                |
| 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.   | I                  | B                  | 47,54,63          |
| If AF is of ≥48 h, OAC therapy is recommended for at least 4 weeks after immediate/emergency cardioversion, similar to patients undergoing elective cardioversion.  | I                  | B                  | 63                |
| In patients at high risk of stroke, OAC therapy with a VKA (INR 2.0–3.0) is recommended to be continued long-term.  | I                  | B                  | 47,54,63          |
| As an alternative to anticoagulation prior to cardioversion, TOE-guided cardioversion is recommended to exclude thrombus in the left atrium or left atrial appendage.   | I                  | B                  | 42                |
| For patients undergoing TOE-guided cardioversion who have no identifiable thrombus, cardioversion is recommended immediately after anticoagulation with heparin, and heparin should be continued until OAC therapy has been established, which should be maintained for at least 4 weeks after cardioversion. | I                  | B                  | 42                |
| For patients undergoing a TOE-guided strategy in whom thrombus is identified, VKA (INR 2.0–3.0) is recommended for at least 3 weeks, followed by a repeat TOE to ensure thrombus resolution.  | I                  | C                  |                   |
| For patients with atrial flutter undergoing cardioversion, anticoagulation is recommended as for patients with AF.  | I                  | C                  |                   |
| In patients with risk factors for stroke or AF recurrence, OAC therapy should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.   | IIa                | B                  | 63                |
| 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).   | IIa                | C                  |                   |
| If thrombus remains on repeat TOE, an alternative strategy (e.g. rate control) may be considered.   | IIb                | C                  |                   |
| 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.  | IIb                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TOE = transoesophageal echocardiogram; UFH = unfractionated heparin; VKA = vitamin K antagonist.

In patients with AF presenting with an acute stroke or TIA, uncontrolled hypertension should be appropriately managed before antithrombotic treatment is started, and cerebral imaging, CT or magnetic resonance imaging (MRI), should be performed to exclude haemorrhage. In the absence of haemorrhage, anticoagulation should begin after 2 weeks, but, in the presence of haemorrhage, anticoagulation should not be given. In patients with AF and acute TIA, anticoagulation treatment should begin as soon as possible in the absence of cerebral infarction or haemorrhage.

*Silent stroke*

As stroke in patients with AF is primarily embolic, the detection of asymptomatic cerebral emboli would identify patients at high risk of thrombo-embolism. Cerebral imaging studies (CT/MRI) show a higher incidence of silent strokes in AF patients compared with controls in sinus rhythm. Transcranial Doppler ultrasound may identify

asymptomatic patients with an active embolic source or patients with prior stroke who are at high risk of recurrent stroke.

*4.1.6.9 Atrial flutter*

The risk of stroke linked to atrial flutter has been studied retrospectively in a large number of older patients, and was similar to that seen in AF. Thus, thromboprophylaxis in patients with atrial flutter should follow the same guidelines as in AF patients.

**4.1.7 Cardioversion**

Increased risk of thrombo-embolism following cardioversion is well recognized. Therefore, anticoagulation is considered mandatory before elective cardioversion for AF of >48 h or AF of unknown duration. Based on observational cohort studies, VKA treatment (INR 2.0–3.0) should be given for at least 3 weeks



before cardioversion. Thromboprophylaxis is recommended for electrical and pharmacological cardioversion of AF >48 h. VKA should be continued for a minimum of 4 weeks after cardioversion because of risk of thrombo-embolism due to post-cardioversion left atrial/LAA dysfunction (so-called 'atrial stunning'). In patients with risk factors for stroke or AF recurrence, VKA treatment should be continued lifelong irrespective of apparent maintenance of sinus rhythm following cardioversion.

In patients with a definite AF onset <48 h, cardioversion can be performed expediently under the cover of UFH administered i.v. followed by infusion or subcutaneous LMWH. In patients with risk factors for stroke (see Section 4.1.1), OAC should be started after cardioversion and continued lifelong. UFH or LMWH should be continued until the INR is at the therapeutic level (2.0–3.0). No OAC is required in patients without thrombo-embolic risk factors.

In patients with AF >48 h with haemodynamic instability (angina, myocardial infarction, shock, or pulmonary oedema), immediate cardioversion should be performed, and UFH or LMWH should be administered before cardioversion. After cardioversion, OAC should be started and heparin should be continued until the INR is at the therapeutic level (2.0–3.0). Duration of OAC therapy (4 weeks or lifelong) will depend on the presence of risk factors for stroke.

#### 4.1.7.1 Transoesophageal echocardiogram-guided cardioversion

The mandatory 3-week period of OAC prior to cardioversion can be shortened if TOE reveals no LA or LAA thrombus. TOE may not only show thrombus within the LAA or elsewhere in the left atrium, but may also identify spontaneous echo-contrast or complex aortic plaque. A TOE-guided cardioversion strategy is recommended as an alternative to 3-week pre-cardioversion anticoagulation if experienced staff and appropriate facilities are available, and, when early cardioversion is needed, pre-cardioversion OAC is not indicated due to patient choice or potential bleeding risks, or when there is a high risk of LA/LAA thrombus.<sup>42</sup>

If no LA thrombus is detected on TOE, UFH or LMWH should be started prior to cardioversion and continued thereafter until the target INR is achieved with OAC.

If TOE detects a thrombus in the left atrium or LAA, VKA (INR 2.0–3.0) treatment is required for at least 3 weeks and TOE should be repeated. If thrombus resolution is evident, cardioversion can be performed, and post-cardioversion OAC is continued lifelong. If thrombus is still evident, the rhythm control strategy may be changed to a rate control strategy, especially when AF-related symptoms are controlled, since there is a high risk of thrombo-embolism if cardioversion is performed (Figure 5).

#### 4.1.8 Non-pharmacological methods to prevent stroke

The LAA is considered the main site of atrial thrombogenesis. Thus, occlusion of the LAA orifice may reduce the development of atrial thrombi and stroke in patients with AF. Of note, incomplete occlusion may occur in up to 40% of cases during follow-up, and such incomplete LAA occlusion is considered as a risk factor for the occurrence of stroke. In particular, patients with contraindications to chronic anticoagulation therapy might be considered as candidates for LAA occlusion. The PROTECT AF

(WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients with Atrial Fibrillation) trial<sup>62</sup> 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 (rate ratio 0.62; 95% credible interval 0.35–1.25). There was a higher rate of adverse safety events in the intervention group than in the control group, due mainly to periprocedural complications.

## 4.2 Rate and rhythm management

### 4.2.1 Acute rate and rhythm management

The acute management of patients with AF is driven by acute protection against thrombo-embolic events and acute improvement of cardiac function. The severity of AF-related symptoms should drive the decision for acute restoration of sinus rhythm (in severely compromised patients) or acute management of the ventricular rate (in most other patients).

#### 4.2.1.1 Acute rate control

An inappropriate ventricular rate and irregularity of the rhythm can cause symptoms and severe haemodynamic distress in AF patients. Patients with a rapid ventricular response usually need acute control of their ventricular rate. In stable patients, this can be achieved by oral administration of  $\beta$ -blockers or non-dihydropyridine calcium channel antagonists. In severely compromised patients, i.v. verapamil or metoprolol can be very useful to slow atrioventricular node conduction rapidly. In the acute setting, the target ventricular rate should usually be 80–100 bpm. In selected patients, amiodarone may be used, especially in those with severely depressed LV function. 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 cardioversion or placement of a temporary pacemaker lead in the right ventricle.

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 4.3.2.

#### 4.2.1.2 Pharmacological cardioversion

Many episodes of AF terminate spontaneously within the first hours or days. If medically indicated (e.g. in severely compromised patients), in patients who remain symptomatic despite adequate rate control, or in patients in whom rhythm control therapy is pursued, pharmacological cardioversion of AF may be initiated by a bolus administration of an antiarrhythmic drug.

The conversion rate with antiarrhythmic drugs is lower than with DCC, but does not require conscious sedation or anaesthesia, 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. Repeat oral pharmacological cardioversion ('pill-in-the-pocket' therapy)<sup>67</sup> may be appropriate for selected ambulatory patients once the safety of such an intervention has been established (see page 26). Several agents are available for pharmacological cardioversion (Table 12).

**Flecainide** given i.v. to patients with AF of short duration (especially <24 h) has an established effect (67–92% at 6 h) on restoring sinus rhythm. The usual dose is 2 mg/kg over 10 min. The majority of patients convert within the first hour after i.v. administration. It is rarely effective for termination of atrial flutter or persistent AF.

Oral administration of flecainide may be effective for recent-onset AF. Recommended doses are 200–400 mg (see also 'pill-in-the-pocket' approach). Flecainide should be avoided in patients with underlying heart disease involving abnormal LV function and ischaemia.

Several placebo-controlled randomized studies have demonstrated the efficacy of **propafenone** in converting recent-onset AF to sinus rhythm. Within a few hours, the expected conversion rate was between 41 and 91% after i.v. use (2 mg/kg over 10–20 min). The corresponding early conversion rates in placebo-treated patients were 10–29%. Propafenone has only a limited efficacy for conversion of persistent AF and for atrial flutter. Similar to flecainide, propafenone should be avoided in patients

with underlying heart disease involving abnormal LV function and ischaemia. In addition, owing to its weak  $\beta$ -blocking properties, propafenone should be avoided in severe obstructive lung disease. The time to conversion varies from 30 min to 2 h. Propafenone is also effective if administered orally (conversion between 2 and 6 h).

Cardioversion with **amiodarone** occurs several hours later than with flecainide or propafenone. The approximate conversion rate at 24 h in placebo-treated patients was 40–60%, with an increase to 80–90% after amiodarone treatment. In the short and medium term, amiodarone does not achieve cardioversion. At 24 h the drug has demonstrated better effect compared with control in some but not all randomized studies.

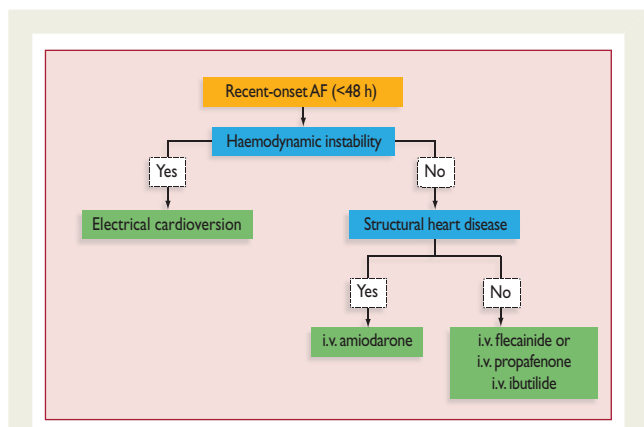
In patients with recent-onset AF, **ibutilide** in one or two infusions of 1 mg over 10 min each, with a wait of 10 min between doses, has demonstrated conversion rates within 90 min of ~50% in several well-designed randomized studies, placebo controlled or with a control group of drugs with known little effect. The time to conversion is ~30 min. The most important side effect is polymorphic ventricular tachycardia, most often non-sustained, but DCC may be needed, and the QTc interval is expected to increase by ~60 ms. Ibutilide is, however, more effective for conversion of atrial flutter than AF.

**Table 12** Drugs and doses for pharmacological conversion of (recent-onset) AF

| Drug        | Dose   | Follow-up dose  | Risks  |
|-------------|--|---|--|
| Amiodarone  | 5 mg/kg i.v. over 1 h                              | 50 mg/h   | Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.   |
| Flecainide  | 2 mg/kg i.v. over 10 min,<br>or<br>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.               |
| Ibutilide   | 1 mg i.v. over 10 min                              | 1 mg i.v. over 10 min after waiting for 10 min                | Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.  |
| Propafenone | 2 mg/kg i.v. over 10 min,<br>or<br>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. |
| Vernakalant | 3 mg/kg i.v. over 10 min                           | Second infusion of 2 mg/kg i.v. over 10 min after 15 min rest | So far only evaluated in clinical trials; recently approved. <sup>68–70</sup>  |

<sup>a</sup>Vernakalant has recently been recommended for approval by the European Medicines Agency for rapid cardioversion of recent-onset AF to sinus rhythm in adults ( $\leq 7$  days for non-surgical patients;  $\leq 3$  days for surgical patients).<sup>68,69</sup> A direct comparison with amiodarone in the AVRO trial (Phase III prospective, randomized, double-blind, Active-controlled, multi-center, superiority study of Vernakalant injection versus amiodarone in subjects with Recent Onset atrial fibrillation), vernakalant was more effective than amiodarone for the rapid conversion of AF to sinus rhythm (51.7% vs. 5.7% at 90 min after the start of treatment;  $P < 0.0001$ ).<sup>70</sup> It is to be given as an initial i.v. infusion (3 mg/kg over 10 min), followed by 15 min of observation and a further i.v. infusion (2 mg/kg over 10 min), if necessary. Vernakalant is contraindicated in patients with systolic blood pressure  $< 100$  mm Hg, severe aortic stenosis, heart failure (class NYHA III and IV), ACS within the previous 30 days, or QT interval prolongation. Before its use, the patients should be adequately hydrated. ECG and haemodynamic monitoring should be used, and the infusion can be followed by DCC if necessary. The drug is not contraindicated in patients with stable coronary artery disease, hypertensive heart disease, or mild heart failure. The clinical positioning of this drug has not yet been determined, but it is likely to be used for acute termination of recent-onset AF in patients with lone AF or AF associated with hypertension, coronary artery disease, or mild to moderate (NYHA class I–II) heart failure.

ACS = acute coronary syndrome; AF = atrial fibrillation; DCC = direct current cardioversion; i.v. = intravenous; N/A = not applicable; NYHA, New York Heart Association; p.o. = per os; QRS = QRS duration; QT = QT interval; T-U = abnormal repolarization (T-U) waves.



**Figure 6** Direct current conversion and pharmacological cardioversion of recent-onset AF in patients considered for pharmacological cardioversion. AF = atrial fibrillation; i.v. = intravenous.

Other drugs (see footnote <sup>a</sup> in Table 12)

One study comparing the effect of placebo vs. two different dosages of **sotalol** found conversion rates of 14% (2/14 patients), 11% (2/11 patients), and 13% (2/16 patients). These differences were not significant.

In one study in 79 patients with AF (but no control group), 13% converted to sinus rhythm after i.v. **β-blocker** (metoprolol) treatment. No relevant reports have been published for atenolol, carvedilol, bisoprolol, propranolol, timolol, or esmolol.

No randomized controlled trial of sufficient size comparing **verapamil** with placebo has been published. In studies comparing verapamil with flecainide, esmolol, or propafenone, 6, 12, and 14%, respectively, converted to sinus rhythm, in 17, 24, and 29 patients given verapamil.

**Digoxin** is ineffective for AF termination. In one study in 239 patients with AF of <7 days duration, the conversion rate at 16 h was 46% in placebo-treated patients and 51% in patients given digoxin; two other studies, in 40 and 82 patients, found conversion rates (placebo vs. digoxin) of 40% vs. 47% and 14% vs. 32%, respectively.

In conclusion, there is good evidence that digoxin has no effect. Although evidence is less comprehensive for verapamil, the reported conversion rates point to a negligible effect. In one study sotalol did not have any effect, and there are no data for ajmaline. Metoprolol did not have any effect in the one study reported, and there are no data for the other β-blocking agents.

*Comparisons between drugs*

Several comparisons have been made between flecainide and propafenone, but only one study demonstrated better conversion rates of flecainide (90 and 64%, respectively). Ibutilide converted 71% of patients compared with 49% on propafenone, but 10% in the ibutilide group experienced non-sustained ventricular tachycardia.

From these studies, no clear conclusions can be drawn regarding the difference in the effect on conversion of these drugs. The choice may therefore be made on the basis of contraindications, side effects, and/or costs.

In summary, in suitable patients with recent-onset AF (generally <48 h duration), a trial of pharmacological cardioversion to sinus

**Recommendations for pharmacological cardioversion**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. flecainide or propafenone is recommended for cardioversion of recent-onset AF.  | I                  | A                  | 71–73             |
| In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.   | I                  | A                  | 74–76             |
| 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.   | IIa                | B                  | 67                |
| In patients with recent-onset AF, structural heart disease, but without hypotension or manifest congestive heart failure, ibutilide may be considered. Serum electrolytes and the QTc interval must be within the normal range, and the patients must be closely monitored during and for 4 h after the infusion because of risk of proarrhythmia. | IIb                | A                  | 71,77             |
| Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B), other β-blocking agents and ajmaline (LoE C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.   | III                | A B C              |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; LoE = level of evidence; i.v. = intravenous.

rhythm can be offered with i.v. flecainide or propafenone (when there is little or no underlying structural heart disease) or amiodarone (when there is structural disease) (Figure 6). The anticipated conversion rate is ≥50% within ~15–120 min. Ibutilide is effective, but the risk of serious proarrhythmia is not negligible.<sup>2</sup>

4.2.1.3 ‘Pill-in-the-pocket’ approach

In-hospital oral propafenone converted 55 of 119 (45%) patients at 3 h compared with 22 of 121 (18%) patients on placebo. In smaller studies, both propafenone and flecainide demonstrated a similar effect.

