

## 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Kirchhof, Paulus; Benussi, Stefano; Kotecha, Dipak; Ahlsson, Anders; Atar, Dan; Casadei, Barbara; Castella, Manuel; Diener, Hans-Christoph; Heidbuchel, Hein; Hendriks, Jeroen; Hindricks, Gerhard; Manolis, Antonis S.; Oldgren, Jonas; Popescu, Bogdan Alexandru; Schotten, Ulrich; Van Putte, Bart; Vardas, Panagiotis; Agewall, Stefan; Camm, John; Baron Esquivias, Gonzalo

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# 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

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) of the ESC

Endorsed by the European Stroke Organisation (ESO)

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180	<b>Abbreviations and acronyms</b>	
181	ABC	age, biomarkers, clinical history
182	ACE	angiotensin-converting enzyme
183	ACS	acute coronary syndromes
184	AF	atrial fibrillation
185	AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
186	AFNET	German Competence NETwork on Atrial Fibrillation
187	AHRE	atrial high rate episodes
188	ARB	angiotensin receptor blocker
189	ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
190	ARNI	angiotensin receptor neprilysin inhibition
191	ATRIA	AnTicoagulation and Risk factors In Atrial fibrillation
192	AXAFA	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation
193		catheter Ablation: Comparison to vitamin K antagonist therapy
194	BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
195	BMI	body mass index
196	bpm	beats per minute
197	CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial
198	CAD	coronary artery disease
199	CHA <sub>2</sub> DS <sub>2</sub> -VASc	Congestive Heart failure, hypertension, Age $\geq 75$ (doubled), Diabetes, Stroke (doubled),
200		Vascular disease, Age 65–74, and Sex (female)
201	CHADS <sub>2</sub>	Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled)
202	CI	confidence interval
203	CKD	chronic kidney disease
204	CrCl	creatinine clearance
205	CT	computed tomography
206	DIG	Digitalis Investigation Group
207	EACTS	European Association for Cardio-Thoracic Surgery
208	EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial
209	ECG	electrocardiogram/electrocardiography
210	EHRA	European Heart Rhythm Association
211	ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–
212		Thrombolysis in Myocardial Infarction 48
213	EORP	EURObservational Research Programme
214	FAST	Atrial Fibrillation Catheter Ablation vs Surgical Ablation Treatment
215	FEV1	forced expiratory volume in 1 second
216	GDF-15	growth differentiation factor 15
217	GFR	glomerular filtration rate
218	GFR	glomerular filtration rate
219	GUCH	grown up congenital heart disease
220	HARMONY	A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in
221		Combination in Patients With Paroxysmal Atrial Fibrillation
222	HAS-BLED	hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or
223		predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)
224	HFmrEF	heart failure with mid-range ejection fraction
225	HFpEF	heart failure with preserved ejection fraction
226	HFrfEF	heart failure with reduced ejection fraction
227	HR	hazard ratio
228	INR	international normalized ratio
229	LA	left atrium/atrial
230	LAA	left atrial appendage
231	LAAOS	Left Atrial Appendage Occlusion Study
232	LV	left ventricular
233	LVEF	left ventricular ejection fraction
234	LVH	left ventricular hypertrophy
235	MANTRA-PAF	Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial
236		Fibrillation
237	MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute
238		Coronary Syndrome
239	MRI	magnetic resonance imaging

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240	NOAC	non-vitamin K antagonist oral anticoagulant
241	NYHA	New York Heart Association
242	OAC	oral anticoagulation/oral anticoagulant
243	OR	odds ratio
244	ORBIT	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
245	PCI	percutaneous coronary intervention
246	PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial
247		
248	PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial
249	PVI	pulmonary vein isolation
250	RACE	Rate Control Efficacy in Permanent Atrial Fibrillation
251	RATE-AF	Rate Control Therapy Evaluation in Permanent Atrial Fibrillation
252	RCT	randomized controlled trial
253	RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein ablation: assessment of different peri-proCedUral anticoagulation sTrategies
254		
255	RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
256	ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
257		
258	RR	risk ratio
259	SD	standard deviation
260	SPAF	Stroke Prevention in Atrial Fibrillation
261	TIA	transient ischaemic attack
262	TIMI	Thrombolysis In Myocardial Infarction
263	TOE	transoesophageal echocardiography
264	TTR	time in therapeutic range
265	UFH	unfractionated heparin
266	US	United States
267	VKA	vitamin K antagonist
268	WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing
269		
270	WPW	Wolff-Parkinson-White syndrome
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272		

## 1 Preamble

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) and by the European Association for Cardio-Thoracic Surgery (EACTS), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the 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 website (<http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC, including representation from the European Heart Rhythm Association (EHRA), and EACTS as well as by the European Stroke Organisation (ESO) to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the EACTS and ESO. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (<http://www.escardio.org/guidelines>). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and EACTS and updated. The Task Force received its entire financial support from the ESC and EACTS without any involvement from the healthcare industry.

The ESC 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. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by EACTS and ESO-appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG, EACTS and ESO for publication in the *European Heart Journal*, *Europace*, and in the *European Journal of Cardio-Thoracic Surgery* as well as in the *International Journal of Stroke (TBC)*. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC and EACTS Guidelines covers not only integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. 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.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC and EACTS Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC and EACTS Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

333 **Table 1** Classes of recommendations

Table 1: Classes of Recommendations		
Classes of Recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

334  
335  
336 **Table 2** Levels of evidence

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

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339  
340 **2 Introduction**

341 Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of  
342 the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Furthermore,  
343 the number of patients with AF is predicted to rise steeply in the coming years. To meet the growing demand for  
344 effective care of patients with AF, new information is continually generated and published, and the last few  
345 years have seen substantial progress. It therefore seems timely to publish this 2<sup>nd</sup> edition of the ESC guidelines  
346 on AF.

347  
348 Reflecting the multidisciplinary input into the management of patients with AF, the Task Force includes  
349 cardiologists with varying subspecialty expertise, cardiac surgeons, stroke neurologists, and specialist nurses  
350 amongst its members. Supplementing the evidence review as outlined in the preamble, this task force identified  
351 three PICOT questions on relevant topics for the guideline. The ESC commissioned external systematic reviews  
352 to answer these three questions. These reviews informed specific recommendations.

353  
354 Further to adhering to the standards for generating recommendations that is common to all ESC guidelines (see  
355 preamble), this task force discussed each draft recommendation during web-based conference calls dedicated to  
356 specific chapters, followed by consensus modifications and an online vote on each recommendation. Only  
357 recommendations that were supported by at least 75% of the task force members were included in the guideline.

358  
359 We hope that this guideline will help to deliver good care to all patients with AF based on the current state-of-  
360 the-art evidence in 2016.

361  
362 **3 Epidemiology and impact for patients**

### 3.1. Incidence and prevalence of atrial fibrillation

In 2010, the estimated numbers of men and women with atrial fibrillation (AF) worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries.<sup>1,2</sup> One in four middle-aged adults in Europe and the United States (US) will develop AF.<sup>3-5</sup> By 2030, 14–17 million AF patients are anticipated in the European Union, with 120,000–215,000 newly diagnosed patients per year.<sup>2,6,7</sup> Estimates suggest an AF prevalence of approximately 3% in adults age 20 years or older,<sup>8,9</sup> with more AF in elderly persons<sup>1</sup> and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, diabetes mellitus, and chronic kidney disease (CKD).<sup>7,10-15</sup> The increase in AF prevalence can be attributed to better detection of silent AF<sup>16-18</sup> and increasing age and conditions predisposing to AF.<sup>19</sup>

### 3.2. Morbidity, mortality, and healthcare burden of atrial fibrillation

AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men<sup>20-22</sup> (Table 3). Death due to stroke can largely be mitigated by anticoagulation, while other cardiovascular deaths, for example due to heart failure and sudden death, remain common even in AF patients treated according to the current evidence-base.<sup>23</sup> AF is also associated with increased morbidity, such as heart failure and stroke.<sup>21,24,25</sup> Contemporary studies show that 20–30% of patients with an ischaemic stroke have AF diagnosed before, during, or after the initial event.<sup>17,26,27</sup> White matter lesions in the brain, cognitive impairment,<sup>28-30</sup> decreased quality of life,<sup>31,32</sup> and depressed mood<sup>33</sup> are common in AF patients, and between 10% and 40% of AF patients are hospitalized each year.<sup>23,34,35</sup>

The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK, and between \$6.0 and \$26.0 billion in the US for 2008,<sup>36,37</sup> driven by AF-related complications (e.g. stroke) and AF-related treatment costs (e.g. hospitalizations). These costs will increase dramatically unless AF is prevented and treated in a timely and effective manner.

**Table 3 Cardiovascular morbidity and mortality associated with AF**

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure, or stroke
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with ‘silent’, paroxysmal AF
Hospitalizations	10–40% of AF patients are hospitalized every year
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions
LV dysfunction and heart failure	LV dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia increase even in anticoagulated patients. Brain white matter lesions are more common in AF patients than in patients without AF

AF = atrial fibrillation; LV = left ventricular.

### 3.3. Impact of evidence-based management on outcomes in atrial fibrillation patients

Figure 1 depicts the major milestones in the management of AF. Despite these advances, substantial morbidity remains. Oral anticoagulation (OAC) with vitamin K antagonists (VKAs) or non-VKA oral anticoagulants (NOACs) markedly reduces stroke and mortality in AF patients.<sup>38,39</sup> Other interventions such as rhythm control and rate control improve AF-related symptoms and may preserve cardiac function, but have not demonstrated a reduction in long-term morbidity or mortality.<sup>40,41</sup>



**Figure 1** Timeline of major landmarks in AF management, including treatment of concomitant conditions and prevention (green), anticoagulation (blue), rate and rhythm control (orange and red), and surgical therapy (purple).

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy; NOAC = non-vitamin K antagonist oral anticoagulant; PUFA = polyunsaturated fatty acid; PVI = pulmonary vein isolation; QoL = quality of life; RACE = Rate Control Efficacy in Permanent Atrial Fibrillation; RF = radiofrequency; SR = sinus rhythm; VKA = vitamin K antagonist.

In contemporary, well-controlled, randomized clinical trials in AF, the average annual stroke rate is about 1.5% and the annualized death rate is around 3%.<sup>40</sup> In real life, the annual mortality can be different (both higher and lower).<sup>42</sup> A minority of these deaths are related to stroke, while sudden cardiac death and death from progressive heart failure are more frequent, emphasizing the need for interventions beyond anticoagulation.<sup>43, 44</sup>

Furthermore, AF is also associated with high rates of hospitalization, commonly for AF management, but often also for heart failure, myocardial infarction, and treatment-associated bleeding.<sup>34, 45</sup>

### 3.4. Gender

In both developed and developing countries, the age-adjusted incidence and prevalence of AF are lower in women, while the risk of death in women with AF is similar to or higher than that in men with AF.<sup>1, 46, 47</sup> Female AF patients who have additional stroke risk factors (particularly older age) are also at greater risk than men of having a stroke,<sup>48, 49</sup> even those anticoagulated with warfarin<sup>50</sup> (see Chapter 8 for details). Women with diagnosed AF can be more symptomatic than men and are typically older with more comorbidities.<sup>51, 52</sup> Bleeding risk on anticoagulation is similar in both sexes,<sup>49, 50, 53</sup> but women appear less likely to receive specialist care and rhythm control therapy,<sup>54</sup> while the outcomes of catheter ablation or AF surgery are comparable to those in men.<sup>55, 56</sup> These observations highlight the need to offer effective diagnostic tools and therapeutic management equally in women and men.

#### Recommendations relating to gender

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
AF clinicians must offer effective diagnostic tools and therapeutic management to women and men equally to prevent stroke and death	I	A	39, 46, 57
Catheter or surgical ablation techniques should be regarded as equally effective in women and men	Ila	B	55, 56

428 AF = atrial fibrillation

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

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

431 <sup>c</sup>Reference(s) supporting recommendations.

432

## 433 **4 Pathophysiological and genetic aspects that guide management**

### 434 **4.1. Genetic predisposition**

435 AF, especially early-onset AF, has a strong heritable component, independent of concomitant cardiovascular  
 436 conditions.<sup>58,59</sup> A few young AF patients suffer from inherited cardiomyopathies or channelopathies mediated  
 437 by disease-causing mutations. These monogenic diseases also convey a risk for sudden death (see Chapter 5).  
 438 Up to one-third of AF patients carry common genetic variants that predispose to AF, albeit with a relatively low  
 439 added risk. At least 14 of these common variants, often single nucleotide polymorphisms, are known to increase  
 440 the risk of prevalent AF in populations.<sup>60-62</sup> The most important variants are located close to the paired-like  
 441 homeodomain transcription factor 2 gene on chromosome 4q25.<sup>63,64</sup> These variants modify the risk of AF up to  
 442 sevenfold.<sup>64</sup> Several of the AF risk variants are also associated with cardioembolic or ischaemic stroke, possibly  
 443 due to silent AF (see section 4.1).<sup>62,65,66</sup> Changes in atrial action potential characteristics,<sup>67-70</sup> atrial remodelling,  
 444 and modified penetration of rare gene defects<sup>61</sup> have been suggested as potential mechanisms mediating  
 445 increased AF risk in carriers of common gene variants. Genetic variants could in the future become useful for  
 446 patient selection of rhythm control strategies,<sup>71-73</sup> but it is currently unknown whether common gene variants  
 447 differentially affect the efficacy of antiarrhythmic drugs or rate control medication.<sup>74</sup> While genomic analysis  
 448 may provide an opportunity to improve diagnosis and management of AF in the future,<sup>75,76</sup> routine genetic  
 449 testing for common gene variants associated with AF cannot be recommended at present.<sup>77</sup>  
 450

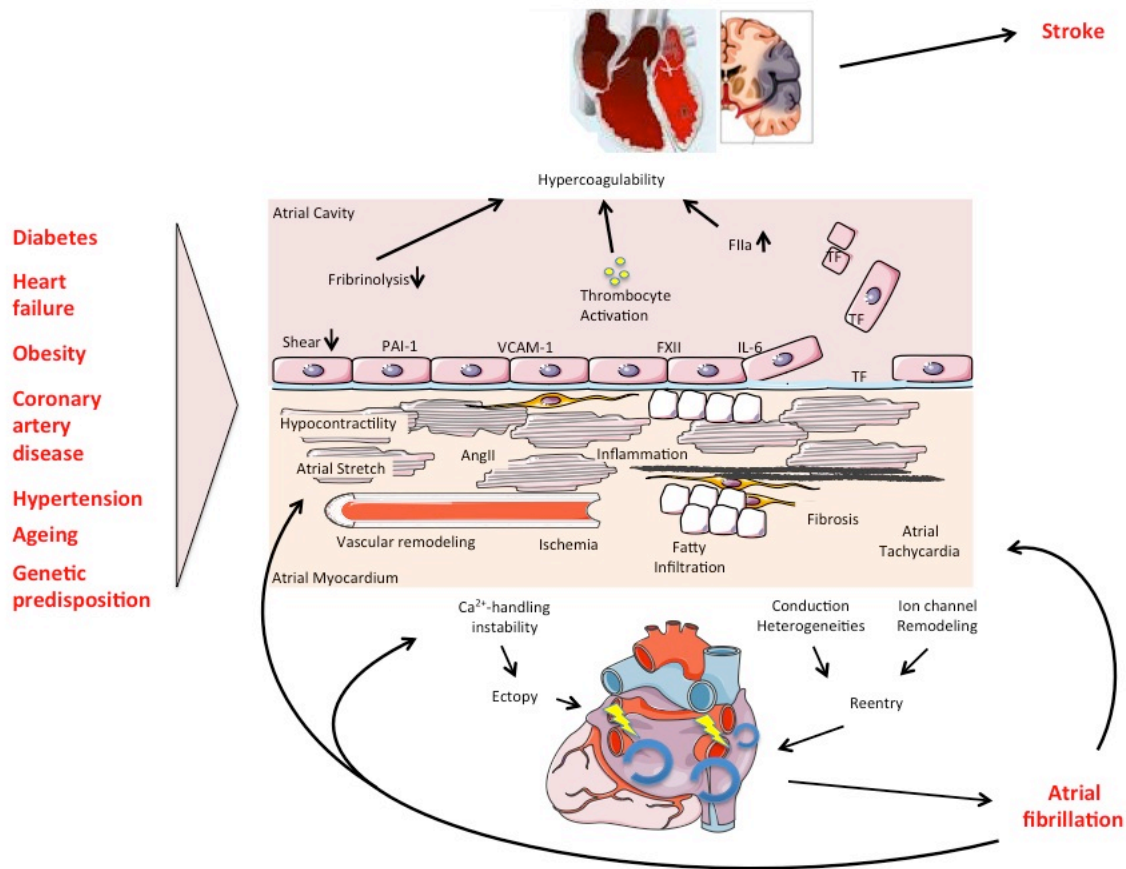
### 451 **4.2. Mechanisms leading to atrial fibrillation**

#### 452 **4.2.1. Remodelling of atrial structure and ion channel function**

453 External stressors such as structural heart disease, hypertension, possibly diabetes, but also AF itself induce a  
 454 slow but progressive process of structural remodelling in the atria (*Figure 2*). Activation of fibroblasts,  
 455 enhanced connective tissue deposition, and fibrosis are the hallmarks of this process.<sup>78-80</sup> In addition, atrial fatty  
 456 infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis, and amyloidosis are found in AF patients  
 457 with concomitant conditions predisposing to AF.<sup>81-84</sup> Structural remodelling results in electrical dissociation  
 458 between muscle bundles and local conduction heterogeneities,<sup>85</sup> favouring reentry and perpetuation of the  
 459 arrhythmia.<sup>86</sup> In many patients, the structural remodelling process occurs before the onset of AF.<sup>78</sup> As some of  
 460 the structural remodelling will be irreversible, early initiation of treatment seems desirable.<sup>87</sup> *Table 4* gives an  
 461 overview of the most relevant pathophysiological alterations in atrial tissue associated with AF, and lists  
 462 corresponding clinical conditions that can contribute to these changes.

463 The functional and structural changes in atrial myocardium and stasis of blood, especially in the left  
 464 atrial appendage (LAA), generate a prothrombotic milieu. Furthermore, even short episodes of AF lead to  
 465 myocardial damage and expression of prothrombotic factors on the atrial endothelial surface, and activation of  
 466 platelets and inflammatory cells, and contribute to a generalized prothrombotic state.<sup>88,89</sup> The atrial and  
 467 systemic activation of the coagulation system can partially explain why short episodes of AF convey a long-  
 468 term stroke risk.





469  
470

471 **Figure 2** Major mechanisms causing AF that can be considered when guiding therapy. The various aetiological  
 472 factors (left) cause a complex array of pathophysiological changes in the atria, including stretch-induced atrial  
 473 fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodelling, ischaemia, ion channel  
 474 dysfunction, and Ca<sup>2+</sup>-instability. These changes enhance both ectopy and conduction disturbances, increasing  
 475 the propensity of the atria to develop or maintain AF. At the same time, some of these alterations are involved in  
 476 the occurrence of the hypercoagulable state associated with AF. For example, hypocontractility reduces local  
 477 endothelial shear stress, which increases PAI-1 expression, and ischaemia-induced inflammation enhances the  
 478 expression of endothelial adhesion molecules or promotes shedding of endothelial cells, resulting in tissue factor  
 479 exposure to the blood stream. These changes contribute to the thrombogenic milieu in the atria of AF patients.  
 480 AF in itself can aggravate many of the mechanisms shown, which may explain the progressive nature of the  
 481 arrhythmia.  
 482 AngII = angiotensin II; TF = tissue factor; FXII = factor XII; IL-6 = interleukin 6; PAI-1 = plasminogen  
 483 activator inhibitor 1; VCAM-1 = vascular cell adhesion molecule 1.

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487

**Table 4** Pathophysiological alterations in atrial tissue associated with AF and clinical conditions that could contribute to such alterations

Pathophysiological alteration	Clinical conditions contributing to the alteration	Proarrhythmic mechanism/functional consequence	References
<i>Changes of the extracellular matrix, fibroblast function, and fat cells</i>			
Interstitial and replacement fibrosis	AF (especially forms with a high AF burden), hypertension, heart failure, valvular heart disease (via pressure and volume overload)	Electrical dissociation, conduction block, enhanced AF complexity	78, 79, 90, 91
Inflammatory infiltration		Profibrotic responses, enhanced AF complexity	81
Fatty infiltration	Obesity (fatty infiltration)	Profibrotic/proinflammatory responses, localized conduction	82, 92

Amyloid deposition	Ageing, heart failure, CAD (via atrial scarring), genetic factors	block Conduction disturbances	83, 93
<b><i>Ion channel alterations</i></b>			
Ion channel remodelling	AF (especially forms with a high AF burden), genetic predisposition to AF	AF cycle shortening (if due to atrial tachycardia), AF cycle length prolongation (if due to heart failure), enhanced heterogeneity of atrial repolarization	94-96
Ca <sup>2+</sup> handling instability	AF (especially forms with a high AF burden), possibly heart failure and hypertension (possibly through increased sympathetic activation)	Enhanced propensity to ectopy	97, 98
Gap-junction redistribution	AF	Conduction disturbances	99
<b><i>Myocyte alterations</i></b>			
Apoptosis and necrosis	CAD, heart failure (through cardiomyocyte death and atrial scarring)	May induce replacement fibrosis	100
Myocyte hypertrophy	Atrial dilatation, AF	Aggravates conduction disturbances	84, 101
<b><i>Endothelial and vascular alterations</i></b>			
Microvascular changes	Atherosclerosis, CAD and peripheral artery disease, possibly AF	Aggravation of atrial ischaemia, heterogeneity of electrical function, structural remodelling	102
Endocardial remodelling		Enhanced risk for thrombus formation	103, 104
<b><i>Changes of the autonomic nervous system</i></b>			
Sympathetic hyperinnervation	Heart failure, hypertension	Enhanced propensity to ectopy	80, 105

488 AF = atrial fibrillation; CAD = coronary artery disease.

489

### 490 3.2.1. Electrophysiological mechanisms of atrial fibrillation

491 AF provokes a shortening of the atrial refractory period and AF cycle length during the first days of the  
 492 arrhythmia, largely due to downregulation of the Ca<sup>2+</sup>-inward current and upregulation of inward rectifier K<sup>+</sup>  
 493 currents.<sup>94, 95</sup> Structural heart disease, in contrast, tends to prolong the atrial refractory period, illustrating the  
 494 heterogeneous nature of mechanisms that cause AF in different patients.<sup>96</sup> Hyperphosphorylation of various  
 495 Ca<sup>2+</sup> handling proteins may contribute to enhanced spontaneous Ca<sup>2+</sup> release events and triggered activity,<sup>97, 98</sup>  
 496 thus causing ectopy and promoting AF. Although the concept of Ca<sup>2+</sup> handling instability has been challenged  
 497 recently,<sup>106, 107</sup> it may mediate AF in structurally remodelled atria and explain how altered autonomic tone can  
 498 generate AF.<sup>80, 105</sup>

499  
 500 ***Focal initiation and maintenance of AF:*** The seminal observation by Haissaguerre et al<sup>108</sup> was that a focal  
 501 source in the pulmonary veins can trigger AF, and ablation of this source can extinguish the arrhythmia. The  
 502 mechanism of focal activity might involve both triggered activity and localized reentry.<sup>109, 110</sup> Hierarchic  
 503 organization of AF with rapidly activated areas driving the arrhythmia has been documented in patients with  
 504 paroxysmal AF,<sup>111, 112</sup> but is more challenging in patients with persistent AF.<sup>113</sup>

505  
 506 ***The multiple wavelet hypothesis and rotors as sources of AF:*** Moe and Abildskov<sup>114</sup> proposed that AF can be  
 507 perpetuated by continuous conduction of several independent wavelets propagating through the atrial  
 508 musculature in a seemingly chaotic manner. As long as the number of wavefronts does not decline below a  
 509 critical level, they will be capable of sustaining the arrhythmia. Numerous experimental and clinical  
 510 observations can be reconciled with the multiple wavelet hypothesis.<sup>115</sup> All localized sources of AF (ectopic

511 foci, rotors, or other stable reentry circuits) cause fibrillatory conduction remote from the source, which is  
512 difficult to distinguish from propagation sustaining AF by multiple wavelets, and either of these phenomena  
513 may generate ‘rotors’ picked up by intracardiac<sup>116,117</sup> or body surface<sup>117</sup> recordings.  
514  
515

## 516 **5 Diagnosis and timely detection of atrial fibrillation**

### 517 **5.1. Overt and silent atrial fibrillation**

518 The diagnosis of AF requires rhythm documentation using an electrocardiogram (ECG), with the typical pattern  
519 of AF. ECG-documented AF was the entry criterion in trials forming the evidence for these guidelines. By  
520 accepted convention, an episode lasting at least 30 seconds is diagnostic. Individuals with AF may be  
521 symptomatic or asymptomatic (‘silent AF’). Many AF patients have both symptomatic and asymptomatic  
522 episodes of AF.<sup>118-121</sup>

523 Silent, undetected AF is common,<sup>120, 122</sup> with severe consequences such as stroke and death.<sup>123-125</sup>  
524 Prompt recording of an ECG is an effective and cost-effective method to document chronic forms of AF.<sup>126</sup> The  
525 technology to detect paroxysmal, self-terminating AF episodes is rapidly evolving (see Chapter 5 for a  
526 definition of AF patterns). There is good evidence that prolonged ECG monitoring enhances the detection of  
527 undiagnosed AF, for 72 hours after a stroke,<sup>27, 127</sup> for even longer periods,<sup>18, 128</sup> or by daily short-term ECG  
528 recording in patients over 75 years of age<sup>129</sup> (*Web Addenda Figure 1*). Ongoing studies will determine whether  
529 such early detection alters management (e.g. initiation of anticoagulation) and improves outcomes.

530 Once the ECG diagnosis of AF has been established, further ECG monitoring can inform management  
531 in the context of: (1) a change in symptoms or new symptoms; (2) suspected progression of AF; (3) monitoring  
532 of drug effects on ventricular rate; and (4) ECG monitoring of antiarrhythmic drug effects or catheter ablation  
533 for rhythm control.  
534

### 535 **5.2. Screening for silent atrial fibrillation**

#### 536 **5.2.1. Screening for atrial fibrillation by electrocardiogram in the community**

537 Undiagnosed AF is common, especially in older populations and in patients with heart failure.<sup>130</sup> Opportunistic  
538 screening for silent AF seems cost-effective in elderly populations (e.g. > 65 years),<sup>131</sup> and similar effects have  
539 been reported using single-lead ECG screening in other at-risk populations.<sup>132, 133</sup> Screening of elderly  
540 populations (mean age 64 years) yielded a prevalence of 2.3% for chronic forms of AF in 122,571 participants  
541 using either short-term ECG or pulse palpation (followed by ECG in those with an irregular pulse).<sup>134</sup>  
542 Previously undiagnosed AF was found in 1.4% of those aged > 65 years, suggesting a number needed to screen  
543 of 70. These findings encourage the further evaluation of systematic AF screening programmes in at-risk  
544 populations.  
545

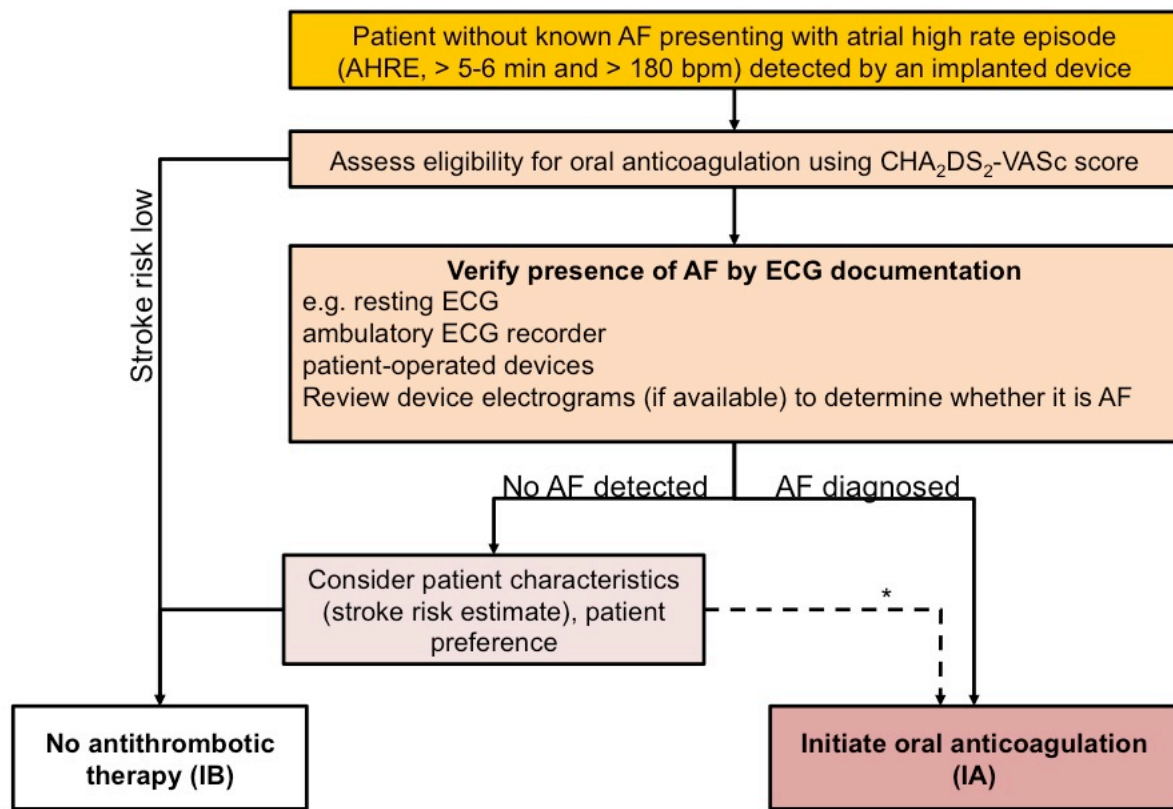
#### 546 **5.2.2. Prolonged monitoring for paroxysmal atrial fibrillation**

547 Paroxysmal AF is often missed.<sup>120</sup> Repeated daily ECG recordings increased the detection of silent,  
548 asymptomatic paroxysmal AF in an unselected Swedish population aged > 75 years.<sup>120, 135</sup> Several patient-  
549 operated devices<sup>136, 137</sup> and extended continuous ECG monitoring using skin patch recorders<sup>138</sup> have been  
550 validated for detection of paroxysmal AF.<sup>139</sup> The detection rate of asymptomatic AF by new technologies such  
551 as smartphone cases with ECG electrodes, smart watches, and blood pressure machines with AF detection  
552 algorithms, has not yet been formally evaluated against an established arrhythmia detection method.<sup>140</sup>  
553

#### 554 **5.2.3. Patients with pacemakers and implanted devices**

555 Implanted pacemakers or defibrillators with an atrial lead allow continuous monitoring of atrial rhythm. Using  
556 this technology, patients with atrial high rate episodes (AHRE) can be identified. Depending on the risk profile  
557 of the population studied, such AHRE are detected in 10–15% of pacemaker patients.<sup>141</sup> AHRE are associated  
558 with an increased risk of overt AF (hazard ratio [HR] 5.56; 95% confidence interval [CI] 3.78–8.17;  $P < 0.001$ )  
559 and ischaemic stroke or systemic embolism (HR 2.49; 95% CI 1.28–4.85;  $P = 0.007$ ). The stroke risk in AHRE  
560 patients seems lower than the stroke risk in patients with diagnosed AF, and not all AHRE represent AF.<sup>142</sup>  
561 Strokes often occur without AHRE detected within 30 days before the event.<sup>143-147</sup> Consequently, it is unclear  
562 whether AHRE imply the same therapeutic requirements as overt AF,<sup>148</sup> and the benefit of OAC in patients with  
563 AHRE is being evaluated in ongoing clinical trials (e.g. ARTESiA [NCT01938248] and NOAH  
564 [NCT02618577]). At present, pacemakers and implanted devices should be interrogated on a regular basis for  
565 AHRE, and patients with AHRE should undergo further assessment of stroke risk factors and for overt AF,

566 including ECG monitoring (Figure 3).<sup>149</sup>



\*In rare individual circumstances, oral anticoagulation may be considered in patients with AHRE, but without diagnosed AF. This clearly needs discussion with the patient and careful evaluation of perceived benefit and risk.

**Figure 3** Management of AHRE detected on an implanted device. Adapted from the report of the 3rd AFNET/EHRA consensus conference.<sup>150</sup>

AF = atrial fibrillation; AFNET = German Competence NETwork on Atrial Fibrillation; AHRE = atrial high rate episodes; bpm = beats per minute; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); ECG = electrocardiogram; EHRA = European Heart Rhythm Association.

**5.2.4. Detection of atrial fibrillation in stroke survivors**

Sequential stratified ECG monitoring detected AF in 24% (95% CI 17–31) of stroke survivors,<sup>151</sup> and in 11.5% (95% CI 8.9%–14.3%) in another meta-analysis,<sup>17</sup> with large variations depending on the timing, duration, and method of monitoring. AF detection is not uncommon in unselected stroke patients (6.2%, 95% CI 4.4–8.3),<sup>128</sup> but is more likely in patients with cryptogenic stroke implanted with loop recorders or who have had ECG monitors for several weeks.<sup>18, 128, 152</sup> Cryptogenic stroke is defined as a stroke in which the cause could not be identified after extensive investigations.<sup>153</sup> A broader definition is embolic stroke of undetermined source.<sup>154</sup> Several studies have also found AF in patients in whom another competing cause for stroke has been identified clinically (e.g. hypertension or carotid artery stenosis).<sup>27, 127</sup> Hence, prolonged ECG monitoring seems reasonable in all survivors of an ischaemic stroke without an established diagnosis of AF.

**Recommendations for screening for AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients > 65 years of age	I	B	130, 134, 155
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours	I	B	27, 127

It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy	I	B	141, 156
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent AF	IIa	B	18, 128
Systematic ECG screening may be considered to detect AF in patients aged > 75 years, or those at high stroke risk	IIb	B	130, 135, 157

587 AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable  
588 cardioverter defibrillator; TIA = transient ischaemic attack.

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

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

591 <sup>c</sup>Reference(s) supporting recommendations.

592

### 593 5.3. Electrocardiogram detection of atrial flutter

594 Right atrial isthmus-dependent flutter has a typical ECG pattern and ventricular rate.<sup>158</sup> The prevalence of atrial  
595 flutter is less than one-tenth of the prevalence of AF.<sup>159</sup> Atrial flutter often coexists with or precedes AF.<sup>160</sup> In  
596 typical, isthmus-dependent flutter, P waves will often show a 'saw tooth' morphology, especially in the inferior  
597 leads (II, III, aVF). The ventricular rate can be variable (usual ratio of atrial to ventricular contraction 4:1 to 2:1,  
598 in rare cases 1:1) and macro-reentrant tachycardias may be missed in stable 2:1 conduction. Vagal stimulation  
599 or intravenous adenosine may be helpful to unmask atrial flutter. The management of atrial flutter is discussed  
600 in Section 12.7. Left or right atrial macro-reentrant tachycardia is usually confined to patients after catheter  
601 ablation for AF, AF surgery, or after open heart surgery.<sup>158</sup>

602

## 603 6 Classification of atrial fibrillation

### 604 6.1. Atrial fibrillation pattern

605 In many patients, AF progresses from short, infrequent episodes to longer and more frequent attacks. Over time,  
606 many patients will develop sustained forms of AF. In a small proportion of patients, AF will remain paroxysmal  
607 over several decades (2–3% of AF patients).<sup>161</sup> The distribution of paroxysmal AF recurrences is not random,  
608 but clustered.<sup>162</sup> AF may also regress from persistent to paroxysmal AF. Furthermore, asymptomatic recurrences  
609 of AF are common in patients with symptomatic AF.<sup>120</sup>

610

611 Based on presentation, duration, and spontaneous termination of AF episodes, five types of AF are  
612 traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF  
613 (*Table 5*). If patients suffer from both paroxysmal and persistent AF episodes, the more common type should be  
614 used for classification. Clinically determined AF patterns do not correspond well to the AF burden measured by  
615 long-term ECG monitoring.<sup>163</sup> Even less is known about the response to therapy in patients with long-standing  
616 persistent AF or long-standing paroxysmal AF. Despite these inaccuracies, the distinction between paroxysmal  
617 and persistent AF has been used in many trials and therefore still forms the basis of some recommendations.

