

# 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)

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

### Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

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**SD** For the **Supplementary Data** which include background information and detailed discussion of the data that have provided the basis for the Guidelines see *European Heart Journal* online.

## Keywords

Guidelines • atrial fibrillation • anticoagulation • vitamin K antagonists • non-vitamin K antagonist oral anticoagulants • left atrial appendage occlusion • rate control • rhythm control • cardioversion • antiarrhythmic drugs • catheter ablation • pulmonary vein isolation • left atrial ablation • AF surgery • upstream therapy • ABC pathway • screening • stroke • recommendations

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**Abbreviations and acronyms**

Abbreviations and acronyms

4S-AF	Stroke risk, Symptom severity, Severity of AF burden, Substrate severity
AAD	Antiarrhythmic drug
ABC	Atrial fibrillation Better Care [includes A (avoid stroke), B (better symptom control), and C (cardiovascular risk factors and comorbid conditions management)]
ABC-bleeding	Age, Biomarkers (haemoglobin, cTnT hs T, GDF-15), and Clinical history (prior bleeding)
ABC-stroke	Age, Biomarkers, Clinical history (stroke risk score)
ACS	Acute coronary syndromes

ACTIVE W	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events trial
AF	Atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFL	Atrial flutter
AHRE	Atrial high-rate episode
AMICA	Atrial Fibrillation Management in Congestive Heart Failure With Ablation
ARCADIA	AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ARREST-AF	Aggressive Risk Factor Reduction Study – Implication for AF
AST	Aspartate aminotransferase
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation (score)
ATTICUS	Apixaban for treatment of embolic stroke of undetermined source
AVERROES	Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
b.i.d.	bis in die (twice a day)
BP	Blood pressure
bpm	Beats per minute
C <sub>2</sub> HEST	CAD/COPD (1 point each), Hypertension (1 point), Elderly ( ≥75 years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point) (score)
CABANA	Catheter ABlation vs. ANtiarrhythmic Drug Therapy for Atrial Fibrillation
CAD	Coronary artery disease
CAPTAF	Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation
CASTLE-AF	Catheter Ablation vs. Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation
CATCH-ME	Characterizing AF by Translating its Causes into Health Modifiers in the Elderly
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome
CHA <sub>2</sub> DS <sub>2</sub> -VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female)
CHADS <sub>2</sub>	CHF history, Hypertension history, Age ≥75 y, Diabetes mellitus history, Stroke or TIA symptoms previously
CHF	Congestive heart failure
CI	Confidence interval
CIED	Cardiac implantable electronic device
CKD	Chronic kidney disease
COP-AF	Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery

COPD	Chronic obstructive pulmonary disease	NOAC	Non-vitamin K antagonist oral anticoagulant
CPAP	Continuous positive airway pressure	NSAID	Non-steroidal anti-inflammatory drug
CrCl	Creatinine clearance	NYHA	New York Heart Association
CRT	Cardiac resynchronization therapy	o.d.	omni die (once daily)
CT	Computed tomography	OAC	Oral anticoagulant
CTI	Cavotricuspid isthmus	OPTIMAS	OPTimal TIMing of Anticoagulation after Stroke
cTnT-hs	High-sensitivity troponin T	OSA	Obstructive sleep apnoea
DAPT	Dual antiplatelet therapy	PACES	Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG
EAST	Early treatment of Atrial fibrillation for Stroke prevention Trial	PAD	Peripheral artery disease
ECG	Electrocardiogram	PCI	Percutaneous coronary intervention
EHRA	European Heart Rhythm Association	PCORI	Patient-Centred Outcomes Research Institute
ELAN	Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation	PIONEER AF-PCI	OPen-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention
ENGAGE AF-TIMI 48	Effective aNticoaGulation with factor XA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48	PREVAIL	Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
ENTRUST-AF PCI	Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention	PRO	Patient-reported outcome
ESC	European Society of Cardiology	PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation
GARFIELD-AF	Global Anticoagulant Registry in the FIELD - Atrial Fibrillation	PVI	Pulmonary vein isolation
GDF-15	Growth differentiation factor-15	QoL	Quality of life
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly	QRS	QRS interval
HCM	Hypertrophic cardiomyopathy	QTc	Corrected QT interval
HF	Heart failure	RACE	Race Control Efficacy in Permanent Atrial Fibrillation
HFpEF	Heart failure with preserved ejection fraction	RCT	Randomized controlled trial
HFrEF	Heart failure with reduced ejection fraction	RE-DUAL	Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
HR	Hazard ratio	RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonary vein ablation: assessment of different peri-procedural anticoagulation strategies
i.v.	intravenous	REHEARSE-AF	REmote HEArt Rhythm Sampling using the AliveCor hear monitor to screen for Atrial Fibrillation
ICH	Intracranial haemorrhage	RE-LY	Randomized Evaluation of Long Term Anticoagulant Therapy
IMPACT-AF	Integrated Management Program Advancing Community Treatment of Atrial Fibrillation	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
INR	International normalized ratio	SAME-TT <sub>2</sub> R <sub>2</sub>	Sex (female), Age (<60 years), Medical history, Treatment, Tobacco use, Race (non-Caucasian) (score)
LA	Left atrium/atrial	SBP	Systolic blood pressure
LAA	Left atrial appendage	START	Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in AF
LEGACY	Long-term Effect of Goal-directed weight management on an Atrial fibrillation Cohort: a 5-Year follow-up study		
LGE-CMR	Late gadolinium contrast-enhanced cardiac magnetic resonance		
LMWH	Low-molecular-weight heparin		
LV	Left ventricular		
LVEF	Left ventricular ejection fraction		
LVH	Left ventricular hypertrophy		
mAFA	Mobile AF App		
MANTRA-PAF	Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation		
MRI	Magnetic resonance imaging		
NDCC	Non-dihydropyridine calcium channel blocker		

STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiography
TTR	Time in therapeutic range
UFH	Unfractionated heparin
US	United States of America
VHD	Valvular heart disease
VKA	Vitamin K antagonist
WOEST	What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting

## 1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organizations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EurObservational Research Programme of international

registries of cardiovascular diseases and interventions which are essential to assess, diagnostic/therapeutic processes, use of resources and adherence to Guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC has developed and embedded, in some of its guidelines, a set of quality indicators (QIs) which are tools to evaluate the level of implementation of the Guidelines and may be used by the ESC, hospitals, healthcare providers and professionals to measure clinical practice as well as used in educational programmes, alongside the key messages from the Guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined below.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (<http://www.escardio.org/guidelines>). This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

**Table 1** Classes of recommendations

	Definition	Wording to use	
Classes of recommendations	<b>Class I</b>	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
	<b>Class II</b>	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
	<b>Class III</b>	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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**Table 2** Levels of evidence

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

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The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists, and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access the full text version of the Guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate, and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

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

## 2 Introduction

Atrial fibrillation (AF) poses significant burden to patients, physicians, and healthcare systems globally. Substantial research efforts and resources are being directed towards gaining detailed information about the mechanisms underlying AF, its natural course and effective treatments (see also the *ESC Textbook of Cardiovascular Medicine: CardioMed*) and new evidence is continuously generated and published.

The complexity of AF requires a multifaceted, holistic, and multidisciplinary approach to the management of AF patients, with their active involvement in partnership with clinicians. Streamlining the care of patients with AF in daily clinical practice is a challenging but essential requirement for effective management of AF. In recent years, substantial progress has been made in the detection of AF and its management, and new evidence is timely integrated in this third edition of the ESC guidelines on AF. The 2016 ESC AF Guidelines introduced the concept of the five domains to facilitate an integrated structured approach to AF care and promote consistent, guideline-adherent management for all patients. The Atrial Fibrillation Better Care (ABC) approach in the 2020 ESC AF Guidelines is a continuum of this approach, with the goal to further improve the structured management of AF patients, promote patient values, and finally improve patient outcomes.

Reflecting the multidisciplinary input into the management of patients with AF and interpretation of new evidence, the Task Force includes cardiologists with varying subspecialty expertise, cardiac surgeons, methodologists, and specialist nurses amongst its members.

Further to adhering to the standards for generating recommendations that are common to all ESC guidelines (see *preamble*), this Task Force discussed each draft recommendation during web-based conference calls dedicated to specific chapters, followed by consensus modifications and an online vote on each recommendation. Only recommendations that were supported by at least 75% of the Task Force members were included in the Guidelines.



## 2.1 What is new in the 2020 Guidelines?

### New recommendations

Recommendations	Class <sup>a</sup>
<b>Recommendations for diagnosis of AF</b>	
ECG documentation is required to establish the diagnosis of AF. A standard 12-lead ECG recording or a single-lead ECG tracing of $\geq 30$ s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.	I
<b>Recommendations for structured characterization of AF</b>	
Structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of AF patients at different healthcare levels, inform treatment decision making, and facilitate optimal management of AF patients.	IIa
<b>Recommendations for screening to detect AF</b>	
When screening for AF it is recommended that: <ul style="list-style-type: none"> <li>• The individuals undergoing screening are informed about the significance and treatment implications of detecting AF.</li> <li>• A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF.</li> <li>• Definite diagnosis of AF in screen-positive cases is established only after the physician reviews the single-lead ECG recording of <math>\geq 30</math> s or 12-lead ECG and confirms that it shows AF.</li> </ul>	I
<b>Recommendations about integrated AF management</b>	
It is recommended to routinely collect PROs to measure treatment success and improve patient care.	I
<b>Recommendations for the prevention of thrombo-embolic events in AF</b>	
For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score $\geq 3$ ) for early and more frequent clinical review and follow-up.	IIa
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors	I
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made 4 - 6 months after the index evaluation.	IIa
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.	III
<b>Recommendations for cardioversion</b>	
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thrombo-embolic risk.	I
For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc ( $>500$ ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.	III
<b>Recommendations for rhythm control/catheter ablation of AF</b>	
<i>General recommendations</i>	
For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient.	I
Repeated PVI procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI.	IIa
<i>AF catheter ablation after antiarrhythmic drug therapy failure</i>	
AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF.	IIa
<i>First-line therapy</i>	
AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic: <ul style="list-style-type: none"> <li>• Paroxysmal AF episodes, or</li> <li>• Persistent AF without major risk factors for AF recurrence as an alternative to AAD class I or III, considering patient choice, benefit, and risk.</li> </ul>	IIa IIIb

Continued

<i>Techniques and technologies</i>	
Use of additional ablation lesions beyond PVI (low voltage areas, lines, fragmented activity, ectopic foci, rotors, and others) may be considered but is not well established.	<b>IIb</b>
<i>Lifestyle modification and other strategies to improve outcomes of ablation</i>	
Strict control of risk factors and avoidance of triggers are recommended as part of rhythm control strategy.	<b>I</b>
<b>Recommendations for stroke risk management peri-cardioversion</b>	
It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.	<b>I</b>
In patients with AF duration of >24 h undergoing cardioversion, therapeutic anticoagulation should be continued for at least 4 weeks even after successful cardioversion to sinus rhythm (beyond 4 weeks, the decision about long-term OAC treatment is determined by the presence of stroke risk factors).	<b>IIa</b>
In patients with a definite duration of AF ≤24 h and a very low stroke risk (CHA <sub>2</sub> DS <sub>2</sub> -VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted.	<b>IIb</b>
<b>Recommendations for stroke risk management peri-catheter ablation</b>	
In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and:	<b>I</b>
<ul style="list-style-type: none"> <li>• Preferably, therapeutic OAC for at least 3 weeks before ablation, or</li> <li>• Alternatively, the use of TOE to exclude LA thrombus before ablation.</li> </ul>	<b>IIa</b>
For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended.	<b>I</b>
<b>Recommendations for long-term AADs</b>	
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.	<b>I</b>
In AF patients treated with flecainide for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered.	<b>IIa</b>
Sotalol may be considered for long-term rhythm control in patients with normal LV function or with ischaemic heart disease if close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is provided.	<b>IIb</b>
<b>Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in AF</b>	
Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.	<b>I</b>
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.	<b>I</b>
Opportunistic screening for AF is recommended in hypertensive patients.	<b>I</b>
Opportunistic screening for AF should be considered in patients with OSA.	<b>IIa</b>
<b>Recommendations for patients with AF and an ACS, PCI, or CCS</b>	
<i>Recommendations for AF patients with ACS</i>	
In AF patients with ACS undergoing an uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and a P2Y <sub>12</sub> inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	<b>I</b>
<i>Recommendations in AF patients with a CCS undergoing PCI</i>	
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	<b>I</b>
<b>Recommendations for the management of active bleeding on OAC</b>	
Four-factor prothrombin complex concentrates should be considered in AF patients on VKA who develop a severe bleeding complication.	<b>IIa</b>
<b>Recommendations for the management of AF during pregnancy</b>	
<i>Acute management</i>	
In pregnant women with HCM, cardioversion should be considered for persistent AF.	<b>IIa</b>
Ibutilide or flecainide i.v. may be considered for termination of AF in stable patients with structurally normal hearts.	<b>IIb</b>
<i>Long-term management (oral administration of drugs)</i>	
Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail.	<b>IIa</b>
Digoxin or verapamil should be considered for rate control if beta-blockers fail.	<b>IIa</b>

Continued

Recommendations for postoperative AF	
Long-term OAC therapy to prevent thrombo-embolic events should be considered in patients at risk for stroke with postoperative AF after non-cardiac surgery, considering the anticipated net clinical benefit of OAC and informed patient preferences.	IIa
Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery.	III
Recommendations pertaining to sex-related differences in AF	
Women with symptomatic paroxysmal or persistent AF should be offered timely access to rhythm control therapies, including AF catheter ablation, when appropriate for medical reasons.	IIa
Recommendations for quality measures in AF	
The introduction of tools to measure quality of care and identify opportunities for improved treatment quality and AF patient outcome should be considered by practitioners and institutions.	IIa

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AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; CCS = chronic coronary syndrome; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); CrCl = creatinine clearance; ECG = electrocardiogram; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; HCM = hypertrophic cardiomyopathy; i.v. = intravenous; LA = left atrium/atrial; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; OSA = obstructive sleep apnoea; PCI = percutaneous coronary intervention; PRO = patient-reported outcome; PVI = pulmonary vein isolation; QTc = corrected QT interval; TOE = transoesophageal echocardiography; VKA = vitamin K antagonist therapy.  
<sup>a</sup>Class of recommendation.