According to one medium-size trial, oral propafenone (450–600 mg) or flecainide (200–300 mg) can be administered by the patient safely (1/569 episodes resulting in atrial flutter with rapid conduction) and effectively (94%, 534/569 episodes) out of hospital.<sup>67</sup>

This approach may be used in selected, highly symptomatic patients with infrequent (e.g. between once per month and once per year) recurrences of AF. In order to implement the 'pill-in-the-pocket' technique, patients should be screened for indications and contraindications, and the efficacy and safety of oral treatment should be tested in hospital. Patients should be instructed to take flecainide or propafenone when symptoms of AF occur.

#### 4.2.1.4 Direct current cardioversion

DCC is an effective method of converting AF to sinus rhythm.

##### Procedure

Unless adequate anticoagulation has been documented for 3 weeks or AF is < 48 h from a definite onset, a TOE should be performed to rule out atrial thrombi (see Figure 5). A pacing catheter or external pacing pads may be needed if asystole or bradycardia occurs.

Successful DCC is usually defined as termination of AF, documented as the presence of two or more consecutive P waves after shock delivery. 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 DCC for AF when biphasic waveforms were used.

Currently, two conventional positions are commonly used for electrode placement. Several studies have shown that anteroposterior electrode placement is more effective than anterolateral placement.<sup>78</sup> If initial shocks are unsuccessful for terminating the arrhythmia, the electrodes should be repositioned and cardioversion repeated.

Outpatient/ambulatory DCC 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, but has been largely abandoned as a means for cardioversion, except when implanted defibrillation devices are present.

##### 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 thrombo-embolism, 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.

##### Cardioversion in patients with implanted pacemakers and defibrillators

The electrode paddle should be at least 8 cm from the pacemaker battery, and the anteroposterior paddle positioning is recommended.

### Recommendations for direct current cardioversion

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| Immediate DCC 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. | I                  | C                  |                   |
| Immediate DCC is recommended for patients with AF involving pre-excitation when rapid tachycardia or haemodynamic instability is present.   | I                  | B                  | 82                |
| Elective DCC should be considered in order to initiate a long-term rhythm control management strategy for patients with AF.   | IIa                | B                  | 46, 78, 83        |
| Pre-treatment with amiodarone, flecainide, propafenone, ibutilide, or sotalol should be considered to enhance success of DCC and prevent recurrent AF.  | IIa                | B                  | 79–81             |
| Repeated DCC may be considered in highly symptomatic patients refractory to other therapy.  | IIb                | C                  |                   |
| Pre-treatment with $\beta$ -blockers, diltiazem or verapamil may be considered for rate control, although the efficacy of these agents in enhancing success of DCC or preventing early recurrence of AF is uncertain.     | IIb                | C                  |                   |
| DCC is contraindicated in patients with digitalis toxicity.   | III                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; DCC = direct current cardioversion.

Biphasic shocks are preferred because they require less energy for AF termination. In pacemaker-dependent patients, an increase in pacing threshold should be anticipated. These patients should be monitored carefully. After cardioversion, the device should be interrogated and evaluated to ensure normal function.

##### Recurrence after cardioversion

Recurrences after DCC can be divided into three phases:

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

**Table 13** General characteristics of rhythm control and rate control trials in patients with AF<sup>86–92</sup>

| Trial           | Ref | Patients (n) | Mean age (years) | Mean follow-up (years) | Inclusion criteria   | Primary outcome parameter   | Patients reaching primary outcome (n) |                  |       |
|-----------------|-----|--------------|------------------|------------------------|--|---|---------------------------------------|------------------|-------|
|                 |     |              |                  |                        |  |   | Rate control                          | Rhythm control   | P     |
| PIAF (2000)     | 92  | 252          | 61.0             | 1.0                    | Persistent AF (7–360 days)   | Symptomatic improvement   | 76/125 (60.8%)                        | 70/127 (55.1%)   | 0.32  |
| AFFIRM (2002)   | 86  | 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)     | 87  | 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)     | 88  | 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  |
| HOT CAFÉ (2004) | 89  | 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)   | 90  | 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) | 91  | 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 CAFÉ = 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.

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, ibutilide, sotalol, flecainide, and propafenone increases the likelihood of restoration of sinus rhythm.<sup>79–81</sup>

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.

### 4.3 Long-term management

#### General management

Clinical management of patients with AF involves the following five objectives:

- (1) Prevention of thrombo-embolism.
- (2) Symptom relief.
- (3) Optimal management of concomitant cardiovascular disease.
- (4) Rate control.
- (5) 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. For patients with symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control, while the long-term goal may be to restore sinus rhythm. If rate control offers inadequate symptomatic relief, restoration of sinus rhythm becomes a clear long-term goal. Early cardioversion may be necessary if AF causes hypotension or worsening of heart failure. In contrast, amelioration of symptoms by rate control in older patients may steer the clinician away from attempts to restore sinus rhythm.

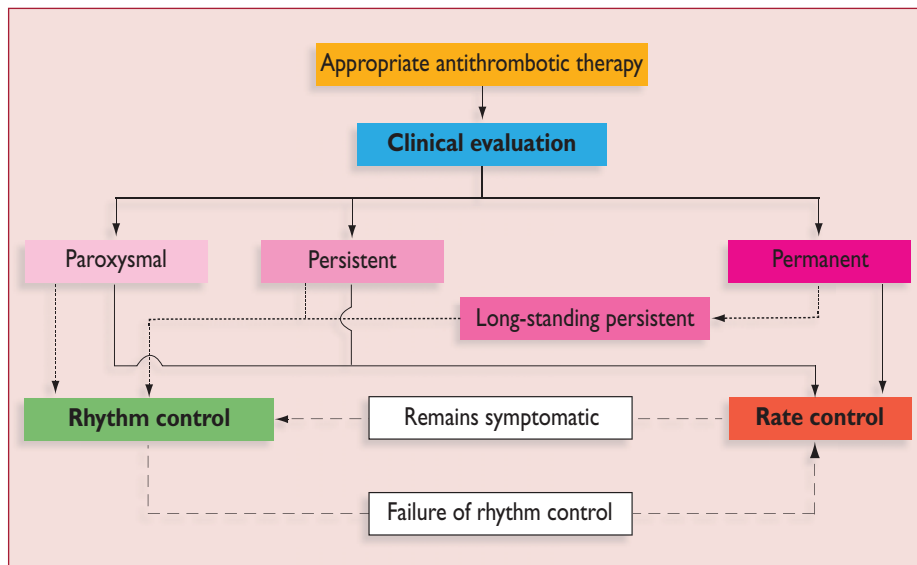


**Table 14 Comparison of adverse outcomes in rhythm control and rate control trials in patients with AF**

| Trial           | Ref | Deaths from all causes (in rate/rhythm) | Deaths from cardiovascular causes | Deaths from non-cardiovascular causes | Stroke | Thrombo-embolic events | Bleeding |
|-----------------|-----|---|-----------------------------------|---------------------------------------|--------|------------------------|----------|
| PIAF (2000)     | 92  | 4                                       | 1/1                               | 1 <sup>a</sup>                        | ND     | ND                     | ND       |
| AFFIRM (2002)   | 86  | 666 (310/356)                           | 167/164                           | 113/165                               | 77/80  | ND                     | 107/96   |
| RACE (2002)     | 87  | 36                                      | 18/18                             | ND                                    | ND     | 14/21                  | 12/9     |
| STAF (2003)     | 88  | 12 (8/4)                                | 8/3                               | 0/1                                   | 1/5    | ND                     | 8/11     |
| HOT CAFÉ (2004) | 89  | 4 (1/3)                                 | 0/2                               | 1/1                                   | 0/3    | ND                     | 5/8      |
| AF-CHF (2008)   | 90  | 228/217                                 | 175/182                           | 53/35                                 | 11/9   | ND                     | ND       |

<sup>a</sup>Total 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.



**Figure 7** 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.

**4.3.1 Rate and rhythm control**

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.

Depending on the patient’s course, the strategy initially chosen may prove insufficient and may then be supplemented by rhythm control drugs or interventions. It is likely that long-lasting AF renders maintenance of sinus rhythm more difficult,<sup>23,84–85</sup> but clinical data on the usefulness and benefit of early rhythm control therapy are lacking. Nonetheless, it is likely that a window of opportunity to maintain sinus rhythm exists early in the course of management of a patient with AF.

**Recommendations for rate and rhythm control of AF**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| Rate control should be the initial approach in elderly patients with AF and minor symptoms (EHRA score I).   | I                  | A                  | 86–87, 90         |
| Rate control should be continued throughout a rhythm control approach to ensure adequate control of the ventricular rate during recurrences of AF.     | I                  | A                  | 86                |
| Rhythm control is recommended in patients with symptomatic (EHRA score ≥2) AF despite adequate rate control.   | I                  | B                  | 3, 46, 93–94, 96  |
| Rhythm control in patients with AF and AF-related heart failure should be considered for improvement of symptoms.                                      | IIa                | B                  | 93–94, 97         |
| Rhythm control as an initial approach should be considered in young symptomatic patients in whom catheter ablation treatment has not been ruled out.   | IIa                | C                  |                   |
| Rhythm control should be considered in patients with AF secondary to a trigger or substrate that has been corrected (e.g. ischaemia, hyperthyroidism). | IIa                | C                  |                   |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

*Clinical trials comparing rate control with rhythm control*

Randomized trials comparing outcomes of rhythm vs. rate control strategies in patients with AF are summarized in Tables 13 and 14.<sup>86–92</sup> Among these, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) found no difference in all-cause mortality (primary outcome) or stroke rate between patients assigned to one strategy or the other.<sup>86</sup> The RATE Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) trial found rate control not inferior to rhythm control for prevention of cardiovascular mortality and morbidity (composite endpoint).<sup>87</sup> The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial observed no difference in cardiovascular mortality (primary outcome) between patients with an LVEF ≤ 35%, symptoms of congestive heart failure, and a history of AF randomized to rate or rhythm control, or in the secondary outcomes including death from any cause and worsening of heart failure.<sup>90</sup>

*Patient-tailored therapy*

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

**Recommendations for acute rate control**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| 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. | I                  | A                  | 100               |
| In the acute setting, i.v. administration of digitalis or amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the setting of hypotension.   | I                  | B                  | 101               |
| In pre-excitation, preferred drugs are class I antiarrhythmic drugs or amiodarone.   | I                  | C                  |                   |
| When pre-excited AF is present, β-blockers, non-dihydropyridine calcium channel antagonists, digoxin, and adenosine are contraindicated.   | III                | C                  |                   |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation; i.v. = intravenous.

future and how successful rhythm control is expected to be (Figure 7). 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 6), 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.

*Effects on quality of life*

The AFFIRM, RACE, the Pharmacologic Intervention in Atrial Fibrillation (PIAF) trial, and the Strategies of Treatment of Atrial Fibrillation (STAF) trial found no differences in quality of life with rhythm control compared with rate control. Yet, quality of life is significantly impaired in patients with AF compared with healthy controls, and post-hoc analyses suggest that maintenance of sinus rhythm may improve quality of life and be associated with improved survival.

The instruments to assess AF-related quality of life in the trials have been far from optimal. The most frequently used Medical Outcomes Study Short-Form health survey (SF-36) questionnaire is a tool to measure general quality of life but not AF-related symptoms. Newer questionnaires are more AF specific (University of Toronto AF Severity Scale and the Canadian Cardiovascular Society Severity in AF scales, the latter being very similar to the EHRA score<sup>3,41</sup>) and many disease-specific instruments to assess quality of life in AF are under clinical evaluation. These may be

**Recommendations for long-term rate control**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| 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.            | I                  | B                  | 100               |
| In patients who experience symptoms related to AF during activity, the adequacy of rate control should be assessed during exercise, and therapy should be adjusted to achieve a physiological chronotropic response and to avoid bradycardia.   | I                  | C                  |                   |
| In pre-excitation AF, or in patients with a history of AF, preferred drugs for rate control are propafenone or amiodarone.  | I                  | C                  |                   |
| It is reasonable to initiate treatment with a lenient rate control protocol aimed at a resting heart rate <110 bpm.   | IIa                | B                  | 98                |
| 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. | IIa                | B                  | 98                |
| It is reasonable to achieve rate control by administration of dronedarone in non-permanent AF except for patients with NYHA class III–IV or unstable heart failure.   | IIa                | B                  | 95, 99, 103       |
| Digoxin is indicated in patients with heart failure and LV dysfunction, and in sedentary (inactive) patients.   | IIa                | C                  |                   |
| Rate control may be achieved by administration of oral amiodarone when other measures are unsuccessful or contraindicated.  | IIb                | C                  |                   |
| Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.  | III                | B                  | 104               |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; bpm = beats per minute; LV = left ventricular; NYHA = New York Heart Association.

**Table 15 Drugs for rate control**

|  | Intravenous administration              | Usual oral maintenance dose      |
|--|---|----------------------------------|
| <b>β-Blockers</b>                                      |   |                                  |
| Metoprolol CR/XL                                       | 2.5–5 mg                                | 100–200 mg o.d. (ER)             |
| Bisoprolol   | N/A                                     | 2.5–10 mg o.d.                   |
| Atenolol   | N/A                                     | 25–100 mg o.d.                   |
| Esmolol  | 10 mg                                   | N/A                              |
| Propranolol  | 1 mg                                    | 10–40 mg t.i.d.                  |
| Carvedilol   | N/A                                     | 3.125–25 mg b.i.d.               |
| <b>Non-dihydropyridine calcium channel antagonists</b> |   |                                  |
| Verapamil  | 5 mg                                    | 40 mg b.d. to 360 mg (ER) o.d.   |
| Diltiazem  | N/A                                     | 60 mg t.d.s. to 360 mg (ER) o.d. |
| <b>Digitalis glycosides</b>                            |   |                                  |
| Digoxin  | 0.5–1 mg                                | 0.125 mg–0.5 mg o.d.             |
| Digitoxin  | 0.4–0.6 mg                              | 0.05 mg–0.1 mg o.d.              |
| <b>Others</b>  |   |                                  |
| Amiodarone   | 5 mg/kg in 1 h, and 50 mg/h maintenance | 100 mg–200 mg o.d.               |
| Dronedarone <sup>a</sup>                               | N/A                                     | 400 mg b.i.d.                    |

ER = extended release formulations; N/A = not applicable.

<sup>a</sup>Only in patients with non-permanent atrial fibrillation.

better tools to assess quality of life and symptoms, but they have not been used in major trials.

*Effects on heart failure and left ventricular function*

Development of heart failure was not different between rate control and rhythm control therapy groups in the AFFIRM, RACE, or AF-CHF trials.<sup>86–87,90</sup> Substudies in the RACE trial and echocardiographic assessment of highly selected patients with heart failure undergoing extensive catheter ablation for AF suggest that LV function may deteriorate less or even improve in patients undergoing rhythm control management,<sup>93,94</sup> but the AFFIRM echocardiographic analysis did not identify such an effect. Heart failure may develop or deteriorate during either type of treatment for AF due to progression of underlying cardiac disease, inadequate control of the ventricular rate at the time of recurrent AF, or antiarrhythmic drug toxicity. Hence, while selected patients may show better LV function on rhythm control therapy, this motivation to pursue maintenance of sinus rhythm needs to be individualized.

*Effects on mortality and hospitalization*

None of the rate vs. rhythm trials demonstrated the benefit of rhythm control therapy on mortality that was expected at the outset of the trials.<sup>86–87,90</sup> A post-hoc analysis of the AFFIRM database has suggested that deleterious effects of antiarrhythmic drugs (a mortality increase of 49%) may have offset the benefits of sinus rhythm (which was associated with a 53% reduction in mortality),

while an analysis of the RACE database suggested that underlying heart disease impacts prognosis more than AF itself.

#### Implications of the rhythm vs. rate control studies

There is a clear disconnect between the deleterious outcome in AF patients compared with those in sinus rhythm and the perceived benefits of sinus rhythm maintenance on one hand (see Section 2.1) and the outcome of virtually all 'rate vs. rhythm' trials on the other hand.<sup>86,87,90</sup> The outcome of the ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter) study (see Section 4.3.5.1) is a first signal that safely maintained sinus rhythm may prevent relevant outcomes in AF,<sup>95</sup> but this trial alone cannot reconcile the disconnect. One may conclude that rate control is a reasonable strategy in elderly patients, in whom the level of symptoms related to AF is deemed acceptable (EHRA score = 1). Rhythm control therapy is reasonable to ameliorate symptoms, but should not result in cessation of antithrombotic therapy, rate control therapy, or therapy of underlying heart disease. There is a clear need for a controlled trial to assess the effects of catheter ablation and safe antiarrhythmic drugs as novel means for sinus rhythm maintenance on severe cardiovascular outcomes compared with rate control.

