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

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of: European Heart Rhythm Association [†] and the European Stroke Organisation (ESO)+

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

AAD	antiarrhythmic drug
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome(s)
ACT	activated clotting time
AF	atrial fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy of life questionnaire
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFNET	German Competence NETwork on Atrial Fibrillation
AF-QoL	quality of life questionnaire for patients with atrial fibrillation
AHRE	atrial high rate episodes
AP	action potential
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ARREST-AF	Aggressive Risk Factor Reduction Study for Atrial Fibrillation
ASD	atrial septal defect
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial
AV	atrioventricular
AVERROES	Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
AXAFA	Anticoagulation using the direct factor Xa inhibitor apixaban during Atrial Fibrillation catheter Ablation: Comparison to vitamin K antagonist therapy

BAFTA	Birmingham Atrial Fibrillation Treatment of the Aged Study
b.i.d.	twice daily
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
CABANA	Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial
CAD	coronary artery disease
CARE-HF	CArdiac REsynchronisation in Heart Failure
CFAE	complex fractionated atrial electrograms
$CHADs_2$	Congestive heart failure, Hypertension, Age $\geq$75, Diabetes, Stroke (doubled)
CHA_2DS_2-VASc	Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female)
CI	confidence interval
CKD	chronic kidney disease
CMP	Cox maze procedure
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRP	C-reactive protein
CRT	cardiac resynchronization therapy
CT	computed tomography
cTnT	cardiac troponin T
CV	cardiovascular
DIG	Digitalis Investigation Group

EAD	early afterdepolarization
EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EHRA	European Heart Rhythm Association
ENGAGE AF-TIMI	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction
EORP	EURObservational Research Programme
ESUS	embolic stroke of undetermined source
FAST	Atrial Fibrillation Catheter Ablation vs Surgical Ablation Treatment
FDA	US Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GDF-15	growth differentiation factor 15
GFR	glomerular filtration rate
GI	gastrointestinal
GP	general practitioner
GUCH	grown up congenital heart disease
HARMONY	A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation
HAS-BLED	hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
IART	intra-atrial reentrant tachycardia

ICB	intracranial bleed
ICD	implantable cardioverter defibrillator
ICD code	International Classification of Diseases code
ICM	insertable cardiac monitor
ICH	intracranial haemorrhage
IHD	ischaemic heart disease
INR	international normalized ratio
IQR	interquartile range
ITT	intention to treat
IV	intravenous
LA	left atrium/atrial
LAA	left atrial appendage
LAAOS	Left Atrial Appendage Occlusion Study
LMWH	low-molecular-weight heparin
LQT	long QT
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVOTO	left ventricular outflow tract obstruction
MACE	major adverse cardiac events
MANTRA-PAF	Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
MDRD	Modification of Diet in Renal Disease
MERLIN	Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome
MH	major haemorrhages
mEHRA	modified EHRA

MI	myocardial infarction
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NIHSS	National Institutes of Health Stroke Scale
NNH	number needed to harm
NNT	number needed to treat
NOAC	non-vitamin K antagonist oral anticoagulant
NT-proBNP	N-terminal fragment B-type natriuretic peptide
NYHA	New York Heart Association
OAC	oral anticoagulation
o.d.	once daily
OR	odds ratio
OSA	obstructive sleep apnoea
PAFAC	Prevention of Atrial Fibrillation After Cardioversion
PCC	prothrombin complex concentrates
PCI	percutaneous coronary intervention
PITX2	paired-like homeodomain transcription factor 2
PREFER in AF	PREvention oF thromboembolic events - European Registry in Atrial Fibrillation
PREVAIL	Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients with AF Versus Long Term Warfarin Therapy trial
PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF trial
PUFA	polyunsaturated fatty acid
VI	pulmonary vein isolation
QALYs	quality adjusted life years
QoL	quality of life
RACE	Rate Control Efficacy in Permanent Atrial Fibrillation