### Changes in the recommendations

Recommendations about integrated AF management			
2020	Class <sup>a</sup>	2016	Class <sup>a</sup>
To optimize shared decision making about specific AF treatment option(s) in consideration, it is recommended that: <ul style="list-style-type: none"> <li>Physicians inform the patient about advantages/limitations and benefit/risks associated with considered treatment option(s); and</li> <li>Discuss the potential burden of the treatment with the patient and include the patient's perception of treatment burden in the treatment decision.</li> </ul>	I	Placing patients in a central role in decision making should be considered in order to tailor management to patient preferences and improve adherence to long-term therapy	IIa
Recommendations for the prevention of thrombo-embolic events in AF			
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.	I	Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.	IIa
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are: <ul style="list-style-type: none"> <li>Switching to a NOAC but ensuring good adherence and persistence with therapy; or</li> <li>Efforts to improve TTR (e.g. education/counselling and more frequent INR checks).</li> </ul>	I  IIa	AF patients already on treatment with a VKAs may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contraindications to NOAC (e.g. prosthetic valve).	IIb
Recommendations for rhythm control/catheter ablation of AF			
<i>AF catheter ablation after drug therapy failure</i>			
AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with: <ul style="list-style-type: none"> <li>Paroxysmal AF, or</li> <li>Persistent AF without major risk factors for AF recurrence, or</li> <li>Persistent AF with major risk factors for AF recurrence.</li> </ul>	I	Catheter or surgical 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

Continued

<i>First-line therapy</i>			
AF catheter ablation:			
<ul style="list-style-type: none"> <li>Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status.</li> </ul>	I	AF ablation should be considered in symptomatic patients with AF and HFrEF to improve symptoms and cardiac function when tachycardiomyopathy is suspected.	IIa
<ul style="list-style-type: none"> <li>Should be considered in selected AF patients with HFrEF to improve survival and reduce HF hospitalization.</li> </ul>	IIa		
<i>Techniques and technologies</i>			
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.	I	Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryotherapy balloon catheters.	IIa
If patient has a history of CTI-dependent atrial flutter or if typical atrial flutter is induced at the time of AF ablation, delivery of a CTI lesion may be considered.	IIb	Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if documented or occurring during the AF ablation	IIa
<i>Lifestyle modification and other strategies to improve outcomes of ablation</i>			
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.	I	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>Recommendations for stroke risk management peri-cardioversion</b>			
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety as warfarin.	I	Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa
<b>Recommendations for stroke risk management peri-catheter ablation</b>			
After AF catheter ablation, it is recommended that: <ul style="list-style-type: none"> <li>Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and</li> <li>Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.</li> </ul>	I	All patients should receive oral anticoagulation for at least 8 weeks after catheter ablation.	IIa
<b>Recommendations for long-term antiarrhythmic drugs</b>			
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.	I	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
<b>Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF</b>			
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	BP control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding	IIa
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.	IIa	Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting intense sports participation can promote AF	I
Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms.	IIb	OSA treatment should be optimized to reduce AF recurrences and improve AF treatment results.	IIa
<b>Recommendations for stroke prevention in AF patients after ICH</b>			
In AF patients at high risk of ischaemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: <ul style="list-style-type: none"> <li>A trauma-related ICH</li> <li>Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits</li> </ul>	IIa	After ICH oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled.	IIb

Continued

**Recommendations for postoperative AF**

Long-term OAC therapy to prevent thrombo-embolic events may be considered in patients at risk for stroke with postoperative AF after cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.

**IIb**

Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk.

**IIa**

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AAD = antiarrhythmic drug; AF = atrial fibrillation; BP = blood pressure; CTI = cavotricuspid isthmus; HFrEF = heart failure with reduced ejection fraction; ICH = intracranial haemorrhage; INR = international normalized ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant or oral anticoagulation; PVI = pulmonary vein isolation; TTR = time in therapeutic range; VKA = vitamin K antagonist.

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

## 3 Definition and diagnosis of atrial fibrillation

### 3.1 Definition

**Table 3** Definition of atrial fibrillation

	Definition
<b>AF</b>	A supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. <i>Electrocardiographic characteristics of AF include:</i> <ul style="list-style-type: none"> <li>● Irregularly irregular R-R intervals (when atrioventricular conduction is not impaired),</li> <li>● Absence of distinct repeating P waves, and</li> <li>● Irregular atrial activations.</li> </ul>
	<b>Currently used terms</b>
<b>Clinical AF</b>	<i>Symptomatic or asymptomatic AF</i> that is documented by surface ECG. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or entire 12-lead ECG. <sup>1,2</sup>
<b>AHRE, subclinical AF</b>	Refers to individuals <i>without symptoms attributable to AF</i> , in whom <i>clinical AF is NOT previously detected (that is, there is no surface ECG tracing of AF)</i> , see also <a href="#">section 3.3</a> . <b>AHRE</b> - events fulfilling programmed or specified criteria for AHRE that are detected by CIEDs with an atrial lead allowing automated continuous monitoring of atrial rhythm and tracings storage. CIED-recorded AHRE need to be visually inspected because some AHRE may be electrical artefacts/false positives. <b>Subclinical AF</b> includes AHRE confirmed to be AF, AFL, or an AT, or AF episodes detected by insertable cardiac monitor or wearable monitor and confirmed by visually reviewed intracardiac electrograms or ECG-recorded rhythm.

Device-programmed rate criterion for AHRE is  $\geq 175$  bpm, whereas there is no specific rate limit for subclinical AF.

The criterion for AHRE duration is usually set at  $\geq 5$  min (mainly to reduce the inclusion of artefacts), whereas a wide range of subclinical AF duration cut-offs (from 10 - 20 seconds to  $>24$  hours) is reported in studies of the association of subclinical AF with thromboembolism. The reported duration refers to either the longest single episode or, more commonly, total duration of AHRE/subclinical AF during the specified monitoring period.

Although not completely identical, the terms AHRE and subclinical AF are often used interchangeably (in this document the amalgamated term AHRE/subclinical AF will be used for practicality).<sup>3-5</sup> Whereas a large body of high-quality evidence from RCTs informing the management of AF patients pertains exclusively to 'clinical' AF (that is, the ECG documentation of AF was a mandatory inclusion criterion in those RCTs), data on optimal management of AHRE and subclinical AF are lacking. For this reason, AF is currently described as either 'clinical' or 'AHRE/subclinical', until the results of several ongoing RCTs expected to inform the management of AHRE and 'subclinical' AF are available.

AHRE = atrial high-rate episode; AF = atrial fibrillation; ECG = electrocardiogram; AFL = atrial flutter; AT = atrial tachycardia; bpm = beats per minute; CIED = cardiac implantable electronic device; ECG = electrocardiogram; RCT = randomized controlled trial.

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### 3.2 Diagnostic criteria for atrial fibrillation

The diagnosis of AF requires rhythm documentation with an electrocardiogram (ECG) tracing showing AF. By convention, an episode lasting at least 30 s is diagnostic for clinical AF.<sup>6</sup>

#### Recommendations for diagnosis of AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
ECG documentation is required to establish the diagnosis of AF. <ul style="list-style-type: none"> <li>A standard 12-lead ECG recording or a single-lead ECG tracing of <math>\geq 30</math> s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.<sup>6</sup></li> </ul>	<b>I</b>	<b>B</b>

AF = atrial fibrillation; ECG = electrocardiogram.  
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

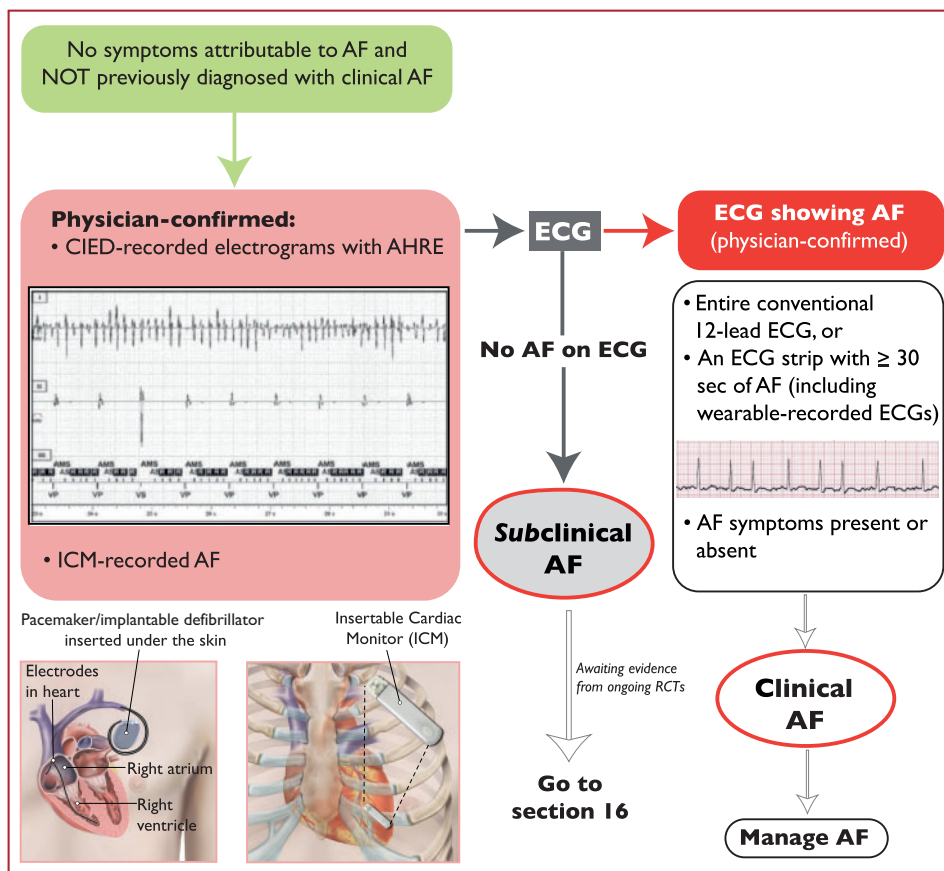
### 3.3 Diagnosis of atrial high-rate episodes/subclinical atrial fibrillation

Various implanted devices and wearable monitors allow detection of atrial high-rate episodes (AHRE) /subclinical AF (Figure 1).<sup>3</sup> Owing to a short monitoring, detection of AHRE/subclinical AF via external ECG is less likely.<sup>7</sup>

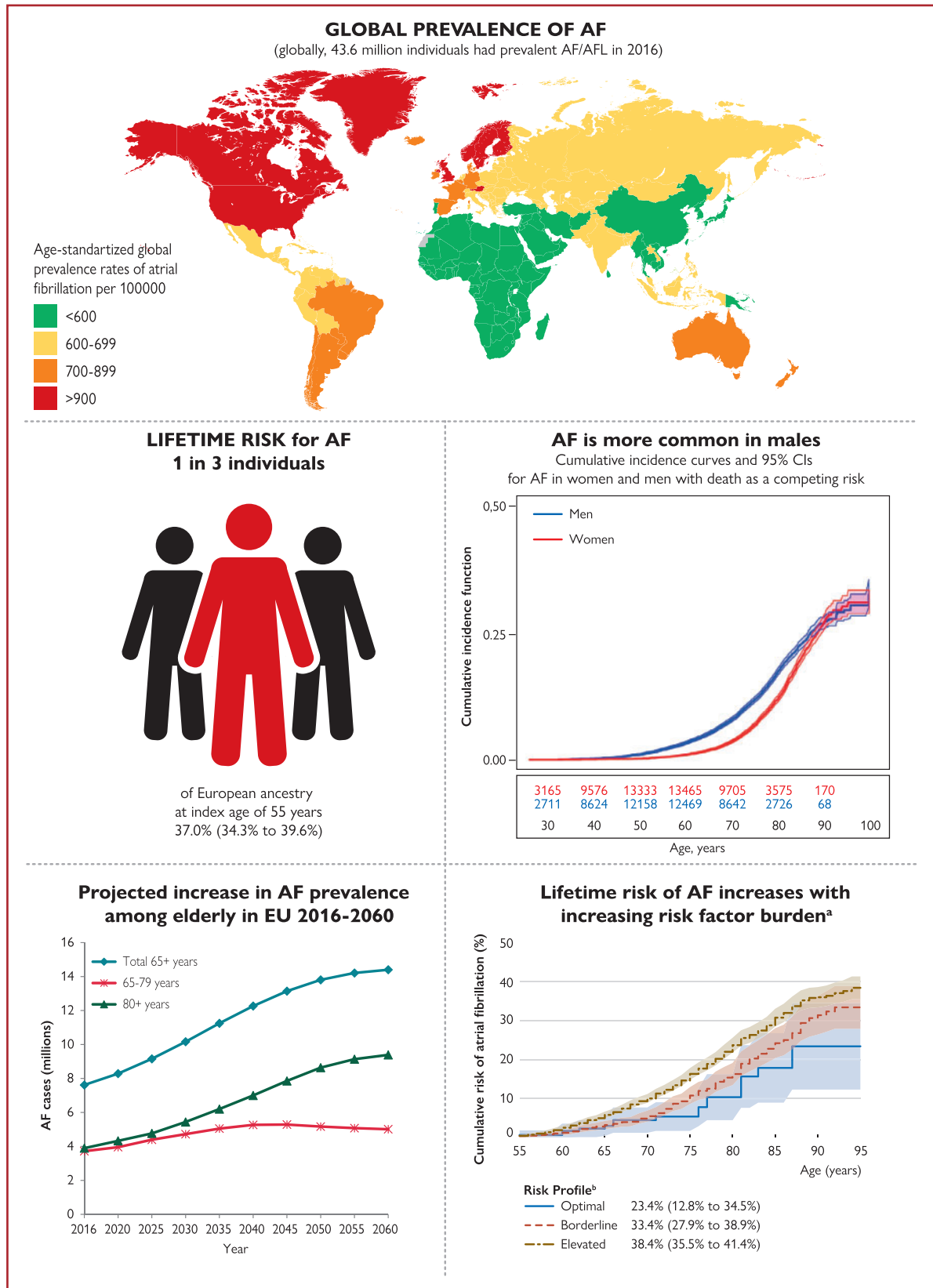
When AHRE/subclinical AF is detected by a device/wearable, inspection of the stored electrograms/ECG rhythm strips is recommended to exclude artefacts or other causes of inappropriate detection.<sup>8,9</sup>

## 4 Epidemiology

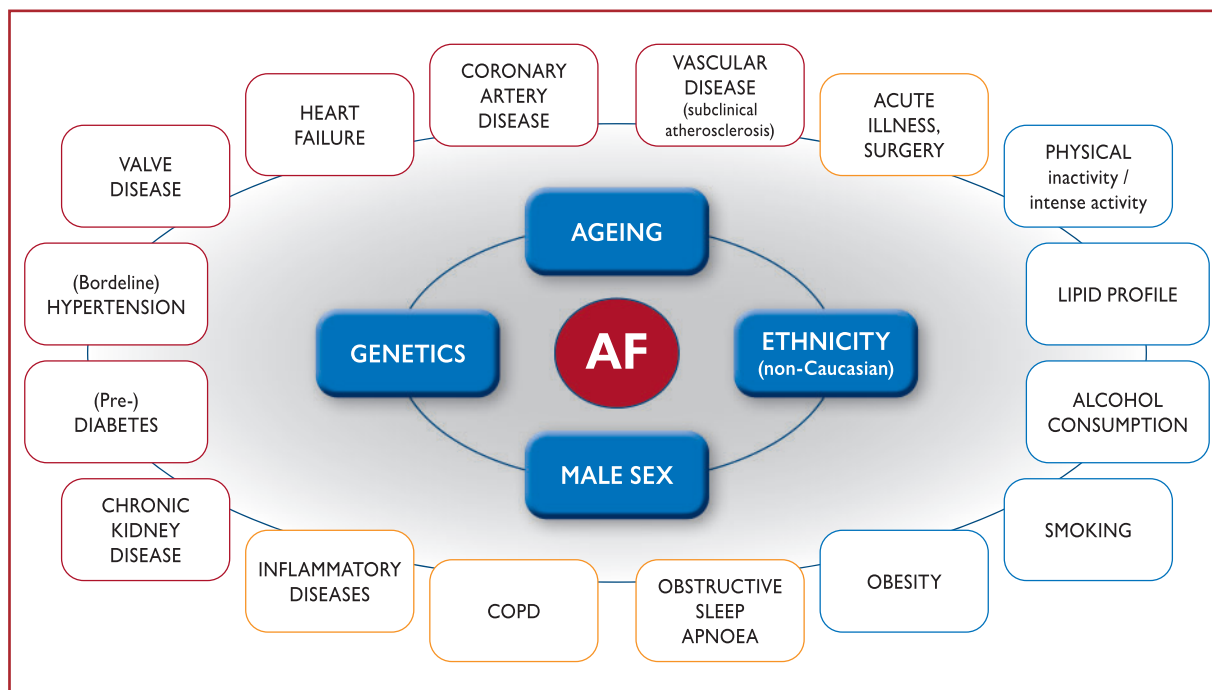
Worldwide, AF is the most common sustained cardiac arrhythmia in adults<sup>10</sup> (Figure 2, upper panel). AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy (Figure 2, lower panel) (Supplementary section 1).