618 There is some evidence suggesting that AF burden may influence stroke risk<sup>44, 124, 164</sup> and could modify  
619 the response to rhythm control therapy.<sup>76, 165</sup> The evidence for this is weak. Therefore, AF burden should not be  
620 a major factor in deciding on the usefulness of an intervention that is deemed suitable for other reasons.

621

622 **Table 5** Patterns of AF

AF pattern	Definition
<b>First diagnosed AF</b>	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
<b>Paroxysmal AF</b>	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days. <sup>a</sup> Most AF episodes that are cardioverted within 24-48 hours should be considered paroxysmal. <sup>a</sup>
<b>Persistent AF</b>	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
<b>Long-standing persistent AF</b>	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
<b>Permanent AF</b>	AF 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 would be re-classified as 'long-standing persistent AF'.

623 AF = atrial fibrillation.

624 <sup>a</sup>The distinction between paroxysmal and persistent AF is often not made correctly without access to long-term  
625 monitoring.<sup>163</sup> Hence, this classification alone is often insufficient to select specific therapies. If both persistent  
626 and paroxysmal episodes are present, the predominant pattern should guide the classification.  
627

## 628 6.2. Atrial fibrillation types reflecting different causes of the arrhythmia

629 The risk of developing AF is increased in a variety of physiological and disease states, and the historic term  
630 'lone AF' is probably misleading and should be avoided.<sup>166</sup> Although the pattern of AF may be the same, the  
631 mechanisms underpinning AF vary substantially between patients<sup>167</sup> (Table 6). This suggests that stratifying AF  
632 patients by underlying drivers of AF could inform management, for example, considering cardiac and systemic  
633 comorbidity (e.g. diabetes and obesity<sup>168</sup>), lifestyle factors (e.g. activity level, smoking, alcohol intake<sup>169, 170</sup>),  
634 markers of cardiac structural remodelling (e.g. fibrosis<sup>171-173</sup> or electrocardiographic parameters of AF  
635 complexity<sup>174</sup>), or genetic background. Table 6 provides such a taxonomy, informed by expert consensus,<sup>76, 120,</sup>  
636 <sup>175</sup> but without much evidence to underpin its clinical use.<sup>176</sup> Systematic research defining the major drivers of  
637 AF is clearly needed to better define different types of AF.<sup>176</sup>  
638

639 **Table 6 Clinical types of AF (modified from the report on the 4<sup>th</sup> AFNET/EHRA consensus conference<sup>76</sup>)<sup>a</sup>**

AF type	Clinical presentation	Possible pathophysiology
AF secondary to structural heart disease	AF in patients with LV systolic or diastolic dysfunction, long-standing hypertension with LVH, and/or other structural heart diseases. The onset of AF in these patients is a common cause of hospitalization and a predictor of poor outcome	Increased atrial pressure and atrial structural remodelling, together with activation of the sympathetic and renin-angiotensin system
Focal AF	Patients with repetitive atrial runs and frequent, short episodes of paroxysmal AF. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, and/or atrial tachycardia deteriorating in AF	Localized triggers, in most cases originating from the pulmonary veins, initiate AF. AF due to one or a few reentrant drivers is also considered to be part of this type of AF
Polygenic AF	AF in carriers of common gene variants that have been associated with early onset AF	Currently under study. The presence of some gene variants may also influence treatment outcomes
Postoperative AF	New onset of AF (usually self-terminating) after major (typically cardiac) surgery in patients who were in sinus rhythm before surgery and had no history of AF	Acute factors: inflammation, atrial oxidative stress, high sympathetic tone, electrolyte changes, and volume overload, possibly interacting with a pre-existing substrate
AF in patients with mitral stenosis or prosthetic heart valves	AF in patients with mitral stenosis, after mitral valve surgery and in some cases other valvular disease	Left atrial pressure (stenosis) and volume (regurgitation) load are the main drivers of atrial enlargement and structural atrial remodelling in these patients
AF in athletes	Usually paroxysmal, related to duration and intensity of training	Increased vagal tone and atrial volume
Monogenic AF	AF in patients with inherited cardiomyopathies, including channelopathies	The arrhythmogenic mechanisms responsible for sudden death are likely to contribute to the occurrence of AF in these patients

640 AF = atrial fibrillation; LV = left ventricular; LVH = left ventricular hypertrophy.

641 <sup>a</sup>It is recognized that these types of AF will overlap in clinical practice, and that their impact for management  
642 needs to be evaluated systematically.  
643

## 644 6.3. Symptom burden in atrial fibrillation

645 Patients with AF have significantly poorer quality of life than healthy controls, experiencing a variety of  
 646 symptoms including lethargy, palpitations, dyspnoea, chest tightness, sleeping difficulties, and psychosocial  
 647 distress.<sup>32, 177-180</sup> Improved quality of life has been noted with both pharmacological and interventional  
 648 therapies,<sup>181-185</sup> but there are limited data to compare the benefit of different treatments.<sup>32, 186</sup> Assessment of  
 649 quality of life is further constrained by a lack of cross-validation of the several AF-specific quality-of-life  
 650 tools.<sup>187-191</sup> With regard to symptom assessment, the European Heart Rhythm Association (EHRA) suggested  
 651 the EHRA symptom scale (*Table 7*) to describe symptom severity in AF patients.<sup>192</sup> A similar scale (the  
 652 Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale) is used in Canada.<sup>193</sup> The EHRA scale  
 653 has been used and validated.<sup>194-199</sup> A modification was proposed in 2014, subdividing EHRA class 2 into mild  
 654 (2a) or moderate (2b) impact.<sup>199</sup> As symptoms in class 2b ('troubling' symptoms) identified patients with a  
 655 health utility benefit of rhythm control in that study, this modification may provide a threshold for potential  
 656 treatment decisions, but this remains to be tested. While some AF patients had no or minimal symptoms (25–  
 657 40%), many (15–30%) reported severe or disabling symptoms.<sup>194, 196</sup> The EHRA scale should be used to guide  
 658 symptom-orientated treatment decisions and for longitudinal patient profiling.

660 **Table 7 Modified EHRA symptom scale (modified from Wynn et al<sup>199</sup>)**

Modified EHRA score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF <sup>a</sup>
2b	Moderate	Normal daily activity not affected <sup>a</sup>
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

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

662 <sup>a</sup>EHRA class 2a and 2b can be differentiated by evaluating whether patients are functionally affected by their  
 663 AF symptoms. AF-related symptoms are most commonly fatigue/tiredness and exertional shortness of breath, or  
 664 less frequently palpitations and chest pain.<sup>42, 194, 200-202</sup>

#### 666 Recommendation on use of the modified EHRA symptom scale

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Use of the modified EHRA symptom scale is recommended in clinical practice and research studies to quantify AF-related symptoms	I	C	192, 199

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

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

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

670 <sup>c</sup>Reference(s) supporting recommendations.

## 672 7 Detection and management of risk factors and concomitant cardiovascular diseases

673 Many cardiovascular diseases and concomitant conditions increase the risk of developing AF (*Table 8*),  
 674 recurrent AF, and AF-associated complications. Identification of such conditions, their prevention and treatment  
 675 is an important leverage to prevent AF and its disease burden. Knowledge of these factors and their management  
 676 is hence important for optimal management of AF patients.<sup>203, 204</sup>

677 **Table 8 Cardiovascular and other conditions independently associated with AF**

Characteristic/comorbidity	Association with AF
Genetic predisposition (based on multiple common gene variants associated with AF) <sup>64</sup>	HR range 0.4–3.2

Older age <sup>19</sup> 50–59 years 60–69 years 70–79 years 80–89 years	HR: 1.00 (reference) 4.98 (95% CI 3.49–7.10) 7.35 (95% CI 5.28–10.2) 9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none <sup>19</sup>	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs. none <sup>19</sup>	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs. none <sup>205</sup>	RR 2.42 (95% CI 1.62–3.60)
Myocardial infarction vs. none <sup>19</sup>	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction <sup>206, 207</sup> hypothyroidism subclinical hyperthyroidism overt hyperthyroidism	(reference: euthyroid) HR 1.23 (95% CI 0.77–1.97) RR 1.31 (95% CI 1.19–1.44) RR 1.42 (95% CI 1.22–1.63)
Obesity <sup>19, 208</sup> none (BMI < 25 kg/m <sup>2</sup> ) overweight (BMI 25–30 kg/m <sup>2</sup> ) obese (BMI ≥ 31 kg/m <sup>2</sup> )	HR: 1.00 (reference) 1.13 (95% CI 0.87–1.46) 1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs. none <sup>19</sup>	HR 1.25 (95% CI 0.98–1.60)
Chronic obstructive pulmonary disease <sup>209</sup> FEV1 ≥ 80% 60–80% < 60%	RR:  1.00 (reference) 1.28 (95% CI 0.79–2.06) 2.53 (95% CI 1.45–4.42)
Obstructive sleep apnoea vs. none <sup>210</sup>	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease <sup>211</sup> none stage 1 or 2 stage 3 stage 4 or 5	OR: 1.00 (reference) 2.67 (95% CI 2.04–3.48) 1.68 (95% CI 1.26–2.24) 3.52 (95% CI 1.73–7.15)
Smoking <sup>212</sup> never former current	HR: 1.00 (reference) 1.32 (95% CI 1.10–1.57) 2.05 (95% CI 1.71–2.47)
Alcohol consumption <sup>213</sup> None 1–6 drinks/week 7–14 drinks/week 15–21 drinks/week > 21 drinks/week	RR: 1.00 (reference) 1.01 (95% CI 0.94–1.09) 1.07 (95% CI 0.98–1.17) 1.14 (95% CI 1.01–1.28) 1.39 (95% CI 1.22–1.58)
Habitual vigorous exercise <sup>214</sup> Non-exercisers < 1 day/week 1–2 days/week 3–4 days/week 5–7 days/week	RR: 1.00 (reference) 0.90 (95% CI 0.68–1.20) 1.09 (95% CI 0.95–1.26) 1.04 (95% CI 0.91–1.19) 1.20 (95% CI 1.02–1.41)

680 AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; FEV1 = forced expiratory volume in  
681 1 second; HR = hazard ratio; OR = odds ratio; RR = risk ratio  
682

## 683 7.1. Heart failure

684 Heart failure and AF coincide in many patients.<sup>215–217</sup> They are linked by similar risk factors and share a  
685 common pathophysiology.<sup>218</sup> Heart failure and AF can cause and exacerbate each other through mechanisms  
686 such as structural cardiac remodelling, activation of neurohormonal mechanisms, and rate-related impairment of  
687 left ventricular (LV) function. Patients with AF and concomitant heart failure, both with preserved ejection  
688 fraction (LV ejection fraction [LVEF] ≥ 50%) and reduced ejection fraction (LVEF < 40%),<sup>219, 220</sup> suffer from a  
689 worse prognosis, including increased mortality.<sup>16, 221</sup> The recent ESC Guidelines on heart failure<sup>222</sup> have also  
690 introduced a new category of heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%), although  
691 data on AF patients in this group are currently limited. Prevention of adverse outcomes and maintenance of a  
692 good quality of life are the aims of management in all patients with AF and concomitant heart failure, regardless



693 of LVEF.<sup>223</sup> The general approach to AF management does not differ between heart failure patients and others,  
694 but a few considerations are worthwhile to consider. Of note, the only therapy with proven prognostic value in  
695 these patients is anticoagulation, and appropriate OAC should be prescribed in all patients at risk of stroke (see  
696 Chapter 8).

697  
698 **7.1.1. Patients with atrial fibrillation and heart failure with reduced ejection**  
699 **fraction**

700 In addition to OAC, standard heart-failure therapy should be used in patients with heart failure with reduced  
701 ejection fraction (HFrEF), as detailed in the ESC Guidelines.<sup>222</sup> This includes angiotensin-converting enzyme  
702 (ACE) inhibitors or angiotensin receptor blockers (ARBs), mineralocorticoid antagonists, defibrillators and  
703 cardiac resynchronization therapy,<sup>218</sup> in addition to combined angiotensin receptor neprilysin inhibition (ARNI)  
704 in patients able to tolerate an ACE inhibitor or ARB with ongoing symptoms.<sup>224</sup>

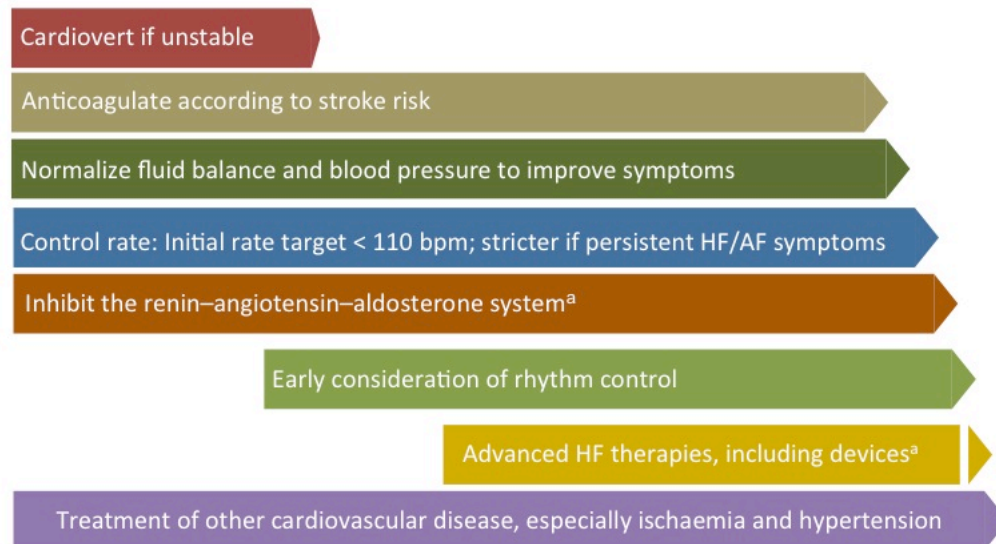
705 Rate control of AF is discussed in detail in Chapter 9. In brief, only beta-blockers and digoxin are  
706 suitable in HFrEF because of the negative inotropic potential of verapamil and diltiazem. Beta-blockers are  
707 usually the first-line option in patients with clinically stable HFrEF, although a meta-analysis using individual  
708 patient data from randomized controlled trials (RCTs) found no reduction in mortality from beta-blockers versus  
709 placebo in those with AF at baseline (HR 0.97, 95% CI 0.83–1.14).<sup>23</sup> Digoxin is commonly prescribed in  
710 clinical practice but no head-to-head RCTs in AF patients have been performed. In a meta-analysis of  
711 observational studies, digoxin had a neutral effect on mortality in patients with AF and concomitant heart failure  
712 (adjusted observational studies HR 0.90, 95% CI 0.70–1.16; propensity-matched observational studies RR 1.08,  
713 95% CI 0.93–1.26).<sup>225</sup> Initial and combination rate-control therapy for AF in HFrEF should therefore take  
714 account of individual patient characteristics and symptoms; beta-blocker initiation should be delayed in patients  
715 with acute decompensated heart failure, and digoxin has more adverse effects in patients with renal impairment  
716 (see Chapter 9).

717 Patients with AF and HFrEF who present with severe symptoms may require rhythm control therapy in  
718 addition to rate control therapy. For patients who develop HFrEF as a result of rapid AF (tachycardiomyopathy),  
719 a rhythm control strategy is preferred, based on several relatively small patient cohorts and trials reporting  
720 improved LV function after restoration of sinus rhythm.<sup>185, 226-228</sup> The diagnosis of tachycardiomyopathy can be  
721 challenging, and at times requires restoration of sinus rhythm.<sup>229</sup> Catheter ablation may be a useful method to  
722 restore LV function and quality of life in AF patients with HFrEF,<sup>185, 226-228</sup> but further data are needed. *Figure 4*  
723 summarizes the approach to patients with AF and heart failure.

## Management of patients presenting acutely with AF and heart failure

Acute management

Chronic management



**Figure 4** Initial management of newly diagnosed with AF and heart failure. Adapted from Kotecha and Piccini.<sup>218</sup>

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibition; bpm = beats per minute; HF = heart failure.

<sup>a</sup>In patients with heart failure and reduced ejection fraction; also consider combined ARNI in patients able to tolerate an ACE inhibitor or ARB with ongoing symptoms.

### 7.1.2. Atrial fibrillation patients with heart failure with preserved ejection fraction

The diagnosis of heart failure with preserved ejection fraction (HFpEF) in patients with AF is problematic because of the difficulty in separating symptoms that are due to HF from those due to AF. Although diagnostic differentiation can be achieved by cardioversion and clinical reassessment, this option is often not appropriate in this group, particularly as a specific therapy that improves prognosis in HFpEF is currently lacking. Echocardiography can support detection of HFpEF in patients with symptomatic AF by providing evidence of relevant structural heart disease (e.g. LV hypertrophy [LVH]) and/or measurement of diastolic dysfunction. Reduced early diastolic myocardial velocity  $e'$  by tissue Doppler reflects impaired LV relaxation, while the ratio of  $E/e'$  has demonstrated a significant correlation with invasive measurement of LV filling pressures.<sup>230-234</sup> Natriuretic peptide levels are part of the diagnostic assessment of HFpEF,<sup>222</sup> although natriuretic peptide levels are elevated in AF patients and the optimum diagnostic cut-off is still unknown.<sup>235</sup> The management of patients with AF and concomitant HFpEF should focus on control of fluid balance and concomitant conditions such as hypertension and ischaemia.

### 7.1.3. Atrial fibrillation patients with heart failure with mid-range ejection fraction

HFmrEF is a recently defined entity, describing patients with symptoms and signs of heart failure, LVEF 40–49%, elevated levels of natriuretic peptides, and either LV hypertrophy, left atrial (LA) enlargement, or evidence of diastolic dysfunction.<sup>222</sup> However, diagnosis is more difficult in patients with AF, as natriuretic peptides are elevated in AF and LA dilatation is common, regardless of concomitant heart failure. LVEF is also variable and difficult to assess in AF patients because of AF-induced reduction in systolic LV function and

753 variable cardiac cycle length. Further study of this group is required before particular treatment strategies in AF  
754 patients with HFmrEF can be recommended.

755

#### 756 **7.1.4. Prevention of atrial fibrillation in heart failure**

757 Retrospective analyses from large randomized trials have reported a lower incidence of new-onset AF in  
758 patients treated with ACE inhibitors/ARBs compared with placebo.<sup>236-238</sup> The reduced incidence of AF with  
759 ACE inhibitors/ARBs is less evident in patients with HFpEF<sup>239</sup> and is lost in patients without heart failure.<sup>240-242</sup>  
760 Nephilysin inhibition does not seem to add to this effect.<sup>224</sup> Beta-blocker therapy was associated with a 33%  
761 reduction in the adjusted odds of incident AF in HFrEF patients pretreated with ACE inhibitors/ARBs,  
762 reinforcing the importance of beta-blocker therapy in HFrEF patients in sinus rhythm.<sup>23</sup> Eplerenone, a  
763 mineralocorticoid receptor antagonist, also reduced the risk of new-onset AF in patients with LVEF ≤ 35%,  
764 New York Heart Association (NYHA) Class II, and pretreatment with ACE inhibitors/ARBs and beta-  
765 blockers.<sup>243</sup>

766

## 767 **7.2. Hypertension**

### 768 **7.2.1. Treatment of hypertension to prevent incident atrial fibrillation**

769 Inhibition of the renin–angiotensin–aldosterone system can prevent structural remodelling and recurrent AF.<sup>236,</sup>  
770 <sup>244</sup> A recent analysis of the Danish healthcare database with long-term monitoring of the effect of different  
771 antihypertensive agents on the occurrence of overt AF suggests a beneficial effect of ACE inhibitors or  
772 ARBs.<sup>245</sup> Secondary analyses of ACE inhibitors or ARBs in patients with heart failure or LVH show a lower  
773 incidence of new-onset AF.<sup>238, 246</sup>

774

### 775 **7.2.2. Blood pressure control in patients with atrial fibrillation**

776 Hypertension is a stroke risk factor in AF, and uncontrolled high blood pressure enhances the risk of stroke and  
777 bleeding events and may lead to recurrent AF. Good blood-pressure control should therefore form an integral  
778 part of the management of AF patients.<sup>247</sup> In patients with established AF, but without LV dysfunction or heart  
779 failure, ARBs do not prevent recurrent AF better than placebo.<sup>240, 241</sup> ACE inhibitors or ARBs may reduce  
780 recurrent AF after cardioversion when coadministered with antiarrhythmic drug therapy compared with an  
781 antiarrhythmic drug alone.<sup>248, 249</sup> Meta-analyses driven by these studies suggested a lower risk of recurrent  
782 AF,<sup>236-238, 250</sup> but at least one controlled trial failed to demonstrate benefit.<sup>240, 251</sup>

783

## 784 **7.3. Valvular heart disease**

785 Valvular heart disease is independently associated with incident AF.<sup>252</sup> Approximately 30% of patients with AF  
786 have some form of valvular heart disease, often detected only by echocardiography.<sup>201, 253-255</sup> AF worsens  
787 prognosis in patients with severe valvular heart disease,<sup>256</sup> including those undergoing surgery or transcatheter  
788 interventions for aortic or mitral valve disease.<sup>257-262</sup> Valvular heart disease can be associated with an increased  
789 thromboembolic risk, which probably also adds to the stroke risk in AF patients.<sup>263</sup> Similar to heart failure,  
790 valvular disease and AF interact and sustain each other through volume and pressure overload,  
791 tachycardiomyopathy, and neurohumoral factors.<sup>264-270</sup> When valve dysfunction is severe, AF can be regarded as  
792 a marker for progressive disease, thus favouring valve repair or replacement.<sup>271</sup>

793

794 Traditionally, patients with AF have been dichotomized into ‘valvular’ and ‘non-valvular’ AF.<sup>272</sup>  
795 Although slightly different definitions have been used, valvular AF mainly refers to AF patients that have either  
796 rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves. In fact, while AF implies  
797 an incremental risk for thromboembolism in patients with mitral valve stenosis,<sup>263, 273, 274</sup> there is no clear  
798 evidence that other valvular diseases, including mitral regurgitation or aortic valve disease, need to be  
799 considered when choosing an anticoagulant or indeed to estimate stroke risk.<sup>275</sup> We have therefore decided to  
800 replace the historic term ‘non-valvular’ AF with reference to the specific underlying conditions.

801

### 801 **Recommendations for patients with valvular heart disease and AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
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	IIa	C	276

Mitral valvotomy should be considered for asymptomatic patients with severe mitral stenosis and suitable valve anatomy who have new-onset AF	Ila	C	
--	-----	---	--

802 AF = atrial fibrillation; LV = left ventricular.

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

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

805 <sup>c</sup>Reference(s) supporting recommendations.

806

807

## 808 7.4. Diabetes mellitus

809 Diabetes and AF frequently coexist because of associations with other risk factors.<sup>277-283</sup> Diabetes is a risk factor  
 810 for stroke and other complications in AF.<sup>284</sup> In patients with AF, a longer duration of diabetes appears to confer  
 811 a higher risk of thromboembolism, albeit without greater risk of OAC-related bleeding.<sup>285</sup> Unfortunately,  
 812 intensive glycaemic control does not affect the rate of new-onset AF,<sup>284</sup> while treatment with metformin seems  
 813 to be associated with a decreased long-term risk of AF in diabetic patients<sup>286</sup> and may even lower long-term  
 814 stroke risk.<sup>13</sup> Diabetic retinopathy, a measure of disease severity, does not increase the risk of ocular bleeding in  
 815 anticoagulated patients.<sup>287</sup>  
 816

## 817 7.5. Obesity and weight loss

### 818 7.5.1. Obesity as a risk factor

819 Obesity increases the risk for AF (risk ratio 1.5–1.8),<sup>288-291</sup> with a progressive increase according to body mass  
 820 index.<sup>288, 290-292</sup> Obese patients may have more LV diastolic dysfunction, increased sympathetic activity and  
 821 inflammation, and increased fatty infiltration of the atria.<sup>293-295</sup> Obesity may also be a risk factor for ischaemic  
 822 stroke, thromboembolism, and death in AF patients.<sup>292</sup>  
 823

824

### 824 7.5.2. Weight reduction in obese patients with atrial fibrillation

825 Intensive weight-reduction management in addition to management of other cardiovascular risk factors (in the  
 826 range of 10–15 kg weight loss achieved) led to fewer AF recurrences and symptoms compared with an approach  
 827 based on general advice in obese patients with AF.<sup>203, 204, 296</sup> Improved cardiorespiratory fitness can further  
 828 decrease AF burden in obese patients with AF.<sup>297</sup> Although the findings in these studies have to be confirmed,  
 829 they underpin the positive effect of weight reduction in obese patients.  
 830

831

### 831 7.5.3. Catheter ablation in obese patients

832 Obesity may increase the rate of AF recurrence after catheter ablation,<sup>298-301</sup> with obstructive sleep apnoea as an  
 833 important potential confounder. Obesity has also been linked to a higher radiation dose and complication rate  
 834 during AF ablation.<sup>302, 303</sup> Notably, the symptomatic improvement after catheter ablation of AF in obese patients  
 835 seems comparable to the improvement in normal-weight patients.<sup>298</sup> In view of the potential to reduce AF  
 836 episodes by weight reduction (see Section 6.5.2.), AF ablation should be offered to obese patients in conjunction  
 837 with lifestyle modifications that lead to weight reduction.  
 838

839

### 839 Recommendation for obese patients with AF

840

841 AF = atrial fibrillation.

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF burden and symptoms	IIa	B	204, 288, 296

842

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

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

845 <sup>c</sup> Reference(s) supporting recommendation(s)

846

## 847 7.6. Chronic obstructive pulmonary disease, sleep apnoea, and other respiratory 848 diseases

849 AF has been associated with obstructive sleep apnoea.<sup>304, 305</sup> Multiple pathophysiological mechanisms can  
 850 contribute to AF in obstructive sleep apnoea, including autonomic dysfunction, hypoxia, hypercapnia, and  
 851 inflammation.<sup>96, 304-307</sup> Obstructive sleep apnoea exaggerates intrathoracic pressure changes, which in itself and  
 852 via vagal activation can provoke shortening of the atrial action potential and induce AF. Risk factor reduction  
 853 and continuous positive airway pressure ventilation can reduce AF recurrence.<sup>308-312</sup> It seems reasonable to  
 854 consider obstructive sleep apnoea screening in AF patients with risk factors. Obstructive sleep apnoea treatment  
 855 should be optimized to improve AF treatment results in appropriate patients. Servo-controlled pressure support  
 856 therapy should not be used in HFrEF patients with predominantly central sleep apnoea (of which 25% had  
 857 concomitant AF).<sup>313</sup>

858 Patients with chronic obstructive pulmonary disease often suffer from atrial tachycardias, which need  
 859 to be differentiated from AF by ECG. Agents used to relieve bronchospasm, notably theophyllines and beta-  
 860 adrenergic agonists, may precipitate AF and make control of the ventricular response rate difficult. Non-  
 861 selective beta-blockers, sotalol, propafenone, and adenosine should be used with caution in patients with  
 862 significant bronchospasm, while they can safely be used in patients with chronic obstructive pulmonary disease.  
 863 Beta-1 selective blockers (e.g. bisoprolol, metoprolol, and nebivolol), diltiazem, and verapamil are often  
 864 tolerated and effective (see Chapter 9).

#### 865 **Recommendations for patients with AF and respiratory diseases**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Correction of hypoxaemia and acidosis should be considered as initial management for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease	IIa	C	
Interrogation for clinical signs of obstructive sleep apnoea in all AF patients should be considered	IIa	B	304, 305, 314, 315
Obstructive sleep apnoea treatment should be optimized to reduce AF recurrences and improve AF treatment results	IIa	B	307-311

867 AF = atrial fibrillation.

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

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

870 <sup>c</sup>Reference(s) supporting recommendations.

871

#### 872 **7.7. Chronic kidney disease**

873 AF is present in 15–20% of patients with CKD.<sup>316</sup> The definition of CKD in most AF trials is relatively strict.  
 874 Although an estimated creatinine clearance (CrCl) rate of < 60 mL/min is indicative of CKD, a number of trials  
 875 in AF patients have used CrCl < 50 mL/min to adapt NOAC dosage, usually estimated using the Cockcroft–Gault  
 876 formula. CrCl in AF patients can deteriorate over time.<sup>317</sup> The management of OAC in patients with CKD is  
 877 discussed in Section 8.2.4.

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#### 879 **Recommendations for patients with kidney disease and AF**

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Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy	I	A	316, 318-321
All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect kidney disease	IIa	B	

881 AF = atrial fibrillation.

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

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

884 <sup>c</sup>Reference(s) supporting recommendations.

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## 8 Integrated management of patients with atrial fibrillation

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Most patients access the healthcare system initially through pharmacists, community health workers, or primary care physicians. As AF is often asymptomatic, these healthcare professionals are important stakeholders to enable adequate detection of AF and to ensure consistent management. The initial assessment should be performed at the point of first contact with the healthcare system, and is feasible in most healthcare settings (when an ECG is available). We propose to consider five domains in the initial assessment of patients presenting with newly diagnosed AF (*Figure 5*). These domains are:

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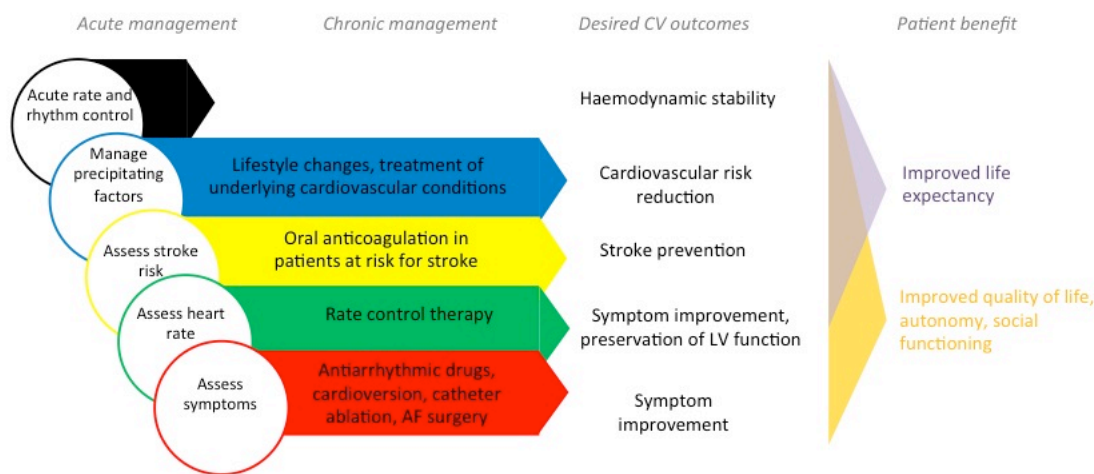
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1. Haemodynamic instability or limiting, severe symptoms
2. Presence of precipitating factors (e.g. thyrotoxicosis, sepsis, or postoperative AF) and underlying cardiovascular conditions
3. Stroke risk and need for anticoagulation
4. Heart rate and need for rate control
5. Symptom assessment and decision for rhythm control



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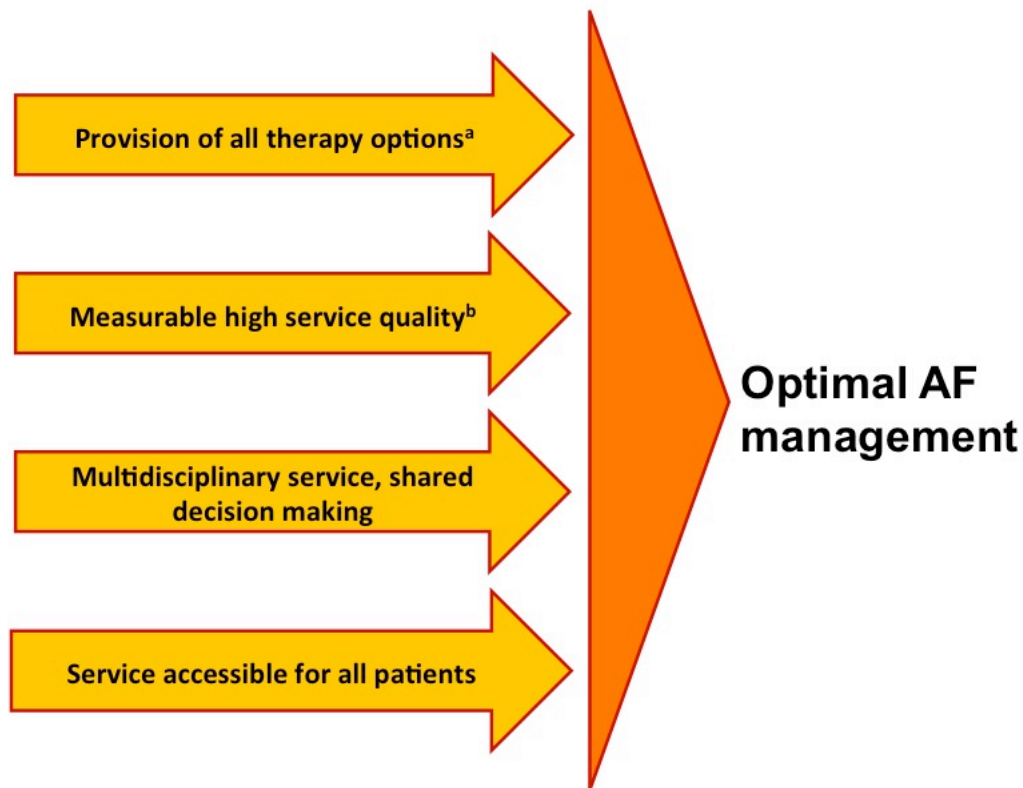
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**Figure 5** Acute and chronic management of AF patients, desired cardiovascular outcomes, and patient benefits. Adapted from the report on the 4th AFNET/EHRA consensus conference.<sup>76</sup> AF = atrial fibrillation; AFNET = German Competence NETwork on Atrial Fibrillation; EHRA = European Heart Rhythm Association.

An integrated, structured approach to AF care, as applied successfully to other domains of medicine,<sup>322-324</sup> will facilitate consistent, guideline-adherent AF management for all patients<sup>325</sup> (*Figure 6*), with the potential to improve outcomes.<sup>42, 326, 327</sup> Such approaches are consistent with the Innovative Care for Chronic Conditions Framework proposal put forward by the World Health Organization.<sup>328</sup> Review by an AF service, or at least referral to a cardiologist, will usually be required after the initial assessment to fully evaluate the effect of AF on cardiovascular health.<sup>329</sup> There may also be reasons for early or urgent referral (*Table 9*). Integrated care of all patients with newly diagnosed AF should help to overcome the current shortcomings of AF management, such as underuse of anticoagulation, access to rate and rhythm control therapy, and inconsistent approaches to cardiovascular risk reduction. Integrated AF care requires the cooperation of primary care physicians, cardiologists, cardiac surgeons, AF specialists, stroke specialists, allied health practitioners and patients,

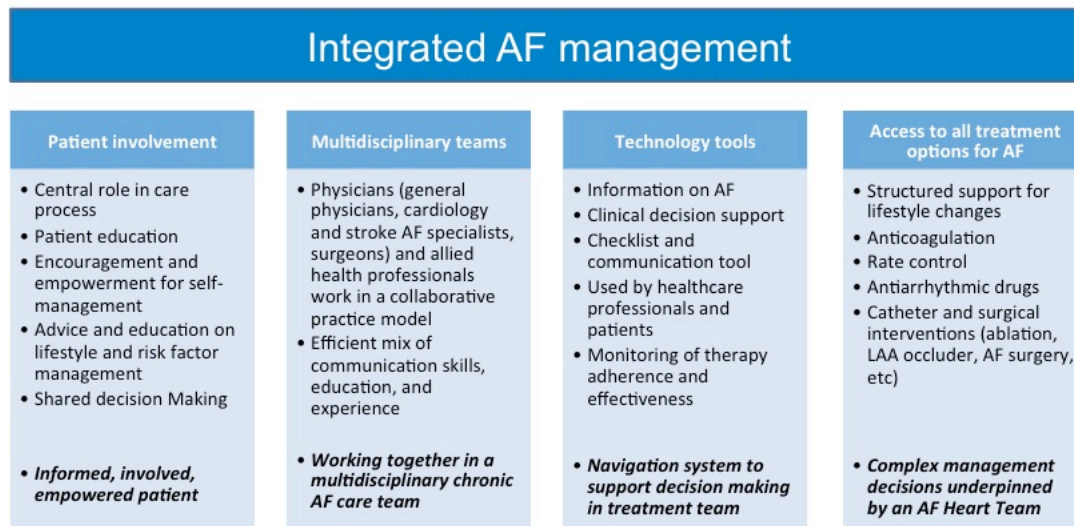
915 encompassing lifestyle interventions, treatment of underlying cardiovascular diseases and AF-specific therapy  
916 (Figure 7).