RCT	randomized controlled trial
RealiseAF	Real-life global survey evaluating patients with Atrial Fibrillation
RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonaRy vein ablation: assessment of different peri-proCedUral anticoagulation sTrategies
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
RF	radiofrequency
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	risk ratio
rtPA	recombinant tissue plasminogen activator
RV	right ventricle
SAFE	Screening for AF in the Elderly study
SAH	subarachnoid hemorrhage
SAN	sinoatrial node
SBP	systolic blood pressure
SD	standard deviation
SDH	subdural haemorrhage
SE	systemic embolism
SERVE-HF	Treatment of sleep-disordered breathing with predominant central sleep apnoea by adaptive Servo-ventilation in patients with Heart Failure
SF-36	short form 36 health survey questionnaire
SNP	single nucleotide polymorphism
SPAF	Stroke Prevention in Atrial Fibrillation
SR	sinus rhythm
STS	Society of Thoracic Surgeons
TAVI	transcatheter aortic valve replacement

TIA	transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TOE	transoesophageal echocardiography
TTE	transthoracic echocardiography
TTR	time in therapeutic range
UFH	unfractionated heparin
VKA	vitamin K antagonist
VT	ventricular tachycardia
WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing
WPW	Wolff-Parkinson-White syndrome

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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.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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 persons[1] 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 AF[16-18] 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 mood[33] 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]

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.

AF = atrial fibrillation; LV = left ventricular.

2.4 Gender

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

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

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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 characteristics[67-70], atrial remodelling, and modified penetration of rare gene defects[61] 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.

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]

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]

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 surface [107] recordings.

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

Pathophysiological alteration	Clinical conditions contributing to the alteration	Proarrhythmic mechanism/ functional consequence	References
Changes of the extracellular matrix, fibroblast function and fat cells			
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
Ion channel alterations			
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
Ca2+ 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
Myocyte alterations			

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]

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 age[129]. (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 recorders[138] 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 AF[148] and the benefit of OAC in patients with AHRE is being evaluation 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.

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 CHA_2DS_2-VASc risk factors	IIb	B	130, 135, 155

AF = atrial fibrillation; AHRE = atrial high rate episodes; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

4.3 ECG detection of atrial flutter

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

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 patients[166] (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 obesity[167]), lifestyle factors (e.g. activity level, smoking, alcohol intake[168, 169]), markers of cardiac structural remodelling (e.g. fibrosis[170-172] or electrocardiographic parameters of AF complexity[173]), 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

847 symptoms in class 2b ('troubling' symptoms) identified patients with a health utility benefit of
848 rhythm control in that study, this modification may provide a threshold for potential treatment
849 decisions, but this remains to be tested. While some AF patients had no or minimal symptoms
850 (25-40%), many (15-30%) reported severe or disabling symptoms.[193, 195] The EHRA scale
851 should be used to guide symptom-oriented treatment decisions and for longitudinal patient
852 profiling.

853

854 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

855 [a] Class of recommendation

856 [b] Level of evidence

857 [c] Reference(s) supporting recommendation(s)

858

859 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

860 * EHRA class 2a and 2b can be differentiated by evaluating whether patients are functionally
861 affected by their AF symptoms. AF-related symptoms are most commonly fatigue / tiredness
862 and exertional shortness of breath, or less frequently palpitations and chest pain.[42, 193, 199-201]
863 Modified from [198]

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

865

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] 50–59 years 60–69 years 70–79 years 80–89 years	HR: 1.00 (reference) 4.98 (95% CI 3.49–7.10) 7.35 (95% CI 5.28–10.2) 9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none[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] hypothyroidism subclinical hyperthyroidism overt hyperthyroidism	(reference: euthyroid) HR 1.23 (95% CI 0.77-1.97) RR 1.31 (95% CI 1.19–1.44) RR 1.42 (95% CI 1.22–1.63)
Obesity[19, 207] none (BMI <25 kg/m²) overweight (BMI 25–30 kg/m²) obese (BMI ≥31 kg/m²)	HR: 1.00 (reference) 1.13 (95% CI 0.87–1.46) 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] FEV1 % ≥80% 60–80% <60%	RR: 1.00 (reference) 1.28 (95% CI 0.79–2.06) 2.53 (95% CI 1.45–4.42)
Obstructive sleep apnoea vs. none[209]	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease[210] none stage 1 to 2 stage 3 stage 4 to 5	OR: 1.00 (reference) 2.67 (95% CI 2.04–3.48) 1.68 (95% CI 1.26–2.24) 3.52 (95% CI 1.73–7.15)