**Figure 1** Diagnosis of AHRE/subclinical AF. CIEDs with an atrial lead can monitor atrial rhythm and store the tracings. ICMs have no intracardiac leads but continuously monitor cardiac electrical activity by recording and analysing a single-lead bipolar surface ECG based on a specific algorithm. Left-bottom image: pacemaker with a right atrial lead, and a ventricular lead in the right ventricular apex. In addition to pacing at either site, these leads can sense activity in the respective cardiac chamber. The device can also detect pre-programmed events, such as AHRE. Right-bottom image: subcutaneous ICM: these devices have no intra-cardiac leads and essentially record a single, bipolar, surface ECG, with inbuilt algorithms for detection of AHRE or AF. AF = atrial fibrillation; AHRE = atrial high rate episode; CIED = cardiac implantable electronic device; ECG = electrocardiogram; ICM = insertable cardiac monitor; RCT = randomized clinical trial.



**Figure 2** Epidemiology of AF: prevalence (upper panel)<sup>10–20</sup>; and lifetime risk and projected rise in the incidence and prevalence (lower panel).<sup>21–34</sup> AF = atrial fibrillation; AFL = atrial flutter; BP = blood pressure; CI = confidence interval; EU = European Union. <sup>a</sup>Smoking, alcohol consumption, body mass index, BP, diabetes mellitus (type 1 or 2), and history of myocardial infarction or heart failure. <sup>b</sup>Risk profile: *optimal* - all risk factors are negative or within the normal range; *borderline* - no elevated risk factors but >1 borderline risk factor; *elevated* - >1 elevated risk factor.



**Figure 3** Summary of risk factors for incident AF<sup>10,22,33,35–72</sup> (*Supplementary Table 1* for full list). AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease.

The currently estimated prevalence of AF in adults is between 2% and 4%,<sup>10</sup> and a 2.3-fold rise<sup>11</sup> is expected,<sup>12,13</sup> owing to extended longevity in the general population and intensifying search for undiagnosed AF.<sup>15</sup> Increasing age is a prominent AF risk factor, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD),<sup>21</sup> obesity, and obstructive sleep apnoea (OSA) is also important;<sup>22–26</sup> modifiable risk factors are potent contributors to AF development and progression<sup>27,28</sup> (*Figure 3*). The age-adjusted incidence, prevalence, and lifetime risk of AF are lower in women vs. men and in non-Caucasian vs. Caucasian cohorts.<sup>10,14–20</sup> A previous lifetime AF risk estimate of 1 in 4 individuals<sup>29,30</sup> was recently revised to 1 in 3 individuals of European ancestry at index age of 55 years.<sup>31,32</sup> The AF lifetime risk depends on age, genetic, and (sub)clinical factors.<sup>10,33,34</sup> The observed impact of clinical risk factor burden/multiple comorbidity on AF risk (*Figure 3*, lower panel<sup>31</sup>) suggests that an early intervention and modifiable risk factor control could reduce incident AF.

#### 4.1 Prediction of incident atrial fibrillation

Identifying individuals at higher risk of developing AF in the community could facilitate targeting of preventive interventions and screening programmes for early AF detection, for example in high-risk subgroups such as post-stroke patients.<sup>73</sup> Various predictive scores for new-onset AF have been proposed (*Supplementary Table 2*), but none has been widely used in clinical practice.

#### 4.2 Pathophysiology of atrial fibrillation

A complex interplay of triggers, perpetuators, and substrate development eventually resulting in AF occurrence is shown in *Supplementary Figure 1*.

### 5 Clinical features of atrial fibrillation

Clinical presentation of AF and AF-related outcomes are shown in *Figure 4* (see also *Supplementary section 2* and *Supplementary Box 1*).

### 6 Atrial fibrillation subtypes, burden, and progression

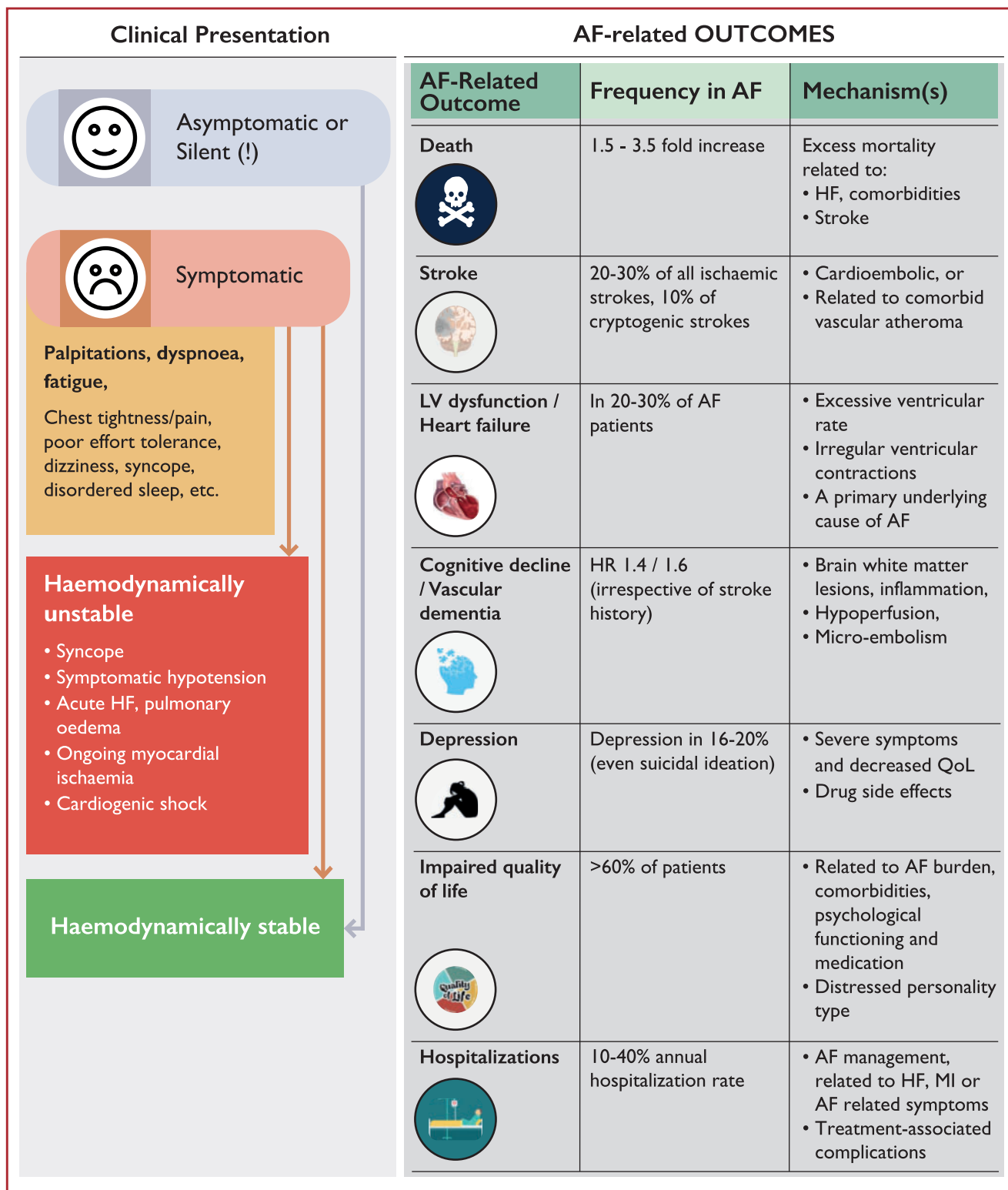
#### 6.1 Classification of atrial fibrillation

Different AF classifications have been proposed but, traditionally, five patterns of AF are distinguished, based on presentation, duration, and spontaneous termination of AF episodes (*Table 4*).<sup>143</sup>

In patients experiencing both paroxysmal and persistent AF episodes, the more common type should be used for classification. However, clinically determined AF patterns do not correspond well to the AF burden measured by long-term ECG monitoring.<sup>144–146</sup>

Other classifications of AF reflect the presence of symptoms (asymptomatic AF is diagnosed with an opportune 12-lead ECG or rhythm strip in asymptomatic patients) or underlying cause of AF





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**Figure 4** Clinical presentation of AF and AF-related outcomes.<sup>10,31,74–140</sup> AF = atrial fibrillation; HF = heart failure; HR = Hazard Ratio; LV = left ventricle; MI = myocardial infarction; QoL = quality of life.

Patients with AF may have various symptoms<sup>92,108,109,128,131</sup> but 50–87% are initially asymptomatic,<sup>75,82,88,111,117,120,125,127</sup> with possibly a less favourable prognosis.<sup>79,82,87,88,117,119,127,134,139</sup> First-onset AF symptoms are less well studied,<sup>92,105,108,109,127</sup> may change with treatment<sup>119</sup> and AF recurrences are commonly asymptomatic.<sup>113</sup>

**Stroke/systolic embolism:** annual AF-related stroke risk in AF patients depends on comorbidities.<sup>78,84,85,91,106,112</sup> Cardioembolic strokes associated with AF are usually severe, highly recurrent, often fatal, or with permanent disability.<sup>108,3,115</sup> In a population-based registry, patients with new-onset AF also had increased rates of systemic embolism.<sup>89</sup>

**Figure 4** Continued

**Left ventricular (LV) dysfunction and HF:** multiple AF-associated mechanisms/myocardial alterations may lead to LV dysfunction and HF,<sup>102,138</sup> resulting in a high prevalence and incidence of HF among AF patients. Sharing common risk factors, AF and HF often coexist, or may precipitate/exacerbate each other, resulting in significantly greater mortality than either condition alone.<sup>140</sup>

**Hospitalization:** approximately 30% of AF patients have at least one, and 10% have  $\geq 2$ , hospital admissions annually,<sup>99,110,129</sup> being twice as likely to be hospitalized as age- and sex-matched non-AF individuals (37.5% vs. 17.5%, respectively).<sup>98</sup> In a nationwide cohort, AF was the main cause for admission in 14% of hospitalized patients but their in-hospital mortality was <1%.<sup>101</sup> The most common reasons for hospitalization of AF patients were cardiovascular disorders (49%), non-cardiovascular causes (43%) and bleeding (8%).<sup>129</sup>

**Quality of life (QoL) and functional status:** >60% of AF patients have significantly impaired QoL/exercise tolerance,<sup>81,88,136</sup> but only 17% have disabling symptoms.<sup>88</sup> QoL is significantly lower in women,<sup>81,107,114,124</sup> young individuals, and those with comorbidities.<sup>118</sup> AF burden<sup>100</sup> may also affect QoL, but only psychological functioning consistently predicted symptoms and QoL.<sup>136</sup> Patients with AF more often developed anxiety disorders,<sup>126</sup> had a higher burden of depressive symptoms,<sup>123</sup> and poorer QoL with a Distressed personality type (Type D).<sup>103</sup> Key symptom and QoL drivers are important to identify optimal AF treatment. It is also important to confirm that symptoms are related to AF or, if absent, to exclude a subconscious adaptation to living with suboptimal physical capacity by asking for breathlessness or fatigue on exertion and recording possible improvements after cardioversion.

**Cognitive impairment/dementia:** AF may lead to cognitive impairment ranging from mild dysfunction to dementia<sup>97,104,141</sup> via clinically apparent or silent stroke or insufficiently understood stroke-independent pathways.<sup>94,96,97,122</sup> Magnetic resonance imaging (MRI) studies have shown that AF is associated with a greater than twofold increase in the odds of having silent cerebral ischaemia.<sup>90,121,142</sup> A recent expert consensus paper summarized the available data.<sup>86</sup>

**Mortality:** AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men,<sup>77,80,130,137</sup> with an overall 3.5-fold mortality risk increase.<sup>31</sup> Whereas the mechanistic explanation for this association is multifaceted, associated comorbidities play an important role.<sup>95</sup> In a recent study, the most common causes of death among AF patients were HF (14.5%), malignancy (23.1%), and infection/sepsis (17.3%), whereas stroke-related mortality was only 6.5%.<sup>76</sup> These and other recent data indicate that, in addition to anticoagulation and HF treatment, comorbid conditions need to be actively treated in the endeavour to reduce AF-related mortality.<sup>77,93,116,133</sup>

**Table 4** Classification of AF

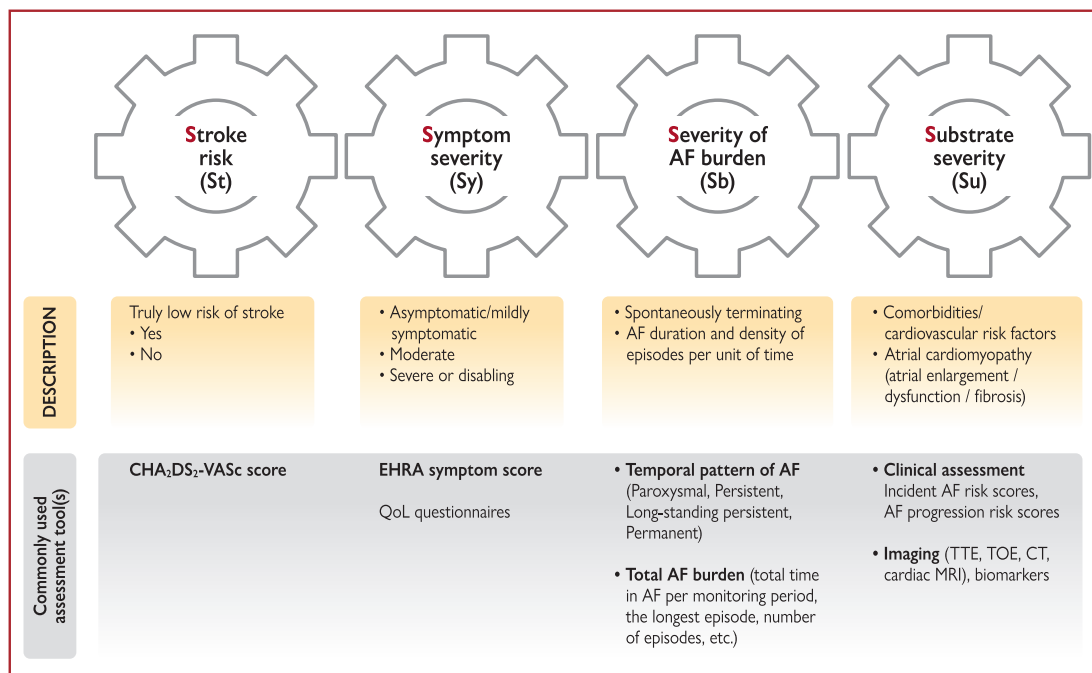
AF pattern	Definition
<b>First diagnosed</b>	AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
<b>Paroxysmal</b>	AF that terminates spontaneously or with intervention within 7 days of onset.
<b>Persistent</b>	AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after $\geq 7$ days
<b>Long-standing persistent</b>	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
<b>Permanent</b>	AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term should not be used in the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.
Terminology that should be abandoned	
<b>Lone AF</b>	A historical descriptor. Increasing knowledge about the pathophysiology of AF shows that in every patient a cause is present. Hence, this term is potentially confusing and should be abandoned. <sup>147</sup>
<b>Valvular/non-valvular AF</b>	Differentiates patients with moderate/severe mitral stenosis and those with mechanical prosthetic heart valve(s) from other patients with AF, but may be confusing <sup>148</sup> and should not be used.
<b>Chronic AF</b>	Has variable definitions and should not be used to describe populations of AF patients.