917  
918 **Figure 6** Achieving optimal management of AF patients.  
919 AF = atrial fibrillation.

920 <sup>a</sup>On-site or through institutionalized cooperation.

921 <sup>b</sup>Safety outcomes should be collected in published and monitored central databases.



**Figure 7** Fundamentals of integrated care in AF patients.  
AF = atrial fibrillation; LAA = left atrial appendage.

**Table 9** Clinical signs calling for urgent involvement of a specialized AF service.<sup>a</sup>

Haemodynamic instability
Uncontrollable rate
Symptomatic bradycardia not amenable to reduced dosing of rate control agents
Severe angina or worsening left ventricular function
Transient ischemic attack or stroke

AF = atrial fibrillation

<sup>a</sup>Anticoagulation should be initiated early in all suitable patients and will not routinely require specialist input.

## 8.1. Evidence supporting integrated atrial fibrillation care

Several structured approaches to AF care have been developed. Some evidence underpins their use, while more research is needed into the best way of delivering integrated AF care. Integrated AF management in an RCT increased the use of evidence-base care and reduced by approximately one-third the composite outcome of cardiovascular hospitalization and cardiovascular death over a mean follow-up of 22 months (14.3% vs. 20.8%, HR 0.65; 95% CI 0.45–0.93;  $P = 0.017$ ) compared with usual care in a large tertiary care centre.<sup>330</sup> Integrated AF management appeared cost-effective in that study.<sup>331</sup> However, an Australian RCT showed only a marginal effect on unplanned admissions and death using integrated AF care limited to the initial care period, possibly emphasizing the need for sustained integration of AF care.<sup>332</sup> Two observational studies of integrated AF care found fewer hospitalizations,<sup>333, 334</sup> one study showed fewer cases of stroke,<sup>333</sup> and a further non-randomized study identified a trend for a lower rate of the composite outcome of death, cardiovascular hospitalization, and AF-related emergency visits.<sup>335</sup> More research is needed, and integrated AF care is likely to require different designs in different healthcare settings.

## 8.2. Components of integrated atrial fibrillation care

### 8.2.1. Patient involvement



946 Patients should have a central role in the care process. As treatment of AF requires patients to change their  
 947 lifestyles and adhere to chronic therapy, at times without an immediately tangible benefit, they need to  
 948 understand their responsibilities in the care process. Physicians and healthcare professionals are responsible for  
 949 providing access to evidence-based therapy, but adherence to therapy is ultimately the responsibility of  
 950 informed and autonomous patients, best described as ‘shared accountability’.<sup>336</sup> Hence, information and  
 951 education of patients and often of their partners and relatives is indispensable to encourage a self-management  
 952 role and to empower patients to participate in shared decision-making,<sup>326, 328</sup> and to support their understanding  
 953 of the disease and the suggested treatments.<sup>337</sup>

### 955 **8.2.2. Multidisciplinary atrial fibrillation teams**

956 Delegation of tasks from specialists to general physicians and from physicians to allied health professionals is a  
 957 fundamental concept of integrated care models. A multidisciplinary AF team approach includes an efficient mix  
 958 of interpersonal and communication skills, education and expertise in AF management, as well as the use of  
 959 dedicated technology. This approach underlines the importance of redesigning daily practice in a way that  
 960 encourages non-specialists and allied professionals to have an important role in educating patients and  
 961 coordinating care, while the specialist remains medically responsible. Cultural and regional differences will  
 962 determine the composition of AF teams.

### 964 **8.2.3. Role of non-specialists**

965 AF patients often initially present to general practitioners or pharmacists. Some physicians in primary care have  
 966 extensive expertise in stroke prevention and initial management of AF patients. Others may seek training to  
 967 acquire such knowledge. Other components of AF management (e.g. assessment of concomitant cardiovascular  
 968 conditions, antiarrhythmic drug therapy, or interventional treatment) often require specialist input. Integrated  
 969 AF care structures should support treatment initiation by non-specialists where appropriate, and provide ready  
 970 access to specialist knowledge to optimize AF care.

### 972 **8.2.4. Technology use to support atrial fibrillation care**

973 Technology, such as decision support software, has the potential to enhance the implementation of evidence-  
 974 based care and improve outcomes, when used to enhance expert advice.<sup>338</sup> Electronic tools can also ensure  
 975 coherent communication within the AF team. With a view to support the wider use of such technology, this  
 976 Task Force is providing tools free of charge, in the form of smartphone apps, to AF healthcare professionals and  
 977 to AF patients.

### 979 **Recommendations for an integrated approach to care**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
An integrated approach with structured organization of care and follow-up should be considered in all patients with AF, aiming to improve guideline adherence and reduce hospitalization and mortality	IIa	B	330-332
Placing patients in a central role in the decision-making should be considered in order to tailor management to patient preferences and improve adherence to chronic therapy	IIa	C	330, 332, 334

980 AF = atrial fibrillation

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

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

983 <sup>c</sup>Reference(s) supporting recommendations.

984

## 985 **8.3. Diagnostic workup of atrial fibrillation patients**

986 AF is often found in patients with other, at times undiagnosed, cardiovascular conditions. Thus, all AF patients  
 987 will benefit from a comprehensive cardiovascular assessment.<sup>339</sup>

988

### 989 **8.3.1. Recommended evaluation in all atrial fibrillation patients**

990 A complete medical history should be taken and all patients should undergo clinical evaluation that includes  
 991 thorough assessment for concomitant conditions, establishing the AF pattern, estimation of stroke risk and AF-  
 992 related symptoms, and assessment of arrhythmia-related complications such as thromboembolism or LV  
 993 dysfunction. A 12-lead ECG is recommended to establish a suspected diagnosis of AF, to determine rate in AF,

and to screen for conduction defects, ischaemia, and signs of structural heart disease. Initial blood tests should evaluate thyroid and kidney function as well as serum electrolytes and full blood count. Transthoracic echocardiography is recommended in all AF patients to guide treatment decisions. Transthoracic echocardiography should be used to identify structural disease (e.g. valvular disease) and assess LV size and function (systolic and diastolic), atrial size, and right heart function.<sup>339, 340</sup> Although biomarkers such as natriuretic peptides are elevated in AF patients, there is insufficient data to suggest that blood-based parameters are independent markers for AF.<sup>341-343</sup>

### 8.3.2. Additional investigations in selected patients with atrial fibrillation

Ambulatory ECG monitoring in AF patients can assess the adequacy of rate control, relate symptoms with AF recurrences, and detect focal induction of bouts of paroxysmal AF. Transoesophageal echocardiography (TOE) is useful to further assess valvular heart disease and to exclude intracardiac thrombi, especially in the LAA, to facilitate early cardioversion or catheter ablation.<sup>344</sup> Patients with symptoms or signs of myocardial ischaemia should undergo coronary angiography or stress testing as appropriate. In patients with AF and signs of cerebral ischaemia or stroke, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain is recommended to detect stroke and support decisions regarding acute management and long-term anticoagulation. Delayed-enhancement MRI of the left atrium using gadolinium contrast,<sup>345-347</sup> T1 mapping using cardiac MRI,<sup>347</sup> and intracardiac echo<sup>348</sup> may help to guide treatment decisions in AF, but require external validation in multicentre studies.

## 8.4. Structured follow-up

Most AF patients need regular follow-up to ensure continued optimal management. Follow-up may be undertaken in primary care, by specially trained nurses, by cardiologists, or by AF specialists.<sup>325, 330</sup> A specialist should coordinate care and follow-up. Follow-up should ensure implementation of the management plan, continued engagement of the patient, and therapy adaptation where needed.

### Recommendations for diagnostic workup of AF patients

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
ECG documentation is required to establish the diagnosis of AF	I	B	349
A full cardiovascular evaluation, including an accurate history, careful clinical examination, and assessment of concomitant conditions, is recommended in all AF patients	I	C	
Transthoracic echocardiography is recommended in all AF patients to guide management	I	C	339
Long-term ECG monitoring should be considered in selected patients to assess the adequacy of rate control in symptomatic patients and to relate symptoms with AF episodes	Ila	C	

AF = atrial fibrillation; ECG = electrocardiogram.

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

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

<sup>c</sup>Reference(s) supporting recommendations.

## 8.5. Defining goals of atrial fibrillation management

AF management comprises therapies with prognostic impact (anticoagulation and treatment of cardiovascular conditions) and therapies predominantly providing symptomatic benefit (rate control, rhythm control, *Table 10*). Therapies with prognostic benefit need careful explanation to patients when their benefits are not directly felt. Rhythm control therapy can be successful if symptoms are controlled, even when AF recurs. Explaining the expected benefits to each patient at the start of AF management will prevent unfounded expectations and has the potential to optimize quality of life.

**Table 10** Goal-based follow-up

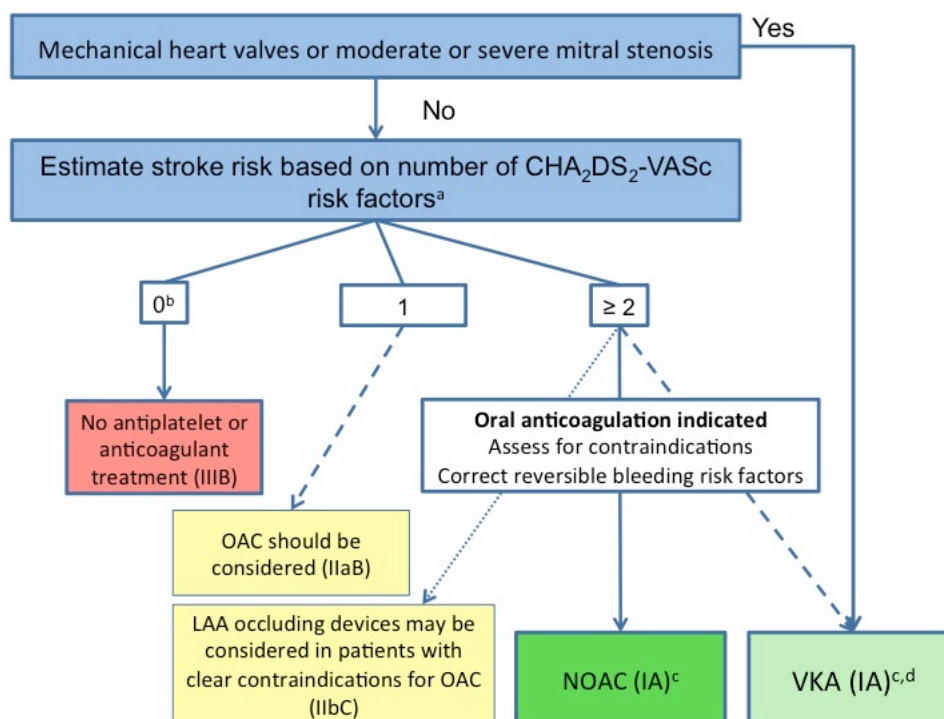
Category	Intervention	Follow-up aspects	Performance indicator (examples)
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Prognostic	Comorbidity control (relevant examples given)	Obesity	Weight loss
		Arterial hypertension	Blood pressure control
		Heart failure	Heart failure therapy
		Coronary artery disease	Statin and antiplatelet therapy Revascularization
		Diabetes	Glycaemic control
	Valvular Heart Disease	Valve repair or replacement	
Prognostic	Anticoagulation	Indication (risk profile; timing, e.g. post-cardioversion); Adherence (NOAC or VKA) and INR (if VKA); NOAC dosing (co- medications, age, weight, renal function)	Stroke Bleeding Mortality
Mainly symptomatic Partly prognostic	Rate control	Symptoms Average resting heart rate < 110 bpm	EHRA score Heart failure status LV function Exercise capacity
Symptomatic at present	Rhythm control	Symptoms vs. side-effects Exclusion of proarrhythmia (PR; QRS; QTc interval)	Hospitalization Therapy complications
Relevant for implementation of and adherence to therapy	Patient education and self-care capabilities	Knowledge (about disease; about treatment; about management goals) Capabilities (what to do if...)	Adherence to therapy Directed evaluation, preferably based on systematic checklists
Relevant for chronic care management	Caregiver involvement	Who? (spouse; GP; home nurse; pharmacist) Clearly spelling out participation roles Knowledge and capabilities	Directed evaluation of task performance (e.g. via patient card) Dispensed medication GP log of follow-up visits

1035 bpm = beats per minute; EHRA = European Heart Rhythm Association; GP = general practitioner; INR =  
1036 international normalized ratio; LV = left ventricular; NOAC = non-vitamin K antagonist oral anticoagulant;  
1037 VKA = vitamin K antagonist.  
1038

## 1039 **9 Stroke prevention therapy in atrial fibrillation patients**

1040 OAC therapy can prevent the majority of ischaemic strokes in AF patients and can prolong life.<sup>38, 39, 42, 194, 201, 329,</sup>  
1041 <sup>350-352</sup> It is superior to no treatment or aspirin in patients with different profiles for stroke risk.<sup>353, 354</sup> The net  
1042 clinical benefit is almost universal, with the exception of patients at very low stroke risk, and OAC should  
1043 therefore be used in most patients with AF (*Figure 8*). Despite this evidence, underuse or premature termination  
1044 of OAC therapy is still common. Bleeding events, both severe and nuisance bleeds, a perceived 'high risk of  
1045 bleeding' on anticoagulation, and the efforts required to monitor and dose-adjust VKA therapy are among the  
1046 most common reasons for withholding or ending OAC.<sup>352, 355-359</sup> However, the considerable stroke risk without  
1047 OAC often exceeds the bleeding risk on OAC, even in the elderly, in patients with cognitive dysfunction, or in  
1048 patients with frequent falls or frailty.<sup>360, 361</sup> The bleeding risk on aspirin is not different to the bleeding risk on  
1049 VKA<sup>362</sup> or NOAC therapy,<sup>354, 363</sup> while VKA and NOACs, but not aspirin, effectively prevent strokes in AF  
1050 patients.<sup>38, 354, 362, 363</sup>  
1051



**Figure 8** Stroke prevention in AF.

AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.

<sup>a</sup>Congestive heart failure, hypertension, age ≥75 years (2 points), diabetes, prior stroke/TIA/embolus (2 points), vascular disease, age 65–74, female sex.

<sup>b</sup>Includes women without other stroke risk factors.

<sup>c</sup>IIaB for women with only one additional stroke risk factor,

<sup>d</sup>IB for patients with mechanical heart valves or mitral stenosis

## 9.1. Prediction of stroke and bleeding risk

### 9.1.1. Clinical risk scores for stroke and systemic embolism

Simple, clinically applicable stroke risk-stratification schemes in AF patients were developed in the late 1990s in small cohort studies and have later been refined and validated in larger populations.<sup>364-368</sup> The introduction of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (*Table 11*) has clearly simplified the initial decision for OAC in AF patients. Since its first incorporation in the ESC guidelines in 2010,<sup>369</sup> it has been widely used.<sup>370</sup> We recommend estimating stroke risk in AF patients based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>368</sup> In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with stroke risk factors (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 or more for men, and 2 or more for women) are likely to benefit from OAC.

**Table 11** Clinical risk factors for stroke, transient ischemic attack, and systemic embolism in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

CHA <sub>2</sub> DS <sub>2</sub> -VASc risk factor	Points
<b>Congestive heart failure</b>	+1
Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	

<b>Hypertension</b> Resting blood pressure > 140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
<b>Age 75 years or older</b>	+2
<b>Diabetes mellitus</b> Fasting glucose > 125 mg/dL or treatment with oral hypoglycaemic agent and/or insulin	+1
<b>Previous stroke, transient ischemic attack, or thromboembolism</b>	+2
<b>Vascular disease</b> Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
<b>Age 65 to 74 years</b>	+1
<b>Sex category (female)</b>	+1

1076 CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled),  
1077 Vascular disease, Age 65–74, and Sex (female).

1078  
1079 Other, less established risk factors for stroke include unstable international normalized ratio (INR) and low time  
1080 in therapeutic range (TTR) in patients treated with VKAs; previous bleed or anaemia; alcohol excess and other  
1081 markers for decreased therapy adherence; CKD; elevated high-sensitivity troponin T; and elevated N-terminal  
1082 pro-B-type natriuretic peptide.

### 1084 9.1.2. Anticoagulation in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in men and 2 1085 in women

1086 Controlled trials studying OAC in AF patients have been enriched for patients at high risk of stroke,<sup>38, 39, 42, 194,</sup>  
1087 <sup>201, 329, 351, 352</sup> and hence there is strong evidence that patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score of 2 or more in  
1088 men, and 3 or more in women benefit from OAC. Fortunately, we now have a growing evidence-base regarding  
1089 stroke risk in patients with one clinical risk factor (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 for men, and 2 for women),  
1090 although this relies largely on observed stroke rates in patients not receiving OAC. In many of these patients,  
1091 anticoagulation seems to provide a clinical benefit.<sup>371-375</sup> The rates of stroke and thromboembolism vary  
1092 considerably in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 1 or 2 due to differences in outcomes, populations, and  
1093 anticoagulation status (*Web Addenda Table 1*).<sup>371, 376, 377, 1041</sup> OAC should be considered for men with a  
1094 CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 and women with a score of 2, balancing the expected stroke reduction, bleeding  
1095 risk, and patient preference. Importantly, age (65 years and older) conveys a relatively high and continuously  
1096 increasing stroke risk that also potentiates other risk factors (such as heart failure and sex). Hence, an  
1097 individualized weighing of risk, as well as patient preferences, should inform the decision to anticoagulate  
1098 patients with only one CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factor, apart from female sex. Female sex does not appear to  
1099 increase stroke risk in the absence of other stroke risk factors (*Web Addenda Table 1*).<sup>378, 379</sup>

1100 Measurement of cardiac troponin (high-sensitivity troponin T or I) and N-terminal pro-B-type  
1101 natriuretic peptide may provide additional prognostic information in selected AF patients.<sup>380-382</sup> Biomarker-  
1102 based risk scores may in the future prove helpful to better stratify patients (e.g. those at a truly low risk of  
1103 stroke).<sup>75, 382</sup>

### 1104 1105 9.1.3. Clinical risk scores for bleeding

1106 Several bleeding risk scores have been developed, mainly in patients on VKAs. These include HAS-BLED  
1107 (hypertension, abnormal renal/liver function [1 point each], stroke, bleeding history or predisposition, labile  
1108 INR, elderly [>65 years], drugs/alcohol concomitantly [1 point each]), ORBIT (Outcomes Registry for Better  
1109 Informed Treatment of Atrial Fibrillation), and more recently, the ABC (age, biomarkers, clinical history)  
1110 bleeding score, which also makes use of selected biomarkers.<sup>383-385</sup> Stroke and bleeding risk factors overlap  
1111 (compare *Table 11* and *Table 12*). For example, older age is one of the most important predictors of both  
1112 ischaemic stroke and bleeding in AF patients.<sup>386, 387</sup> A high bleeding risk score should generally not result in  
1113 withholding OAC. Rather, bleeding risk factors should be identified and treatable factors corrected (see Section  
1114 8.5). *Table 12* provides details of modifiable bleeding risk factors.

1115  
1116 **Table 12** Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on  
1117 bleeding risk scores.

<b>Modifiable bleeding risk factors</b>
Hypertension (especially when systolic blood pressure is > 160 mmHg) <sup>a,b,c</sup>

Labile INR (in patients on vitamin K antagonists) or time in therapeutic range < 60% <sup>a</sup>
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs <sup>a,d</sup>
Excess alcohol (≥ 8 drinks/week) <sup>a,b</sup>
<b>Potentially modifiable bleeding risk factors</b>
Anaemia <sup>b,c,d</sup>
Impaired renal function <sup>a,b,c,d</sup>
Impaired liver function <sup>a,b</sup>
Reduced platelet count or function <sup>b</sup>
<b>Non-modifiable bleeding risk factors</b>
Age <sup>e</sup> (> 65 years) <sup>a</sup> (≥ 75 years) <sup>b,c,d</sup>
History of major bleeding <sup>a,b,c,d</sup>
Previous stroke <sup>a,b</sup>
Dialysis-dependent CKD or renal transplant <sup>a,c</sup>
Cirrhotic liver disease <sup>a</sup>
Malignancy <sup>b</sup>
Genetic factors <sup>b</sup>
<b>Biomarker-based bleeding risk factors</b>
High-sensitivity troponin T <sup>e</sup>
Growth differentiation factor-15 <sup>e</sup>
Serum creatinine/estimated CrCL <sup>e</sup>

- 1118 ABC = age, biomarkers, clinical history; ATRIA = AnTicoagulation and Risk factors In Atrial fibrillation; CKD  
 1119 = chronic kidney disease; CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver  
 1120 function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol  
 1121 concomitantly (1 point each); INR = international normalized ratio; ORBIT = Outcomes Registry for Better  
 1122 Informed Treatment of Atrial Fibrillation; TTR = time in therapeutic range; VKA = vitamin K antagonist.  
 1123 <sup>a</sup>Derived from the HAS-BLED score.<sup>384</sup>  
 1124 <sup>b</sup>Derived from the HEMORR<sub>2</sub>HAGES score.<sup>383</sup>  
 1125 <sup>c</sup>Derived from the ATRIA score.<sup>385</sup>  
 1126 <sup>d</sup>Derived from the ORBIT score.<sup>388</sup>  
 1127 <sup>e</sup>Derived from the ABC bleeding score.<sup>387</sup>

1128  
 1129 **Recommendations for prediction of stroke and bleeding risk**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
The CHA <sub>2</sub> DS <sub>2</sub> -VASc score is recommended for stroke risk prediction in patients with AF	I	A	368, 371, 386
Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable factors for major bleeding	IIa	B	384, 386, 387, 389-392
Biomarkers such as high-sensitivity troponin and N-terminal pro-B-type natriuretic peptide may be considered to further refine stroke and bleeding risk in AF patients	IIb	B	380-382, 387, 393

- 1130 AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled),  
 1131 Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); OAC = oral anticoagulation.  
 1132 <sup>a</sup>Class of recommendation.  
 1133 <sup>b</sup>Level of evidence.  
 1134 <sup>c</sup>Reference(s) supporting recommendations.  
 1135

1136 **9.2. Stroke prevention**  
 1137 **9.2.1. Vitamin K antagonists**

- 1138 Warfarin and other VKAs were the first anticoagulants used in AF patients. VKA therapy reduces risk of stroke  
 1139 by two-thirds and mortality by one-quarter compared with control (aspirin or no therapy).<sup>38</sup> VKAs have been  
 1140 used in many patients throughout the world with good outcomes,<sup>394-396</sup> and this is reflected in the warfarin arms  
 1141 of the NOAC trials (see Section 8.2.2.). The use of VKAs is limited by the narrow therapeutic interval,  
 1142 necessitating frequent monitoring and dose adjustments, but VKAs, when delivered with adequate TTR, are

1143 effective for stroke prevention in AF patients. Clinical parameters can help to identify patients who are likely to  
1144 achieve a decent TTR on VKA therapy.<sup>397</sup> These have been summarized in the SAME-TT<sub>2</sub>R<sub>2</sub> score. Patients who  
1145 fare well on this score, when treated with a VKA, have on average a higher TTR than patients who do not fare  
1146 well on the score.<sup>398, 399</sup> VKAs are currently the only treatment with established safety in AF patients with  
1147 rheumatic mitral valve disease and/or a mechanical heart valve prosthesis.<sup>400</sup>

### 1148 1149 **9.2.2. Non-vitamin K antagonist oral anticoagulants**

1150 NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, and  
1151 rivaroxaban, are suitable alternatives to VKAs for stroke prevention in AF (*Table 13*). Their use in clinical  
1152 practice is increasing rapidly.<sup>401</sup> All NOACs have a predictable effect (onset and offset) without need for regular  
1153 anticoagulation monitoring. The phase III trials have been conducted with carefully selected doses of the  
1154 NOACs, including clear rules for dose reduction that should be followed in clinical practice (*Table 13*).

#### 1155 *Apixaban*

1156 In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial  
1157 Fibrillation) trial,<sup>319</sup> apixaban reduced stroke or systemic embolism by 21% compared with warfarin, combined  
1158 with a 31% reduction in major bleeding and an 11% reduction in all-cause mortality (all statistically significant).  
1159 Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on  
1160 apixaban. Rates of gastrointestinal bleeding were similar between the two treatment arms.<sup>402</sup>

1161 Apixaban is the only NOAC that has been compared with aspirin in AF patients: apixaban significantly  
1162 reduced stroke or systemic embolism by 55% compared with aspirin, with no significant difference in rates of  
1163 major bleeding or intracranial haemorrhage.<sup>354, 403</sup>

#### 1164 *Dabigatran*

1165 In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study,<sup>318, 404</sup> dabigatran 150 mg  
1166 twice daily reduced stroke and systemic embolism by 35% compared with warfarin without a significant  
1167 difference in major bleeding events. Dabigatran 110 mg twice daily was non-inferior to warfarin for prevention  
1168 of stroke and systemic embolism, with 20% fewer major bleeding events. Both dabigatran doses significantly  
1169 reduced haemorrhagic stroke and intracranial haemorrhage. Dabigatran 150 mg twice daily significantly  
1170 reduced ischaemic stroke by 24% and vascular mortality by 12%, while gastrointestinal bleeding was  
1171 significantly increased by 50%. There was a non-significant numerical increase in the rate of myocardial  
1172 infarction with both dabigatran doses,<sup>318, 404</sup> which has not been replicated in large post-authorization  
1173 analyses.<sup>396</sup> These data have also replicated the benefit of dabigatran over VKAs found in the RE-LY trial in  
1174 patients enriched for the higher dabigatran dose (150 mg twice daily).<sup>396</sup>

#### 1175 *Edoxaban*

1176 In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–  
1177 Thrombolysis in Myocardial Infarction 48) trial,<sup>321</sup> edoxaban 60 mg once daily and edoxaban 30 mg once daily  
1178 (with dose reductions in certain patients according to *Table 13*), were compared with adjusted-dose warfarin.<sup>405</sup>  
1179 Edoxaban 60 mg once daily was non-inferior to warfarin (primary outcome, HR 0.87; 97.5% CI 0.73–1.04; *P* =  
1180 0.08). In an on-treatment analysis, edoxaban 60 mg once daily significantly reduced stroke or systemic  
1181 embolism by 21% and significantly reduced major bleeding events by 20% compared with warfarin, while  
1182 edoxaban 30 mg once daily was non-inferior to warfarin for prevention of stroke and systemic embolism but  
1183 significantly reduced major bleeding events by 53%. Cardiovascular death was reduced in patients randomized  
1184 to edoxaban 60 mg once daily or edoxaban 30 mg once daily compared with warfarin. Only the higher dose  
1185 regimen has been approved for stroke prevention in AF.

#### 1186 *Rivaroxaban*

1187 In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K  
1188 Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial,<sup>320</sup> patients were  
1189 randomized to rivaroxaban 20 mg once daily or VKA, with a dose adjustment to 15 mg daily for those with  
1190 estimated CrCl 30–49 mL/min by the Cockcroft–Gault formula. Rivaroxaban was non-inferior to warfarin for the  
1191 prevention of stroke and systemic embolism in the intent-to-treat analysis, while the per-protocol on-treatment  
1192 analysis achieved statistical superiority with a 21% reduction in stroke or systemic embolism compared with  
1193 warfarin. Rivaroxaban did not reduce the rates of mortality, ischaemic stroke, or major bleeding events  
1194 compared to VKA. There was an increase in gastrointestinal bleeding events, but a significant reduction in  
1195 haemorrhagic stroke and intracranial haemorrhage with rivaroxaban compared with warfarin. Comparable event  
1196 rates have been reported in post-authorization analyses, which are part of the post-approval risk-management  
1197 process.<sup>406, 407</sup>

1202 **Table 13** NOACs compared with warfarin in controlled trials

	<b>Dabigatran (RE-LY)</b>	<b>Rivaroxaban (ROCKET-AF)</b>	<b>Apixaban (ARISTOTLE)</b>	<b>Edoxaban (ENGAGE AF-TIMI 48)</b>
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	66 fasting, 80–100 with food	50	62
Time to peak levels, h	3	2–4	3	1–2
Half-life, h	12–17	5–13	9–14	10–14
Excretion	80% renal	66% liver, 33% renal	27% renal	50% renal
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily
Dose reduction in selected patients		Rivaroxaban 15 mg once daily if CrCl 30–49 mL/min	Apixaban 2.5 mg twice daily if at least 2 of age $\geq$ 80 years, body weight $\leq$ 60 kg or serum creatinine level $\geq$ 1.5 mg/dL (133 $\mu$ mol/L)	Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: CrCl 30–50 mL/min, body weight $\leq$ 60 kg, concomitant use of verapamil or quinidine or dronedarone
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind	Randomized, double-blind
Number of patients	18,113	14,264	18,201	21,105
Follow-up period, years	2	1.9	1.8	2.8
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg twice daily or 110 mg twice daily)	Dose-adjusted warfarin vs. rivaroxaban 20 mg once daily	Dose-adjusted warfarin vs. apixaban 5 mg twice daily	Dose-adjusted warfarin vs. edoxaban (60 mg once daily or 30 mg once daily)
Age, years	Mean $\pm$ SD 71.5 $\pm$ 8.7	Median 73; IQR 65–78	Median 70; IQR 63–76	Median 72; IQR 64–78
Men, %	63.6	60.3	64.5	61.9
CHADS <sub>2</sub> score (mean)	2.1	3.5	2.1	2.8

1203



	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30
	<i>n</i> = 6022	<i>n</i> = 6076	<i>n</i> = 6015	<i>n</i> = 7133	<i>n</i> = 7131	<i>n</i> = 9081	<i>n</i> = 9120	<i>n</i> = 7036	<i>n</i> = 7035	<i>n</i> = 7034
	Event rate, %/year	Event rate, %/year (RR vs. warfarin)	Event rate, %/year (RR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year	Event rate, %/year (HR vs. warfarin)	Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; <i>P</i> for non-inferiority and superiority < 0.001)	1.54 (0.89, 0.73–1.09; <i>P</i> for non-inferiority < 0.001)	2.42	2.12 (0.88, 0.75–1.03; <i>P</i> for non-inferiority < 0.001, <i>P</i> for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; <i>P</i> < 0.001 for non-inferiority, <i>P</i> = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; <i>P</i> < 0.001 for non-inferiority, <i>P</i> = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; <i>P</i> = 0.005 for non-inferiority, <i>P</i> = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; <i>P</i> = 0.03)	1.34 (1.10, 0.88–1.37; <i>P</i> = 0.42)	1.42	1.34 (0.94; 0.75–1.17; <i>P</i> = 0.581)	1.05	0.97 (0.92, 0.74–1.13; <i>P</i> = 0.42)	1.25	1.25 (1.00, 0.83–1.19; <i>P</i> = 0.97)	1.77 (1.41, 1.19–1.67; <i>P</i> < 0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; <i>P</i> < 0.001)	0.12 (0.31, 0.17–0.56; <i>P</i> < 0.001)	0.44	0.26 (0.59; 0.37–0.93; <i>P</i> = 0.024)	0.47	0.24 (0.51, 0.35–0.75; <i>P</i> < 0.001)	0.47	0.26 (0.54, 0.38–0.77; <i>P</i> < 0.001)	0.16 (0.33, 0.22–0.50; <i>P</i> < 0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; <i>P</i> = 0.41)	2.92 (0.80, 0.70–0.93; <i>P</i> = 0.003)	3.45	3.60 (1.04; 0.90–2.30; <i>P</i> = 0.58)	3.09	2.13 (0.69, 0.60–0.80; <i>P</i> < 0.001)	3.43	2.75 (0.80, 0.71–0.91; <i>P</i> < 0.001)	1.61 (0.47, 0.41–0.55; <i>P</i> < 0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; <i>P</i> < 0.001)	0.23 (0.29, 0.19–0.45; <i>P</i> < 0.001)	0.74	0.49 (0.67; 0.47–0.93; <i>P</i> = 0.02)	0.80	0.33 (0.42, 0.30–0.58; <i>P</i> < 0.001)	0.85	0.39 (0.47, 0.34–0.63; <i>P</i> < 0.001)	0.26 (0.30, 0.21–0.43; <i>P</i> < 0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; <i>P</i> < 0.001)	1.13 (1.04, 0.82–1.33; <i>P</i> = 0.74)	1.24	2.00 (1.61; 1.30–1.99; <i>P</i> < 0.001)	0.86	0.76 (0.89, 0.70–1.15; <i>P</i> = 0.37)	1.23	1.51 (1.23, 1.02–1.50; <i>P</i> = 0.03)	0.82 (0.67, 0.53–0.83; <i>P</i> < 0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94–1.71; <i>P</i> = 0.12)	0.82 (1.29, 0.96–1.75; <i>P</i> = 0.09)	1.12	0.91 (0.81; 0.63–1.06; <i>P</i> = 0.12)	0.61	0.53 (0.88, 0.66–1.17; <i>P</i> = 0.37)	0.75	0.70 (0.94, 0.74–1.19; <i>P</i> = 0.60)	0.89 (1.19, 0.95–1.49; <i>P</i> = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; <i>P</i> = 0.051)	3.75 (0.91, 0.80–1.03; <i>P</i> = 0.13)	2.21	1.87 (0.85; 0.70–1.02; <i>P</i> = 0.07)	3.94	3.52 (0.89, 0.80–0.99; <i>P</i> = 0.047)	4.35	3.99 (0.92, 0.83–1.01; <i>P</i> = 0.08)	3.80 (0.87, 0.79–0.96; <i>P</i> = 0.006)

1204 AF = atrial fibrillation; CHADS<sub>2</sub> = Cardiac failure, Hypertension, Age, Diabetes, Stroke (Doubled); CrCl = creatinine clearance; HR = hazard ratio; IQR = interquartile range (25<sup>th</sup> to 75<sup>th</sup> quartiles); RR = risk ratio; SD = standard deviation.