#### 4.3.2 Long-term rate control

An irregular rhythm and a rapid ventricular rate in AF can cause symptoms including palpitations, dyspnoea, fatigue, and dizziness. Adequate control of the ventricular rate may reduce symptoms and improve haemodynamics, by allowing enough time for ventricular filling and prevention of tachycardiomyopathy.

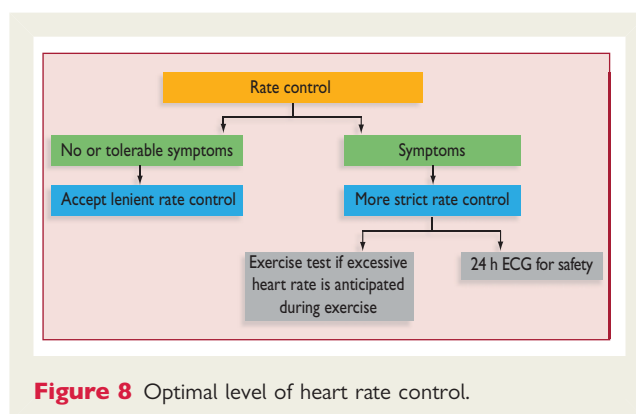
#### Intensity of rate control therapy

The optimal level of heart rate control with respect to morbidity, mortality, quality of life, and symptoms remains unknown. Previous guidelines recommended strict rate control aiming at a resting heart rate between 60–80 bpm and 90–115 bpm during moderate exercise, based on the type of therapy applied in the AFFIRM trial.<sup>86</sup> Strict rate control therapy required implantation of a pacemaker for symptomatic bradycardia in 147 patients (7.3%) in the AFFIRM trial, while higher resting heart rates were not associated with an adverse prognosis. The recently published RACE II (Rate Control Efficacy in permanent atrial fibrillation) trial did not identify a benefit of stringent rate control over lenient rate control therapy in 614 patients randomized to either of these two therapy strategies.<sup>98</sup> Lenient rate control used a resting heart rate <110 bpm in AF as the therapeutic target, while strict rate control aimed at a resting heart rate of <80 bpm and an adequate increase in heart rate upon moderate exertion.<sup>98</sup> The primary composite outcome was reached in 81 patients (38 in the lenient and 43 in the strict rate control group). Symptoms, adverse events, and quality of life were similar in both groups. Patients assigned to lenient rate control had fewer hospital visits. The trial has shown that in the patients enrolled in RACE II, presumably patients without severe symptoms due to a high ventricular rate, a lenient rate control therapy approach is reasonable.

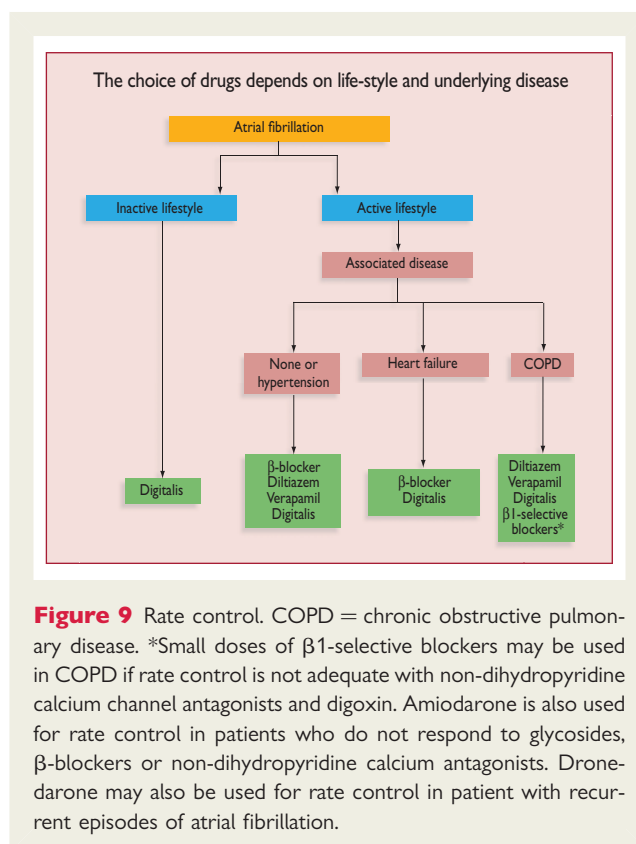
#### 4.3.3 Pharmacological rate control

##### Drugs used for pharmacological rate control

The main determinants of the ventricular rate during AF are the conduction characteristics and refractoriness of the



**Figure 8** Optimal level of heart rate control.



**Figure 9** Rate control. COPD = chronic obstructive pulmonary disease. \*Small doses of  $\beta$ 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,  $\beta$ -blockers or non-dihydropyridine calcium antagonists. Dronedarone may also be used for rate control in patient with recurrent episodes of atrial fibrillation.

atrioventricular node and the sympathetic and parasympathetic tone. Drugs commonly used are  $\beta$ -blockers, non-dihydropyridine calcium channel antagonists, and digitalis. Acute treatment is described in Section 4.2.1. Combinations of drugs may be necessary. Dronedarone 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  $\beta$ -blocker and digitalis may be beneficial in patients with heart failure.

Rate control drugs include (Table 15):

- **$\beta$ -Blockers** may be especially useful in the presence of high adrenergic tone or symptomatic myocardial ischaemia occurring in association with AF. During chronic treatment  $\beta$ -blockers have been shown to be effective and safe in several studies

**Recommendation for atrioventricular node ablation in AF patients**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| 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. | <b>IIa</b>         | <b>B</b>           | 106,107           |
| 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).   | <b>IIa</b>         | <b>B</b>           | 105, 108–110      |
| 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.  | <b>IIa</b>         | <b>C</b>           |                   |
| 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.  | <b>IIa</b>         | <b>C</b>           |                   |
| 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.   | <b>IIb</b>         | <b>C</b>           |                   |
| 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.                                    | <b>IIb</b>         | <b>C</b>           |                   |
| 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.   | <b>III</b>         | <b>C</b>           |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

**Recommendations for pacemakers after atrioventricular node ablation**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| 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. | <b>IIb</b>         | <b>C</b>           |                   |
| In patients with paroxysmal AF and normal LV function, implantation of a dual-chamber (DDD) pacemaker with mode-switch function may be considered after AV node ablation.                          | <b>IIb</b>         | <b>C</b>           |                   |
| In patients with persistent or permanent AF and normal LV function, implantation of a single-chamber (VVR) pacemaker may be considered after AV node ablation.                                     | <b>IIb</b>         | <b>C</b>           |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; AV = atrioventricular; CRT = cardiac resynchronization therapy; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

compared with placebo and digoxin. In AFFIRM, β-blockers were commonly used to achieve strict rate control. Dosages of commonly used β-blockers are given in *Table 15*.

- **Non-dihydropyridine calcium channel antagonists** (verapamil and diltiazem) are effective for acute and chronic rate control of AF. The drugs should be avoided in patients with systolic heart failure because of their negative inotropic effect.
- **Digoxin** and digitoxin are effective for control of heart rate at rest, but not during exercise. In combination with a β-blocker either may be effective in patients with or without heart failure. Digoxin may cause (life-threatening) adverse effects and should therefore be instituted cautiously. Interactions with other drugs may occur.
- **Dronedaron** is effective as a rate-controlling drug for chronic treatment, significantly decreasing the heart rate at rest and during exercise. The effects of dronedaron are additive to those of other rate control agents. It also successfully reduces the heart rate during AF relapses,<sup>99</sup> but is not currently approved for permanent AF.
- **Amiodarone** is an effective rate control drug. Intravenous amiodarone is effective and well tolerated in haemodynamically ill patients. Amiodarone may also be instituted for chronic treatment when conventional measures are ineffective, but it may cause severe extracardiac adverse events including thyroid dysfunction and bradycardia. Amiodarone, usually initiated for rhythm control, may continue to be used inadvertently for rate control when patients have lapsed into permanent AF. Unless safer agents are unsuitable, amiodarone should be discontinued in this setting.

Other class I antiarrhythmic drugs are not effective for rate control. Sotalol should not be used solely for rate control,



**Table 16** Suggested doses and main caveats for commonly used antiarrhythmic drugs

| Drug           | Dose   | Main contraindications and precautions  | ECG features prompting lower dose or discontinuation | AV nodal slowing                       |
|----------------|--|---|--|--|
| Disopyramide   | 100–250 mg t.i.d.  | Contraindicated in systolic heart failure. Caution when using concomitant therapy with QT-prolonging drugs.   | QT interval >500 ms                                  | None                                   |
| Flecainide     | 100–200 mg b.i.d.  | Contraindicated if creatinine clearance <50 mg/mL, in coronary artery disease, reduced LV ejection fraction.  | QRS duration increase >25% above baseline            | None                                   |
| Flecainide XL  | 200 mg o.d.  | Caution in the presence of conduction system disease.   |  |  |
| Propafenone    | 150–300 mg t.i.d.  | Contraindicated in coronary artery disease, reduced LV ejection fraction.   | QRS duration increase >25% above baseline            | Slight                                 |
| Propafenone SR | 225–425 mg b.i.d.  | Caution in the presence of conduction system disease and renal impairment.  |  |  |
| d,l-Sotalol    | 80–160 mg b.i.d.   | Contraindicated in the presence of significant LV hypertrophy, systolic heart failure, pre-existing QT prolongation, hypokalaemia creatinine clearance <50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose.   | QT interval >500 ms                                  | Similar to high-dose $\beta$ -blockers |
| Amiodarone     | 600 mg o.d. for 4 weeks, 400 mg o.d. for 4 weeks, then 200 mg o.d. | Caution when using concomitant therapy with QT-prolonging drugs, heart failure. Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced.   | QT interval >500 ms                                  | 10–12 bpm in AF                        |
| Dronedarone    | 400 mg b.i.d.  | Contraindicated in NYHA class III–IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, powerful CYP3A4 inhibitors, and creatinine clearance <30 mg/mL. Caution when using concomitant therapy with QT-prolonging drugs, heart failure. Dose of digitoxin/digoxin should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect reduced renal function. | QT interval >500 ms                                  | 10–12 bpm in AF                        |

AF = atrial fibrillation; AV = atrioventricular; bpm = beats per minute; CYP = cytochrome P; ECG = electrocardiogram; LV = left ventricular; NYHA = New York Heart Association.

although its additional rate control properties may be valuable when it is used primarily for rhythm control.

#### How to establish rate control

The outcome of RACE II, and previous observations in non-randomized studies, suggest that an initially lenient rate control approach should be used, aiming at a resting heart rate of <110 bpm. The dose of rate control drugs can be increased and drugs can be combined until this target has been achieved. If patients remain symptomatic, especially if complaints relate to excessive rate or irregularity, a stricter rate control target should be pursued. The ventricular rate should be reduced until the patient becomes asymptomatic or symptoms become tolerable, or when it is recognized that symptoms are due to the underlying disease rather than the ventricular rate or rhythm. 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. If symptoms are exercise-related, an exercise test may be performed (Figure 8). The

choice of drugs for rate control depends on age, underlying heart disease, and the goal of treatment (Figure 9). In patients who remain symptomatic on strict rate control therapy, rhythm control therapy may be considered.

#### 4.3.4 Atrioventricular node ablation and modification

Atrioventricular node ablation provides highly effective control of ventricular rate in patients with AF. Complete heart block is achieved by selective catheter-mediated destruction of the atrioventricular node or His bundle, with radiofrequency current serving as the predominant source of ablation energy.

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. In such patients, atrioventricular node ablation improves quality of life and renders mortality similar to death rates in the general population. Selection of the appropriate cardiac implant

(VVI, DDD, cardiac resynchronization therapy; pacemaker, or implantable cardioverter-defibrillator) depends on the type of AF (paroxysmal, permanent, or persistent), the presence and severity of associated cardiovascular disease, LVEF, and the presence and severity of heart failure symptoms. It is reasonable to assume that patients with reduced LV function may require biventricular pacing after atrioventricular node ablation to prevent deterioration of LV function. In patients without LV dysfunction, it is not established at present whether biventricular pacing is needed: some data suggest that biventricular pacing may be beneficial,<sup>105</sup> while others demonstrate similar benefits with right ventricular pacing.

#### *Atrioventricular node modification for rate control*

Small and preliminary studies suggested that catheter-based radio-frequency modification of atrioventricular nodal conduction properties may reduce ventricular rate and AF-related symptoms. However, the procedure has no defined endpoint, and atrioventricular node ablation and pacemaker implantation appear superior. Therefore, atrioventricular node modification without permanent pacemaker insertion is rarely used.

### 4.3.5 Long-term rhythm control

#### 4.3.5.1 Antiarrhythmic drugs to maintain sinus rhythm

The main motivation to initiate rhythm control therapy is relief of AF-related symptoms. Conversely, asymptomatic patients (or those who become asymptomatic with adequate rate control therapy) should not generally receive antiarrhythmic drugs.

The following illustrates 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

Individual drugs are discussed below and their main disadvantages are listed in *Table 16*.

**β-Blockers** are only modestly effective in preventing recurrent AF except in the context of thyrotoxicosis and exercise-induced AF. In a randomized trial in 394 patients, individuals assigned to metoprolol had a 47.7% AF relapse rate compared with 59.9% in controls ( $P = 0.005$ ). The perceived 'antiarrhythmic effect' may also be explained by improved rate control that may render recurrent AF silent (see Section 3.5).

#### *Efficacy of antiarrhythmic drugs in preventing recurrent atrial fibrillation*

In a recent meta-analysis of 44 randomized controlled trials comparing antiarrhythmic drugs against control (placebo or no treatment),<sup>111</sup> sodium channel blockers with fast (disopyramide, quinidine) or slow (flecainide, propafenone) binding kinetics, and agents causing either pure potassium channel blockade (dofetilide), potassium channel

blockade plus β-blockade (sotalol), or mixed ion channel blockade plus antisympathetic effects (amiodarone) significantly reduced the rate of recurrent AF. Overall, the likelihood of maintaining sinus rhythm is approximately doubled by the use of antiarrhythmic drugs.<sup>112</sup> Amiodarone was superior to class I agents and sotalol.

In the meta-analysis, 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.<sup>111</sup> 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 [odds ratio (OR) 2.39; 95% CI 1.03–5.59;  $P = 0.04$ ; number needed to harm = 109].

Flecainide, propafenone, sotalol, and amiodarone are frequently used in most European countries. Quinidine, the first sodium channel blocker available, has been used less in recent years due to its QT-prolonging effect and subsequent risk of drug-induced torsades de pointes. Disopyramide is little used except for vagally induced AF, and cibenzoline and hydroquinidine are only used in a few European countries. Dronedarone, a new antiarrhythmic drug specifically developed for the management of AF, is now available in many European countries, North America, and elsewhere.

**Flecainide** approximately doubles the likelihood of maintaining sinus rhythm. Flecainide was initially evaluated for paroxysmal AF, but is also used to maintain sinus rhythm after DCC. It can be safely administered in patients without significant structural heart disease, but should not be used in patients with coronary artery disease or in those with reduced LVEF. Precautions should be observed when using flecainide in the presence of intraventricular conduction delay, particularly left bundle branch block.

Upon initiation of flecainide therapy, regular ECG monitoring is recommended. An increase in QRS duration of >25% on therapy compared with baseline is a sign of potential risk of proarrhythmia when the drug should be stopped or the dose reduced. Similarly, when the flecainide dose is increased, QRS duration should be monitored. Concomitant atrioventricular node blockade (see Section 4.3.1) is recommended because of the potential of flecainide and propafenone to convert AF to atrial flutter, which then may be conducted rapidly to the ventricles.

**Propafenone** prevents recurrent AF. In addition, propafenone has a weak β-adrenoreceptor blocking effect. It can be safely administered in patients without significant structural heart disease. By analogy to flecainide, propafenone should not be used in patients with coronary artery disease or reduced LVEF. Precautions similar to those for flecainide should also be observed with propafenone.

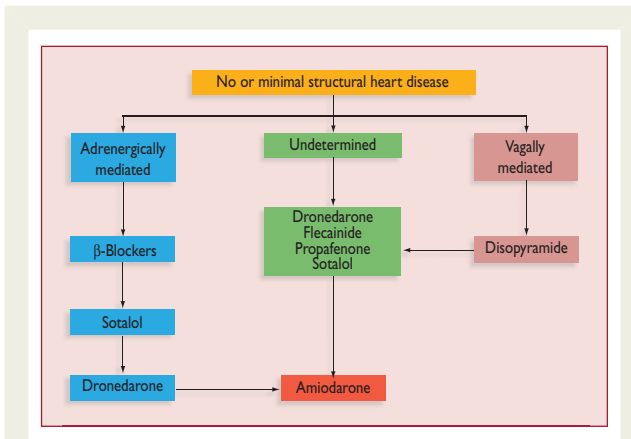
**Quinidine** was among the first cardiovascular drugs to undergo prospective systematic testing. In controlled trials quinidine improved maintenance of sinus rhythm. However, a meta-analysis demonstrated that quinidine increased mortality, very probably due to ventricular proarrhythmia secondary to QT interval prolongation (torsade de pointes). Quinidine is now largely abandoned.

