
TITLE PAGE



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)

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and the European Stroke Organisation (ESO)+

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197

198

199 Abbreviations and acronyms (to be checked by MW at final phase)

200

201 AAD antiarrhythmic drug

202

203 ACE angiotensin-converting enzyme

204

205 ACEI angiotensin-converting enzyme inhibitor

206

207 ACS acute coronary syndrome(s)

208

209 ACT activated clotting time

210

211 AF atrial fibrillation

212

213 AFEQT Atrial Fibrillation Effect on QualiTy of life questionnaire

214

215 AFFIRM Atrial Fibrillation Follow-up Investigation of Rhythm Management

216

217 AFNET German Competence NETwork on Atrial Fibrillation

218

219 AF-QoL quality of life questionnaire for patients with atrial fibrillation

220

221 AHRE atrial high rate episodes

222

223 AP action potential

224

225 aPTT activated partial thromboplastin time

226

227 ARB angiotensin receptor blocker

228

229 ARISTOTLE Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

230

231 ARREST-AF Aggressive Risk Factor Reduction Study for Atrial Fibrillation

232

233

234 ASD atrial septal defect

235

236 ASSERT Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial

237

238 AV atrioventricular

239

240 AVERROES Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment

241

242 AXAFA Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy

243

244

245

246

247

248

249	BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
250		
251	<i>b.i.d.</i>	twice daily
252		
253	BMI	body mass index
254		
255	BNP	B-type natriuretic peptide
256		
257	BP	blood pressure
258		
259	bpm	beats per minute
260		
261	CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation
262		Trial
263		
264	CAD	coronary artery disease
265		
266	CARE-HF	CARDiac RESynchronisation in Heart Failure
267		
268	CFAE	complex fractionated atrial electrograms
269		
270	CHADS ₂	Congestive heart failure, Hypertension, Age ≥ 75 , Diabetes, Stroke
271		(doubled)
272		
273	CHA ₂ DS ₂ -VASc	Congestive Heart failure, hypertension, Age ≥ 75 (doubled), Diabetes,
274		Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)
275		
276	CI	confidence interval
277		
278	CKD	chronic kidney disease
279		
280	CMP	Cox maze procedure
281		
282	CNS	central nervous system
283		
284	COPD	chronic obstructive pulmonary disease
285		
286	CrCl	creatinine clearance
287		
288	CRP	C-reactive protein
289		
290	CRT	cardiac resynchronization therapy
291		
292	CT	computed tomography
293		
294	cTnT	cardiac troponin T
295		
296	CV	cardiovascular
297		
298		
299	DIG	Digitalis Investigation Group
300		

301	EAD	early afterdepolarization
302		
303	EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial
304		
305	ECG	electrocardiogram
306		
307	eGFR	estimated glomerular filtration rate
308		
309	EHRA	European Heart Rhythm Association
310		
311	ENGAGE AF-TIMI	Effective Anticoagulation with Factor Xa Next Generation in Atrial
312		Fibrillation-Thrombolysis in Myocardial Infarction
313		
314	EORP	EURObservational Research Programme
315		
316	ESUS	embolic stroke of undetermined source
317		
318	FAST	Atrial Fibrillation Catheter Ablation vs Surgical Ablation Treatment
319		
320	FDA	US Food and Drug Administration
321		
322	FEV1	forced expiratory volume in 1 second
323		
324	GDF-15	growth differentiation factor 15
325		
326	GFR	glomerular filtration rate
327		
328	GI	gastrointestinal
329		
330	GP	general practitioner
331		
332	GUCH	grown up congenital heart disease
333		
334	HARMONY	A Study to Evaluate the Effect of Ranolazine and Dronedarone When
335		Given Alone and in Combination in Patients With Paroxysmal Atrial
336		Fibrillation
337		
338	HAS-BLED	hypertension, abnormal renal/liver function, stroke, bleeding history or
339		predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly
340		
341	HCM	hypertrophic cardiomyopathy
342		
343	HF	heart failure
344		
345	HFpEF	heart failure with preserved ejection fraction
346		
347	HFrEF	heart failure with reduced ejection fraction
348		
349	HR	hazard ratio
350		
351	IART	intra-atrial reentrant tachycardia
352		

353	ICB	intracranial bleed
354		
355	ICD	implantable cardioverter defibrillator
356		
357	ICD code	International Classification of Diseases code
358		
359	ICM	insertable cardiac monitor
360		
361	ICH	intracranial haemorrhage
362		
363	IHD	ischaemic heart disease
364		
365	INR	international normalized ratio
366		
367	IQR	interquartile range
368		
369	ITT	intention to treat
370		
371	IV	intravenous
372		
373	LA	left atrium/atrial
374		
375	LAA	left atrial appendage
376		
377	LAAOS	Left Atrial Appendage Occlusion Study
378		
379	LMWH	low-molecular-weight heparin
380		
381	LQT	long QT
382		
383	LV	left ventricular
384		
385	LVEF	left ventricular ejection fraction
386		
387	LVH	left ventricular hypertrophy
388		
389	LVOTO	left ventricular outflow tract obstruction
390		
391	MACE	major adverse cardiac events
392		
393	MANTRA-PAF	Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
394		
395		
396	MDRD	Modification of Diet in Renal Disease
397		
398	MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome
399		
400		
401	MH	major haemorrhages
402		
403	mEHRA	modified EHRA
404		

405	MI	myocardial infarction
406		
407	MRI	magnetic resonance imaging
408		
409	mRNA	messenger ribonucleic acid
410		
411	NIHSS	National Institutes of Health Stroke Scale
412		
413	NNH	number needed to harm
414		
415	NNT	number needed to treat
416		
417	NOAC	non-vitamin K antagonist oral anticoagulant
418		
419	NT-proBNP	N-terminal fragment B-type natriuretic peptide
420		
421	NYHA	New York Heart Association
422		
423	OAC	oral anticoagulation
424		
425	<i>o.d.</i>	once daily
426		
427	OR	odds ratio
428		
429	OSA	obstructive sleep apnoea
430		
431	PAFAC	Prevention of Atrial Fibrillation After Cardioversion
432		
433	PCC	prothrombin complex concentrates
434		
435	PCI	percutaneous coronary intervention
436		
437	PITX2	paired-like homeodomain transcription factor 2
438		
439	PREFER in AF	PREvention oF thromboembolic events - European Registry in Atrial Fibrillation
440		
441		
442	PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial
443		
444		
445	PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial
446		
447		
448	PUFA	polyunsaturated fatty acid
449		
450	VI	pulmonary vein isolation
451		
452	QALYs	quality adjusted life years
453		
454	QoL	quality of life
455		
456	RACE	Rate Control Efficacy in Permanent Atrial Fibrillation

457		
458	RCT	randomized controlled trial
459		
460	RealiseAF	Real-life global survey evaluating patients with Atrial Fibrillation
461		
462	RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarin in
463		pulmonaRy vein ablation: assessment of different peri-proCedUral
464		anticoagulation sTrategies
465		
466	RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
467		
468	RF	radiofrequency
469		
470	ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with
471		Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial
472		Fibrillation
473		
474	RR	risk ratio
475		
476	rtPA	recombinant tissue plasminogen activator
477		
478	RV	right ventricle
479		
480	SAFE	Screening for AF in the Elderly study
481		
482	SAH	subarachnoid hemorrhage
483		
484	SAN	sinoatrial node
485		
486	SBP	systolic blood pressure
487		
488	SD	standard deviation
489		
490	SDH	subdural haemorrhage
491		
492	SE	systemic embolism
493		
494	SERVE-HF	Treatment of sleep-disordered breathing with predominant central sleep
495		apnoea by adaptive Servo-ventilation in patients with Heart Failure
496		
497	SF-36	short form 36 health survey questionnaire
498		
499	SNP	single nucleotide polymorphism
500		
501	SPAF	Stroke Prevention in Atrial Fibrillation
502		
503	SR	sinus rhythm
504		
505	STS	Society of Thoracic Surgeons
506		
507	TAVI	transcatheter aortic valve replacement
508		

509	TIA	transient ischaemic attack
510		
511	TIMI	Thrombolysis in Myocardial Infarction
512		
513	TOE	transoesophageal echocardiography
514		
515	TTE	transthoracic echocardiography
516		
517	TTR	time in therapeutic range
518		
519	UFH	unfractionated heparin
520		
521	VKA	vitamin K antagonist
522		
523	VT	ventricular tachycardia
524		
525	WOEST	What is the Optimal antiplatelet and anticoagulant therapy in patients with
526		oral anticoagulation and coronary Stenting
527		
528	WPW	Wolff-Parkinson-White syndrome
529		
530		
531		
532		

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1. Preamble

Preamble will be added at a later stage.

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.	
<i>Class IIa</i>	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
<i>Class IIb</i>	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

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.

2. Epidemiology and impact for patients

2.1 Incidence and prevalence of atrial fibrillation

In 2010 the estimated number 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.^{1, 2} One in four middle-aged adults in Europe and the US will develop AF.³⁻⁵ By 2030, 14–17 million AF patients are expected in the EU, with 120,000–215,000 new patients per year.^{2, 6, 7} Estimates suggest an AF prevalence of approximately 3% in adults 20 years or above^{8, 9}, with more AF in elderly persons¹ and in patients suffering from conditions such as hypertension, heart failure, coronary artery disease, valvular heart disease, diabetes mellitus or chronic kidney disease.^{7, 10-15} The increase in AF prevalence can be attributed to both better detection of silent AF¹⁶⁻¹⁸ and to increasing age and conditions predisposing to AF.¹⁹

2.2 Morbidity, mortality, and healthcare burden of AF

AF is independently associated with a two-fold increased risk of all-cause mortality in women and 1.5-fold increase in men.²⁰⁻²² (see 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.²³ AF is also associated with increased morbidity, such heart failure and stroke.^{21, 24, 25} Contemporary studies show that 20-30% of patients with an ischaemic stroke have AF diagnosed before, during, or after the initial event.^{17, 26, 27} White matter lesions in the brain, cognitive impairment,²⁸⁻³⁰ decreased quality of life^{31, 32} and depressed mood³³ are common in AF patients, and between 10-40% of AF patients are hospitalized per year.^{23, 34, 35}

The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK and between 5 and 21 billion Euros in the US for 2008,^{36, 37} driven by AF-related complications (e.g. stroke) and AF-related treatment cost (e.g. hospitalizations). This cost will increase dramatically unless AF is prevented and treated in a timely and effective manner.

2.3 Impact of evidence-based management on outcomes in AF 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 or non-vitamin K antagonist oral anticoagulants (NOACs) markedly reduces stroke and mortality in AF

patients.^{38, 39} Other interventions such as rhythm control or rate control improve AF-related symptoms and may preserve cardiac function, but have not demonstrated reduction in long-term morbidity or mortality.^{40, 41}

In contemporary, well-controlled, randomized clinical AF trials, the average annual stroke rate is about 1.5% and annualized death rate is around 3%.⁴⁰ In real life the annual mortality can be different (both higher and lower).⁴² A minority of these deaths are related to stroke, while sudden cardiac death and progressive heart failure death are more frequent, emphasizing the need for interventions beyond anticoagulation.^{43, 44} Furthermore, AF is also associated with high rates of hospitalization, commonly for AF management but often also for heart failure, myocardial infarction, or treatment-associated bleeding.^{34, 45}

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595 **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 and stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of stroke patients 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.
Left ventricular dysfunction and heart failure	Left ventricular 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 increased even in anticoagulated patients. Brain white matter lesions are more common in AF patients than in controls.

596 AF = atrial fibrillation; LV = left ventricular.

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598

599 2.4 Gender

600 Age-adjusted incidence and prevalence of AF are lower in women, while the risk of death is
 601 similar or higher than men in developed and developing countries.^{1, 46, 47} Women suffering from
 602 AF and with additional stroke risk factors (particularly age) are also at greater risk of developing
 603 a stroke^{48, 49}, even in patients anticoagulated with warfarin⁵⁰ (see Chapter 8 for details). Women
 604 with diagnosed AF can be more symptomatic than men and typically older with more
 605 comorbidities.^{51, 52} Bleeding risk on anticoagulation is similar in men and women,^{49, 50, 53} but
 606 women appear to receive less specialist care and rhythm control therapy⁵⁴, while the outcomes
 607 of catheter ablation or AF surgery are comparable to men.^{55, 56} These observations highlight the
 608 need to offer effective diagnostic tools and therapeutic management in both women and men
 609 equally.

610

611 Recommendations relating to gender

Recommendations	Class ^a	Level ^b	Refs ^c
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.	IIa	B	55, 56

612 AF = atrial fibrillation

613 ^a Class of recommendation614 ^b Level of evidence615 ^c Reference(s) supporting recommendation(s)

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3. Pathophysiological and genetic aspects that guide management

3.1 Genetic predisposition

AF, especially early-onset AF, has a strong heritable component, independent of concomitant cardiovascular conditions.^{58, 59} A few young AF patients suffer from inherited cardiomyopathies or channelopathies mediated by disease-causing mutations. These monogenic diseases also convey a risk for sudden death (see Chapter 5). Up to a third of AF patients carry common genetic variants that predispose them to AF, albeit with a relatively low added risk. At least 14 of these common variants, often single nucleotide polymorphisms (SNP), are known to increase the risk of prevalent AF in populations.⁶⁰⁻⁶² The most important variants are located close to the PITX2 gene on chromosome 4q25.^{63, 64} These variants modify the AF risk up to 7-fold.⁶⁴ Several of the AF risk variants are also associated with cardioembolic or ischaemic stroke, possibly due to silent AF (see below).^{62, 65, 66} Changes in atrial action potential characteristics⁶⁷⁻⁷⁰, atrial remodelling, and modified penetration of rare gene defects⁶¹ have been suggested as potential mechanisms mediating increased AF risk in carriers of common gene variants. Genetic variants could in the future become useful for patient selection of rhythm control strategies,⁷¹⁻⁷³ but it is currently unknown whether common gene variants differentially affect the efficacy of antiarrhythmic drugs or rate control medication.⁷⁴ While genomic analysis can provide an opportunity to improve diagnosis and management of AF in the future,^{75, 76} routine genetic testing for common gene variants associated with AF cannot be recommended at present.⁷⁷

3.2 Mechanisms leading to AF

3.2.1 Remodelling of atrial structure and ion channel function

External stressors such as structural heart disease, hypertension, possibly diabetes, but also AF itself induce a slow but progressive process of structural remodelling in the atria (Figure 2). Activation of fibroblasts, enhanced connective tissue deposition and fibrosis are the hallmarks of this process.⁷⁸⁻⁸⁰ In addition, atrial fatty infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis, and amyloidosis are found in AF patients with concomitant conditions predisposing to AF.⁸¹⁻⁸⁴ Structural remodelling results in electrical dissociation between muscle bundles and local conduction heterogeneities,⁸⁵ favouring re-entry and perpetuation of the arrhythmia.⁸⁶ In many patients, the structural remodelling process occurs before the onset of AF.⁷⁸ As some of the structural remodelling will be irreversible, early initiation of treatment seems desirable.⁸⁷

Table 4 gives an overview of the most relevant pathophysiological alterations in atrial tissue associated with AF, and lists corresponding clinical conditions that can contribute to these changes.

The functional and structural changes in atrial myocardium and stasis of blood, especially in the left atrial appendage, generate a prothrombotic milieu. Furthermore, even short episodes of AF lead to myocardial damage and expression of prothrombotic factors on the atrial endothelial surface, activation of platelets and inflammatory cells, and contribute to a generalized prothrombotic state.^{88, 89} The atrial and systemic activation of the coagulation system can partially explain why short episodes of AF convey a long-term stroke risk.

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3.2.2 Electrophysiological mechanisms of AF

AF provokes a shortening of the atrial refractory period and AF cycle length during the first days of the arrhythmia, largely due to downregulation of the Ca^{2+} -inward current and upregulation of inward rectifier K^{+} currents.^{90, 91} Structural heart disease, in contrast, tends to prolong the atrial refractory period, illustrating the heterogeneous nature of mechanisms that cause AF in different patients.⁹² Hyperphosphorylation of various Ca^{2+} handling proteins may contribute to enhanced spontaneous Ca^{2+} release events and triggered activity,^{93, 94} thus triggering ectopy and promoting AF. Although the concept of Ca^{2+} handling instability has recently been challenged^{95, 96} it may mediate AF in structurally remodelled atria (see above) and explain how altered autonomic tone can generate AF.^{80, 97}

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Focal initiation and maintenance of AF: The seminal observation by Haissaguerre was that a focal source in the pulmonary veins can trigger AF, and ablation of this source can extinguish the arrhythmia.⁹⁸ The mechanism of focal activity might involve both triggered activity and localized reentry.^{99, 100} Hierarchic organization of AF with rapidly activated areas driving the arrhythmia has been documented in patients with paroxysmal AF,^{101, 102} but is more challenging in patients with persistent AF.¹⁰³

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The multiple wavelet hypothesis and rotors as sources of AF: Moe proposed that AF can be perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner.¹⁰⁴ As long as the number of wavefronts does not decline below a critical level, they will be capable of sustaining the arrhythmia.

Numerous experimental and clinical observations can be reconciled with the multiple wavelet hypothesis.¹⁰⁵ All localized sources of AF (ectopic foci, rotors, or other stable re-entry circuits) cause fibrillatory conduction remote from the source which is difficult to distinguish from propagation sustaining AF by multiple wavelets, and either of these phenomena may generate “rotors” picked up by intracardiac^{106, 107} or body surface¹⁰⁷ recordings.

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

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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, 108, 109
Inflammatory infiltration		Profibrotic responses, enhanced AF complexity	81
Fatty infiltration	Obesity (fatty infiltration)	Profibrotic / proinflammatory responses, localized conduction block	82, 110
Amyloid deposition	Aging, heart failure, coronary artery disease (via atrial scarring), genetic factors	Conduction disturbances	83, 111
<i>Ion channel alterations</i>			
Ion channel remodelling	Atrial fibrillation (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	90-92
Ca ²⁺ handling instability	AF (especially forms with a high AF burden), possibly heart failure and hypertension (possibly through increased sympathetic activation)	Enhanced propensity to ectopy	93, 94
Gap-junction redistribution	AF	Conduction disturbances	112
<i>Myocyte alterations</i>			

Apoptosis and necrosis	Coronary artery disease, heart failure (through cardiomyocyte death and atrial scarring)	May induce replacement fibrosis	113
Myocyte hypertrophy	Atrial dilatation, AF	Aggravates conduction disturbances	84, 114

Endothelial and vascular alterations

Microvascular changes	Atherosclerosis, coronary and peripheral artery disease, possibly atrial fibrillation	Aggravation of atrial ischaemia, heterogeneity of electrical function, structural remodelling	115
Endocardial remodelling		Enhanced risk for thrombus formation	116, 117

Changes of the autonomic nervous system

Sympathetic hyperinnervation	Heart failure, hypertension	Enhanced propensity to ectopy	80, 97
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693 AF = atrial fibrillation

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4. Diagnosis and timely detection of AF

4.1 Overt and silent AF

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

Silent, undetected AF is common,^{120, 122} with severe consequences such as stroke and death.¹²³⁻¹²⁵ Prompt recording of an ECG is an effective and cost-effective method to document chronic forms of AF.¹²⁶ The technology to detect paroxysmal, self-terminating AF episodes is rapidly evolving (see Chapter 5 for a definition of AF patterns). There is good evidence that prolonged ECG monitoring enhances detection of undiagnosed AF, for 72 hours after a stroke,^{27, 127} even longer periods,^{18, 128} or by daily short-term ECG in patients over 75 years of age¹²⁹. (online Figure A). Ongoing studies will determine whether such early detection alters management – e.g. initiation of anticoagulation – and improves outcomes.

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

4.2 Screening for silent AF

4.2.1 Screening for AF by ECG in the community

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

4.2.2 Prolonged monitoring for paroxysmal AF

Paroxysmal AF is often missed.¹²⁰ Repeated daily ECG recordings increased detection of silent, asymptomatic paroxysmal AF in an unselected Swedish population aged >75 years.^{120, 135} Several patient-operated devices^{136, 137} and extended continuous ECG monitoring using skin patch recorders¹³⁸ have been validated for detection of paroxysmal AF.¹³⁹ The detection rate of asymptomatic AF by new technologies such as smartphone cases with ECG electrodes, smart watches and blood pressure machines with AF detection algorithms, has not yet been formally evaluated against an established arrhythmia detection method.¹⁴⁰

4.2.3 Patients with pacemakers and implanted devices

Implanted pacemakers or defibrillators with an atrial lead allow continuous monitoring of atrial rhythm. Using this technology, patients with atrial high rate episodes (AHRE) can be identified. Depending on the risk profile of the population studied, such atrial high rate episodes are detected in 10–15% of pacemaker patients.¹⁴¹ AHRE are associated with an increased risk of overt AF (HR 5.56; CI 3.78–8.17; $P < 0.001$) and ischaemic stroke or systemic embolism (HR 2.49; CI 1.28–4.85; $P = 0.007$). The stroke risk in AHRE patients seems lower than the stroke risk in patients with diagnosed AF and not all AHRE represent AF.¹⁴² Strokes often occur without AHRE detected within 30 days before the event.^{143–147} Consequently, it is unclear whether AHRE imply the same therapeutic requirements as overt AF¹⁴⁸ and the benefit of OAC in patients with AHRE is being evaluated in ongoing clinical trials (e.g. ARTESiA, NCT01938248 and NOAH, NCT02618577). At present, pacemakers and implanted devices should be interrogated on a regular basis for AHRE, and patients with AHRE should undergo further assessment of stroke risk factors and for overt AF, including ECG monitoring (Figure 3).¹⁴⁹

4.2.4 Detection of AF in stroke survivors

Sequential stratified ECG monitoring detected AF in 24% of stroke survivors (95% CI 17–31%)¹⁵⁰, and in 11.5% in another meta-analysis (95% CI 8.9%–14.3%)¹⁷, 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%)¹²⁸, but is more likely in patients with cryptogenic stroke implanted with loop recorders or with ECG monitors for several weeks.^{18, 128}

Cryptogenic stroke is defined as a stroke in which the cause could not be identified after extensive investigations.¹⁵¹ A broader definition is ‘embolic stroke of undetermined source’ (ESUS).¹⁵² 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).^{27, 127} Hence, prolonged ECG monitoring seems reasonable in all survivors of an ischaemic stroke without an established diagnosis of AF.

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767 Recommendations for screening for AF

Recommendations	Class ^a	Level ^b	Refs ^c
Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age	I	B	130, 134, 153
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, 154
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation	IIa	B	18, 128
Systematic ECG screening may be considered to detect AF in patients aged >75 years or with at least two CHA₂DS₂-VASc risk factors	IIb	B	130, 135, 155

768 AF = atrial fibrillation; AHRE = atrial high rate episodes; CHA₂DS₂-VASc = Congestive Heart
 769 failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age
 770 65–74, and Sex (female); ECG = electrocardiogram; ICD = implantable cardioverter defibrillator;
 771 TIA = transient ischaemic attack

772 ^a Class of recommendation

773 ^b Level of evidence

774 ^c Reference(s) supporting recommendation(s)

775

776

777 4.3 **ECG detection of atrial flutter**

778 Right atrial isthmus dependent flutter has a typical ECG pattern and ventricular rate.¹⁵⁶ The
779 prevalence of atrial flutter is less than 1/10 of the prevalence of AF.¹⁵⁷ Atrial flutter often
780 coexists with or precedes AF.¹⁵⁸ In typical, isthmus-dependent flutter, P waves will often show a
781 “saw tooth” morphology, especially in the inferior leads (II, III, aVF). The ventricular rate can be
782 variable (usual ratio of atrial to ventricular contraction 4:1 to 2:1, in rare cases 1:1) and macro-
783 reentrant tachycardias may be missed in stable 2:1 conduction. Vagal stimulation or
784 intravenous adenosine may be helpful to unmask atrial flutter. The management of atrial flutter
785 is discussed in Section 12.7. Left or right atrial macro-reentrant tachycardia is usually confined
786 to patients after catheter ablation for AF, AF surgery, or after open heart surgery.¹⁵⁶

787

5. Classification of AF

5.1 AF pattern

In many patients, AF progresses from short, infrequent episodes, to longer and more frequent attacks. Over time, many patients will develop sustained forms of AF. In a small proportion of patients, AF will remain paroxysmal over several decades (2–3% of AF patients).¹⁵⁹ The distribution of paroxysmal AF recurrences is not random, but clustered.¹⁶⁰ AF may also regress from persistent to paroxysmal AF. Furthermore, asymptomatic recurrences of AF are common in patients with symptomatic AF.¹⁶¹

Based on presentation, duration and spontaneous termination of AF episodes, five types of AF are traditionally distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (Table 5). If patients suffer from both paroxysmal and persistent AF episodes, the more common type should be used for classification. Clinically determined AF patterns do not correspond well to the AF burden measured by long-term ECG monitoring.¹⁶² Even less is known about the response to therapy in patients with long-standing persistent AF or long-standing paroxysmal AF. Despite these inaccuracies, the distinction between paroxysmal and persistent AF has been used in many trials and therefore still forms the basis of some recommendations.