Smoking[211]	HR:
never	1.00 (reference)
former	1.32 (95% CI 1.10–1.57)
current	2.05 (95% CI 1.71–2.47)
Alcohol[212]	RR:
None	1.00 (reference)
1 to 6 drinks/week	1.01 (95% CI 0.94–1.09)
7 to 14 drinks/week	1.07 (95% CI 0.98–1.17)
15 to 21 drinks/week	1.14 (95% CI 1.01–1.28)
>21 drinks/week	1.39 (95% CI 1.22–1.58)
Habitual vigorous exercise[213]	RR:
Non-exercisers	1.00 (reference)
<1 day/week	0.90 (95% CI 0.68−1.20)
1−2 days/week	1.09 (95% CI 0.95−1.26)
3−4 days/week	1.04 (95% CI 0.91−1.19)
5−7 days/week	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

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 ≥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).

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 Guidelines[221]. This includes ACE inhibitors/ARBs, mineralocorticoid antagonists, defibrillators and cardiac resynchronisation therapy[217], 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 tachycardiomoypathy 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 HFpEF[221], 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 HFpEF[238] 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 mineralocortcoid receptor antagonist, also reduced new-onset AF in patients with LVEF ≤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 disease[258], 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)

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]

6.5 Obesity and weight loss

6.5.1 Obesity as a risk factor

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

6.5.2 Weight reduction in AF patients

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

6.5.3 Catheter ablation in obese patients

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

Recommendations	Class [a]	Level [b]	Refs[c]

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

Recommendations for obese patients with AF

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

6.6 COPD, sleep apnoea, and other respiratory diseases

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

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

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.	IIa	B	310, 311, 320, 321
Obstructive sleep apnoea treatment should be optimized to reduce AF recurrences and improve AF treatment results.	IIa	B	313-317

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

6.7 Chronic kidney disease

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

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.	IIa	B	

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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 patients[332] (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).

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

Anticoagulation should be initiated early in all suitable patients and will not routinely require specialist input. AF = atrial fibrillation.

7.1 Evidence supporting integrated AF care

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

7.2 Components of integrated AF care

Patient involvement: Patients should have a central role in the care process. Since treatment of AF requires patients to change their lifestyle and to adhere to chronic therapy, at times without an immediately tangible benefit, they need to understand their responsibilities in the 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.

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.	IIa	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.	IIa	C	337, 339, 341

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

7.3 Diagnostic workup of AF patients

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

7.3.1 Recommended evaluation in all AF patients

A complete medical history should be taken and all patients should undergo clinical evaluation that includes thorough assessment for concomitant conditions, establishing the AF pattern, estimation of stroke risk and AF related symptoms, and assessment of arrhythmia-related complications such as thromboembolism or left ventricular dysfunction. A 12-lead ECG is recommended to establish a suspected diagnosis of AF, to determine rate in AF, to screen for conduction defects, ischemia, and signs of structural heart disease. Initial blood tests should evaluate thyroid and kidney function, as well as serum electrolytes and full blood count. Transthoracic echocardiography (TTE) is recommended in all AF patients to guide treatment decisions. TTE should assess for structural disease (e.g. valvular disease), left ventricular size and function (systolic and diastolic), atrial size, and right heart function.[347] Although biomarkers such as natriuretic peptides are elevated in AF patients, there is insufficient data to suggest that blood based parameters are independent markers for AF.[348-350]

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 contrast[352-354], T1 mapping using cardiac MRI[354] and intracardiac echo[355] 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

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

7.5 Defining Goals of AF management

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

TABLE 10: Goal-based follow-up

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 Hospitalization Therapy complications
Rhythm control	Symptomatic at present	Symptoms vs. side effects Exclusion of pro-arrhythmia (PR; QRS; QTc interval)	
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

bpm = beats per minute; GP = general practitioner; INR = international normalized ratio; LV = left ventricular; EHRA = European Heart Rhythm Association AF symptoms scale; NOAC = non-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 VKA[369] 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 CHA_2DS_2-VASc score has clearly simplified the initial decision for OAC in AF patients. Since its first implementation into the ESC guidelines in 2010[376], it has been widely used.[377] We recommend to estimate stroke risk in AF patients based on the CHA_2DS_2-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. CHA_2DS_2-VASc score of 1 or more for men, and 2 or more for women) are likely to benefit from OAC.