1206 RRs and HRs compared to warfarin therapy are presented with 95% confidence intervals and *P*-values.

1207

1208 **9.2.3. Non-vitamin K antagonist oral anticoagulants or vitamin K antagonists**

1209 Both VKAs and NOACs are effective for the prevention of stroke in AF. A meta-analysis<sup>39</sup> based on the high-  
 1210 dose treatment groups of the pivotal studies of warfarin versus NOACs included 42,411 patients receiving a  
 1211 NOAC and 29,272 receiving warfarin. NOACs in these dosages significantly reduced stroke or systemic  
 1212 embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73–0.91;  $P < 0.0001$ ), mainly driven by a  
 1213 reduction in haemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64;  $P < 0.0001$ ). Mortality was 10% lower in  
 1214 patients randomized to NOAC therapy (RR 0.90; 95% CI 0.85–0.95;  $P = 0.0003$ ) and intracranial haemorrhage  
 1215 was halved (RR 0.48; 95% CI 0.39–0.59;  $P < 0.0001$ ), while gastrointestinal bleeding events were more  
 1216 frequent (RR 1.25; 95% CI 1.01–1.55;  $P = 0.04$ ).<sup>39</sup> The stroke reduction with NOACs was consistent in all  
 1217 evaluated subgroups, while there was a suggestion of greater relative reduction in bleeding with NOACs at  
 1218 centres with poor INR control (interaction  $P = 0.022$ ). Notably, the substantial reduction in intracranial  
 1219 haemorrhage by NOACs compared with warfarin seems unrelated to poor or good INR control.<sup>408, 409</sup>

1220

1221 **9.2.4. Oral anticoagulation in atrial fibrillation patients with chronic kidney disease**  
1222

1223 CKD is associated with stroke and bleeding in large data sets.<sup>410, 411</sup> Anticoagulation can be safely used in AF  
 1224 patients with moderate or moderate-to-severe CKD (glomerular filtration rate [GFR]  $\geq 15$  mL/min): the SPAF  
 1225 (Stroke Prevention in Atrial Fibrillation) III trial randomized 805/1936 participants with stage 3 CKD (estimated  
 1226 GFR  $< 59$  mL/min/1.73 m<sup>2</sup>), and reported good outcomes on warfarin (INR 2–3).<sup>412</sup> This finding is supported by  
 1227 a large Swedish database, in which stroke risk was lower in CKD patients with AF treated with warfarin  
 1228 (adjusted HR 0.76; 95% CI 0.72–0.80),<sup>413</sup> while bleeding was also slightly increased, especially during therapy  
 1229 initiation.<sup>414</sup> In a meta-analysis of the major NOAC trials, patients with mild or moderate CKD suffered fewer  
 1230 strokes, systemic emboli, or major bleeding events on NOACs than on warfarin.<sup>415</sup> Kidney function should be  
 1231 regularly monitored in AF patients on OAC to allow dose adaptation for those on NOACs (Table 14) and to  
 1232 refine risk estimation.<sup>416</sup>

1233

1234 **Table 14** Inclusion criteria, dose adjustments, and outcomes in patients with chronic kidney disease in the  
 1235 four major randomized trials comparing NOACs with warfarin in patients with AF. Adapted from Hart  
 1236 *et al.*<sup>316</sup>

	Dabigatran (RE-LY) <sup>318, 425</sup>	Rivaroxaban (ROCKET-AF) 320, 426	Apixaban (ARISTOTLE) <sup>319, 427</sup>	Edoxaban (ENGAGE AF- TIMI 48) <sup>321</sup>
Renal clearance	80%	35%	25%	50%
Number of patients	18,113	14,264	18,201	21,105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg or 30 mg once daily
Exclusion criteria for CKD	CrCl $< 30$ mL/min	CrCl $< 30$ mL/min	Serum creatinine $> 2.5$ mg/dL or CrCl $< 25$ mL/min	CrCl $< 30$ mL/min
Dose adjustment with CKD	None	15 mg once daily if CrCl $< 30$ –49 mL/min	2.5 mg twice daily if serum creatinine $\geq 1.5$ mg/dL plus age $\geq 80$ years or weight $\leq 60$ kg	30 mg or 15 mg once daily if CrCl $< 50$ mL/min
Per cent of patients with CKD	20% with CrCl 30–49 mL/min	21% with CrCl 30–49 mL/min	15% with CrCl 30–50 mL/dL	19% with CrCl $< 50$ mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction of major haemorrhages compared with warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

	estimated GFR > 80 mL/min with either dose			
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1237 AF = atrial fibrillation; CKD = chronic kidney disease; CrCl = creatinine clearance; GFR = glomerular filtration  
1238 rate; NA = not available; NOAC = non-vitamin K antagonist oral anticoagulant.

1239

### 1240 9.2.5. Oral anticoagulation in atrial fibrillation patients on dialysis

1241 Approximately one in eight dialysis patient suffers from AF, with an incidence rate of 2.7/100 patient-years.<sup>417</sup>  
1242 AF is associated with increased mortality in patients on dialysis.<sup>417</sup> There are no randomized trials assessing  
1243 OAC in haemodialysis patients,<sup>418</sup> and no controlled trials of NOACs in patients with severe CKD (CrCl < 25–  
1244 30 mL/min).<sup>318-321</sup> Warfarin use was associated either with a neutral or increased risk of stroke in database  
1245 analyses of patients on dialysis,<sup>419-421</sup> including a population-based analysis in Canada (adjusted HR for stroke  
1246 1.14; 95% CI 0.78–1.67, adjusted HR for bleeding 1.44; 95% CI 1.13–1.85).<sup>422</sup> In contrast, data from Denmark  
1247 suggest a benefit of OAC in patients on renal replacement therapy.<sup>423</sup> Hence, controlled studies of  
1248 anticoagulants (both VKAs and NOACs) in AF patients on dialysis are needed.<sup>424</sup>

1249

### 1250 9.2.6. Patients with atrial fibrillation requiring kidney transplantation

1251 There are no randomized trials assessing OAC in patients after kidney transplantation. The prescription of  
1252 NOAC therapy should be guided by the estimated GFR of the transplanted kidney. Potential pharmacokinetic  
1253 interactions of OAC with immunosuppressive agents should be considered.

1254

1255

### 1256 9.2.7. Antiplatelet therapy as an alternative to oral anticoagulants

1257 The evidence supporting antiplatelet monotherapy for stroke prevention in AF is very limited.<sup>38, 428-430</sup> VKA  
1258 therapy prevents stroke, non-central nervous system embolus, myocardial infarction, and vascular death better  
1259 than single or dual antiplatelet therapy with aspirin and clopidogrel (annual risk of 5.6% for aspirin and  
1260 clopidogrel vs. 3.9% with VKA therapy).<sup>431</sup> Even greater benefits were seen in VKA-treated patients with a high  
1261 TTR.<sup>432</sup> Antiplatelet therapy increases bleeding risk, especially dual antiplatelet therapy (2.0% vs. 1.3% with  
1262 antiplatelet monotherapy;  $P < 0.001$ ),<sup>433</sup> with bleeding rates that are similar to those on OAC.<sup>354, 362, 431, 434</sup> Thus,  
1263 antiplatelet therapy cannot be recommended for stroke prevention in AF patients.

1264

### 1265 Recommendations for stroke prevention in patients with AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
<b>Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or more</b>	I	A	38, 318-321, 354, 404
<b>Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 or more</b>	I	A	38, 318-321, 354, 404
<b>Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, considering individual characteristics and patient preferences</b>	IIa	B	371, 375-377
<b>Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2, considering individual characteristics and patient preferences</b>	IIa	B	371, 376, 377
<b>Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves</b>	I	B	274, 435-440
<b>When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist</b>	I	A	39, 318-321, 404
<b>When patients are treated with a vitamin K antagonist, time</b>	I	A	395, 432, 441-444

<b>in therapeutic range (TTR) should be kept as high as possible and closely monitored</b>			
<b>AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contraindication (e.g. prosthetic valve)</b>	IIb	A	39, 318, 319, 404, 408
<b>Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition</b>	III (harm)	B	429, 445
<b>In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention</b>	III (harm)	B	368, 371, 376, 377
<b>Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk</b>	III (harm)	A	38, 429, 430
<b>NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C)</b>	III (harm)	B/C	318-321, 400, 404

1266 AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled),  
 1267 Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized  
 1268 ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in  
 1269 therapeutic range; VKA = vitamin K antagonist.

1270 <sup>a</sup>Class of recommendation.

1271 <sup>b</sup>Level of evidence.

1272 <sup>c</sup>Reference(s) supporting recommendations.

1273

### 1274 9.3. Left atrial appendage occlusion and exclusion

#### 1275 9.3.1. Left atrial appendage occlusion devices

1276 Interventional LAA occlusion,<sup>446-449</sup> and limited experience with percutaneous LAA ligation, has mainly been  
 1277 reported in observational studies and registries. Only one device (Watchman®) has been compared with VKA  
 1278 therapy in randomized trials (PROTECT AF [Watchman Left Atrial Appendage System for Embolic Protection  
 1279 in Patients With AF trial], see *Web Addenda Table 2*; and PREVAIL [Prospective Randomized Evaluation of  
 1280 the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial]).<sup>449-451</sup> In  
 1281 these data sets, LAA occlusion was non-inferior to VKA treatment for the prevention of stroke in AF patients  
 1282 with moderate stroke risk, with a possibility of lower bleeding rates in the patients who continued follow-up.<sup>452</sup>  
 1283 <sup>453</sup> These data were confirmed in a patient-level meta-analysis of the two trials and their associated registries.<sup>453</sup>  
 1284 LAA occlusion may also reduce stroke risk in patients with contraindications to OAC.<sup>454, 455</sup> The implantation  
 1285 procedure can cause serious complications,<sup>446, 456-458</sup> with high event rates reported in analyses from insurance  
 1286 databases and systematic reviews, possibly identifying a certain degree of reporting bias.<sup>446, 456</sup> A large recent  
 1287 European registry reported a high rate of implantation success (98%), with an acceptable procedure-related  
 1288 complication rate of 4% at 30 days.<sup>459</sup> Most patients who historically would be considered unsuitable for OAC  
 1289 therapy seem to do relatively well on contemporarily managed OAC.<sup>396, 407, 460</sup> Adequately powered controlled  
 1290 trials are urgently needed to inform the best use of these devices, including LAA occluders in patients who are  
 1291 truly unsuitable for OAC or in patients who suffer a stroke on OAC, randomized comparisons of LAA occluders  
 1292 with NOACs, and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion.

1293

#### 1294 9.3.2. Surgical left atrial appendage occlusion or exclusion

1295 Surgical LAA occlusion or exclusion concomitant to cardiac surgery has been performed for many decades and  
 1296 with various techniques. Multiple observational studies indicate the feasibility and safety of surgical LAA  
 1297 occlusion/exclusion, but only limited controlled trial data are available.<sup>461-464</sup> Residual LAA flow or incomplete  
 1298 LAA exclusion can increase stroke risk.<sup>465</sup> In most studies, LAA occlusion/exclusion was performed during  
 1299 other open heart surgery, and more recently in combination with surgical ablation of AF<sup>463</sup> or as a stand-alone  
 1300 thoracoscopic procedure. One randomized trial evaluating the role of concomitant AF surgery and LAA  
 1301 occlusion reported in 2015, without a clear benefit of LAA exclusion for stroke prevention in the subgroup  
 1302 undergoing AF surgery.<sup>466</sup> A large randomized trial is currently underway.<sup>467</sup>

1303

#### 1304 Recommendations for occlusion or exclusion of the LAA

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention	I	B	461, 462
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause)	IIb	B	449, 453, 454
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery	IIb	B	463
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic ablation surgery	IIb	B	468

1305 AF = atrial fibrillation; LAA = left atrial appendage.

1306 <sup>a</sup>Class of recommendation.

1307 <sup>b</sup>Level of evidence.

1308 <sup>c</sup>Reference(s) supporting recommendations.

1309

## 1310 9.4. Secondary stroke prevention

1311 The most important risk factors for stroke in patients with AF are advanced age and previous cardioembolic  
1312 stroke or TIA,<sup>382</sup> emphasizing the need for OAC in these patients. The highest risk of recurrent stroke is in the  
1313 early phase after a first stroke or TIA.<sup>469, 470</sup>

1314

### 1315 9.4.1. Treatment of acute ischaemic stroke

1316 Systemic thrombolysis with recombinant tissue plasminogen activator (rtPA) is an effective and approved  
1317 medical treatment for acute ischaemic stroke in patients presenting within 4.5 hours of symptom onset.<sup>471</sup>

1318 Systemic thrombolysis is contraindicated in patients on therapeutic OAC.<sup>472, 473</sup> Recombinant tissue  
1319 plasminogen activator can be given in patients treated with a VKA if the INR is below 1.7,<sup>474</sup> or in dabigatran-  
1320 treated patients with a normal activated partial thromboplastin time and last intake of drug > 48 hours previously  
1321 (based on expert consensus).<sup>472</sup> Whether specific NOAC antidotes<sup>475</sup> could be used followed by systemic  
1322 thrombolysis needs to be investigated. Thrombectomy can be performed in anticoagulated patients with distal  
1323 occlusion of the internal carotid artery or middle cerebral artery in a 6-hour window.<sup>476</sup>

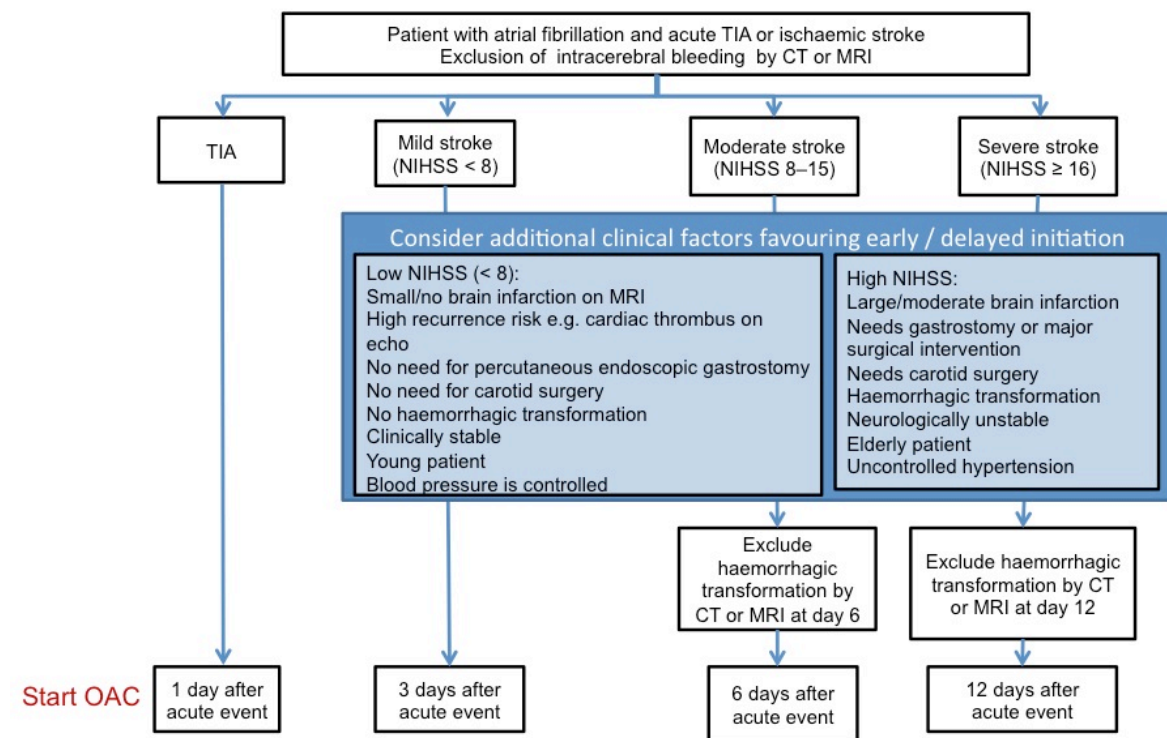
1324

### 1325 9.4.2. Initiation of anticoagulation after transient ischaemic attack or ischaemic 1326 stroke

1327 Data on the optimal use of anticoagulants (heparin, low-molecular-weight heparin, heparinoid, VKA, NOAC) in  
1328 the first days after a stroke are scarce. Parenteral anticoagulants seem to be associated with a non-significant  
1329 reduction in recurrent ischaemic stroke when administered 7 to 14 days after the acute stroke (odds ratio [OR]  
1330 0.68; 95% CI 0.44–1.06), with a significant increase in symptomatic intracranial bleeding (OR 2.89; 95% CI  
1331 1.19–7.01), and a similar rate of death or disability at final follow-up.<sup>477</sup> It seems likely that the bleeding risk on  
1332 parenteral anticoagulation exceeds the stroke prevention benefit in the first days after a large stroke, whereas  
1333 patients with a TIA or a small stroke may benefit from early (immediate) initiation or continuation of  
1334 anticoagulation. Therefore, we propose to initiate anticoagulation in AF patients between 1 and 12 days after an  
1335 ischaemic stroke, depending on its severity (*Figure 9*).<sup>478</sup> We suggest repeat brain imaging to determine the  
1336 optimal initiation of anticoagulation in patients with a large stroke at risk for haemorrhagic transformation.  
1337 Long-term OAC with a VKA<sup>363, 479–481</sup> or NOAC<sup>482</sup> conveys benefits in AF patients who survived a stroke.  
1338 NOACs seem to convey slightly better outcomes, mainly driven by fewer intracranial haemorrhages and  
1339 haemorrhagic strokes (OR 0.44, 95% CI 0.32–0.62).<sup>482</sup> Detailed data for edoxaban have not yet been  
1340 published.<sup>321</sup> If a patient suffers a stroke or TIA whilst taking an anticoagulant, switching to another  
1341 anticoagulant should be considered.

1342

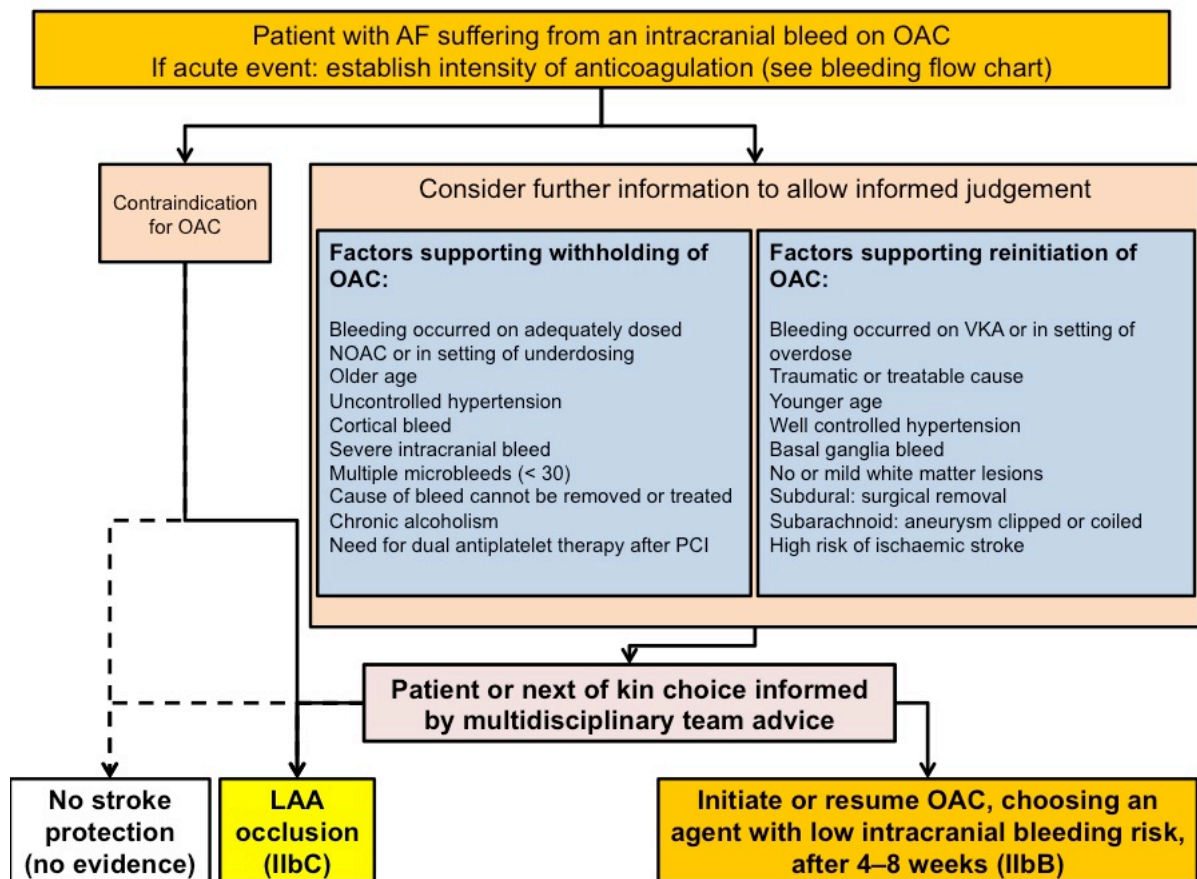
1343 **Figure 9** Initiation or continuation of anticoagulation in AF patients after a stroke or TIA. This approach is  
 1344 based on consensus rather than prospective data.



1345 AF = atrial fibrillation; CT = computed tomography; MRI = magnetic resonance imaging; NIHSS = National  
 1346 Institutes of Health stroke severity scale (available at [http://www.strokecenter.org/wp-](http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf)  
 1347 [content/uploads/2011/08/NIH\\_Stroke\\_Scale.pdf](http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf)); OAC = oral anticoagulation; TIA = transient ischaemic  
 1348 attack.  
 1349

### 1350 9.4.3. Initiation of anticoagulation after intracranial haemorrhage

1352 No prospective studies have investigated the benefit or risk of the initiation of OAC after intracranial  
 1353 haemorrhage,<sup>483</sup> and patients with a history of intracranial bleeding were excluded from the randomized trials  
 1354 comparing NOACs with VKAs. The available evidence indicates that anticoagulation in patients with AF can be  
 1355 reinitiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor (e.g. uncontrolled  
 1356 hypertension) has been treated, and that such treatment leads to fewer recurrent (ischaemic) strokes and lower  
 1357 mortality.<sup>460, 484</sup> If anticoagulation is resumed, it seems reasonable to consider anticoagulants with a low  
 1358 bleeding risk.<sup>39</sup> *Figure 10* depicts a consensus opinion on the initiation or resumption of OAC after an  
 1359 intracranial haemorrhage. We recommend a multidisciplinary decision with input from stroke  
 1360 physicians/neurologists, cardiologists, neuroradiologists, and neurosurgeons.



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### Recommendations for secondary stroke prevention

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Anticoagulation with heparin or low-molecular-weight heparin immediately after ischaemic stroke is not recommended in AF patients	III (harm)	A	477
In patients who suffer a transient ischemic attack or stroke while on anticoagulation, adherence to therapy should be assessed and optimized	IIa	C	
In patients who suffer a moderate-to-severe ischaemic stroke while on anticoagulation, anticoagulation should be interrupted for 3–12 days based on a multidisciplinary assessment of acute stroke and bleeding risk	IIa	C	
In AF patients who suffer a stroke, aspirin should be considered for prevention of secondary stroke until the initiation or resumption of oral anticoagulation.	IIa	B	485
Systemic thrombolysis with a recombinant tissue plasminogen activator is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if activated partial thromboplastin time is outside the normal range)	III (harm)	C	472, 474
NOACs are recommended in preference to VKAs or aspirin in AF patients with a previous stroke	I	B	363, 482
After TIA or stroke, combination therapy of OAC and an	III (harm)	B	486

antiplatelet is not recommended			
After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled	IIb	B	483, 484, 487

1369

1370

1371 AF = atrial fibrillation; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral  
1372 anticoagulant; OAC = oral anticoagulation; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

1373 <sup>a</sup>Class of recommendation.

1374 <sup>b</sup>Level of evidence.

1375 <sup>c</sup>Reference(s) supporting recommendations.

1376

## 1377 **9.5. Strategies to minimize bleeding on anticoagulant therapy**

1378 In a meta-analysis of 47 studies, the overall incidence of major bleeding with VKAs was 2.1 (range 0.9–3.4) per  
1379 100 patient-years in controlled trials and 2.0 (range 0.2–7.6) per 100 patient-years for observational data sets.<sup>488</sup>

1380 Minimizing treatable bleeding risk factors (see *Table 12*) seems paramount to reduce the bleeding rate on  
1381 anticoagulants.

1382

### 1383 **9.5.1. Uncontrolled hypertension**

1384 Uncontrolled blood pressure increases the risk of bleeding on OAC.<sup>53</sup> Hence, keeping systolic blood pressure  
1385 well controlled is of particular relevance in anticoagulated patients with AF. Treatment according to current  
1386 guidelines is recommended in patients with known hypertension.<sup>489</sup>

1387

### 1388 **9.5.2. Previous bleeding event**

1389 History of bleeding events and the presence of anaemia are important parts of the assessment of all patients  
1390 receiving OAC. The majority of bleeding events are gastrointestinal. Compared with warfarin, the risk of  
1391 gastrointestinal bleeds was increased for dabigatran 150 mg twice daily,<sup>396, 490</sup> rivaroxaban 20 mg once daily,<sup>491</sup>  
1392 and edoxaban 60 mg once daily.<sup>321</sup> The risk of gastrointestinal bleeds was comparable to warfarin on dabigatran  
1393 110 mg twice daily<sup>490</sup> and on apixaban 5 mg twice daily.<sup>319</sup> Recent observational analyses do not replicate these  
1394 findings, suggesting a smaller effect.<sup>396, 492, 493</sup> In patients in whom the source of bleeding has been identified and  
1395 corrected, OAC can be reinitiated. This also appears true for patients who have had an intracranial haemorrhage,  
1396 once modifiable bleeding risk factors (e.g. uncontrolled hypertension) have been corrected.<sup>460, 484</sup>

1397

### 1398 **9.5.3. Labile international normalized ratio and adequate non-vitamin K 1399 antagonist oral anticoagulant dosing**

1400 TTR on VKA therapy is an important predictor of major haemorrhage.<sup>432, 441, 494</sup> Therefore we recommend  
1401 targeting the INR between 2.0 and 3.0 in patients on VKAs, maintaining a high TTR (e.g.  $\geq 70\%$ <sup>494</sup>), and to  
1402 consider switching to a NOAC when a high TTR cannot be sustained.<sup>444</sup> NOAC dosing should follow the dose-  
1403 reduction criteria evaluated in the clinical trials, considering renal function, age, and weight. Patient information  
1404 and empowerment, best delivered through integrated AF management, seem paramount to achieve this goal.

1405

### 1406 **9.5.4. Alcohol abuse**

1407 Alcohol excess is a risk factor for bleeding in anticoagulated patients,<sup>384</sup> mediated by poor adherence, liver  
1408 disease, variceal bleeding, and risk of major trauma. Severe alcohol abuse and binge drinking habits should be  
1409 corrected in patients eligible for OAC.

1410

### 1411 **9.5.5. Falls and dementia**

1412 Falls and dementia are associated with increased mortality in AF patients,<sup>495</sup> without evidence that these  
1413 conditions markedly increase the risk of intracranial haemorrhage.<sup>495, 496</sup> Hence, anticoagulation should only be  
1414 withheld from patients with severe uncontrolled falls (e.g. epilepsy or advanced multisystem atrophy with  
1415 backwards falls), or in selected patients with dementia where compliance and adherence cannot be ensured by a  
1416 caregiver.

1417

### 1418 **9.5.6. Genetic testing**



1419 In addition to food and drug interactions, multiple genetic variations affect the metabolism of VKAs.<sup>497</sup> The  
1420 systematic use of genetic information for adjustment of VKA dosage has been evaluated in several controlled  
1421 clinical studies.<sup>498-500</sup> Genetic testing has little effect on TTR or bleeding risk on warfarin, and is not  
1422 recommended for clinical use at present.<sup>501</sup>

1423

### 1424 **9.5.7. Bridging periods off oral anticoagulation**

1425 Most cardiovascular interventions (e.g. percutaneous coronary intervention or pacemaker implantation) can be  
1426 performed safely on continued OAC. When interruption of OAC is required, bridging does not seem to be  
1427 beneficial, except in patients with mechanical heart valves. In a randomized trial of 1884 patients with AF,  
1428 interruption of anticoagulation was non-inferior to heparin administration for the outcome of arterial  
1429 thromboembolism (incidence of 0.4% and 0.3%, respectively) and resulted in a lower risk of major bleeding  
1430 (1.3% and 3.2%, respectively).<sup>502</sup> A short interruption or continued OAC should be considered in patients at  
1431 highest risk of stroke.

1432

## 1433 **9.6. Management of bleeding events in anticoagulated patients with atrial fibrillation**

### 1434 **9.6.1. Management of minor, moderate, and severe bleeding**

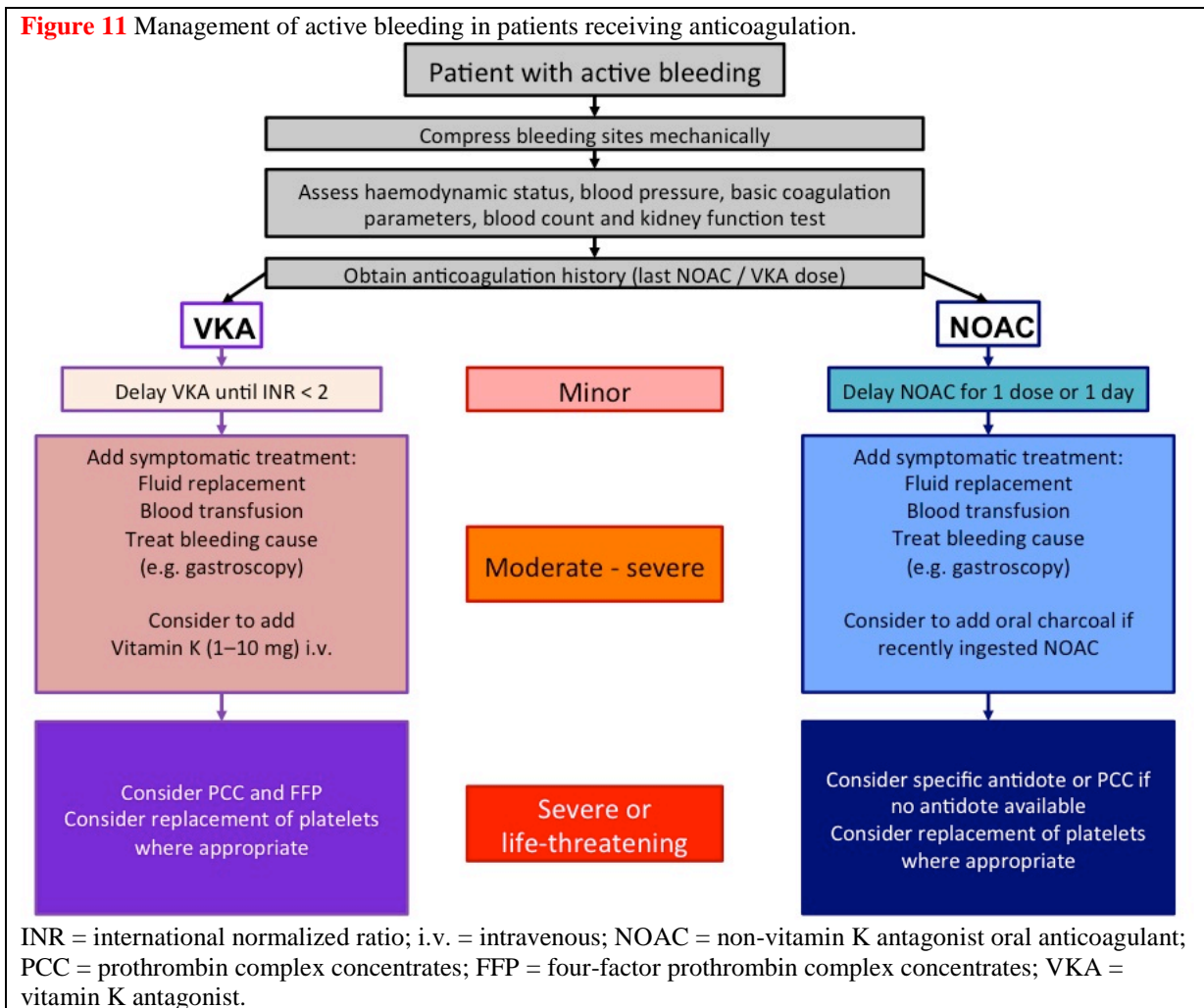
1435 General assessment of an anticoagulated patient with AF experiencing a bleeding event should include  
1436 assessment of bleeding site, onset, and severity of the bleeding, the time-point of last intake of OAC and other  
1437 antithrombotic drugs, and other factors influencing bleeding risk such as CKD, alcohol abuse, and concurrent  
1438 medications. Laboratory tests should include haemoglobin, haematocrit, platelet count, renal function, and for  
1439 VKA patients, prothrombin time, activated partial thromboplastin time, and INR. Coagulation tests do not  
1440 provide much information in patients on NOACs, except for activated partial thromboplastin time in the case of  
1441 dabigatran. More specific coagulation tests do exist, including diluted thrombin time (HEMOCLLOT) for  
1442 dabigatran and calibrated quantitative anti-factor Xa assays for factor Xa inhibitors.<sup>503</sup> However, these tests are  
1443 not always readily available and are often unnecessary for bleeding management.<sup>504</sup>

1444 We propose a simple scheme to manage bleeding events in patients on OAC (*Figure 11*). Minor  
1445 bleeding events should be treated with supportive measures such as mechanical compression or minor surgery to  
1446 achieve haemostasis. In patients receiving VKAs, the next dose of VKA can be postponed. NOACs have a short  
1447 plasma half-life of approximately 12 hours and improved haemostasis is expected within 12–24 hours after a  
1448 delayed or omitted dose. Treatment of moderate bleeding events may require blood transfusions and fluid  
1449 replacement. Specific diagnostic and treatment interventions directed against the cause of the bleeding (e.g.  
1450 gastroscopy) should be performed promptly. If the intake of NOAC was recent (< 2–4 h), charcoal  
1451 administration and/or gastric lavage will reduce further exposure. Dialysis clears dabigatran but is not effective  
1452 for the other NOACs.

1453 Immediate reversal of the antithrombotic effect is indicated in severe or life-threatening bleeding  
1454 events. An agreed, the institutional procedure for the management of life-threatening bleeds should be  
1455 documented and accessible at all times to ensure adequate initial management. For VKAs, administration of  
1456 fresh frozen plasma restores coagulation more rapidly than vitamin K, and prothrombin complex concentrates  
1457 achieve even faster blood coagulation.<sup>505</sup> Registry data suggest that the combination of plasma and prothrombin  
1458 complex concentrates is associated with the lowest case fatality following intracranial haemorrhage on VKA  
1459 treatment with an INR  $\geq 1.3$ .<sup>506</sup> In a multicentre randomized trial of 188 patients, four-factor prothrombin  
1460 complex concentrates achieved more rapid INR reversal and effective haemostasis than plasma in patients  
1461 undergoing urgent surgical or invasive procedures.<sup>507</sup> Administration of prothrombin complex concentrates may  
1462 also be considered for severe bleeding on NOAC treatment if specific antidotes are not available.

1463 Several antidotes to NOACs are under development. Idarucizumab (approved in 2015 by the US Food  
1464 and Drug Administration and the European Medicines Agency) is a clinically available humanized antibody  
1465 fragment that binds dabigatran and rapidly and dose-dependently reverses the effects without over-correction or  
1466 thrombin generation.<sup>475</sup> Andexanet alpha, a modified recombinant human factor Xa that lacks enzymatic  
1467 activity, reverses the anticoagulant activity of apixaban and rivaroxaban in healthy probands within minutes  
1468 after administration and for the duration of infusion, with a transient increase in markers of coagulation activity  
1469 of uncertain clinical relevance.<sup>508</sup> Another agent under development is ciraparantag (PER977), an antidote  
1470 targeted to reverse both direct thrombin and factor Xa inhibitors as well as the indirect inhibitor enoxaparin.<sup>509</sup>  
1471 The clinical usefulness of these specific antidotes needs further evaluation.

1472

1473 **Figure 11** Management of active bleeding in patients receiving anticoagulation.

1478

### 1479 9.6.2. Oral anticoagulation in atrial fibrillation patients at risk of or having a 1480 bleeding event

1481 While anticoagulation therapy should be paused to control active bleeding, absolute contraindications to long-  
1482 term OAC after a bleeding episode are rare. When nuisance bleeds are the reason to stop OAC, a change from  
1483 one anticoagulant to another seems reasonable. Many causes or triggers of major bleeding events can be treated  
1484 and/or eliminated, including uncontrolled hypertension, gastrointestinal ulcers, and intracranial aneurysms.  
1485 Reinitiation of anticoagulation after a bleeding event is often clinically justified.<sup>460, 510</sup> Difficult decisions,  
1486 including the discontinuation and recommencement of OAC, should be taken by a multidisciplinary team,  
1487 balancing estimated risk of recurrent stroke and bleeding, and considering the bleeding risk of different stroke  
1488 prevention therapies. LAA exclusion or occlusion might be an alternative in selected patients.

1489

#### 1490 Recommendations for management of bleeding

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding	IIa	B	511
When dabigatran is used, a reduced dose of dabigatran (110 mg twice daily) may be considered in patients > 75 years to reduce the risk of bleeding	IIb	B	490
In patients at high risk of gastrointestinal bleeding, a VKA or another NOAC should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily	IIa	B	321, 396, 402, 405, 490, 492, 493, 512

Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC	IIa	C	
Genetic testing before the initiation of VKA therapy is not recommended.	III (no benefit)	B	<sup>497</sup>
Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke-prevention interventions, improved management of factors that contributed to bleeding, and stroke risk	IIa	B	<sup>460</sup>
In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the underlying cause is resolved	I	C	

1491 AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation;

1492 VKA = vitamin K antagonist

1493 <sup>a</sup>Class of recommendation.