There is some evidence suggesting that AF burden may influence stroke risk^{44, 124, 163} and could modify the response to rhythm control therapy.^{76, 164} The evidence for this is weak. Therefore, AF burden should not be a major factor deciding on the usefulness of an intervention that is deemed suitable for other reasons.

TABLE 5: Patterns of atrial fibrillation

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days.* Most AF episodes that are cardioverted within 24-48 hours should be considered as paroxysmal.*

Persistent AF	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.
Long-standing persistent AF	Continuous AF lasting for ≥ 1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	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'.

*The distinction between paroxysmal and persistent AF is often not made correctly without access to long-term monitoring.¹⁶² This classification alone is hence often not sufficient to select specific therapies. If both persistent and paroxysmal episodes are present, the predominant AF pattern should guide the classification.

AF=atrial fibrillation

5.2 AF types reflecting different causes of AF

The risk of developing AF is increased in a variety of physiological and disease states, and the historic term 'lone AF' is probably misleading and should be avoided.¹⁶⁵ Although the pattern of AF may be the same, the mechanisms underpinning AF vary substantially between patients¹⁶⁶ (Table 6). This suggests that stratifying AF patients by underlying drivers of AF could inform management, e.g. considering cardiac and systemic comorbidity (e.g. diabetes and obesity¹⁶⁷), lifestyle factors (e.g. activity level, smoking, alcohol intake^{168, 169}), markers of cardiac structural remodelling (e.g. fibrosis¹⁷⁰⁻¹⁷² or electrocardiographic parameters of AF complexity¹⁷³), or genetic background. Table 6 provides such a taxonomy, informed by expert consensus^{76, 120, 174}, but without much evidence to underpin its clinical use.¹⁷⁵ Systematic research defining the major drivers of AF is clearly needed to better define different types of AF.¹⁷⁵

TABLE 6: Clinical types of AF

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 left ventricular hypertrophy, 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 atrial fibrillation. 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 prior 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.

It is recognized that these types of AF will overlap in clinical practice, and that their impact for management needs to be evaluated systematically. Modified from ⁷⁶.

AF = atrial fibrillation; LV = left ventricular.

5.3 Symptom burden in AF

Patients with AF have significantly poorer quality of life than healthy controls, experiencing a variety of symptoms including lethargy, palpitations, dyspnoea, chest tightness, sleeping difficulties, and psychosocial distress.^{32, 176-179} Improved quality of life has been noted with both pharmacological and interventional therapies,¹⁸⁰⁻¹⁸⁴ but there are limited data to compare the benefit of different treatments.^{32, 185} Assessment of quality of life is further constrained by a lack of cross-validation of the several AF-specific QoL tools.¹⁸⁶⁻¹⁹⁰ With regard to symptom assessment, the European Heart Rhythm Association (EHRA) suggested the EHRA symptom scale (Table 7) to describe symptom severity in AF patients.¹⁹¹ A similar scale (CCS-SAF) is used in Canada.¹⁹² The EHRA scale has been used and validated.¹⁹³⁻¹⁹⁸ A modification was proposed in 2014, subdividing EHRA class 2 into mild (2a) or moderate (2b) impact.¹⁹⁸ As

symptoms in class 2b ('troubling' symptoms) identified patients with a health utility benefit of rhythm control in that study, this modification may provide a threshold for potential treatment decisions, but this remains to be tested. While some AF patients had no or minimal symptoms (25-40%), many (15-30%) reported severe or disabling symptoms.^{193, 195} The EHRA scale should be used to guide symptom-oriented treatment decisions and for longitudinal patient profiling.

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Recommendations on use of the modified EHRA symptom scale

Recommendations	Class ^a	Level ^b	Refs ^c
The use of the modified EHRA symptom scale is recommended in clinical practice and research studies to quantify AF-related symptoms.	I	C	191, 198

^a Class of recommendation

^b Level of evidence

^c Reference(s) supporting recommendation(s)

858

TABLE 7: Modified EHRA symptom scale

mEHRA score	Symptoms	Description
1	None	AF does not cause any symptoms.
2a	Mild	Normal daily activity not affected by symptoms related to AF*
2b	Moderate	Normal daily activity not affected*
3	Severe	Normal daily activity affected
4	Disabling	Normal daily activity discontinued

* EHRA class 2a and 2b can be differentiated by evaluating whether patients are functionally affected by their AF symptoms. AF-related symptoms are most commonly fatigue / tiredness and exertional shortness of breath, or less frequently palpitations and chest pain.^{42, 193, 199-201}

Modified from ¹⁹⁸

AF = atrial fibrillation; mEHRA = modified European Heart Rhythm Association

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6. Detection and management of risk factors and concomitant cardiovascular diseases

Many cardiovascular diseases and concomitant conditions increase the risk of developing AF (Table 8), recurrent AF, and AF-associated complications. Identification of such conditions, their prevention and treatment is an important leverage to prevent AF and its disease burden. Knowledge of these factors and their management is hence important for optimal management of AF patients.^{202, 203}

TABLE 8: Cardiovascular and other conditions independently associated with atrial fibrillation

Characteristic/comorbidity	Association with AF: hazard ratio (HR) or risk ratio (RR)
Genetic predisposition (based on multiple common gene variants associated with AF) ⁶⁴	HR range 0.4 – 3.2
Older age ¹⁹	HR:
50–59 years	1.00 (reference)
60–69 years	4.98 (95% CI 3.49–7.10)
70–79 years	7.35 (95% CI 5.28–10.2)
80–89 years	9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none ¹⁹	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs. none ¹⁹	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs. none ²⁰⁴	RR 2.40 (95% CI 1.62–3.60)
Myocardial infarction vs. none ¹⁹	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction ^{205, 206}	(reference: euthyroid)
hypothyroidism	HR 1.23 (95% CI 0.77–1.97)
subclinical hyperthyroidism	RR 1.31 (95% CI 1.19–1.44)
overt hyperthyroidism	RR 1.42 (95% CI 1.22–1.63)
Obesity ^{19, 207}	HR:
none (BMI <25 kg/m ²)	1.00 (reference)
overweight (BMI 25–30 kg/m ²)	1.13 (95% CI 0.87–1.46)
obese (BMI ≥31 kg/m ²)	1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs. none ¹⁹	HR 1.25 (95% CI 0.98–1.60)
Chronic obstructive pulmonary disease ²⁰⁸	RR:
FEV1 % ≥80%	1.00 (reference)
60–80%	1.28 (95% CI 0.79–2.06)
<60%	2.53 (95% CI 1.45–4.42)
Obstructive sleep apnoea vs. none ²⁰⁹	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease ²¹⁰	OR:
none	1.00 (reference)
stage 1 to 2	2.67 (95% CI 2.04–3.48)
stage 3	1.68 (95% CI 1.26–2.24)
stage 4 to 5	3.52 (95% CI 1.73–7.15)

Smoking ²¹¹ never former current	HR: 1.00 (reference) 1.32 (95% CI 1.10–1.57) 2.05 (95% CI 1.71–2.47)
Alcohol ²¹² None 1 to 6 drinks/week 7 to 14 drinks/week 15 to 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 ²¹³ 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)

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

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6.1 Heart failure

Heart failure (HF) and atrial fibrillation (AF) coincide in many patients.^{214–216} They are linked by similar risk factors and share a common pathophysiology.²¹⁷ HF and AF can cause and exacerbate each other through mechanisms such as, structural cardiac remodelling, activation of neurohormonal mechanisms, and rate-related impairment of LV function. Patients with AF and concomitant HF, both with preserved ejection fraction (HFpEF; LVEF $\geq 50\%$) and reduced ejection fraction (HFrEF; LVEF $< 40\%$)^{218, 219}, suffer from worse prognosis, including increased mortality.^{16, 220} The recent ESC Guidelines on Heart Failure have also introduced a new category of HF with mid-range ejection fraction (HFmrEF; LVEF 40–49%)²²¹, although data on AF patients in this group are currently limited. Prevention of adverse outcomes and maintenance of a good quality of life are the aims of management in all patients with AF and concomitant HF, regardless of LVEF.²²² The general approach to AF management does not differ between HF patients and others, but a few considerations are worthwhile to consider. Of note, the only therapy with proven prognostic value in these patients is anticoagulation therapy, and appropriate OAC should be prescribed in all patients at risk of stroke (see Chapter 8).

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6.1.1 Patients with AF and HFrEF

In addition to oral anticoagulation, standard HF therapy should be used in patients with HFrEF, as detailed in the ESC Guidelines²²¹. This includes ACE inhibitors/ARBs, mineralocorticoid antagonists, defibrillators and cardiac resynchronisation therapy²¹⁷, in addition to combined angiotensin receptor neprilysin inhibition (ARNI) in patients able to tolerate an ACE inhibitor or ARB with ongoing symptoms.²²³

Rate control of AF is discussed in detail in Chapter 9. In brief, only beta-blockers and digoxin are suitable in HFrEF due to the negative inotropic potential of verapamil and diltiazem. Beta-blockers are usually the first-line option in patients with clinically stable HFrEF, although an individual patient data meta-analysis of RCTs found no reduction in mortality from beta-blockers versus placebo in those with AF at baseline (HR 0.97, 95% CI 0.83-1.14).²³ Digoxin is commonly prescribed in clinical practice but no head-to-head RCTs in AF patients have been performed. In meta-analysis of observational studies, digoxin had a neutral effect on mortality in patients with AF and concomitant HF (adjusted observational studies HR 0.90, 95% CI 0.70-1.16; propensity-matched observational studies RR 1.08, 95% CI 0.93-1.26).²²⁴ Initial and combination rate control therapy for AF in HFrEF should therefore take account of individual patient characteristics and symptoms; beta-blocker initiation should be delayed in patients with acute decompensated HF, and digoxin has more adverse effects in patients with renal impairment (see Chapter 9).

Patients with AF and HFrEF who present with severe symptoms may require rhythm control therapy in addition to rate control. For patients who develop HFrEF as a result of rapid AF (tachycardiomyopathy), a rhythm control strategy is preferred, based on several relatively small patient cohorts and trials reporting improved LV function after restoration of sinus rhythm.^{184, 225-227} The diagnosis of tachycardiomyopathy can be challenging, and can at times require restoration of sinus rhythm.²²⁸ Catheter ablation may be a useful method to restore LV function and quality of life in AF patients with HFrEF^{184, 225-227}, but further data are needed. Figure 5 summarizes the approach to patients with AF and HF.

6.1.2 AF patients with HFpEF

The diagnosis of HFpEF in patients with AF is problematic due to the difficulty in separating out symptoms that are due to HF, or as a consequence of AF. Although diagnostic differentiation can be achieved by cardioversion and clinical reassessment, this option is often not appropriate in this patient group, particularly as specific therapy that improves prognosis in HFpEF is currently lacking. Echocardiography can support detection of HFpEF in symptomatic AF

patients by providing evidence of relevant structural heart disease (e.g. LV hypertrophy) 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.²²⁹⁻²³³ Natriuretic peptide levels are part of the diagnostic assessment of HFpEF²²¹, although in AF patients natriuretic peptide levels are elevated and the optimum diagnostic cut-off is still unknown.²³⁴ The management of patients with AF and concomitant HFpEF should focus on control of fluid balance and concomitant conditions, such as hypertension and ischaemia.

6.1.3 AF patients with HFmrEF

HFmrEF is a recently defined entity, describing patients with symptoms and signs of HF, LVEF 40-49%, elevated levels of natriuretic peptides and either LV hypertrophy, LA enlargement or evidence of diastolic dysfunction.²²¹ However, diagnosis is more difficult in patients with AF, as natriuretic peptides are elevated in AF and LA dilatation common, regardless of concomitant HF. LVEF is also variable and difficult to assess in AF patients due to AF-induced reduction in systolic LV function and variable cardiac cycle length. Further study of this group of patients is required before particular treatment strategies in AF patients with HFmrEF can be recommended.

6.1.4 Prevention of AF in heart failure

Retrospective analyses from large randomized trials have reported a lower incidence of new-onset AF in patients treated with ACE inhibitors and ARBs compared with placebo.²³⁵⁻²³⁷ The reduced incidence of AF with ACE inhibitors and ARBs is less evident in patients with HFpEF²³⁸ and is lost in patients without heart failure.²³⁹⁻²⁴¹ Neprilysin inhibition does not seem to add to this effect.²²³ Beta-blocker therapy was associated with a 33% reduction in the adjusted odds of incident AF in HFrEF patients pretreated with ACE inhibitors/ARB, reinforcing the importance of beta-blocker therapy in HFrEF patients in sinus rhythm.²³ Eplerenone, a mineralocorticoid receptor antagonist, also reduced new-onset AF in patients with LVEF $\leq 35\%$, NYHA Class II and pretreatment with ACE inhibitors/ARB and beta-blockers.²⁴²

6.2 Hypertension

6.2.1 Treatment of hypertension to prevent incident AF

Inhibition of the renin-angiotensin-aldosterone system can prevent structural remodelling and recurrent AF.^{235, 243} A recent analysis of the Danish healthcare database with long-term monitoring of the effect of different antihypertensive agents on the occurrence of overt AF suggests a beneficial effect of ACE inhibitors or ARBs.²⁴⁴ Secondary analyses of ACE inhibitors or ARBs in patients with heart failure or left ventricular hypertrophy show a lower incidence of new-onset AF.^{237, 245}

6.2.2 Blood pressure control in patients with AF

Hypertension is a stroke risk factor in AF, and uncontrolled high blood pressure enhances the risk of stroke and of bleeding events and may lead to recurrent AF. Good blood pressure control should therefore be an integral part of the management of AF patients.²⁴⁶ In patients with established AF, but without LV dysfunction or heart failure, ARBs do not prevent recurrent AF better than placebo.^{239, 240} ACE inhibitors or ARBs may reduce recurrent AF after cardioversion when co-administered with antiarrhythmic drug therapy compared with an antiarrhythmic drug alone.^{247, 248} Meta-analyses driven by these studies suggested less recurrent AF,^{235, 237, 249, 250} but at least one controlled trial failed to demonstrate benefit.^{251, 252}

6.3 Valvular heart disease

Valvular heart disease is independently associated with incident AF.²⁵³ Approximately 30% of patients with AF have some form of valvular heart disease, often only detected by echocardiography.²⁵⁴⁻²⁵⁷ AF worsens prognosis in patients with severe valvular heart disease²⁵⁸, including those undergoing surgery or transcatheter interventions for aortic or mitral valve disease.²⁵⁹⁻²⁶⁴ Valvular heart disease can be associated with an increased thromboembolic risk, which probably also adds to the stroke risk in AF patients.²⁶⁵ Similar to heart failure, valvular disease and AF interact and sustain each other through volume and pressure overload, tachycardiomyopathy, and neurohumoral factors.²⁶⁶⁻²⁷² When valve dysfunction is severe, AF can be regarded as a marker for progressive disease, thus favouring valve repair or replacement.²⁷³

Traditionally, patients with AF have been dichotomized into 'valvular' and 'non-valvular' AF.²⁷⁴ Although slightly different definitions have been used, "valvular AF" mainly referred to AF

patients that have either rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves. In fact, while AF implies an incremental risk for thromboembolism in patients with mitral valve stenosis,^{265, 275, 276} there is no clear evidence that other valvular diseases, including mitral regurgitation or aortic valve disease, need to be considered when choosing an anticoagulant or indeed to estimate stroke risk.²⁷⁷ We have therefore decided to replace the historic term “non-valvular AF” with reference to the specific underlying conditions.

Recommendations for patients with valvular heart disease and AF

Recommendations	Class ^a	Level ^b	Refs ^c
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with mitral stenosis or mechanical heart valves and atrial fibrillation.	I	B	276, 278-281
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	282
Mitral valvotomy may be considered for asymptomatic patients with severe mitral stenosis and suitable valve anatomy who have new-onset AF.	IIb	C	

AF = atrial fibrillation; INR = international normalized ratio; LV = left ventricular

^a Class of recommendation

^b Level of evidence

^c Reference(s) supporting recommendation(s)

1007

1008

6.4 Diabetes mellitus

Diabetes and AF frequently co-exist because of associations with other risk factors,²⁸³⁻²⁸⁹

Diabetes is a risk factor for stroke and other complications in AF patients.²⁹⁰ In patients with

AF, a longer duration of diabetes appears to confer a higher risk of thromboembolism, albeit

without greater risk of OAC-related bleeding.²⁹¹ Unfortunately, intensive glycaemic control does

not affect the rate of new-onset AF,²⁹⁰ while treatment with metformin seems to be associated

with a decreased long-term risk of AF in diabetic patients,²⁹² and may even lower long-term

stroke risk.¹³ Diabetic retinopathy, a measure of disease severity, does not increase the risk of

ocular bleeding in anticoagulated patients.²⁹³

1018

1019 **6.5 Obesity and weight loss**1020 **6.5.1 Obesity as a risk factor**

1021 Obesity increases the risk for AF (risk ratio 1.5–1.8),²⁹⁴⁻²⁹⁷ with a progressive increase
 1022 according to body mass index^{294, 296-298} Obese patients may have more left ventricular diastolic
 1023 dysfunction, increased sympathetic activity and inflammation, or increased fatty infiltration of the
 1024 atria.²⁹⁹⁻³⁰¹ Obesity may also be a risk factor for ischaemic stroke, thromboembolism and death
 1025 in AF patients.²⁹⁸

1026

1027 **6.5.2 Weight reduction in AF patients**

1028 Intensive weight reduction management on top of management of other cardiovascular risk
 1029 factors (in the range of 10-15 kg weight loss achieved) led to less AF recurrences and
 1030 symptoms compared to general advice in obese patients with AF.^{202, 203, 302} Improved
 1031 cardiorespiratory fitness can further decrease AF burden in obese patients with AF.³⁰³ Although
 1032 the findings in these studies have to be confirmed, they underpin the positive effect of weight
 1033 reduction in obese patients.

1034

1035 **6.5.3 Catheter ablation in obese patients**

1036 Obesity may increase the AF recurrence rate after catheter ablation³⁰⁴⁻³⁰⁷ with obstructive sleep
 1037 apnoea as an important potential confounder. Obesity has also been linked to a higher
 1038 radiation dose and complication rate during AF ablation.^{308, 309} Notably, the symptomatic
 1039 improvement after catheter ablation of AF in obese patients seems comparable to the
 1040 improvement in normal-weight patients.³⁰⁴ In view of the potential to reduce AF episodes by
 1041 weight reduction (see above), AF ablation should be offered to obese patients in conjunction
 1042 with lifestyle modifications that lead to weight reduction.

1043

1044

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

203, 294, 302

1045 Recommendations for obese patients with AF

1046 AF = atrial fibrillation

1047 ^a Class of recommendation

1048 ^b Level of evidence

1049 ^c Reference(s) supporting recommendation(s)

1050

1051 6.6 COPD, sleep apnoea, and other respiratory diseases

1052 AF has been associated with obstructive sleep apnoea (OSA).^{310, 311} Multiple pathophysiological
 1053 mechanisms can contribute to AF in OSA, including autonomic dysfunction, hypoxia,
 1054 hypercapnia and inflammation.^{92, 310-313} OSA exaggerates intrathoracic pressure changes,
 1055 which in itself and via vagal activation can provoke shortening of the atrial action potential and
 1056 induce AF. Risk factor reduction and continuous positive airway pressure ventilation can reduce
 1057 AF recurrence.³¹⁴⁻³¹⁸ It seems reasonable to consider OSA screening in AF patients with risk
 1058 factors. OSA treatment should be optimized to improve AF treatment results in appropriate
 1059 patients. Servo-controlled pressure support therapy should not be used in HFrEF patients with
 1060 predominantly central sleep apnoea (of which 25% had concomitant AF).³¹⁹

1061 Patients with COPD often suffer from atrial tachycardias which need to be differentiated from AF
 1062 by ECG. Agents used to relieve bronchospasm, notably theophyllines and beta-adrenergic
 1063 agonists, may precipitate AF and make control of the ventricular response rate difficult. Non-
 1064 selective beta-blockers, sotalol, propafenone, and adenosine should be used with caution in
 1065 patients with significant bronchospasm, while they can safely be used in patients with COPD.
 1066 Beta-1 selective blockers (e.g. bisoprolol, metoprolol and nebivolol), diltiazem and verapamil are
 1067 often tolerated and effective (see Chapter 9).

1068

1069 Recommendations for patients with AF and respiratory diseases

Recommendations	Class ^a	Level ^b	Refs ^c
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.	Ila	B	310, 311, 320, 321
Obstructive sleep apnoea treatment should be optimized to reduce AF recurrences and improve AF treatment results.	Ila	B	313-317

1070 AF = atrial fibrillation

1071 ^a Class of recommendation

1072 ^b Level of evidence

1073 ^c Reference(s) supporting recommendation(s)

1074

1075 6.7 Chronic kidney disease

1076 Atrial fibrillation is present in 15–20% of patients with chronic kidney disease (CKD).³²² The
 1077 definition of CKD in most AF trials is relatively strict. Although an estimated creatinine clearance
 1078 (CrCl) <60 ml/min is indicative of CKD, a number of trials in AF patients have used a CrCl<50
 1079 ml/min to adapt NOAC dosage, usually estimated by the Cockcroft-Gault formula. CrCl in AF
 1080 patients can deteriorate over time.³²³ The management of OAC in patients with CKD is
 1081 discussed in Section 8.2.

1082

1083 Recommendations for patients with kidney disease and AF

Recommendations	Class ^a	Level ^b	Refs ^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	324-328
All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect kidney disease.	Ila	B	

1084 AF = atrial fibrillation

1085 ^a Class of recommendation

1086 ^b Level of evidence

1087 ^c Reference(s) supporting recommendation(s)

1088

7. Integrated management of patients with AF

Most patients access the healthcare system initially through pharmacists, community health workers or primary care physicians. As atrial fibrillation 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 health care system, and is feasible in most health care settings (when an ECG is available). We propose to consider five domains in the initial assessment of patients presenting with newly diagnosed AF (Figure 4). These domains are:

1. Haemodynamic instability or limiting, severe symptoms
2. Presence of precipitating factors (e.g. thyrotoxicosis, sepsis, or postoperative AF) and of 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

An integrated, structured approach to AF care, as applied successfully to other domains of medicine,³²⁹⁻³³¹ will facilitate consistent, guideline-adherent AF management for all patients³³² (see Figure 6), with the potential to improve outcomes.^{42, 333, 334} Such approaches are consistent with the Innovative Care for Chronic Conditions Framework proposal by the World Health Organization.³³⁵ Review by an AF service or at least referral to a cardiologist will usually be required after the initial assessment to fully assess the impact of AF for cardiovascular health.³³⁶ There may also be reasons for early or urgent referral (Table 9). Integrated care of all patient with newly diagnosed AF should help to overcome the current shortcomings of AF management, such as underuse of anticoagulation, inadequate use of, and access to rate and rhythm control therapy, and inconsistent approaches to cardiovascular risk reduction. Integrated AF care requires cooperation of primary care physicians, cardiologists, cardiac surgeons, AF specialists, stroke specialists, allied health practitioners and patients, encompassing lifestyle interventions, treatment of underlying cardiovascular diseases, anticoagulation, rate control, and rhythm control therapy in selected patients (Figure 4).