TABLE 11: Clinical risk factors for stroke, transient ischemic attack, and systemic embolism in the CHA_2DS_2-VASc score.

CHA_2DS_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.

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 CHA_2DS_2-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. CHA_2DS_2-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 CHA_2DS_2-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 patients[384-386] and biomarker-based risk scores may in the future prove helpful to better identify patients at a truly low risk of stroke.[386, 387]

Supplementary Table: Reported rates of stroke, often including transient ischemic attack, systemic embolism and pulmonary embolism, in AF patients with CHA_2DS_2-VASc of 1 in men and 2 in women.

	population	Event rate in patients with CHA_2DS_2-VASc = 1 (men) and 2 (women)	
		without anticoagulation	on anticoagulation
Lip[375]	European patients seen by cardiologists admitted to hospital	0.6 (0 - 3.4, men and women)	
Poli[388]	AF patients enrolled in anticoagulation clinics in Italy		0.8 (men and women)
Olesen[389]	Danish population admitted to hospital	1.6 (men and women)	1.3 (men and women)
Olesen[378]	Danish population admitted to hospital	1.45 (men and women)	
Friberg[390]	Swedish population admitted to hospital	0.9	
Guo[391]	Chinese AF patients	0.9 (men and women)	
Coppens[392]	AVERRROES CHADSVASC = 1 randomized to aspirin	0.9 (men and women)	
Forslund[393]	AF patients in the Stockholm region	0.3-0.5 (men and women)	0.0 - 0.3 (men and women)
Chao[379]	Taiwanese AF patients	2.5 (men), 2.75 (women)	
Lip[380]	Danish population admitted to hospital	1.2 (men)	1.0 - 1.1 (men and women)
Friberg[382]	Swedish population	0.5 - 0.7 (men)	
van den Ham[394]	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)			

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]

[a] Derived from the HAS-BLED score[396]; [b] Derived from the HEMORR$_2$HAGES score[395]; [c] Derived from the ATRIA score[397]; [d] Derived from the ORBIT score[398]; [e] Derived from the ABC bleeding score[399].

Recommendations for stroke and bleeding risk prediction

Recommendations	Class [a]	Level [b]	Refs [c]
The CHA_2DS_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

8.2 Stroke prevention

8.2.1 Vitamin K antagonists

Warfarin and other VKA were the first anticoagulants used in AF patients. VKA therapy reduces stroke by two thirds and mortality by a quarter compared to control (aspirin or no therapy).[38] VKA have been used in many patients throughout the world with good outcomes [405-407], and this 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-TT_2R_2 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]

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.

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 Cockroft-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

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Outcomes (% per year)												
	Warfarin	Dabigatran 150	Dabigatran 110	Warfarin	Rivaroxaban	Warfarin	Apixaban	Warfarin	Edoxaban 60	Edoxaban 30	Warfarin	Watchman device
	n = 6022	n = 6076	n = 6015	n = 7133	n = 7131	n = 9081	n = 9120	n = 7036	n = 7035	n = 7034	n = 244	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)

AF = atrial fibrillation; b.i.d. = bis in die (twice daily); CHADS2 = congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA [doubled]; CI = confidence interval; CrI = credible interval; CrCl = creatinine clearance; HR = hazard ratio; ITT = intention-to-treat; o.d. = once daily; PP = posterior probabilities; RR = relative 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-analysis[39] 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 m^2), 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 patients[431], 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-

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

8.2.6 **Patients with AF requiring kidney transplantation**

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

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 CHA_2DS_2-VASc score of two or more, women with a CHA_2DS_2-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 CHA_2DS_2-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

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); NOAC = non-vitamin K antagonist oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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 ablation[473] 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]