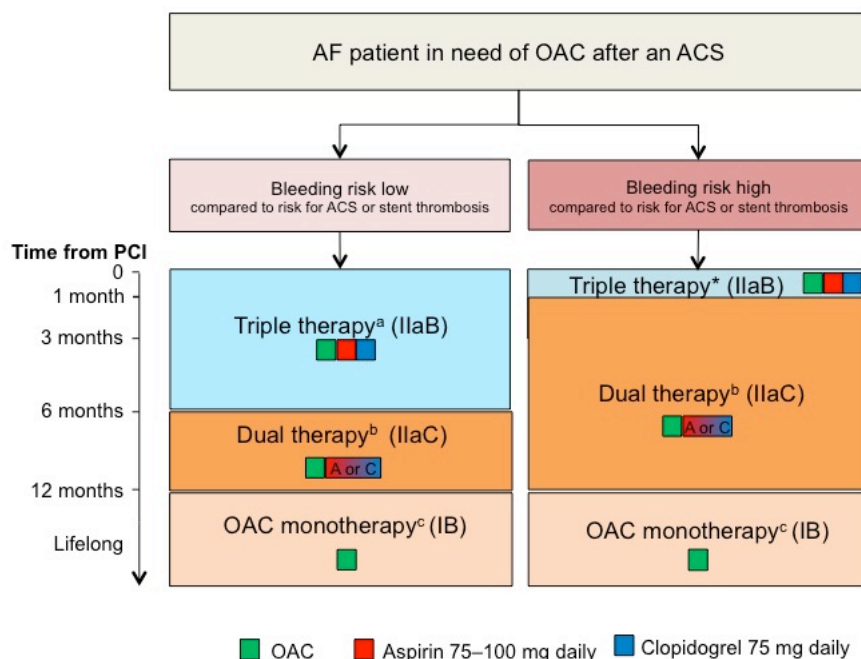
1494 <sup>b</sup>Level of evidence.

1495 <sup>c</sup>Reference(s) supporting recommendations.

1496

### 1497 **9.7. Combination therapy with oral anticoagulants and antiplatelets**

1498 Approximately 15% of AF patients in contemporary trials<sup>513</sup> and registries<sup>514-516</sup> have a history of myocardial  
 1499 infarction. Between 5% and 15% of AF patients will require stenting at some point in their lives. This scenario  
 1500 requires careful consideration of antithrombotic therapy, balancing bleeding risk, stroke risk, and risk of acute  
 1501 coronary syndromes (ACS).<sup>516</sup> Co-prescription of OAC with antiplatelet therapy, in particular triple therapy,  
 1502 increases the absolute risk of major haemorrhage.<sup>445, 517, 518</sup> A recent meta-analysis involving 30,866 patients  
 1503 with a recent ACS evaluated the effects of adding NOAC therapy to single (4135 patients) or dual (26,731  
 1504 patients) antiplatelet therapy.<sup>519</sup> The addition of a NOAC increased the bleeding risk by 79–134%, while  
 1505 reducing recurrent ischaemic events only marginally in patients without AF. OAC monotherapy, and not  
 1506 combination therapy with antiplatelets, is recommended in AF patients with stable CAD but without an ACS  
 1507 and/or coronary intervention in the previous 12 months. In patients treated for ACS and in those receiving a  
 1508 coronary stent, short-term triple combination therapy of OAC, clopidogrel, and aspirin seems warranted (*Figure*  
 1509 *12*).



1510

1511 **Figure 12** Antithrombotic therapy after an ACS in AF patients requiring anticoagulation.

1512 ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K

1513 antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

1514 <sup>a</sup>Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not

1515 receiving a stent or patients at a longer time from the index event.

1516 <sup>b</sup>OAC plus single antiplatelet.1517 <sup>c</sup>Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high

1518 risk of coronary events.

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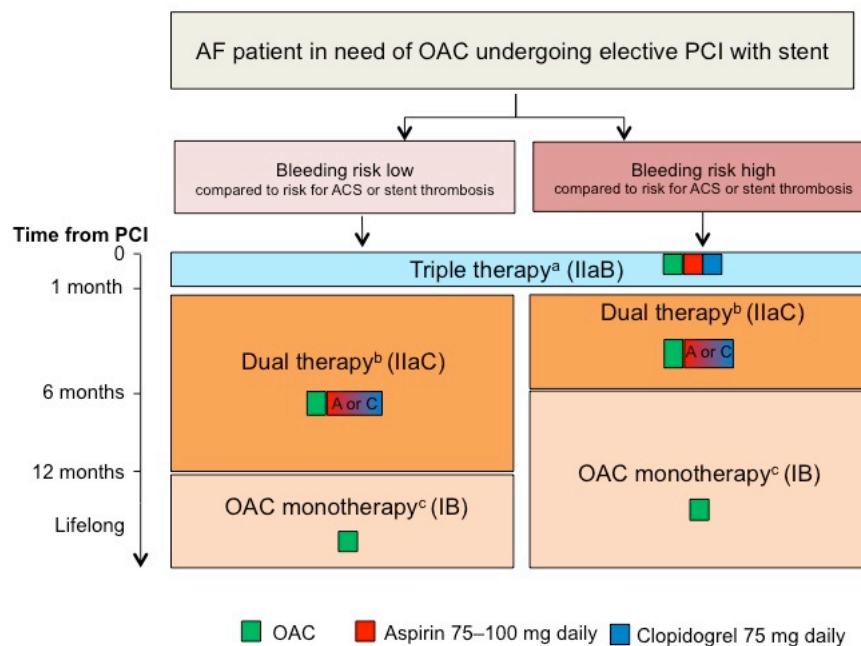
### 9.7.1. Antithrombotic therapy after acute coronary syndromes and percutaneous coronary intervention in patients requiring oral anticoagulation

The optimal combination antithrombotic therapy or duration of combination therapy for AF patients undergoing percutaneous coronary intervention is not known, but the continued bleeding risk suggests a short duration. Expert consensus,<sup>520</sup> reviewed and reconsidered by this Task Force, suggests the following principles: AF patients at risk for stroke, patients with mechanical valves, and patients with recent or recurrent deep vein thrombosis or pulmonary embolism should continue OAC during and after stenting. In general, a short period of triple therapy (OAC, aspirin, clopidogrel) is recommended, followed by a period of dual therapy (OAC plus a single antiplatelet) (Figure 13). When a NOAC is used, the consensus recommendation is that the lowest dose effective for stroke prevention in AF should be considered. Dose reduction beyond the dosing regimens tested in the phase III trials is not currently recommended, and awaits assessment in ongoing controlled trials. The combination of aspirin, clopidogrel, and low-dose rivaroxaban (2.5 mg twice daily) is not recommended for stroke prevention in AF.<sup>521</sup>

The use of prasugrel or ticagrelor as part of triple therapy should be avoided unless there is a clear need for these agents (e.g. stent thrombosis on aspirin plus clopidogrel), given the lack of evidence and the greater risk of major bleeding compared with clopidogrel.<sup>522, 523</sup> Ongoing trials will inform about such combination therapies in the future.

The omission of aspirin while maintaining clopidogrel and OAC has been evaluated in the WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary

1540 StenTing) trial, in which 573 anticoagulated patients undergoing percutaneous coronary intervention (70% with  
 1541 AF) were randomized to either dual therapy with OAC and clopidogrel (75 mg once daily) or to triple therapy  
 1542 with OAC, clopidogrel, and aspirin.<sup>524</sup> Bleeding was lower in the dual versus triple therapy arm, driven by fewer  
 1543 minor bleeding events. The rates of myocardial infarction, stroke, target vessel revascularization, and stent  
 1544 thrombosis did not differ (albeit with low event numbers), but all-cause mortality was lower in the dual therapy  
 1545 group at 1 year (2.5% vs. triple 6.4%). Although the trial was too small to assess ischaemic outcomes, dual  
 1546 therapy with OAC and clopidogrel may emerge in the future as an alternative to triple therapy in patients with  
 1547 AF and ACS and/or coronary intervention.<sup>525</sup>



1548  
 1549 **Figure 13** Antithrombotic therapy after percutaneous intervention in AF patients requiring anticoagulation.  
 1550 ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K  
 1551 antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.

1552 <sup>a</sup>Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.

1553 <sup>b</sup>OAC plus single antiplatelet.

1554 <sup>c</sup>Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high  
 1555 risk of coronary events.

1556

### 1557 Recommendations for combination therapy with oral anticoagulants and antiplatelets

1558

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
After elective coronary stenting for stable coronary artery disease in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events	IIa	B	522, 524
After an ACS with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel, and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events	IIa	C	520

After an ACS without stent implantation in AF patients at risk of stroke, dual therapy with an oral anticoagulant and aspirin or clopidogrel should be considered for up to 12 months to prevent recurrent coronary and cerebral ischaemic events	IIa	C	
The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding	IIa	B	520
Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy with aspirin in selected patients.	IIb	C	524, 525

1559 ACS = acute coronary syndromes; AF = atrial fibrillation

1560 <sup>a</sup>Class of recommendation.

1561 <sup>b</sup>Level of evidence.

1562 <sup>c</sup>Reference(s) supporting recommendations.

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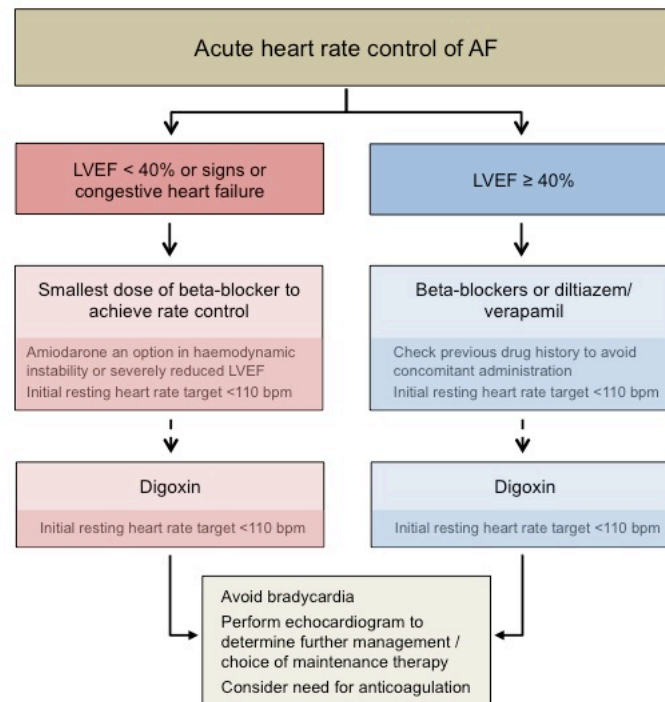
## 1564 **10 Rate control therapy in AF**

1565 Rate control is an integral part of the management of AF patients, and is often sufficient to improve AF-related  
 1566 symptoms. Compared with stroke prevention and rhythm control, very little robust evidence exists to inform the  
 1567 best type and intensity of rate control treatment, with the majority of data derived from short-term crossover  
 1568 trials and observational studies.<sup>41, 526-528</sup> Pharmacological rate control can be achieved for acute or long-term rate  
 1569 control with beta-blockers, digoxin, the calcium channel blockers diltiazem and verapamil, or combination  
 1570 therapy (*Table 15*). A number of antiarrhythmic drugs also have rate-limiting properties (amiodarone,  
 1571 dronedarone, sotalol, and to some extent propafenone), but they should only be used in patients needing rhythm  
 1572 control therapy (see Chapter 10).

1573

### 1574 **10.1. Acute rate control**

1575 In the setting of acute new-onset AF, patients are often in need of heart rate control. Physicians should evaluate  
 1576 underlying causes of elevated heart rate, such as infection, endocrine imbalance, anaemia, and pulmonary  
 1577 embolism. For acute rate control, beta-blockers and diltiazem/verapamil are preferred over digoxin because of  
 1578 their rapid onset of action and effectiveness at high sympathetic tone.<sup>528-532</sup> The choice of drug (*Table 15*) and  
 1579 target heart rate will depend on patient characteristics, symptoms, LVEF and haemodynamics, but a lenient  
 1580 initial approach to heart rate seems acceptable. Combination therapy may be required (*Figure 14*). In patients  
 1581 with evidence of HFrEF, beta-blockers, digitalis (digoxin or digitoxin), or their combination should be used,<sup>218,</sup>  
 1582 <sup>533</sup> as diltiazem and verapamil can have negative inotropic effects in patients with LVEF < 40%.<sup>222, 534, 535</sup> In  
 1583 critically ill patients and those with severely impaired LV systolic function, intravenous amiodarone can be used  
 1584 where excess heart rate is leading to haemodynamic instability.<sup>536-538</sup> Urgent cardioversion should be considered  
 1585 in unstable patients (see Chapter 10.2).



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1590

**Figure 14** Acute heart rate control of AF.

See Table 15 for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.  
AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

## 1591 10.2. Long-term pharmacological rate control

### 1592 10.2.1. Beta-blockers

1593 Beta-adrenoreceptor blocker monotherapy is often the first-line rate-controlling agent,<sup>539</sup> largely based on  
1594 observations of better acute heart rate control than digoxin. Interestingly, the prognostic benefit of beta-blockers  
1595 seen in HFrEF patients with sinus rhythm is lost in those with AF. In an individual patient-level meta-analysis  
1596 of RCTs, beta-blockers did not reduce all-cause mortality compared to placebo in those with AF at baseline (HR  
1597 0.97; 95% CI 0.83–1.14;  $P = 0.73$ ), whereas there was a clear benefit in patients with sinus rhythm (HR 0.73;  
1598 95% CI 0.67–0.80;  $P < 0.001$ ).<sup>23</sup> The study, which included 3066 participants with HFrEF and AF, showed  
1599 consistency across all subgroups and outcomes, with no heterogeneity between the 10 RCTs included ( $I^2 = 0\%$ ).  
1600 Despite this lack of prognostic benefit in HFrEF, this Task Force still considers beta-blockers as a useful first-  
1601 line rate control agent across all AF patients, based on the potential for symptomatic and cardiac function  
1602 improvement as a result of rate control, the lack of harm from published studies, and the good tolerability profile  
1603 across all ages in sinus rhythm and in AF.<sup>23, 540</sup>

1604

### 1605 10.2.2. Non-dihydropyridine calcium channel blockers

1606 Verapamil or diltiazem provides reasonable rate control in AF patients.<sup>541</sup> They should be avoided in patients  
1607 with HFrEF because of their negative inotropic effects.<sup>222, 534, 535</sup> Verapamil or diltiazem can improve  
1608 arrhythmia-related symptoms,<sup>526</sup> in comparison with beta-blockers, which reduced exercise capacity and  
1609 increased B-type natriuretic peptide in one small trial of low-risk patients with preserved LVEF.<sup>542</sup>

1610

### 1611 10.2.3. Digitalis

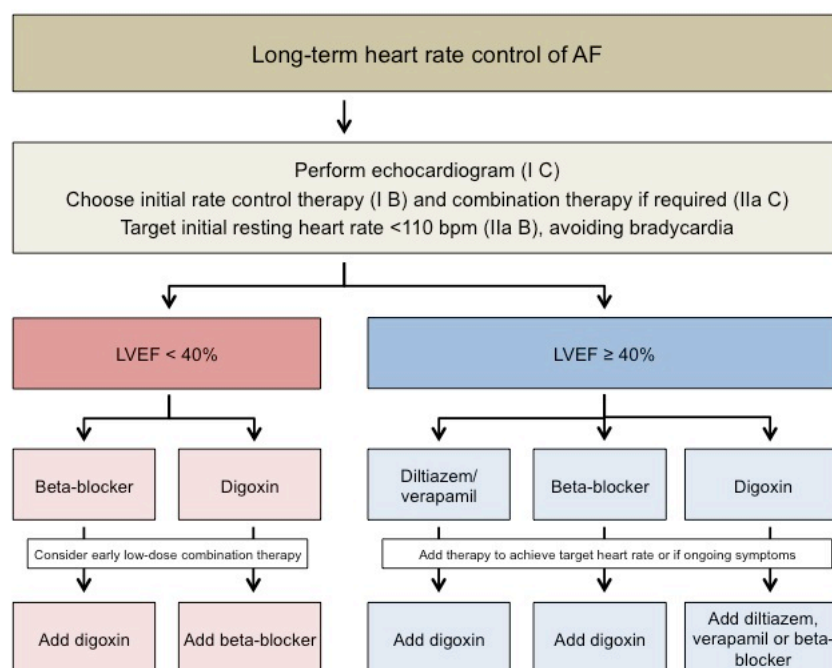
1612 Cardiac glycosides such as digoxin and digitoxin have been in use for over two centuries, although prescriptions  
1613 have been declining steadily over the past 15 years.<sup>543</sup> In the randomized Digitalis Investigation Group (DIG)  
1614 trial, digoxin had no effect on mortality compared to placebo in HFrEF patients in sinus rhythm (RR 0.99; 95%

1615 CI 0.91–1.07), but reduced hospital admissions (RR 0.72; 95% CI 0.66–0.79).<sup>544, 545</sup> There have been no head-  
 1616 to-head RCTs of digoxin in AF patients.<sup>546</sup> Observational studies have associated digoxin use with excess  
 1617 mortality in AF patients,<sup>547-549</sup> but this association is likely due to selection and prescription biases rather than  
 1618 harm caused by digoxin,<sup>550-553</sup> particularly as digoxin is commonly prescribed to sicker patients.<sup>225</sup> In a  
 1619 crossover mechanistic trial of 47 patients with HFrEF and AF, there were no differences in heart rate, blood  
 1620 pressure, walking distance, or LVEF between carvedilol and digoxin, although beta-blockers did result in higher  
 1621 B-type natriuretic peptide levels, combination carvedilol/digoxin improved LVEF, and digoxin withdrawal  
 1622 reduced LVEF.<sup>554</sup> Comparisons with other rate control therapies are based on small, short-duration studies that  
 1623 identify no or marginal differences in exercise capacity, quality of life, or LVEF compared to digoxin.<sup>526, 554-558</sup>  
 1624 Lower doses of digoxin ( $\leq 250 \mu\text{g}$  once daily), corresponding to serum digoxin levels of 0.5–0.9 ng/mL, may be  
 1625 associated with better prognosis.<sup>225</sup>

#### 1627 10.2.4. Amiodarone

1628 Amiodarone can be useful for rate control as a last resort. The wide array of extracardiac adverse effects  
 1629 associated with amiodarone renders it a reserve agent in patients whose heart rate cannot be controlled with  
 1630 combination therapy (e.g. beta-blocker or verapamil/diltiazem combined with digoxin).

1631  
 1632 In summary, there is equipoise for the use of different rate control agents in AF. The choice of beta-blocker,  
 1633 diltiazem/verapamil, digoxin, or combination therapy should be made on an individual basis, after consideration  
 1634 of patient characteristics and patient preference. All available therapies have the potential for adverse effects and  
 1635 patients should initially be treated with a low dose and uptitrated to achieve symptom improvement. In practice,  
 1636 achieving a heart rate  $< 110$  bpm will often require combination therapy (*Figure 15*). The benefit of different  
 1637 rate control strategies on symptoms, quality of life, and other intermediate outcomes is under investigation.<sup>559</sup>



1638  
 1639 **Figure 15** Long-term heart rate control of AF.

1640 See *Table 15* for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.  
 1641 AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

1642

### 1643 10.3. Heart rate targets in atrial fibrillation



1644 The optimal heart rate target in AF patients is unclear. The RACE (Rate Control Efficacy in Permanent Atrial  
 1645 Fibrillation) II study randomized 614 patients with permanent AF to either a target heart rate < 80 bpm at rest  
 1646 and < 110 bpm during moderate exercise, or to a lenient heart rate target of < 110 bpm. There was no difference  
 1647 in a composite of clinical events (14.9% in the strict rate control group, 12.9% in the lenient group),<sup>560</sup> NYHA  
 1648 class, or hospitalizations.<sup>560, 561</sup> Similar results were found in a pooled analysis of the AFFIRM (Atrial  
 1649 Fibrillation Follow-up Investigation of Rhythm Management) and RACE trials (1091 participants), albeit with  
 1650 smaller heart rate differences and without randomization.<sup>562</sup> It is worthwhile to note that many ‘adequately rate-  
 1651 controlled’ patients (resting heart rate 60–100 bpm) are severely symptomatic, calling for additional  
 1652 management.<sup>194</sup> Nonetheless, lenient rate control is an acceptable initial approach, regardless of heart failure  
 1653 status, unless symptoms call for stricter rate control.  
 1654

#### 1655 10.4. Atrioventricular node ablation and pacing

1656 Ablation of the atrioventricular node/His bundle and implantation of a VVI pacemaker can control ventricular  
 1657 rate when medications fail to control rate and symptoms. It is a relatively simple procedure with a low  
 1658 complication rate and low long-term mortality risk,<sup>563, 564</sup> especially when the pacemaker is implanted a few  
 1659 weeks before the AV nodal ablation and the initial pacing rate after ablation is set at 70–90 bpm.<sup>565, 566</sup> The  
 1660 procedure does not worsen LV function<sup>567</sup> and may even improve LVEF in selected patients.<sup>568-570</sup> In some  
 1661 patients in heart failure treated with biventricular pacing (cardiac resynchronization therapy), AF can  
 1662 terminate,<sup>571</sup> although such a ‘rhythm control’ effect of cardiac resynchronization therapy is likely to be small  
 1663 and clearly needs confirmation.<sup>572</sup> AV nodal ablation renders patients pacemaker-dependent for the rest of their  
 1664 lives, limiting AV nodal ablation and pacing to patients whose symptoms cannot be managed by rate controlling  
 1665 medication or by reasonable rhythm control interventions. The choice of pacing therapy (right ventricular or  
 1666 biventricular pacing with or without an implantable defibrillator) will depend on individual patient  
 1667 characteristics, including LVEF.<sup>573, 574</sup>  
 1668

#### 1669 Recommendations for rate control

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Beta-blocker, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥ 40%	I	B	225, 526, 528, 531, 532, 541, 555, 575
Beta-blocker and/or digoxin are recommended to control heart rate in AF patients with LVEF < 40%	I	B	23, 225, 526, 533, 554, 575, 576
Combination therapy comprising different rate controlling agents should be considered if a single agent does not achieve the necessary heart rate target	IIa	C	23, 554, 577
In cases of haemodynamic instability or severe depression in LVEF, amiodarone may be considered for acute control of heart rate	IIb	B	536-538
In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs should not routinely be used for rate control	III (harm)	A	41, 578, 579
A resting heart rate of < 110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy	IIa	B	560
Rhythm rather than rate control strategies should be considered as the preferred management in pre-excited AF and AF during pregnancy	IIa	C	
Atrioventricular node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, accepting that these patients will become pacemaker dependent	IIa	B	184, 564, 569

1670 AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

1671 Digitoxin is a suitable alternative to digoxin, where available. In patients with heart failure with reduced ejection  
 1672 fraction (LVEF < 40%), recommended beta-blockers are bisoprolol, carvedilol, long-acting metoprolol, and  
 1673 nebivolol.

1674 <sup>a</sup>Class of recommendation.

1675 <sup>b</sup> Level of evidence.1676 <sup>c</sup> Reference(s) supporting recommendations.

1677

1678 **Table 15 Rate control therapy in AF**

Therapy	Acute intravenous rate control	Long-term oral rate control	Side-effect profile	Comments
<b>Beta-blockers<sup>a</sup></b>				
Bisoprolol	Not available	1.25–20 mg once daily or split	Most common reported adverse symptoms are lethargy, headache, peripheral oedema, upper respiratory tract symptoms, gastrointestinal upset, and dizziness. Adverse effects include bradycardia, atrioventricular block, and hypotension	Bronchospasm is rare – in cases of asthma, recommend beta-1 selective agents (avoid carvedilol). Contraindicated in acute cardiac failure and a history of severe bronchospasm
Carvedilol	Not available	3.125–50 mg twice daily		
Metoprolol	2.5–10 mg intravenous bolus (repeated as required)	100–200 mg total daily dose (according to preparation)		
Nebivolol	N/A	2.5–10 mg once daily or split		
Esmolol	0.5 mg intravenous bolus over 1 min; then 0.05–0.25 mcg/kg/min			
<b>Calcium-channel blockers</b>				
Diltiazem	15–25 mg intravenous bolus (repeated as required)	60 mg three times daily up to 360 mg total daily dose (120–360 mg once daily modified release)	Most common reported adverse symptoms are dizziness, malaise, lethargy, headache, hot flushes, gastrointestinal upset, and oedema. Adverse effects include bradycardia, atrioventricular block, and hypotension (prolonged hypotension possible with verapamil)	Use with caution in combination with beta-blockers. Reduce dose with hepatic impairment and start with smaller dose in renal impairment. Contraindicated in LV failure with pulmonary congestion or LVEF < 40%
Verapamil	2.5–10 mg intravenous bolus (repeated as required)	40–120 mg three times daily (120–480 mg once daily modified release)		
<b>Cardiac glycosides</b>				
Digoxin	0.5 mg intravenous bolus (0.75–1.5 mg over 24 h in divided doses)	0.0625–0.25 mg daily dose	Most common reported adverse symptoms are gastrointestinal upset, dizziness, blurred vision, headache, and rash. In toxic states (serum levels > 2 ng/mL), digoxin is proarrhythmic and can aggravate heart failure, particularly with coexistent hypokalaemia	High plasma levels associated with increased risk of death. Check renal function before starting and adapt dose in patients with CKD. Contraindicated in accessory conducting pathways, ventricular tachycardia, and hypertrophic cardiomyopathy with outflow tract obstruction
Digitoxin	0.4–0.6 mg intravenous bolus	0.05–0.3 mg daily dose		
<b>Specific indications</b>				
Amiodarone	300 mg	200 mg daily	Hypotension,	Suggested as

intravenously diluted in 250 mL 5% dextrose over 30–60 min (preferably via central venous cannula)<sup>b</sup>

bradycardia, nausea, QT prolongation, pulmonary toxicity, skin discolouration, thyroid dysfunction, corneal deposits, and cutaneous reaction with extravasation

adjunctive therapy in patients where heart rate control cannot be achieved using combination therapy

1679 AF = atrial fibrillation; CKD = chronic kidney disease; LV = left ventricular; LVEF = left ventricular ejection  
1680 fraction.

1681 <sup>a</sup>A number of other beta-blockers are also available, but are not recommended as specific rate control therapy in  
1682 AF. These include atenolol (25–100 mg once daily with a short biological half-life), propranolol (non-selective,  
1683 1 mg over 1 min and repeat up to 3 mg at 2-min intervals [acute] or 10–40 mg three times daily [long-term]), or  
1684 labetalol (non-selective, 1–2 mg/min [acute]).

1685 <sup>b</sup>If ongoing requirement for amiodarone, follow with 900 mg intravenous over 24 hours diluted in 500–1000 mL  
1686 via a central venous cannula.

1687

## 1688 **11 Rhythm control therapy in atrial fibrillation**

1689 Restoring and maintaining sinus rhythm is an integral part of AF management. Antiarrhythmic drugs  
1690 approximately double the rate of sinus rhythm compared with placebo.<sup>580-584</sup> Catheter ablation or combination  
1691 therapy is often effective when antiarrhythmic drugs fail.<sup>226, 585-587</sup> Although many clinicians believe that  
1692 maintaining sinus rhythm can improve outcomes in AF patients,<sup>588</sup> all trials that have compared rhythm control  
1693 to rate control (with appropriate anticoagulation) therapy have resulted in neutral outcomes.<sup>41, 578, 579, 582, 589-593</sup>

1694 Whether modern rhythm control management involving catheter ablation, combination therapy, and early  
1695 therapy leads to a reduction in major cardiovascular events (e.g. stroke and cardiovascular death) is currently  
1696 under investigation (e.g. in the EAST [Early treatment of Atrial fibrillation for Stroke prevention Trial] –  
1697 AFNET 4<sup>40</sup> and CABANA [Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial]<sup>594</sup>  
1698 trials). For now, rhythm control therapy is indicated to improve symptoms in AF patients who remain  
1699 symptomatic on adequate rate control therapy.

1700

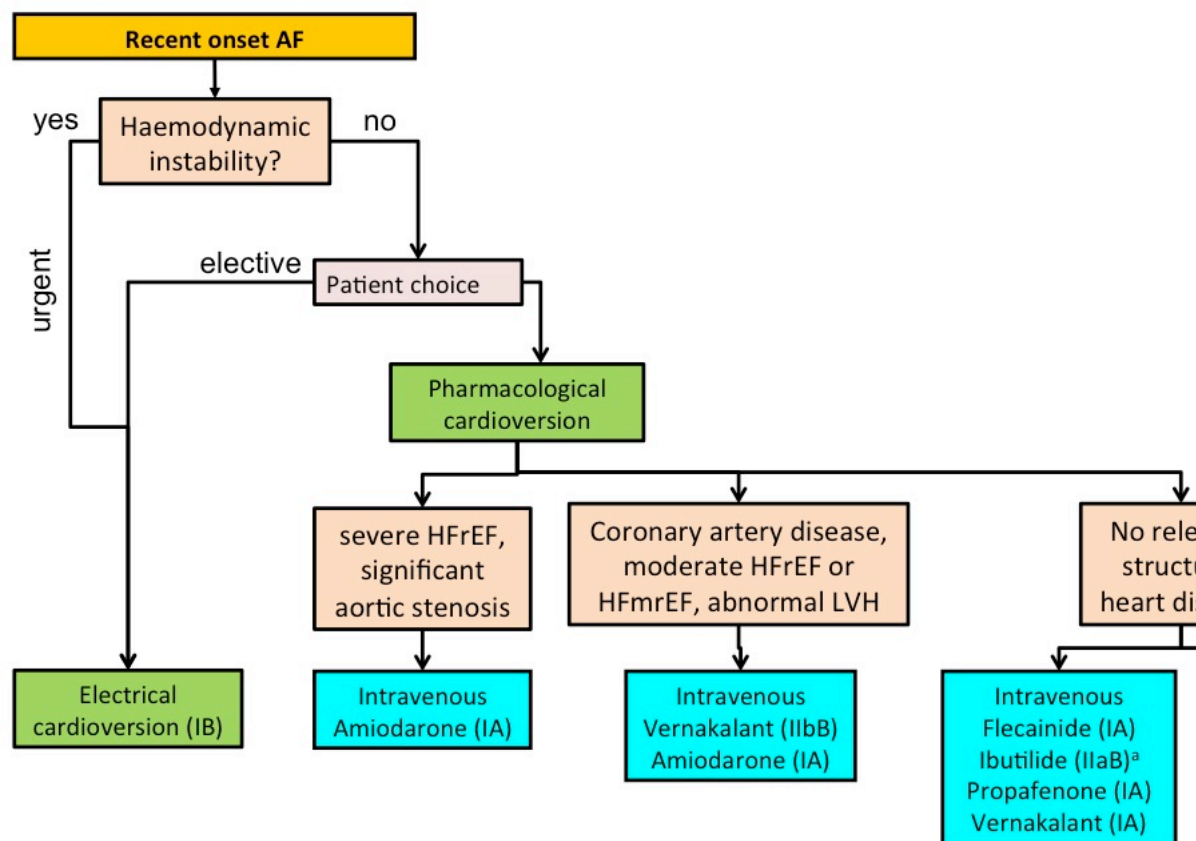
### 1701 **11.1. Acute restoration of sinus rhythm**

#### 1702 **11.1.1. Antiarrhythmic drugs for acute restoration of sinus rhythm**

##### 1703 **(‘pharmacological cardioversion’)**

1704 Antiarrhythmic drug can restore sinus rhythm in patients with AF (pharmacological cardioversion) as  
1705 shown in small controlled trials, meta-analyses,<sup>41, 584, 595, 596</sup> and in a few larger controlled trials.<sup>597-605</sup>  
1706 Outside of Europe, dofetilide is available and can convert recent-onset AF.<sup>606</sup> Pharmacological cardioversion  
1707 restores sinus rhythm in approximately 50% of patients with recent-onset AF (*Table 16*).<sup>607-609</sup> In the short term,  
1708 electrical cardioversion restores sinus rhythm quicker and more effectively than pharmacological cardioversion  
1709 and is associated with shorter hospitalization.<sup>609-613</sup> Pharmacological cardioversion, conversely, does not require  
1710 sedation or fasting (*Figure 16*).

1711 Flecainide and propafenone are effective for pharmacological cardioversion,<sup>595, 602-605, 614, 615</sup> but their  
1712 use is restricted largely to patients without structural heart disease. Ibutilide is an alternative where available,  
1713 but carries a risk of torsades de pointes.<sup>615</sup> Vernakalant<sup>602-605</sup> can be given to patients with mild heart failure  
1714 (NYHA Class I or II), including those with ischaemic heart disease, provided they do not present with  
1715 hypotension or severe aortic stenosis.<sup>616-618</sup> Amiodarone can be used in patients with heart failure and in patients  
1716 with ischaemic heart disease (although patients with severe heart failure were excluded in most of the AF  
1717 cardioversion trials).<sup>596</sup> Amiodarone also slows heart rate by 10–12 bpm after 8–12 hours when given  
1718 intravenously.<sup>596</sup> Both amiodarone and flecainide appear more effective than sotalol in restoring sinus  
1719 rhythm.<sup>600, 601, 619</sup>



1720

1721 **Figure 16** Rhythm control management of acute AF.1722 AF = atrial fibrillation; HFmrEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with  
1723 reduced ejection fraction.1724 <sup>a</sup>Ibutilide should not be used in patients with long QT interval.

1725

1726 **11.1.2. 'Pill in the pocket' cardioversion performed by patients**

1727 In selected patients with infrequent symptomatic episodes of paroxysmal AF, a single bolus of oral flecainide  
1728 (200–300 mg) or propafenone (450–600 mg) can be self-administered by the patient at home ('pill in the pocket'  
1729 therapy) to restore sinus rhythm, after safety has been established in the hospital setting.<sup>620</sup> This approach seems  
1730 marginally less effective than hospital-based cardioversion,<sup>621</sup> but is practical and provides control and  
1731 reassurance to selected patients.

1732

1733 **Table 16** Antiarrhythmic drugs for pharmacological cardioversion

Drug	Route	First dose	Follow-up dose	Risks	References
<b>Flecainide</b>	Oral	200–300 mg	N/A	Avoid in patients with IHD and/or significant structural heart disease. Hypotension, atrial flutter with 1:1 conduction, QT prolongation	595, 598
	IV	1.5–2 mg/kg over 10 min			
<b>Amiodarone</b>	IV <sup>a</sup>	5–7 mg/kg over 1–2 h	50 mg/h to a maximum of 1.0 g over 24 h	Phlebitis, hypotension, bradycardia/AV block. Will slow ventricular rate. Delayed conversion to sinus rhythm (8–12 h)	596–601
<b>Propafenone</b>	IV	1.5–2 mg/kg over 10 min		Avoid in patients with IHD and/or significant structural heart disease. Hypotension, atrial flutter with 1:1	622–625

	Oral	450–600 mg		conduction, QRS prolongation (mild)	
<b>Ibutilide<sup>b</sup></b>	IV	1 mg over 10 min	1 mg over 10 min after waiting for 10 min	Avoid in patients with QT prolongation, hypokalemia, severe LVH, or low ejection fraction. QT prolongation, polymorphic ventricular tachycardia/torsades de pointes (3–4% of patients). Will slow ventricular rate	614, 615
<b>Vernakalant</b>	IV	3 mg/kg over 10 min	2 mg/kg over 10 min after waiting for 15 min	Avoid in patients with systolic blood pressure < 100 mmHg, recent (< 30 days) ACS, NYHA Class III and IV heart failure, QT interval prolongation (uncorrected QT > 440 ms), and severe aortic stenosis. Hypotension, non-sustained ventricular arrhythmias, QT and QRS prolongation	602-605, 618

1734 ACS = acute coronary syndromes; IHD = ischaemic heart disease; IV = intravenous; LVH = left ventricular  
 1735 hypertrophy; NYHA = New York Heart Association.

1736 <sup>a</sup>Use a large peripheral vessel and change to oral amiodarone within 24 h of IV (central line) administration.

1737 <sup>b</sup>Ibutilide is only available in selected European countries.