AF = atrial fibrillation.

(e.g. postoperative AF, see [section 11.19](#)). Classifying AF by underlying drivers could inform management, but the evidence in support of the clinical use of such classification is lacking ([Supplementary Table 3](#)). Terms that should no longer be used to describe AF are listed in [Table 4](#).

Recommendations for AF management are not based on the temporal AF patterns, except for the restoration of sinus rhythm.<sup>143,149,150</sup> It is very unlikely that a simple but comprehensive

AF classification will be proposed, given the multiplicity of factors relevant for its management, advances in AF monitoring, multiplicity of risk assessment tools, evolving treatments, and complexity of AF itself. Indeed, a paradigm shift from classification towards a *structured characterization* of AF, addressing specific domains with treatment and prognostic implications has been recently proposed.<sup>151</sup> Such a scheme would streamline the assessment of AF patients at any healthcare level, thus facilitating communication among physicians,



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**Figure 5** 4S-AF scheme as an example of structured characterization of AF.<sup>151</sup> AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CT = computed tomography; EHRA = European Heart Rhythm Association; LA = left atrium; MRI = magnetic resonance imaging; QoL = quality of life; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

treatment decision making, and optimal management of AF patients, and should become a standard in clinical practice when reporting an AF case.

The proposed 4S-AF scheme (Stroke risk, Symptom severity, Severity of AF burden, Substrate severity) includes four AF-related domains (Figure 5).<sup>151</sup> The currently used assessment tools/classifications pertinent to specific domains (e.g. stroke risk scores, symptom scores, clinical factors, imaging modalities, etc.) can be easily fitted in, but the 4S-AF has great potential for future refinements guided by advances in technology, and the most appropriate descriptors of AF domains are yet to be defined. Given the descriptors of AF included in the 4S-AF scheme, the structured characterization of AF patients using 4S-AF could also provide prognostic information, but the clinical utility and prognostic value of the 4S-AF scheme needs extensive validation in different AF cohorts and clinical settings.

**Recommendations for structured characterization of AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of AF patients at different healthcare levels, inform treatment decision-making, and facilitate optimal management of AF patients. <sup>151</sup>	IIa	C

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

**6.2 Definition and assessment of atrial fibrillation burden**

The term ‘burden’ refers to various AF aspects (e.g. epidemiological, economic).<sup>144</sup> Regarding continuous device-based monitoring, ‘AF burden’ is currently defined as the overall time spent in AHRE/sub-clinical AF during a specified monitoring period (e.g. 1 day). Both the time in AF and the monitoring period should be acknowledged when reporting AF burden (most studies reported the maximum time spent in AF over a 24-h period), but optimal measures are yet to be determined.<sup>152</sup> The term ‘AF burden’ is different from ‘burden of AF’, the latter referring to AF consequences.

Clinical AF burden is routinely determined by AF temporal pattern<sup>146</sup> (Table 4) and intermittent ECG monitoring,<sup>153</sup> neither corresponding well to the long-term ECG monitoring. The relationship of clinical AF burden with specific outcomes is not well characterized,<sup>154</sup> but may be associated with higher risk of incident HF<sup>155</sup> and all-cause mortality,<sup>156</sup> while the association with quality of life (QoL) is complex and data about cognitive impairment/dementia are lacking.<sup>86</sup> Recent randomized controlled trial (RCT) data consistently showed significantly lower residual thrombo-embolic risk among anticoagulated patients with paroxysmal vs. persistent AF,<sup>156–159</sup> whereas earlier trial-based<sup>160</sup> and observational data<sup>161,162</sup> are contradictory. Among non-anticoagulated patients, stroke risk was lower with paroxysmal than non-paroxysmal AF,<sup>156</sup> and a greater total AF burden (but not the longest AF episode) was independently associated with higher thrombo-embolic event rates.<sup>163</sup> Clinical AF burden may influence the response to rhythm control therapy.<sup>164,165</sup> The presence of >6 h of AF per week (especially when progressing to >24 h weekly) was associated with increased mortality, especially in women.<sup>166</sup>

Available evidence on the association of AF burden with AF-related outcomes is insufficient to guide treatment and should not be a major factor in treatment decisions. Comprehensive management of modifiable cardiovascular risk factors/comorbidity reduces AF burden (section 10.3).

### 6.3 Atrial fibrillation progression

Transition from paroxysmal to non-paroxysmal AF (or from subclinical to clinical AF)<sup>154,167–169</sup> is often characterized by advancing atrial structural remodelling or worsening of atrial cardiomyopathy.<sup>170,171</sup>

Assessment of AF progression depends on duration of rhythm monitoring and underlying substrate.<sup>172,173</sup> Reported annual rates of paroxysmal AF progression range from <1% to 15% (up to 27–36% in studies with ≥10-year follow-up).<sup>169,174</sup> Risk factors for AF progression include age, HF, hypertension, CKD, chronic pulmonary diseases, diabetes mellitus, previous stroke, and left atrial (LA) size,<sup>167</sup> whereas the added predictive value of biomarkers is presently not well defined. Older age is associated with permanent AF,<sup>82,117,154</sup> and various triggers may also play a role, with different progression patterns resulting from their interaction with substrate remodelling.<sup>171</sup> Progression to persistent/permanent AF is associated with adverse cardiovascular events, hospitalizations, and death,<sup>166</sup> but it is unclear whether AF progression is a determinant of adverse prognosis or rather a marker of an underlying progressive disease/substrate.<sup>175,176</sup> The true impact of different therapeutic interventions at different disease stages on AF progression and associated outcomes is also less well defined.

### 6.4 Atrial cardiomyopathy: definition, classification, clinical implications, and diagnostic assessment

Important progress in understanding AF mechanisms and thrombogenicity reconsiders the role of atrial cardiomyopathy (i.e. atrial structural, architectural, contractile, or electrophysiological changes with potentially relevant clinical manifestations).<sup>170</sup>

Clinical classification of atrial cardiomyopathy should be based on the atrial structure, morphology, electrical and mechanical function, and the diagnosis could be based on easily accessible parameters (e.g. aetiology, the prothrombotic state,<sup>177</sup> and abnormal LA volume/function).<sup>178</sup> Major clinical issues in AF (i.e. prevention of thromboembolic complications and AF progression) are influenced by atrial remodelling; and, importantly, AF is not only a risk factor for but also a marker of atrial cardiomyopathy, which could explain the lack of temporal relationship between detected AF and stroke.<sup>179</sup>

The diagnostic algorithm for atrial cardiomyopathy should follow a stepwise approach, identifying risk factors for atrial cardiomyopathy,<sup>170</sup> atrial electrical and mechanical dysfunction,<sup>180</sup> and increased thrombotic risk.<sup>181</sup> More data are needed to define prognostic and treatment implications of different atrial cardiomyopathy morpho-functional forms.

## 7 Screening for atrial fibrillation

Multiple factors (i.e. increasing AF prevalence, previously unknown AF detection in about 10% of all ischaemic strokes,<sup>4,182</sup> high prevalence of asymptomatic AF,<sup>117</sup> potential to prevent AF-related strokes

with appropriate treatment and increasing availability of AF detection tools) have fuelled international initiatives to implement screening for AF in clinical practice.<sup>172</sup>

Asymptomatic clinical AF has been independently associated with increased risk of stroke and mortality compared with symptomatic AF.<sup>82,117,127,183</sup> Data derived from studies of incidentally detected asymptomatic AF are the closest possible approximation of the risk of stroke and death in screen-detected AF subjects, because delaying treatment to discern a natural history would be unethical. Observational data suggest that screen-detected AF responds to treatment similarly to AF detected by routine care,<sup>183</sup> thus favouring AF screening.

Although AF fulfils many of the criteria for disease screening<sup>184</sup> (Supplementary Figure 2), RCT data to confirm the health benefits from screening for AF and inform the choice of optimal screening programmes and strategies for its implementation are scarce.<sup>185,186</sup> Advances in wearable technology will likely yield inexpensive and practical options for AF detection and AF burden assessment in the near future.

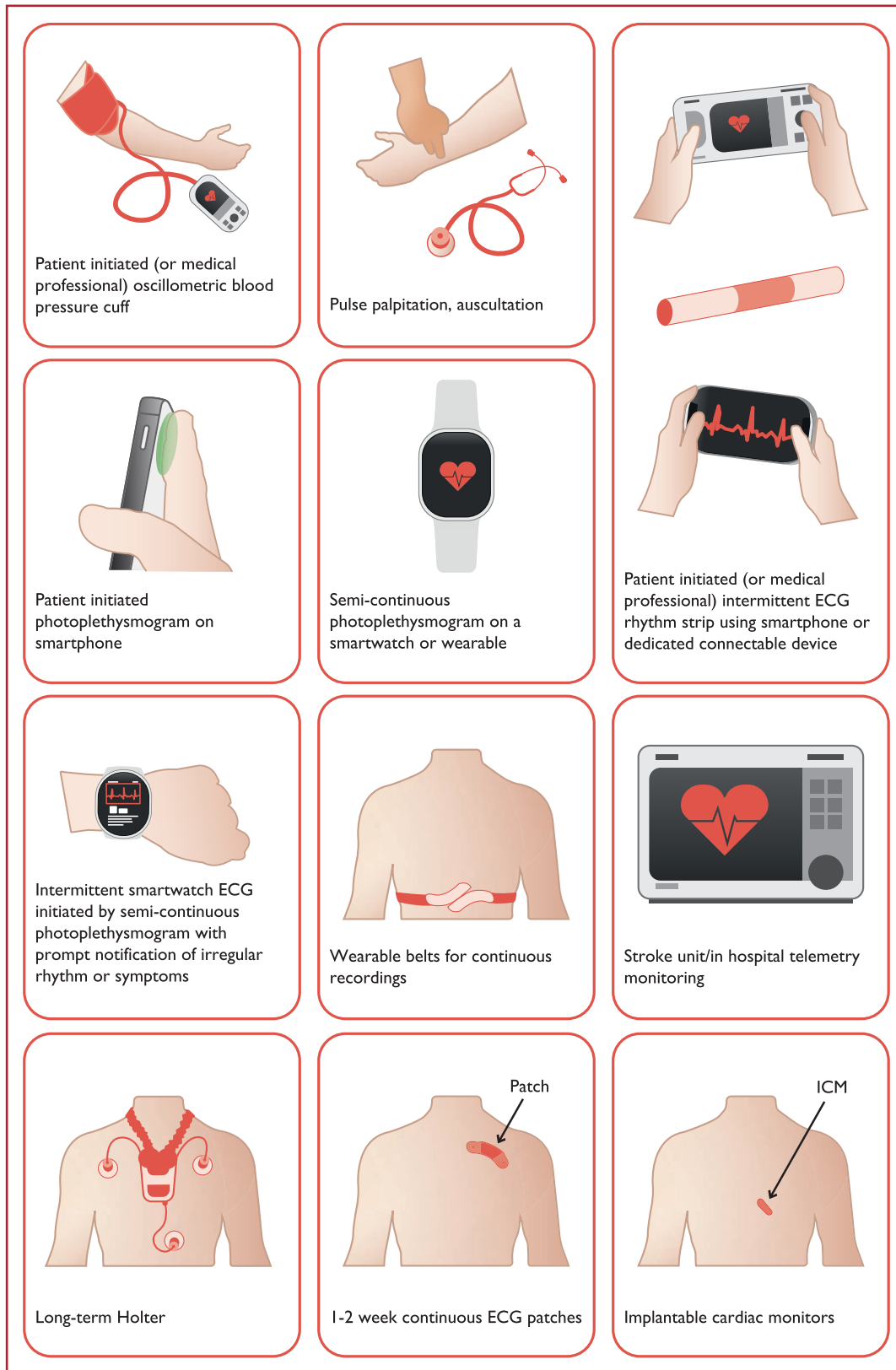
### 7.1 Screening tools

The systems used for AF screening are shown in Table 5 and Figure 6.<sup>173,187</sup>

Mobile health technologies are rapidly developing for AF detection and other purposes (>100 000 mHealth apps and ≥400 wearable activity monitors are currently available).<sup>197</sup> Caution is needed in their clinical use, as many are not clinically validated. Several studies evaluated AF detection using smartwatches,<sup>198,199</sup> thus opening new perspectives for AF detection targeting specific populations at risk. Machine learning and artificial intelligence may be capable of identifying individuals with previous AF episodes from a sinus rhythm ECG recording,<sup>200</sup> which would be a major technological breakthrough in AF detection.<sup>200</sup>

The Apple Heart study<sup>201</sup> included 419 297 self-enrolled smart-watch app users (mean age 40 years) in the United States of America (USA), of whom 0.5% received an irregular pulse notification (0.15% of those aged <40 years, 3.2% among those aged >65 years). Subsequent (notification-triggered) 1-week ECG patch monitoring revealed AF in 34% of monitored participants. The Huawei Heart study<sup>202</sup> included 187 912 individuals (mean age 35 years, 86.7% male), of whom 0.23% received a 'suspected AF' notification. Of those effectively followed up, 87.0% were confirmed as having AF, with the positive predictive value of photoplethysmography signals being 91.6% [95% confidence interval (CI) 91.5–91.8]. Of those with identified AF, 95.1% entered an integrated AF management programme using a mobile AF App (mAFA).