1121 **TABLE 9: Clinical signs calling for urgent involvement of a specialized AF service.**

Clinical conditions calling for urgent involvement of a specialized AF service
Haemodynamic instability
Uncontrollable rate
Symptomatic bradycardia not amenable to reduction of rate control agents
Severe angina or worsening left ventricular function
Transient ischemic attack or stroke

1122 Anticoagulation should be initiated early in all suitable patients and will not routinely require

1123 specialist input. AF = atrial fibrillation.

1124

1125 **7.1 Evidence supporting integrated AF care**

1126 Several structured approaches to AF care have been developed. Some evidence underpins
 1127 their use, while more research is needed into the best way of delivering integrated AF care.
 1128 Integrated AF management in an RCT increased the use of evidence-base care and reduced a
 1129 composite of cardiovascular hospitalization and cardiovascular death over a mean follow-up of
 1130 22 months by approximately 1/3 (14.3% versus 20.8%, hazard ratio 0.65; 95% CI 0.45–0.93; P
 1131 = 0.017) compared to usual care in a large tertiary care centre.³³⁷ Integrated AF management
 1132 appeared cost-effective in that study.³³⁸ However, an Australian RCT showed only a marginal
 1133 effect on unplanned admissions and death by an integration of AF care limited to the initial care
 1134 period, possibly emphasizing the need for sustained integration of AF care.³³⁹ Two
 1135 observational studies of integrated AF care found reduced hospitalizations,^{340, 341} one study
 1136 showed reduced stroke,³⁴⁰ and a further non-randomized study identified a trend for a lower
 1137 composite of death, cardiovascular hospitalization and AF-related emergency visits.³⁴² More
 1138 research is needed, and integrated AF care is likely to require different designs in different
 1139 health care settings.

1140

1141 **7.2 Components of integrated AF care**

1142 **Patient involvement:** Patients should have a central role in the care process. Since treatment
 1143 of AF requires patients to change their lifestyle and to adhere to chronic therapy, at times
 1144 without an immediately tangible benefit, they need to understand their responsibilities in the
 1145 care process. Physicians and health care professionals are responsible to provide access to

evidence-based therapy, but adherence to therapy is ultimately the responsibility of informed and autonomous patients, best described as shared accountability.³⁴³ Hence, information and education of patients and often of their partners and relatives is indispensable to encourage a self-management role and to empower patients to participate in shared decision making,^{333, 335} and to support their understanding of the disease and the suggested treatments.³⁴⁴

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

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

Technology use to support AF care: Technology such as decision support software has the potential to enhance the implementation of evidence-based care and improve outcomes, when used to enhance expert advice.³⁴⁵ Electronic tools can also ensure coherent communication within the AF team. With a view to support the wider use of such technology, this task force is providing tools free of charge in the form of smartphone apps to AF health care professionals and to AF patients.

1178 Recommendations for an integrated approach to care

Recommendations	Class ^a	Level ^b	Refs ^c
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 to reduce hospitalization and mortality.	Ila	B	337-339
Placing patients in a central role in decision making should be considered to tailor management to patient preferences and to improve adherence to chronic therapy.	Ila	C	337, 339, 341

1179 AF = atrial fibrillation

1180 ^a Class of recommendation1181 ^b Level of evidence1182 ^c Reference(s) supporting recommendation(s)

1183

1184

1185 7.3 Diagnostic workup of AF patients

1186 AF is often found in patients with other, at times undiagnosed cardiovascular conditions. Thus,
 1187 all AF patients will benefit from a comprehensive cardiovascular assessment.³⁴⁶

1188

1189 7.3.1 Recommended evaluation in all AF patients

1190 A complete medical history should be taken and all patients should undergo clinical evaluation

1191 that includes thorough assessment for concomitant conditions, establishing the AF pattern,

1192 estimation of stroke risk and AF related symptoms, and assessment of arrhythmia-related

1193 complications such as thromboembolism or left ventricular dysfunction. A 12-lead ECG is

1194 recommended to establish a suspected diagnosis of AF, to determine rate in AF, to screen for

1195 conduction defects, ischemia, and signs of structural heart disease. Initial blood tests should

1196 evaluate thyroid and kidney function, as well as serum electrolytes and full blood count.

1197 Transthoracic echocardiography (TTE) is recommended in all AF patients to guide treatment

1198 decisions. TTE should assess for structural disease (e.g. valvular disease), left ventricular size

1199 and function (systolic and diastolic), atrial size, and right heart function.³⁴⁷ Although biomarkers

1200 such as natriuretic peptides are elevated in AF patients, there is insufficient data to suggest that

1201 blood based parameters are independent markers for AF.³⁴⁸⁻³⁵⁰

1202

7.3.2 Additional investigations in selected patients with AF

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 left atrial appendage, to facilitate early cardioversion or catheter ablation.³⁵¹ 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 or MRI of the brain are recommended to detect stroke and to support decisions regarding acute management and long-term anticoagulation. Delayed-enhancement magnetic resonance imaging (MRI) of the left atrium using gadolinium contrast³⁵²⁻³⁵⁴, T1 mapping using cardiac MRI³⁵⁴ and intracardiac echo³⁵⁵ may help to guide treatment decisions in AF, but require external validation in multicentre studies.

7.4 Structured follow-up

Most AF patients need regular follow-up to ensure continued management. AF patient follow-up may be undertaken in primary care, by specially trained nurses, by cardiologists, or by AF specialists.^{332, 337} 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 ^a	Level ^b	Refs ^c
ECG documentation is required to establish the diagnosis of AF.	I	B	356
A full cardiovascular evaluation including an accurate history, careful clinical examination, and assessment of concomitant conditions is recommended in all AF patients.	I	C	
A transthoracic echocardiogram is recommended in all AF patients to guide management.	I	C	346
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.	IIa	C	

AF = atrial fibrillation; ECG = electrocardiogram

1226 ^a Class of recommendation

1227 ^b Level of evidence

1228 ^c Reference(s) supporting recommendation(s)

1229

1230

1231 7.5 Defining Goals of AF management

1232 AF management comprises therapies with prognostic impact (anticoagulation and treatment of
1233 cardiovascular conditions) and therapies predominantly providing symptomatic benefit (rate
1234 control, rhythm control, Table 10). Therapies with prognostic benefit need careful explanation to
1235 patients when their benefits are not directly felt. Rhythm control therapy can be successful if
1236 symptoms are controlled, even when AF recurs. Explaining the expected benefits to each AF
1237 patient at the start of AF management will prevent unfounded expectations and has the
1238 potential to optimize quality of life.

1239

1240 **TABLE 10: Goal-based follow-up**

Intervention	Category	Follow-up aspects	Performance indicator (examples)
Anticoagulation	Prognostic	Indication (risk profile; timing, e.g. post-cardioversion) Adherence (if NOAC) INR (if VKA) NOAC dosing (co-medications; age; weight; renal function)	Stroke Bleeding Mortality
Comorbidity control	Prognostic	Obesity Arterial hypertension Heart failure Coronary Artery disease Diabetes etc.	Weight loss Blood pressure control Heart failure therapy and hospitalizations Statin and antiplatelet therapy Adequate revascularization Glycaemic control
Rate control	Mainly symptomatic Partly prognostic	Symptoms Average resting heart rate <110 bpm	EHRA score Heart failure status LV function Exercise capacity
Rhythm control	Symptomatic at present	Symptoms vs. side effects Exclusion of pro-arrhythmia (PR; QRS; QTc interval)	Hospitalization Therapy complications
Patient education and self-care capabilities	Relevant for implementation of and adherence to therapy	Knowledge (about disease; about treatment; about management goals) Capabilities (what to do if...)	Adherence to therapy Directed evaluation, preferably based on systematic checklists
Caregiver involvement	Relevant for chronic care management	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

1241 bpm = beats per minute; GP = general practitioner; INR = international normalized ratio; LV =
1242 left ventricular; EHRA = European Heart Rhythm Association AF symptoms scale; NOAC = non-
1243 vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist

8. Stroke prevention therapy in AF patients

Oral anticoagulation (OAC) can prevent the majority of ischemic strokes in AF patients and prolong life^{38, 39, 193, 200, 336, 357-359}, and is superior to no treatment or aspirin in patients with different stroke risk profiles.^{360, 361} The benefit is almost universal, with the exception of patients at very low stroke risk, and OAC should therefore be used in most patients with AF. Despite this evidence, underuse or premature termination of therapy with OAC is still common. Bleeding events, both severe and nuisance bleeds, a perceived 'high risk of bleeding' on anticoagulation, and the impact of adherence to VKA therapy are among the most common reasons for withholding or ending OAC.^{359, 362-366} However, the considerable stroke risk without OAC often exceeds the bleeding risk on OAC, even in the elderly, patients with cognitive dysfunction, or those with frequent falls or frailty.^{367, 368} The bleeding risk on aspirin is not different to the bleeding risk on VKA³⁶⁹ or NOAC therapy,^{361, 370} while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients.^{38, 361, 369, 370}

8.1 Stroke and bleeding risk prediction

8.1.1 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.³⁷¹⁻³⁷⁵ The introduction of the CHA₂DS₂-VASc score has clearly simplified the initial decision for OAC in AF patients. Since its first implementation into the ESC guidelines in 2010³⁷⁶, it has been widely used.³⁷⁷ We recommend to estimate stroke risk in AF patients based on the CHA₂DS₂-VASc score (Table 11).³⁷⁵ In general, patients without clinical stroke risk factors do not need antithrombotic therapy, while patients with stroke risk factors (i.e. CHA₂DS₂-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 CHA₂DS₂-VASc score.

CHA ₂ DS ₂ -VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of left ventricular dysfunction	+1

Hypertension Resting BP > 140/90 mmHg on at least 2 occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose > 125 mg/dL or treatment with oral hypoglycaemic agent and/or insulin	+1
Prior stroke, TIA, or thromboembolism	+2
Vascular disease Prior myocardial infarction, peripheral arterial disease, or aortic plaque	+1
Age 65 to 74 years	+1
Sex category (female)	+1

Other, less validated clinical risk factors for stroke include: Unstable INRs and low time in therapeutic range in patients treated with vitamin K antagonists; prior bleed or anaemia; alcohol excess and other markers for decreased therapy adherence; chronic kidney disease; elevated high-sensitivity Troponin T; and elevated NT-proBNP.

1275

8.1.2 Anticoagulation in patients with a CHA₂DS₂-VASc score of 1 in men and 2 in women

Controlled trials studying OAC in AF patients have been enriched for patients at high risk for stroke^{38, 39, 193, 200, 336, 357-359}, and hence there is strong evidence that patients with a CHA₂DS₂-VASc risk score of 2 or more in men, and 3 or more in women benefit from OAC. Fortunately, we now have a growing evidence-base regarding stroke risk in patients with one clinical risk factor (i.e. CHA₂DS₂-VASc score of 1 for men, and 2 for women), although this largely relies on observed stroke rates in patients not receiving OAC. In many of these patients, anticoagulation seems to provide a clinical benefit.³⁷⁸⁻³⁸¹ Stroke rates in these patients vary from 0.3 – 2.75 % per year without anticoagulation (Supplementary Table)^{378, 382, 383} (Add Hemingway CPRD data when published), and OAC should be considered for these patients, balancing the expected stroke reduction, bleeding risk and patient preference. Importantly, age (65 years and older) conveys a relatively high and continuously increasing stroke risk that also potentiates other risk factors

(such as heart failure and gender). Hence, an individualized weighing of risk, as well as patient preferences should inform the decision to anticoagulate patients with only one CHA₂DS₂-VASC stroke risk factor apart from female sex.

Measurement of cardiac troponin (high sensitive troponin T or I) and NT-proBNP may provide additional prognostic information in selected AF patients³⁸⁴⁻³⁸⁶ and biomarker-based risk scores may in the future prove helpful to better identify patients at a truly low risk of stroke.^{386, 387}

1295

1296

Supplementary Table: Reported rates of stroke, often including transient ischemic attack, systemic embolism and pulmonary embolism, in AF patients with CHA₂DS₂-VASC of 1 in men and 2 in women.

	population	Event rate in patients with CHA ₂ DS ₂ -VASC = 1 (men) and 2 (women)	
		without anticoagulation	on anticoagulation
Lip³⁷⁵	European patients seen by cardiologists admitted to hospital	0.6 (0 - 3.4, men and women)	
Poli³⁸⁸	AF patients enrolled in anticoagulation clinics in Italy		0.8 (men and women)
Olesen³⁸⁹	Danish population admitted to hospital	1.6 (men and women)	1.3 (men and women)
Olesen³⁷⁸	Danish population admitted to hospital	1.45 (men and women)	
Friberg³⁹⁰	Swedish population admitted to hospital	0.9	
Guo³⁹¹	Chinese AF patients	0.9 (men and women)	
Coppens³⁹²	AVERRROES CHADSVASC = 1 randomized to aspirin	0.9 (men and women)	
Forslund³⁹³	AF patients in the Stockholm region	0.3-0.5 (men and women)	0.0 - 0.3 (men and women)
Chao³⁷⁹	Taiwanese AF patients	2.5 (men), 2.75 (women)	
Lip³⁸⁰	Danish population admitted to hospital	1.2 (men)	1.0 - 1.1 (men and women)
Friberg³⁸²	Swedish population	0.5 - 0.7 (men)	
van den Ham³⁹⁴	UK population collected in primary care	0.8 - 1.9 (men and women)	
Allan / Hemingway (commissioned by	UK population collected in primary care	0.5 (men), 0.4 (women)	0.8 (men), 0.4 (women)

ESC to inform this guideline)			
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8.1.3 Clinical risk scores for bleeding

Several bleeding risk scores have been developed, mainly in patients on VKA, such as HAS-BLED, ORBIT, and more recently the ABC bleeding score that also makes use of selected biomarkers.³⁹⁵⁻³⁹⁷ Stroke and bleeding risk factors overlap (compare Table 11 and Table 12). Importantly, the two major clinical factors associated with bleeding, higher age and prior stroke, are also two of the most important stroke risk factors. A high bleeding risk score should generally not result in withholding OAC. Rather, bleeding risk factors should be identified and treatable factors should be corrected (see Section 8.5). Table 12 illustrates the modifiable bleeding risk factors.

TABLE 12: Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores.

Modifiable bleeding risk factors
Hypertension (especially when systolic blood pressure is >160 mmHg) ^{a,b,c}
Labile international normalized ratio (in patients on vitamin K antagonists) or time in therapeutic range <60% ^a
Medication predisposing to bleeding, such as antiplatelet agents and NSAIDs ^{a,d}
Excess alcohol (≥8 drinks/week) or drug usage ^{a,b}
Anaemia ^{b,c,d}
Potentially modifiable bleeding risk factors
Impaired renal function ^{a,b,c,d}
Impaired liver function ^{a,b}
Reduced platelet count or function ^b
Non-modifiable bleeding risk factors
Age ^e (>65 years) ^a (≥75 years) ^{b,c,d}

History of stroke ^{a,b}
Prior major bleeding ^{a,b,c,d}
Dialysis dependent chronic kidney disease or renal transplant ^{a,c}
Cirrhotic liver disease ^a
Malignancy ^b
Genetic factors ^b
Biomarker-based bleeding risk factors
High sensitive Troponin T ^e
Growth differentiation factor-15 ^e

1313 ^a Derived from the HAS-BLED score³⁹⁶; ^b Derived from the HEMORR₂HAGES score³⁹⁵; ^c

1314 Derived from the ATRIA score³⁹⁷; ^d Derived from the ORBIT score³⁹⁸; ^e Derived from the ABC
1315 bleeding score³⁹⁹.

1316
1317 Recommendations for stroke and bleeding risk prediction

Recommendations	Class ^a	Level ^b	Refs ^c
The CHA ₂ DS ₂ -VASc score is recommended for stroke risk prediction in patients with AF	I	A	375, 378, 390
Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable factors for major bleeding.	IIa	B	390, 396, 399-403
Troponin and NT-ProBNP measurements may be considered to further refine stroke and bleeding risk in AF patients	IIb	B	384-386, 399, 404

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1319

1320 8.2 Stroke prevention

1321 8.2.1 Vitamin K antagonists

1322 Warfarin and other VKA were the first anticoagulants used in AF patients. VKA therapy reduces
1323 stroke by two thirds and mortality by a quarter compared to control (aspirin or no therapy).³⁸
1324 VKA have been used in many patients throughout the world with good outcomes ⁴⁰⁵⁻⁴⁰⁷, and this
1325 is reflected in the warfarin arms of the NOAC trials (see below). The use of VKAs is limited by

the narrow therapeutic interval, necessitating frequent monitoring and dose adjustments, but VKA, when delivered with adequate time in therapeutic range (TTR), is effective for stroke prevention in AF patients. Clinical parameters can help to identify patients who are likely to achieve a decent time in therapeutic range on VKA therapy.⁴⁰⁸ These have been summarized in the SAME-TT₂R₂ score. Patients who fare well on this score, when treated with VKA, have on average a higher TTR than patients who do not fare well on the score.^{409, 410} VKA are currently the only treatment with established safety in AF patients with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis.⁴¹¹

8.2.2 Non-vitamin K antagonist oral anticoagulants

NOACs, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban, are suitable alternatives to VKA for stroke prevention in AF (Table 13). Their use in clinical practice is rapidly increasing.⁴¹² All NOACs have a predictable effect (onset and offset) without need for regular anticoagulation monitoring. The phase III trials have been conducted with carefully selected doses of the NOACs, including clear rules for dose reduction that should be followed in clinical practice (Table 13.)

Apixaban: In the ARISTOTLE trial,³²⁶ apixaban reduced stroke or systemic embolism by 21% compared with warfarin, combined with a 31% reduction in major bleeding and an 11% reduction in all-cause mortality (all significant). Rates of haemorrhagic stroke and intracranial haemorrhage, but not of ischaemic stroke, were lower on apixaban than on warfarin. Gastrointestinal bleeding was similar between the treatment.⁴¹³ Apixaban is the only NOAC that has been compared to aspirin in AF patients: Apixaban significantly reduced stroke or systemic embolism by 55% compared with aspirin, with no significant difference in rates of major bleeding or intracranial haemorrhage.^{414, 415}

Dabigatran: In the RELY study,^{416, 417} dabigatran 150 mg twice daily reduced stroke and systemic embolism by 35% without significant difference in major bleeding events compared to warfarin. Dabigatran 110 mg twice daily was non-inferior to warfarin for prevention of stroke and systemic embolism, with 20% fewer major bleeding events. Both dabigatran doses significantly reduced haemorrhagic stroke and intracranial haemorrhage. Dabigatran 150 mg twice daily significantly reduced ischaemic stroke by 24% and vascular mortality by 12%, while gastrointestinal bleeding was significantly increased by 50%. There was a non-significant

numerical increase in myocardial infarction with both dabigatran doses^{416, 417} which has not been replicated in large post-authorization analyses.⁴⁰⁷ These data have also replicated the benefit of dabigatran over VKA found in the RE-LY trial in patients enriched for the higher dabigatran dose (150 mg twice daily).⁴⁰⁷

1363

Edoxaban: In the ENGAGE AF-TIMI 48 trial,³²⁸ edoxaban 60 mg once daily and edoxaban 30 mg once daily (with dose reductions in certain patients according to table 13) were compared to adjusted-dose warfarin.⁴¹⁸ Edoxaban 60mg once daily was non-inferior to warfarin (primary outcome, hazard-ratio 0.87; 97.5% CI 0.73–1.04; P = 0.08). In an on-treatment analysis, edoxaban 60 mg once daily significantly reduced stroke or systemic embolism by 21% and significantly reduced major bleeding events by 20% compared to warfarin, while edoxaban 30 mg once daily was non-inferior to warfarin for prevention of stroke and systemic embolism but significantly reduced major bleeding events by 53%. Cardiovascular death was reduced in patients randomised to edoxaban 60 mg once daily or edoxaban 30 mg once daily compared to warfarin. Only the higher dose regime has been approved for stroke prevention in AF.

1374

Rivaroxaban: In the ROCKET-AF trial,³²⁷ patients were randomized to rivaroxaban 20 mg once daily or VKA, with a dose adjustment to 15 mg daily for those with estimated creatinine clearance 30–49 mL/min by the Cockcroft-Gault formula. Rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism in the intention-to-treat analysis while the per-protocol on-treatment analysis achieved statistical superiority with a 21% reduction of stroke or systemic embolism compared to warfarin. Rivaroxaban did not reduce the rates of mortality, ischaemic stroke or major bleeding events compared to VKA. There was an increase in gastrointestinal bleeding events, but a significant reduction in haemorrhagic stroke and intracranial haemorrhage with rivaroxaban compared to warfarin. Comparable event rates have been reported in post-authorization analyses, which are part of the post-approval risk management process.^{419, 420}

1386 TABLE 13: Newer stroke prevention therapies that have been compared to vitamin K antagonist therapy in controlled trials

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)	Watchman device (PROTECT AF)
Pharmacokinetics					
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor	Percutaneous closure of left atrial appendage
Bioavailability, %	6	60–80	50	62	N/A
Time to peak levels, hours	3	2–4	3	1–2	N/A
Half-life, hours	12–17	5–13	9–14	10–14	N/A
Excretion	80% renal	2/3 liver, 1/3 renal	27% renal	50% renal	N/A
Dose	150 mg b.i.d or 110 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d. or 30 mg o.d.	N/A
Dose reduction in selected patients		Rivaroxaban 15 mg o.d. if CrCl 30–49 mL/min	Apixaban 2.5 mg b.i.d. if at least 2 of age ≥ 80 years, body weight ≤ 60 kg or serum creatinine level ≥ 1.5 mg/dL (133 µmol/L)	Edoxaban 60 mg reduced to 30 mg o.d., and Edoxaban 30 mg reduced to 15 mg o.d., if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤ 60 kg, concomitant use of verapamil or quinidine or dronedarone	N/A
Study characteristics					
Study design	Randomized, open-label	Randomized, double-blind	Randomized, double-blind	Randomized, double-blind	Randomized, unblinded (2:1)
Number of patients	18 113	14 264	18 201	21 105	707
Follow-up period, years	2	1.9	1.8	2.8	3.8
Randomized groups	Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg b.i.d., 110 mg b.i.d.)	Dose-adjusted warfarin vs. rivaroxaban 20 mg o.d.	Dose-adjusted warfarin vs. apixaban 5 mg b.i.d.	Dose-adjusted warfarin vs. edoxaban (60 mg o.d., 30 mg o.d.)	Dose-adjusted warfarin vs. Watchman device
Baseline patient characteristics					
Age, years	71.5 ± 8.7 (mean ± SD)	73 (65–78) [median (interquartile range)]	70 (63–76) [median (interquartile range)]	72 (64–78) [median (interquartile range)]	Watchman: 71.7 ± 8.8; Warfarin: 72.7 ± 9.2 (mean ± SD)
Male sex, %	63.6	60.3	64.5	61.9	Watchman: 70.4; Warfarin: 70.1
CHADS2 (mean)	2.1	3.5	2.1	2.8	Watchman: 2.2; Warfarin: 2.3