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

AF = atrial fibrillation; LAA = left atrial appendage

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

8.4 Secondary stroke prevention

The most important risk factors for stroke in patients with AF are advanced age or prior cardioembolic stroke / TIA[386], emphasizing the need for OAC in these patients. The highest risk of recurrent stroke is in the early phase after a first stroke or TIA.[479, 480]

8.4.1 Treatment of acute ischaemic stroke

Systemic thrombolysis with rtPA is an effective and approved medical treatment of acute ischaemic stroke in patients presenting within 4.5 hours of symptom onset.[481] Systemic thrombolysis is contraindicated in patients on therapeutic OAC.[482, 483] RtPA can be given in patients treated with VKA if the INR is below 1.7,[484] or in dabigatran-treated patients with a normal aPTT and last intake of drug >48 hours previously (based on expert consensus).[482] 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 NOAC[493] 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.

8.4.4 Competing causes of stroke or TIA

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

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.	IIa	B	[500]

AF= atrial fibrillation; aPTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low molecular weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; rtPA = recombinant tissue plasminogen activator; TIA = transient ischaemic attack; VKA = vitamin K antagonist

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

8.5 Strategies to minimize bleeding on anticoagulant therapy

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

8.5.1 Uncontrolled hypertension

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

8.5.2 Prior bleeding

History of bleeding events and the presence of anaemia are important parts of the assessment of all patients receiving OAC. The majority of bleeding events are gastrointestinal. Compared to warfarin the risk of gastrointestinal bleeds was increased for dabigatran 150 mg twice daily,[407, 503] rivaroxaban 20 mg once daily[504] and edoxaban 60 mg once daily.[328] The risk of gastrointestinal bleeds was comparable to warfarin on dabigatran 110 mg twice daily[503] and on 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]

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.

8.5.4 Alcohol abuse

Alcohol excess is a risk factor for bleeding in anticoagulated patients[396], 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.

8.5.5 Falls and dementia

Falls and dementia are associated with increased mortality in AF patients[509], 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.

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]

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 (HEMOCLOT) 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.

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.

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	

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

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

8.7 Combination therapy with oral anticoagulants and antiplatelets

Approximately 15% of AF patients in contemporary trials[527] and registries[528-530] have a history of a prior myocardial infarction. 5–15% of AF patients will require stenting at some point in their lives. This scenario requires careful consideration of antithrombotic therapy, balancing bleeding risk, stroke risk, and the risk of acute coronary syndromes (ACS).[530] Co-prescription of OAC with antiplatelet therapy, in particular triple therapy, increases the absolute risk of major 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).

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 consensus[534], 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

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

Recommendations for combination therapy

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.	IIa	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.	IIa	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.	IIa	C	
The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding.	IIa	B	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

ACS = acute coronary syndromes; AF = atrial fibrillation.

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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]

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 symptoms[541], in comparison to beta-blockers which reduced exercise capacity and increased BNP in one small trial of low-risk patients with preserved LVEF.[557]

Cardiac glycosides, such as **digoxin** and **digitoxin**, have been in use for over two centuries[558], 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 patients[563-565], 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]

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

function[583] and may even improve LVEF in selected patients.[584-586] In some patients in heart failure treated with biventricular pacing (CRT), AF can terminate [587], 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]

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 ≥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

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

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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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.

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

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 EAST[40] and CABANA[613] 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] Vernakalant[621-624] 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.

TABLE 16: Antiarrhythmic drugs for pharmacological cardioversion

Drug	Route	1st dose	Follow-up dose	Risks	Reference
Flecainide	Oral IV	200–300 mg 1.5 - 2 mg/kg over 10 min	N/A	Avoid in patients with IHD and/or significant structural heart disease. Hypotension, atrial flutter with 1:1 conduction, QT prolongation	614, 617
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 Oral	1.5 - 2 mg/kg over 10 min 450–600 mg		Avoid in patients with IHD and/or significant structural heart disease. Hypotension, atrial flutter with 1:1 conduction, QRS prolongation (mild)	641-644
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

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

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

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] sotalol[649], ibutilide[651], or vernakalant [652] can improve efficacy of electrical cardioversion, and similar effects are likely for flecainide [602] and propafenone[653]. Neither beta-blockers,[654] verapamil, diltiazem [655-657], 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 patients[660] 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 guidelines [376] 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 ablation [667] 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 sleep[76]) 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 trial[118]). 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 patients [683] 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).