**Amiodarone** prevents recurrent AF better than propafenone and sotalol. The number of patients needed to treat is 3 with amiodarone, 4 with flecainide, 5 with dofetilide and propafenone, and 8

with sotalol.<sup>111</sup> Amiodarone is a good therapeutic option in patients with frequent, symptomatic AF recurrences despite therapy with other antiarrhythmic drugs. Unlike most other agents, amiodarone can be safely administered in patients with structural heart disease, including patients with heart failure.<sup>113</sup> The risk of drug-induced torsade de pointes is lower with amiodarone than with 'pure' potassium channel blockers, possibly due to multiple ion channel inhibition.<sup>114</sup> However, drug-induced proarrhythmia is seen with amiodarone,<sup>114</sup> and the QT interval should be monitored closely.

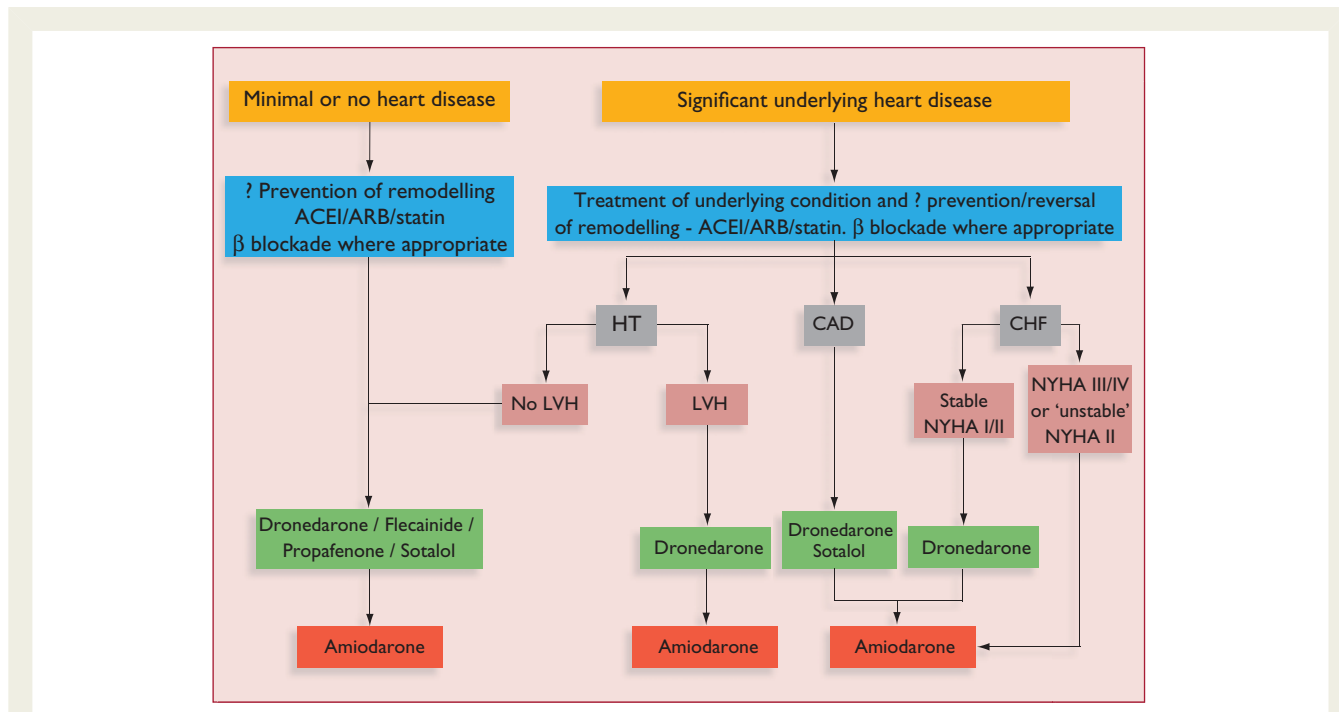
**Sotalol** prevents recurrent AF as effectively as the fixed dose quinidine–verapamil combination,<sup>83</sup> but less effectively than amiodarone. In the Sotalol Amiodarone atrial Fibrillation Efficacy Trial (SAFE-T), the efficacy of sotalol to maintain sinus rhythm was not inferior to amiodarone in the subgroup of patients with ischaemic heart disease ( $P = 0.53$ ).<sup>46</sup> Drug-induced proarrhythmia with sotalol is due to excessive prolongation of the QT interval<sup>115</sup> and/or bradycardia. Careful monitoring for QT prolongation<sup>115</sup> and abnormal TU waves<sup>114</sup> is mandatory. In patients reaching a QT interval >500 ms, sotalol should be stopped or the dose reduced. Women, and patients with marked LV hypertrophy, severe bradycardia, ventricular arrhythmias, renal dysfunction, or with hypokalaemia or magnaemia are at increased risk of proarrhythmia.<sup>45</sup>

**Dronedarone** is a multichannel blocker that inhibits the sodium, potassium, and calcium channels, and has non-competitive antiadrenergic activity. Similarly to sotalol, propafenone, and flecainide, its efficacy to maintain sinus rhythm is lower than that of amiodarone.<sup>116</sup> In the DIONYSOS (randomized Double blind trial



**Figure 10** 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 (adrenergic or vagally mediated). Antiarrhythmic agents are listed in alphabetical order within each treatment box.

to evaluate efficacy and safety of drOnedarone [400 mg b.i.d.] versus amiodarone [600 mg q.d. for 28 days, then 200 mg q.d. thereafter] for at least 6 months for the maintenance of sinus rhythm in patients with atrial fibrillation) study in 504 patients with persistent AF, dronedarone was less efficacious but also less toxic than amiodarone. The primary composite endpoint events (recurrence of AF and



**Figure 11** 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.

study drug discontinuation) occurred in 75 and 59% of patients treated with dronedarone and amiodarone, respectively [hazard ratio (HR) 1.59; 95% CI 1.28–1.98;  $P < 0.0001$ ]. AF recurrence was more common in the dronedarone arm compared with amiodarone (36.5% vs. 24.3%). Premature drug discontinuation tended to be less frequent with dronedarone (10.4% vs. 13.3%). The main safety endpoint occurred in 39.3 and 44.5% of patients treated with dronedarone and amiodarone, respectively (HR 0.80; 95% CI 0.60–1.07;  $P = 0.129$ ), and were due mainly to fewer thyroid, neurological, skin, and ocular events in the dronedarone group.

The safety profile of dronedarone is advantageous in patients without structural heart disease and in stable patients with heart disease. Specifically, dronedarone appears to have a low potential for proarrhythmia.<sup>95,99</sup> Dronedarone was shown in two large pivotal trials to be superior to placebo in maintaining sinus rhythm in patients with recurrent AF.<sup>99</sup> Combining data from the two trials, the median time to the first episode of AF was 53 days in the placebo group, compared with 116 days in the dronedarone group (HR 0.75; CI 0.65–0.87;  $P < 0.0001$ ). Dronedarone significantly reduced the ventricular rate during the first recurrence of AF or atrial flutter.

The ANtiarrhythmic trial with DRonedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrease (ANDROMEDA) trial in patients in sinus rhythm and advanced heart failure was stopped prematurely due to increased mortality with dronedarone.<sup>117</sup> This trial evaluated the use of dronedarone in patients with symptomatic (NYHA class II–IV) heart failure, who in addition had severe LV dysfunction and at least one NYHA class III–IV episode requiring hospitalization in the past month. The deaths in the dronedarone group were due predominantly to worsening heart failure, and there was no evidence of proarrhythmia or an increased incidence of sudden death.

The ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg b.i.d. for the prevention of cardiovascular Hospitalisation or death from any cause in patiENts with Atrial fibrillation/atrial flutter) study<sup>95</sup> recruited 4628 patients, and randomized patients with paroxysmal or persistent AF or flutter and cardiovascular risk factors to treatment with dronedarone 400 mg twice daily or placebo. Primary outcome events (all-cause death or cardiovascular hospitalization) occurred in 734 (31.9%) patients randomized to dronedarone and in 917 (39.4%) patients randomized to placebo (HR 0.76; 95% CI 0.69–0.84;  $P < 0.0001$ ). There was a numerical, but not significant, reduction in deaths in the dronedarone group (HR 0.84; 95% CI 0.66–1.08;  $P = 0.18$ ). The rate of cardiovascular mortality was lower in the dronedarone group (2.7% vs. 3.9%; HR 0.71; 95% CI 0.51–0.98). Rates of death presumed due to heart failure were not different between groups (HR 0.95; 95% CI 0.49–1.85;  $P = 0.89$ ). Post-hoc analysis demonstrated a reduction in stroke risk in patients receiving dronedarone, which was independent of underlying antithrombotic therapy. Results in several subgroups of patients (i.e. patients with heart failure or coronary disease) were consistent with the overall results.

*Choice of antiarrhythmic drugs*

Antiarrhythmic therapy for recurrent AF is recommended on the basis of choosing safer, although possibly less efficacious,

**Recommendation for choice of antiarrhythmic drug for AF control**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup>    |
|---|--------------------|--------------------|----------------------|
| The following antiarrhythmic drugs are recommended for rhythm control in patients with AF, depending on underlying heart disease:   |                    |                    |                      |
| • amiodarone  | I                  | A                  | 46, 111, 125         |
| • dronedarone   | I                  | A                  | 95, 99               |
| • flecainide  | I                  | A                  | 111, 127             |
| • propafenone   | I                  | A                  | 111, 125             |
| • d,l-sotalol   | I                  | A                  | 46, 83, 111          |
| Amiodarone is more effective in maintaining sinus rhythm than sotalol, propafenone, flecainide (by analogy), or dronedarone (LoE A), but because of its toxicity profile should generally be used when other agents have failed or are contraindicated (LoE C). | I                  | A<br>C             | 46, 111, 121, 125    |
| 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.   | I                  | B                  | 126                  |
| In patients without significant structural heart disease, initial antiarrhythmic therapy should be chosen from dronedarone, flecainide, propafenone, and sotalol.   | I                  | A                  | 95, 99, 111, 125–127 |
| β-Blockers are recommended for prevention of adrenergic AF.   | I                  | C                  |                      |
| 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.  | IIa                | C                  |                      |
| Dronedarone should be considered in order to reduce cardiovascular hospitalizations in patients with non-permanent AF and cardiovascular risk factors.  | IIa                | B                  | 95, 99               |
| β-blockers should be considered for rhythm (plus rate) control in patients with a first episode of AF.  | IIa                | C                  |                      |
| Disopyramide may be considered in patients with vagally mediated AF.  | IIb                | B                  | 111, 118, 119        |
| Dronedarone is not recommended for treatment of AF in patients with NYHA class III and IV, or with recently unstable (decompensation within the prior month) NYHA class II heart failure.   | III                | B                  | 117, 122             |
| 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.  | III                | C                  |                      |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; AV = atrioventricular; LoE = level of evidence; NYHA = New York Heart Association.

medication before resorting to more effective but less safe therapy. AF occurring in patients with little or no underlying cardiovascular disease can be treated with almost any antiarrhythmic drug that is licensed for AF therapy. Most patients with AF will receive  $\beta$ -blockers initially for rate control. Amiodarone is reserved for those who have failed treatment with other antiarrhythmic drugs or have significant structural heart disease.

*Patients with atrial fibrillation and minimal or no heart disease (lone atrial fibrillation).* In patients with no or minimal heart disease,  $\beta$ -blockers represent a logical first attempt to prevent recurrent AF when the arrhythmia is clearly related to mental or physical stress (adrenergic AF). Since  $\beta$ -blockers are not very effective in many other patients with 'lone AF', flecainide, propafenone, sotalol, or dronedarone is usually prescribed. Disopyramide, which has marked anticholinergic effects, may be useful in vagally mediated AF (Figure 10).<sup>118,119</sup>

*Patients with underlying heart disease.* Cardiovascular disease has conventionally been divided into a variety of pathophysiological substrates: hypertrophy, ischaemia, and congestive heart failure (Figure 11). For each of these it has been recommended that specific drugs be avoided. Studies of flecainide and propafenone in patients with AF or other arrhythmias have shown substantial toxicity, and this has been attributed to proarrhythmic and/or negative inotropic effects. Sotalol is known to prolong the QT interval and to induce torsades de pointes in susceptible patients, who probably include those with marked LV hypertrophy and heart failure. Studies in post-myocardial infarction patients suggest that sotalol may be used relatively safely in coronary artery disease. For most patients with significant structural heart disease, particularly heart failure and LV hypertrophy, only amiodarone has been available in Europe (whereas dofetilide has also been available in North America). There is an emerging concern that amiodarone may not be safe for long-term use in patients with NYHA class III heart failure.<sup>120</sup>

It is challenging to make recommendations concerning the choice between amiodarone and dronedarone for patients with structural heart disease. In its favour, amiodarone has been used for many years without the emergence of any consistent and obvious cardiac toxicity. On the other hand, general toxicity relating to amiodarone is considerable when used at higher doses, but less so when given at  $\leq 200$  mg per day. Amiodarone has not been evaluated in a large-scale placebo-controlled randomized controlled trial similar to ATHENA, but several meta-analyses<sup>111,113,121,122</sup> and mixed treatment effect modelling<sup>123</sup> have failed to identify a beneficial effect 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, and stable NYHA class I–II heart failure. Patients with NYHA class III or IV, or recently unstable heart failure, should not receive dronedarone. There are no systematically collected data regarding the use of dronedarone in patients with documented LV hypertrophy or hypertrophic cardiomyopathy.

*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.

*Patients with coronary artery disease.* Patients who have coronary artery disease should not receive flecainide<sup>124</sup> 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.

*Patients with heart failure.* Dronedarone and amiodarone are the only agents available in Europe that can be safely administered in patients with stable NYHA class I–II heart failure. Dronedarone is contraindicated in patients with NYHA class III–IV or recently (within the previous 4 weeks) decompensated heart failure.<sup>117</sup> In such patients, amiodarone should be used.

The results of recent trials, in particular those of ATHENA, have led to a shift towards a new therapeutic paradigm in patients with AF. Prevention of repeated hospitalizations, as demonstrated in ATHENA, may be more important to patient and physician alike compared with sinus rhythm maintenance *per se*, especially when other prognostically relevant therapies (anticoagulation, rate control, therapy of concomitant diseases) are maintained.

Patients enrolled in ATHENA did not have to be symptomatic but many would have been. The trial data are not sufficient to analyse the value of dronedarone specifically in asymptomatic patients. No comparison has been made between dronedarone treatment, other antiarrhythmic agents, or rate control in asymptomatic patients, and therefore there is insufficient evidence to recommend its routine use in such patients.

#### 4.3.5.2 Left atrial catheter ablation

Ablation strategies have been deployed with the intention of 'curing' AF in several patient populations. Long-term follow-up of these patients suggests that while sinus rhythm is better preserved than with antiarrhythmic drugs, late recurrences are not uncommon.<sup>128</sup> The majority of studies have recruited patients with symptomatic paroxysmal AF and no or minimal structural heart disease.

#### Indications

In general, catheter ablation should be reserved for patients with AF which remains symptomatic despite optimal medical therapy, including rate and rhythm control. Whether to undertake an ablation procedure in a symptomatic patient should take into account:

- (1) The stage of atrial disease (i.e. AF type, LA size, AF history).
- (2) The presence and severity of underlying cardiovascular disease.
- (3) Potential treatment alternatives (antiarrhythmic drugs, rate control).
- (4) Patient preference.