Outcomes (% per year)												
	Warfarin n = 6022	Dabigatran 150 n = 6076	Dabigatran 110 n = 6015	Warfarin n = 7133	Rivaroxaban n = 7131	Warfarin n = 9081	Apixaban n = 9120	Warfarin n = 7036	Edoxaban 60 n = 7035	Edoxaban 30 n = 7034	Warfarin n = 244	Watchman device n = 463
		(RR, 95% CI; P value)	(RR, 95% CI; P value)		(HR, 95% CI; P value)		(HR, 95% CI; P value)		(HR, 95% CI; P value)	(HR, 95% CI; P value)		(Rate ratio, 95% CrI; PP)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; P for non- inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; P for non- inferiority <0.001)	2.4	2.1 (0.88, 0.75–1.03; P for non- inferiority <0.001, P for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; P <0.001 for non-inferiority, P = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; P <0.001 for non- inferiority, P = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; P = 0.005 for non- inferiority, P = 0.10 for superiority)	2.2	1.5 (0.68, 0.42– 1.37; PP > 99% for non- inferiority, PP = 83% for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; P = 0.03)	1.34 (1.10, 0.88–1.37; P = 0.42)	1.42	1.34 (0.94; 0.75–1.17; P = 0.581)	1.05	0.97 (0.92, 0.74–1.13; P = 0.42)	1.25	1.25 (1.00, 0.83–1.19; P = 0.97)	1.77 (1.41, 1.19–1.67; P <0.001)	1.1	1.4 (1.26, 0.72– 3.28; PP = 78 for non- inferiority, PP = 15% for superiority)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; P <0.001)	0.12 (0.31, 0.17–0.56; P <0.001)	0.44	0.26 (0.59; 0.37–0.93; P = 0.024)	0.47	0.24 (0.51, 0.35–0.75; P <0.001)	0.47	0.26 (0.54, 0.38–0.77; P <0.001)	0.16 (0.33, 0.22–0.50; P <0.001)	1.1	0.2 (0.15, 0.03– 0.49; PP > 99 for non- inferiority, PP = 99 for superiority)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; P = 0.41)	2.92 (0.80, 0.70–0.93; P = 0.003)	3.4	3.6 (P = 0.58)	3.09	2.13 (0.69, 0.60–0.80; P <0.001)	3.43	2.75 (0.80, 0.71–0.91; P <0.001)	1.61 (0.47, 0.41–0.55; P <0.001)	7.4	4.8
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; P <0.001)	0.23 (0.29, 0.19–0.45; P <0.001)	0.70	0.5 (0.67; 0.47–0.93; P = 0.02)	0.80	0.33 (0.42, 0.30–0.58; P <0.001)	0.85	0.39 (0.47, 0.34–0.63; P <0.001)	0.26 (0.30, 0.21–0.43; P <0.001)	–	–
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; P <0.001)	1.13 (1.04, 0.82–1.33; P = 0.74)	1.24	2.00 (P <0.001)	0.86	0.76 (0.89, 0.70–1.15; P = 0.37)	1.23	1.51 (1.23, 1.02–1.50; P = 0.03)	0.82 (0.67, 0.53–0.83; P <0.001)	–	–
Myocardial infarction	0.64	0.81 (1.27, 0.94–1.71; P = 0.12)	0.82 (1.29, 0.96–1.75; P = 0.09)	1.12	0.91 (0.81; 0.63–1.06; P = 0.12)	0.61	0.53 (0.88, 0.66–1.17; P = 0.37)	0.75	0.70 (0.94, 0.74–1.19; P = 0.60)	0.89 (1.19, 0.95–1.49; P = 0.13)	–	–
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; P = 0.051)	3.75 (0.91, 0.80–1.03; P = 0.13)	2.21	1.87 (0.85; 0.70–1.02; P = 0.07)	3.94	3.52 (0.89, 0.80–0.99; P = 0.047)	4.35	3.99 (0.92, 0.83–1.01; P = 0.08)	3.80 (0.87, 0.79–0.96; P = 0.006)	4.8	3.2 (HR, 95% CI; 0.66, 0.45– 0.98, P = 0.04)

1388 AF = atrial fibrillation; b.i.d. = bis in die (twice daily); CHADS2 = congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA [doubled]; CI = confidence
1389 interval; CrI = credible interval; CrCI = creatinine clearance; HR = hazard ratio; ITT = intention-to-treat; o.d. = once daily; PP = posterior probabilities; RR = relative
1390 risk; SD = standard deviation; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

8.2.3 NOACs or vitamin K antagonists

Both VKA and NOACs are effective treatments to prevent stroke in AF patients. A meta-analysis³⁹ based on the high-dose treatment groups of the pivotal studies of warfarin versus NOACs included 42,411 patients receiving a NOAC and 29,272 patients receiving warfarin. NOACs in these dosages significantly reduced stroke or systemic embolic events by 19% compared to warfarin (RR 0.81; 95% CI 0.73–0.91; $P < 0.0001$), mainly driven by a reduction in haemorrhagic stroke (0.49; 0.38–0.64; $P < 0.0001$). Mortality was 10% lower in patients randomized to NOAC therapy (0.90; 0.85–0.95; $P = 0.0003$), and intracranial haemorrhage was halved (0.48; 0.39–0.59; $P < 0.0001$), while gastrointestinal bleeding events were increased (1.25; 1.01–1.55; $P = 0.04$).³⁹ The stroke reduction with NOACs was consistent in all evaluated subgroups, while there was a suggestion of greater relative reduction in bleeding with NOACs at centres with poor INR control (interaction $P = 0.022$). Notably, the substantial reduction in intracranial haemorrhage by NOACs compared to warfarin seems unrelated to poor or good INR control.^{421, 422}

8.2.4 Oral anticoagulation in AF patients with CKD

CKD is associated with stroke and bleeding in large data sets.^{423, 424} Anticoagulation can be safely used in AF patients with moderate or moderate-severe CKD (GFR ≥ 15 ml/min): the SPAF III trial randomized 805/1936 participants with stage 3 CKD (eGFR < 59 ml/min/1.73 m²), with good outcomes on warfarin (INR 2–3).⁴²⁵ This is supported by a large Swedish data base where stroke risk was lower in CKD patients with AF treated with warfarin (adjusted HR 0.76; CI 0.72–0.80)⁴²⁶, while bleeding was also slightly increased, especially during therapy initiation.⁴²⁷ In a meta-analysis of the major NOAC trials, patients with mild or moderate CKD suffered less stroke systemic emboli or major bleeding events on NOACs than on warfarin.⁴²⁸ Kidney function should be regularly monitored in AF patients on oral anticoagulation to allow dose adaption for those on NOACs eliminated by the kidney (Table 14) and to refine risk estimation.⁴²⁹

8.2.5 Oral anticoagulation in AF patients on dialysis

Approximately one in eight dialysis patient suffers from AF, with an incidence rate of 2.7/100 patient-years.⁴³⁰ AF increases mortality in dialysis patients.⁴³⁰ There are no randomized trials assessing OAC in haemodialysis patients⁴³¹, and no controlled trials of NOACs in patients with severe CKD (CrCl < 25 –30 ml/min).^{325–328} Warfarin use was associated either with a neutral or increased risk of stroke in database analyses of dialysis patients^{432–434} including a population-

1424 based analysis in Canada (adjusted hazard ratio for stroke 1.14; 95% confidence interval 0.78–
1425 1.67, adjusted hazard ratio for bleeding 1.44; 95% confidence interval 1.13–1.85).⁴³⁵ In
1426 contrast, data from Denmark suggest a benefit of OAC in patients on renal replacement
1427 therapy.⁴³⁶ Hence, controlled studies of anticoagulants (both VKA and NOAC) in AF patients on
1428 dialysis are needed.⁴³⁷

1429

1430 8.2.6 Patients with AF requiring kidney transplantation

1431 There are no randomized trials in patients after kidney transplantation assessing OAC. The
1432 prescription of NOAC therapy should be guided by the eGFR of the transplanted kidney.
1433 Potential pharmacokinetic interactions of OAC with immunosuppressive agents should be
1434 considered.

1435

TABLE 14: Inclusion criteria, dose adjustment, and outcomes in patients with chronic kidney disease in the 4 major randomized trials comparing NOACs with warfarin in patients with AF

	Dabigatran (RE-LY) ^{325, 438}	Rivaroxaban (ROCKET-AF) 327, 439	Apixaban (ARISTOTLE) ^{326, 440}	Edoxaban (ENGAGE AF-TIMI 48) ⁴⁴¹
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 ≥1.5 mg/dl plus age ≥80 years or weight ≤60 kg	30 mg or 15 mg once daily if CrCl <50 ml/min
Percent 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 to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 ml/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

AF = atrial fibrillation; CKD = chronic kidney disease; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; NA = not available; NOAC = non-vitamin K antagonist oral anticoagulant; *o.d.* = once daily. Adapted from Hart *et al.*³²²

8.2.7 Antiplatelet therapy as an alternative to oral anticoagulants

The evidence supporting antiplatelet monotherapy for stroke prevention in AF is very limited.^{38, 389, 442, 443} VKA therapy prevents stroke, non CNS embolus, myocardial infarction, and vascular

death better than single or dual antiplatelet therapy with aspirin and clopidogrel (annual risk of 5.6% for aspirin and clopidogrel vs. 3.9% with VKA therapy).⁴⁴⁴ Even greater benefits were seen in those VKA-treated patients with high TTR.⁴⁴⁵ Antiplatelet therapy increases bleeding risk, especially combination therapy (2.0% vs. 1.3%; $P < 0.001$)⁴⁴⁶, with bleeding rates that are similar to those on OAC.^{414, 444, 447, 448} Thus, antiplatelet therapy cannot be recommended for stroke prevention in AF patients.

Recommendations for stroke prevention in patients with AF

Recommendations	Class ^a	Level ^b	Refs ^c
Oral anticoagulation therapy to prevent thromboembolism is recommended for all patients with AF and an increased risk of stroke, i.e. men with a CHA₂DS₂-VASc score of two or more, women with a CHA₂DS₂-VASc score of three or more and patients with mitral stenosis or mechanical heart valves.	I	A	38, 326-328, 414, 416, 417
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 vitamin K antagonists.	I	A	39, 326-328, 416, 417
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	445, 449-453
Oral anticoagulation to prevent thromboembolism should be considered in patients with a CHA₂DS₂-VASc risk score of one in men or two in women, considering individual characteristics and patient preferences.	IIa	B	378, 382, 383
AF patients already on treatment with VKA 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).	IIb	A	39, 326, 416, 417, 454
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	389, 455
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	375, 378, 382, 383
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 389, 443

NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) are not recommended in patients with mechanical heart valves (LOE B) or moderate to severe mitral stenosis (LOE C).	III (harm)	B/C	326-328, 411, 416, 417
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1454 AF = atrial fibrillation; CHA₂DS₂-VASc = Congestive Heart failure, hypertension, Age ≥75
 1455 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); NOAC
 1456 = non-vitamin K antagonist oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K
 1457 antagonist

1458 ^a Class of recommendation

1459 ^b Level of evidence

1460 ^c Reference(s) supporting recommendation(s)

1461

8.3 Left atrial appendage occlusion and exclusion

8.3.1 Left atrial appendage occlusion devices

Interventional left atrial appendage (LAA) occlusion,⁴⁵⁶⁻⁴⁵⁹ and limited experience with percutaneous LAA ligation, has mainly been reported in observational studies and registries. Only one device (Watchman®) was compared to VKA therapy in one controlled trial (PROTECT AF) and one study with a randomized study group and a non-randomized cohort (PREVAIL).⁴⁵⁹⁻⁴⁶¹ In these data sets, LAA occlusion was non-inferior to VKA for the prevention of stroke in AF patients with moderate stroke risk, with a possibility of lower bleeding in those patients who continued follow-up.^{462, 463} These data were confirmed in a patient-level meta-analysis of the two trials and their associated registries.⁴⁶³ LAA occlusion may also reduce stroke risk in patients with contraindications to OAC.^{464, 465} The implantation procedure can cause serious complications^{456, 466-468} with high rates reported in analyses from insurance databases and systematic reviews, possibly identifying a certain degree of reporting bias.^{456, 466} A large recent European registry reported high implantation success (98%) with an acceptable procedure-related complication rate of 4% at 30 days.⁴⁶⁹ Most patients who would historically be considered unsuitable for OAC therapy seem to do relatively well on contemporarily managed OAC.^{407, 420, 470} Urgently needed to inform the best use of LAA occluders are adequately powered controlled trials evaluating LAA occluders in patients who are truly unsuitable for OAC or in patients who suffer a stroke on OAC, randomized comparisons of LAA occluders with NOACs, and assessment of the minimal antiplatelet therapy acceptable after LAA occlusion.

8.3.2 Surgical LAA occlusion or exclusion

Surgical LAA occlusion or exclusion concomitant to cardiac surgery has been performed for many decades and with various techniques. Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available.⁴⁷¹⁻⁴⁷⁴ Residual LAA flow or incomplete LAA exclusion can increase stroke risk.⁴⁷⁵ In most studies, LAA occlusion/exclusion was performed during other open heart surgery, and more recently in combination with surgical AF ablation⁴⁷³ or as a stand-alone thoracoscopic procedure. One randomized trial evaluating the role of concomitant AF surgery and LAA occlusion has reported in 2015, without a clear benefit of LAA exclusion for stroke prevention in the subgroup of patients undergoing AF surgery.⁴⁷⁶ A large randomized trial is currently underway.⁴⁷⁷

1495

1496 Recommendations for occlusion / exclusion of the LAA

Recommendations	Class ^a	Level ^b	Refs ^c
After surgical occlusion / exclusion of the LAA, it is recommended to continue anticoagulation in AF patients at risk of stroke for stroke prevention.	I	B	471, 472
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment, e.g. those with a prior life-threatening bleeding without a reversible cause.	IIb	B	459, 463, 464
Surgical occlusion / exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.	IIb	B	473
Surgical occlusion / exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic ablation surgery.	IIb	B	478

1497 AF = atrial fibrillation; LAA = left atrial appendage

1498 ^a Class of recommendation1499 ^b Level of evidence1500 ^c Reference(s) supporting recommendation(s)

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1502

1503 8.4 **Secondary stroke prevention**

1504 The most important risk factors for stroke in patients with AF are advanced age or prior
 1505 cardioembolic stroke / TIA³⁸⁶, emphasizing the need for OAC in these patients. The highest risk
 1506 of recurrent stroke is in the early phase after a first stroke or TIA.^{479, 480}

1507

1508 8.4.1 **Treatment of acute ischaemic stroke**

1509 Systemic thrombolysis with rtPA is an effective and approved medical treatment of acute
 1510 ischaemic stroke in patients presenting within 4.5 hours of symptom onset.⁴⁸¹ Systemic
 1511 thrombolysis is contraindicated in patients on therapeutic OAC.^{482, 483} RtPA can be given in
 1512 patients treated with VKA if the INR is below 1.7,⁴⁸⁴ or in dabigatran-treated patients with a
 1513 normal aPTT and last intake of drug >48 hours previously (based on expert consensus).⁴⁸²
 1514 Whether specific NOAC antidotes^{485, 486} could be used followed by systemic thrombolysis,

needs to be investigated. Thrombectomy can be performed in anticoagulated patients with distal occlusion of the internal carotid artery or middle cerebral artery in a six-hour time window.⁴⁸⁷

8.4.2 Initiation of anticoagulation after TIA or ischaemic stroke

Data on the optimal use of anticoagulants (heparin, low molecular weight heparins, heparinoids, VKA, NOACs) in the first days after a stroke are scarce. Parenteral anticoagulants seem to be associated with a non-significant reduction in recurrent ischaemic stroke when administered 7 to 14 days after the acute stroke (OR 0.68; CI: 0.44–1.06), a significant increase in symptomatic intracranial bleeding (OR 2.89; CI 1.19–7.01), and a similar rate of death or disability at final follow up.⁴⁸⁸ It seems likely that the bleeding risk on parenteral anticoagulation exceeds the stroke prevention benefit in the first days after a large stroke, while patients with a TIA or a small stroke may benefit from early (immediate) initiation or continuation of anticoagulation. Therefore, we propose to initiate anticoagulation in AF patients between 1 and 12 days after an ischemic stroke, depending on its severity (Figure 9).⁴⁸⁹ We suggest repeat brain imaging to determine the optimal initiation of anticoagulation in patients with a large stroke at risk for haemorrhagic transformation. Long-term OAC with VKA^{370, 490-492} or a NOAC⁴⁹³ conveys benefits in AF patients who survived a stroke. NOACs seem to convey slightly better outcomes, mainly driven by fewer intracranial haemorrhages and haemorrhagic strokes (OR 0.44, 95% CI .032-0.62).⁴⁹³ Detailed data for edoxaban have not yet been published.³²⁸ If a patient suffers a stroke or TIA whilst taking an anticoagulant, switching to another anticoagulant should be considered.

8.4.3 Initiation of anticoagulation after intracranial haemorrhage

No prospective studies have investigated the benefit or risk of the initiation of OAC after intracranial haemorrhage,⁴⁹⁴ and patients with a history of intracranial bleeding were excluded from the randomized trials comparing NOACs with VKA. The available evidence indicates that anticoagulation in patients with AF can be reinitiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor (e.g. uncontrolled hypertension) has been treated, and that such treatment leads to less recurrent (ischemic) strokes and lower mortality.^{470, 495} If anticoagulation is resumed, it seems reasonable to consider anticoagulants with a low bleeding risk.³⁹ Figure 10 depicts a consensus opinion on the initiation or resumption of OAC after an intracranial haemorrhage. We recommend a multidisciplinary decision with input from stroke physicians/neurologists, cardiologists, neuroradiologists, and neurosurgeons.

1548

1549 8.4.4 **Competing causes of stroke or TIA**

1550 A patient with AF and symptomatic high-degree stenosis of the internal carotid artery should be
 1551 operated and not stented to minimize the need for combination therapy with OAC and
 1552 antiplatelets. In patients undergoing endarterectomy, co-medication with aspirin is only required
 1553 prior to surgery and for 10 days post procedure.⁴⁹⁶

1554

1555 Recommendations for secondary stroke prevention

Recommendations	Class ^a	Level ^b	Refs ^c
Anticoagulation with heparin or LMWH immediately after ischaemic stroke is not recommended in AF patients.	III (harm)	A	488
In patients who suffer a TIA 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 secondary stroke prevention until the initiation or resumption of oral anticoagulation.	IIa	B	497
Systemic thrombolysis with rtPA is not recommended if the INR is above 1.7 (or for patients on dabigatran, if aPTT is outside normal range).	III (harm)	C	482, 484
NOACs are recommended in preference to VKA or aspirin in AF patients with a prior stroke.	I	B	370, 493
After TIA or stroke, combination therapy of oral anticoagulation and antiplatelet therapy is not recommended.	III (harm)	B	498
After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided that the cause of bleeding or the relevant risk factor has been treated or controlled.	IIb	B	494, 495, 499

Patients with AF and symptomatic high-degree stenosis of the internal carotid artery should be operated and not stented, in order to avoid combination therapy with antiplatelets and an oral anticoagulant.	Ila	B	500
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1556 AF= atrial fibrillation; aPTT = activated partial thromboplastin time; INR = international
 1557 normalized ratio; LMWH = low molecular weight heparin; NOAC = non-vitamin K antagonist oral
 1558 anticoagulant; rtPA = recombinant tissue plasminogen activator; TIA = transient ischaemic
 1559 attack; VKA = vitamin K antagonist

1560 ^a Class of recommendation

1561 ^b Level of evidence

1562 ^c Reference(s) supporting recommendation(s)

1563

1564

1565 8.5 Strategies to minimize bleeding on anticoagulant therapy

1566 In a meta-analysis of 47 studies, the overall incidence of major bleeding with vitamin K
 1567 antagonists was 2.1 per 100 patient-years in controlled trials (range 0.9–3.4) and 2.0 per 100
 1568 patient-years for observational data sets (range 0.2–7.6).⁵⁰¹ Minimizing treatable bleeding risk
 1569 factors (see Table 12) seems paramount to reduce the bleeding rate on anticoagulants.

1570

1571 8.5.1 Uncontrolled hypertension

1572 Uncontrolled blood pressure increases the bleeding risk on OAC.⁵³ Hence, keeping systolic
 1573 blood pressure well controlled is of particular relevance in anticoagulated AF patients. In
 1574 patients with known hypertension, treatment according to current guidelines is recommended.⁵⁰²

1575

1576 8.5.2 Prior bleeding

1577 History of bleeding events and the presence of anaemia are important parts of the assessment
 1578 of all patients receiving OAC. The majority of bleeding events are gastrointestinal. Compared
 1579 to warfarin the risk of gastrointestinal bleeds was increased for dabigatran 150 mg twice
 1580 daily,^{407, 503} rivaroxaban 20 mg once daily⁵⁰⁴ and edoxaban 60 mg once daily.³²⁸ The risk of
 1581 gastrointestinal bleeds was comparable to warfarin on dabigatran 110 mg twice daily⁵⁰³ and on
 1582 apixaban 5 mg twice daily,³²⁶ Recent observational analyses do not replicate these findings,

suggesting a smaller effect.^{407, 505, 506} In patients in whom the source of bleeding has been identified and corrected, OAC can be reinitiated. This also appears true for patients who have suffered an intracranial haemorrhage, once modifiable bleeding risk factors (e.g. uncontrolled hypertension) have been corrected.^{470, 507}

1587

1588 8.5.3 **Labile INR and adequate NOAC dosing**

Time in therapeutic range (TTR) on VKA is an important predictor of major haemorrhage.^{449, 508} Therefore we recommend targeting the INR between 2.0 to 3.0 in patients on VKA with a high TTR (e.g. >70%), and to consider switching to a NOAC when a high TTR cannot be maintained.⁴⁵² NOAC dosing should follow the dose reduction criteria evaluated in the clinical trials, considering renal function, age, and weight. Patient information and empowerment, best delivered through integrated AF management, seem paramount to achieve this goal.

1595

1596 8.5.4 **Alcohol abuse**

Alcohol excess is a risk factor for bleeding in anticoagulated patients³⁹⁶, mediated by poor adherence, liver disease, variceal bleeding and risk of major trauma. Severe alcohol abuse and binge drinking habits should be corrected in patients eligible for OAC.

1600

1601 8.5.5 **Falls and dementia**

Falls and dementia are associated with increased mortality in AF patients⁵⁰⁹, without evidence that these conditions markedly increase the risk of intracranial hemorrhage.^{509, 510} Hence, anticoagulation should only be withheld from patients with severe uncontrolled falls (e.g. epilepsy or advanced multi-system atrophy with backwards falls), or in selected dementia patients where compliance and adherence cannot be ensured by a caregiver.

1607

1608 8.5.6 **Genetic testing**

In addition to food and drug interactions, multiple genetic variations affect the metabolism of VKA.⁵¹¹ The systematic use of genetic information for adjustment of VKA dosage has been evaluated in several controlled clinical studies.⁵¹²⁻⁵¹⁴ Genetic testing has little impact on TTR or bleeding risk on warfarin, and is not recommended for clinical use at present.⁵¹⁵

1613

8.5.7 Bridging periods off OAC

Most cardiovascular interventions (e.g. PCI or pacemaker implantation) can safely be performed on continued OAC. When interruption of OAC is required, bridging does not seem beneficial, except in patients with mechanical heart valves. In a randomised trial of 1884 AF patients, interruption of anticoagulation was non-inferior to heparin administration for the outcome of arterial thromboembolism (incidence of 0.4% and 0.3%, respectively) and resulted in lower risk of major bleeding (1.3% and 3.2%, respectively).⁵¹⁶ A short interruption or continued OAC should be considered in patients at highest stroke risk.

8.6 Management of bleeding events in anticoagulated AF patients

8.6.1 Management of minor, moderate and severe bleeding

General assessment of an anticoagulated AF patient experiencing a bleeding event should include assessment of bleeding site, onset and severity of the bleeding, the time-point of last intake of OAC and other antithrombotic drugs, and other factors influencing bleeding risk such as chronic kidney disease, alcohol abuse and concurrent medications. Laboratory tests should include haemoglobin, haematocrit, platelet count, renal function, and for VKA patients, prothrombin time, activated partial thromboplastin time and INR. Coagulation tests do not provide much information in NOAC patients, except for aPTT in the case of dabigatran. More specific coagulation tests do exist, including diluted thrombin time (HEMOCLLOT) for dabigatran and calibrated quantitative anti-FXa assays for factor Xa inhibitors.⁵¹⁷ However, these tests are not always readily available and are often unnecessary for bleeding management.⁵¹⁸

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

Immediate reversal of the antithrombotic effect is indicated in severe or life-threatening bleeding events. An agreed, institutional procedure for the management of life-threatening bleeds should

be documented and accessible at all times to ensure adequate initial management. For VKA, administration of fresh frozen plasma restores coagulation more rapidly than vitamin K, and prothrombin complex concentrates (PCC) achieve even faster blood coagulation.⁵¹⁹ Registry data suggest that the combination of plasma and PCC is associated with the lowest case fatality following intracranial haemorrhage on VKA with INR ≥ 1.3 .⁵²⁰ In a multicentre randomised trial of 188 patients, four-factor PCC achieved more rapid INR reversal and effective haemostasis than plasma in patients undergoing urgent surgical or invasive procedures.⁵²¹ Administration of PCC may also be considered for severe bleeding on NOAC treatment, if specific antidotes are not available.