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.[669] 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.

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 Flecainide slow release	100–150 mg twice daily 200 mg once daily	Contraindicated if creatinine clearance <50 mg/mL, liver disease, ischemic heart disease or reduced LV ejection 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
Propafenone Propafenone SR	150–300 mg three times daily 225–425 mg twice daily	Contraindicated in IHD or reduced LV ejection 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
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

AAD = antiarrhythmic drug; AF = atrial fibrillation; AV = atrioventricular; bpm = beats per minute; IHD = ischaemic heart disease; LV = left ventricular; NYHA = New York Heart Association; SAN = sinoatrial node

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 cardioversion[698-700], 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 prevention [242], at present there is no robust evidence to make any recommendation for the use of aldosterone antagonists for secondary prevention of AF.[720-722]

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.	IIa	B	202, 203, 302, 318 *2 further RCTs due to publish in summer (CAST, AMICA)*
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.	IIa	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.	IIa	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_2DS_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

AAD = antiarrhythmic drug; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; AV = atrioventricular; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); ECG = electrocardiogram; NOAC = non-vitamin K antagonist oral anticoagulant; TOE = transoesophageal echocardiography

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

10.3 Catheter ablation

Since the initial description of triggers in the pulmonary veins that initiate paroxysmal AF,[740] catheter ablation of AF has developed from a specialized, experimental procedure into a common treatment to prevent recurrent AF.[605, 741] This is primarily achieved through isolation of the pulmonary veins, probably requiring complete isolation for full effectiveness[742], and additional ablation in the posterior left atrial wall. AF ablation, when performed in experienced centres by adequately trained teams, is more effective than antiarrhythmic drug therapy in maintaining sinus rhythm, and the complication rate, though not negligible, is comparable to the complication rate of AAD.[603, 743](Add five year MANTRA_PAF data when published)

10.3.1 Indications

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

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 (≈ 5%), and seems even less common after cryoballoon ablation[760], 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 PVI[742] 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.

10.3.3 **Outcome and complications**

The rhythm outcome after catheter ablation of AF is difficult to predict in individual patients.[172, 226, 738, 754] Most patients require more than one procedure to achieve symptom control. [738, 752, 754] In general, better rhythm outcome and lower procedure related complications can be expected in younger patients with a short AF history and frequent, short AF episodes in the absence of significant structural heart disease.[770] Catheter ablation is more effective than AAD therapy in maintaining sinus rhythm (Online Figure B).[(*)771] Sinus rhythm without severely symptomatic recurrences of AF is found in up to 70% of patients with paroxysmal AF (Add MANTRA-PAF 5 yr outcomes when published), and around 50% in persistent AF.[738, 754, 762] Very late recurrence of AF after years of sinus rhythm is not uncommon and may reflect disease progression, with important implications for continuation of AF therapies.[754] Multiple parameters have been identified as risk factors for recurrence after catheter ablation of AF, but their predictive power is weak. The decision for catheter ablation thus should be based on a shared decision making process [772] (see chapter 7), following thorough explanation of the potential benefits and risks, and of the alternatives such as AAD or acceptance of current symptoms without rhythm control therapy.[773]

(*)*Add ref to commissioned meta-analysis when published: Systematic review and meta-analysis of randomised trials that compare ablation to antiarrythmic drugs in patients with persistent atrial fibrillation. Authors: Guy Amit, Alma Adler, Onikepe Owolabi, Juan P. Casas, Jonathan Nyong, David Prieto-Merino, Pablo Perel, Pier Lambiase and Carlos A. Morillo*