1738

### 1739 11.1.3. Electrical cardioversion

1740 Synchronized direct current electrical cardioversion quickly and effectively converts AF to sinus rhythm and is  
 1741 the method of choice in severely haemodynamically compromised patients with new-onset AF (*Figure 16*).<sup>626-</sup>  
 1742 <sup>628</sup> Electrical cardioversion can be performed safely in sedated patients treated with intravenous midazolam  
 1743 and/or propofol. Continuous monitoring of blood pressure and oximetry during the procedure is important.<sup>629</sup>  
 1744 Skin burns may occasionally be observed. Intravenous atropine or isoproterenol or temporary transcutaneous  
 1745 pacing should be available to mitigate post-cardioversion bradycardia. Biphasic defibrillators are more effective  
 1746 than monophasic waveforms, and have become industry standard.<sup>626, 628</sup> Anterior–posterior electrode positions  
 1747 generate a stronger shock field in the left atrium than anterolaterally positioned electrodes, and restore sinus  
 1748 rhythm more effectively.<sup>626, 627, 630</sup>

1749 Pretreatment with amiodarone (requiring a few weeks of therapy),<sup>631, 632</sup> sotalol,<sup>631</sup> ibutilide,<sup>633</sup> or  
 1750 vernakalant<sup>634</sup> can improve efficacy of electrical cardioversion, and similar effects are likely for flecainide<sup>584</sup>  
 1751 and propafenone.<sup>635</sup> Beta-blockers,<sup>636</sup> verapamil, diltiazem,<sup>637-639</sup> and digoxin<sup>640, 641</sup> do not reliably terminate AF  
 1752 or facilitate electrical cardioversion. When antiarrhythmic drug therapy is planned to maintain sinus rhythm  
 1753 after cardioversion, it seems prudent to start therapy 1–3 days before cardioversion (amiodarone: a few weeks)  
 1754 to promote pharmacological conversion and to achieve effective drug levels.<sup>584, 601</sup>

1755

### 1756 11.1.4. Anticoagulation in patients undergoing cardioversion

1757 Cardioversion carries an inherent risk of stroke in non-anticoagulated patients,<sup>642</sup> which is reduced substantially  
 1758 by the administration of anticoagulation.<sup>643</sup> Immediate initiation of anticoagulation is important in all patients  
 1759 scheduled for cardioversion.<sup>644-646</sup> Patients who have been in AF for longer than 48 hours should start OAC at  
 1760 least 3 weeks before cardioversion and continue it for 4 weeks afterwards (in patients without a need for long-  
 1761 term anticoagulation), and continue it indefinitely in patients at risk of stroke. This practice has never been  
 1762 evaluated in controlled trials, but seemed safe in a large observational data set from Finland.<sup>647</sup> When early  
 1763 cardioversion is desired, TOE can exclude the majority of left atrial thrombi, allowing immediate  
 1764 cardioversion.<sup>648, 649</sup> Ongoing studies will inform about the safety and efficacy of newly initiated anticoagulation  
 1765 using NOACs in patients scheduled for electrical cardioversion.

1766

## 1767 11.2. Long-term antiarrhythmic drug therapy

1768 The aim of antiarrhythmic drug therapy is improvement in AF-related symptoms.<sup>41, 580</sup> Hence, the decision to  
 1769 initiate long-term antiarrhythmic drug therapy needs to balance symptom burden, possible adverse drug  
 1770 reactions, and patient preferences. The principles of antiarrhythmic drug therapy outlined in the 2010 ESC AF  
 1771 guidelines<sup>369</sup> are still relevant and should be observed:

- 1772 1. Treatment is aimed at reducing AF-related symptoms;
- 1773 2. Efficacy of antiarrhythmic drugs to maintain sinus rhythm is modest;

- 1774 3. Clinically successful antiarrhythmic drug therapy may reduce rather than eliminate the recurrence of  
1775 AF;  
1776 4. If one antiarrhythmic drug ‘fails’, a clinically acceptable response may be achieved with another agent;  
1777 5. Drug-induced proarrhythmia or extra-cardiac side-effects are frequent;  
1778 6. Safety rather than efficacy considerations should primarily guide the choice of antiarrhythmic drug.  
1779

1780 Antiarrhythmic drug therapy approximately doubles sinus rhythm maintenance compared with no therapy.<sup>580</sup>  
1781 There is no appreciable effect on mortality or cardiovascular complications, but rhythm control therapy can  
1782 slightly increase the risk of hospitalizations (often for AF).<sup>41, 578, 579, 582, 589-593</sup> To reduce the risk of side-  
1783 effects,<sup>201, 580</sup> a shorter duration of antiarrhythmic drug therapy seems desirable. As an example, short-term  
1784 treatment (4 weeks) with flecainide for 4 weeks after cardioversion of AF was well-tolerated and prevented  
1785 most (80%) AF recurrences when compared with long-term treatment.<sup>584</sup> Short-term antiarrhythmic drug  
1786 therapy is also used to avoid early AF recurrences after catheter ablation<sup>650</sup> and may be reasonable in patients  
1787 deemed at increased risk of antiarrhythmic drug side-effects or in those with a low perceived risk of recurrent  
1788 AF.

1789 In addition to antiarrhythmic drug therapy and catheter ablation (see Section 10.3), management of  
1790 concomitant cardiovascular conditions can reduce symptom burden in AF and facilitate maintenance of sinus  
1791 rhythm.<sup>203, 204, 296, 312</sup> This includes weight reduction, blood pressure control, heart failure treatment, increasing  
1792 cardiorespiratory fitness, and other measures (see Chapter 6).  
1793

### 1794 11.2.1. Selection of antiarrhythmic drugs for long-term therapy: Safety first!

1795 Usually, the safety of antiarrhythmic drug therapy determines the initial choice of antiarrhythmic drugs (*Figure*  
1796 *17*). The following major antiarrhythmic drugs are available to prevent AF:  
1797

1798 **Amiodarone** is an effective multichannel blocker, reduces ventricular rate, and is safe in patients with heart  
1799 failure.<sup>582, 651</sup> Torsades de pointes proarrhythmia can occur, and QT interval and TU waves should be monitored  
1800 on therapy (see *Table 17*).<sup>652</sup> Amiodarone often causes extracardiac side-effects, especially on long-term  
1801 therapy,<sup>653, 654</sup> rendering it a second-line treatment in patients who are suitable for other antiarrhythmic drugs.  
1802 Amiodarone appears less suitable to episodic short-term therapy (unless after catheter ablation),<sup>655</sup> probably  
1803 because of its long biological half-life.  
1804

1805 **Dronedarone** maintains sinus rhythm, reduces ventricular rate, and prevents cardiovascular hospitalizations  
1806 (mostly due to AF) and cardiovascular death in patients with paroxysmal or persistent AF or flutter who had at  
1807 least one relevant cardiovascular comorbidity.<sup>583, 588, 656</sup> Dronedarone increases mortality in patients with  
1808 recently decompensated heart failure (with or without AF)<sup>657</sup> and in patients with permanent AF in whom sinus  
1809 rhythm is not restored.<sup>658</sup> Dronedarone moderately increases serum creatinine, reflecting a reduction in  
1810 creatinine excretion rather than a decline in kidney function.<sup>659</sup>  
1811

1812 **Flecainide** and **propafenone** are effective in preventing recurrent AF.<sup>581, 584, 620</sup> They should only be used in  
1813 patients without significant ischaemic heart disease or heart failure to avoid the risk of life-threatening  
1814 ventricular arrhythmias.<sup>660</sup> High ventricular rates resulting from the conversion of AF into atrial flutter with 1:1  
1815 conduction by flecainide or propafenone can be prevented by preadministering a beta-blocker, verapamil, or  
1816 diltiazem.  
1817

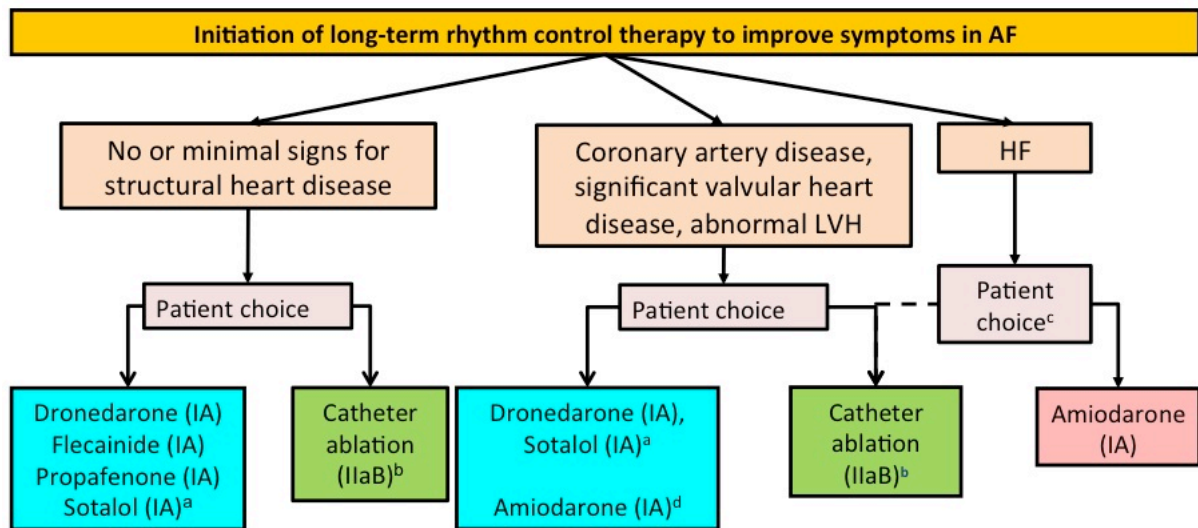
1818 **Quinidine** and **disopyramide** have been associated with an increase in all-cause mortality (OR 2.39; 95% CI  
1819 1.03–5.59; number needed to harm 109; 95% CI 34–4985) at 1-year follow-up,<sup>580, 661</sup> likely due to ventricular  
1820 arrhythmias (torsades de pointes).<sup>580, 661</sup> Although this proarrhythmic effect is more common at higher doses,  
1821 they are less commonly used for rhythm control in AF. Disopyramide may be useful in ‘vagally mediated’ AF  
1822 (e.g. AF occurring in athletes and/or during sleep<sup>76</sup>), and has been shown to reduce LV outflow gradient and  
1823 improve symptoms in patients with hypertrophic cardiomyopathy.<sup>662-664</sup>  
1824

1825 **Sotalol** has a relevant risk of torsades de pointes (1% in the Prevention of Atrial Fibrillation After Cardioversion  
1826 [PAFAC] trial<sup>118</sup>). Its d-enantiomer is associated with an increased mortality compared to placebo in patients  
1827 with LV dysfunction post-myocardial infarction,<sup>665</sup> probably due to ventricular arrhythmias (OR 2.47; 95% CI  
1828 1.2–5.05; number needed to harm 166; 95% CI 61–1159).<sup>580, 665</sup> On the other hand, d,l sotalol has been used in  
1829 AF patients without safety signals in two controlled trials.<sup>581, 601</sup>  
1830

1831 **Dofetilide** is another potassium channel blocker that is mainly available outside of Europe. Dofetilide restores  
1832 and maintains sinus rhythm in heart failure patients<sup>666</sup> and occasionally in patients refractory to other  
1833 antiarrhythmic drugs.<sup>667</sup>

1834

1835 Overall, it seems prudent to limit the use of quinidine, disopyramide, dofetilide, and sotalol to specific  
 1836 situations. Similarly, combinations of QT-prolonging antiarrhythmic drugs should generally be avoided (*Table*  
 1837 *17*).



1838

1839 **Figure 17** Initiation of rhythm control therapy in symptomatic patients.

1840 AF = atrial fibrillation; HF = heart failure; LVH = left ventricular hypertrophy;

1841 <sup>a</sup>Sotalol requires careful evaluation of proarrhythmic risk.

1842 <sup>b</sup>Catheter ablation should isolate pulmonary veins and can be performed using radiofrequency or cryoballoon catheters.

1843 <sup>c</sup>Catheter ablation as a first-line therapy is usually reserved for heart failure patients with tachycardiomyopathy.

1844 <sup>d</sup>Amiodarone is a second-choice therapy in many patients because of its extracardiac side-effects.

1845

1846

### 1847 11.2.2. Twelve-lead electrocardiogram as a tool to identify patients at risk of 1848 proarrhythmia

1849 Identifying patients at risk of proarrhythmia can help to mitigate the proarrhythmic risk of antiarrhythmic  
 1850 drugs.<sup>668</sup> In addition to the clinical characteristics mentioned above, monitoring PR, QT, and QRS durations  
 1851 during initiation of antiarrhythmic drug therapy can identify patients at higher risk of drug-induced  
 1852 proarrhythmia on longer-term treatment.<sup>669-671</sup> In addition, the presence of ‘abnormal TU waves’ is a sign of  
 1853 imminent torsades de pointes.<sup>652</sup> Periodic ECG analysis for proarrhythmia signs has been used successfully in  
 1854 recent antiarrhythmic drug trials.<sup>118, 584, 672</sup> Specifically, ECG monitoring was used systematically on days 1–3 in  
 1855 patients receiving flecainide, propafenone, or sotalol to identify those at risk of proarrhythmia.<sup>118, 584, 601</sup> Based  
 1856 on this evaluated practice, we suggest to record an ECG in all patients before initiation of antiarrhythmic drugs.  
 1857 Scheduled ECGs during the initiation period seem reasonable (*Table 17*).

1858

1859 **Table 17** Oral antiarrhythmic drugs used for maintaining sinus rhythm after cardioversion.

Drug	Dose	Main contraindications and precautions	Warning signs warranting discontinuation	Atrioventricular nodal slowing	Suggested ECG monitoring during initiation
Amiodarone	600 mg in divided doses for 4 weeks, 400 mg for 4 weeks, then 200 mg once daily	Caution when using concomitant therapy with QT-prolonging drugs and in patients with sinoatrial node or atrioventricular node and conduction disease. The dose of VKAs and of digitalis should be reduced. Increased risk of myopathy with statins. Caution in patients with pre-existing liver disease	QT prolongation > 500 ms	10–12 bpm in AF	Baseline, 1 week, 4 weeks
Dronedarone	400 mg twice daily	Contraindicated in NYHA class III or IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, or powerful CYP3A4 inhibitors (e.g. verapamil, diltiazem, azole antifungal agents), and when CrCl < 30 mg/mL. The dose of digitalis, beta-blockers, and of some statins should be reduced. Elevations in serum creatinine of 0.1–0.2 mg/dL are common and do not reflect a decline in renal function. Caution in patients with pre-existing liver disease	QT prolongation > 500 ms	10–12 bpm in AF	Baseline, 1 week, 4 weeks
Flecainide	100–150 mg twice daily	Contraindicated if CrCl < 50 mg/mL, liver disease, IHD, or reduced LVEF.	QRS duration increases > 25% above baseline	None	Baseline, day 1, day 2–3
Flecainide slow release	200 mg once daily	Caution in the presence of sinoatrial node or atrioventricular node or conduction system disease. CYP2D6 inhibitors (e.g. fluoxetine, tricyclic) increase plasma concentration			
Propafenone	150–300 mg three times daily	Contraindicated in IHD or reduced LV ejection fraction. Caution in the presence of sinoatrial node or atrioventricular node and conduction system disease, renal or liver impairment, and asthma. Increases concentration of digitalis and warfarin	QRS duration increase > 25% above baseline	Slight	Baseline, day 1, day 2–3
Propafenone SR	225–425 mg twice daily				
d,l sotalol	80–160 mg twice daily	Contraindicated in the presence of significant LV hypertrophy, systolic heart failure, asthma, pre-existing QT prolongation, hypokalaemia, CrCl < 50 mg/mL. Moderate renal dysfunction requires careful adaptation of dose	QT interval > 500 ms, QT prolongation by > 60 ms upon therapy initiation	Similar to high-dose blockers	Baseline, day 1, day 2–3



1860 AF = atrial fibrillation; bpm = beats per minute; CrCl = creatinine clearance; ECG = electrocardiogram; IHD =  
 1861 ischaemic heart disease; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York  
 1862 Heart Association; VKA = vitamin K antagonist.

1863

### 1864 11.2.3. New antiarrhythmic drugs

1865 Several compounds that inhibit the ultrarapid potassium current ( $I_{Kur}$ ) and other inhibitors of atypical ion  
 1866 channels are in clinical development.<sup>673-675</sup> They are not available for clinical use at present. The antianginal  
 1867 compound ranolazine inhibits potassium and sodium currents and increases glucose metabolism at the expense  
 1868 of free fatty acid metabolism, thereby enhancing efficient use of oxygen.<sup>676, 677</sup> Ranolazine was safe in patients  
 1869 with non-ST-segment elevation myocardial infarction and unstable angina evaluated in the MERLIN  
 1870 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome)  
 1871 trial.<sup>678</sup> In a post-hoc analysis of continuous ECG recordings obtained during the first 7 days after  
 1872 randomization, patients assigned to ranolazine had a trend towards fewer episodes of AF than those on placebo  
 1873 (75 [2.4%] vs. 55 [1.7%] patients;  $P = 0.08$ ).<sup>679</sup> In the HARMONY (A Study to Evaluate the Effect of  
 1874 Ranolazine and Dronedaron When Given Alone and in Combination in Patients With Paroxysmal Atrial  
 1875 Fibrillation) trial, the highest tested dose of a combination of ranolazine (750 mg twice daily) and dronedarone  
 1876 (225 mg twice daily) slightly reduced AF burden in 134 subjects with paroxysmal AF and dual-chamber  
 1877 pacemakers.<sup>680</sup> Small, open-label studies suggest that ranolazine might enhance the antiarrhythmic effect of  
 1878 amiodarone for cardioversion,<sup>681-683</sup> whereas the results from a controlled trial of ranolazine and the ranolazine-  
 1879 dronedarone combination to prevent AHRE in pacemaker patients were ambiguous.<sup>684</sup> At present, there is  
 1880 insufficient evidence to recommend ranolazine as an antiarrhythmic drug, alone or in combination with other  
 1881 antiarrhythmic drugs. Of note, the ‘funny channel blocker’ ivabradine, which is used for angina and heart  
 1882 failure, increases the risk of AF.<sup>685</sup>

1883

### 1884 11.2.4. Antiarrhythmic effects of non-antiarrhythmic drugs

1885 ACE inhibitors or ARBs appear to prevent new-onset AF in patients with LV dysfunction and in hypertensive  
 1886 patients with LV hypertrophy.<sup>219, 236, 237, 239, 246, 250, 686</sup> Nephilysin inhibition needs to be studied further, but does  
 1887 not seem to enhance this effect.<sup>224</sup> A Danish cohort study also suggested that initial treatment of uncomplicated  
 1888 hypertension with ACE inhibitors or ARBs reduces incident AF compared with other hypertensive agents.<sup>245</sup>  
 1889 ARB therapy did not reduce the AF burden in patients with AF without structural heart disease.<sup>241</sup> Thus, ACE  
 1890 inhibitors or ARBs are unlikely to have a relevant direct antiarrhythmic effect. However, it might be justified to  
 1891 consider adding ACE inhibitors or ARB therapy to antiarrhythmic drugs to reduce AF recurrences after  
 1892 cardioversion.<sup>248, 249, 687</sup>

1893

1894 Compared with placebo, beta-blockers are associated with a reduced risk of new-onset AF in patients  
 1895 with reduced ejection fraction and sinus rhythm.<sup>23</sup> Beta-blockers have also been reported to reduce symptomatic  
 1896 AF recurrences,<sup>580, 636, 688</sup> but this finding may be driven by the beneficial effect of rate control, which will  
 1897 render AF more often asymptomatic.

1898

1899 Perioperative statin therapy appeared to reduce the risk of postoperative AF in a number of small  
 1900 RCTs<sup>689, 690</sup>; however, an adequately powered placebo-controlled trial has shown no effect of perioperative  
 1901 rosuvastatin therapy on postoperative AF.<sup>691</sup> Statin treatment does not prevent AF in other settings.<sup>692, 693</sup>  
 1902 Similarly, polyunsaturated fatty acids failed to show convincing benefit.<sup>241, 694-698</sup> The role of aldosterone  
 1903 antagonists in the management of AF has not been extensively investigated in humans; although preliminary  
 1904 evidence from trials of eplerenone is encouraging for primary prevention,<sup>243</sup> at present there is no robust  
 1905 evidence to make any recommendation for the use of aldosterone antagonists for secondary prevention of AF.<sup>699-701</sup>

1906

1907

### 1908 Recommendations for rhythm control therapy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>d</sup>
<b>General recommendations</b>			
Management of cardiovascular risk factors and avoidance of AF triggers should be pursued in patients on rhythm control therapy to facilitate maintenance of sinus rhythm	IIa	B	203, 204, 296, 312
Rhythm control therapy is indicated for symptom improvement in patients with AF	I	B	120, 586, 601
With the exception of AF associated with haemodynamic instability, the choice between electrical and pharmacological cardioversion	IIa	C	

should be guided by patient and physician preferences			
<b>Cardioversion of AF</b>			
Electrical cardioversion of AF is recommended in patients with acute haemodynamic instability to acutely restore cardiac output	I	B	612, 702-704
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy	I	B	584, 601, 627, 628, 648, 705
Pretreatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to enhance success of electrical cardioversion and prevent recurrent AF	Ila	B	248, 584, 633
In patients with no history of ischaemic or structural heart disease, flecainide, propafenone, or vernakalant are recommended for pharmacological cardioversion of new-onset AF	I	A	602-605, 614, 618, 622, 706, 707
In patients with no history of ischaemic or structural heart disease, ibutilide should be considered for pharmacological conversion of AF	Ila	B	
In selected patients with recent-onset AF and no significant structural or ischaemic heart disease, a single oral dose of flecainide or propafenone (the 'pill in the pocket' approach) should be considered for patient-led cardioversion, following safety assessment	Ila	B	620, 621
In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF	I	A	597-601
Vernakalant may be considered as an alternative to amiodarone for pharmacological conversion of AF in patients without hypotension, severe heart failure, or severe structural heart disease (especially aortic stenosis)	Ilb	B	602-605, 616, 618
<b>Stroke prevention in patients designated for cardioversion of AF</b>			
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter	Ila	B	708, 709
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion	I	B	648, 708
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus, as an alternative to preprocedural anticoagulation when early cardioversion is planned	I	B	648, 708
Early cardioversion can be performed without TOE in patients with a definite duration of AF < 48 hours	Ila	B	648
In patients at risk for stroke (e.g. presence of CHA <sub>2</sub> DS <sub>2</sub> -VASc factors), anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion	I	B	353, 710
In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks	I	C	
A repeat TOE to ensure thrombus resolution should be considered before cardioversion	Ila	C	
<b>Antiarrhythmic drugs for the long-term maintenance of sinus rhythm/prevention of recurrent AF</b>			

The choice of antiarrhythmic drug needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden	I	A	41, 580
Dronedaron, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A	581, 583, 584, 588, 601
Dronedaron is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure	I	A	583, 588
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure	I	B	596-598
Amiodarone is more effective in preventing AF recurrences than other antiarrhythmic drugs but extracardiac toxic effects are common and increase with time. For this reason, other antiarrhythmic drugs should be considered first	IIa	C	596-598
Patients on antiarrhythmic drug therapy should be periodically evaluated to confirm their eligibility for treatment	IIa	C	583, 588, 657, 658, 660
ECG recording during the initiation of antiarrhythmic drug therapy should be considered to monitor heart rate, detect QRS and QT interval prolongation, and the occurrence of atrioventricular block	IIa	B	584 582, 583, 588, 601
Antiarrhythmic drug therapy is not recommended in patients with prolonged QT interval (> 0.5 s) or with significant sinoatrial node disease or atrioventricular node dysfunction who do not have a functioning permanent pacemaker	III (harm)	C	
Adding atrial-based bradycardia pacing to drug treatment that induces or exacerbates sinus node dysfunction should be considered to allow continuation of antiarrhythmic drug therapy in patients in whom AF ablation is declined or not indicated	IIa	B	711, 712
Continuation of antiarrhythmic drug therapy beyond the blanking period after AF ablation should be considered to maintain sinus rhythm when recurrences seem likely	IIa	B	713
<b>Antiarrhythmic effects of non-antiarrhythmic drugs</b>			
ACE inhibitors, ARBs, and beta-blockers should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction	IIa	A	23, 219, 236, 237, 239, 250, 714
ACE inhibitors and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with LV hypertrophy	IIa	B	238, 246, 686, 714
Pretreatment with ACE inhibitors or ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion and receiving antiarrhythmic drug therapy	IIb	B	236, 237, 248, 249
ARBs or ACE inhibitors are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.	III (no benefit)	B	241, 697

1907 ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHA<sub>2</sub>DS<sub>2</sub>-  
1908 VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular  
1909 disease, Age 65–74, and Sex (female); ECG = electrocardiogram; NOAC = non-vitamin K antagonist oral  
1910 anticoagulant; TOE = transoesophageal echocardiography.

1911 <sup>a</sup>Class of recommendation.

1912 <sup>b</sup>Level of evidence.

1913 <sup>c</sup>Reference(s) supporting recommendations.

1914

1915 **11.3. Catheter ablation**

1916 Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF,<sup>108</sup> catheter ablation  
 1917 of AF has developed from a specialized, experimental procedure into a common treatment to prevent recurrent  
 1918 AF.<sup>587, 715</sup> This is primarily achieved through isolation of the pulmonary veins, probably requiring complete  
 1919 isolation for full effectiveness,<sup>716</sup> and additional ablation in the posterior left atrial wall. AF ablation, when  
 1920 performed in experienced centres by adequately trained teams, is more effective than antiarrhythmic drug  
 1921 therapy in maintaining sinus rhythm, and the complication rate, though not negligible, is similar to the  
 1922 complication rate for antiarrhythmic drugs.<sup>585, 717, 1042</sup>

### 1924 11.3.1. Indications

1925 Catheter ablation of AF is effective in restoring and maintaining sinus rhythm in patients with symptomatic  
 1926 paroxysmal, persistent, and probably long-standing persistent AF – in general as second-line treatment after  
 1927 failure of or intolerance to antiarrhythmic drug therapy. In such patients, catheter ablation is more effective than  
 1928 antiarrhythmic drug therapy.<sup>185, 586, 713, 717-720</sup> As first-line treatment for paroxysmal AF, randomized trials  
 1929 showed only modestly improved rhythm outcome with catheter ablation compared to antiarrhythmic drug  
 1930 therapy.<sup>585, 721-723</sup> Complication rates were similar, but ablation was performed in expert centres, justifying  
 1931 catheter ablation as first-line therapy in selected patients with paroxysmal AF who ask for interventional  
 1932 therapy. Fewer data are available reporting the effectiveness and safety of catheter ablation in patients with  
 1933 persistent or long-standing persistent AF, but all point to lower recurrence rates after catheter ablation compared  
 1934 to antiarrhythmic drug therapy with or without cardioversion.<sup>185, 717, 723-726, 1039</sup> In patients who experience  
 1935 symptomatic recurrences of AF despite antiarrhythmic drug therapy, all RCTs showed better sinus rhythm  
 1936 maintenance with catheter ablation than on antiarrhythmic drugs.<sup>586, 713, 727, 728</sup> There is no current indication for  
 1937 catheter ablation to prevent cardiovascular outcomes (or desired withdrawal of anticoagulation), or to reduce  
 1938 hospitalization.<sup>40, 594</sup>

### 1940 11.3.2. Techniques and technologies

1941 Complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter  
 1942 ablation,<sup>716, 729-731</sup> achievable by point-by-point radiofrequency ablation, linear lesions encircling the pulmonary  
 1943 veins, or cryoballoon ablation, with similar outcomes.<sup>732-734</sup> Complete isolation of the pulmonary veins has  
 1944 better rhythm outcomes than incomplete isolation.<sup>716</sup> PVI was initially tested in patients with paroxysmal AF,  
 1945 but appears to be non-inferior to more extensive ablation in persistent AF as well.<sup>729, 735</sup> More extensive  
 1946 ablations have been used in patients with persistent AF, but there are insufficient data to guide the use of these at  
 1947 present.<sup>117, 718, 719, 735-737</sup> Extended ablation procedures (beyond PVI) consistently require longer procedures and  
 1948 more ionizing radiation, potentially creating risk for patients. Left atrial macro-reentrant tachycardia is relatively  
 1949 uncommon after PVI ( $\approx 5\%$ ). It also seems even less common after cryoballoon ablation,<sup>734</sup> but may occur in up  
 1950 to 25% of patients after left atrial substrate modification ablation, often due to incomplete ablation lines. Thus,  
 1951 for patients with persistent AF, ablation of complex fractionated electrograms, ablation of rotors, or routine  
 1952 deployment of linear lesions or other additional ablations does not seem justified in the first procedure.<sup>735, 738, 739</sup>  
 1953 However, additional ablation on top of complete PVI<sup>716</sup> may be considered in patients with recurrent AF after  
 1954 the initial ablation procedure.<sup>719, 740, 741</sup> In patients with documented right atrial isthmus-dependent flutter  
 1955 undergoing AF ablation, right atrial isthmus ablation is recommended. Adenosine testing to identify patients in  
 1956 need of additional ablation remains controversial after evaluation in several reports.<sup>739, 742-744</sup> Ablation of so-  
 1957 called ‘rotors’ guided by body surface mapping or endocardial mapping is under evaluation and cannot be  
 1958 recommended for routine clinical use at present.

### 1960 11.3.3. Outcome and complications

1961 The rhythm outcome after catheter ablation of AF is difficult to predict in individual patients.<sup>173, 227, 713, 728</sup> Most  
 1962 patients require more than one procedure to achieve symptom control.<sup>713, 726, 728</sup> In general, better rhythm  
 1963 outcome and lower procedure-related complications can be expected in younger patients with a short history of  
 1964 AF and frequent, short AF episodes in the absence of significant structural heart disease.<sup>745</sup> Catheter ablation is  
 1965 more effective than antiarrhythmic drug therapy in maintaining sinus rhythm (*Web Addenda Figure 2*).<sup>746, 1039</sup>  
 1966 Sinus rhythm without severely symptomatic recurrences of AF is found in up to 70% of patients with  
 1967 paroxysmal AF, and around 50% in persistent AF.<sup>713, 728, 735, 1042</sup> Very late recurrence of AF after years of sinus  
 1968 rhythm is not uncommon and may reflect disease progression, with important implications for continuation of  
 1969 AF therapies.<sup>728</sup> Multiple variables have been identified as risk factors for recurrence after catheter ablation of  
 1970 AF, but their predictive power is weak. The decision for catheter ablation thus should be based on a shared  
 1971 decision-making process<sup>747</sup> (see Chapter 7), following thorough explanation of the potential benefits and risks,  
 1972 and of the alternatives such as antiarrhythmic drug or acceptance of current symptoms without rhythm control  
 1973 therapy.<sup>175</sup>

1974 *Complications of catheter ablation for AF*

1975 There is a clear need to systematically capture complications in clinical practice to improve the quality of AF  
 1976 ablation procedures.<sup>175</sup> The median length of hospital stay in AF patients undergoing their first ablation as part  
 1977 of the EURObservational Research Programme (EORP) was 3 days (interquartile range 2–4 days), based on  
 1978 data from 1391 patients from hospitals performing at least 50 ablations per year. Five to seven per cent of  
 1979 patients will suffer severe complications after catheter ablation of AF, and 2–3% will experience life-threatening  
 1980 but usually manageable complications.<sup>727, 748-750</sup> Intraprocedural death has been reported, but is rare (< 0.2%).<sup>751</sup>  
 1981 The most important severe complications are stroke/TIA (< 1%), cardiac tamponade (1–2%), pulmonary vein  
 1982 stenosis, and severe oesophageal injury leading to atrio-oesophageal fistula weeks after ablation (*Table 18*).  
 1983 ‘Silent strokes’ (i.e. white matter lesions detectable by brain MRI), have been observed in around 10% of  
 1984 patients treated with radiofrequency and cryoballoon ablation.<sup>752</sup> The clinical relevance of this observation is  
 1985 unclear.<sup>749</sup> Post-procedure complications include stroke, with the highest risk within the first week,<sup>753</sup> late  
 1986 pericardial tamponade several days after catheter ablation,<sup>751</sup> and oesophageal fistulas, which usually become  
 1987 apparent 7–30 days after ablation. Timely detection of atrio-oesophageal fistulas can be life-saving and should  
 1988 be based on the typical triad of infection without a clear focus, retrosternal pain, and stroke or TIA.<sup>748</sup>  
 1989

1990 **Table 18** Complications related to catheter ablation of AF

Complication severity	Complication type	Rate <sup>727, 748, 750, 754-759</sup>
Life-threatening complications	Periprocedural death	< 0.2%
	Oesophageal injury (perforation/fistula) <sup>a</sup>	< 0.5%
	Periprocedural stroke (including TIA/air embolism)	< 1%
	Cardiac tamponade	1–2%
Severe complications	Pulmonary vein stenosis	< 1%
	Persistent phrenic nerve palsy	1–2%
	Vascular complications	2–4%
	Other severe complications	≈ 1%
Other moderate or minor complications		1–2%
Unknown significance	Asymptomatic cerebral embolism (silent stroke) <sup>b</sup>	5–20%
	Radiation exposure	

1991 AF = atrial fibrillation; TIA = transient ischaemic attack.

1992 <sup>a</sup>Oesophageal fistula should be suspected in patients presenting with the triad of unspecific signs of infection,  
 1993 chest pain, and stroke or TIA in the first weeks after an ablation procedure. It requires immediate therapy.

1994 <sup>b</sup>< 10% for cryoablation or radiofrequency ablation, > 20% for phased radiofrequency ablation

1995

1996 **11.3.4. Anticoagulation – before, during, and after ablation**

1997 Patients anticoagulated with VKAs should continue therapy during ablation (with an INR of 2–3).<sup>760</sup>

1998 Anticoagulation with NOACs is an alternative to warfarin.<sup>478, 761-765</sup> There is no safety signal from observational  
 1999 cohorts treated with uninterrupted NOAC therapy undergoing catheter ablation in experienced centres.<sup>761, 763, 766,</sup>

2000 <sup>767</sup> The first controlled trial, enrolling around 200 patients, has recently been published,<sup>768</sup> as well as several  
 2001 observational data sets.<sup>761, 769, 770</sup> Ongoing studies compare uninterrupted VKA with NOAC therapy in AF

2002 patients undergoing ablation (e.g. AXAFA – AFNET 5 [Apixaban During Atrial Fibrillation Catheter Ablation:  
 2003 Comparison to Vitamin K Antagonist Therapy – Anticoagulation using the direct factor Xa inhibitor apixaban

2004 during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy; NCT02227550] and  
 2005 RE-CIRCUIT [Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein

2006 ablation: assessment of different peri-procedural anticoagulation strategies; NCT02348723]). During ablation,  
2007 heparin should be given to maintain an activated clotting time > 300 seconds. Anticoagulation should be  
2008 maintained for at least 8 weeks after ablation for all patients. The true incidence of thromboembolic events after  
2009 catheter ablation has never been systematically studied and the expected stroke risk has been adopted from non-  
2010 ablation AF cohorts. Although observational studies suggest a relatively low stroke rate in the first few years  
2011 after catheter ablation of AF,<sup>737, 771-776</sup> the long-term risk of recurrent AF and the safety profile of  
2012 anticoagulation in ablated patients need to be considered. In the absence of controlled trial data, OAC after  
2013 catheter ablation should follow general anticoagulation recommendations, regardless of the presumed rhythm  
2014 outcome.

### 2016 **11.3.5. Ablation of atrial fibrillation in heart failure patients**

2017 Catheter ablation, compared with amiodarone therapy, significantly reduces recurrent AF in AF patients with  
2018 HFrEF.<sup>777</sup> Selected patients with HFrEF and AF can achieve recovery of LV systolic function after catheter  
2019 ablation (probably reflecting tachycardiomyopathy). Several smaller trials suggest improved LV function after  
2020 catheter ablation in HFrEF patients<sup>185, 226-228, 778, 779</sup> and reduced hospitalizations,<sup>720, 777</sup> especially in patients  
2021 without a previous myocardial infarction.<sup>780</sup> Larger trials are warranted to confirm these findings. Catheter  
2022 ablation can be demanding in these patients. Thus, indications for catheter ablation in HFrEF patients should be  
2023 carefully balanced, and the procedures performed in experienced centres.