When AF is detected by a screening tool, including mobile or wearable devices, a single-lead ECG tracing of ≥30 s or 12-lead ECG showing AF analysed by a physician with expertise in ECG rhythm interpretation is necessary to establish a definitive diagnosis of AF (devices capable of ECG recording enable direct analysis of the device-provided tracings). When AF detection is not based on an ECG recording (e.g. with devices using photoplethysmography) or in case of uncertainty in the interpretation of device-provided ECG tracing, a confirmatory ECG diagnosis has to be obtained using additional ECG recording (e.g. 12-lead ECG, Holter monitoring, etc.)



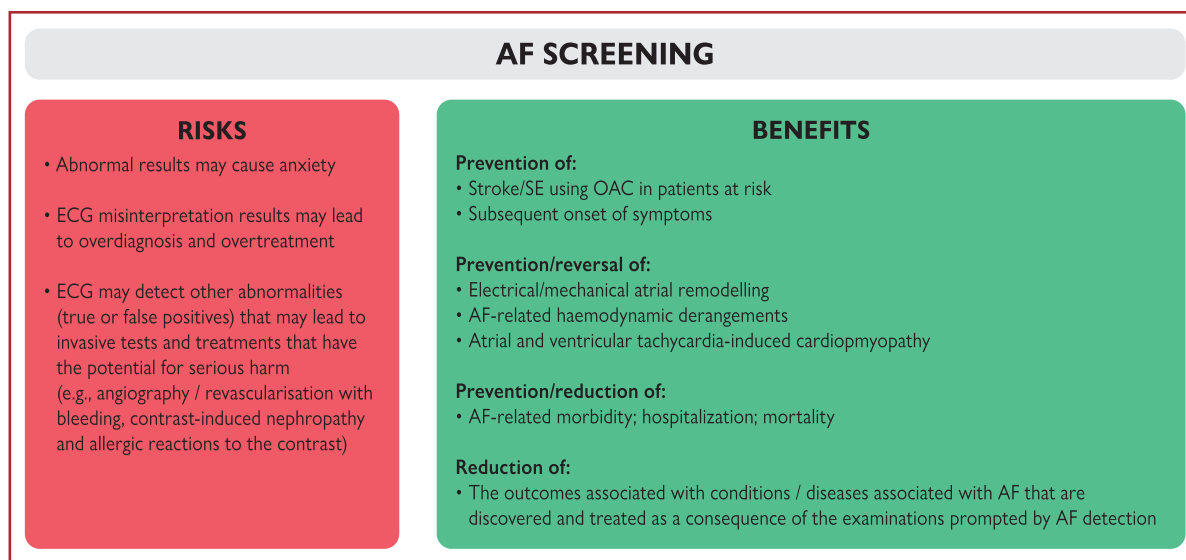
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**Figure 6** Systems used for AF screening. Pulse palpation, automated BP monitors, single-lead ECG devices, PPG devices, other sensors (using seismocardiography, accelerometers, and gyroscopes, etc.) used in applications for smartphones, wrist bands, and watches. Intermittent smartwatch detection of AF is possible through PPG or ECG recordings. Smartwatches and other ‘wearables’ can passively measure pulse rate from the wrist using an optical sensor for PPG and alerting the consumer of a pulse irregularity (based on a specific algorithm for AF detection analysing pulse irregularity and variability).<sup>172,173,188–196</sup> AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram; PPG = photoplethysmography.

**Table 5** Sensitivity and specificity of various AF screening tools considering the 12-lead ECG as the gold standard<sup>173</sup>

	Sensitivity	Specificity
Pulse taking <sup>203</sup>	87 - 97%	70 - 81%
Automated BP monitors <sup>204–207</sup>	93 - 100%	86 - 92%
Single lead ECG <sup>208–211</sup>	94 - 98%	76 - 95%
Smartphone apps <sup>188,189,191,195,212,213</sup>	91.5 - 98.5%	91.4 - 100%
Watches <sup>196,198,213,214</sup>	97 - 99%	83 - 94%

AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram.

**Figure 7** Potential benefits from and risks of screening for AF. AF = atrial fibrillation; ECG = electrocardiogram; OAC = oral anticoagulant; SE = systemic embolism.

The data reported in Table 5 should be interpreted with caution, as assessment of sensitivity and specificity in many studies was based on small observational cohorts, with a substantial risk of bias due to signal selection. Moreover, there is a continuous evolution of algorithms and technologies available in commercial devices.

Two recent meta-analyses reported that screening for AF using an ECG would not detect more cases than would screening with pulse palpation.<sup>215</sup>

## 7.2 Screening types and strategies

Commonly used AF screening types and strategies<sup>172,173,216</sup> include opportunistic or systematic screening of individuals above a certain age (usually  $\geq 65$  years) or with other characteristics suggestive of increased stroke risk, using intermittent single-point or repeated 30-s ECG recording over 2 weeks. The appropriate frequency of monitoring using smartphones or watches is undefined. Primary care, pharmacies, or community screening during special events is a good setting for AF screening.<sup>172,173</sup> Overall, there was no significant difference between systematic vs. opportunistic or general practice vs. community screening in a meta-analysis, but repeated heart associated with significantly better effectiveness compared with single assessment.<sup>215</sup> Importantly, a structured referral of screen-detected or suspected AF cases for further clinical evaluation should be organized, to provide an appropriate management.

## 7.3 Benefits from and risks of screening for atrial fibrillation

Potential advantages and disadvantages of detecting a previously undiagnosed AF through screening are shown in Figure 7.<sup>173</sup>

Screening can also highlight cases of known suboptimally managed AF.<sup>217</sup> Intermittent ECG recording increased new AF detection four-fold.<sup>217</sup> In the REHEARSE-AF (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) controlled study using a smartphone/tablet-based single-lead ECG system twice weekly over 12 months vs. routine care resulted in a 3.9-fold increase in AF detection in patients aged  $\geq 65$  years.<sup>218</sup> Appropriate patient information and screening programme organization with rapid ECG clarification may reduce anxiety induced by suspicion of abnormality.

## 7.4 Cost-effectiveness of screening for atrial fibrillation

Higher AF-related medical costs justify strategies to identify and treat undiagnosed AF.<sup>219</sup> Opportunistic AF screening is associated with lower costs than systematic screening.<sup>173</sup> Appropriate choice of the screening tool and setting is important,<sup>220</sup> and a favourable cost-effectiveness profile has been estimated for screening programmes based on pulse palpation, hand-held ECG devices, and

smartphones with pulse photoplethysmography algorithms.<sup>172</sup> Both systematic and opportunistic screening are more cost-effective than routine practice for patients  $\geq 65$  years, with opportunistic screening more likely to be cost-effective than systematic population screening.<sup>1491</sup>

## 7.5 Screening in high-risk populations

### 7.5.1 Elderly

The risk of AF (often asymptomatic) and stroke increase with age,<sup>82,127,221</sup> thus justifying AF screening in the elderly. Opportunistic AF screening seems to be cost-effective in elderly populations ( $\geq 65$  years)<sup>222</sup> and among 75–76-year-old individuals undergoing a 2-week intermittent ECG screening.<sup>223</sup>

Pulse palpation and/or short-term ECG among the elderly ( $\geq 65$  years) yielded an AF prevalence of 4.4%, with previously undiagnosed AF in 1.4%, suggesting a number needed to screen of 70.<sup>224</sup> Repeated hand-held ECG recordings over 2 weeks in an unselected population aged 75–76 years increased the detection of asymptomatic AF up to 7.4% in subjects with  $\geq 2$  stroke risk factors.<sup>225</sup>

#### Recommendations for screening to detect AF

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients $\geq 65$ years of age. <sup>188,211,223,225</sup>	I	B
It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE. <sup>c224,226</sup>	I	B
When screening for AF it is recommended that: <sup>217,218</sup> <ul style="list-style-type: none"> <li>• The individuals undergoing screening are informed about the significance and treatment implications of detecting AF.</li> <li>• A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF.</li> <li>• Definite diagnosis of AF in screen-positive cases is established only after physician reviews the single-lead ECG recording of <math>\geq 30</math> s or 12-lead ECG and confirms that it shows AF.</li> </ul>	I	B
Systematic ECG screening should be considered to detect AF in individuals aged $\geq 75$ years, or those at high risk of stroke. <sup>212,224,227</sup>	IIa	B

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AF = atrial fibrillation; AHRE = atrial high-rate episode; ECG = electrocardiogram.

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

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

<sup>c</sup>See sections 3.2 and 3.3 for diagnostic criteria for AF and AHRE, and section 16 for the management of patients with AHRE.

## 8 Diagnostic assessment in atrial fibrillation

Often occurring in patients with cardiovascular risk factors/comorbidities, AF may sometimes be a marker of undiagnosed conditions. Hence, all AF patients will benefit from a comprehensive cardiovascular assessment (Figure 8).

The 'standard package' for diagnostic evaluation of AF patients should include complete medical history and assessment of concomitant conditions, AF pattern, stroke risk, AF-related symptoms, thrombo-embolism, and LV dysfunction.<sup>143</sup> A 12-lead ECG is recommended in all AF patients, to establish the diagnosis of AF, assess ventricular rate during AF, and check for the presence of conduction defects, ischaemia, or signs of structural heart disease. Laboratory tests (thyroid and kidney function, serum electrolytes, full blood count) and transthoracic echocardiography (LV size and function, LA size, valvular disease, and right heart size and systolic function) are needed to guide treatment. Based on the patient's characteristics, specific additional information can be obtained. Most AF patients need regular follow-up (primary care) to ensure continued optimal management.

### 8.1 Symptoms and quality of life

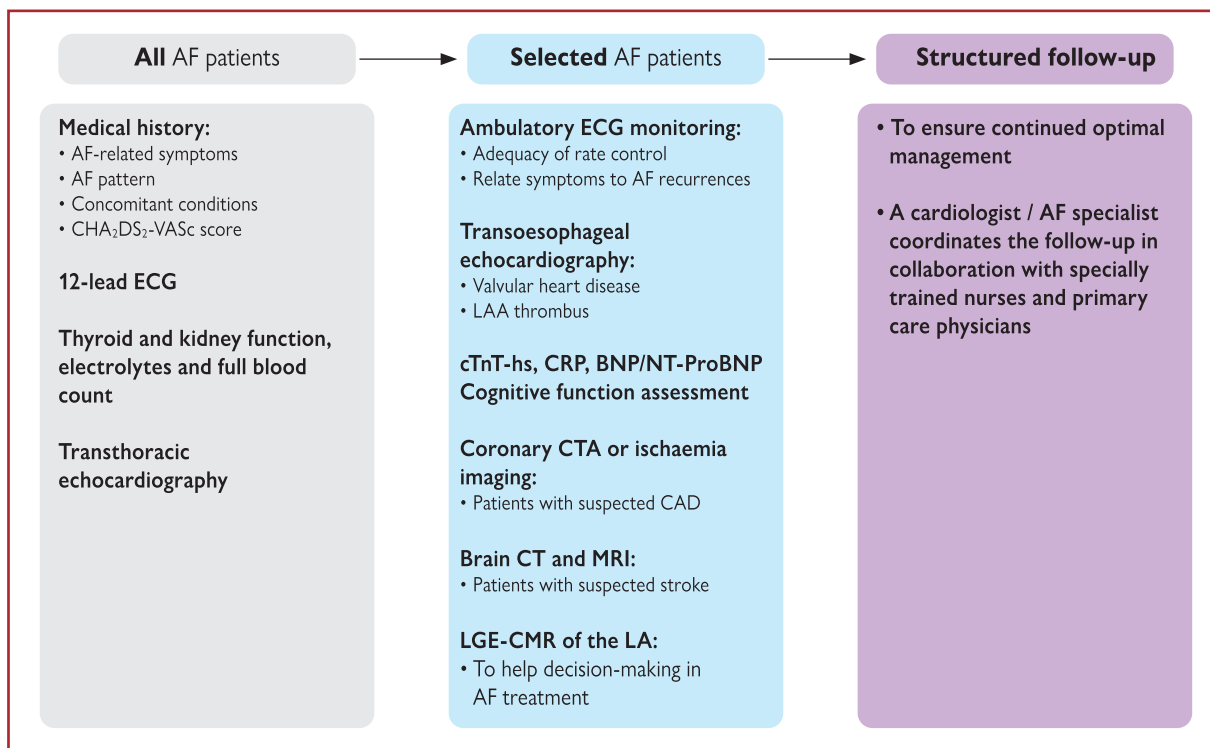
As symptoms related to AF may range from none to disabling, and rhythm control treatment decisions (including catheter ablation) are influenced by symptom severity, symptom status should be characterized using the European Heart Rhythm Association (EHRA) symptom scale<sup>228</sup> (Table 6), and the relation of symptoms (especially if non-specific, such as shortness of breath, fatigue, chest discomfort, etc.) to AF should be elucidated because symptoms may also result from undiagnosed or suboptimally managed concomitant cardiovascular risk factors or pathological conditions.<sup>229</sup>

In selected AF patients, long-term ECG monitoring is recommended to assess the adequacy of rate control or to relate symptoms with AF episodes. Sometimes the association of symptoms with AF can be established only retrospectively, after successful rhythm control intervention. In selected patients, a trial of sinus rhythm using cardioversion and a quantified patient perception of symptoms using a validated assessment tool (Supplementary Table 4) may inform the decision about subsequent AF catheter ablation (section 10.2).

Symptomatic and functional improvement with rhythm control therapies (cardioversion,<sup>232–234</sup> antiarrhythmic medications, and AF catheter-ablation procedures<sup>235–242</sup>) largely depends on sinus rhythm maintenance<sup>243</sup>; however, QoL may improve despite AF recurrences, unless AF burden is high<sup>244</sup> (e.g.  $>2$  h daily<sup>100</sup>) owing to optimized management of cardiovascular risk factors or comorbidities<sup>245</sup> or a treatment expectancy effect. The effect of AF treatment<sup>246,247</sup> is supported by reports of persistently improved QoL 10 years after paroxysmal AF catheter ablation in patients with a low AF progression rate.<sup>248</sup>

### 8.2 Substrate

The substrate for AF relates to LA dilation and fibrosis with subsequent LA dysfunction and delay in electromechanical conduction.



**Figure 8** Diagnostic work-up and follow-up in AF patients. AF = atrial fibrillation; BNP = B-type natriuretic peptide; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CAD = coronary artery disease; CRP = C-reactive protein; CT = computed tomography; CTA = computed tomography angiography; cTnT-hs = high-sensitivity cardiac troponin T; ECG = electrocardiogram; LAA = left atrial appendage; LGE-CMR = late gadolinium contrast-enhanced cardiac magnetic resonance; MRI = magnetic resonance imaging; NT-ProBNP = N-terminal (NT)-prohormone B-type natriuretic peptide.

**Table 6** EHRA symptom scale

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 by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

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Six symptoms, including palpitations, fatigue, dizziness, dyspnoea, chest pain, and anxiety during AF, are evaluated with regard to how it affects the patient's daily activity, ranging from none to symptom frequency or severity that leads to a discontinuation of daily activities.