Complications of catheter ablation for AF. There is a clear need to capture complications in clinical practice systematically to improve the quality of AF ablation procedures.[174] The median length of hospital stay in AF patients undergoing their first ablation as part of the EURObservational Research Programme (EORP) was 3 days (IQR 2–4 days), based on 1391 patients from hospitals performing at least 50 ablations per year. Five to seven percent of patients will suffer severe complications after catheter ablation of AF, and 2–3% life-threatening but usually manageable complications.[753, 774-776] Intraprocedural death has been reported, but is rare (<0.2%).[777] The most important severe complications are: stroke/TIA (<1%), cardiac tamponade (1–2%), pulmonary vein stenosis and severe oesophageal injury leading to atrio-oesophageal fistula weeks after ablation (see Table 18). ‘Silent strokes’, i.e. white matter lesions detectable by brain magnetic resonance imaging, have been observed in around 10% of patients treated with radiofrequency and cryoballoon ablation.[778] The clinical relevance of this observation is unclear.[775] Post-procedure complications include stroke, with the highest risk within the first week,[779] late pericardial tamponade several days after catheter ablation,[777] and oesophageal fistulas which usually become apparent 7 to 30 days after ablation. Timely detection of atrio-esophageal fistulas can be life-saving and should be based on the typical triad 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 published[794], 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.

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 ablation[746].*(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.

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).

10.4 AF Surgery

10.4.1 Concomitant AF surgery

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

10.4.2 Stand-alone rhythm control surgery

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

maintenance of sinus rhythm[478, 840], while also causing more complications such as pneumothorax (10%) and bradycardia requiring pacemaker implantation (3%, Table 19). [841] To improve results in patients with persistent or long-standing persistent AF[478, 842-844], more extensive lesion sets have been performed, connecting lines between the PVI encircling and towards the mitral annulus.[838, 845-848] To improve the generation of transmural lesions[742], endo-epicardial ablation strategies have recently been proposed.[838, 849-851] Although preliminary experience with hybrid simultaneous ablation shows promise, procedural time and bleeding complications are higher.[838, 849]

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%

* The rate of asymptomatic cerebral embolism is unknown

AF = atrial fibrillation

10.5 Choice of rhythm control following treatment failure

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

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.

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 cryothermy 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 *Add ref to commissioned Huffman review when published*

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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

AAD = antiarrhythmic drug; AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized ratio; VKA = vitamin K antagonist

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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 amiodarone[860-862], 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 uptitration 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 BAFTA[369], the NOAC trials[39], 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 death[872] and hypertrophic cardiomyopathy[873]).

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 Ca2+ 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

short QT syndrome (Table 20).[881, 884-886] Penetrance of disease phenotype including AF is variable.[61, 880, 913, 914] Both shortening as well as prolongation of the atrial action potential have been demonstrated as likely mechanisms underlying AF in these diseases. It seems reasonable to consider AAD that reverse the suspected channel defect in AF patients with inherited cardiomyopathies, e.g. a sodium channel blocker in LQT3[880], or quinidine in Brugada syndrome.[915] More importantly, new onset AF in young, otherwise healthy individuals should trigger a careful search for such inherited conditions including clinical history, family history, ECG phenotype, and echocardiography and/or other cardiac imaging.

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

Recommendations for inherited cardiomyopathies

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.	IIa	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.	IIa	B	925
Amiodarone should be considered to achieve rhythm control and maintain sinus rhythm in HCM patients.	IIa	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.	IIa	A	880

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

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

12.3 Sports and atrial fibrillation

Physical activity improves cardiovascular health, which translates in a lower risk of AF.[927] Therefore, physical activity is a cornerstone of preventing AF. Intensive sports practice, especially endurance sports (> 1500 hours of endurance sports practice)[928], increases the risk of AF later in life[929-931], probably mediated by altered autonomic tone, volume load during exercise, atrial hypertrophy and dilatation.[932, 933] This results in a U-shaped relationship of physical activity and incident AF.[927, 931, 934-936] Detraining can reduce AF in models[933] and reduces ventricular arrhythmias in athletes,[937] but the role of detraining for AF in human athletes is unknown. The management of athletes with AF is similar to general AF management, but requires a few special considerations. Clinical risk factors will determine the need for anticoagulation. Sports with direct bodily contact or prone to trauma should be avoided in patients on OAC. Beta-blockers are not well tolerated and at times prohibited, and digoxin, verapamil, and diltiazem are often not potent enough to slow heart rate during exertional AF. Catheter ablation for AF probably has similar outcomes in athletes as in non-athletes,[938, 939] but further data are needed. Pill in the pocket therapy has been used as well.[639] After ingestion of flecainide or propafenone as pill in the pocket, patients should refrain from sports as long as AF persists and until two half-lives of the AAD have elapsed. Prophylactic ablation of the flutter circuit may be considered in athletes treated with sodium channel blockers.[940]