**Table 17** Complications of AF catheter ablation

| Type  | Typical symptoms  | Incidence  | Treatment options and outcome   | How to reduce risks   |
|---|---|--|---|---|
| Thrombo-embolism<br>TIA<br>Stroke                     | Neurological deficit relating to the site of embolus                                      | 0.93%<br>0.2% (0.6%)<br>0.3% (0.28%)   | Consider lysis therapy  | Use irrigated tip catheter<br>Monitor ACT every 30 min and adjust using i.v. heparin bolus  |
| PV stenosis/occlusion                                 | Cough, shortness of breath on exertion, resistant pneumonia, haemoptysis                  | Depending on the ablation site with regards to the PV ostium<br>Up to 10% for focal PV ablation.<br><5% for segmental PV isolation | PV dilatation/recanalization eventually requiring stent implantation<br>Frequent in-stent re-stenosis | Avoid intra-PV ablation and solid-tip ablation  |
| Atrio-oesophageal fistula formation                   | Unexplained fever, dysphagia, seizure   | <1%  | Immediate surgical correction   | Avoid excessive energy delivery at sites neighbouring the posterior LA wall   |
| Tamponade<br>Immediate<br>Late (days after procedure) | Hypotension<br>cardiac arrest   | 0.8%<br>Up to 6% of all procedures<br>Unknown  | Immediate pericardiocentesis  | Avoid direct mechanical trauma during trans-septal puncture<br>Avoid pop formation<br>Avoid excessive contact force   |
| Phrenic nerve injury (mostly right-sided)             | Diaphragmatic paralysis causing shortness of breath on exertion or dyspnoea at rest       | Can be transient   | Wait  | Identify phrenic nerve location in relation to PV ostia by stimulation manoeuvre<br>Avoid stretching the PV ostium (mostly when using balloon catheters)                              |
| Perioesophageal injury                                | Intestinal symptoms (bloating, etc.)  | May be transient<br>Develops hours or days after the procedure<br>1% in cohort of 367 patients                                     | If necessary<br>Dilation of pylorus<br>Botulinum injections   | Unknown   |
| Arteriovenous fistula                                 | Pain at puncture site   | 0.43%  | Compression<br>Surgical correction rarely needed  | Careful puncture technique  |
| Aneurysm formation                                    | Pain at puncture site   | 0.5–0.53%  | Wait<br>Thrombin injection  | Careful puncture technique  |
| Radiation injury                                      | Pain and reddening at radiated site   | Occurs late in follow-up<br>Acute radiation injury very rare   | Treat as burn injury  | Avoid excessive radiation exposure and employ ALARA concept<br>Use 3D mapping technology<br>Use low frame rate pulsed fluoroscopy<br>Optimal adjustment of fluoroscopy exposure rates |
| Mitral valve injury                                   | Entrapment of catheters<br>Extensive scarring after excessive ablation on valvular tissue | Very uncommon  | Gentle catheter retraction while sheath is advanced into the ventricle<br>Surgical removal            | Recognition of the anatomic relationship of the LA/LV anatomy in 3D<br>Monitor signals while manipulating catheters   |
| Acute coronary injury                                 | Chest pain<br>ST elevation<br>Hypotension   | Very rare<br>1/356 patients in single case report  | Standard percutaneous therapy for acute coronary occlusion  | Avoid excessive energy application close to the coronary arteries<br>Avoid intracoronary sinus ablation when possible   |
| Air embolism  | Acute ischaemia<br>Hypotension<br>Atrioventricular block<br>Cardiac arrest                |  | Aspiration of air in long sheaths<br>Watch and wait<br>Pacing<br>Perform CPR if needed                | Careful aspiration of all indwelling sheaths<br>Constant positive pressure on trans-septal sheaths  |
| Haematoma at puncture site                            | Pain<br>Swelling<br>Discolouration  | Frequent   | Compression, in rare cases surgical treatment<br>Sheath removal after normalization of ACT            | Careful compression<br>Sheath removal after normalization of ACT  |
| Death overall   |   | 0.7%   |   |   |

ACT = activated clotting time; AF = atrial fibrillation; ALARA = as low as reasonably achievable; AV = atrioventricular; CPR = cardiopulmonary resuscitation; LA = left atrium; LV = left ventricle; PV = pulmonary vein; TIA = transient ischaemic attack.

**Table 18** Randomized clinical trials of catheter ablation vs. antiarrhythmic drugs or no treatment in AF

| Study   | Reference | Patients (n) | Age, years                          | Type of AF             | Previous use of AAD        | Ablation technique                               | Repeat ablation in the ablation group                 | Crossed to ablation in the AAD group | AF free at 1 year |      |
|---|-----------|--------------|-------------------------------------|------------------------|----------------------------|--|---|--------------------------------------|-------------------|------|
|   |           |              |                                     |                        |                            |  |   |                                      | Ablation          | AAD  |
| Krittayaphong <i>et al.</i> 2003                    | Online    | 30           | 55 ± 10 (ablation)<br>47 ± 15 (AAD) | Paroxysmal, persistent | ≥1 <sup>a</sup>            | PVI + LA lines + CTI ablation + RA lines         | Not stated  | Not stated                           | 79%               | 40%  |
| Wazni <i>et al.</i> 2005 (RAAFT)                    | 134       | 70           | 53 ± 8 (ablation)<br>54 ± 8 (AAD)   | Mainly paroxysmal      | No                         | PVI  | 12% <sup>b</sup>                                      | 49% <sup>c</sup>                     | 87%               | 37%  |
| Stabile <i>et al.</i> 2005 (CACAF) <sup>d</sup>     | Online    | 245          | 62 ± 9 (ablation)<br>62 ± 10 (AAD)  | Paroxysmal, persistent | ≥2                         | PVI + LA lines ± CTI ablation                    | No exact data   | 57%                                  | 56%               | 9%   |
| Oral <i>et al.</i> 2006 <sup>e</sup>                | Online    | 245          | 57 ± 9                              | Persistent             | ≥1 (mean 2.1 ± 1.2)        | CPVA   | 26% for AF; 6% for LA flutter                         | 77%                                  | 74%               | 4%   |
| Pappone <i>et al.</i> 2006 (APAF)                   | 135       | 198          | 55 ± 10 (ablation)<br>57 ± 10 (AAD) | Paroxysmal             | ≥2 (mean 2 ± 1)            | CPVA + CTI ablation                              | 6% for AF; 3% for atrial tachycardia                  | 42%                                  | 86%               | 22%  |
| Jais <i>et al.</i> 2008 (A4 study)                  | 133       | 112          | 51 ± 11                             | Paroxysmal             | ≥1                         | PVI ± LA lines ± CTI ablation                    | Mean 1.8 ± 0.8, median 2 per patient                  | 63%                                  | 89%               | 23%  |
| Forleo <i>et al.</i> 2008 <sup>f</sup>              | Online    | 70           | 63 ± 9 (ablation)<br>65 ± 6 (AAD)   | Paroxysmal, persistent | ≥1                         | PVI ± LA lines ± CTI ablation                    | Not stated  | Not stated                           | 80%               | 43%  |
| Wilber <i>et al.</i> 2010 (Thermocool) <sup>g</sup> | 96        | 167          | 55.5 (ablation)<br>56.1 (AAD)       | Paroxysmal             | ≥1 (mean 1.3) <sup>h</sup> | PVI ± LA lines ± CFAEs ± CTI ablation ± RA lines | 12.6% within 80 days after 1st procedure <sup>i</sup> | 59% <sup>c</sup>                     | 66%               | 16%  |
| Packer <i>et al.</i> 2010 (STOP-AF) <sup>j</sup>    | Online    | 245          | 56.7 (ablation)<br>56.4 (AAD)       | Paroxysmal             | ≥1 <sup>b</sup>            | Cryo-PVI ± LA lines                              | 19% within 90 days after 1st procedure                | 79%                                  | 69.9%             | 7.3% |

<sup>a</sup>No previous use of amiodarone, but 'failed' drugs included β-blockers, calcium channel antagonists, and digitalis, in addition to class IA and IC agents.

<sup>b</sup>Excluding amiodarone.

<sup>c</sup>After 1 year; not allowed during formal 1-year follow-up.

<sup>d</sup>All patients in the ablation arm were treated with antiarrhythmic drugs.

<sup>e</sup>Patients in the control group received amiodarone and had up to two electrical cardioversions if required during the first 3 months; amiodarone was discontinued if patients were in sinus rhythm after 3 months.

<sup>f</sup>With type 2 diabetes mellitus.

<sup>g</sup>Follow-up 9 months.

<sup>h</sup>Patients who received amiodarone in the previous 6 months were excluded.

<sup>i</sup>Considered treatment failure.

<sup>j</sup>Presented at the Sessions of the American College of Cardiology in 2010.

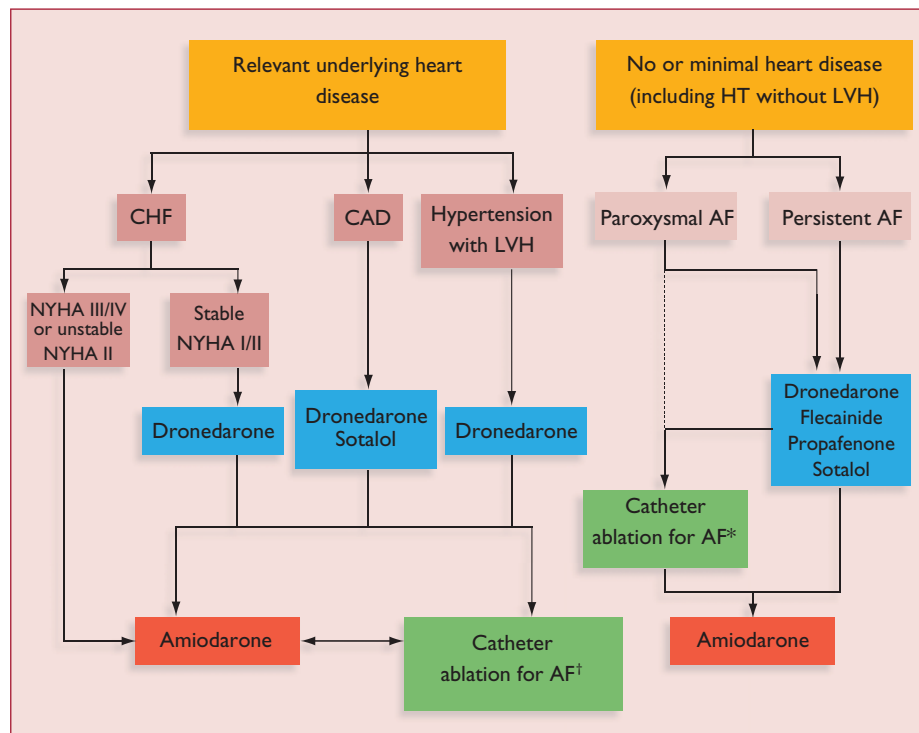
A4 = Atrial Fibrillation Ablation versus Antiarrhythmic Drugs; AAD = antiarrhythmic drugs; AF = atrial fibrillation; APAF = Ablation for Paroxysmal Atrial Fibrillation study; CACAF = Catheter Ablation for the Cure of Atrial Fibrillation study; CPVA = circumferential pulmonary vein ablation; CTI = cavotricuspid isthmus; LA = left atrial; PVI = pulmonary vein isolation; RA = right atrial; RAAFT = Radiofrequency Ablation Atrial Fibrillation Trial; STOP-AF = Sustained Treatment Of Paroxysmal Atrial Fibrillation. Online = references available on the dedicated Atrial Fibrillation Guidelines page of the European Society of Cardiology Web Site ([www.escardio.org/guidelines](http://www.escardio.org/guidelines)).

For the individual patient with symptomatic AF, there must be sufficient potential benefit to justify a complex ablation procedure associated with possibly severe complications. Operator experience is an important consideration when considering ablation as a treatment option. The studies cited in support of the recommendations have been almost exclusively performed by highly experienced operators and expert staff working in specialized institutions, but in clinical practice more junior and less experienced operators may be involved in many institutions.

Catheter ablation is usually undertaken in patients with symptomatic paroxysmal AF that is resistant to at least one antiarrhythmic drug. This practice is supported by the results of multiple single-centre randomized studies and by multicentre prospective studies comparing antiarrhythmic drug treatment with catheter ablation, showing a significantly better rhythm outcome after ablation (Table 18). In addition, meta-analyses of studies performed mostly in patients with paroxysmal AF, comparing antiarrhythmic drugs and catheter ablation, have also shown a clearly better rhythm outcome after catheter ablation.<sup>96,131–135</sup> However, most of these studies have included patients already resistant to antiarrhythmic drug treatment, and the follow-up was relatively short.

Data on a direct comparison of antiarrhythmic drug treatment and catheter ablation as first-line therapy in patients with symptomatic paroxysmal AF are scarce,<sup>134</sup> but separate analyses of the efficacy of antiarrhythmic drugs and of LA catheter ablation in AF imply greater benefit from ablation.<sup>131</sup> However, considering the potential of AF catheter ablation to achieve rhythm control in symptomatic patients with paroxysmal AF and minimal or no heart disease, and the relative safety of the technique when performed by experienced operators, ablation may be considered as an initial therapy in selected patients (Figure 12).

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. Since amiodarone treatment may be associated with serious and frequent adverse effects, especially during long-term treatment, it is reasonable to consider catheter ablation as an alternative to amiodarone treatment in younger patients.



**Figure 12** 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.

### Recommendations for left atrial ablation

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup>                |
|--|--------------------|--------------------|----------------------------------|
| 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.  | I                  | B                  | 33                               |
| Catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication.  | IIa                | A                  | 96, 131, 132, 133, 135, 137, 138 |
| Ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option.  | IIa                | B                  | 33                               |
| 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. | IIa                | C                  |                                  |
| Continuation of OAC therapy post-ablation is recommended in patients with 1 'major' ('definitive') or ≥2 'clinically relevant non-major' risk factors (i.e. CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2).  | IIa                | B                  | 136                              |
| Catheter ablation of AF in patients with heart failure may be considered when antiarrhythmic medication, including amiodarone, fails to control symptoms.  | IIb                | B                  | 93, 94                           |
| 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.   | IIb                | B                  | 131                              |
| Catheter ablation of AF may be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs.   | IIb                | C                  |                                  |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; i.v. = intravenous; LMWH = low molecular weight heparin; OAC = oral anticoagulant; UFH = unfractionated heparin.

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. These procedures are long and technically challenging, and are associated with greater risk than PV isolation alone. Whether amiodarone therapy or catheter ablation should be performed after failure of less toxic antiarrhythmic drug treatment should be carefully evaluated in individual patients. Among other factors, patient age, type and severity of organic heart disease, LA size, co-morbidities, and patient preference should be considered. There is evidence that patients with AF-related co-morbidity may gain from a primary ablation strategy; for example, patients with heart failure benefit from LA ablation as the ejection fraction and functional endpoints such as exercise tolerance may improve significantly.<sup>93,94</sup>

The benefit of AF ablation has not been demonstrated in asymptomatic patients.

#### Pre-ablation assessment

Prior to an ablation procedure all patients should undergo a 12-lead ECG and/or Holter recording to demonstrate the nature of the arrhythmia, and a transthoracic echocardiogram to identify/exclude underlying structural heart disease. Additional imaging studies, e.g. MRI or CT, demonstrate individual three-dimensional geometry and provide some quantification of atrial fibrosis. To lower the risk of thrombo-embolic events during any LA ablation procedure, an LA thrombus (usually within the LAA) should be excluded. Appropriate anticoagulation should be employed to 'bridge' the time (≤48 h is recommended) between exclusion of LAA thrombus by TOE and the procedure itself.

#### Trigger elimination by pulmonary vein isolation

Triggered AF episodes initiated by 'focal firing' from within the PVs led to the strategy of electrically isolating these triggers from the atrial substrate. This was achieved by circumferential mapping catheters that were positioned within the PV ostia to guide ablation and target the 'connecting' fibres by 'segmental' ablation. Since a characteristic PV potential is also seen during sinus rhythm in PVs, the ablation procedure can be carried out in the absence of any active 'firing' of the PV trigger. Segmental lesions to ablate the fibres connecting the left atrium and PV were placed close to the PV ostia, risking ostial stenosis and/or occlusion. In addition, AF recurrence rates were reported to be due to electrical re-conduction to and from the PVs, but some were also due to 'ostial' triggers in the presence of more distally isolated PVs.

#### Linear pulmonary vein isolation and circumferential pulmonary vein ablation

In order to facilitate ablation and reduce the risk of PV stenosis, ablation sites were moved further towards the atrial ('antral' or 'ostial') side, forming a long lesion around one or both ipsilateral PVs. The placement of these lesions underlined the previously made observation that the PV antrum could also serve as a substrate for maintenance of AF. There is now strong evidence suggesting that the PVs and the antrum are in fact critical for maintenance of AF, rendering the distinction between 'trigger' and 'substrate modification' inadequate to explain the role of the PVs. Following PV isolation of all veins, 54% of patients can no longer sustain induced AF, suggesting that in a significant proportion of patients with paroxysmal AF, the PVs form the substrate maintaining AF.

Circumferential PV ablation is a purely anatomical approach that does not require the endpoint of electrical disconnection of the encircled area. Since no simultaneous mapping within the PVs is performed, only a single trans-septal puncture is required. No waiting time is required after successful isolation, thereby shortening the procedure time. Using this technique, up to 45% of PVs are not isolated, PV–LA conduction persists, and PVs remain potentially arrhythmogenic. In addition, organized arrhythmias are more common after this type of ablation. A recent study reports that incomplete encircling lesions ('gaps') were the most predictive factor for the development of organized arrhythmias. This finding argues further in favour of achieving complete lesions.

#### *Endpoint of pulmonary vein isolation*

A recent expert consensus stated that ablation strategies that target the PVs and/or the PV antrum are the cornerstone for most AF ablation procedures. If the PVs are targeted, complete electrical PV isolation should be the goal of the procedure.<sup>33</sup> For such procedures, complete isolation of all PVs is currently the most accepted and best endpoint. Further evidence of the need for PV isolation is provided by studies that have evaluated AF recurrence after ablation and demonstrated that the majority of patients with AF recurrence demonstrate PV re-connection. Repeat PV isolation has been associated with the elimination of all AF in up to 90% of selected patients during short- to medium-term follow-up.