Several antidotes against NOACs are under development. Idarucizumab (FDA and EMA approved in 2015) is a clinically available humanized antibody fragment that binds dabigatran and rapidly and dose-dependently reverses the effects without over-correction or thrombin generation.⁴⁸⁵ Andexanet alpha, a modified recombinant human factor Xa which lacks enzymatic activity, has been shown to reverse the anticoagulant activity of apixaban and rivaroxaban in healthy probands within minutes after administration and for the duration of infusion, with a transient increase in markers of coagulation activity of uncertain clinical relevance.⁵²² Another agent under development is Ciraparantag (PER977), an antidote targeted to reverse of both direct thrombin and factor Xa inhibitors as well as the indirect inhibitor enoxaparin.⁵²³ The clinical usefulness of these specific antidotes needs further evaluation.

1666

1667 8.6.2 OAC in AF patients at risk or suffering a bleeding event

While anticoagulation therapy should be paused to control active bleeding, absolute contraindications to long-term OAC after a bleeding episode are rare. When nuisance bleeds are the reason to stop OAC, a change from one anticoagulant to another seems reasonable. Many causes or triggers of major bleeding events can be treated and/or eliminated, including uncontrolled hypertension, gastrointestinal ulcers, or intracranial aneurysms. Reinitiation of anticoagulation after a bleeding event is often clinically justified.^{470, 524} Difficult decisions including the discontinuation and recommencement of OAC should be taken by a multidisciplinary team, balancing estimated risk of recurrent stroke and bleeding, and considering the bleeding risk of different stroke prevention therapies. Left atrial appendage exclusion or occlusion might be an alternative in selected patients.

1678

1679

1680 Recommendations for management of bleeding

Recommendations	Class ^a	Level ^b	Refs ^c
Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding.	IIa	B	525
When dabigatran is used, reduced dose of dabigatran (110 mg twice daily) may be considered in patients >75 years to reduce the risk of bleeding.	IIb	B	503
In patients at high risk of gastrointestinal bleeding, VKA or another NOAC should be preferred over dabigatran 150 mg BD or rivaroxaban 20 mg OD, or edoxaban 60 mg OD.	IIa	B	328, 407, 413, 418, 503, 505, 506, 526
Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for oral anticoagulation.	IIa	C	
Genetic testing prior to the initiation of VKA therapy is not recommended.	III (no benefit)	B	511
Reinitiation of oral anticoagulation 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	470
In AF patients with severe active bleeding events, it is recommended to interrupt oral anticoagulation therapy until the underlying cause is resolved.	I	C	

1681 AF = atrial fibrillation; GI = gastrointestinal; VKA = vitamin K antagonist

1682 ^a Class of recommendation1683 ^b Level of evidence1684 ^c Reference(s) supporting recommendation(s)

1685

1686 8.7 Combination therapy with oral anticoagulants and antiplatelets

1687 Approximately 15% of AF patients in contemporary trials⁵²⁷ and registries⁵²⁸⁻⁵³⁰ have a history of
1688 a prior myocardial infarction. 5–15% of AF patients will require stenting at some point in their
1689 lives. This scenario requires careful consideration of antithrombotic therapy, balancing bleeding
1690 risk, stroke risk, and the risk of acute coronary syndromes (ACS).⁵³⁰ Co-prescription of OAC
1691 with antiplatelet therapy, in particular triple therapy, increases the absolute risk of major
1692 haemorrhage.^{455, 531, 532} A recent meta-analysis comprising 30,866 patients with a recent ACS

evaluated the effects of adding NOAC therapy to single (4,135 patients) or dual (26,731 patients) antiplatelet therapy.⁵³³ NOAC addition increased the bleeding risk by 79-134%, while reducing recurrent ischemic events only marginally in patients without AF. In AF patients with stable coronary artery disease but without an ACS and/or coronary intervention in the last 12 months, OAC monotherapy is recommended, and not combination therapy with antiplatelets. In patients treated for ACS and in those receiving a coronary stent, short-term triple combination therapy of OAC, clopidogrel and aspirin seems warranted (Figure 12).

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8.7.1 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 PCI is not known, but the continued bleeding risk suggests a short duration. Expert consensus⁵³⁴, reviewed and reconsidered by this task force, suggests the following principles: AF patients at risk for stroke, patients with mechanical valves, and 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 single antiplatelet, Figure 13). Where a NOAC is used, the consensus recommendation is that the lowest dose that is effective for stroke prevention in AF should be considered. Dose reduction beyond the dosing regimes 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.⁵³⁵

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 with aspirin plus clopidogrel), given the lack of evidence and the greater risk of major bleeding observed with clopidogrel.^{536, 537} 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 trial randomizing 573 anticoagulated patients undergoing PCI (70% with AF) either to dual therapy with OAC and clopidogrel (75 mg daily), or to triple therapy with OAC, clopidogrel, and aspirin.⁵³⁸ Bleeding was lower in the dual than in the triple therapy arm, driven by less minor bleeding. The rates of myocardial infarction, stroke, target vessel revascularization, or stent thrombosis did not differ (albeit with low event numbers), but all-cause mortality was lower in the dual therapy group at 1 year (2.5% vs. triple 6.4%). Although the trial was too small to

1726 assess ischaemic outcomes, dual therapy with OAC and clopidogrel may emerge in the future
 1727 as an alternative to triple therapy in patients with AF and ACS and/or coronary intervention.⁵³⁹

1728

1729 Recommendations for combination therapy

1730

Recommendations	Class ^a	Level ^b	Refs ^c
After elective coronary stenting with 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 ischemic events.	Ila	B	536, 538
After an acute coronary syndrome with stent insertion 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 ischemic events.	Ila	C	540
After an acute coronary syndrome without stent insertion 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 ischemic events.	Ila	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.	Ila	B	540
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	538, 539

1731 ACS = acute coronary syndromes; AF = atrial fibrillation.

1732 ^a Class of recommendation

1733 ^b Level of evidence

1734 ^c Reference(s) supporting recommendation(s)

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9. Rate control therapy in AF

Rate control is an integral part of the management in AF patients, and is often sufficient to improve AF-related symptoms. Compared to stroke prevention and rhythm control, very little robust evidence exists to inform the best type and intensity of rate control treatment, with the majority of data derived from short-term crossover trials and observational studies.^{41, 541-543} Pharmacological rate control can be achieved with beta-blockers, digoxin, the calcium channel blockers diltiazem or verapamil, or combination therapy, both for patients requiring acute and long-term rate control (see Table 15). A number of antiarrhythmic drugs also have rate-limiting properties (amiodarone, dronedarone, sotalol and to some extent propafenone), but they should only be used in patients needing rhythm control therapy (see Chapter 10)

9.1 Acute rate control

In the setting of acute new-onset AF, patients are often in need of heart rate control. Physicians should evaluate underlying causes of elevated heart rate, such as infection, endocrine imbalance, anaemia and pulmonary embolism. For acute rate control, beta-blockers and diltiazem/verapamil are preferred over digoxin due to their rapid onset of action and effectiveness at high sympathetic tone.⁵⁴³⁻⁵⁴⁷ The choice of agent (see Table 15) and target heart rate will depend on patient characteristics, symptoms, LVEF and haemodynamics, but a lenient initial approach seems acceptable. Combination therapy may be required (see Figure 14). In patients with evidence of HFrEF, beta-blockers, digitalis (digoxin or digitoxin) or their combination should be used,^{217, 548} as diltiazem and verapamil can have negative inotropic effects in patients with LVEF <40%.^{221, 549, 550} In critically ill patients and those with severely impaired left ventricular systolic function, intravenous amiodarone can be used where excess heart rate is leading to haemodynamic instability.⁵⁵¹⁻⁵⁵³ Urgent cardioversion should be considered in unstable patients (see Chapter 10.2).

9.2 Long-term pharmacological rate control

Beta adrenoreceptor blocker monotherapy is often the first-line rate-controlling agent,⁵⁵⁴ largely based on observations of better acute heart rate control than digoxin. Interestingly, the prognostic benefit of beta blockers seen in HFrEF patients with sinus rhythm is lost in those with AF. In an individual patient-level meta-analysis of RCTs, beta-blockers did not reduce all-cause mortality compared to placebo in those with AF at baseline (hazard ratio 0.97; 0.83–1.14; P =

0.73), while there was a clear benefit in patients with sinus rhythm (hazard ratio 0.73; 0.67–0.80; $P < 0.001$).²³ The study included 3066 participants with HFrEF and AF, showed consistency across all subgroups and outcomes, with no heterogeneity between the ten RCTs included ($I^2=0\%$). Despite this lack of prognostic benefit in HFrEF, this Taskforce still considers beta-blockers as a useful first-line rate control agent across all AF patients, based on the potential for symptomatic and cardiac function improvement as a result of rate control, the lack of harm from published studies and the good tolerability profile across all ages in sinus rhythm and AF.^{23, 555}

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Verapamil or **diltiazem** provide reasonable rate control in AF patients.⁵⁵⁶ They should be avoided in patients with HFrEF due to their negative inotropic effects.^{221, 549, 550} Verapamil or diltiazem can improve arrhythmia-related symptoms⁵⁴¹, in comparison to beta-blockers which reduced exercise capacity and increased BNP in one small trial of low-risk patients with preserved LVEF.⁵⁵⁷

1783

Cardiac glycosides, such as **digoxin** and **digitoxin**, have been in use for over two centuries⁵⁵⁸, although prescriptions have been steadily declining over the past 15 years.⁵⁵⁹ In the randomized DIG trial, digoxin had no impact on mortality compared to placebo in HFrEF patients in sinus rhythm (risk ratio 0.99; 95% CI 0.91–1.07), but reduced hospital admissions (risk ratio 0.72; 95% CI 0.66–0.79).^{560, 561} There have been no head-to-head RCTs of digoxin in AF patients.⁵⁶² Observational studies have associated digoxin use with excess mortality in AF patients⁵⁶³⁻⁵⁶⁵, but this association is likely due to selection and prescription biases rather than harm caused by digoxin,⁵⁶⁶⁻⁵⁶⁹ particularly as digoxin is commonly prescribed to sicker patients.²²⁴ In a crossover mechanistic trial of 47 patients with HFrEF and AF, there were no differences in heart rate, blood pressure, walking distance or LVEF between carvedilol and digoxin, although beta-blockers did result in higher BNP levels, combination carvedilol/digoxin improved LVEF, and digoxin withdrawal reduced LVEF.⁵⁷⁰ Comparisons with other rate control therapy are based on small, short duration studies that identify no or marginal differences in exercise capacity, quality of life or LVEF compared to digoxin.^{541, 570-574} Lower doses of digoxin (≤ 250 micrograms daily), corresponding to serum digoxin levels of 0.5-0.9 ng/mL, may be associated with better prognosis.²²⁴

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

In summary, there is equipoise for the use of different rate control agents in AF. The choice of beta-blocker, diltiazem/verapamil, digoxin or combination therapy should be made on an individual basis, after consideration of patient characteristics and patient preference. All available therapies have the potential for adverse effects and patients should initially be treated with a low dose and uptitrated to achieve symptom improvement. In practice, achieving a heart rate <110 bpm will often require combination therapy (Figure 15). The benefit of different rate control strategies on symptoms, quality of life and other intermediate outcomes are under investigation.⁵⁷⁵

9.3 Heart rate targets in AF

The optimal heart rate target in AF patients is unclear. The RACE II study randomized 614 patients with permanent AF to either a target heart rate <80 bpm at rest and <110 bpm during moderate exercise, or to a lenient heart rate target < 110 bpm. There was no difference in a composite of clinical events (14.9% in the strict rate control group, 12.9% in the lenient group)⁵⁷⁶, NYHA class or hospitalizations.^{576, 577} Similar results were found in a pooled analysis of the AFFIRM and RACE trials (1091 participants), albeit with smaller heart rate differences and without randomization.⁵⁷⁸ It is worthwhile to note that many 'adequately rate controlled' patients (resting heart rate 60–100 bpm) are severely symptomatic, calling for additional management.¹⁹³ Nonetheless, lenient rate control is an acceptable initial approach, regardless of HF status, unless symptoms call for stricter rate control.

9.4 Atrioventricular node ablation and pacing

Ablation of the atrioventricular (AV) node / His bundle and implantation of a VVI pacemaker can control ventricular rate when medications fail to control rate and symptoms. It is a relatively simple procedure with a low complication rate and low long-term mortality risk^{579, 580}, especially when the pacemaker is implanted a few weeks prior to the AV nodal ablation and the initial pacing rate after ablation is set at 70-90 bpm.^{581, 582} The procedure does not worsen LV

function⁵⁸³ and may even improve LVEF in selected patients.⁵⁸⁴⁻⁵⁸⁶ In some patients in heart failure treated with biventricular pacing (CRT), AF can terminate⁵⁸⁷, although such a “rhythm control” effect of CRT is likely to be small and clearly needs confirmation.⁵⁸⁸ AV nodal ablation renders patients pacemaker-dependent for the rest of their lives, limiting AV nodal ablation and pacing to patients whose symptoms cannot be managed by rate controlling medication or by reasonable rhythm control interventions. The choice of pacing therapy (right ventricular or biventricular pacing with or without implantable defibrillator) will depend on individual patient characteristics including LVEF.^{589, 590}

1841

1842 Recommendations for rate control

Recommendations	Class ^a	Level ^b	Refs ^c
Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF $\geq$ 40%.	I	B	224, 541, 543, 546, 547, 556, 591, 592
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF <40%.	I	B	23, 224, 548, 570, 592-594
Combination therapy of different rate controlling agents should be considered if a single agent does not achieve the necessary heart rate target.	IIa	C	23, 570, 595
In cases of haemodynamic instability or severe depression in LVEF, amiodarone may be considered for acute control of heart rate.	IIb	B	551-553
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, 596, 597
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	576
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	183, 580, 585

1843 AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction. In
 1844 patients with HFrEF (LVEF <40%), recommended beta-blockers are bisoprolol, carvedilol, long-
 1845 acting metoprolol and nebivolol. Digoxin is a suitable alternative to digoxin, where available.

1846 ^a Class of recommendation

1847 ^b Level of evidence

1848 ^c Reference(s) supporting recommendation(s)

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1852 TABLE 15: Rate control therapy in AF

1853

Therapy	Acute intravenous rate control	Long-term oral rate control	Side effect profile	Comments
Beta-blockers				
Bisoprolol	N/A	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	N/A	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	N/A		
Calcium-channel blockers				
Diltiazem	15–25 mg intravenous bolus (repeated as required)	60 mg 3 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 left ventricular failure with pulmonary congestion or LVEF <40%.
Verapamil	2.5–10 mg intravenous bolus (repeated as required)	40–120 mg 3 times daily (120–480 mg once daily modified release)		
Cardiac glycosides				
Digoxin	0.5 mg intravenous bolus (0.75–1.5 mg over 24 hours 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	High plasma levels associated with increased risk of death. Check renal function before starting and adapt dose in patients with

Digitoxin	0.4–0.6 mg intravenous bolus	0.05–0.3 mg daily dose	ng/mL), digoxin is proarrhythmic and can aggravate heart failure, particularly with co-existent hypokalaemia.	chronic kidney disease. Contraindicated in accessory conducting pathways, ventricular tachycardia and hypertrophic cardiomyopathy with outflow tract obstruction.
Specific indications				
Amiodarone	300 mg intravenously diluted in 250 mL 5% dextrose over 30–60 minutes (preferably via central venous cannula) *	200 mg daily	Hypotension, bradycardia, nausea, QT prolongation, pulmonary toxicity, skin discoloration, thyroid dysfunction, corneal deposits and cutaneous reaction with extravasation.	Suggested as adjunctive therapy in patients where heart rate control cannot be achieved by combination therapy.

1854 AF = atrial fibrillation. A number of other beta-blockers are also available, but not
1855 recommended as specific rate control therapy in AF, such as atenolol (25-100 mg once daily
1856 with a short biological half-life), propranolol (nonselective, 1 mg over 1 minute and repeat up to
1857 3 mg at 2 minute intervals [acute] or 10-40 mg three times daily [long-term]), or labetalol
1858 (nonselective, 1–2 mg/minute [acute]). * If ongoing requirement for amiodarone, follow with 900
1859 mg intravenous over 24 hours diluted in 500–1000 mL via a central venous cannula.
1860

10. Rhythm control therapy in AF

Restoring and maintaining sinus rhythm is an integral part of AF management. Antiarrhythmic drugs (AAD) approximately double the sinus rhythm rate compared to placebo.⁵⁹⁸⁻⁶⁰² Catheter ablation or combination therapy is often effective when antiarrhythmic drugs fail.^{225, 603-605} Although many clinicians believe that maintaining sinus rhythm can improve outcomes in AF patients,⁶⁰⁶ all trials that have compared rhythm control therapy to rate control (with appropriate anticoagulation) have resulted in neutral outcomes.^{41, 597, 600, 607-612} Whether modern rhythm control management involving catheter ablation, combination therapy, and early therapy, leads to a reduction in major cardiovascular events (e.g. stroke and cardiovascular death) is currently under investigation (e.g. in the EAST⁴⁰ and CABANA⁶¹³ trials). For now, rhythm control therapy is indicated to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy.

10.1 Acute restoration of sinus rhythm

10.1.1 Antiarrhythmic drugs (AAD) for acute restoration of sinus rhythm ('pharmacological cardioversion')

AAD can restore sinus rhythm in patients with AF (pharmacological cardioversion) as shown in small controlled trials, meta analyses^{41, 602, 614, 615} and a few larger controlled trials.⁶¹⁶⁻⁶²⁴

Outside of Europe, dofetilide is available and can convert recent-onset AF.⁶²⁵ Pharmacological cardioversion using different AADs (Table 16) restores sinus rhythm in approximately 50% of patients with recent-onset AF.⁶²⁶⁻⁶²⁸ In the short term, electrical cardioversion restores sinus rhythm quicker and more effectively than pharmacological cardioversion and is associated with shorter hospitalization.⁶²⁸⁻⁶³² Pharmacological cardioversion, conversely, does not require sedation or fasting (Figure 16).

Flecainide and propafenone are effective for pharmacological cardioversion^{614, 621-624, 633, 634}, but their use is largely restricted to patients without structural heart disease. Ibutilide is an alternative where available, but carries a risk of torsades de pointes.⁶³⁴ Vernakalant⁶²¹⁻⁶²⁴ can be given to patients with mild heart failure (NYHA Class I-II) or a history of ischaemic heart disease.⁶³⁵⁻⁶³⁷ Amiodarone can be used in patients with heart failure and in patients with ischaemic heart disease (though patients with severe heart failure were excluded in most of AF

cardioversion trials).⁶¹⁵ Amiodarone also slows heart rate by 10–12 bpm on average, but restores sinus rhythm more slowly (8–12 hours when given intravenously).⁶¹⁵ Both amiodarone and flecainide appear more effective than sotalol in restoring sinus rhythm.^{619, 620, 638}

10.1.2 ‘Pill in the pocket’ cardioversion performed by patients

In selected patients with infrequent symptomatic episodes of paroxysmal AF, a single bolus of oral flecainide (200–300 mg), or propafenone (450–600 mg) can be self-administered by the patient at home (‘pill in the pocket’ therapy) to restore sinus rhythm, after safety has been established in the hospital setting.⁶³⁹ This approach seems marginally less effective than hospital-based cardioversion, or continuous AAD,⁶⁴⁰ but is practical and provides control and reassurance to selected patients.

1906 **TABLE 16: Antiarrhythmic drugs for pharmacological cardioversion**

Drug	Route	1 st dose	Follow-up dose	Risks	Reference
Flecainide	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	614, 617
	IV	1.5 - 2 mg/kg over 10 min			
Amiodarone	IV*	5–7 mg/kg over 1–2 hours	50 mg/hour to a maximum of 1.0 gr over 24 hours	Phlebitis, hypotension, bradycardia/AV block. Will slow ventricular rate. Delayed conversion to sinus rhythm (8–12 hours)	615-620
Propafenone	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 conduction, QRS prolongation (mild)	641-644
	Oral	450–600 mg			
Ibutilide	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.	633, 634
Vernakalant	IV	3 mg/kg over 10 min	2 mg/kg over 10 min after waiting for 15 min	Avoid in patients with SBP <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	621-624, 637

1907 * use a large peripheral vessel and change to oral amiodarone within 24 hours of IV (central
 1908 line) administration. Ibutilide is only available in selected European countries.

1909 ACS = acute coronary syndrome; AV = atrioventricular; IHD = ischaemic heart disease; IV =
 1910 intravenous; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; SBP =
 1911 systolic blood pressure

1912

10.1.3 Electrical cardioversion

Synchronized direct current electrical cardioversion quickly and effectively converts AF to sinus rhythm and is the method of choice in severely haemodynamically compromised patients with new-onset AF (Figure 16).⁶⁴⁵⁻⁶⁴⁷ Electrical cardioversion can be safely performed in sedated patients treated with intravenous midazolam and/or propofol. Continuous monitoring of blood pressure and oximetry during the procedure is important. Skin burns may be occasionally observed. Intravenous atropine or isoproterenol or temporary transcutaneous pacing should be available to mitigate post-cardioversion bradycardia. Biphasic defibrillators are more effective than monophasic wave forms, and have become industry standard.^{645, 647} Anterior-posterior electrode positions generate a stronger shock field in the left atrium than anterolaterally positioned electrodes, and restore sinus rhythm more effectively.^{645, 646, 648}

Pre-treatment with amiodarone (requiring a few weeks of therapy),^{649, 650} sotalol⁶⁴⁹, ibutilide⁶⁵¹, or vernakalant⁶⁵² can improve efficacy of electrical cardioversion, and similar effects are likely for flecainide⁶⁰² and propafenone⁶⁵³. Neither beta-blockers,⁶⁵⁴ verapamil, diltiazem⁶⁵⁵⁻⁶⁵⁷, nor digoxin^{658, 659} terminate AF or facilitate electrical cardioversion. When AAD therapy is planned to maintain sinus rhythm after cardioversion, it seems prudent to start therapy 1-3 days before cardioversion (amiodarone: a few weeks), to promote pharmacological conversion and to achieve effective drug levels.^{602, 620}

10.1.4 Anticoagulation in patients undergoing cardioversion

Cardioversion carries an inherent risk of stroke in non-anticoagulated patients⁶⁶⁰ which is substantially reduced by anticoagulation.⁶⁶¹ Immediate initiation of OAC is important in all patients scheduled for cardioversion.⁶⁶²⁻⁶⁶⁴ Patients who have been in AF for longer than 48 hours should start oral anticoagulation at least 3 weeks before cardioversion and continue it for 4 weeks after cardioversion (in patients without a need for long-term anticoagulation), and indefinitely in patients at risk of stroke. This practice has never been evaluated in controlled trials, but seemed safe in a large observational data set from Finland.⁶⁶⁵ When early cardioversion is desired, transoesophageal echocardiography can exclude the majority of left atrial thrombi allowing immediate cardioversion.⁶⁶⁶ Ongoing studies will inform about the safety and efficacy of newly initiated anticoagulation using NOACs in patients scheduled for electrical cardioversion.

10.2 Long-term antiarrhythmic drug therapy

The aim of AAD therapy is improvement of AF-related symptoms.^{41, 598} Hence, the decision to initiate long-term AAD therapy needs to balance symptom burden, possible adverse drug reactions, and patient preferences. The principles of AAD therapy outlined in the 2010 ESC AF guidelines³⁷⁶ are still relevant and should be observed:

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

Antiarrhythmic drug therapy approximately doubles sinus rhythm maintenance compared to no therapy.⁵⁹⁸ There is no appreciable effect on mortality or cardiovascular complications, but rhythm control therapy can slightly increase hospitalizations (often for AF).^{41, 597, 600, 607-612} To reduce the risk of side effects^{200, 598}, a shorter duration of AAD therapy seems desirable. As an example, short-term treatment (4 weeks) with flecainide for four weeks after cardioversion of AF was well-tolerated and prevented most (80%) AF recurrence when compared to long-term treatment.⁶⁰² Short-term antiarrhythmic drug therapy is also used to avoid early AF recurrences after catheter ablation⁶⁶⁷ and may be reasonable in patients deemed at increased risk of AAD side effects or in those with a low perceived risk of recurrent AF.