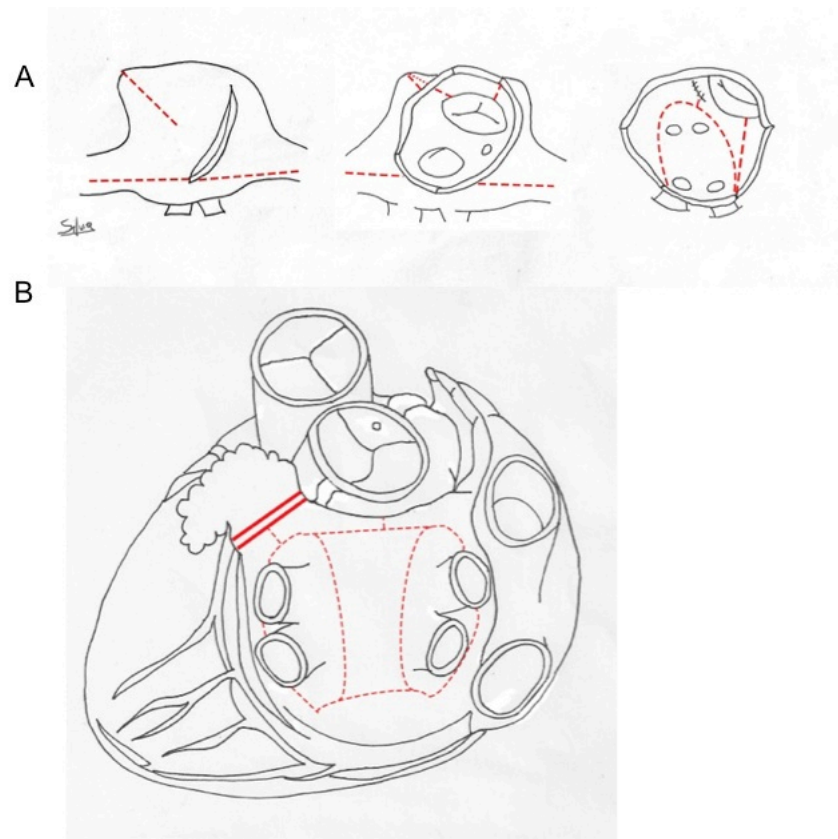
### 2025 **11.3.6. Follow-up after catheter ablation**

2026 Patients and physicians involved in the follow-up after catheter ablation should know the signs and symptoms of  
2027 late complications to allow swift referral for treatment. Patient should also be aware that symptomatic and  
2028 asymptomatic AF recurrences are frequent after catheter ablation.<sup>119, 781, 782</sup> In line with the primary goal of  
2029 rhythm control therapy, asymptomatic episodes should generally not trigger further rhythm control therapy.  
2030 Patients should be seen at least once by a rhythm specialist in the first 12 months after ablation. Further rhythm  
2031 control options should be considered in patients with symptomatic recurrences, including discussion in a Heart  
2032 Team (*Figure 17*).

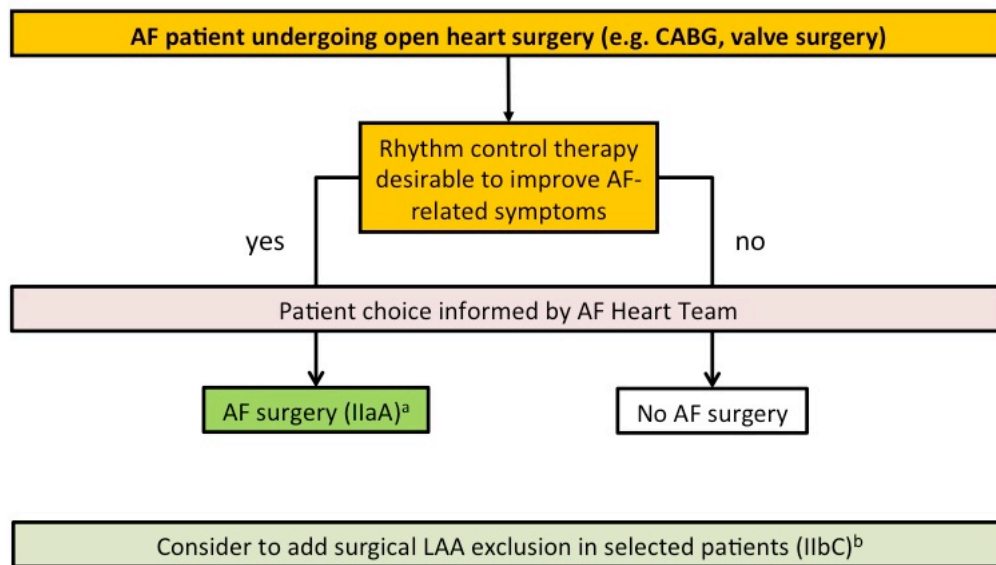
## 2034 **11.4. Atrial fibrillation surgery**

### 2035 **11.4.1. Concomitant atrial fibrillation surgery**

2036 The Cox maze procedure was first performed 30 years ago as a ‘cut-and-sew’ technique, including isolation of  
2037 the posterior left atrium, a connection to the posterior mitral annulus, a cavotricuspid connection, a cavocaval  
2038 connection, and exclusion of the LAA (*Figure 18*).<sup>783</sup> Thereby, the Cox maze procedure creates an electrical  
2039 labyrinth (maze) of passages through which the sinoatrial node impulse finds a route to the atrioventricular node  
2040 while preventing fibrillatory conduction. The Cox maze procedure and other, often simpler, forms of AF surgery  
2041 have mainly been used in patients undergoing other open heart surgical procedures.<sup>461, 466, 784-798</sup> In a systematic  
2042 review commissioned for these guidelines, concomitant AF surgery resulted in greater freedom from AF, atrial  
2043 flutter, and atrial tachycardia (RR 1.94, 95% CI 1.51–2.49;  $n = 554$  from seven RCTs) (*Web Addenda Figure*  
2044 *3*).<sup>1040</sup> Patients undergoing the Cox maze procedure required pacemaker implantation more often (RR 1.69, 95%  
2045 CI 1.12–2.54;  $n = 1631$  from 17 RCTs), without a detectable difference in other outcomes or complications.  
2046 These findings are underpinned by an analysis of Society of Thoracic Surgeons database comprising 67,389  
2047 patients in AF: mortality or major morbidity was not affected by concomitant AF surgery (adjusted OR 1.00;  
2048 95% CI 0.83–1.20), but pacemaker implantation was more frequent (adjusted OR 1.26; 95% CI 1.07–1.49).<sup>799</sup>  
2049 Predictors of AF recurrence after surgery include left atrial dilatation, older age, > 10-year history of AF, and  
2050 non-paroxysmal AF.<sup>800-804</sup> Regarding AF type, surgical PVI seems effective in paroxysmal AF.<sup>805</sup> Batrial lesion  
2051 patterns may be more effective in persistent and long-standing persistent AF.<sup>797, 803, 806</sup> The suggested  
2052 management of patients with AF-related symptoms undergoing cardiac surgery is displayed in *Figure 19*, with  
2053 an important contribution of the AF Heart Team to advise and inform patient choice.



2054  
2055 **Figure 18** A. Surgical lesion sets for the biatrial Cox maze procedure. Left and middle panel: right atrial lesions.  
2056 Right panel: left atrial lesions.  
2057 B: Left atrial lesions in a thoracoscopic minimally invasive surgical procedure (dashed lines), including left  
2058 appendage exclusion (double line).



2059

2060 **Figure 19** Surgical rhythm control in patients undergoing cardiac surgery.2061 AF = atrial fibrillation; CABG = coronary artery bypass graft; LAA = left atrial appendage; PVI = pulmonary  
2062 vein isolation.2063 <sup>a</sup>AF surgery may be PVI in paroxysmal AF and biatrial maze in persistent or long-standing persistent AF.2064 <sup>b</sup>Oral anticoagulation should be continued in patients at risk of stroke irrespective of AF surgery or LAA  
2065 exclusion.

2066

2067

2068

**11.4.2. Stand-alone rhythm control surgery**2069 Current technology (e.g. bipolar radiofrequency or cryotherapy) renders the procedure easier and more  
2070 reproducible and feasible via a mini-thoracotomy.<sup>786, 807, 808</sup> Thoracoscopic PVI with bipolar radiofrequency2071 prevents recurrence of paroxysmal AF (69–91% freedom from arrhythmias at 1 year, see *Figure 18B* for lesion  
2072 set),<sup>468, 809, 810</sup> and seems effective in patients refractory to catheter ablation.<sup>811</sup> The average length of hospital2073 stay for thoracoscopic ablation varies from 3.6 to 6.0 days.<sup>468, 812, 813</sup> The FAST (Atrial Fibrillation Catheter2074 Ablation vs Surgical Ablation Treatment) trial,<sup>468</sup> and another smaller trial,<sup>814</sup> suggested that thoracoscopic AF2075 surgery could be more effective than catheter ablation for the maintenance of sinus rhythm,<sup>468, 814</sup> while also2076 causing more complications (*Table 19*).<sup>815</sup> To improve results,<sup>468, 816-818</sup> more extensive lesion sets have been2077 performed, connecting lines between the PVI encircling and towards the mitral annulus.<sup>812, 819-822</sup> To improve the2078 generation of transmural lesions,<sup>716</sup> endo-epicardial ablation strategies have recently been proposed.<sup>812, 823-825</sup>2079 Although preliminary experience with hybrid simultaneous ablation shows promise, procedural time and rates of  
2080 bleeding complications are higher.<sup>812, 823</sup>

2081

2082

**Table 19** Complications of thoracoscopic AF surgery

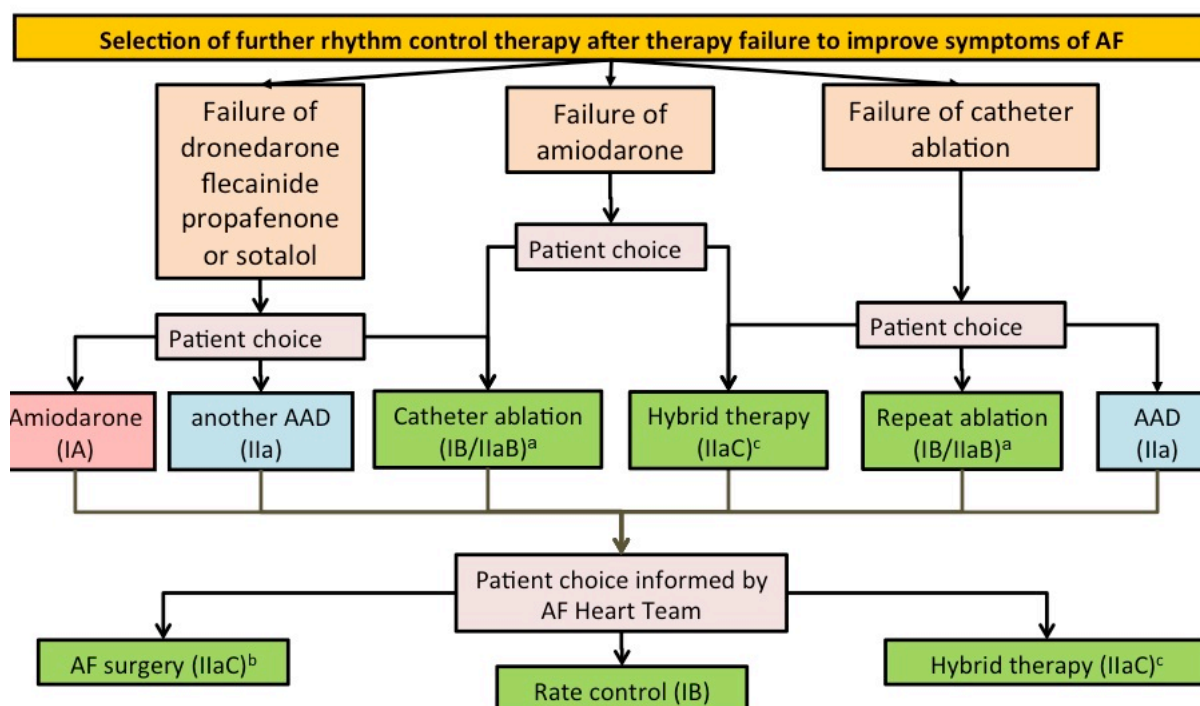
Complication	Rate <sup>468, 815, 822, 826</sup>
Conversion to sternotomy	0–1.6%
Pacemaker implantation	0–3.3%
Drainage for pneumothorax	0–3.3%
Pericardial tamponade	0–6.0%
Transient ischaemic attack <sup>a</sup>	0–3.0%



2083 AF = atrial fibrillation.  
 2084 <sup>a</sup>The rate of asymptomatic cerebral embolism is unknown  
 2085

### 2086 11.5. Choice of rhythm control following treatment failure

2087 There is insufficient evidence on which to base clear recommendations on how to treat patients with recurrent  
 2088 AF after catheter ablation. Early recurrences of AF or atrial tachycardias after ablation (occurring within 8  
 2089 weeks) may be treated with cardioversion. Many of the published series of patients undergoing AF ablation  
 2090 included those who failed antiarrhythmic drug therapy. Thus, considering ablation therapy in patients who have  
 2091 symptomatic recurrences on antiarrhythmic drug therapy is often reasonable. Alternatively, trialling another  
 2092 antiarrhythmic drug can be considered. Combining antiarrhythmic drug with ablation ('hybrid therapy', see  
 2093 Section 11) should be considered based on the different and possibly synergistic effects of these drugs with AF  
 2094 ablation, possibly benefitting patients in whom either treatment alone was previously ineffective. Rate control  
 2095 without rhythm control, surgical ablation, or repeat catheter ablation should be considered as well as third-line  
 2096 options (Figure 20). Patient preferences and local access to therapy are important considerations to inform the  
 2097 therapy choice in patients who are in need of further rhythm control therapy after an initial therapy failure.



2098  
 2099 **Figure 20** Choice of rhythm control approaches following treatment failure.  
 2100 AAD = antiarrhythmic drug; AF = atrial fibrillation; PVI = pulmonary vein isolation.  
 2101 <sup>a</sup> catheter ablation should target PVI. Class I level B for paroxysmal AF and Class IIa level B for persistent AF.  
 2102 <sup>b</sup> AF surgery may be PVI (e.g. in paroxysmal AF) or maze surgery (e.g. in therapy-refractory or long-standing  
 2103 persistent AF).  
 2104 <sup>c</sup> Hybrid therapy involves combination of antiarrhythmic drugs, catheter ablation, and/or AF surgery.  
 2105

### 2106 11.6. The atrial fibrillation Heart Team

2107 In view of the complexity of the different treatment options in patients with failed rhythm control therapy but  
 2108 who still require or demand further rhythm control therapy, this Task Force proposes that decisions involving  
 2109 AF surgery or extensive AF ablation should be based on advice from an AF Heart Team. This will also apply to  
 2110 reversal to a rate control strategy in patients with severe (EHRA III or IV) AF symptoms. An AF Heart Team  
 2111 should consist of a cardiologist with expertise in antiarrhythmic drug therapy, an interventional  
 2112 electrophysiologist, and a cardiac surgeon with expertise in appropriate patient selection, techniques, and

2113 technologies for interventional or surgical AF ablation. Such AF Heart Teams – and a collaborative  
 2114 infrastructure supporting a continued interaction between physicians delivering continued care, AF  
 2115 cardiologists, interventional electrophysiologists, and AF surgeons – should be established to provide optimal  
 2116 advice and ultimately to improve rhythm outcomes for patients in need of advanced and complex rhythm control  
 2117 interventions.

2118

2119 **Recommendations for catheter ablation of AF and AF surgery**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre	I	A	585-587, 713, 727
Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF-ablation procedure if previously documented or occurring during the AF ablation	Ila	B	827
Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk	Ila	B	585
All patients should receive oral anticoagulation for stroke prevention for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation.	Ila	B/C	727
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high risk of stroke	Ila	C	
When catheter ablation of AF is planned, continuation of oral anticoagulation with VKA (IIaB) or NOAC (IIaC) should be considered during the procedure, maintaining effective anticoagulation	Ila	B/C	760, 768
Catheter ablation should target complete isolation of the pulmonary veins using radiofrequency ablation or cryotherapy balloon catheters	Ila	B	585, 715, 716, 734, 735
AF ablation should be considered in symptomatic patients with AF and heart failure with reduced ejection fraction to improve symptoms and cardiac function when tachycardiomyopathy is suspected	Ila	C	185, 226-228, 720, 777-779, 828
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia	Ila	C	829, 830
Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to antiarrhythmic drug therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team	Ila	C	468, 735, 777, 831, 832, 1040
Minimally invasive surgery with epicardial pulmonary vein isolation should be considered in patients with symptomatic AF when catheter ablation has failed. Decisions on such patients should be supported by an AF Heart Team	Ila	B	468 812, 819, 823
Maze surgery, possibly via a minimally invasive approach, performed by an adequately trained operator in an experienced centre, should be considered by an AF Heart Team as a treatment option for patients with symptomatic refractory persistent AF or post-ablation AF to improve symptoms	Ila	C	808, 832

Maze surgery, preferably biatrial, should be considered in patients undergoing cardiac surgery to improve symptoms attributable to AF, balancing the added risk of the procedure and the benefit of rhythm control therapy	IIa	A	461, 466, 790, 791, 796, 797
Concomitant biatrial maze or pulmonary vein isolation surgery may be considered in asymptomatic AF patients undergoing cardiac surgery	IIb	C	796, 797, 833

2120 AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

2121 <sup>a</sup>Class of recommendation.

2122 <sup>b</sup>Level of evidence.

2123 <sup>c</sup>Reference(s) supporting recommendations.

2124

## 2125 **12 Hybrid rhythm control therapy**

2126 AF has many different drivers, which are only partially targeted by antiarrhythmic drug or catheter ablation.<sup>96</sup>

2127 Hence, combination or 'hybrid' rhythm control therapy seems reasonable, although there is little evidence  
2128 supporting its use.

2129

### 2130 **12.1. Combining antiarrhythmic drugs and catheter ablation**

2131 Antiarrhythmic drug therapy is commonly given for 8–12 weeks after ablation to reduce early recurrences of AF  
2132 after catheter ablation, supported by a recent controlled trial where amiodarone halved early AF recurrences  
2133 compared with placebo.<sup>650</sup> Prospective studies have not been done, but a meta-analysis of the available (weak)  
2134 evidence suggests slightly better prevention of recurrent AF in patients treated with antiarrhythmic drugs after  
2135 catheter ablation.<sup>713</sup> Many patients are treated with antiarrhythmic drug therapy after catheter ablation (most  
2136 often amiodarone or flecainide),<sup>587</sup> and this seems a reasonable option in patients with recurrent AF after  
2137 ablation. It seems common sense to consider antiarrhythmic drug therapy in patients who are in need of further  
2138 rhythm control therapy after catheter ablation, but controlled trials to confirm this are desirable.

2139 Combining cavotricuspid isthmus ablation and antiarrhythmic drugs may lead to improved rhythm  
2140 control without the need for left atrial ablation in patients who develop 'drug-induced atrial flutter' on therapy  
2141 with flecainide, propafenone, or amiodarone,<sup>834-836</sup> although recurrent AF is a concern in the long term.<sup>837, 838</sup>

2142

### 2143 **12.2. Combining antiarrhythmic drugs and pacemakers**

2144 In selected patients with sick sinus syndrome and fast ventricular response during AF paroxysms requiring rate  
2145 control therapy, the addition of a pacemaker not only optimizes rate control but may also help to control  
2146 rhythm.<sup>711, 712</sup> Moreover, when antiarrhythmic drug treatment leads to sinus node dysfunction and bradycardia,  
2147 pacing may permit uptitration of the antiarrhythmic drug dose. Such strategies have never been prospectively  
2148 investigated and the existing populations studied are highly selected.<sup>839, 840</sup> Some patients with AF-induced  
2149 bradycardia may benefit from catheter ablation of AF, obviating the need for antiarrhythmic drugs and  
2150 pacemaker implantation.<sup>829, 830</sup>

2151

## 2152 **13 Specific situations**

### 2153 **13.1. Frail and 'elderly' patients**

2154 Many AF patients present at an older age (e.g. > 75 or > 80 years). There are no studies suggesting that  
2155 cardiovascular risk reduction is less effective in these 'elderly' AF patients than in younger patients. Rather, age  
2156 is one of the strongest predictors/risk factors for ischaemic stroke in AF (*Table 11*).<sup>382</sup> Good data are available to  
2157 support the use of anticoagulants in older patients from BAFTA (Birmingham Atrial Fibrillation Treatment of  
2158 the Aged Study),<sup>362</sup> the NOAC trials,<sup>39</sup> and from analyses in elderly Americans (Medicare).<sup>396</sup> Elderly AF  
2159 patients are at higher risk of stroke and thus are more likely to benefit from OAC than younger patients,<sup>841</sup> and  
2160 yet OAC is still underutilized in the elderly.<sup>220, 842</sup> Although the evidence base is smaller for other treatment  
2161 options in AF, the available data support the use of available rate and rhythm control interventions, including  
2162 pacemakers and catheter ablation, without justification to discriminate by age group. Individual patients at older  
2163 age may present with multiple comorbidities including dementia, a tendency to falls, CKD, anaemia,  
2164 hypertension, diabetes, and cognitive dysfunction. Such conditions may limit quality of life more than AF-  
2165 related symptoms. Impairment of renal and hepatic function and multiple simultaneous medications make drug  
2166 interactions and adverse drug reactions more likely. Integrated AF management and careful adaptation of drug  
2167 dosing seem reasonable to reduce complications of AF therapy in such patients.<sup>843</sup>

2168

### 2169 **13.2. Inherited cardiomyopathies, channelopathies, and accessory pathways**

2170 Several inherited cardiac conditions are associated with early-onset AF (*Table 20*). Treatment of the underlying  
 2171 cardiac condition is an important contribution to AF management in these young patients (see also ESC  
 2172 guidelines on the sudden cardiac death<sup>844</sup> and hypertrophic cardiomyopathy<sup>845</sup>).

2173

2174 **Table 20** Inherited cardiomyopathies, channelopathies, and pathways associated with AF

2175

Syndrome	Gene	Functional alteration	AF prevalence	References
Long QT syndrome	KCNQ1 KCNH2 SCN5A ANK2 others	IKs <input type="checkbox"/> IKr <input type="checkbox"/> INa <input type="checkbox"/> INa,K <input type="checkbox"/> Various effects	5–10%	846-850
Brugada syndrome	SCN5A GPDIL SCN1B CACNA1C CACNB2b others	INa <input type="checkbox"/> INa <input type="checkbox"/> INa <input type="checkbox"/> ICa <input type="checkbox"/> ICa <input type="checkbox"/> others	10–20%	851-855
Short QT syndrome	KCNH2 KCNQ1 KCNJ2 CACNA1C CACNB2b	IKr <input type="checkbox"/> IKs <input type="checkbox"/> IK1 <input type="checkbox"/> ICa <input type="checkbox"/> ICa <input type="checkbox"/>	Up to 70%	853, 856-858
Catecholaminergic ventricular tachycardia	RYR2 CASQ2	Abnormal Ca <sup>2+</sup> release from sarcoplasmic reticulum	Variable but significant	859-861
Hypertrophic cardiomyopathy	Sarcomeric genes		5–15%	862-864
Wolff–Parkinson–White syndrome	PRKAG		Variable	865
Holt–Oram syndrome	TBX5		Variable	866
Arrhythmogenic right ventricular cardiomyopathy	Several desmosomal genes, unknown gene loci		>40% in patients with VTs	867, 868

2176 AF = atrial fibrillation.

2177

#### 2178 **13.2.1. Wolff–Parkinson–White syndrome**

2179 Patients with pre-excitation and AF are at risk of rapid conduction across the accessory pathway, resulting in a  
 2180 fast ventricular rate, possibly ventricular fibrillation, and sudden death. In AF patients with evidence of an  
 2181 antegrade accessory pathway, catheter ablation of the pathway is recommended.<sup>869, 870</sup> This procedure is safe and  
 2182 effective and may be considered as a prophylactic treatment strategy.<sup>871, 872</sup> In AF patients surviving a sudden  
 2183 death event with evidence of an accessory pathway, urgent catheter ablation of the pathway is recommended.<sup>869</sup>

2184 A documented short pre-excited RR interval (< 250 ms) during spontaneous or induced AF is one of the risk  
 2185 markers for sudden death in Wolff–Parkinson–White syndrome (WPW) syndrome, in addition to a history of  
 2186 symptomatic tachycardia, the presence of multiple accessory pathways, and Ebstein’s anomaly. Intravenous  
 2187 procainamide, propafenone, or ajmaline can be used to acutely slow ventricular rate,<sup>873, 874</sup> whereas digoxin,  
 2188 verapamil, and diltiazem are contraindicated.<sup>875</sup> Intravenous amiodarone should be used with caution, as there  
 2189 are case reports of accelerated ventricular rhythms and ventricular fibrillation in patients with pre-excited AF  
 2190 receiving intravenous amiodarone infusion.<sup>876</sup>

2191

#### 2192 **13.2.2. Hypertrophic cardiomyopathy**

2193 AF is the most common arrhythmia in patients with hypertrophic cardiomyopathy, affecting approximately one-  
 2194 quarter of this population.<sup>877</sup> Observational data highlight a high stroke risk in hypertrophic cardiomyopathy

2195 patients with AF, confirming the need for OAC.<sup>878</sup> While there is more experience with VKAs, there are no data  
 2196 to suggest that NOACs cannot be used in these patients.<sup>845</sup> Studies of rate or rhythm control medications in  
 2197 patients with hypertrophic cardiomyopathy are relatively scarce. Beta-blockers and diltiazem or verapamil seem  
 2198 reasonable treatment options for rate control in these patients. In the absence of significant LV outflow tract  
 2199 obstruction, digoxin can be used alone or in combination with beta-blockers.<sup>845</sup> Amiodarone seems a safe  
 2200 antiarrhythmic drug in AF patients with hypertrophic cardiomyopathy,<sup>879</sup> and expert opinion suggests that  
 2201 disopyramide may be beneficial in those with outflow tract obstruction. AF ablation is effective to suppress  
 2202 symptomatic AF recurrences.<sup>880-884</sup> Surgical treatment of AF may be appropriate in patients with hypertrophic  
 2203 cardiomyopathy undergoing surgery (e.g. for LV outflow tract obstruction or mitral valve surgery), but  
 2204 experience is limited.

### 2205 2206 **13.2.3. Channelopathies and arrhythmogenic right ventricular cardiomyopathy**

2207 Many channelopathies and inherited cardiomyopathies are associated with AF. AF prevalence ranges from 5%  
 2208 to 20% in patients with long QT syndrome or Brugada syndrome, and is up to 70% in short QT syndrome  
 2209 (Table 20).<sup>853, 856-858</sup> Penetrance of disease phenotype including AF is variable.<sup>61, 852, 885, 886</sup> Both shortening as  
 2210 well as prolongation of the atrial action potential have been demonstrated as likely mechanisms underlying AF  
 2211 in these diseases. It seems reasonable to consider antiarrhythmic drugs that reverse the suspected channel defect  
 2212 in AF patients with inherited cardiomyopathies (e.g. a sodium channel blocker in LQT3<sup>852</sup> and quinidine in  
 2213 Brugada syndrome<sup>887</sup>). More importantly, new-onset AF in young, otherwise healthy individuals should trigger  
 2214 a careful search for such inherited conditions, including clinical history, family history, ECG phenotype, and  
 2215 echocardiography and/or other cardiac imaging.

2216 Monogenic defects only account for 3–5% of all patients with AF, even in younger populations.<sup>846, 848,</sup>  
 2217 <sup>888-890</sup> Furthermore, there is no clear link between detected mutations and specific outcomes or therapeutic needs.  
 2218 For these reasons, genetic testing is not recommended in the general AF population.<sup>77</sup> Other guidelines have  
 2219 described the indications for genetic testing in patients with inherited arrhythmogenic diseases.<sup>844, 891</sup>

### 2220 2221 **Recommendations for inherited cardiomyopathies**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
<b>WPW syndrome</b>			
Catheter ablation of the accessory pathway in WPW patients with AF and rapid conduction over the accessory pathway is recommended to prevent sudden cardiac death	I	B	892-894
Catheter ablation of the accessory pathway is recommended without delay in WPW patients who survive sudden cardiac death	I	C	869
Asymptomatic patients with overt pre-excitation and AF should be considered for accessory pathway ablation after careful counselling	IIa	B	872, 895
<b>Hypertrophic cardiomyopathy</b>			
Lifelong oral anticoagulation to prevent stroke is recommended in hypertrophic cardiomyopathy patients who develop AF	I	B	878
Restoration of sinus rhythm by electrical or pharmacological cardioversion to improve symptoms is recommended in hypertrophic cardiomyopathy patients with symptomatic new-onset AF	I	B	845
In haemodynamically stable hypertrophic cardiomyopathy patients with AF, ventricular rate control using beta-blockers and diltiazem/verapamil is recommended	I	C	845
Treatment of LV outflow tract obstruction should be considered in AF patients with hypertrophic cardiomyopathy to improve symptoms	IIa	B	896
Amiodarone should be considered to achieve rhythm control and maintain sinus rhythm in hypertrophic cardiomyopathy patients	IIa	C	845, 897
<b>Inherited cardiomyopathies and channelopathies</b>			
Targeted genetic testing should be considered in patients with AF and a suspicion of inherited cardiomyopathies or channelopathies based on clinical history, family history, or electrocardiographic phenotype	IIa	A	852

2223 AF = atrial fibrillation; LV = left ventricular; WPW = Wolff–Parkinson–White syndrome.

2224 <sup>a</sup>Class of recommendation.

2225 <sup>b</sup>Level of evidence.

2226 <sup>c</sup>Reference(s) supporting recommendations.

2227

2228 **13.3. Sports and atrial fibrillation**

2229 Physical activity improves cardiovascular health, which translates into a lower risk of AF.<sup>898</sup> Therefore, physical  
 2230 activity is a cornerstone of preventing AF. Intensive sports practice, especially endurance sports (> 1500 h of  
 2231 endurance sports practice),<sup>899</sup> increases the risk of AF later in life,<sup>900-902</sup> probably mediated by altered autonomic  
 2232 tone, volume load during exercise, atrial hypertrophy, and dilatation.<sup>903,904</sup> This results in a U-shaped  
 2233 relationship of physical activity and incident AF.<sup>214,898,902,905,906</sup> Detraining can reduce AF in models<sup>904</sup> and  
 2234 reduces ventricular arrhythmias in athletes,<sup>907</sup> but the role of detraining for AF in human athletes is unknown.  
 2235 The management of athletes with AF is similar to general AF management, but requires a few special  
 2236 considerations. Clinical risk factors will determine the need for anticoagulation. Sports with direct bodily  
 2237 contact or prone to trauma should be avoided in patients on OAC. Beta-blockers are not well tolerated and at  
 2238 times prohibited, and digoxin, verapamil, and diltiazem are often not potent enough to slow heart rate during  
 2239 exertional AF. Catheter ablation for AF probably has similar outcomes in athletes as in non-athletes,<sup>908,909</sup> but  
 2240 further data are needed. Pill-in-the-pocket therapy has been used as well.<sup>620</sup> After ingestion of flecainide or  
 2241 propafenone as pill-in-the-pocket, patients should refrain from sports as long as AF persists and until two half-  
 2242 lives of the antiarrhythmic drug have elapsed. Prophylactic ablation of the flutter circuit may be considered in  
 2243 athletes treated with sodium channel blockers.<sup>910</sup>

2244

2245 **Recommendations for physical activity in patients with AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting, more intense sports participation can promote AF	I	A	214, 898, 900-902, 905, 906
AF ablation should be considered to prevent recurrent AF in athletes	IIa	B	908, 909
The ventricular rate while exercising with AF should be evaluated in every athlete (by symptoms and/or by monitoring), and titrated rate control should be instituted	IIa	C	
After ingestion of pill-in-the-pocket Class I antiarrhythmic drugs, patients should refrain from sports as long as AF persists and until two half-lives of the antiarrhythmic drug have elapsed	IIa	C	620

2246 AF = atrial fibrillation.

2247 <sup>a</sup>Class of recommendation.2248 <sup>b</sup>Level of evidence.2249 <sup>c</sup>Reference(s) supporting recommendations.

2250

2251 **13.4. Pregnancy**

2252 AF in pregnant women is rare and is usually associated with pre-existing heart disease. AF is associated with  
 2253 increased complications for the mother and foetus.<sup>911,912</sup> Better treatment of congenital heart diseases will  
 2254 probably increase the incidence of AF during pregnancy in the future.<sup>913</sup> Pregnant women with AF should be  
 2255 managed as high-risk pregnancies in close collaboration with cardiologists, obstetricians, and neonatologists.

2256

2257 **13.4.1. Rate control**

2258 Owing to a lack of specific data, beta-blockers, verapamil, diltiazem, and digoxin all carry a US Food and Drug  
 2259 Administration pregnancy safety category of C (benefits may outweigh risk), except for atenolol (category D:  
 2260 positive evidence of risk). Their use should be at the lowest dose and for the shortest time required. None of the  
 2261 agents are teratogenic, but they readily cross the placenta.<sup>914</sup> Beta-blockers are commonly used in clinical  
 2262 practice (e.g. for management of gestational hypertension and pre-eclampsia), but may be associated with  
 2263 intrauterine growth retardation,<sup>915</sup> and hence growth scans after 20 weeks gestation are recommended. Digoxin  
 2264 is considered safe for maternal and foetal arrhythmias.<sup>916</sup> There are insufficient data to comment on verapamil or  
 2265 diltiazem, hence rate control using beta-blockers and/or digoxin is recommended.<sup>917</sup> With regards to  
 2266 breastfeeding, all rate control agents are present in breast milk, although levels of beta-blockers, digoxin, and  
 2267 verapamil are too low to be considered harmful. Diltiazem will be present at high levels and should be  
 2268 considered second-line treatment.<sup>918</sup>

2269

2270 **13.4.2. Rhythm control**

2271 Rhythm control therapy in pregnant patients with AF has only been reported in case studies. Amiodarone is  
 2272 associated with severe adverse foetal side-effects and should only be considered for emergency situations.<sup>919</sup>  
 2273 Flecainide and sotalol can both be used for conversion of foetal arrhythmias without major adverse effects,<sup>920</sup>  
 2274 and thus are likely to be safe to treat maternal symptomatic AF. Electrical cardioversion can be effective for  
 2275 restoration of sinus rhythm when tachyarrhythmia is causing haemodynamic instability, with low rates of  
 2276 adverse outcomes for both mother and foetus.<sup>921</sup> However, in view of the risk of foetal distress, electrical  
 2277 cardioversion should only be carried out where facilities are available for foetal monitoring and emergency  
 2278 caesarean section. As with other emergencies during pregnancy, patients should receive 100% oxygen,  
 2279 intravenous access should be established early, and the mother should be positioned in the left lateral position to  
 2280 improve venous return.<sup>922</sup>

2281

### 2282 13.4.3. Anticoagulation

2283 VKAs should be avoided in the first trimester because of teratogenic effects, and in the 2–4 weeks preceding  
 2284 delivery to avoid foetal bleeding. Low-molecular-weight heparins are a safe substitute, as they do not cross the  
 2285 placenta.<sup>923</sup> In the third trimester, frequent laboratory checks for adequate anticoagulation (e.g. every 10–14  
 2286 days) and corresponding dose adjustments are advised, given that in some women high doses of both VKA and  
 2287 heparin may be needed to maintain adequate anticoagulation. Pregnant patients with AF and mechanical  
 2288 prosthetic valves who elect to stop VKA treatment in consultation with their specialist team between 6 and 12  
 2289 weeks of gestation, should receive continuous, dose-adjusted unfractionated heparin or dose-adjusted  
 2290 subcutaneous low-molecular-weight heparin. As only limited data are available about teratogenesis for NOACs,  
 2291 these drugs should be avoided during pregnancy.

2292

### 2293 Recommendations during pregnancy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Electrical cardioversion 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 the foetus	I	C	
Anticoagulation is recommended in pregnant patients with AF at risk of stroke. To minimize teratogenic risk and intrauterine bleeding, dose-adjusted heparins are recommended during the first trimester of pregnancy and in the 2–4 weeks before delivery. Vitamin K antagonists or heparin can be used in the remaining parts of the pregnancy	I	B	923
NOACs should be avoided in pregnancy and in women planning a pregnancy	III (harm)	C	

2294 NOAC = non-vitamin K antagonist oral anticoagulants

2295 <sup>a</sup>Class of recommendation.