Despite exclusion of triggers initiating AF, most patients with persistent or long-standing persistent AF may need additional substrate modification. The conceptual basis for substrate modification by compartmentalization of the atria is based on the multiple wavelet hypothesis (see Section 2.2.2). Linear ablation is performed connecting anatomical or functional electrical obstacles in order to transect these regions and thereby prevent re-entry. A variety of different linear configurations have been investigated; however, prediction of which line is more suitable in a given patient remains elusive.

Linear ablation lesions may need to be transmural in order to accomplish complete conduction block. This is often difficult to achieve.

#### *Alternative ablation technologies and energy sources for pulmonary vein isolation*

To overcome the limitation of sequential, 'point-by-point' lesion creation and the imminent risk of incomplete lesion formation, several 'single-shot' devices have been proposed to achieve PV isolation, ideally with one (or few) energy application. Different devices either on the basis of balloon technology, or expandable circumferential or mesh designs, have been studied, mostly in patients with paroxysmal AF in the absence of structural heart disease or significant dilatation of the left atrium. While these devices operate mostly using radiofrequency current in monopolar or bipolar fashion, alternative energy sources are available, such as cryothermia, ultrasound, and laser energy. Since no randomized trial data yet exist, superiority over the 'conventional' sequential ablation has not been demonstrated. Potentially causing excessive collateral damage such as atrio-oesophageal fistula formation, all of these devices still have to be shown to be 'safe and simple'.

#### *Right atrial flutter ablation*

Any clinical evidence of common atrial flutter should prompt the placement of a linear lesion to produce bidirectional block in the inferior right atrial isthmus connecting the tricuspid annulus to the inferior caval vein as an additional step during catheter ablation of AF.

#### *Alternative techniques for substrate modification*

Atrial tissue generating **complex fractionated atrial electrograms** (CFAEs) has been ablated, without any attempt to isolate the PVs. While reports from single centres are favourable, prospective randomized trials have not shown benefit. Interestingly, arrhythmia recurrences after such procedures are dominated by arrhythmias originating in the PVs. Several groups have described radiofrequency ablation of **ganglionic plexi** as an add-on to PV isolation. The value of this technique is not yet established.

#### *Complications*

Catheter ablation of AF is associated with significant complications (Table 17).<sup>129–131</sup> Major complications are defined as those that result in permanent injury or death, require intervention for treatment, or prolong or require hospitalization. It must be emphasized that rarer complications with significant sequelae can also occur, especially when using energy sources other than radiofrequency.

#### *Follow-up considerations*

**Anticoagulation.** Initially post-ablation, LMWH or i.v. UFH should be used as a bridge to resumption of systemic anticoagulation, which should be continued for a minimum of 3 months,<sup>136</sup> although some centres do not interrupt anticoagulation for the ablation procedure. Thereafter, the individual stroke risk (see Section 4.1) of the patient should determine whether oral anticoagulation should be continued. Discontinuation of warfarin therapy post-ablation is generally not recommended in patients at risk for stroke (see Section 4.1), as AF is a chronically progressing arrhythmia, especially in patients at risk for stroke (see Section 3).

**Monitoring for atrial fibrillation recurrences.** The assessment of clinical mid- and long-term outcome after AF ablation remains a subject of discussion. Symptom-based follow-up may be sufficient, as symptom relief is the main aim of AF ablation. To obtain information to compare success rates following different procedures and to improve ablation techniques, systematic, standardized ECG monitoring is needed.<sup>3</sup> Expert consensus recommends an initial follow-up visit at 3 months, with 6 monthly intervals thereafter for at least 2 years.<sup>33</sup> The true recurrence rate will be markedly underestimated (see Section 3.4).

#### *Results of meta-analysis and randomized trials of ablation vs. antiarrhythmic medication*

Although medical therapy remains the foundation of the treatment of AF, catheter ablation is assuming an increasingly greater role. A recent meta-analysis found a 77% success rate for catheter ablation strategies vs. 52% for antiarrhythmic medication.<sup>131</sup> Similar results have been reported in other meta-analyses,<sup>134,140,141</sup> 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 (OR 9.74; 95% CI 3.98–23.87;  $P < 0.001$ ).<sup>140</sup>



### Recommendations for surgical ablation of AF

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| Surgical ablation of AF should be considered in patients with symptomatic AF undergoing cardiac surgery.  | IIa                | A                  | 139, 141, 142     |
| Surgical ablation of AF may be performed in patients with asymptomatic AF undergoing cardiac surgery if feasible with minimal risk.   | IIb                | C                  |                   |
| 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. | IIb                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation.

Several prospective multicentre trials have now confirmed the superiority of catheter ablation compared with antiarrhythmic medication. Many patients enrolled in the ablation arms underwent multiple procedures, underlining the current limitations of the procedure. Besides reconnection of previously isolated PVs, iatrogenic atrial re-entrant tachycardia due to incomplete lines of ablation is the major cause of post-ablation arrhythmia, which may require another ablation procedure. Results from ongoing prospective multicentre trials in patient subgroups such as AF in congestive heart failure [e.g. Catheter Ablation versus STandard conventional treatment in patients with LV dysfunction and Atrial Fibrillation (CASTLE-AF), AF Management In Congestive heart failure with Ablation (AMICA)] are still pending. There is no evidence so far that successful AF ablation will result in reduced mortality, but a large prospective worldwide trial is already underway [Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA)]. It is conceivable that AF ablation embedded in a comprehensive rhythm control intervention is most effective and most beneficial when performed early during the course of disease.<sup>23</sup> The clinical benefit of such an 'early rhythm control therapy' is tested in the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST). Both trials are expected to report in 2015.

#### 4.3.5.3 Surgical ablation

AF is an independent risk factor for poor outcome after cardiac surgery and is associated with higher perioperative mortality, particularly in patients with LVEF of >40%.<sup>139</sup> Preoperative AF is a marker for increased surgical risk of mitral repair, and predicts late adverse cardiac events and stroke. Although the independent contribution of AF to late survival is uncertain, restoration of sinus rhythm improves outcome.<sup>139</sup> Compared with catheter-based techniques, surgical ablation can easily achieve complete isolation with transmural lesions and also allows LAA exclusion/excision.

#### Surgical incisions

'Cut-and-sew' techniques are used to isolate the PVs, extending to the mitral annulus, right and LAAs, and coronary sinus. The technique is known as the 'maze procedure' in reference to the complex branching passage through which the sinoatrial node impulse finds a route to the atrioventricular node.

Freedom from AF is 75–95% up to 15 years after the procedure. In patients with mitral valve disease, valve surgery alone is unsuccessful in reducing recurrent AF or stroke, but a concomitant maze procedure produces similar outcomes compared with patients in sinus rhythm and has favourable effects on restoration of effective LA contraction.

The procedure is complex, with risk of mortality and significant complications, and consequently has been sparsely adopted.<sup>143,144</sup> Surgical PV isolation is effective in restoring sinus rhythm in permanent AF associated with mitral valve disease.

#### Alternative energy sources

Alternative energy sources can replicate the maze lines of atrial conduction block without surgical incision, permitting faster and less invasive procedures without need of heart arrest. In small, randomized studies, these techniques demonstrate increased rates of sinus rhythm and walking distance, and reduced plasma brain natriuretic peptide concentrations and stroke rate.<sup>140</sup>

**Radiofrequency:** sinus rhythm is restored in ~85% of cases at 1 year and 52% at 5 years. The duration of AF and the LA size are predictive of recurrence.

**Cryoablation** induces transmural lesions by freezing atrial tissue. Freedom from AF is 87% at 1 year.

**High-intensity focused ultrasound** results in deep heating, coagulation necrosis, and conduction block. Freedom from AF or flutter is 86% at 18 months.

Factors reducing success of the procedure include large LA size, advanced age, longer duration of AF (permanent vs. paroxysmal AF), hypertension, and sleep apnoea.<sup>33</sup>

Other advances, including thoracoscopic access and video assistance, show promise but have not been formally compared against stand-alone surgical treatment of AF.

#### Role of the autonomic nervous system

Ganglionated plexus ablation and vagal denervation are methods for controlling or curing paroxysmal AF. Long-term success is not yet established and initial studies show no advantage over PV isolation alone.

#### Treatment after surgical ablation

Reverse remodelling takes place after surgical ablation and is frequently complicated by arrhythmia. Antiarrhythmic and anticoagulation drugs are continued for at least 3 months and withdrawal is based on clinical, ECG, and echocardiographic assessment at 3-, 6-, and 12-month follow-up.

## 4.4 Upstream therapy

Upstream therapy to prevent or delay myocardial remodelling associated with hypertension, heart failure, or inflammation (e.g. after cardiac surgery) may deter the development of new AF (primary prevention) or, once established, its rate of recurrence or progression to permanent AF (secondary prevention).<sup>143</sup>

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.

#### 4.4.1 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

ACEIs and ARBs inhibit the arrhythmogenic effects of angiotensin II, which include stimulation of atrial fibrosis and hypertrophy, uncoupling gap junctions, impaired calcium handling, alteration of ion channels, activation of mediators of oxidative stress, and promotion of inflammation. There is good experimental evidence of antifibrillatory and antifibrotic actions of ACEIs and ARBs in various AF models.<sup>144,145</sup>

##### Primary prevention

**Congestive heart failure.** Several retrospective analyses from large randomized trials in LV dysfunction and heart failure have reported a lower incidence of new-onset AF in patients treated with ACEIs and ARBs compared with placebo. Several meta-analyses of these studies have shown a significant 30–48% reduction in risk of AF associated with ACEI and ARB therapies.<sup>145–148</sup> This benefit of ACEIs and ARBs is less evident in patients with heart failure and preserved systolic function.<sup>149</sup>

**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.<sup>147</sup> This trend was mainly driven by a marked 33% reduction in the incidence of new-onset AF observed with losartan compared with atenolol (6.8 vs. 10.1 per 1000 person-years) in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study, which enrolled patients with LV hypertrophy.<sup>150</sup> Nevertheless, subsequent reports from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial<sup>151</sup> and two retrospective analyses from administrative databases in the USA and the UK have suggested that ACEI- or ARB-based treatment for hypertension can delay the occurrence of AF, including the usual care setting.

**Cardiovascular risk factors.** The effects are less clear in patients with multiple risk factors including hypertension, diabetes mellitus, coronary artery disease, cerebrovascular disease, PAD, hypercholesterolaemia, etc., such as those enrolled in the Heart Outcomes Prevention Evaluation (HOPE) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials.<sup>143</sup> In these trials, ramipril and telmisartan, respectively, had no protective effect on new-onset AF compared with placebo.

##### Secondary prevention

Several relatively small prospective randomized controlled trials have demonstrated that therapy with ACEIs or ARBs 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.<sup>152,153</sup> Meta-analyses driven by these studies have reported a significant 45–50% reduction in RR of recurrent AF.<sup>145–148</sup> Conversely, a double-blind, placebo-controlled study—Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF)—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.<sup>154</sup>

Evidence to support the use of ACEIs or ARBs in patients with paroxysmal or persistent AF who are not undergoing electrical cardioversion remains controversial. The results of randomized controlled trials in patients with hypertension have pointed to a lower incidence of recurrent paroxysmal AF with ARB- or ACEI-based therapy compared with atenolol or amlodipine or when added to amiodarone.<sup>145</sup> Several relatively small studies have reported some benefit from ACEI/ARB treatment in patients with minor underlying cardiac pathology (mainly hypertension without LV hypertrophy) and paroxysmal or recent-onset persistent AF.<sup>155,156</sup>

However, the largest secondary prevention study, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Atrial Fibrillation (GISSI-AF), in 1442 patients with cardiovascular risk factors (mainly hypertension, 85%) and paroxysmal or recently cardioverted persistent AF, demonstrated no effect of valsartan added on top of optimal medical therapy (including antiarrhythmic drugs and ACEIs) on the primary endpoint of time to first AF recurrence (HR 0.99; 95% CI 0.85–1.15;  $P = 0.84$ ) and the number of patients with more than one AF recurrence (26.9% vs. 27.9%) compared with placebo at 1-year follow-up.<sup>157</sup> There was also no added benefit from valsartan in a small proportion of patients without co-existing cardiovascular disease but with dilated left atria.

The preliminary results of the Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) II study in 318 patients with hypertension and paroxysmal AF showed no benefit of treatment with candesartan compared with amlodipine on the frequency and duration of AF recurrence detected by daily transtelephonic monitoring or progression to persistent AF (8% vs. 14%) during 1 year of follow-up. Retrospective analyses have found no beneficial effect of therapy with ACEIs or ARBs on recurrent AF after PV ablation.

##### Effects on major cardiovascular outcomes

An important observation from the LIFE study was that, compared with atenolol, losartan-based therapy improved major cardiovascular outcomes in patients with AF. Thus, the occurrence of the primary composite endpoint of cardiovascular mortality, stroke, and myocardial infarction was reduced by 42%, as were its components (42% reduction in cardiovascular death and 45% reduction in stroke), and there was a trend towards lower all-cause mortality. However, neither the VALUE<sup>151</sup> nor the GISSI-AF<sup>157</sup> study has shown improved outcome with ARB-based therapy compared with amlodipine or placebo. In the Atrial fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events—Irbesartan arm (ACTIVE I) in 9016 patients with AF and risk factors, therapy with irbesartan did not reduce the primary composite endpoint of stroke, myocardial infarction, and vascular death, but significantly reduced hospitalizations for heart failure.

In summary, there is a sustained reduction in new-onset AF in patients with significant underlying heart disease (e.g. LV dysfunction and hypertrophy) treated with ACEIs or ARBs, but evidence is less robust in patients with moderate structural heart disease and

recurrent AF. No superiority of one class of renin–angiotensin–aldosterone system inhibitors over another has been convincingly demonstrated.<sup>146,147,155</sup> The antiarrhythmic effect of ACEIs and ARBs on AF either as a primary endpoint or as part of larger mortality and morbidity studies will be assessed in several ongoing trials.

**4.4.2 Aldosterone antagonists**

Patients with primary hyperaldosteronism have a 12-fold higher risk of developing AF than their matched counterparts with essential hypertension. Increased aldosterone levels have been reported in patients with AF. Pre-treatment with spironolactone in a dog AF model reduced the amount of atrial fibrosis and inducibility of AF. The role of aldosterone antagonists has not been specifically studied in humans, but preliminary data suggest that spironolactone reduces the incidence of recurrent AF after electrical cardioversion in patients with hypertension and mild LV dysfunction. Several trials with spironolactone and eplerenone are ongoing.

**4.4.3 Statins**

Inflammation can be a key mechanism for some forms of AF. Increased levels of C-reactive protein and inflammatory cytokines (interleukin-1β and 6, and tumour necrosis factor-α) in patients with new-onset or recurrent AF have been reported in epidemiological and observational studies.

**Recommendations for primary prevention of AF with ‘upstream’ therapy**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| ACEIs and ARBs should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.                           | IIa                | A                  | 145–149           |
| ACEIs and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with left ventricular hypertrophy.          | IIa                | B                  | 147, 150, 151     |
| Statins should be considered for prevention of new-onset AF after coronary artery bypass grafting, isolated or in combination with valvular interventions. | IIa                | B                  | 161, 162          |
| Statins may be considered for prevention of new-onset AF in patients with underlying heart disease, particularly heart failure.                            | IIb                | B                  | 164, 165          |
| Upstream therapies with ACEIs, ARBs, and statins are not recommended for primary prevention of AF in patients without cardiovascular disease.              | III                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker.

**Recommendations for secondary prevention of AF with ‘upstream’ therapy**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| Pre-treatment with ACEIs and ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion <i>and</i> receiving antiarrhythmic drug therapy.   | IIb                | B                  | 145–147, 152–153  |
| ARBs or ACEIs may be useful for prevention of recurrent paroxysmal AF or in patients with persistent AF in the absence of significant structural heart disease if these agents are indicated for other reasons (e.g. hypertension). | IIb                | B                  | 145, 155–156      |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker.