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.	IIa	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.	IIa	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.	IIa	C	639

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

12.4 Pregnancy

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

12.4.1 Rate control

Due to a lack of specific data, beta-blockers, verapamil, diltiazem, and digoxin all carry an FDA pregnancy safety category of C (benefits may outweigh risk), except for atenolol (category D: positive evidence of risk). Their use should be at the smallest dose and for the shortest time required. None of the agents are teratogenic, but readily cross the placenta.[944] Beta-blockers are commonly used in clinical practice (e.g. for management of gestational hypertension and pre-eclampsia), but may be associated with intrauterine growth retardation[945] 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]

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]

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.

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	

AF = atrial fibrillation; VKA = vitamin K antagonist

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

12.5 Postoperative AF

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

12.5.1 Prevention of postoperative AF

Beta-blockers reduce postoperative AF and supraventricular tachycardias, albeit with high heterogeneity and moderate risk of bias in a systematic review of published studies (most commonly studied was propranolol, with AF in 16.3% of the treatment group compared to 31.7% in the control group).[955] In the majority of these studies, beta-blockers were administered postoperatively, a regimen supported in a recent meta-analysis.[958] Amiodarone reduced the incidence of postoperative AF compared to a beta-blocker regimen in several meta-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]

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 AF[988], 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.

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-up[991], 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.

Recommendations for preventing postoperative AF

Recommendations	Class [a]	Level [b]	Refs [c]

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] Biatrial 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

tachycardia[1007] 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]

12.6.4 **Atrial tachyarrhythmias after Tetralogy of Fallot correction**

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

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 $CHA_2DS_2VAS_C \geq 1$.	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]**

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

12.7 Management of atrial flutter

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

Ablation of the cavotricuspid isthmus for isthmus-dependent right atrial atrial flutter (either the common counterclockwise atrial flutter or the less common clockwise atrial flutter) restores and maintains sinus rhythm with a success rate over 90–95%.[1032] It may also reduce AF recurrences in selected patients,[1033, 1034] and help to prevent hospitalizations.[1034, 1035] Isthmus ablation is 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]

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	

AF = atrial fibrillation

[a] Class of recommendation

[b] Level of evidence

[c] Reference(s) supporting recommendation(s)

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 making[772] 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 process[772], 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.	IIa	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.	IIa	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 trial[1059] 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.

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.

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.

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.

14.8 Left atrial occlusion

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

14.9 Anticoagulation in AF patients after a bleeding or stroke event

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

14.10 Comparison of rate control agents

Although the use of rate control therapy is very common in AF patients, robust data comparing rate control therapies are scant, with the majority of studies being small, uncontrolled trials over short periods of follow-up. Some studies are funded (e.g. RATE-AF[575]) and will investigate the potential benefits of different rate controlling agents, characteristics or biomarkers that can help to personalize the use of rate control, and the adverse event profile of specific drugs in defined groups of patients (for example, AF with HFrEF).

14.11 Combination therapy for rhythm control

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

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

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

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

14.13 Catheter ablation in persistent and long-standing persistent AF

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

14.14 Optimal technique for repeat catheter ablation

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

14.15 Anticoagulation after “successful” catheter ablation

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

14.16 Thoracoscopic “stand alone” AF surgery

Minimally invasive epicardial ablation surgery for the treatment of stand-alone AF was reported a decade ago.[1063] The procedure has since evolved towards a totally thoracoscopic procedure[1064], and lesion sets were extended to a complete left atrial maze.[848] With such rapid development and the coexistence of different techniques and lesion sets, scientific evidence on long-term results is still limited. Randomized trials using a standardized procedure are urgently needed to clearly define the benefits and risks of thoracoscopic AF ablation, and to further support decisions of the AF Heart Team.

14.17 Surgical exclusion of the left atrial appendage

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

14.18 Concomitant AF surgery

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

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