To measure treatment effects, QoL and symptom questionnaires should be sensitive to changes in AF burden. The EHRA symptom scale is a physician-assessed tool for quantification of AF-related symptoms that is used to guide symptom-driven AF treatment decisions,<sup>228</sup> and has been related to adverse outcomes in more symptomatic patients (score 3-4) versus those with a score of 1-2.<sup>228,230</sup> However, it does not consider the symptom dimensions such as anxiety, treatment concerns, and medication adverse effects that are captured by general QoL scales,<sup>230</sup> or the patient-reported symptom-related outcomes. As discrepancies between patient-reported and physician-assessed outcomes are frequently observed,<sup>231</sup> the AF-related treatment decisions also need to be informed by a quantified patient perception of symptoms, but further research is needed to identify optimal tool(s) for capturing this information.

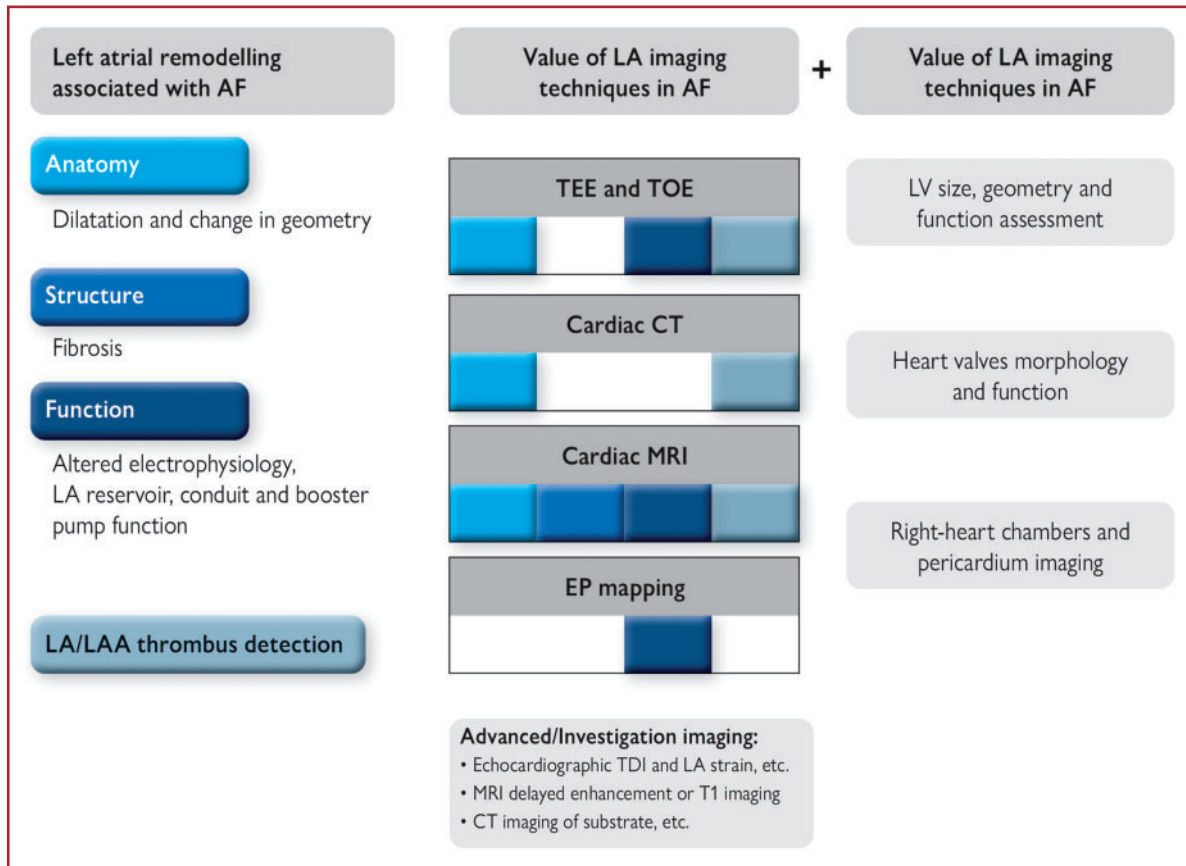
AF = atrial fibrillation; EHRA = European Heart Rhythm Association; QoL = quality of life.

Non-invasive, multimodality imaging can provide all needed information (Figure 9).<sup>249,250</sup>

In selected patients, transoesophageal echocardiography (TOE) can be used to evaluate valvular heart disease (VHD) or left atrial appendage (LAA) thrombus; CT coronary angiography can be

performed for assessment of CAD; CT/MRI of the brain can be performed when stroke is suspected. Specific predictors of stroke have been suggested: LA dilation, spontaneous LA contrast, reduced LA strain, LAA thrombus, low peak LAA velocity (<20 cm/s), and LAA non-chicken wing configuration (on CT).<sup>250</sup>





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**Figure 9** Imaging in AF. Anatomical imaging provides the LA size, shape, and fibrosis. Most accurate assessment of LA dilation is obtained by CMR or CT. For routine assessment, two-dimensional (2D) or (preferably) three-dimensional (3D) transthoracic echocardiography is used. The 3D echocardiographic normal volume values are 15 - 42 mL/m<sup>2</sup> for men and 15 - 39 mL/m<sup>2</sup> for women.<sup>250</sup> Assessment of LA fibrosis with LGE-CMR has been described but only rarely applied in clinical practice.<sup>251</sup> Functional imaging includes TDI and strain. TDI measures the velocities of the myocardium in diastole and systole, whereas LA strain reflects active LA contraction. The PA-TDI interval reflects the atrial electromechanical delay (total LA conduction time, the time interval between the P-wave on the ECG and the A' [atrial peak velocity] on TDI) and reflects LA strain.<sup>252</sup> LA wall infiltration by epicardial fat is a potential early marker of inflammation and can be detected with CT or cardiac MRI.<sup>253</sup> Before AF ablation, the pulmonary vein anatomy can be visualized with CT or CMR. AF = atrial fibrillation; CT = computed tomography; EP = electrophysiology; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; LGE-CMR = late gadolinium contrast-enhanced cardiac magnetic resonance; MRI = magnetic resonance imaging; TDI = tissue doppler imaging; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

**Recommendations for diagnostic evaluation of patients with AF**

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
In patients with AF, it is recommended to: <ul style="list-style-type: none"> <li>Evaluate AF-related symptoms (including fatigue, tiredness, exertional shortness of breath, palpitations, and chest pain) and quantify the patient symptom status using the modified EHRA symptom scale before and after initiation of treatment.<sup>230,232</sup></li> <li>Evaluate AF-related symptoms before and after cardioversion of persistent AF to aid rhythm control treatment decisions.<sup>230,232</sup></li> </ul>	I	C

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

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

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

## 9 Integrated management of patients with atrial fibrillation

### 9.1 Definitions and components of integrated management of atrial fibrillation patients

Integrated management of AF patients requires a coordinated and agreed patient-individualized care pathway to deliver optimized treatment (Figure 10) by an interdisciplinary team (Figure 11). Central to this approach is the patient; treatment options should be discussed, and the management plan agreed in discussion with healthcare professionals. Treatment is subject to change over time with the development of new risk factors, symptoms, disease progression, and the advent of new treatments.

### 9.2 Multidisciplinary atrial fibrillation teams

Integrated AF management requires a coordinated multidisciplinary team (Figure 11) composed according to individual patient needs and local availability of services. Complex patients would benefit from a multidisciplinary team that includes relevant specialists, as well as their primary care physician (for post-discharge care) and their family/carer. Involvement of patient and family/carers is integral to the success of AF management.

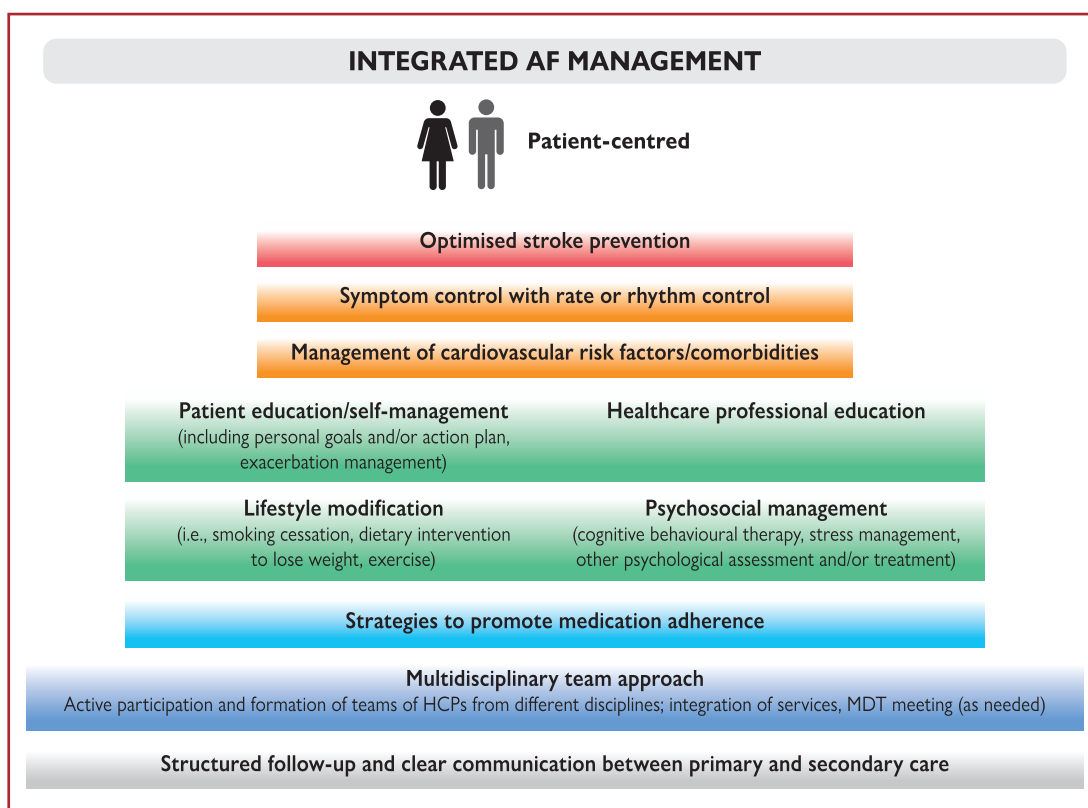
### 9.2.1 Role of healthcare systems and budget constraints

Optimized AF treatment requires a well-structured healthcare system and significant financial resources.<sup>254</sup> Allocation of resources will vary due to differing healthcare system structures and budget constraints in diverse geographies. The significant inequalities in the access to AF management-related resources are documented in the recent ESC Atlas on Cardiovascular Disease.<sup>255</sup> It is important to consider optimizing use of available resources to reduce stroke, improve symptoms, and treat comorbidities.

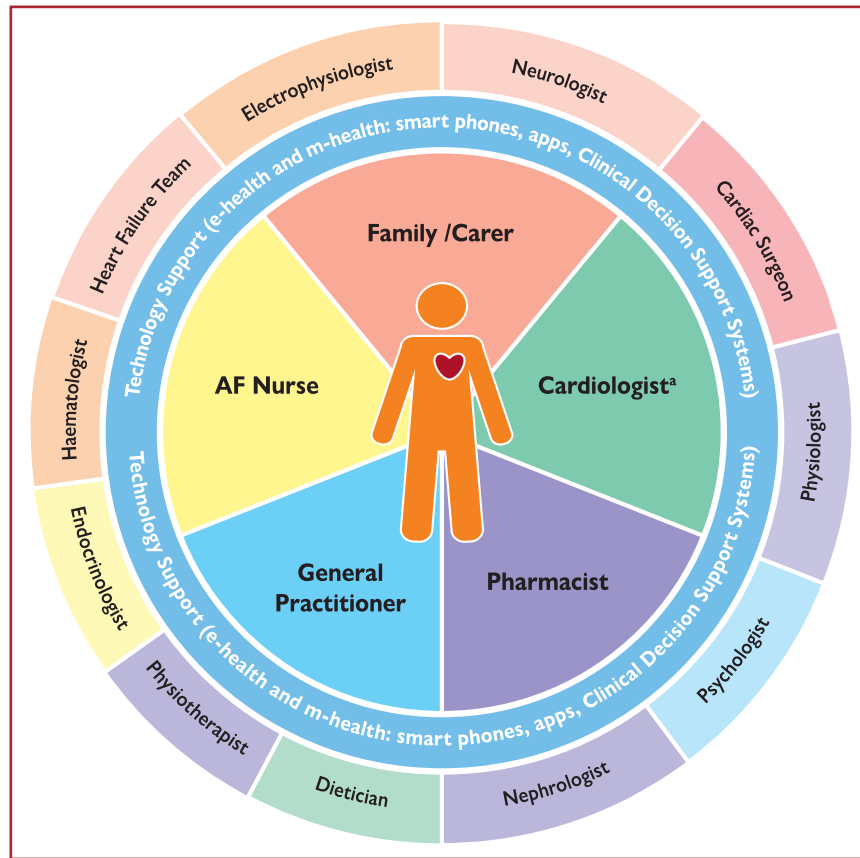
### 9.3 Patient involvement and shared decision making

#### 9.3.1 Patient values and preferences

Exploring patient's values, goals, and preferences should be the first step of shared decision making.<sup>256,257</sup> Qualitative research demonstrates recurring discordance between caregivers reporting shared decision making and patients experiencing a paternalistic model,<sup>109,258–261</sup> and a misperception that many prefer not to be involved in decision making, rather deferring to their physician.<sup>259,262–266</sup> For shared decision making,<sup>261</sup> the importance attached by the patient to stroke prevention and rhythm control and the respective risk of death, stroke, and major bleeding, as well as the burden of treatment, should be thoroughly assessed and respected.<sup>257,264,266–268</sup>



**Figure 10** Components of integrated AF management. AF = atrial fibrillation; HCP = healthcare professional; MDT = multidisciplinary team.



**Figure 11** Integrated AF management team (an example). The figure gives an example on the potential composition of AF teams showing a variety of different specialists supporting individual patients as needed. AF = atrial fibrillation. <sup>a</sup>According to local standards, this could be a general cardiologist with special interest in arrhythmias/AF or an electrophysiologist.

### 9.3.2 Patient education

Patient knowledge about AF and its management is often limited<sup>257,269–272</sup> particularly when first diagnosed, when the majority of treatment decisions are discussed and made.

Information on useful resources to help educate AF patients<sup>273</sup> can be found in the *ESC Textbook of Cardiovascular Medicine*, but education alone is often insufficient to produce and maintain medication adherence and lifestyle modifications.

### 9.4 Healthcare professional education

A mixed-methods approach has been used when targeting healthcare professionals including individual needs assessment followed by bespoke education and training, whether by smart technology, online resources, or upskilling face-to-face workshops or a combination.<sup>274</sup> The mAFA, integrating clinical-decision support and education for healthcare professionals, has been successfully piloted and subsequently tested in an outcome RCT.<sup>275</sup> Education alone is insufficient to change healthcare-professional behaviour.<sup>276</sup> In the Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF) trial,<sup>277</sup> a multifaceted educational intervention including healthcare-professional education and feedback resulted in a significant increase in the proportion of patients treated with oral anticoagulant (OAC) therapy.