The preventive effect of statins on AF is thought to be the net benefit derived from improvement of lipid metabolism and prevention of process of atherosclerosis, anti-inflammatory and antioxidant actions, reduction of endothelial dysfunction and neurohormonal activation, altered membrane fluidity, and ion channel conductance.<sup>158</sup> Statins are employed in regulating the variety of metalloproteinases, the effect that may play the role in regulating structural remodelling associated with AF, e.g. dilatation and fibrosis. In animal models of AF, statins have been demonstrated to attenuate electrical and structural atrial remodelling and reduce inducibility of AF.<sup>159</sup>

*Primary prevention*

High-quality studies of statins in AF are sparse, and most evidence comes from the observational studies and retrospective analyses.<sup>159</sup> Some studies, particularly in patients with LV dysfunction and heart failure, have shown a 20–50% reduction in the incidence of new-onset AF, but reports in patients with hypertension, coronary artery disease, and ACS were less consistent, although the overall trend was in favour of statin use.<sup>159</sup> There is evidence that statins may reduce the occurrence of AF in patients with permanent pacemakers by 57%, but the studies were retrospective and too small to support the use of statins specifically for prevention of AF in pacemaker patients.<sup>160</sup>

**Post operative atrial fibrillation.** Several retrospective, observational, and randomized controlled studies,<sup>159</sup> including the Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3) trial<sup>161</sup> and a recent systematic review,<sup>162</sup> have reported a lower incidence of post-operative AF in association with statin therapy. However, several large retrospective analyses reported no reduction in the incidence of post-operative AF and even hinted at their proarrhythmic potential. Nevertheless,

with all studies in the surgical setting pooled together (three randomized controlled trials and 10 observational studies including a total of 17 643 patients), the OR for any AF was 0.78 (95% CI 0.67–0.90;  $P < 0.001$ ) and 0.66 (95% CI 0.51–0.84;  $P < 0.001$ ) for new-onset AF in favour of statins.<sup>162</sup> A dose-dependent effect of statins was observed.

#### Secondary prevention

Statins have been reported to be more effective for prevention of paroxysmal AF or recent-onset AF than in patients with recurrent persistent AF or after LA ablation.<sup>159</sup> Randomized controlled trials showed no benefit from statin therapy after cardioversion.<sup>163</sup> Consequently, meta-analyses of the efficacy of statins in prevention of AF in different clinical settings have yielded different results depending on the type of studies and study populations.<sup>164,165</sup> The greatest effect was seen in earlier, observational studies.

In summary, evidence in support of the use of statins for primary or secondary prevention of AF, except for post-operative AF, is insufficient to produce any robust recommendation. There is as yet no consensus regarding the intensity and duration of treatment and type of statins.

#### 4.4.4 Polyunsaturated fatty acids

Omega-3 or *n*-3 PUFAs (mainly eicosapentaenoic acid and docosahexaenoic acid) are universal constituents of biological membranes, where they produce a stabilizing effect, counteract stretch-induced shortening of cardiac refractoriness, reduce membrane fluorescence anisotropy by increasing membrane fluidity, and reduce oxidative stress.<sup>161</sup> In addition, PUFAs produce direct electrophysiological effects on several ion channels, including the sodium and ultra-rapid potassium currents, and the sodium–calcium exchanger. In experiments, PUFAs reduced atrial electrical remodelling and attenuated structural changes in the atria.<sup>159</sup>

#### Primary prevention

**General population.** Reports from epidemiological studies have been controversial.<sup>159</sup> While the Cardiovascular Health Study and Kuopio Ischaemic Heart Disease Risk Factor Study have reported significant reductions in risk of AF by 30–35% associated with greater intake of PUFAs, other large, population-based studies failed to reproduce these results. There is limited evidence to suggest that the preventive effect on AF may depend on the use of a specific acid, e.g. docosahexaenoic acid.

**Post-operative AF.** Although the initial reports from two open-label studies have suggested that treatment with PUFAs was associated with a significantly lower incidence of AF after coronary artery bypass grafting, these results have not been reproduced in double-blind, placebo-controlled, randomized controlled trials.<sup>166,167</sup> There was no difference in time spent in AF and length of hospital stay between groups.

#### Secondary prevention

There is limited evidence of the efficacy of PUFAs in secondary prevention in AF, and the results are controversial. One retrospective analysis has shown that the use of PUFA supplements was

associated with a lower incidence of AF recurrence after PV isolation. The preliminary results from two small size randomized controlled trials have demonstrated no effect of treatment with PUFAs starting 1–4 weeks before electrical cardioversion on the subsequent recurrence rate during 6 months to 1-year follow-up. Several prospective, randomized clinical trials are under way. At present, there is no robust evidence to make any recommendation for the use of PUFAs for primary or secondary prevention of AF.

### Recommendations for rate control during AF with heart failure

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup>  |
|--|--------------------|--------------------|--------------------|
| β-Blockers are recommended as first-line therapy to control the ventricular rate in patients with heart failure and low LVEF.  | I                  | A                  | 169, 171           |
| Where monotherapy is inadequate for heart rate control, digoxin should be added.   | I                  | B                  | 171, 172           |
| In haemodynamically unstable patients with acute heart failure and low LVEF, amiodarone is recommended as the initial treatment.   | I                  | B                  | 173                |
| If an AP is excluded, digoxin is recommended as an alternative to amiodarone to control the heart rate in patients with AF and acute systolic heart failure.   | I                  | C                  |                    |
| AV node ablation should be considered to control the heart rate when other measures are unsuccessful or contraindicated in patients with permanent AF and an indication for CRT (NYHA class III–IV, LVEF ≤35%, and QRS width ≥130 ms). | IIa                | B                  | 105, 109, 110, 174 |
| In patients with heart failure and preserved LVEF, a non-dihydropyridine calcium channel antagonist may be considered.   | IIb                | C                  |                    |
| A β-blocker may be considered as an alternative to a non-dihydropyridine calcium channel antagonist in heart failure with preserved ejection fraction.   | IIb                | C                  |                    |
| A non-dihydropyridine calcium channel antagonist is not recommended to control the heart rate in patients with systolic heart failure.   | III                | C                  |                    |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; AP = accessory pathway; AV = atrioventricular; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.



## 5. Specific populations

### 5.1 Heart failure

Several mechanisms operating in heart failure can predispose to AF by creating either a substrate or a trigger for this arrhythmia.<sup>44,168</sup> AF constitutes a strong and independent risk factor for the development of heart failure, and both conditions frequently co-exist,<sup>44</sup> partly because of common risk factors.

Development 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:<sup>44</sup>

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

#### Recommendations for rhythm control of AF in heart failure

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup>   |
|---|--------------------|--------------------|---------------------|
| DCC 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. | I                  | C                  |                     |
| In patients with AF and severe (NYHA class III or IV) or recent ( $\leq 4$ weeks) unstable heart failure, the use of antiarrhythmic therapy to maintain sinus rhythm should be restricted to amiodarone.          | I                  | C                  |                     |
| Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF, or to facilitate electrical cardioversion of AF.   | IIa                | B                  | 46, 74, 80, 175     |
| In patients with AF and stable heart failure (NYHA class I, II) dronedarone should be considered to reduce cardiovascular hospitalizations.   | IIa                | C                  |                     |
| For patients with heart failure and symptomatic persistent AF despite adequate rate control, electrical cardioversion and rhythm control may be considered.   | IIb                | B                  | 90, 93, 94, 97, 176 |
| Catheter ablation (pulmonary vein isolation) may be considered in heart failure patients with refractory symptomatic AF.  | IIb                | B                  | 93, 94              |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; DCC = direct current cardioversion; NYHA = New York Heart Association.

As in other conditions in which ventricular rate control is required,  $\beta$ -adrenoreceptor 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  $\beta$ -blocker may be more effective than a single drug for heart-rate control at rest. Therapy with  $\beta$ -blockers alone or in combination with digoxin was associated with lower mortality rates compared with treatment with digoxin alone.<sup>169</sup>  $\beta$ -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  $\beta$ -blockers.<sup>170</sup>

Although diltiazem effectively controls excessive heart rate during exercise, it adversely suppresses myocardial contraction and increases the risk of heart failure. Nonetheless, 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.<sup>90</sup> 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 4.3.5.3).<sup>93,94</sup>

The prevention of thrombo-embolism is covered in Section 4.1, 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.

### 5.2 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.<sup>177,178</sup> There are increasing data showing that AF is 2–10 times more prevalent in active or former competitive athletes and those performing intense recreational endurance sports.<sup>179,180</sup> 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). The role of performance-enhancing drugs is largely unknown.

The therapeutic goal of rate control is difficult to reach in athletes:  $\beta$ -blockers are not well tolerated (or are even 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 sodium channel-blocking drugs as monotherapy in athletes with AF.<sup>181</sup> These drugs may lead to (slow) 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.



**Recommendations for AF in athletes**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| 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. | <b>IIa</b>         | <b>C</b>           |                   |
| Isthmus ablation should be considered in competitive or leisure-time athletes with documented atrial flutter, especially when therapy with flecainide or propafenone is intended.  | <b>IIa</b>         | <b>C</b>           |                   |
| Where appropriate, AF ablation should be considered to prevent recurrent AF in athletes.   | <b>IIa</b>         | <b>C</b>           |                   |
| 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.                       | <b>III</b>         | <b>C</b>           |                   |
| It is not recommended to allow physical sports activity when symptoms due to haemodynamic impairment (such as dizziness) are present.  | <b>III</b>         | <b>C</b>           |                   |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation.

Continuation of drug therapy for AF will often be required despite successful ablation ('hybrid therapy').

In some athletes with paroxysmal AF, flecainide or propafenone can be used for acute conversion (the 'pill-in-the-pocket' approach; see Section 4.2.1.2).<sup>67</sup> 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. In others, non-pharmacological options such as catheter ablation can be considered.<sup>182</sup>

Anticoagulation may be necessary depending on the presence of risk factors for thrombo-embolic events (see Section 4.1). However, anticoagulation cannot be used in individuals participating in sporting activities with a risk of bodily collision.

**5.3 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.<sup>64</sup> 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.

**Recommendations for AF in valvular heart disease**

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| OAC therapy (INR 2.0–3.0) is indicated in patients with mitral stenosis and AF (paroxysmal, persistent, or permanent).   | <b>I</b>           | <b>C</b>           |                   |
| OAC therapy (INR 2.0–3.0) is recommended in patients with AF and clinically significant mitral regurgitation.  | <b>I</b>           | <b>C</b>           |                   |
| 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. | <b>IIa</b>         | <b>C</b>           |                   |
| 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.        | <b>IIa</b>         | <b>C</b>           |                   |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation; INR = international normalized ratio; LA = left atrial; LV = left ventricular; OAC = oral anticoagulant.

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 4.1).

**5.4 Acute coronary syndromes**

AF occurs in 2–21% of patients with ACS.<sup>49</sup> The widespread use of PCI, especially during the acute phase, has been associated with a decline in the incidence of AF. Similarly, the use of ACEIs, ARBs, or β-blockers early after acute myocardial infarction has probably reduced the incidence of AF.<sup>49</sup> AF is more commonly associated with ACS in older patients and those with heart failure, higher heart rates on admission, and LV dysfunction, and is independent of the mode of reperfusion therapy (none, thrombolysis, or PCI).<sup>49</sup> AF complicating ACS is associated with increased in-hospital and long-term mortality, and increases the risk of ischaemic stroke during hospitalization and follow-up. Specific recommendations for the management of patients with AF in the setting of ACS are based primarily on consensus, since adequate trial data do not exist.

Urgent DCC may be considered in ACS patients presenting with AF and intractable ischaemia or haemodynamic instability. I.v. β-blocker or non-dihydropyridine calcium antagonist therapy may be indicated for rate control in patients with ACS to reduce

**Recommendations for AF in acute coronary syndrome**

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| DCC is recommended for patients with severe haemodynamic compromise or intractable ischaemia, or when adequate rate control cannot be achieved with pharmacological agents in patients with ACS and AF.                   | I                  | C                  |                   |
| Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF in patients with ACS.  | I                  | C                  |                   |
| Intravenous β-blockers are recommended to slow a rapid ventricular response to AF in patients with ACS.   | I                  | C                  |                   |
| 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. | IIa                | C                  |                   |
| Intravenous administration of digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with heart failure.   | IIb                | C                  |                   |
| Administration of flecainide or propafenone is not recommended in patients with AF in the setting of ACS.   | III                | B                  | 124               |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation, ACS = acute coronary syndrome; DCC = direct current cardioversion.

myocardial oxygen demand. Digoxin and/or i.v. amiodarone is an appropriate alternative for patients with ACS associated with severe LV dysfunction and heart failure. For details on anticoagulation management of AF patients with ACS, as well as recommendations, see Section 4.1.

**5.5 Diabetes mellitus**

Diabetes and AF frequently co-exist because of associations such as coronary artery disease, hypertension, and LV dysfunction, and possibly as a result of autonomic dysfunction and ion channelopathy. Community studies demonstrate the presence of diabetes in 13% of patients with AF. Diabetes is an independent risk factor (RR 1.4–1.8) for incident AF. The presence of diabetes confers an adverse prognosis in AF with an increase in death and cardiovascular events. A comprehensive approach to risk management, including blood pressure control, statin therapy, etc., is desirable. The significance of diabetes is recognized in each of the major stroke

**Recommendations for diabetes mellitus**

| Recommendation   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| AF patients with diabetes are recommended to undergo full assessment and management of all cardiovascular risk factors, including blood pressure, lipids, etc. | I                  | C                  |                   |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation.

risk stratification schemes, and antithrombotic therapy is recommended in diabetic subjects (see Section 4.1).

**5.6 The elderly**

The prevalence of AF is ~10% at the age of 80 years, and 18% in those aged ≥85 years. In the primary care setting, the Screening for AF in the Elderly (SAFE) study<sup>43</sup> found that opportunistic screening by the general practitioner, followed by an ECG when the pulse was irregular, is as effective as systematic screening with an ECG.

All patients aged >75 years with AF have an individual yearly risk of thrombo-embolism >4%, a level above which prescription of a VKA is preferred unless there is too high a bleeding risk. Of the individual components of the CHADS<sub>2</sub> score, age ≥75 carries a worse prognosis for stroke and mortality, over hypertension, diabetes, or heart failure (see the CHA<sub>2</sub>DS<sub>2</sub>VASc score in Section 4.1.1).

In general, VKA treatment is reasonably tolerated in the elderly.<sup>56</sup> Randomized controlled trials with VKA in AF have shown sustained reductions in ischaemic stroke and cardiovascular events, with only a slight increase in serious bleeds, resulting in a clear positive net effect of VKA in the elderly, compared with aspirin. In contrast, the beneficial effect of antiplatelet therapy on ischaemic stroke appears to decrease with age and was no longer apparent at the age of 77 years (see Section 4.1 for recommendations).

DCC is little used in the elderly because sinus rhythm is often difficult to maintain.<sup>183</sup> For rate control, β-blockers and non-

**Recommendations for AF in the elderly**

| Recommendation   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| Every patient aged 65 years and older who attends their general practitioner should be screened by checking the pulse, followed by an ECG in case of irregularity. | I                  | B                  | 43                |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 ECG = electrocardiogram.

dihydropyridine calcium channel antagonists are effective.  $\beta$ -Blockers can be used cautiously for elderly patients with COPD.

An elderly patient with AF differs considerably from younger patients:

- Fragile, multiple co-morbidities, including cardiovascular and non-cardiac disease.
- High incidence and prevalence rates of AF.
- Higher thrombo-embolic and bleeding risks.
- Most often permanent and not recurrent (paroxysmal and/or persistent) AF.
- Atypical symptoms and complaints are common.
- Less sensitive to sympathetic effects on ventricular response rates in AF ('aged' conduction system).
- More sensitive to proarrhythmic effects of drugs (decreased renal and hepatic function).
- More often underdiagnosed than in younger patients.

### 5.7 Pregnancy

AF is rare during pregnancy in women without previously detected AF and without pre-existing heart disease. In patients with previously diagnosed AF, 52% experienced new episodes during pregnancy; in addition more foetal complications occur in those women who develop arrhythmias during pregnancy. AF during pregnancy is well tolerated in most patients without congenital or valvular disease.

#### Rate control drugs

$\beta$ -Blockers cross the placenta and are associated with various adverse effects including intra-uterine growth retardation, neonatal respiratory depression, bradycardia, and hypoglycaemia, especially if treatment is initiated early in pregnancy (i.e. 12–24 weeks). In pregnancies complicated by hypertension and treated with propranolol, no congenital anomalies were seen,<sup>184</sup> but growth retardation has been reported. Atenolol given in the first trimester, but not later, has been associated with foetal growth retardation. A meta-analysis in patients with hypertension assessing risks of  $\beta$ -receptor blockers in pregnancy found a borderline increase in 'small for gestational age' infants. Digoxin crosses the placenta freely, and digitalis intoxication in the mother has been associated with foetal death. Limited data exist for verapamil and diltiazem, but oral use for rate control is generally safe.

#### Drugs for atrial fibrillation conversion

Flecainide has been used for converting foetal arrhythmias without negative effects. Amiodarone has demonstrated negative foetal effects when used in pregnant women, and should only be used in urgent situations. All drugs should, if possible, be avoided during the period of organogenesis in the first trimester of pregnancy.

#### Direct current cardioversion

Several case reports have demonstrated successful cardioversion of maternal AF, without harm to the foetus. Energy requirements in pregnant and non-pregnant women are similar.

#### Anticoagulation

VKA can be teratogenic and in many cases should be substituted with UFH or LMWH for the first trimester.<sup>185</sup> In one systematic review, foetal malformations associated with warfarin occurred in

6.4% of cases when given throughout the pregnancy, compared with no events when the treatment was changed to heparins between weeks 6 and 12. Warfarin crosses the placenta freely, and the foetus may be overdosed even when the mother is in the therapeutic INR range.