In addition to AAD therapy and catheter ablation (see below), management of concomitant cardiovascular conditions can reduce symptom burden in AF and facilitate maintenance of sinus rhythm.^{202, 203, 302, 318} This includes weight reduction, blood pressure control, heart failure treatment, increasing cardiorespiratory fitness, and other measures (see Chapter 6).

10.2.1 Selection of antiarrhythmic drugs for long-term therapy: Safety first!

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

Amiodarone is an effective multi-channel blocker, reduces ventricular rate, and is safe in patients with heart failure.^{600, 668} Torsades de pointes proarrhythmia can occur, and QT interval and TU waves should be monitored on therapy (see below).⁶⁶⁹ Amiodarone often causes extracardiac side effects common especially on long-term therapy,^{670, 671} rendering amiodarone a second-line treatment in patients who are suitable for other AADs. Amiodarone appears less suitable to episodic short term therapy (unless after catheter ablation),⁶⁷² probably due to its long biological half life.

Dronedarone maintains sinus rhythm, reduces ventricular rate, and prevents cardiovascular hospitalizations (mostly due to AF) and cardiovascular death in patients with paroxysmal or persistent AF or flutter who had at least one relevant cardiovascular comorbidity.^{601, 606, 673} Dronedarone increases mortality in patients with recently decompensated heart failure (with or without AF),⁶⁷⁴ and in patients with permanent AF in whom sinus rhythm is not restored.⁶⁷⁵ Dronedarone moderately increases serum creatinine, reflecting a reduction in creatinine excretion rather than a decline in kidney function.⁶⁷⁶

Flecainide and **propafenone** are effective in preventing recurrent AF.^{599, 602, 639} They should only be used in patients without significant ischaemic heart disease or heart failure to avoid the risk of life-threatening ventricular arrhythmias.⁶⁷⁷ High ventricular rates resulting from the conversion of AF into atrial flutter with 1:1 conduction by flecainide or propafenone can be prevented by pre-administering a beta-blocker, verapamil, or diltiazem.

Quinidine and **disopyramide** have been associated with an increase in all-cause mortality (OR 2.39; 95% CI 1.03–5.59; NNH 109; 95% CI 34–4985) at 1 year follow-up,^{598, 678} likely due to ventricular arrhythmias (torsades de pointes).^{598, 678} Although this proarrhythmic effect is more common at higher doses, they are less commonly used for rhythm control in AF. Disopyramide may be useful in 'vagally mediated' AF (e.g. AF occurring in athletes and/or during sleep⁷⁶) and has been shown to reduce left ventricular outflow gradient and improve symptoms in patients with hypertrophic cardiomyopathy.⁶⁷⁹⁻⁶⁸¹

Sotalol has a relevant risk of torsades de pointes (1% in the PAFAC trial¹¹⁸). Its d-enantiomer is associated with an increased mortality compared to placebo in patients with left ventricular dysfunction post-myocardial infarction,⁶⁸² probably due to ventricular arrhythmias (OR 2.47; 95% CI 1.2–5.05; NNH 166; 95% CI 61–1159).^{598, 682} On the other hand, d,l sotalol has been used in AF patients without safety signals in two controlled trials.^{599, 620}

Dofetilide is another potassium channel blocker that is mainly available outside of Europe. Dofetilide restores and maintains sinus rhythm in heart failure patients⁶⁸³ and occasionally in patients refractory to other antiarrhythmic drugs.⁶⁸⁴

Overall, it seems prudent to limit the use of quinidine, disopyramide, dofetilide, or sotalol to specific situations. Similarly, combinations of QT prolonging AADs should generally be avoided (see Table 17).

2015

10.2.2 The 12-lead ECG as a tool to identify patients at risk for proarrhythmia

Identifying patients at risk for proarrhythmia can help to mitigate the proarrhythmic risk of AADs.⁶⁸⁵ In addition to the clinical characteristics mentioned above, monitoring PR, QT and QRS durations during initiation of AAD therapy can identify patients at higher risk for drug-induced proarrhythmia on longer-term treatment.⁶⁸⁶⁻⁶⁸⁸ In addition, the presence of 'abnormal TU waves' is a sign of imminent torsades de pointes.⁶⁸⁹ Periodic ECG analysis for proarrhythmia signs has been successfully used in recent AAD trials.^{118, 602, 689} Specifically, ECG monitoring was systematically used on days 1–3 in patients receiving flecainide, propafenone, or sotalol to identify patients who are at risk of proarrhythmia.^{118, 602, 620} Based on this evaluated practice, this Task Force suggests that an ECG should be recorded in all patients before initiation of AAD. Repeat ECGs should be considered 1-3 days after initiation of therapy with flecainide, propafenone, or sotalol (see Table 17). In patients on dronedarone or amiodarone, a repeat ECG at one and four weeks after initiation of therapy seems reasonable.

2029

TABLE 17: Oral AADs used for maintaining sinus rhythm after cardioversion.

Drug	Dose	Main contraindications and precautions	Warning signs warranting discontinuation	AV 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 SAN or AV node and conduction disease. The dose of vitamin K antagonists 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–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 creatinine clearance <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 creatinine clearance <50 mg/mL, liver disease, ischemic heart disease or reduced LVEjection fraction. Caution in the presence of SAN or AV node or conduction system disease. CYP2D6 inhibitors (eg	QRS duration increases >25% above baseline	None	baseline, day 1, day 2-3
Flecainide slow release	200 mg once daily				
Propafenone	150–300 mg three times daily	Contraindicated in IHD or reduced LVEjection fraction. Caution in the presence of SAN or AV node and conduction system disease, renal or liver impairment, and asthma. Increases concentration of	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, creatinine clearance <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

2031 AAD = antiarrhythmic drug; AF = atrial fibrillation; AV = atrioventricular; bpm = beats per minute;

2032 IHD = ischaemic heart disease; LV = left ventricular; NYHA = New York Heart Association; SAN

2033 = sinoatrial node

2034

10.2.3 New antiarrhythmic drugs

Several compounds that inhibit the ultrarapid potassium current (I_{Kur}) and other inhibitors of atypical ion channels are in clinical development.⁶⁹⁰⁻⁶⁹² They are not available for clinical use at present. The antianginal compound ranolazine inhibits potassium and sodium currents and increases glucose metabolism at the expense of free fatty acid metabolism, thereby enhancing efficient use of oxygen.^{693, 694} Ranolazine was safe in patients with non–ST segment elevation myocardial infarction and unstable angina evaluated in the MERLIN trial.⁶⁹⁵ In a post-hoc analysis of continuous ECG recordings obtained during the first 7 days after randomization, patients assigned to ranolazine tended to have fewer episodes of AF (75 [2.4%] vs. 55 [1.7%] patients, $P = 0.08$).⁶⁹⁶ In the HARMONY trial the highest tested dose of a combination of ranolazine (750 mg *b.i.d.*) and dronedarone (225 mg *b.i.d.*) slightly reduced AF burden in 134 subjects with paroxysmal AF and dual chamber pacemakers.⁶⁹⁷ Small, open-label studies suggest that ranolazine might enhance the antiarrhythmic effect of amiodarone for cardioversion⁶⁹⁸⁻⁷⁰⁰, while a controlled trial of ranolazine and the ranolazine-dronedarone combination to prevent atrial high rate episodes in pacemaker patients was ambiguous.⁷⁰¹ At present, there is insufficient evidence to recommend ranolazine as an AAD, alone or in combination with other AADs. Of note, the “funny channel blocker” ivabradine, which is used for angina and heart failure, increases the risk of AF.⁷⁰²

10.2.4 Antiarrhythmic effects of non-antiarrhythmic drugs

ACEI or ARB appear to prevent new-onset AF in patients with left ventricular dysfunction and in hypertensive patients with LV hypertrophy.^{218, 235, 236, 238, 703-707} Neprilysin inhibition needs to be studied further, but does not seem to enhance this effect.²²³ A Danish cohort study also suggested that initial treatment of uncomplicated hypertension with ACEI or ARB reduces incident AF compared to other hypertensive agents.²⁴⁴ ARB therapy did not reduce the AF burden in patients with AF without structural heart disease.²⁴⁰ Thus, ACEI or ARB are unlikely to have a relevant direct antiarrhythmic effect. However, it might be justified to consider adding ACEI or ARB therapy to AAD to reduce AF recurrences after cardioversion.^{247, 248, 708}

Compared to placebo, beta-blockers are associated with a reduced new-onset AF in patients with reduced ejection fraction and sinus rhythm.⁷⁰⁹ Beta-blockers have also been reported to reduce symptomatic AF recurrences,^{598, 654, 710} but this finding may be driven by the beneficial effect of rate control which will render AF more often asymptomatic.

Perioperative statin therapy appeared to reduce postoperative AF by a number of small randomized clinical trials;^{711, 712} however, an adequately powered placebo-controlled trial has shown no impact of perioperative rosuvastatin therapy on postoperative AF.^(Add ref when published <http://www.escardio.org/about/press/press-releases/esc14-barcelona/Pages/hotline-five-stics.aspx>) Similarly, statin treatment does not prevent AF in other settings.^{713, 714} Similarly, polyunsaturated fatty acids failed to show convincing benefit.^{240, 715-719} The role of aldosterone antagonists in the management of AF has not been extensively investigated in humans; although preliminary evidence from trials of eplerenone are encouraging for primary prevention²⁴², at present there is no robust evidence to make any recommendation for the use of aldosterone antagonists for secondary prevention of AF.⁷²⁰⁻⁷²²

2077

2078 Recommendations for rhythm control therapy

Recommendations	Class ^a	Level ^b	Refs ^d
General recommendations			
Management of cardiovascular risk factors and avoidance of AF triggers should be pursued in patients on rhythm control therapy in order to facilitate maintenance of sinus rhythm.	Ia	B	202, 203, 302, 318 <i>2 further RCTs due to publish in summer (CAST, AMICA)</i>
Rhythm control therapy is indicated for symptom improvement in patients with AF.	I	B	120, 604, 723
With the exception of AF associated with haemodynamic instability, the choice between electrical and pharmacological cardioversion should be guided by patient and physician preference.	Ia	C	
Cardioversion of AF			
Electrical cardioversion of AF is recommended in patients with acute hemodynamic instability to acutely restore cardiac output.	I	B	631, 724-726
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	602, 620, 646, 666, 727, 728
Pre-treatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to enhance success of electrical cardioversion and prevent recurrent AF.	Ia	B	602, 651, 729

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	621-624, 633, 637, 730-732
In patients with no history of ischaemic or structural heart disease, ibutilide should be considered for pharmacological conversion of AF.	IIa	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.	IIa	B	639, 640
In patients with ischaemic and/or structural heart disease, amiodarone is recommended for cardioversion of AF.	I	A	616-620
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).	IIb	B	621-624, 635, 637
Stroke prevention in patients designated for cardioversion of AF			
Anticoagulation with heparin or a NOAC should be initiated as soon as possible prior to every cardioversion of AF or atrial flutter.	IIa	B	733, 734
For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of three weeks prior to cardioversion.	I	B	666, 733
Transoesophageal echocardiography is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned.	I	B	666, 733
Early cardioversion can be performed without a TOE in patients with a definite duration of AF <48 hours.	IIa	B	666
In patients at risk for stroke (e.g. presence of CHA ₂ DS ₂ -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	360, 735
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 prior to cardioversion.	IIa	C	
AAD for the long-term maintenance of sinus rhythm/prevention of recurrent AF			
The choice of AAD 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, 598

Dronedarone, 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	599, 601, 602, 606, 620
Dronedarone is recommended for prevention of recurrent symptomatic AF in patients with stable coronary artery disease, and without heart failure.	I	A	601, 606
Amiodarone is recommended for prevention of recurrent symptomatic AF in patients with heart failure.	I	B	615-617
Amiodarone is more effective in preventing AF recurrences than other AAD but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first.	IIa	C	615-617
Patients on AAD therapy should be periodically evaluated to confirm their eligibility for treatment.	IIa	C	601, 606, 674, 675, 677
ECG recording during the initiation of AAD therapy should be considered to monitor heart rate, detect QRS and QT interval prolongation and the occurrence of AV block.	IIa	B	602 600, 601, 606, 620
AAD therapy is not recommended in patients with prolonged QT interval (>0.5 s) or those with significant sinoatrial node disease or AV 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 AAD therapy in patients in whom AF ablation is declined or not indicated.	IIa	B	736, 737
Continuation of AAD therapy beyond the blanking period after AF ablation should be considered to maintain sinus rhythm when recurrences seem likely.	IIa	B	738
Antiarrhythmic effects of non-antiarrhythmic drugs			
ACEI, ARB and beta-blockers should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.	IIa	A	23, 218, 235, 236, 238, 703-705
ACEIs and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with left ventricular hypertrophy.	IIa	B	237, 705, 707, 739
Pre-treatment with ACEIs or ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion and receiving antiarrhythmic drug therapy.	IIb	B	235, 236, 247, 248

ARBs or ACEIs are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.	III (no benefit)	B	240, 718
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2079 AAD = antiarrhythmic drug; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial
 2080 fibrillation; ARB = angiotensin receptor blocker; AV = atrioventricular; CHA₂DS₂-VASc =
 2081 Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled),
 2082 Vascular disease, Age 65–74, and Sex (female); ECG = electrocardiogram; NOAC = non-
 2083 vitamin K antagonist oral anticoagulant; TOE = transoesophageal echocardiography

2084 ^a Class of recommendation

2085 ^b Level of evidence

2086 ^c Reference(s) supporting recommendation(s)

2087

2088

2089 10.3 Catheter ablation

2090 Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF,⁷⁴⁰
 2091 catheter ablation of AF has developed from a specialized, experimental procedure into a
 2092 common treatment to prevent recurrent AF.^{605, 741} This is primarily achieved through isolation of
 2093 the pulmonary veins, probably requiring complete isolation for full effectiveness⁷⁴², and
 2094 additional ablation in the posterior left atrial wall. AF ablation, when performed in experienced
 2095 centres by adequately trained teams, is more effective than antiarrhythmic drug therapy in
 2096 maintaining sinus rhythm, and the complication rate, though not negligible, is comparable to the
 2097 complication rate of AAD.^{603, 743}(Add five year MANTRA_PAF data when published)

2098

2099 10.3.1 Indications

2100 Catheter ablation of AF is effective in restoring and maintaining sinus rhythm patients with
 2101 symptomatic paroxysmal, persistent, and probably long-standing persistent AF - in general as
 2102 second-line treatment after failure of or intolerance to antiarrhythmic drug therapy (AAD). In
 2103 such patients, catheter ablation is more effective than antiarrhythmic drug therapy.^{184, 604, 738, 743-}
 2104 ⁷⁴⁶ As first-line treatment for paroxysmal AF, randomized trials showed only modestly improved
 2105 rhythm outcome with catheter ablation compared to AAD therapy.^{603, 747-749} Complication rates
 2106 were similar, but ablation was performed in expert centres, justifying catheter ablation as first
 2107 line therapy in selected patients with paroxysmal AF who ask for interventional therapy. There is

less data reporting the effectiveness and safety of catheter ablation in patients with persistent or long-standing persistent AF, but all point to lower recurrence rates after catheter ablation compared to AAD therapy with or without cardioversion.^{184, 743, 749-752} **add systematic review** In patients who suffer from symptomatic recurrences of AF despite antiarrhythmic drug therapy, all randomized controlled trials showed better sinus rhythm maintenance with catheter ablation than on AAD.^{604, 738, 753, 754} There is no current indication for catheter ablation to prevent cardiovascular outcomes (or desired withdrawal of anticoagulation), or to reduce hospitalization.^{40, 613}

2116

2117 10.3.2 Techniques and technologies

Complete pulmonary vein isolation (PVI) on an atrial level is the best documented target for catheter ablation^{742, 755-757}, achievable by point-by-point radiofrequency ablation, linear lesions encircling the pulmonary veins, or cryoballoon ablation with similar outcomes.⁷⁵⁸⁻⁷⁶⁰ Complete isolation of the pulmonary veins has better rhythm outcomes than incomplete isolation.⁷⁴² Pulmonary vein isolation was initially tested in patients with paroxysmal AF, but appears to be non-inferior to more extensive ablation in persistent AF as well.^{761, 762} More extensive ablations have been used in patients with persistent AF, but there is insufficient data to guide the use of these at present.^{107, 744, 745, 762-764} Extended ablation procedures (beyond PVI) consistently require longer procedures and more ionizing radiation, potentially creating risk for patients. Left atrial macro-reentrant tachycardia is relatively uncommon after pulmonary vein isolation ($\approx 5\%$), and seems even less common after cryoballoon ablation⁷⁶⁰, but may occur in up to 25% of patients after left atrial substrate modification ablation, often due to incomplete ablation lines. Thus, for patients with persistent AF, ablation of complex fractionated electrograms (CFAE) or routine deployment of linear lesions or other additional ablations does not seem justified in the first procedure.^{762, 765} However, additional ablation on top of complete PVI⁷⁴² may be considered in patients with recurrent AF after the initial ablation procedure.^{745, 766, 767} In patients with documented right atrial isthmus dependent flutter undergoing AF ablation, right atrial isthmus ablation is recommended. Adenosine testing to identify patients in need for additional ablation remains controversial after evaluation in two controlled trials.^{768, 769} Ablation of so-called 'rotors' guided by body surface mapping or endocardial mapping is under evaluation and cannot be recommended for routine clinical use at present.

2139

2140 10.3.3 Outcome and complications

2141 The rhythm outcome after catheter ablation of AF is difficult to predict in individual patients.^{172,}
 2142 ^{226, 738, 754} Most patients require more than one procedure to achieve symptom control. ^{738, 752, 754}
 2143 In general, better rhythm outcome and lower procedure related complications can be expected
 2144 in younger patients with a short AF history and frequent, short AF episodes in the absence of
 2145 significant structural heart disease.⁷⁷⁰ Catheter ablation is more effective than AAD therapy in
 2146 maintaining sinus rhythm (Online Figure B).^{(*)771} Sinus rhythm without severely symptomatic
 2147 recurrences of AF is found in up to 70% of patients with paroxysmal AF (Add MANTRA-PAF 5 yr outcomes
 2148 when published), and around 50% in persistent AF.^{738, 754, 762} Very late recurrence of AF after years
 2149 of sinus rhythm is not uncommon and may reflect disease progression, with important
 2150 implications for continuation of AF therapies.⁷⁵⁴ Multiple parameters have been identified as
 2151 risk factors for recurrence after catheter ablation of AF, but their predictive power is weak. The
 2152 decision for catheter ablation thus should be based on a shared decision making process ⁷⁷²
 2153 (see chapter 7), following thorough explanation of the potential benefits and risks, and of the
 2154 alternatives such as AAD or acceptance of current symptoms without rhythm control therapy.⁷⁷³
 2155 *(*)Add ref to commissioned meta-analysis when published: Systematic review and meta-analysis of randomised trials that*
 2156 *compare ablation to antiarrhythmic drugs in patients with persistent atrial fibrillation. Authors: Guy Amit, Alma Adler, Onikepe*
 2157 *Owolabi, Juan P. Casas, Jonathan Nyong, David Prieto-Merino, Pablo Perel, Pier Lambiase and Carlos A. Morillo*

2158

2159 **Complications of catheter ablation for AF.** There is a clear need to capture complications in
 2160 clinical practice systematically to improve the quality of AF ablation procedures.¹⁷⁴ The median
 2161 length of hospital stay in AF patients undergoing their first ablation as part of the
 2162 EURObservational Research Programme (EORP) was 3 days (IQR 2–4 days), based on 1391
 2163 patients from hospitals performing at least 50 ablations per year. Five to seven percent of
 2164 patients will suffer severe complications after catheter ablation of AF, and 2–3% life-threatening
 2165 but usually manageable complications.^{753, 774-776} Intraprocedural death has been reported, but is
 2166 rare (<0.2%).⁷⁷⁷ The most important severe complications are: stroke/TIA (<1%), cardiac
 2167 tamponade (1–2%), pulmonary vein stenosis and severe oesophageal injury leading to atrio-
 2168 oesophageal fistula weeks after ablation (see Table 18). ‘Silent strokes’, i.e. white matter
 2169 lesions detectable by brain magnetic resonance imaging, have been observed in around 10% of
 2170 patients treated with radiofrequency and cryoballoon ablation.⁷⁷⁸ The clinical relevance of this
 2171 observation is unclear.⁷⁷⁵ Post-procedure complications include stroke, with the highest risk
 2172 within the first week,⁷⁷⁹ late pericardial tamponade several days after catheter ablation,⁷⁷⁷ and
 2173 oesophageal fistulas which usually become apparent 7 to 30 days after ablation. Timely
 2174 detection of atrio-esophageal fistulas can be life-saving and should be based on the typical triad
 2175 of infection without a clear focus, retrosternal pain and stroke or TIA.⁷⁷⁴

TABLE 18: Complications related to catheter ablation of AF

Complication severity	Complication	Rate ^{753, 774, 776, 780-785}
Life-threatening complications	Periprocedural death	<0.2%
	Oesophageal injury (perforation/fistula)**	<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) *	5–20%
	Radiation exposure	

* <10% for cryo/radiofrequency ablation, >20% for phased radiofrequency ablation

** Oesophageal fistula should be suspected in patients presenting with the trias of unspecific signs of infection, chest pain, and stroke or TIA in the first weeks after an ablation procedure. It requires immediate therapy.

AF = atrial fibrillation; TIA = transient ischaemic attack

10.3.4 Anticoagulation – before / during / after ablation

Patients anticoagulated with vitamin K antagonists should continue therapy during ablation (INR 2–3).⁷⁸⁶ Anticoagulation with NOACs is an alternative to warfarin.^{489, 787-791} There is no safety signal from observational cohorts treated with uninterrupted NOAC therapy undergoing catheter ablation in experienced centres.^{787, 789, 792, 793} The first controlled trial, enrolling around 200 patients, has recently been published⁷⁹⁴, as well as several observational data sets.^{787, 795, 796} Ongoing studies compare uninterrupted VKA with NOAC therapy in AF ablation patients (e.g. AXAFA – AFNET 5, NCT02227550 or RE-CIRCUIT, NCT02348723). During ablation, heparin should be given to maintain activated clotting time (ACT) > 300 seconds. Anticoagulation

should be maintained for at least 8 weeks after ablation for all patients. The true incidence of thromboembolic events after catheter ablation has never been systematically studied and the expected stroke risk has been adopted from non-ablation AF cohorts. Although observational studies suggest a relatively low stroke rate in the first few years after catheter ablation of AF,^{764, 797-802} the long-term risk of recurrent AF and the safety profile of anticoagulation in ablated patients need to be considered. In the absence of controlled trial data, oral anticoagulation after catheter ablation should follow general anticoagulation recommendations, regardless of the presumed rhythm outcome.

2202

2203 10.3.5 AF ablation in heart failure patients

Catheter ablation prevents recurrent AF slightly better than amiodarone therapy in AF patients with heart failure. Selected patients with HFrEF and AF can achieve recovery of left ventricular systolic function after catheter ablation (probably reflecting tachycardiomyopathy), and there are several smaller trials suggesting improved LV function after catheter ablation of HFrEF^{184, 225-227, 803, 804} (Awaiting full publication <http://www.acc.org/about-acc/press-releases/2015/03/16/11/26/heart-failure-patients-fare-better-with-catheter-ablation-than-amiodarone>). The available data suggest improved LV function and reduced hospitalization in HFrEF patients undergoing AF ablation⁷⁴⁶ (Awaiting full publication <http://www.acc.org/about-acc/press-releases/2015/03/16/11/26/heart-failure-patients-fare-better-with-catheter-ablation-than-amiodarone>), especially in patients without a prior myocardial infarction.⁸⁰⁵ Larger trials are warranted to confirm these findings. Catheter ablation can be demanding in these patients. Thus, indications for catheter ablation in HFrEF patients should be carefully balanced, and procedures performed in experienced centres.