### 9.5 Adherence to treatment

Factors affecting adherence to treatment can be grouped into *patient-related* (e.g. demographics, comorbidities, cognitive impairment, polypharmacy, treatment side-effects, psychological health, patient understanding of the treatment regimen), *physician-related* (knowledge, awareness of guidelines, expertise, multidisciplinary team approach), and *healthcare system-related* (work-setting, access to treatments, cost) factors.<sup>278</sup>

Ensuring patients are appropriately informed about treatment options, how to adhere to treatment, potential consequences of non-adherence, in addition to managing patient's expectations of treatment goals, are crucial to promote adherence. Regular review by any member of the multidisciplinary team is important to identify non-adherence and implement strategies to improve adherence where appropriate.

### 9.6 Technology tools supporting atrial fibrillation management

Clinical decision support systems are intelligent systems that digitize and provide evidence-based guidelines, clinical pathways, and algorithms facilitating personalized, timely, and evidence-based treatment.

The MobiGuide project<sup>279</sup> and several applications<sup>280–283</sup> (*Supplementary Tables 5 and 6*) have been used to enhance patient

education, improve communication between patients and healthcare professionals, and encourage active patient involvement. The ESC/CATCH-ME (Characterizing AF by Translating its Causes into Health Modifiers in the Elderly) consortium also has a smartphone/tablet app<sup>281</sup> for AF patients, but this is yet to be tested prospectively. A Cochrane review<sup>284</sup> demonstrated that patient decision-support aids reduce decision conflict.<sup>285–288</sup> Nevertheless, contradictory results<sup>277,289,290</sup> illustrate the need for more carefully designed studies, including assessment of the intervention's effect on clinical events.

## 9.7 Advantages of integrated management of atrial fibrillation patients

Limited evidence exists on the effectiveness of integrated management of AF. Available intervention studies vary widely in number and content of 'integrated care' employed. Six studies—one cluster RCT,<sup>291</sup> four RCTs,<sup>277,292–295</sup> and one before-and-after study<sup>294</sup>—of integrated AF management have demonstrated mixed findings (*Supplementary Table 7*). Two studies<sup>292,294</sup> and one meta-analysis<sup>296</sup> report significantly lower rates of cardiovascular hospitalization and death with nurse-led, integrated care, whereas others reported no effect of integrated care on these outcomes. One multifaceted study<sup>277</sup> demonstrated improved OAC rates in the intervention group at 12 months. The IMPACT-AF study<sup>277</sup> found no significant difference in the composite efficacy outcome (unplanned emergency department visit or cardiovascular hospitalization) or the primary safety outcome of major bleeding between intervention and usual care.

## 9.8 Measures (or approaches) for implementation of integrated management

Integrated management of AF requires a change in the current approach to patient care, to focus on moving from a multidisciplinary team to interdisciplinary working, including behaviour change for all AF team members and key stakeholders including patients and their family<sup>297,298</sup> (*Supplementary Figure 3*).

To understand whether integrated AF management has been implemented into clinical practice and had an impact on important outcomes (mortality, stroke, hospitalization, QoL, symptom reduction, etc.), a specific international standard set of outcome measures should be collected (*Supplementary Figure 4*).<sup>299</sup> This would also highlight areas requiring further development.

## 9.9 Treatment burden

Patient-perceived treatment burden<sup>300</sup> is defined as the workload imposed by healthcare on patients and its effect on patient functioning and well-being apart from specific treatment side-effects.<sup>301,302</sup> It includes everything patients do for their health (drug management, self-monitoring, visits to the doctor, laboratory tests, lifestyle changes) and healthcare impact on their social relationships, potentially affecting adherence to treatment,<sup>303,304</sup> QoL, and outcomes

(e.g. hospitalization and survival).<sup>305,306</sup> Patient-perceived treatment burden is influenced by their knowledge about disease.<sup>302</sup> Patients with similar treatment regimens may have very different treatment burden,<sup>307</sup> with only a weak agreement between patient's and physicians' treatment burden evaluation, suggesting that the patient's experience is not shared in depth during consultations.<sup>302,308,309</sup>

Treatment burden can be overwhelming for patients with multiple chronic conditions<sup>301</sup> (e.g. those with three chronic conditions would have to take 6–12 medications daily, visit a healthcare giver 1.2–5.9 times per month, and spend 49.6–71.0 h monthly in healthcare-related activities<sup>310</sup>). Treatment burden in AF patients is largely unknown. In a single-centre prospective study, AF patient-perceived total treatment burden was higher than in patients with other chronic conditions (27.6% vs. 24.3%,  $P=0.011$ ), and 1 in 5 AF patients reported a high treatment burden that could question the sustainability of their treatment. Notably, AF patients attributed the highest proportion of treatment burden to healthcare system-related aspects (e.g. attending appointments etc.) and lifestyle modification requirements. Female sex and younger age were independently significantly associated with a higher treatment burden, whereas non-vitamin K antagonist oral anticoagulants (NOACs) and rhythm control reduced the odds for high treatment burden by >50%.<sup>311</sup>

The discussion of treatment burden should be an integral part of shared, informed treatment decision making, and treatment burden can be assessed using a validated questionnaire.<sup>312</sup>

## 9.10 Patient-reported outcomes

There is increasing advocacy for including patient-reported outcomes (PROs) as endpoints in clinical trials<sup>313</sup> and their routine collection<sup>314–316</sup> to improve care and assess treatment success from the patient's perspective. Patients' experience of AF and its management is highly subjective; AF management has become increasingly complex, potentially resulting in significant treatment burden and poorer health-related QoL.

Measuring outcomes that are important to patients, in addition to 'hard' clinical endpoints (death, stroke, major bleeding, etc.), can inform AF management. An international consortium of AF patients and healthcare professionals has identified the following PROs as important to measure for AF: health-related QoL, physical and emotional functioning, cognitive function, symptom severity, exercise tolerance, and ability to work (*Supplementary Figure 4*)<sup>299</sup>; PRO measures can be used to assess these factors and the international standard set of AF outcome measures proposes some tools for assessing PROs.<sup>299</sup> Health informatics systems could help capture PRO data. Despite increasing support for the role of PRO measures in healthcare management, few studies and registries report collecting PRO data using validated tools.<sup>313</sup> Implementation of PRO measures in the management of AF patients is addressed in a dedicated expert consensus paper developed in collaboration with patient representatives by the EHRA.<sup>317</sup>

### Recommendations about integrated AF management

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
To optimize shared decision making about specific AF treatment option(s) in consideration, it is recommended that physicians: <ul style="list-style-type: none"> <li>● Inform the patient about the advantages/limitations and benefit/risks associated with the treatment option(s) being considered; and</li> <li>● Discuss the potential burden of the treatment with the patient and include the patient’s perception of treatment burden in the treatment decision.</li> </ul>	I	C
It is recommended to routinely collect PROs to measure treatment success and improve patient care.	I	C
Integrated management with a structured multidisciplinary approach including healthcare professionals, patients, and their family/carers, should be used in all AF patients to improve clinical outcomes. <small>277,292–294,296,297</small>	IIa	B

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AF = atrial fibrillation; PRO = patient-reported outcome.  
<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.

## 10 Patient management: the integrated ABC pathway

The simple Atrial fibrillation Better Care (ABC) holistic pathway (‘A’ Anticoagulation/Avoid stroke; ‘B’ Better symptom management; ‘C’ Cardiovascular and Comorbidity optimization<sup>318</sup>) streamlines integrated care of AF patients across all healthcare levels and among different specialties. Compared with usual care, implementation of the ABC pathway has been significantly associated with lower risk of all-cause death, composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization,<sup>319</sup> lower rates of cardiovascular events,<sup>320,321</sup> and lower health-related costs.<sup>322</sup> In the prospective, randomized mAFA-II trial, the composite outcome was significantly lowered with ABC pathway management intervention compared with usual care [1.9% vs. 6.0%; hazard ratio (HR) 0.39; 95% CI 0.22 - 0.67; *P* < 0.001].<sup>323</sup>

### 10.1 ‘A’ – Anticoagulation/Avoid stroke

This section refers to AF in the absence of severe mitral stenosis or prosthetic heart valves (for AF with concomitant VHD see [section 11.7](#)).<sup>148</sup>

#### 10.1.1 Stroke risk assessment

Overall, AF increases the risk of stroke five-fold, but this risk is not homogeneous, depending on the presence of specific stroke risk factors/modifiers. Main clinical stroke risk factors have been identified from non-anticoagulated arms of the historical RCTs conducted >20 years ago, notwithstanding that these trials only randomized <10% of patients screened, whereas many common risk factors were not recorded or consistently defined.<sup>324</sup> These data have been supplemented by evidence from large observational cohorts also studying patients who would not have been included in the RCTs. Subsequently, various imaging, blood, and urine biological markers (biomarkers) have been associated with stroke risk ([Table 7](#)).<sup>324,325</sup> In addition, non-paroxysmal AF is associated with an increase in thrombo-embolism (multivariable adjusted HR 1.38; 95% CI 1.19 - 1.61; *P* < 0.001) compared with paroxysmal AF.<sup>156</sup> Notably, many of the risk factors for AF-related complications are also risk factors for incident AF.<sup>33</sup>

Common stroke risk factors are summarized in the clinical risk-factor-based CHA<sub>2</sub>DS<sub>2</sub>-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female)] score ([Table 8](#)).<sup>334</sup>

Stroke risk scores have to balance simplicity and practicality against precision.<sup>354–356</sup> As any clinical risk-factor-based score, CHA<sub>2</sub>DS<sub>2</sub>-VASc performs only modestly in predicting high-risk patients who will sustain thrombo-embolic events, but those identified as low-risk [CHA<sub>2</sub>DS<sub>2</sub>-VASc 0 (males), or score of 1 (females)] consistently have low ischaemic stroke or mortality rates (<1%/year) and do not need any stroke prevention treatment.

Female sex is an age-dependent stroke risk modifier rather than a risk factor per se.<sup>357,358</sup> Observational studies showed that women with no other risk factors (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1) have a low stroke risk, similar to men with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0.<sup>359</sup> The simplified CHA<sub>2</sub>DS<sub>2</sub>-VA score could guide the initial decision about OAC in AF patients, but not considering the sex component would underestimate stroke risk in women with AF.<sup>360,361</sup> In the presence of >1 non-sex stroke risk factor, women with AF consistently have significantly higher stroke risk than men.<sup>353,362</sup>

Many clinical stroke risk factors (e.g. renal impairment, OSA, LA dilatation<sup>291,326,363–365</sup>) are closely related to the CHA<sub>2</sub>DS<sub>2</sub>-VASc components, and their consideration does not improve its predictive value (the relationship of smoking or obesity to stroke risk in AF is also contentious).<sup>366</sup> Various biomarkers [e.g. troponin, natriuretic peptides, growth differentiation factor (GDF)-15, von Willebrand factor] have shown improved performance of biomarker-based over clinical scores in the assessment of residual stroke risk among anticoagulated AF patients<sup>329,367</sup>; notwithstanding, many of these biomarkers (as well as some clinical risk factors) are predictive of both stroke and bleeding<sup>329</sup> or non-AF and non-cardiovascular conditions, often (non-specifically) reflecting simply a sick heart or patient.

More complex clinical scores [e.g. Global Anticoagulant Registry in the FIELD - Atrial Fibrillation (GARFIELD-AF)]<sup>368</sup> and those inclusive of biomarkers [e.g. Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA),<sup>369,370</sup> Intermountain Risk Score,<sup>371</sup> ABC-stroke (Age, Biomarkers, Clinical history)]<sup>372</sup> improve stroke risk prediction modestly but statistically significantly. The ABC-stroke risk score that considers age, previous stroke/transient ischaemic attack (TIA), high-sensitivity troponin T (cTnT-hs) and N-terminal (NT)-prohormone

**Table 7** Stroke risk factors in patients with AF

Most commonly studied clinical risk factors (a systematic review) <sup>324</sup>	Positive studies/All studies	Other clinical risk factors <sup>325</sup>	Imaging biomarkers <sup>291,326–328</sup>	Blood/urine biomarkers <sup>329–332</sup>
Stroke/TIA/systemic embolism	15/16	Impaired renal function/CKD	Echocardiography	Cardiac troponin T and I Natriuretic peptides
Hypertension	11/20	OSA	LA dilatation	Cystatin C
Ageing (per decade)	9/13	HCM	Spontaneous contrast or thrombus in LA	Proteinuria CrCl/eGFR
Structural heart disease	9/13	Amyloidosis in degenerative cerebral and heart diseases	Low LAA velocities	CRP
Diabetes mellitus	9/14	Hyperlipidaemia	Complex aortic plaque	IL-6
Vascular disease	6/17	Smoking	Cerebral imaging	GDF-15
CHF/LV dysfunction	7/18	Metabolic syndrome <sup>333</sup>	Small-vessel disease	von Willebrand factor
Sex category (female)	8/22	Malignancy		D-dimer

CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; GDF-15 = growth differentiation factor-15; IL-6 = interleukin 6; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.

B-type natriuretic peptide has been validated in the cohorts of landmark NOAC trials.<sup>373–375</sup> A biomarker score-guided treatment strategy to reduce stroke and mortality in AF patients is being evaluated in an ongoing RCT (the ABC-AF Study, NCT03753490).

Whereas the routine use of biomarker-based risk scores currently would not substantially add to initial stroke prevention treatment decisions in patients already qualifying for treatment based on the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (and a limited practicality would be accompanied by increased healthcare costs),<sup>355,376,377</sup> biomarkers could further refine stroke risk differentiation among patients initially classified as low risk and those with a single non-sex CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factor.<sup>378</sup>

Studies of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score report a broad range of stroke rates depending on study setting (community vs. hospital), methodology (e.g. excluding patients subsequently treated with OAC would bias stroke rates towards lower levels), ethnicity, and prevalence of specific stroke risk factors in the study population (different risk factors carry different weight, and age thresholds for initiating NOACs may even differ for patients with a different single non-sex stroke risk factor, as follows: age 35 years for HF, 50 years for hypertension or diabetes, and 55 years for vascular disease).<sup>379,380</sup> No RCT has specifically addressed the need for OAC in patients with a single non-sex CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factor (to obtain high event rates and timely complete the study, anticoagulation trials have preferentially included high-risk patients), but an overview of subgroup analyses and observational data suggests that OAC use in such patients confers a positive net clinical benefit when balancing the reduction in stroke against the potential for harm with serious bleeding.<sup>339,381</sup>

For many risk factors (e.g. age), stroke risk is a continuum rather than an artificial low-, moderate-, or high-risk category. Risk factors are dynamic and, given the elderly AF population with multiple (often changing) comorbidities, stroke risk needs to be re-evaluated at each clinical review. Recent studies have shown that patients with a change in their risk profile are more likely to sustain strokes.<sup>382,383</sup> Many initially low-risk patients (>15%) would have ≥1 non-sex CHA<sub>2</sub>DS<sub>2</sub>-

VASc risk factor at 1 year after incident AF,<sup>384–386</sup> and 90% of new comorbidities were evident at 4.4 months after AF was diagnosed.<sup>387</sup>

A Patient-Centred Outcomes Research Institute (PCORI)-commissioned systematic review of 61 studies compared diagnostic accuracy and impact on clinical decision making of available clinical and imaging tools and associated risk factors for predicting thrombo-embolic and bleeding risk in AF patients.<sup>388</sup> The authors concluded that the CHADS<sub>2</sub> (CHF history, Hypertension history, Age ≥75 y, Diabetes mellitus history, Stroke or TIA symptoms previously), CHA<sub>2</sub>DS<sub>2</sub>-VASc, and ABC risk scores have the best evidence for predicting thrombo-embolic risk (moderate strength of evidence for limited prediction ability of each score).