#### Recommendations for AF in pregnancy

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| DCC 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.  | I                  | C                  |                   |
| Protection against thrombo-embolism is recommended throughout pregnancy in AF patients with a high thrombo-embolic risk; the choice of agent (heparin or warfarin) should be made according to the stage of pregnancy.   | I                  | C                  |                   |
| Administration of an oral VKA is recommended from the second trimester, until 1 month before expected delivery.  | I                  | B                  | 185               |
| Subcutaneous administration of LMWH in weight-adjusted therapeutic doses is recommended during the first trimester and during the last month of pregnancy. Alternatively, UFH may be given, to prolong the activated partial thromboplastin time to 1.5 times the control. | I                  | B                  | 185               |
| If rate control is necessary, a $\beta$ -blocker or a non-dihydropyridine calcium channel antagonist should be considered. During the first trimester of pregnancy, the use of $\beta$ -blockers must be weighed against the potential risk of negative foetal effects.    | IIa                | C                  |                   |
| In haemodynamically stable patients with structurally normal hearts, flecainide or ibutilide given intravenously to terminate recent-onset AF may be considered, if arrhythmia conversion is mandatory and DCC considered inappropriate.                                   | IIb                | C                  |                   |
| If rate control is indicated, and $\beta$ -blockers or non-dihydropyridine calcium channel antagonists are contraindicated, digoxin may be considered.   | IIb                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; DCC = direct current cardioversion; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

LMWH does not cross the placenta barrier, and has been used extensively for treatment and prophylaxis of venous thrombo-embolism during pregnancy, without adverse foetal effects. In the third trimester, frequent laboratory checks for adequate anticoagulation (e.g. every 10–14 days) and corresponding dose adjustments are advised, given that in some women high doses of both VKA and heparin may be needed to maintain adequate anticoagulation.

Pregnant patients with AF and mechanical prosthetic valves who elect to stop VKA treatment between 6 and 12 weeks of gestation should receive continuous i.v. UFH, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH, and may start VKA in the second trimester at an only slightly elevated teratogenic risk.

## 5.8 Post-operative atrial fibrillation

AF is the most common complication after cardiac surgery [30% after coronary artery bypass graft (CABG), 40% after valve surgery, and 50% after combined CABG/valve surgery]. The peak incidence of post-operative AF is between post-operative days 2 and 4. A systematic review of 58 studies in 8565 patients has shown that interventions to prevent and/or treat post-operative AF with  $\beta$ -blockers, sotalol, or amiodarone and, less convincingly, atrial pacing, are favoured with respect to outcome (AF, stroke, and length of hospital stay) (OR 0.43; 95% CI 0.37–0.51).<sup>186</sup>

### Prevention of post-operative atrial fibrillation

**$\beta$ -Blocker** therapy is most effective when provided both before and after cardiac surgery compared with only before or after surgery.<sup>186,187,196</sup> Withdrawal of  $\beta$ -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  $\beta_1$ -blocker without intrinsic sympathomimetic activity.

Prophylactic **amiodarone** decreased the incidence of post-operative AF (OR 0.50; 95% CI 0.42–0.59) and significantly shortened the duration of hospital stay, and reduced the incidence of stroke and post-operative ventricular tachyarrhythmia, but not post-operative mortality.<sup>188</sup> AF occurred in fewer amiodarone-treated patients than placebo-treated patients (OR 0.52; 95% CI 0.34–0.69), in patients aged <65 or  $\geq$ 65 years, with CABG only or in valve surgery with or without CABG, and in patients receiving pre-operative  $\beta$ -blockers and in patients who did not receive them. The adverse effects of perioperative prophylactic i.v. amiodarone include an increased probability of post-operative bradycardia and hypotension.<sup>189</sup> A meta-analysis of 14 randomized controlled trials failed to identify any relationship between post-operative AF suppression and the total dose of amiodarone.<sup>190</sup> The beneficial effect of amiodarone has been consistently demonstrated in another systematic review.<sup>186</sup>

**Sotalol** has been reported to reduce the incidence of post-operative AF by 64% compared with placebo, but it had no impact on length of hospital stay, risk of strokes, or mortality.<sup>186</sup> 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.

Hypomagnesaemia is an independent risk factor for post-operative AF. A meta-analysis of 20 randomized trials including 2490 patients showed that prophylactic **i.v. magnesium** reduced the probability of post-operative AF (OR 0.54; 95% CI 0.38–0.75).<sup>191</sup> The clinical impact is not well established.

## Recommendations for post-operative AF

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| Oral $\beta$ -blockers are recommended to prevent post-operative AF for patients undergoing cardiac surgery in the absence of contraindications.                    | I                  | A                  | 186, 187          |
| If used, $\beta$ -blockers (or other oral antiarrhythmic drugs for AF management) are recommended to be continued until the day of surgery.                         | I                  | B                  | 187, 196          |
| Ventricular rate control is recommended in patients with AF without haemodynamic instability.   | I                  | B                  | 196               |
| Restoration of sinus rhythm by DCC is recommended in patients who develop post-operative AF and are haemodynamically unstable.                                      | I                  | C                  |                   |
| Pre-operative administration of amiodarone should be considered as prophylactic therapy for patients at high risk for post-operative AF.                            | IIa                | A                  | 186–188           |
| Unless contraindicated, antithrombotic/anticoagulation medication for post-operative AF should be considered when the duration of AF is $\geq$ 48 h.                | IIa                | A                  | 195               |
| 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. | IIa                | B                  | 195               |
| Antiarrhythmic medications should be considered for recurrent or refractory postoperative AF in an attempt to maintain sinus rhythm.                                | IIa                | C                  |                   |
| Sotalol may be considered for prevention of AF after cardiac surgery, but is associated with risk of proarrhythmia.   | IIb                | A                  | 186               |
| Biatrial pacing may be considered for prevention of AF after cardiac surgery.   | IIb                | A                  | 186               |
| Corticosteroids may be considered in order to reduce the incidence of AF after cardiac surgery, but are associated with risk.                                       | IIb                | B                  | 192               |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; DCC = direct current cardioversion.

The use of **statins** is associated with a 22–34% lower risk of post-operative AF (see Section 4.4).

Several retrospective studies have reported no effect of **ACEIs** and **ARBs** on the occurrence of AF following cardiac surgery. There are also safety concerns about the potential risk of renal dysfunction associated with ACEIs and ARBs early after surgery.

**Corticosteroids** have potent anti-inflammatory effects and their use in AF prevention has been explored in the context of cardiothoracic surgery. Meta-analyses demonstrated that corticosteroid therapy was associated with a 26–45% reduction in post-operative AF and shorter hospital stay.<sup>192</sup> The effect was greater in patients receiving intermediate doses (50–210 mg dexamethasone equivalent) compared with patients on lower or higher doses. Owing to potential adverse effects on glucose metabolism, wound healing, and infection, their use for prevention of AF is 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 (OR 0.57; 95% CI 0.38–0.84;  $P < 0.005$ ),<sup>186</sup> but other studies failed to confirm this.<sup>193</sup> Malfunctioning atrial leads or inappropriate sensing may result in proarrhythmic atrial extra-stimulation that increases the probability of AF.

*Other therapies*

Agents that have been studied in small populations with controversial results include digoxin, verapamil, diltiazem, and naproxen.

*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.<sup>194</sup>

In the highly symptomatic patient or when rate control is difficult to achieve, cardioversion may be performed. DCC is 95% successful but pharmacological cardioversion is more commonly used. Amiodarone and ibutilide were shown to be more effective than placebo in converting post-operative AF to sinus rhythm (section 4.2.1.3).

Short-acting  $\beta$ -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.<sup>195</sup> Standard precautions regarding anticoagulation pericardioversion should be used (see Section 4.1).

### 5.9 Hyperthyroidism

AF occurs in 10–25% of patients, with hyperthyroidism especially in men and the elderly. Treatment is aimed primarily at restoring a euthyroid state, which may be associated with a spontaneous reversion to sinus rhythm. If a rhythm control strategy is selected, thyroid function should be normalized prior to cardioversion to reduce the risk of recurrence. Antiarrhythmic drugs and DCC are generally unsuccessful whilst thyrotoxicosis persists.

$\beta$ -Blockers may be effective in controlling the ventricular rate, and i.v.  $\beta$ -blockers are useful in cases of thyroid storm, when high doses may be required. Non-dihydropyridine calcium channel antagonists, such as diltiazem and verapamil, are alternatives.

Despite lack of specific evidence, OAC therapy is recommended for prevention of systemic embolism, in the presence of risk

### Recommendations for AF in hyperthyroidism

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| In patients with active thyroid disease, antithrombotic therapy is recommended based on the presence of other stroke risk factors.   | I                  | C                  |                   |
| Administration of a $\beta$ -blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.   | I                  | C                  |                   |
| When a $\beta$ -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. | I                  | C                  |                   |
| 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.  | I                  | C                  |                   |
| Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.   | I                  | C                  |                   |

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 AF = atrial fibrillation.

factors for stroke. It remains controversial whether patients with AF associated with previous (treated) thyrotoxicosis are at increased risk of thrombo-embolism, in the absence of risk factors.

The occurrence of hyperthyroidism (as well as asymptomatic changes in thyroid function tests) 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; and 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.

### 5.10 Wolff–Parkinson–White syndrome

Since most APs lack the decremental conduction properties of the atrioventricular node, patients with overt pre-excitation and AF are at risk of frequent 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 4.3.3.



### Recommendations for AF in Wolff-Parkinson-White syndrome

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| Catheter ablation of an overt AP in patients with AF is recommended to prevent SCD.   | I                  | A                  | 30                |
| Immediate referral to an experienced ablation centre for catheter ablation is recommended for patients who survived SCD and have evidence of overt AP conduction.             | I                  | C                  |                   |
| 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. | I                  | B                  | 30                |
| 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.                                | I                  | B                  | 198               |
| Asymptomatic patients with evidence of an overt AP should be considered for catheter ablation of the AP only after a full explanation and careful counselling.                | IIa                | B                  | 198               |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; AP = accessory pathway; ECG = electrocardiogram; SCD = sudden cardiac death.

#### 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. A number of markers identify patients at increased risk, including: shortest pre-excited RR interval <250 ms during spontaneous or induced AF, a history of symptomatic tachycardia, the presence of multiple APs, or Ebstein's anomaly.

Pre-excited tachycardias occurring in patients with other supra-ventricular arrhythmias such as atrial tachycardia or atrial flutter with a bystander AP may present with a one-to-one conduction over the AP, resulting in rapid ventricular activation with the risk of degeneration into VF.

Since the efficacy of catheter ablation of APs is ~95%, this is the management of choice for patients with evidence of antegrade AP conduction and AF.<sup>30</sup> 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, and implantation of an implantable cardioverter-defibrillator after successful ablation is not required. 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).<sup>197</sup> Most patients with asymptomatic pre-excitation have a good prognosis; SCD is rarely the first manifestation of the disease. Approximately 20% of asymptomatic patients will demonstrate a rapid ventricular rate during AF induced during electrophysiological testing. During follow-up very few patients develop symptomatic arrhythmias, or SCD. 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 counselling of the patient (and family) about the natural course and the risk of SCD versus the risk of an ablation procedure.

### 5.11 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%. AF is the major determinant of clinical deterioration. Electrical or pharmacological cardioversion is indicated in the absence of atrial thrombus in patients presenting with acute onset AF.

Amiodarone may be the most effective agent for reducing the occurrence of paroxysmal AF and for preventing recurrence. The value of dronedarone is unknown. Disopyramide combined with a  $\beta$ -blocker has additional value in reducing the outflow tract gradient. In chronic AF, rate control can usually be achieved with  $\beta$ -blockers and verapamil. Atrioventricular nodal ablation with permanent ventricular pacing (to promote late septal

### Recommendations for AF in hypertrophic cardiomyopathy

| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|--|--------------------|--------------------|-------------------|
| Restoration of sinus rhythm by DCC or pharmacological cardioversion is recommended in patients with HCM presenting with recent-onset AF.                                     | I                  | B                  | 200               |
| OAC therapy (INR 2.0–3.0) is recommended in patients with HCM who develop AF unless contraindicated.   | I                  | B                  | 200               |
| Amiodarone (or alternatively, disopyramide plus $\beta$ -blocker) should be considered in order to achieve rhythm control and to maintain sinus rhythm in patients with HCM. | IIa                | C                  |                   |
| Catheter ablation of AF should be considered in patients with symptomatic AF refractory to pharmacological control.  | IIa                | C                  |                   |
| Ablation procedures (with concomitant septal myectomy if indicated) may be considered in patients with HCM and refractory AF.  | IIa                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; DCC = direct current cardioversion; HCM = hypertrophic cardiomyopathy; INR = international normalized ratio.

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 use of radiofrequency catheter ablation for refractory, symptomatic AF in HCM despite medical treatment with various antiarrhythmic agents including amiodarone resulted in 67% of patients being in sinus rhythm, with marked improvement in NYHA functional class in over 3 years post procedure.

Few data exist regarding surgical ablation of AF in patients with HCM. The largest series concerns 10 patients who underwent the maze-III procedure combined with myectomy when LV outflow tract obstruction was present. There was no increase in operative mortality and a high proportion of patients remained in sinus rhythm over a mean follow-up of 15 months.<sup>199</sup> Despite conflicting data, there seems to be an overall beneficial effect of myectomy in reducing the burden of AF in HCM patients.

The decision to implant a cardioverter-defibrillator in patients with AF should be undertaken with caution since it is associated with a higher risk of inappropriate shocks, especially in the first year following implantation.

### 5.12 Pulmonary disease

AF is common in patients with chronic lung disease and has adverse prognostic implications in the context of acute exacerbations associated with hypoxia. Treatment of the underlying pulmonary disease and correction of metabolic imbalance are the primary considerations, as antiarrhythmic therapy and electrical cardioversion are likely to be ineffective until respiratory decompensation has been corrected. Multifocal atrial tachycardia is common in severe COPD and may be mistaken for AF.

Agents used to relieve bronchospasm, notably theophyllines and β-adrenergic agonists, may precipitate AF, and controlling the rate of ventricular response may be difficult in this situation. Non-selective β-blockers, sotalol, propafenone, and adenosine are generally contraindicated in patients with bronchospasm, and non-dihydropyridine calcium channel antagonists are the preferred alternative. β-1 selective blockers (e.g. bisoprolol) in small doses

#### Recommendations for AF in pulmonary disease

| Recommendations   | Class <sup>a</sup> | Level <sup>b</sup> | Ref. <sup>c</sup> |
|---|--------------------|--------------------|-------------------|
| Correction of hypoxaemia and acidosis is recommended initial management for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease.           | I                  | C                  |                   |
| DCC should be attempted in patients with pulmonary disease who become haemodynamically unstable as a consequence of AF.   | I                  | C                  |                   |
| A non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) should be considered to control the ventricular rate in patients with obstructive pulmonary disease who develop AF. | IIa                | C                  |                   |
| β-1 selective blockers (e.g. bisoprolol) in small doses should be considered as an alternative for ventricular rate control.  | IIa                | C                  |                   |
| Theophylline and β-adrenergic agonist agents are not recommended in patients with bronchospastic lung disease who develop AF.   | III                | C                  |                   |
| Non-selective β-blockers, sotalol, propafenone, and adenosine are not recommended in patients with obstructive lung disease who develop AF.   | III                | C                  |                   |

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>References.

AF = atrial fibrillation; DCC = direct current cardioversion.

are often tolerated and effective. Intravenous flecainide may be used to restore sinus rhythm, and DCC should be considered in those who are haemodynamically unstable. In resistant cases, atrio-ventricular nodal ablation and ventricular pacing may be necessary to control the ventricular rate.



The CME text 'Guidelines on the management of atrial fibrillation' is accredited by the European Board for Accreditation in Cardiology (EBAC). EBAC works according to the quality standards of the European Accreditation Council for Continuing Medical Education (EACCME), which is an institution of the European Union of Medical Specialists (UEMS). In compliance with EBAC/EACCME guidelines, all authors participating in this programme have disclosed potential conflicts of interest that might cause a bias in the article. The Organizing Committee is responsible for ensuring that all potential conflicts of interest relevant to the programme are declared to the participants prior to the CME activities.

CME questions for this article are available at: *European Heart Journal* [http://cme.oxfordjournals.org/cgi/hierarchy/oupme\\_node;ehj](http://cme.oxfordjournals.org/cgi/hierarchy/oupme_node;ehj) and European Society of Cardiology <http://www.escardio.org/guidelines>.



Most of the statements in these clinical practice guidelines are supported by published evidence. Only a minority of the publications that support the written text can be listed in the following abridged reference list of the guidelines. A full list of the references, sorted by chapter, is available on the dedicated Atrial Fibrillation Guidelines page of the European Society of Cardiology ([www.escardio.org/guidelines](http://www.escardio.org/guidelines)).

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