2216

2217 10.3.6 Follow-up

Patients and physicians involved in the follow-up after catheter ablation should know the signs/symptoms of late complications to allow swift referral for treatment. Patient should also be aware that symptomatic and asymptomatic AF recurrences are frequent after catheter ablation.^{119, 806, 807} In line with the primary goal of rhythm control therapy, asymptomatic episodes should generally not trigger further rhythm control therapy. Patients should be seen at least once by a rhythm specialist in the first 12 months after ablation. Further rhythm control options should be considered in patients with symptomatic recurrences, including discussion in a heart team (Figure 17).

2226

2227 10.4 **AF Surgery**2228 10.4.1 **Concomitant AF surgery**

2229 Cox maze procedure (CMP) was first performed 30 years ago as a 'cut-and-sew' technique,
 2230 including isolation of the posterior left atrium, a connection to the posterior mitral annulus, a
 2231 cavo-tricuspid connection, a cavo-caval connection and the exclusion of the LAA (Figure 20).⁸⁰⁸
 2232 Thereby, CMP creates an electrical labyrinth (maze) of passages through which the sinoatrial
 2233 node impulse finds a route to the atrioventricular node while preventing fibrillatory conduction.
 2234 CMP and other, often simpler forms of AF surgery have mainly been used in patients
 2235 undergoing other open heart surgical procedures.^{471, 809-824} In a systematic review
 2236 commissioned for this Guideline, concomitant AF surgery prevented recurrent AF (RR 1.94,
 2237 95% CI 1.51-2.49; n=554 from 7 RCTs); Online Figure C. *(Add ref to commissioned Huffman review when*
 2238 *published)* Patients undergoing the Cox maze procedure required pacemaker implantation more
 2239 often (RR 1.69, 95% CI 1.12-2.54; n=1631 from 17 RCTs), without a detectable difference in
 2240 other outcomes or complications. These findings are underpinned by an analysis of STS
 2241 database comprising 67,389 patients in AF: Mortality or major morbidity was not affected by
 2242 concomitant AF surgery (adjusted odds ratio 1.00; 95% CI 0.83–1.20), but pacemaker
 2243 implantation was more frequent (adjusted odds ratio 1.26; 95% CI 1.07–1.49).⁸²⁵ Predictors for
 2244 recurrence of AF after surgery include left atrial dilatation, older age, >10 years history of AF
 2245 and non-paroxysmal AF.⁸²⁶⁻⁸³⁰ Regarding AF type, surgical PVI seems effective in paroxysmal
 2246 AF.⁸³¹ Batrial lesion patterns may be more effective in persistent and long-standing persistent
 2247 AF.^{823, 829, 832} The suggested management of patients with AF-related symptoms undergoing
 2248 cardiac surgery is displayed in Figure 18, with important contribution of the AF Heart Team to
 2249 advise and inform patient choice.

2250

2251 10.4.2 **Stand-alone rhythm control surgery**

2252 Current technology (e.g. bipolar radiofrequency or cryotherapy) renders the procedure easier,
 2253 more reproducible, and feasible via a mini-thoracotomy.^{811, 833, 834} Thoracoscopic pulmonary
 2254 vein isolation (PVI) with bipolar RF prevents recurrence of paroxysmal AF (69–91% freedom
 2255 from arrhythmias at 1 year, see Figure 20B for lesion set),^{478, 835, 836} and seems effective in
 2256 patients refractory to catheter ablation.⁸³⁷ The average length of hospital stay for thoracoscopic
 2257 ablation varies from 3.6–6.0 days.^{478, 838, 839} The FAST trial,⁴⁷⁸ and another smaller trial,⁸⁴⁰
 2258 suggested that thoracoscopic AF surgery could be more effective than catheter ablation for the

2259 maintenance of sinus rhythm^{478, 840}, while also causing more complications such as
 2260 pneumothorax (10%) and bradycardia requiring pacemaker implantation (3%, Table 19).⁸⁴¹ To
 2261 improve results in patients with persistent or long-standing persistent AF^{478, 842-844}, more
 2262 extensive lesion sets have been performed, connecting lines between the PVI encircling and
 2263 towards the mitral annulus.^{838, 845-848} To improve the generation of transmural lesions⁷⁴², endo-
 2264 epicardial ablation strategies have recently been proposed.^{838, 849-851} Although preliminary
 2265 experience with hybrid simultaneous ablation shows promise, procedural time and bleeding
 2266 complications are higher.^{838, 849}

2267

2268 **TABLE 19: Complications of thoracoscopic AF surgery**

Complication	Rate ^{478, 841, 848, 852}
Conversion to sternotomy	0-1.6%
Pacemaker implantation	0-3.3%
Pneumothorax	0-6.2%
Pneumonia (0-1,6%)	0-4.4%
Tamponade (0-9,1%)	0-9.1%
Transient ischaemic attack*	0.6-3.0%

2269 * The rate of asymptomatic cerebral embolism is unknown

2270 AF = atrial fibrillation

2271

2272 10.5 **Choice of rhythm control following treatment failure**

2273 There is insufficient evidence for clear recommendations on how to treat patients with recurrent
 2274 AF after catheter ablation. Early recurrences of AF or atrial tachycardias after ablation (<8
 2275 weeks) may be treated with cardioversion. Many of the published series of AF ablation patients
 2276 included patients who failed antiarrhythmic drug therapy. Thus, considering ablation therapy in
 2277 patients who have symptomatic recurrences on AAD therapy is often reasonable. Alternatively,
 2278 trialling another AAD can be considered. Combining AAD with ablation ('Hybrid therapy', see
 2279 below) should be considered based on the different and possibly synergistic effects of these
 2280 drugs with AF ablation, possibly benefitting patients in whom either treatment alone was
 2281 previously ineffective. Rate control without rhythm control, surgical ablation, or repeat catheter
 2282 ablation should be considered as well as third-line options (Figure 19). Patient preferences and

local access to therapy are important considerations to inform the therapy choice in patients who are in need of further rhythm control therapy after an initial therapy failure.

2285

10.6 The AF Heart Team

In view of the complexity of the different treatment options in patients with failed rhythm control therapy, but still require or demand further rhythm control therapy, this Task Force proposes that decisions involving AF surgery or extensive AF ablation should be based on advice from an AF Heart team. This will also apply to reversal to a rate control strategy in patients with severe (EHRA III-IV) AF symptoms. An AF Heart Team should consist of a cardiologist with expertise in AAD therapy, an interventional electrophysiologist, and a cardiac surgeon with expertise in appropriate patient selection, techniques and technologies for interventional/surgical AF ablation. Such AF Heart teams, and a collaborative infrastructure supporting a continued interaction between physicians delivering continued care, AF cardiologists, interventional electrophysiologists and AF surgeons, should be established to provide optimal advice, and ultimately to improve rhythm outcomes for patients in need for advanced and complex rhythm control interventions.

2299

Recommendations for catheter ablation of AF and AF surgery

Recommendations	Class ^a	Level ^b	Refs ^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	603-605, 738, 753
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.	IIa	B	853
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.	IIa	B	603

All patients should receive oral anticoagulation for stroke prevention for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B/C	753
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high stroke risk.	IIa	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.	IIa	B/C	786, 794
Catheter ablation should target complete isolation of the pulmonary veins using radiofrequency ablation or cryotherapy balloon catheters.	IIa	B	603, 741, 742, 760, 762
Catheter 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	IIa	C	184, 225-227, 746, 803, 804(Awaiting full publication http://www.acc.org/about-acc/press-releases/2015/03/16/11/26/heart-failure-patients-fare-better-with-catheter-ablation-than-amiodarone)
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia.	IIa	C	854, 855
Catheter (IIaB), surgical (IIaC) or hybrid (IIaC) ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team.	IIa	B/C	478, 762, 856, 857 <i>Add ref to commissioned Huffman review when published</i>

2301

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.	IIa	B	478 838, 845, 849
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.	IIa	C	834, 857
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	476, 821 471, 815, 816, 822, 823

Concomitant biatrial maze or pulmonary vein isolation may be considered in asymptomatic AF patients undergoing cardiac surgery.	IIb	C	822, 823, 858
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2302 AAD = antiarrhythmic drug; AF = atrial fibrillation; CHA₂DS₂-VASc = Congestive Heart failure,
2303 hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74,
2304 and Sex (female); INR = international normalized ratio; VKA = vitamin K antagonist

2305 ^a Class of recommendation

2306 ^b Level of evidence

2307 ^c Reference(s) supporting recommendation(s)

2308

11. Hybrid rhythm control therapy

Atrial fibrillation has many different drivers which are only partially targeted by antiarrhythmic drugs or catheter ablation.⁹² Hence, combination or “hybrid” rhythm control therapy seems reasonable, although there is little evidence supporting its use,

11.1 Combining antiarrhythmic drugs and catheter ablation

AAD therapy is commonly given for 8-12 weeks after ablation to reduce early recurrences of AF after catheter ablation, supported by a recent controlled trial where amiodarone halved early AF recurrences compared to placebo.⁸⁵⁹ Prospective studies have not been done, but a meta-analysis of the available (weak) evidence suggest slightly better prevention of recurrent AF in patients treated with AAD after catheter ablation.⁷³⁸ Many patients are treated with AAD therapy after catheter ablation (most often amiodarone or flecainide)⁶⁰⁵, and this seems a reasonable option in patients with recurrent AF after ablation. It seems common sense to consider AAD therapy in patients who are in need of further rhythm control therapy after catheter ablation, but controlled trials are desirable.

Combining cavo-tricuspid isthmus ablation and antiarrhythmic drugs may lead to improved rhythm control without the need for left atrial ablation in patients who develop “drug-induced atrial flutter” on therapy with flecainide, propafenone, or amiodarone⁸⁶⁰⁻⁸⁶², although recurrent AF is a concern in the long term.^{863, 864}

11.2 Combining antiarrhythmic drugs and pacemakers

In selected patients with sick sinus syndrome and fast ventricular response during AF paroxysms requiring rate control therapy, the addition of a pacemaker can not only optimize rate control but also help to control rhythm.^{736, 737} Moreover, when AAD treatment leads to sinus node dysfunction and bradycardia, pacing may permit up titration of AAD dose. Such strategies have never been prospectively investigated and the existing populations studied are highly selected.^{865, 866} Some patients with AF-induced bradycardia may benefit from catheter ablation of AF, obviating the need for AAD and pacemaker implantation.^{854, 855}

12. Specific situations

12.1 Frail and 'elderly' patients

Many AF patients present at older age (e.g. >75 or >80 years old). There are no studies suggesting that cardiovascular risk reduction is less effective in these 'elderly' AF patients than in younger patients. Rather, age is one of the strongest predictors / risk factors for ischemic stroke in AF (Table 11).⁸⁶⁷ There is good data to support the use of anticoagulants in older patients from BAFTA³⁶⁹, the NOAC trials³⁹, and analyses in Elderly Americans (Medicare).⁴⁰⁷ Elderly AF patients are at higher risk of stroke and thus more likely to benefit from OAC than younger patients,⁸⁶⁸ and yet OAC is still underutilized.^{869, 870} Although the evidence base is smaller for other treatment options in AF, the available data support the use of available rate and rhythm control interventions, including pacemakers and catheter ablation, without justification to discriminate by age group. Individual patients at older age may present with multiple comorbidities including dementia, a tendency to falls, chronic kidney disease, anaemia, hypertension, diabetes, cognitive dysfunction, or a tendency to fall. Such conditions may limit quality of life more than AF-related symptoms. Impairment of renal and hepatic function and multiple simultaneous medications make drug interactions and adverse drug reactions more likely. Integrated AF management and careful adaptation of drug dosing seem reasonable to reduce complications of AF therapy in such patients.⁸⁷¹

12.2 Inherited cardiomyopathies, channelopathies and accessory pathways

Several inherited cardiac conditions are associated with early-onset AF (Table 20). Treatment of the underlying cardiac condition is an important contribution to AF management in these young patients (see also ESC guidelines on the sudden cardiac death⁸⁷² and hypertrophic cardiomyopathy⁸⁷³).

TABLE 20: Inherited cardiomyopathies, channelopathies and pathways associated with AF

Syndrome	Gene	Functional alteration	AF prevalence	References
Long QT syndrome	KCNQ1 KCNH2 SCN5A ANK2 others	IKs↓ IKr↓ INa↑ INa,K↓ Various effects	5–10%	874-878
Brugada syndrome	SCN5A GPDIL SCN1B CACNA1C CACNB2b others	INa↓ INa↓ INa↓ ICa↓ ICa↓ others	10–20%	879-883
Short QT syndrome	KCNH2 KCNQ1 KCNJ2 CACNA1C CACNB2b	IKr↑ IKs↑ IK1↑ ICa↓ ICa↓	Up to 70%	881, 884-886
Catecholaminergic VT	RYR2 CASQ2	Abnormal Ca ²⁺ release from sarcoplasmic reticulum	Variable but significant	887-889
Hypertrophic cardiomyopathy	Sarcomeric genes		5–15%	890-892
Wolff-Parkinson-White syndrome	PRKAG		Variable	893
Holt-Oram syndrome	TBX5		Variable	894
Arrhythmogenic right ventricular cardiomyopathy	Several desmosomal genes, unknown gene loci		>40% in patients with VTs	895, 896

AF = atrial fibrillation; VT = ventricular tachycardia

12.2.1 Wolff-Parkinson-White syndrome (WPW)

Patients with pre-excitation and AF are at risk of rapid conduction across the accessory pathway, resulting in fast ventricular rate possibly ventricular fibrillation and sudden death. In AF patients with evidence of an antegrade accessory pathway, catheter ablation of the pathway is recommended.^{897, 898} This procedure is safe and effective and may be considered as a prophylactic treatment strategy.^{899, 900} In AF patients surviving a sudden death event with evidence of an accessory pathway, urgent catheter ablation of the pathway is recommended.⁸⁹⁷ A documented short pre-excited RR interval (<250 ms) during spontaneous or induced AF is one of the risk markers for sudden death in WPW syndrome, in addition to a history of symptomatic tachycardia, the presence of multiple accessory pathways, and Ebstein's anomaly. Intravenous procainamide, propafenone or ajmaline can be used to acutely slow ventricular rate^{901, 902}, whereas digoxin, verapamil or diltiazem are contraindicated.⁹⁰³ Intravenous amiodarone should be used with caution, as there are case reports of accelerated ventricular rhythms and ventricular fibrillation in patients with pre-excited AF receiving intravenous amiodarone infusion.⁹⁰⁴

12.2.2 Hypertrophic cardiomyopathy

AF is the most common arrhythmia in patients with HCM affecting approximately a quarter of the HCM population.⁹⁰⁵ Observational data highlight a high stroke risk in HCM patients with AF, confirming the need for oral anticoagulation.⁹⁰⁶ While there is more experience with VKA, there is no data to suggest that NOACs cannot be used in HCM patients.⁸⁷³ Studies of rate or rhythm control medications in HCM patients are relatively scarce. Beta-blockers and diltiazem or verapamil seem reasonable treatment options for rate control in HCM patients. In the absence of significant LV outflow tract obstruction, digoxin can be used alone or in combination with beta-blockers.⁸⁷³ Amiodarone seems a safe AAD in HCM patients with AF,⁹⁰⁷ and expert opinion suggests that disopyramide may be beneficial in HCM patients with outflow tract obstruction. AF ablation is effective to suppress symptomatic AF recurrences.⁹⁰⁸⁻⁹¹² Surgical treatment of AF may be appropriate in HCM patients undergoing surgery (e.g. for LV outflow tract obstruction or mitral valve surgery), but experience is limited.

12.2.3 Channelopathies and arrhythmogenic right ventricular cardiomyopathy

Many channelopathies or inherited cardiomyopathies are associated with AF. AF prevalence ranges between 5 to 20% in patients with long QT or Brugada syndromes, and up to 70% in

2404 short QT syndrome (Table 20).^{881, 884-886} Penetrance of disease phenotype including AF is
 2405 variable.^{61, 880, 913, 914} Both shortening as well as prolongation of the atrial action potential have
 2406 been demonstrated as likely mechanisms underlying AF in these diseases. It seems
 2407 reasonable to consider AAD that reverse the suspected channel defect in AF patients with
 2408 inherited cardiomyopathies, e.g. a sodium channel blocker in LQT3⁸⁸⁰, or quinidine in Brugada
 2409 syndrome.⁹¹⁵ More importantly, new onset AF in young, otherwise healthy individuals should
 2410 trigger a careful search for such inherited conditions including clinical history, family history,
 2411 ECG phenotype, and echocardiography and/or other cardiac imaging.

2412 Monogenic defects only account for 3–5% of all patients with AF, even in younger populations.
 2413 ^{874, 876, 916-918} Furthermore, there is no clear link between detected mutations and specific
 2414 outcomes or therapeutic needs. For these reasons, genetic testing is not recommended in the
 2415 general AF population.⁷⁷ Other guidelines have described the indications for genetic testing in
 2416 patients with inherited arrhythmogenic diseases.^{919, 920}

2417

2418 Recommendations for inherited cardiomyopathies

2419

Recommendations	Class ^a	Level ^b	Refs ^c
WPW Syndrome			
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	921-923
Catheter ablation of the accessory pathway is recommended without delay in WPW patients who survive sudden cardiac death.	I	C	897
Asymptomatic patients with overt pre-excitation and AF should be considered for accessory pathway ablation after careful counselling.	Ila	B	900, 924
Hypertrophic cardiomyopathy			
Lifelong oral anticoagulation is recommended in HCM patients who develop AF to prevent stroke.	I	B	906
Restoration of sinus rhythm by electrical or pharmacological cardioversion is recommended in HCM patients with symptomatic new-onset AF to improve symptoms.	I	B	873
In haemodynamically stable HCM patients with AF, ventricular rate control using beta-blockers and diltiazem/verapamil is recommended.	I	C	873

Treatment of left ventricular obstruction should be considered in AF patients with HCM to improve symptoms.	Ila	B	925
Amiodarone should be considered to achieve rhythm control and maintain sinus rhythm in HCM patients.	Ila	C	873, 926
Inherited cardiomyopathies and channelopathies			
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.	Ila	A	880

2420 AF = atrial fibrillation; HCM = hypertrophic cardiomyopathy; WPW = Wolff-Parkinson-White
 2421 syndrome

2422 ^a Class of recommendation

2423 ^b Level of evidence

2424 ^c Reference(s) supporting recommendation(s)

2425

2426

2427 12.3 Sports and atrial fibrillation

2428 Physical activity improves cardiovascular health, which translates in a lower risk of AF.⁹²⁷
 2429 Therefore, physical activity is a cornerstone of preventing AF. Intensive sports practice,
 2430 especially endurance sports (> 1500 hours of endurance sports practice)⁹²⁸, increases the risk
 2431 of AF later in life⁹²⁹⁻⁹³¹, probably mediated by altered autonomic tone, volume load during
 2432 exercise, atrial hypertrophy and dilatation.^{932, 933} This results in a U-shaped relationship of
 2433 physical activity and incident AF.^{927, 931, 934-936} Detraining can reduce AF in models⁹³³ and
 2434 reduces ventricular arrhythmias in athletes,⁹³⁷ but the role of detraining for AF in human athletes
 2435 is unknown. The management of athletes with AF is similar to general AF management, but
 2436 requires a few special considerations. Clinical risk factors will determine the need for
 2437 anticoagulation. Sports with direct bodily contact or prone to trauma should be avoided in
 2438 patients on OAC. Beta-blockers are not well tolerated and at times prohibited, and digoxin,
 2439 verapamil, and diltiazem are often not potent enough to slow heart rate during exertional AF.
 2440 Catheter ablation for AF probably has similar outcomes in athletes as in non-athletes,^{938, 939} but
 2441 further data are needed. Pill in the pocket therapy has been used as well.⁶³⁹ After ingestion of
 2442 flecainide or propafenone as pill in the pocket, patients should refrain from sports as long as AF
 2443 persists and until two half-lives of the AAD have elapsed. Prophylactic ablation of the flutter
 2444 circuit may be considered in athletes treated with sodium channel blockers.⁹⁴⁰

- 2445
- 2446 Recommendations for physical activity in patients with AF

Recommendations	Class ^a	Level ^b	Refs ^c
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	927, 929-931, 934-936
AF ablation should be considered to prevent recurrent AF in athletes.	Ila	B	938, 939
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.	Ila	C	
After ingestion of pill in the pocket class 1 antiarrhythmic drugs, patients should refrain from sports as long as AF persists and until two half-lives of the antiarrhythmic drug have elapsed.	Ila	C	639

- 2447 AF = atrial fibrillation

- 2448 ^a Class of recommendation

- 2449 ^b Level of evidence

- 2450 ^c Reference(s) supporting recommendation(s)

2451

2452

- 2453 12.4 **Pregnancy**

- 2454 AF in pregnant women is rare and usually associated with pre-existing heart disease. AF is
- 2455 associated with increased complications for the mother and fetus.^{941, 942} Better treatment of
- 2456 congenital heart diseases will probably increase the incidence of AF during pregnancy in the
- 2457 future.⁹⁴³ Pregnant women with AF should be managed as high risk pregnancies in close
- 2458 collaboration between cardiologists, obstetricians and neonatologists.

2459

- 2460 12.4.1 **Rate control**

- 2461 Due to a lack of specific data, beta-blockers, verapamil, diltiazem, and digoxin all carry an FDA
- 2462 pregnancy safety category of C (benefits may outweigh risk), except for atenolol (category D:
- 2463 positive evidence of risk). Their use should be at the smallest dose and for the shortest time
- 2464 required. None of the agents are teratogenic, but readily cross the placenta.⁹⁴⁴ Beta-blockers
- 2465 are commonly used in clinical practice (e.g. for management of gestational hypertension and
- 2466 pre-eclampsia), but may be associated with intrauterine growth retardation⁹⁴⁵ and hence growth

scans after 20 weeks gestation are recommended. Digoxin is considered safe for maternal and fetal arrhythmias.⁹⁴⁶ There is insufficient data to comment on verapamil or diltiazem, hence rate control using beta-blockers and/or digoxin is recommended.⁹⁴⁷ With regards to breastfeeding, all rate control agents are present in breast milk, although levels of beta-blockers, digoxin and verapamil are too low to be considered harmful. Diltiazem will be present at high levels and should be considered second-line treatment.⁹⁴⁸

2473

12.4.2 Rhythm control

Rhythm control therapy in pregnant AF patients has only been reported in case studies. Amiodarone is associated with severe adverse foetal side effects and should only be considered for emergency situations.⁹⁴⁹ Flecainide and sotalol can both be used for conversion of fetal arrhythmias without major adverse effects,⁹⁵⁰ and are thus likely to be safe to treat maternal symptomatic AF. Electrical cardioversion can be effective for restoration of sinus rhythm when tachyarrhythmia is causing haemodynamic instability, with low rates of adverse outcome for both mother and fetus.⁹⁵¹ However, due to the risk of fetal distress, electrical cardioversion should only be carried out where facilities are available for fetal monitoring and emergency caesarean section. As with other emergencies during pregnancy, patients should receive 100% oxygen, intravenous access should be established early, and the mother should be positioned in the left lateral position to improve venous return.⁹⁵²

2486

12.4.3 Anticoagulation

Vitamin K antagonists should be avoided in the first trimester due to teratogenic effects, and in the 2–4 weeks preceding delivery to avoid fetal bleeding. Low molecular weight heparins are a safe substitute, as they do not cross the placenta.⁹⁵³ In the third trimester, frequent laboratory checks for adequate anticoagulation (e.g. every 10–14 days) and corresponding dose adjustments are advised, given that in some women high doses of both VKA and heparin may be needed to maintain adequate anticoagulation. Pregnant patients with AF and mechanical prosthetic valves who elect to stop VKA treatment in consultation with their specialist team between 6 and 12 weeks of gestation, should receive continuous, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH. Since limited data are available about teratogenesis for NOACs, these drugs should be avoided during pregnancy.