2296 <sup>b</sup>Level of evidence.

2297 <sup>c</sup>Reference(s) supporting recommendations.

2298

### 2299 13.5. Postoperative atrial fibrillation

2300 AF is common after cardiac surgery (occurring in 15–45% of patients),<sup>924-926</sup> and is associated with increased  
 2301 length of hospital stay and higher rates of complications and mortality.<sup>927</sup> Postoperative AF is also not  
 2302 uncommon after other major surgery, especially in elderly patients. The treatment of postoperative AF is mainly  
 2303 based on studies of patients undergoing cardiac surgery, with much less evidence in the non-cardiac surgery  
 2304 setting.

2305

#### 2306 13.5.1. Prevention of postoperative atrial fibrillation

2307 Beta-blockers reduce postoperative AF and supraventricular tachycardias, albeit with high heterogeneity and  
 2308 moderate risk of bias in a systematic review of published studies (the most commonly studied drug was  
 2309 propranolol, with AF in 16.3% of the treatment group vs. 31.7% in the control group).<sup>925</sup> In the majority of these  
 2310 studies, beta-blockers were administered postoperatively, a regimen supported in a recent meta-analysis.<sup>928</sup>  
 2311 Amiodarone reduced the incidence of postoperative AF compared to a beta-blocker regimen in several meta-  
 2312 analyses, also reducing hospital stay.<sup>925, 929-931</sup>

2313 Despite initial reports from meta-analyses,<sup>689, 932, 933</sup> preoperative treatment with statins did not prevent  
 2314 postoperative AF in a prospective controlled trial.<sup>934</sup> Other therapies have also been studied in small, hypothesis-  
 2315 generating trials, but have not demonstrated clear beneficial effects. These include magnesium,<sup>925, 935, 936</sup> n-3  
 2316 polyunsaturated fatty acids,<sup>937-945</sup> colchicine,<sup>946</sup> corticosteroids,<sup>947, 948</sup> and posterior pericardectomy.<sup>949</sup>  
 2317 Postoperative overdrive biatrial pacing has not gained widespread use despite some suggestion of prophylactic  
 2318 effects.<sup>925, 950</sup>  
 2319

### 2320 13.5.2. Anticoagulation

2321 Postoperative AF is associated with an increased early stroke risk, increased morbidity, and 30-day mortality.<sup>927,</sup>  
 2322 <sup>951, 952</sup> In the long term, patients with an episode of postoperative AF have a twofold increase in cardiovascular  
 2323 mortality and a substantially increased risk of future AF and ischaemic stroke compared with patients that  
 2324 remain in sinus rhythm after surgery.<sup>952-958</sup> OAC at discharge has been associated with a reduced long-term  
 2325 mortality in patients with postoperative AF,<sup>959</sup> without evidence from controlled trials. Good quality data are  
 2326 needed to determine whether long-term anticoagulation can prevent strokes in patients with postoperative AF at  
 2327 high stroke risk,<sup>368, 386</sup> and to assess whether short episodes of postoperative AF (e.g. < 48 h) carry a similar risk  
 2328 as longer episodes.<sup>960</sup> The indication and timing of OAC in postoperative AF patients should take into  
 2329 consideration the risk of postoperative bleeding.  
 2330

### 2331 13.5.3. Rhythm control therapy in postoperative atrial fibrillation

2332 In haemodynamically unstable patients, cardioversion and consideration of antiarrhythmic drugs is  
 2333 recommended. Amiodarone or vernakalant have been efficient in converting postoperative AF to sinus  
 2334 rhythm.<sup>603, 950, 961</sup> A recent medium-sized trial randomizing patients with postoperative AF to either rhythm  
 2335 control therapy with amiodarone or to rate control did not find a difference in hospital admissions during a 60-  
 2336 day follow-up,<sup>962</sup> underpinning that the aim of rhythm control therapy should be to improve AF-related  
 2337 symptoms in postoperative AF. In asymptomatic patients and in those with acceptable symptoms, rate control or  
 2338 deferred cardioversion preceded by anticoagulation is a reasonable approach.  
 2339

### 2340 Recommendations for preventing postoperative AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Perioperative oral beta-blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery	I	B	925, 928
Restoration of sinus rhythm by electrical cardioversion or antiarrhythmic drugs is recommended in postoperative AF with haemodynamic instability	I	C	
Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk	IIa	B	368, 386
Antiarrhythmic drugs should be considered for recurrent or symptomatic postoperative AF after cardiac surgery in an attempt to restore sinus rhythm	IIa	C	
Perioperative amiodarone should be considered for prophylactic therapy to prevent AF after cardiac surgery	IIa	A	925
Intravenous vernakalant may be considered for cardioversion of postoperative AF in patients without severe heart failure, hypotension, or severe structural heart disease (especially aortic stenosis)	IIb	B	603
Asymptomatic postoperative AF should initially be managed with rate control and anticoagulation	IIa	B	962

2341 AF = atrial fibrillation.

2342 <sup>a</sup>Class of recommendation.

2343 <sup>b</sup>Level of evidence.

2344 <sup>c</sup>Reference(s) supporting recommendations.

2345

### 2346 13.6. Atrial arrhythmias in grown-up patients with congenital heart disease



2347 Atrial arrhythmias (AF, atrial flutter, atrial tachycardias) often occur late after surgical repair of congenital heart  
 2348 defects, occurring in 15–40% of grown-up patients with congenital heart disease (GUCH). They are associated  
 2349 with heart failure, syncope, thromboembolic events, and sudden death.<sup>963-967</sup> The pathophysiological substrate is  
 2350 complex, associated with hypertrophy, fibrosis, hypoxaemia, chronic haemodynamic overload, and surgical  
 2351 scars and patches. Additionally, related primary anomalies in the conduction pathways can lead to reentrant  
 2352 atrial and ventricular tachycardia, heart block, and sinus node dysfunction.<sup>963</sup> Macro-reentrant atrial tachycardia  
 2353 or atypical atrial flutter may be seen after nearly any surgical procedure involving atriotomy or atrial patches.  
 2354

### 2355 **13.6.1. General management of atrial arrhythmias in grown-up patients with** 2356 **congenital heart disease**

2357 The conventional stroke risk factors should be used to inform decisions on long-term anticoagulation in GUCH  
 2358 patients with AF. In addition, anticoagulation should be considered in GUCH patients with atrial arrhythmias  
 2359 when they present with intracardial repair, cyanosis, Fontan palliation, or systemic right ventricle, in addition to  
 2360 those with conventional stroke risk factors.<sup>968</sup> Beta-blockers, verapamil, diltiazem, and digitalis can be used.  
 2361 Care should be taken to avoid bradycardia and hypotension.

2362 Sodium channel blockers suppress approximately half of atrial arrhythmias in Fontan patients.<sup>969</sup>  
 2363 Amiodarone is more effective, but long-term treatment with an antiarrhythmic drugs carries a high risk of  
 2364 extracardiac side-effects in this relatively young population. Intracardiac thrombi are common in GUCH  
 2365 patients undergoing cardioversion for AF, but also in patients with atrial tachycardias or atrial flutter.<sup>970</sup>  
 2366 Therefore, both a TOE and anticoagulation for a few weeks before the planned cardioversion should be  
 2367 considered.<sup>964</sup> Radiofrequency ablation may be a good option for symptomatic GUCH patients with atrial  
 2368 arrhythmias, especially in those with atrial flutter and other macro-reentrant tachycardias. Interventions should  
 2369 be performed in adequately qualified centres by specialized teams.  
 2370

### 2371 **13.6.2. Atrial tachyarrhythmias and atrial septal defects**

2372 Atrial flutter and fibrillation occur in 14–22% of adults with unoperated atrial septal defects, especially in older  
 2373 patients,<sup>971</sup> and can lead to heart failure.<sup>972</sup> Early repair can reduce but not eliminate the risk of AF.<sup>973</sup> Biatrial  
 2374 volume overload,<sup>974</sup> pulmonary hypertension,<sup>975</sup> and possibly the arrhythmogenic effect of atrial patches can  
 2375 contribute to these arrhythmias.<sup>976</sup> Anticoagulation should be decided based on stroke risk factors. In patients  
 2376 with a history of paroxysmal or persistent AF, AF surgery could be considered at the time of surgical closure, or  
 2377 catheter ablation in patients undergoing interventional atrial septal defect closure. Catheter ablation of late atrial  
 2378 arrhythmias has shown to be effective in 46 consecutive patients after surgical atrial septal defect.<sup>977</sup>  
 2379

### 2380 **13.6.3. Atrial tachyarrhythmias after Fontan operation**

2381 Atrial arrhythmias occur in up to 40% of patients with a Fontan circulation, and can manifest as atrial flutter,  
 2382 primary atrial tachycardia, AF, and accelerated junctional rhythm or junctional tachycardia<sup>978</sup> with or without  
 2383 sinoatrial node dysfunction.<sup>979</sup> Patients with atriopulmonary anastomoses (possibly due to higher atrial volume  
 2384 and pressure load) and those with early postoperative atrial arrhythmias are more likely to develop long-term  
 2385 atrial arrhythmias.<sup>980</sup> Atrial arrhythmias can also be the first manifestation of obstruction of the atriopulmonary  
 2386 anastomosis, a complication that must be identified. Right atrial thrombus formation is common in Fontan  
 2387 patients with atrial arrhythmias and requires oral anticoagulation.<sup>981</sup> Operative conversion to total  
 2388 cavopulmonary artery connection with concomitant arrhythmia surgery can in some patients improve heart  
 2389 failure symptoms and reduce recurrent arrhythmias,<sup>969, 982</sup> with low recurrence rates of clinically apparent atrial  
 2390 arrhythmias in the first few years after repeat surgery.<sup>983-985</sup> Catheter ablation of atrial arrhythmia in Fontan  
 2391 patients has been successful in selected patients.<sup>986</sup>  
 2392

### 2393 **13.6.4. Atrial tachyarrhythmias after tetralogy of Fallot correction**

2394 Approximately one-third of patients after repair of tetralogy of Fallot develop atrial arrhythmias, including intra-  
 2395 atrial reentrant tachycardia, focal atrial tachycardia, and AF.<sup>987</sup> Circuits involving the cavotricuspid isthmus and  
 2396 areas of presumed surgical right atrial scarring have been described as responsible for atrial arrhythmias.  
 2397

### 2398 **Recommendations in patients with GUCH**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Atrial septal defect closure should be considered before the fourth decade of life to diminish the chance of atrial flutter and fibrillation	Ila	C	971, 972, 974

In patients who need surgical closure of an atrial septal defect and who have a history of symptomatic atrial arrhythmia, atrial ablation should be considered at the time of surgical closure	IIa	C	204, 988, 989
Cox maze surgery should be considered in patients with symptomatic AF and an indication for corrective repair of congenital heart defects. All such surgery should be done in experienced centres	IIa	C	988, 990
Oral anticoagulation should be considered in all adult patients with intracardiac repair, cyanosis, Fontan palliation, or systemic right ventricle and a history of AF, atrial flutter, or intra-atrial reentrant tachycardia. In all other congenital heart disease patients with AF, anticoagulation should be considered if the CHA <sub>2</sub> DS <sub>2</sub> -VAS <sub>C</sub> score is $\geq 1$	IIa	C	968
Catheter ablation of atrial arrhythmias associated with congenital heart defects may be considered when performed in experienced centres	IIb	C	991
In patients with congenital heart disease, transoesophageal echocardiography may be considered together with 3-week anticoagulation therapy before cardioversion	IIb	C	964, 970, 988, 990

2399 AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive Heart failure, hypertension, Age  $\geq 75$  (doubled),  
 2400 Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); GUCH = grown-up patients with  
 2401 congenital heart disease; OAC = oral anticoagulation; TOE = transoesophageal echocardiography.

2402 <sup>a</sup>Class of recommendation.

2403 <sup>b</sup>Level of evidence.

2404 <sup>c</sup>Reference(s) supporting recommendations.

2405

### 2406 13.7. Management of atrial flutter

2407 The goals for the management of atrial flutter are similar to those for AF.<sup>992</sup> Based on the available evidence, the  
 2408 stroke risk in patients with atrial flutter is not much different from that in AF.<sup>827</sup> Furthermore, many patients  
 2409 diagnosed with atrial flutter develop AF.<sup>993-995</sup> Thus, anticoagulation should be used in patients with atrial flutter  
 2410 similar to that in patients with AF. Rate control in atrial flutter is achieved with the same medications as in AF,  
 2411 but is often more difficult to achieve. Flecainide, propafenone, dofetilide, and intravenous ibutilide are useful for  
 2412 cardioversion of atrial flutter. They should be combined with a rate-controlling agent to avoid 1:1 conduction of  
 2413 slowing flutter waves to the ventricles. Ibutilide is more effective for conversion of atrial flutter than AF,  
 2414 whereas vernakalant is less effective in converting typical atrial flutter.<sup>996, 997</sup> Electrical cardioversion of atrial  
 2415 flutter can be performed using lower energies (50–100 J) than for AF.<sup>998, 999</sup> Atrial overdrive pacing through  
 2416 pacemaker leads or endocardial or transesophageal catheters can convert atrial flutter to sinus rhythm.<sup>1000, 1001</sup>  
 2417 Anticoagulation and transoesophageal echocardiography around cardioversion or overdrive pacing should be  
 2418 used similar to that in AF.

2419 Ablation of the cavotricuspid isthmus for isthmus-dependent right atrial flutter (either the common  
 2420 counter-clockwise atrial flutter or the less-common clockwise atrial flutter) restores and maintains sinus rhythm  
 2421 with a success rate of 90–95%.<sup>1002</sup> It may also reduce AF recurrences in selected patients,<sup>1003, 1004</sup> and help to  
 2422 prevent hospitalizations.<sup>1004, 1005</sup> Isthmus ablation is comparably safe and more effective than antiarrhythmic  
 2423 drug therapy, and is recommended for recurrent atrial flutter.<sup>585-587, 713</sup> Catheter ablation of left atrial macro-  
 2424 reentrant tachycardia is more complex, with lower success rates and higher recurrence rates.<sup>1006, 1007</sup>

2425

### 2426 Recommendations for management of atrial flutter

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF	I	B	827
Overdrive atrial pacing of atrial flutter should be considered as an alternative to electrical cardioversion, depending on local availability and experience	IIa	B	1000, 1001

Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference	I	B	158
If atrial flutter has been documented before AF ablation, ablation of the cavotricuspid isthmus should be considered as part of the AF ablation procedure	IIa	C	

2427 AF = atrial fibrillation.

2428 <sup>a</sup>Class of recommendation.

2429 <sup>b</sup>Level of evidence.

2430 <sup>c</sup>Reference(s) supporting recommendations.

2431

## 2432 **14 Patient involvement, education and self-management**

2433 A fundamental aspect of a structured AF management programme is the focus on patient-centred care.

2434

### 2435 **14.1. Patient-centred care**

2436 Autonomous, informed patients are better placed to adhere to long-term therapy, and it is very likely that long-term management of chronic conditions such as AF will benefit from informed patients involved in the disease management who are aware of their own responsibilities.<sup>328</sup> Shared decision-making<sup>747</sup> and patient-centred organization of care can help to ensure adherence to management and empower patients, and respect individual patient preferences, needs, and values (see Chapter 7.2).<sup>326, 1008, 1009</sup> Patients in an active role tend to have better health outcomes and care experiences, and engagement itself can be considered as an intermediate outcome, particularly where related to improved clinical outcomes.<sup>1010</sup>

2441

2442

2443

### 2444 **14.2. Integrated patient education**

2445 Education is a prerequisite for informed, involved patients and patient-centred care. However, lack of AF-related knowledge in patients is common, even in those who have received verbal and written information,<sup>32, 1011, 1012</sup> indicating the need to further develop structured patient education. Several patient-information tools have been developed, largely focusing on oral anticoagulation.<sup>1013-1016</sup> Understanding patients' perceptions and attitudes towards AF and its management can improve AF management and related outcomes.<sup>1017</sup> This includes tailored patient education focusing on the disease, symptom recognition, therapy, modifiable risk factors for AF, and self-management activities.<sup>1018, 1019</sup>

2451

2452

### 2453 **14.3. Self-management and shared decision-making**

2454 Self-management is primarily focused on tasks to manage the condition, such as adhering to a therapeutic regimen or modifying behaviour (e.g. resulting in smoking cessation or weight loss).<sup>1020</sup> It requires understanding of the treatment modalities and goals.<sup>350</sup> Within a multidisciplinary team, allied health professionals can guide this interactive process in which communication, trust, and reciprocal respect foster patient engagement.<sup>1021</sup> Shared decision-making should be considered as a routine part of the decision-making process,<sup>747</sup> supported by decision aids where applicable.<sup>1022</sup> Models of care that integrate education, engagement, and shared decision making are now available,<sup>1023</sup> and may be of particular value in the management of AF.

2461

2462

2463

#### **Recommendations for patient involvement, education, and self-management**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Refs <sup>c</sup>
Tailored patient education is recommended in all phases of AF management to support patients' perception of AF and to improve management	I	C	1014, 1017
Patient involvement in the care process should be considered to encourage self-management and responsibility for lifestyle changes	IIa	C	328, 1010
Shared decision-making should be considered to ensure that care is based on the best available evidence and fits the needs, values, and preferences of the patient	IIa	C	747

2464 AF = atrial fibrillation.

2465 <sup>a</sup>Class of recommendation.

2466 <sup>b</sup>Level of evidence.

2467 <sup>c</sup>Reference(s) supporting recommendations.

2468

## 2469 **15 Gaps in evidence**

2470 There are some areas of AF management that are supported by excellent evidence from multiple, adequately  
2471 powered randomized trials (e.g. oral anticoagulation. Other areas, such as rhythm control therapy, integrated AF  
2472 management, and lifestyle modifications are clearly developing the required evidence, while areas such as rate  
2473 control are in dire need of better studies to underpin future guidelines. Here we identify areas in need of further  
2474 research.

2475

### 2476 **15.1. Major health modifiers causing atrial fibrillation**

2477 Atrial fibrillation has different causes in different patients. More research is needed into the major causes (and  
2478 electrophysiological mechanisms) of AF in different patient groups.<sup>176, 1024</sup> Such research should consider the  
2479 major comorbidities associated with AF, and characterize the response to AF therapy in patients with different,  
2480 pathophysiologically distinct types of AF.

2481

### 2482 **15.2. How much atrial fibrillation constitutes a mandate for therapy?**

2483 Technological advances allow screening for an irregular pulse using patient-operated ECG devices,  
2484 smartphones, and a variety of other technologies. These may be very useful to detect silent, undiagnosed AF.<sup>157</sup>  
2485 Adequately powered studies evaluating the diagnostic accuracy of such technologies, the diagnostic yield in  
2486 different populations, the shortest duration of atrial arrhythmias conveying a stroke risk, and ideally the effect of  
2487 ECG screening on outcomes are needed.

2488

### 2489 **15.3. Atrial high-rate episodes and need for anticoagulation**

2490 All of the information on the benefit of OAC has been in patients with AF diagnosed by ECG. Technological  
2491 advances allow ready detection of AHRE in patients with implanted devices and an atrial lead. Such patients are  
2492 at increased stroke risk, but it is unclear whether they benefit from OAC. Controlled trials evaluating OAC in  
2493 AHRE patients are ongoing and will provide evidence on the best antithrombotic therapy in these patients.

2494

### 2495 **15.4. Stroke risk in specific populations**

2496 Several specific AF groups should be studied to better characterize their risk for AF, stroke, and other AF-  
2497 related complications (e.g. patients with one stroke risk factor, and non-Caucasian patients). Confounding  
2498 factors (e.g. different therapy of concomitant cardiovascular diseases) may help to explain the variability in the  
2499 reported rates of incident AF, prevalent AF, and AF complications. This also applies to the effect of gender in  
2500 AF patients.<sup>47</sup>

2501

### 2502 **15.5. Anticoagulation in patients with severe chronic kidney disease**

2503 The use of NOACs has not been tested in patients with creatinine clearance < 30 mL/min, and there is very little  
2504 evidence on the effects of OAC in patients on haemodialysis or on other forms of renal-replacement therapy.  
2505 Studies evaluating OAC in patients with severe chronic kidney disease are needed to inform the best  
2506 management in this patient group at high risk for stroke and bleeding.

2507

### 2508 **15.6. Left atrial appendage occlusion for stroke prevention**

2509 The most common justification for LAA occlusion devices in clinical practice is a perceived high bleeding risk  
2510 and, less often, contraindications for OAC.<sup>459</sup> Unfortunately, LAA occluders have not been tested in such  
2511 populations. Furthermore, LAA occluders have not been compared with NOAC therapy in patients at risk for  
2512 bleeding, or with thoracoscopic LAA clipping. There is a clear need to conduct adequately designed and  
2513 powered trials to define the clinical role of LAA occluders compared with NOAC therapy in patients with  
2514 relative or absolute contraindications for anticoagulation, and/or in those suffering from an ischaemic stroke on  
2515 anticoagulant therapy.

2516

### 2517 **15.7. Anticoagulation in atrial fibrillation patients after a bleeding or stroke event**

2518 At least 2% of anticoagulated patients with AF will experience a serious bleeding event per year. Observational  
2519 data suggest that OAC can be reinitiated even after an intracerebral bleeding event.<sup>460, 484</sup> Controlled studies  
2520 evaluating different anticoagulation and stroke prevention interventions are urgently needed to provide evidence  
2521 on the best management of patients who have suffered a bleeding event that would usually lead to withholding

2522 OAC. Some studies (e.g. APACHE II<sup>1025</sup>) are ongoing, but adequately powered trials are needed. Similarly,  
2523 prospectively collected data are needed on the efficacy and bleeding risk following (re-)initiation of OAC after  
2524 stroke or intracranial bleeding.  
2525

### 2526 **15.8. Anticoagulation and optimal timing of non-acute cardioversion**

2527 Based on retrospective data, previous recommendations on the safe time-window in which a cardioversion can  
2528 be performed in new-onset AF used  $\leq 48$  hours as the ‘gold standard’ for non-protected cardioversion. However,  
2529 new evidence has emerged that initiating precardioversion anticoagulation in patients with AF episodes of  $< 24$   
2530 hours or even  $< 12$  hours would provide even better safety.<sup>642, 647, 1026-1028</sup> Further research is needed to establish  
2531 a clear safety margin in this clinical situation.  
2532

### 2533 **15.9. Competing causes of stroke or transient ischaemic attack in atrial fibrillation** 2534 **patients**

2535 Prospective RCTs have demonstrated the superiority of carotid endarterectomy compared to stenting in patients  
2536 with symptomatic high-degree stenosis of the internal carotid artery.<sup>1029</sup> As endarterectomy minimizes the need  
2537 for combination therapy with OAC and antiplatelets,<sup>1030</sup> this approach has appeal in patients with AF to reduce  
2538 bleeding risk. However, few of these studies included patients with AF. In a large observational study, the  
2539 composite of in-hospital mortality, post-procedural stroke, and cardiac complications was higher in AF patients  
2540 undergoing carotid stenting (457/7668; 6.0%) compared with endarterectomy (4438/51320; 8.6%;  $P <$   
2541 0.0001).<sup>1031</sup> Despite adjustment for baseline risk, this may just reflect the type of patients referred for each  
2542 procedure, and further randomized studies are needed to confirm the optimal treatment strategy in AF patients  
2543 with carotid disease.  
2544

### 2545 **15.10. Anticoagulation in patients with biological heart valves (including transcatheter** 2546 **aortic valve implantation) and non-rheumatic valve disease**

2547 The optimal antithrombotic therapy in the first months after biological valve replacement (including after  
2548 catheter-based valve replacement) is not known. VKAs remain the mainstay during the initial postoperative  
2549 period; NOACs probably deliver the same protection. In patients without AF, many centres use platelet  
2550 inhibitors only. NOACs appear to be equally effective as VKAs in patients with moderate aortic stenosis, based  
2551 on a subanalysis from the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared  
2552 with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial<sup>1032</sup> as well  
2553 as the Loire Valley AF project.<sup>1033</sup> Further data would be helpful to confirm these observations.<sup>1034</sup> The safety  
2554 and efficacy of NOACs in patients with rheumatic mitral valve disease has not been evaluated and should be  
2555 studied.  
2556

### 2557 **15.11. Anticoagulation after ‘successful’ catheter ablation**

2558 In view of the long-term recurrence rates of AF, this Task Force recommends to continue OAC in AF patients  
2559 after ‘successful’ catheter ablation. Nonetheless, observational data suggest that the stroke risk may be lower  
2560 after catheter ablation of AF compared with other AF patients. The ongoing EAST (Early treatment of Atrial  
2561 fibrillation for Stroke prevention Trial) trial will inform in a more general way whether rhythm control therapy  
2562 can reduce stroke rates in anticoagulated AF patients. If confirmed, there may be a place for a controlled trial  
2563 evaluating the termination of OAC therapy at an interval after ‘successful’ catheter ablation.  
2564

### 2565 **15.12. Comparison of rate control agents**

2566 Although the use of rate control therapy is very common in AF patients, robust data comparing rate control  
2567 therapies are scant, with the majority of studies being small uncontrolled trials over short periods of follow-up.  
2568 Some studies are funded (e.g. RATE-AF [Rate Control Therapy Evaluation in Permanent Atrial Fibrillation]<sup>559</sup>)  
2569 and will investigate the potential benefits of different rate controlling agents, characteristics, or biomarkers that  
2570 can help to personalize the use of rate control, and the adverse-event profile of specific drugs in defined groups  
2571 of patients (e.g. AF with HFrEF).  
2572

### 2573 **15.13. Catheter ablation in persistent and long-standing persistent AF**

2574 While a few recent randomized studies support the use of catheter or surgical ablation in patients with persistent  
2575 AF and long-standing persistent AF, there is a clear need for more data evaluating this intervention in  
2576 adequately powered randomized trials.

2577

**2578 15.14. Optimal technique for repeat catheter ablation**

2579 PVI emerges as the most important target for catheter ablation of AF. Although a plethora of different additional  
2580 ablation techniques have been published, their added value is questionable in patients undergoing a first catheter  
2581 ablation, including those with persistent AF.<sup>735</sup> Many patients are in need of multiple catheter-ablation  
2582 procedures, and such interventions often follow local or operator-specific protocols without clear evidence to  
2583 support the choice of ablation target or intervention. There is a clear clinical need to define the best approach in  
2584 patients who are in need of a second ablation procedure.  
2585

**2586 15.15. Combination therapy for maintenance of sinus rhythm**

2587 In the follow-up after initially successful catheter ablation, even when done in experienced centres, many  
2588 patients will experience symptomatic recurrences of AF. These patients are often managed with antiarrhythmic  
2589 drugs. There is a surprising paucity of data evaluating different rhythm control interventions in patients with  
2590 recurrent AF after catheter ablation. Such studies seem reasonable and feasible.  
2591

**2592 15.16. Can rhythm control therapy convey a prognostic benefit in atrial fibrillation patients?**

2593 The progress in rhythm control therapy (catheter ablation, new antiarrhythmic drugs) and observational long-  
2594 term analyses suggest that rhythm control therapy may have a prognostic benefit. Ongoing trials such as  
2595 CABANA and EAST – AFNET 4 will provide initial answers to this important question, but more data are  
2596 needed, in addition to trials of surgical ablation techniques.  
2597  
2598

**2599 15.17. Thoracoscopic ‘stand-alone’ atrial fibrillation surgery**

2600 Minimally invasive epicardial ablation surgery for the treatment of stand-alone AF was reported a decade  
2601 ago.<sup>1035</sup> The procedure has since evolved towards a totally thoracoscopic procedure,<sup>1036</sup> and lesion sets were  
2602 extended to a complete left atrial maze.<sup>822</sup> With such rapid development and the coexistence of different  
2603 techniques and lesion sets, scientific evidence on long-term results is still limited. Randomized trials using a  
2604 standardized procedure are urgently needed to clearly define the benefits and risks of thoracoscopic AF ablation,  
2605 and to further support decisions of the AF Heart Team.  
2606

**2607 15.18. Surgical exclusion of the left atrial appendage**

2608 Exclusion of the LAA has been performed by cardiothoracic surgeons for decades, but prospective randomized  
2609 studies comparing the rate of ischaemic stroke with or without left appendage exclusion are presently lacking.  
2610 The LAAOS (Left Atrial Appendage Occlusion Study) III is currently randomizing cardiac surgery patients with  
2611 AF to undergo concomitant occlusion or no occlusion of the appendage.<sup>467</sup> More data are also needed to confirm  
2612 the safety and efficacy of thoracoscopic exclusion, following early positive observational data.<sup>1037</sup>  
2613

**2614 15.19. Concomitant atrial fibrillation surgery**

2615 Adequately powered randomized trials are needed, employing systematic follow-up, uniform lesion sets and  
2616 energy sources to evaluate the benefits and risks of concomitant AF surgery in symptomatic AF patients. An  
2617 RCT on non-uniform lesion sets with long-term follow-up is due to publish shortly.<sup>1038</sup> These will assist the AF  
2618 Heart Team to decide on optimal therapy for individual patients, including the full repertoire of medical and  
2619 surgical options for the treatment of AF.  
2620

2621 **16 To do and not to do messages from the Guidelines**

2622

Recommendations for diagnosis and screening of AF	Class	Level
ECG documentation is required to establish the diagnosis of AF	I	B
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients > 65 years of age	I	B
In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours	I	B
It is recommended to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes (AHRE). Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy	I	B
Recommendations for general management of AF	Class	Level
Tailored patient education is recommended in all phases of AF management to support patients' perception of AF and to improve management	I	C
A full cardiovascular evaluation, including an accurate history, careful clinical examination, and assessment of concomitant conditions, is recommended in all AF patients	I	C
Use of the modified EHRA symptom scale is recommended in clinical practice and research studies to quantify AF-related symptoms	I	C
Transthoracic echocardiography is recommended in all AF patients to guide management	I	C
The assessment of kidney function by serum creatinine or creatinine clearance is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy	I	A
Recommendations for stroke prevention in AF	Class	Level
The CHA <sub>2</sub> DS <sub>2</sub> -VASc score is recommended for stroke risk prediction in patients with AF	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 2 or more	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 3 or more	I	A
When oral anticoagulation is initiated in a patient with AF who is eligible for a non vitamin-K-antagonist oral anticoagulant (NOAC, apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist	I	A
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves	I	B
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C)	III (harm)	B/C
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored	I	A
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet	III (harm)	B

inhibition		
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention	III (harm)	B
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk	III (harm)	A
After surgical occlusion or exclusion of the left atrial appendage, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention	I	B
Genetic testing before the initiation of vitamin K antagonist therapy is not recommended.	III (no benefit)	B
In AF patients with severe active bleeding events, it is recommended to interrupt oral anticoagulation therapy until the underlying cause is resolved	I	C
NOACs should be avoided in pregnancy and in women planning a pregnancy	III (harm)	C
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF	I	B
Management of typical atrial flutter with ablation of the cavotricuspid isthmus is recommended for patients failing antiarrhythmic drug therapy or as first-line treatment considering patient preference	I	B
Lifelong oral anticoagulation to prevent stroke is recommended in hypertrophic cardiomyopathy patients who develop AF	I	B
Anticoagulation with heparin or low-molecular-weight heparin immediately after ischaemic stroke is not recommended in AF patients	III (harm)	A
Systemic thrombolysis with a recombinant tissue plasminogen activator is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if activated partial thromboplastin time is outside the normal range)	III (harm)	C
After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended	III (harm)	B
<b>Recommendations for rate control of AF</b>	<b>Class</b>	<b>Level</b>
Beta-blocker, digoxin, diltiazem, or verapamil is recommended to control heart rate in AF patients with LVEF $\geq$ 40%	I	B
Beta-blocker and/or digoxin is recommended to control heart rate in AF patients with LVEF < 40%	I	B
In patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), antiarrhythmic drugs should not routinely be used for rate control	III (harm)	A
<b>Recommendations for rhythm control of AF</b>	<b>Class</b>	<b>Level</b>
Rhythm control therapy is indicated for symptom improvement in patients with AF	I	B
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy	I	B
In patients with no history of ischaemic or structural heart disease, flecainide, propafenone, or vernakalant is recommended for pharmacological cardioversion of new-onset AF	I	A



In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF	I	A
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion	I	B
Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus, as an alternative to preprocedural anticoagulation when early cardioversion is planned	I	B
The choice of antiarrhythmic drug needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden	I	A
Dronedarone, flecainide, propafenone, or sotalol is recommended for prevention of recurrent symptomatic AF in patients with normal left ventricular function and without pathological left ventricular hypertrophy.	I	A
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure	I	A
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure	I	B
Antiarrhythmic drug therapy is not recommended in patients with prolonged QT interval (> 0.5 s) or with significant sinoatrial node disease or atrioventricular node dysfunction who do not have a functioning permanent pacemaker	III (harm)	C
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre	I	A
ARBs or ACE inhibitors are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.	III (no benefit)	B
Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting, more intense sports participation can promote AF	I	A

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2624  
2625

**2626 17 A short summary of the management of AF patients**

2627

2628 Here, we provide 17 simple rules to guide diagnosis and management of AF patients according to the 2016  
2629 ESC/EACTS/ESO Guidelines for the management of atrial fibrillation

2630

2631 1. Use ECG screening in at risk populations for atrial fibrillation, especially stroke survivors and the  
2632 Elderly.

2633

2. Document AF by ECG before starting treatment.

2634

2635 3. Evaluate all AF patients by clinical evaluation, ECG, and echocardiogram for underlying  
cardiovascular conditions such as hypertension, heart failure, valvular heart disease, and others.

2636

2637 4. Provide tailored information and education to AF patients to empower them to support AF  
management.

2638

5. Propose life style changes to all suitable AF patients to make their management more effective.

2639

2640 6. Treat underlying cardiovascular conditions adequately, e.g. valve repair or replacement in AF patients  
2641 with significant valvular heart disease, treatment of heart failure, or management of hypertension,  
among others.

2642

2643 7. Use oral anticoagulation in all AF patients unless they are at low risk for stroke based on the  
CHA<sub>2</sub>DS<sub>2</sub>VASc score or have true contraindications for anticoagulant therapy.

2644

2645 8. Anticoagulate patients with atrial flutter similar to atrial fibrillation. Offer isthmus ablation to  
symptomatic flutter patients.

2646

2647 9. Reduce all modifiable bleeding risk factors in all AF patients on oral anticoagulation, e.g. by treating  
2648 hypertension, minimising the duration and intensity of concomitant antiplatelet and NSAID therapy ,  
2649 treating anaemia and eliminating causes for blood loss, maintaining stable INR values in patients on  
vitamin K antagonists, and moderating alcohol intake

2650

2651 10. Check ventricular rate in all AF patients and use rate control medications to achieve lenient rate  
control.

2652

2653 11. Evaluate AF-related symptoms in all AF patients using the modified EHRA score. Whenever patients  
2654 have AF-related symptoms, aim to improve symptoms by adjustment of rate control therapy and by  
offering antiarrhythmic drugs, cardioversion, or catheter or surgical ablation.

2655

2656 12. Select antiarrhythmic drugs based on their safety profile and consider catheter or surgical ablation  
when antiarrhythmic drugs fail.

2657

2658 13. Do not offer routine genetic testing in AF patients unless there is a suspicion for an inherited cardiac  
condition.

2659

14. Do not use antiplatelet therapy for stroke prevention in AF.

2660

2661 15. Do not permanently discontinue oral anticoagulation in AF patients at increased risk of stroke unless  
such a decision is taken by a multidisciplinary team.

2662

2663 16. Do neither use rhythm control therapy in asymptomatic AF patients, nor in patients with permanent  
AF.

2664

2665 17. Do not perform cardioversion or catheter ablation without anticoagulation unless an atrial thrombus has  
been ruled out by transesophageal echocardiogram.

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**2669 18 Web Addenda**

2670 All Web figures and Web tables are available in the Web addenda, available at European Heart Journal online  
2671 and also via the ESC Website (www.escardio.org/guidelines).

2672

**2673 19 Appendix**

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2682

2683 **ESC National Cardiac Societies** actively involved in the review process of the 2016 ESC Guidelines for the  
2684 management of atrial fibrillation developed in collaboration with EACTS

2685

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2719 **20 References**

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