2498

2499 Recommendations during pregnancy

Recommendations	Class ^a	Level ^b	Refs ^c
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 fetus.	I	C	
Anticoagulation is recommended in pregnant AF patients at risk for 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 prior to delivery. Vitamin K antagonists or heparin can be used in the remaining parts of the pregnancy.	I	B	953
Non-vitamin K antagonist oral anticoagulants (NOACs) should be avoided in pregnancy or in women planning a pregnancy.	III (harm)	C	

2500 AF = atrial fibrillation; VKA = vitamin K antagonist

2501 ^a Class of recommendation2502 ^b Level of evidence2503 ^c Reference(s) supporting recommendation(s)

2504

2505

2506 12.5 **Postoperative AF**

2507 AF is common after cardiac surgery (15-45%)⁹⁵⁴⁻⁹⁵⁶ and is associated with increased length of
 2508 hospital stay and higher rates of complications and mortality.⁹⁵⁷ Postoperative AF is also not
 2509 uncommon after other major surgery, especially in elderly patients. The treatment of
 2510 postoperative AF is mainly based on studies of cardiac surgery patients, with much less
 2511 evidence in the non-cardiac surgery setting.

2512

2513 12.5.1 **Prevention of postoperative AF**

2514 Beta-blockers reduce postoperative AF and supraventricular tachycardias, albeit with high
 2515 heterogeneity and moderate risk of bias in a systematic review of published studies (most
 2516 commonly studied was propranolol, with AF in 16.3% of the treatment group compared to
 2517 31.7% in the control group).⁹⁵⁵ In the majority of these studies, beta-blockers were
 2518 administered postoperatively, a regimen supported in a recent meta-analysis.⁹⁵⁸ Amiodarone
 2519 reduced the incidence of postoperative AF compared to a beta-blocker regimen in several meta-
 2520 analyses, also reducing hospital stay.^{955, 959-961}

Despite initial reports from meta-analyses,^{711, 962, 963} preoperative treatment with statins did not prevent postoperative AF in a prospective controlled trial (add ref to STICS when published). Other therapies have also been studied in small, hypothesis generating trials, but have not demonstrated clear beneficial effects. These include magnesium,^{955, 964, 965} n-3 polyunsaturated fatty acids,⁹⁶⁶⁻⁹⁷⁴ colchicine,⁹⁷⁵ corticosteroids^{976, 977} and posterior pericardectomy.⁹⁷⁸ Posteroperative overdrive biatrial pacing has not gained widespread usage despite some suggestion of prophylactic effects.^{955, 979}

2528

2529 12.5.2 Anticoagulation

Postoperative AF is associated with an increased early stroke risk, increased morbidity and 30-day mortality.^{957, 980, 981} In the long-term, patients with an episode of postoperative AF have a two-fold increase in cardiovascular mortality and a substantially increased risk of future AF and ischaemic stroke compared to patients that remain in sinus rhythm after surgery.⁹⁸¹⁻⁹⁸⁷ OAC at discharge has been associated with a reduced long-term mortality in patients with postoperative AF⁹⁸⁸, without evidence from controlled trials. Good quality data are needed to determine whether long-term anticoagulation can prevent strokes in patients with postoperative AF at high stroke risk^{375, 390}, and to assess whether short episodes of postoperative AF (e.g. <48 hours) carry a similar risk as longer episodes.⁹⁸⁹ The indication and timing of OAC in postoperative AF patients should take into consideration the risk of postoperative bleeding.

2540

2541 12.5.3 Rhythm control therapy in postoperative AF

In haemodynamically unstable patients, cardioversion and consideration of AAD is recommended. Amiodarone or vernakalant have been efficient in converting postoperative AF to sinus rhythm.^{622, 979, 990} A recent medium-sized trial randomizing patients with postoperative AF to either rhythm control therapy with amiodarone or to rate control did not find a difference in hospital admissions during a 60 day follow-up⁹⁹¹, underpinning a practice that the aim of rhythm control therapy should be to improve AF-related symptoms in postoperative AF. In asymptomatic patients and in those with acceptable symptoms, rate control or deferred cardioversion preceded by anticoagulation is a reasonable approach.

2550

2551 Recommendations for preventing postoperative AF

Perioperative oral beta-blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery.	I	B	955, 958
Restoration of sinus rhythm by electrical cardioversion or antiarrhythmic medication 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	375, 390
Antiarrhythmic medication 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	955
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	622
Asymptomatic postoperative AF may initially be managed with rate control and anticoagulation.	IIb	C	

AF = atrial fibrillation;

^a Class of recommendation

^b Level of evidence

^c Reference(s) supporting recommendation(s)

12.6 Atrial arrhythmias in grown-up patients with congenital heart disease (GUCH)

Atrial arrhythmias (AF, atrial flutter, atrial tachycardias) often occur late after surgical repair of congenital heart defects, occurring in 15–40% of grown up patients with congenital heart disease (GUCH). They are associated with heart failure, syncope, thromboembolic events and sudden death.⁹⁹²⁻⁹⁹⁶ The pathophysiological substrate is complex, associated with hypertrophy, fibrosis, hypoxaemia, chronic haemodynamic overload, surgical scars and patches. Additionally, related primary anomalies in the conduction pathways can lead to reentrant atrial and ventricular tachycardia, heart block, and sinus node dysfunction.⁹⁹² Macro-reentrant atrial tachycardia or atypical atrial flutter may be seen after nearly any surgical procedure involving atriotomies, involving circuits around surgical scars and patches.

12.6.1 General management of atrial arrhythmias in GUCH patients

The conventional stroke risk factors should be used to inform decisions on long-term anticoagulation in GUCH patients with AF. In addition, anticoagulation should be considered in GUCH patients with atrial arrhythmias when they present with intracardial repair, cyanosis, Fontan palliation or systemic RV in addition to those with conventional stroke risk factors.⁹⁹⁷ Beta-blockers, verapamil, diltiazem, and digitalis can be used. Care should be taken to avoid bradycardia and hypotension.

Sodium channel blockers suppress approximately half of atrial arrhythmias in Fontan patients.⁹⁹⁸ Amiodarone is more effective, but long-term AAD carries a high risk of extracardiac side effects in this relatively young population. Intracardiac thrombi are common in GUCH patients undergoing cardioversion for AF, but also in patients with atrial tachycardias or atrial flutter.⁹⁹⁹ Therefore, both a transoesophageal echocardiogram and anticoagulation for a few weeks prior to the planned cardioversion should be considered.⁹⁹³ Radiofrequency ablation may be a good option for symptomatic GUCH patients with atrial arrhythmias, especially in patients with atrial flutter and other macro-reentrant tachycardias. Interventions should be performed in adequately qualified centres by specialized teams.

12.6.2 Atrial tachyarrhythmias and atrial septal defects

Atrial flutter and fibrillation occur in 14% to 22% of adult patients with unoperated atrial septal defects (ASD), especially in older patients,¹⁰⁰⁰ and can lead to heart failure.¹⁰⁰¹ Early repair can reduce but not eliminate the risk of AF.¹⁰⁰² Batrial volume overload,¹⁰⁰³ pulmonary hypertension,¹⁰⁰⁴ and possibly the arrhythmogenic effect of atrial patches, can contribute to these arrhythmias.¹⁰⁰⁵ Anticoagulation should be decided based on stroke risk factors. In patients with history of paroxysmal or persistent AF, AF surgery could be considered at the time of surgical closure, or catheter ablation in patients undergoing interventional ASD closure devices. Catheter ablation of late atrial arrhythmias has shown to be effective in 46 consecutive patients after surgical ASD.¹⁰⁰⁶

12.6.3 Atrial tachyarrhythmias after Fontan operation

Atrial arrhythmias occur in up to 40% of patients with a Fontan circulation, and can manifest as atrial flutter, primary atrial tachycardia, AF and accelerated junctional rhythm or junctional

tachycardia¹⁰⁰⁷ with or without sinoatrial node dysfunction.¹⁰⁰⁸ Patients with atriopulmonary anastomoses (possibly due to higher atrial volume and pressure load) and those with early postoperative atrial arrhythmias are more likely to develop long-term atrial arrhythmias.¹⁰⁰⁹ Atrial arrhythmias can also be the first manifestation of obstruction of the atrio-pulmonary anastomosis, a complication that must be identified. Right atrial thrombus formation is common in Fontan patients with atrial arrhythmias and requires oral anticoagulation.¹⁰¹⁰ Operative conversion to total cavopulmonary artery connection with concomitant arrhythmia surgery can in some patients improve heart failure symptoms and reduce recurrent arrhythmias,^{998, 1011} with low recurrence rates of clinically apparent atrial arrhythmias in the first few years after repeat surgery.¹⁰¹²⁻¹⁰¹⁴ Catheter ablation of atrial arrhythmia in Fontan patients has been successful in selected patients.¹⁰¹⁵

2612

2613 12.6.4 Atrial tachyarrhythmias after Tetralogy of Fallot correction

2614 Approximately a third of patients after repair of Tetralogy of Fallot develop atrial arrhythmias
 2615 including intra-atrial reentrant tachycardia, focal atrial tachycardia, and AF.¹⁰¹⁶ Circuits involving
 2616 the cavotricuspid isthmus and areas of presumed surgical right atrial scarring have been
 2617 described as responsible for atrial arrhythmias.

2618

2619 Recommendations in patients with grown up congenital heart disease

Recommendations	Class ^a	Level ^b	Refs ^c
Atrial septal defect closure should be considered before the fourth decade of life in order to diminish the chance of atrial flutter and fibrillation.	IIa	C	1000, 1001, 1003
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	203, 1017, 1018
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	1017, 1019
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 CHA ₂ DS ₂ VAS _c ≥1.	IIa	C	997

Catheter ablation of atrial arrhythmias associated with congenital heart defects may be considered when performed in experienced centres.	IIb	C	1020
In patients with congenital heart disease, transoesophageal echocardiography may be considered together with three-week anticoagulation therapy prior to cardioversion.	IIb	C	993, 999, 1017, 1019

2620 AF = atrial fibrillation; CHA₂DS₂-VASc = Congestive Heart failure, hypertension, Age ≥75
 2621 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

2622 ^a Class of recommendation

2623 ^b Level of evidence

2624 ^c Reference(s) supporting recommendation(s)

2625

2626 12.7 Management of atrial flutter

2627

2628 The goals for the management of atrial flutter are similar to those for AF.¹⁰²¹ Based on the
 2629 available evidence, the stroke risk in patients with atrial flutter is not much different from the
 2630 stroke risk in AF.¹⁰²² Furthermore, many patients diagnosed with atrial flutter develop AF.^{1023–1025}
 2631 Thus, anticoagulation should be used in flutter patients similar to AF patients. Rate control in
 2632 atrial flutter is achieved with the same medications as in AF, but is often more difficult to
 2633 achieve. Flecainide, propafenone, dofetilide and intravenous ibutilide are useful for
 2634 cardioversion of atrial flutter. They should be combined with a rate controlling agent to avoid 1:1
 2635 conduction of slowing flutter waves to the ventricles. Ibutilide is more effective for conversion of
 2636 atrial flutter than AF, while vernakalant is less effective in converting typical atrial flutter.^{1026, 1027}
 2637 Electrical cardioversion of atrial flutter can be performed using lower energies (50–100 joules)
 2638 than AF.^{1028, 1029} Atrial overdrive pacing through pacemaker leads, endocardial or
 2639 transesophageal catheters can convert atrial flutter to sinus rhythm.^{1030, 1031} Anticoagulation and
 2640 transoesophageal echocardiography around cardioversion or overdrive pacing should be used
 2641 similar to AF.

2642 Ablation of the cavotricuspid isthmus for isthmus-dependent right atrial atrial flutter (either the
 2643 common counterclockwise atrial flutter or the less common clockwise atrial flutter) restores and
 2644 maintains sinus rhythm with a success rate over 90–95%.¹⁰³² It may also reduce AF recurrences
 2645 in selected patients,^{1033, 1034} and help to prevent hospitalizations.^{1034, 1035} Isthmus ablation is
 2646 comparably safe and more effective than AAD therapy, and is recommended for recurrent atrial

flutter.^{603-605, 738} Catheter ablation of left atrial macro-reentrant tachycardia is more complex with lower success rates and higher recurrence rates.^{1036, 1037}

2649

2650 Recommendations for management of atrial flutter

Recommendations	Class ^a	Level ^b	Refs ^c
For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.	I	B	1022
Overdrive atrial pacing of atrial flutter should be considered as an alternative to electrical cardioversion, depending on local availability and experience.	IIa	B	1030, 1031
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	156
If atrial flutter has been documented prior to AF ablation, ablation of the cavotricuspid isthmus should be considered as part of the AF ablation procedure.	IIa	C	

2651 AF = atrial fibrillation

2652 ^a Class of recommendation

2653 ^b Level of evidence

2654 ^c Reference(s) supporting recommendation(s)

2655

13. Patient involvement, education and self-management

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

13.1 Patient-centred care

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.³³⁵ Shared decision making⁷⁷² and patient-centred organization of care can help to ensure adherence to management and empower patients, and respect individual patient preferences, needs and values (Chapter 7.2).^{333, 1038, 1039} 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.¹⁰⁴⁰

13.2 Integrated patient education

Education is a prerequisite for informed, involved patients and patient-centred care. However, lack of AF-related knowledge in patients is common, even in patients who received verbal and written information^{32, 1041, 1042}, indicating the need to further develop structured patient education. Several patient information tools have been developed, largely focussing on oral anticoagulation.¹⁰⁴³⁻¹⁰⁴⁶ Understanding patients' perceptions and attitudes towards AF its management can improve AF management and related outcomes.¹⁰⁴⁷ This includes tailored patient education focussing on the disease, symptom recognition, therapy, modifiable risk factors for AF and self-management activities.^{1048, 1049}

13.3 Self-management and shared decision making

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.¹⁰⁵⁰ It requires understanding of the treatment modalities and goals.¹⁰⁵¹ Within a multidisciplinary team, allied health professionals can guide this interactive process in which communication, trust and reciprocal respect foster patient engagement.¹⁰⁵² Shared decision making should be considered as a routine part of the decision making process⁷⁷², supported by decision aids where applicable.¹⁰⁵³ Models of care that integrate education, engagement and

shared decision making are now available,¹⁰⁵⁴ and may be of particular value in the management of AF.

Recommendations for patient involvement, education and self-management

Recommendations	Class ^a	Level ^b	Refs ^c
Tailored patient education is recommended in all phases of AF management to support the perception of patients of AF and to improve management.	I	C	1044, 1047
Patient involvement in the care process should be considered to encourage self-management and responsibility for lifestyle changes.	Ila	C	335, 1040
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.	Ila	C	772

AF = atrial fibrillation

^a Class of recommendation

^b Level of evidence

^c Reference(s) supporting recommendation(s)

14. Evidence gaps

There are some areas of AF management that are supported by excellent evidence from multiple, adequately powered randomized trials, mainly antithrombotic therapy. Other areas, such as rhythm control therapy, integrated AF management, or life style modifications are clearly developing the required evidence, while areas such as rate control are in dire need of better studies to underpin future guidelines.

14.1 Major health modifiers causing atrial fibrillation

Atrial fibrillation has different causes in different patients. More research is needed into the major causes (and electrophysiological mechanisms) of AF in different patient groups.^{175, 1055} Such research should consider the major comorbidities associated with AF, and characterize the response to AF therapy in patients with different, pathophysiologically distinct types of AF.

14.2 Stroke rates in less studied populations

Several specific AF patient groups should be studied to better characterize their risk for AF, stroke, and other AF related complications, e.g. patients with one stroke risk factor and non-Caucasian patients. Confounding factors, e.g. different therapy of concomitant cardiovascular diseases, may help to explain the various inconsistencies in the reported rates of incident and prevalent AF as well as variations in AF complication rates in these patients. This also applies to the effect of gender in AF patients.⁴⁷

14.3 Optimal timing of non-acute cardioversion

Based on retrospective data, previous recommendations as to the safe time window in which a cardioversion can be performed in new-onset AF used ≤ 48 hours as the 'gold standard' for non-protected cardioversion. However, new evidence has emerged that initiating pre-cardioversion anticoagulation in patients with AF episodes of < 24 hours or even < 12 hours would provide even better safety.^{660, 665, 1056-1058} Further research is needed to establish a clear safety margin in this clinical situation.

14.4 Anticoagulation in patients with biological heart valves and non-rheumatic valve disease

The optimal antithrombotic therapy in the first months after biological valve replacement is not known. VKAs remain the mainstay during the initial postoperative period, NOACs probably deliver the same protection. In patients without AF, many centres use platelet inhibitors only. NOACs appear to be equally effective as VKA in patients with moderate aortic stenosis, based on a subanalysis from the ROCKET-AF trial¹⁰⁵⁹ as well as the Loire Valley AF project.¹⁰⁶⁰ Further data would be helpful to confirm these observations.¹⁰⁶¹ The safety and efficacy of NOACs in patients with rheumatic mitral valve disease has not been evaluated and should be studied.

2735

2736 14.5 **How much atrial fibrillation constitutes a mandate for therapy?**

All information on the benefit of anticoagulation has been collected in patients with AF diagnosed by ECG. Technological advances allow screening for an irregular pulse using patient-operated ECG devices, smartphones, and a variety of other technologies. These may be very useful to detect silent, undiagnosed AF.¹⁵⁵ Adequately powered studies evaluating the diagnostic accuracy of such technologies, the diagnostic yield in different populations, the shortest duration of atrial arrhythmias conveying a stroke risk, and ideally the impact of ECG screening on outcomes are needed.

2744

2745 14.6 **Atrial high rate episodes and need for anticoagulation**

All information on the benefit of OAC has been collected in patients with AF diagnosed by ECG. Technological advances allow to readily detect atrial high rate episodes (AHRE) in patients with implanted devices and an atrial lead. Such patients are at increased stroke risk, but it is unclear whether they benefit from OAC. Controlled trials evaluating OAC in AHRE patients are ongoing and will inform about the best antithrombotic therapy in these patients.

2751

2752 14.7 **Anticoagulation in patients with severe chronic kidney disease**

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

2758

2759 14.8 Left atrial occlusion

2760 The most common justification for LAA occlusion devices in clinical practice is a perceived high
2761 bleeding risk and, less often, contraindications for OAC.⁴⁶⁹ Unfortunately, LAA occluders have
2762 not been tested in such populations. Furthermore, LAA occluders have not been compared to
2763 NOAC therapy in patients at risk for bleeding, or with thoracoscopic LAA clipping. There is a
2764 clear need to conduct adequately designed and powered trials to define the clinical role of LAA
2765 occluders compared to NOAC therapy in patients with relative or absolute contraindications for
2766 anticoagulation, and/or in those suffering from an ischemic stroke on anticoagulant therapy.

2767

2768 14.9 Anticoagulation in AF patients after a bleeding or stroke event

2769 At least 2% of anticoagulated AF patients will experience a serious bleeding event per year.
2770 Observational data suggest that OAC can be reinitiated even after an intracerebral bleeding
2771 event.^{470, 507} Controlled studies evaluating different anticoagulation and stroke prevention
2772 interventions are urgently needed to inform the best management of patients who have suffered
2773 a bleeding event that would usually lead to withholding OAC. Some studies (e.g. APACHE II
2774 ¹⁰⁶²) are ongoing, but adequately powered trials are needed. Similarly, prospectively collected
2775 data are needed on the efficacy and bleeding risk following (re-)initiation of OAC after stroke or
2776 intracranial bleeding.

2777

2778 14.10 Comparison of rate control agents

2779 Although the use of rate control therapy is very common in AF patients, robust data comparing
2780 rate control therapies are scant, with the majority of studies being small, uncontrolled trials over
2781 short periods of follow-up. Some studies are funded (e.g. RATE-AF⁵⁷⁵) and will investigate the
2782 potential benefits of different rate controlling agents, characteristics or biomarkers that can help
2783 to personalize the use of rate control, and the adverse event profile of specific drugs in defined
2784 groups of patients (for example, AF with HFrEF).

2785

2786 14.11 Combination therapy for rhythm control

2787 In the follow-up after initially successful catheter ablation, even when done in experienced
2788 centres, many patients will experience symptomatic recurrences of AF. These patients are often
2789 managed with AAD. There is a surprising paucity of data evaluating different rhythm control

2790 interventions in patients with recurrent AF after catheter ablation. Such studies seem
2791 reasonable and feasible.

2792

2793 14.12 **Can rhythm control therapy convey a prognostic benefit in AF patients?**

2794 The progress in rhythm control therapy (catheter ablation, new antiarrhythmic drugs) and
2795 observational long-term analyses suggest that rhythm control therapy may have a prognostic
2796 benefit. Ongoing trials such as CABANA and EAST – AFNET 4 will provide initial answers to
2797 this important question, but more data are needed, in addition to trials of surgical ablation
2798 techniques.

2799

2800 14.13 **Catheter ablation in persistent and long-standing persistent AF**

2801 While there are a few recent randomized studies supporting the use of catheter or surgical
2802 ablation in patients with persistent AF and long-standing persistent AF, there is a clear need for
2803 more data evaluating this intervention in adequately powered randomized trials.

2804

2805 14.14 **Optimal technique for repeat catheter ablation**

2806 Pulmonary vein isolation emerges as the most important target for catheter ablation of AF.
2807 Although a plethora of different additional ablation techniques have been published, their added
2808 value is questionable in patients undergoing a first catheter ablation, including those with
2809 persistent AF.⁷⁶² Many patients are in need of multiple catheter ablation procedures, and such
2810 interventions often follow local or operator-specific protocols without clear evidence to support
2811 the choice of ablation target or intervention. There is a clear clinical need to define the best
2812 approach to patients who are in need of a second ablation procedure.

2813

2814 14.15 **Anticoagulation after “successful” catheter ablation**

2815 In view of the long-term recurrence rates of AF, this task force recommends to continue OAC in
2816 AF patients after “successful” catheter ablation. Nonetheless, observational data suggest that
2817 the stroke risk may be lower after catheter ablation of AF compared to other AF patients. The
2818 ongoing EAST trial will inform in a more general way whether rhythm control therapy can reduce
2819 stroke rates in anticoagulated AF patients. If confirmed, there may be a place for a controlled
2820 trial evaluating the termination of OAC therapy at an interval after “successful” catheter ablation.

2821

2822 14.16 **Thoracoscopic “stand alone” AF surgery**

2823 Minimally invasive epicardial ablation surgery for the treatment of stand-alone AF was reported
2824 a decade ago.¹⁰⁶³ The procedure has since evolved towards a totally thoracoscopic
2825 procedure¹⁰⁶⁴, and lesion sets were extended to a complete left atrial maze.⁸⁴⁸ With such rapid
2826 development and the coexistence of different techniques and lesion sets, scientific evidence on
2827 long-term results is still limited. Randomized trials using a standardized procedure are urgently
2828 needed to clearly define the benefits and risks of thoracoscopic AF ablation, and to further
2829 support decisions of the AF Heart Team.

2830

2831 14.17 **Surgical exclusion of the left atrial appendage**

2832 Exclusion of the LAA has been performed by cardiothoracic surgeons for decades, but
2833 prospective randomized studies comparing the rate of ischemic stroke with or without left
2834 appendage exclusion are presently lacking. The Left Atrial Appendage Occlusion Study
2835 (LAAOS) III is currently randomising cardiac surgery patients with AF to undergo concomitant
2836 occlusion or no occlusion of the appendage.⁴⁷⁷ More data are also needed to confirm the
2837 safety and efficacy of thoracoscopic exclusion, following early positive observational data.¹⁰⁶⁵

2838

2839 14.18 **Concomitant AF surgery**

2840 Adequately powered randomized trials are needed, employing systematic follow-up, uniform
2841 lesion sets and energy sources to evaluate the benefits and risks of concomitant AF surgery in
2842 symptomatic AF patients. An RCT on non-uniform lesion sets with long-term follow-up is due to
2843 publish shortly.¹⁰⁶⁶ These will assist the AF Heart Team to decide on optimal therapy for
2844 individual patients, including the full repertoire of medical and surgical options for the treatment
2845 of AF.

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(There will be some references that can be updated before publication that currently only have DOIs)

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4882 Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular
4883 Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA)

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