### 10.1.2 Bleeding risk assessment

When initiating antithrombotic therapy, potential risk for bleeding also needs to be assessed. Non-modifiable and partially modifiable bleeding risks (Table 9) are important drivers of bleeding events in synergy with modifiable factors.<sup>389</sup> Notably, a history of falls is not an independent predictor of bleeding on OAC (a modelling study estimated that a patient would need to fall 295 times per year for the benefits of ischaemic stroke reduction with OAC to be outweighed by the potential for serious bleeding).<sup>390</sup>

Modifiable and non-modifiable bleeding risk factors have been used to formulate various bleeding risk scores,<sup>368,391–395</sup> generally with a modest predictive ability for bleeding events.<sup>396,397</sup> Studies comparing specific bleeding risk scores provided conflicting findings.<sup>393,394,398</sup> Various biomarkers have been proposed as bleeding risk predictors, but many have been studied in anticoagulated trial cohorts (while bleeding risk assessment is needed at all parts of the patient pathway—when initially not using OAC, if taking aspirin, and, subsequently, on OAC). Additionally, biomarkers are non-specifically predictive of stroke, death, HF, etc.<sup>399,400</sup> or even non-cardiovascular conditions (e.g. glaucoma),<sup>401</sup> and the availability of some biomarkers is limited in routine clinical practice.

The biomarker-based ABC-bleeding risk score [Age, Biomarkers (GDF-15, cTnT-hs, haemoglobin) and Clinical history (prior

**Table 8** CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>334</sup>

CHA <sub>2</sub> DS <sub>2</sub> -VASc score		Points awarded	Comment
Risk factors and definitions			
<b>C</b>	<b>Congestive heart failure</b> Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1	Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging <sup>335</sup> ; HCM confers a high stroke risk <sup>336</sup> and OAC is beneficial for stroke reduction. <sup>337</sup>
<b>H</b>	<b>Hypertension</b> or on antihypertensive therapy	1	History of hypertension may result in vascular changes that predispose to stroke, and a well-controlled BP today may not be well-controlled over time. <sup>324</sup> Uncontrolled BP - the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120 - 129/<80 mmHg. <sup>338</sup>
<b>A</b>	<b>Age 75 years or older</b>	2	Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards. <sup>339</sup> Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥75 years.
<b>D</b>	<b>Diabetes mellitus</b> Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1	Diabetes mellitus is a well-established risk factor for stroke, and more recently stroke risk has been related to duration of diabetes mellitus (the longer the duration of diabetes mellitus, the higher the risk of thromboembolism <sup>340</sup> ) and presence of diabetic target organ damage, e.g. retinopathy. <sup>341</sup> Both type 1 and type 2 diabetes mellitus confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged <65 years with type 2 diabetes mellitus compared to patients with type 1 diabetes mellitus. <sup>342</sup>
<b>S</b>	<b>Stroke</b> Previous stroke, TIA, or thromboembolism	2	Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischaemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including haemorrhagic stroke) are at very high risk of subsequent ischaemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation. <sup>343-345</sup>
<b>V</b>	<b>Vascular disease</b> Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1	Vascular disease (PAD or myocardial infarction) confers a 17 - 22% excess risk, particularly in Asian patients. <sup>346-348</sup> Angiographically significant CAD is also an independent risk factor for ischaemic stroke among AF patients (adjusted incidence rate ratio 1.29, 95% CI 1.08 - 1.53). <sup>349</sup> Complex aortic plaque on the descending aorta, as an indicator of significant vascular disease, is also a strong predictor of ischaemic stroke. <sup>350</sup>
<b>A</b>	<b>Age 65 - 74 years</b>	1	See above. Recent data from Asia suggest that the risk of stroke may rise from age 50 - 55 years upwards and that a modified CHA <sub>2</sub> DS <sub>2</sub> -VASc score may be used in Asian patients. <sup>351,352</sup>
<b>Sc</b>	<b>Sex category (female)</b>	1	A stroke risk modifier rather than a risk factor. <sup>353</sup>
<b>Maximum score</b>		<b>9</b>	

AF = atrial fibrillation; BP = blood pressure; CAD = coronary artery disease; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); CI = confidence interval; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICH = intracranial haemorrhage; LV = left ventricular; LVEF = left ventricular ejection fraction; OAC = oral anticoagulant; PAD = peripheral artery disease; RCT = randomized controlled trial; TIA = transient ischaemic attack.

**Table 9** Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years	Extreme frailty ± excessive risk of falls <sup>a</sup>	Hypertension/elevated SBP	GDF-15
Previous major bleeding	Anaemia	Concomitant antiplatelet/NSAID	Cystatin C/CKD-EPI
Severe renal impairment (on dialysis or renal transplant)	Reduced platelet count or function	Excessive alcohol intake	cTnT-hs
Severe hepatic dysfunction (cirrhosis)	Renal impairment with CrCl <60 mL/min	Non-adherence to OAC	von Willebrand factor (+ other coagulation markers)
Malignancy	VKA management strategy <sup>b</sup>	Hazardous hobbies/occupations	
Genetic factors (e.g. CYP 2C9 polymorphisms)		Bridging therapy with heparin	
Previous stroke, small-vessel disease, etc.		INR control (target 2.0 - 3.0), target TTR >70% <sup>c</sup>	
Diabetes mellitus		Appropriate choice of OAC and correct dosing <sup>d</sup>	
Cognitive impairment/dementia			

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.

<sup>a</sup>Walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate.

<sup>b</sup>Increased INR monitoring, dedicated OAC clinics, self-monitoring/self-management, educational/behavioural interventions.

<sup>c</sup>For patients receiving VKA treatment.

<sup>d</sup>Dose adaptation based on patient's age, body weight, and serum creatinine level.

**Table 10** Clinical risk factors in the HAS-BLED score<sup>395</sup>

Risk factors and definitions		Points awarded
<b>H</b>	<b>Uncontrolled hypertension</b> SBP >160 mmHg	1
<b>A</b>	<b>Abnormal renal and/or hepatic function</b> Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
<b>S</b>	<b>Stroke</b> Previous ischaemic or haemorrhagic <sup>a</sup> stroke	1
<b>B</b>	<b>Bleeding history or predisposition</b> Previous major haemorrhage or anaemia or severe thrombocytopenia	1
<b>L</b>	<b>Labile INR<sup>b</sup></b> TTR <60% in patient receiving VKA	1
<b>E</b>	<b>Elderly</b> Aged >65 years or extreme frailty	1
<b>D</b>	<b>Drugs or excessive alcohol drinking</b> Concomitant use of antiplatelet or NSAID; and/or excessive <sup>c</sup> alcohol per week	1 point for each
<b>Maximum score</b>		<b>9</b>

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SBP = systolic blood pressure; INR = international normalized ratio; NSAID = Non-steroidal anti-inflammatory drug; TTR = time in therapeutic range; VKA = vitamin K antagonist.

<sup>a</sup>Haemorrhagic stroke would also score 1 point under the 'B' criterion.

<sup>b</sup>Only relevant if patient receiving a VKA.

<sup>c</sup>Alcohol excess or abuse refers to a high intake (e.g. >14 units per week), where the clinician assesses there would be an impact on health or bleeding risk.

bleeding)]<sup>375,402</sup> reportedly outperformed clinical scores, but in another study there was no long-term advantage of ABC-bleeding over HAS-BLED score (Table 10), whereas HAS-BLED was better in identifying patients at low risk of bleeding (HAS-BLED 0–2).<sup>403</sup> In the PCORI-commissioned systematic review,<sup>388</sup> encompassing 38 studies of bleeding risk prediction, the HAS-BLED score had the best evidence for predicting bleeding risk (moderate strength of evidence), consistent with other systematic reviews and meta-analyses comparing bleeding risk prediction approaches.<sup>404–406</sup>

A high bleeding risk score should not lead to withholding OAC, as the net clinical benefit of OAC is even greater amongst such patients. However, the formal assessment of bleeding risk informs management of patients taking OAC, focusing attention on modifiable bleeding risk factors that should be managed and (re)assessed at every patient contact, and identifying high-risk patients with non-modifiable bleeding risk factors who should be reviewed earlier (for instance in 4 weeks rather than 4–6 months) and more frequently.<sup>389,407</sup> Identification of 'high bleeding risk' patients is also needed when determining the antithrombotic strategy in specific AF patient groups, such as those undergoing percutaneous coronary intervention (PCI).

Overall, bleeding risk assessment based solely on modifiable bleeding risk factors is an inferior strategy compared with formal bleeding risk assessment using a bleeding risk score,<sup>408–410</sup> thus also considering the interaction between modifiable and non-modifiable bleeding risk factors. Bleeding risk is dynamic, and attention to the change in bleeding risk profile is a stronger predictor of major bleeding events compared with simply relying on baseline bleeding risk. In a recent study, there was a 3.5-fold higher risk of major bleeding in the first 3 months amongst patients who had a change in their bleeding risk profile.<sup>389</sup>

In the mAFA-II trial, prospective dynamic monitoring and reassessment using the HAS-BLED score (together with holistic App-based management) was associated with fewer major bleeding events, mitigated modifiable bleeding risk factors, and increased OAC uptake; in contrast, bleeding rates were higher and OAC use overall decreased by 25% in the 'usual care' arm when comparing baseline with 12 months.<sup>411</sup>

### 10.1.3 Absolute contraindications to oral anticoagulants

The few absolute contraindications to OAC include active serious bleeding (where the source should be identified and treated), associated comorbidities (e.g. severe thrombocytopenia <50 platelets/µL, severe anaemia under investigation, etc.), or a recent high-risk bleeding event such as intracranial haemorrhage (ICH). Non-drug options may be considered in such cases (section 11.4.3).

### 10.1.4 Stroke prevention therapies

#### 10.1.4.1 Vitamin K antagonists

Compared with control or placebo, vitamin K antagonist (VKA) therapy (mostly warfarin) reduces stroke risk by 64% and mortality by 26%,<sup>412</sup> and is still used in many AF patients worldwide. VKAs are currently the only treatment with established safety in AF patients with rheumatic mitral valve disease and/or an artificial heart valve.

The use of VKAs is limited by the narrow therapeutic interval, necessitating frequent international normalized ratio (INR) monitoring and dose adjustments.<sup>413</sup> At adequate time in therapeutic range [(TTR) >70%], VKAs are effective and relatively safe drugs. Quality of VKA management (quantified using the TTR based on the Rosendaal method, or the percentage of INRs in range) correlates with haemorrhagic and thrombo-



embolic rates.<sup>414</sup> At high TTR values, the efficacy of VKAs in stroke prevention may be similar to NOACs, whereas the relative safety benefit with NOACs is less affected by TTR, with consistently lower serious bleeding rates (e.g. ICH) seen with NOACs compared with warfarin, notwithstanding that the absolute difference is small.<sup>415,416</sup>

Numerous factors (including genetics, concomitant drugs, etc.) influence the intensity of VKA anticoagulant effect; the more common ones have been used to derive and validate the SAMe-TT<sub>2</sub>R<sub>2</sub> {Sex [female], Age [<60 years], Medical history of  $\geq 2$  comorbidities [hypertension, diabetes mellitus, CAD/myocardial infarction, peripheral artery disease (PAD), HF, previous stroke, pulmonary disease, and hepatic or renal disease], Treatment [interacting drugs, e.g. amiodarone], Tobacco use, Race [non-Caucasian]} score,<sup>417</sup> which can help to identify patients who are less likely to achieve a good TTR on VKA therapy (score >2) and would do better with a NOAC. If such patients with SAMe-TT<sub>2</sub>R<sub>2</sub>>2 are prescribed a VKA, greater efforts to improve TTR, such as more intense regular reviews, education/counselling, and frequent INR monitoring are needed or, more conveniently, the use of a NOAC should be reconsidered.<sup>418</sup>

#### 10.1.4.2 Non-vitamin K antagonist oral anticoagulants

In four pivotal RCTs, apixaban, dabigatran, edoxaban, and rivaroxaban have shown non-inferiority to warfarin in the prevention of stroke/systemic embolism.<sup>419–422</sup> In a meta-analysis of these RCTs, NOACs were associated with a 19% significant stroke/systemic embolism risk reduction, a 51% reduction in haemorrhagic stroke,<sup>423</sup> and similar ischaemic stroke risk reduction compared with VKAs, but NOACs were associated with a significant 10% reduction in all-cause mortality (Supplementary Table 8). There was a non-significant 14% reduction in major bleeding risk, significant 52% reduction in ICH, and 25% increase in gastrointestinal bleeding with NOACs vs. warfarin.<sup>423</sup>

The major bleeding relative risk reduction with NOACs was significantly greater when INR control was poor (i.e. centre-based TTR<66%). A meta-analysis of the five NOAC trials [RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy), 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), J-ROCKET AF, ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial

Fibrillation—Thrombolysis in Myocardial Infarction 48)] showed that, compared with warfarin, standard-dose NOACs were more effective and safer in Asians than in non-Asians.<sup>424</sup> In the AVERROES [Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment] trial of AF patients who refused or were deemed ineligible for VKA therapy, apixaban 5 mg b.i.d. (twice a day) significantly reduced the risk of stroke/systemic embolism with no significant difference in major bleeding or ICH compared with aspirin.<sup>425</sup>

Post-marketing observational data on the effectiveness and safety of dabigatran,<sup>426,427</sup> rivaroxaban,<sup>428,429</sup> apixaban,<sup>430</sup> and edoxaban<sup>431</sup> vs. warfarin show general consistency with the respective RCT. Given the compelling evidence about NOACs, AF patients should be informed of this treatment option.

Persistence to NOAC therapy is generally higher than to VKAs, being facilitated by a better pharmacokinetic profile of NOACs<sup>432</sup> (Supplementary Table 9) and favourable safety and efficacy, especially amongst vulnerable patients including the elderly, those with renal dysfunction or previous stroke, and so on.<sup>433</sup> Whereas patients with end-stage renal dysfunction were excluded from the pivotal RCTs, reduced dose regimens of rivaroxaban, edoxaban, and apixaban are feasible options for severe CKD [creatinine clearance (CrCl) 15–30 mL/min using the Cockcroft-Gault equation].<sup>434,435</sup> Considering that inappropriate dose reductions are frequent in clinical practice,<sup>436</sup> thus increasing the risks of stroke/systemic embolism, hospitalization, and death, but without decreasing bleeding risk,<sup>437</sup> NOAC therapy should be optimized based on the efficacy and safety profile of each NOAC in different patient subgroups (Table 11).

#### 10.1.4.3 Other antithrombotic drugs

In the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel was less effective than warfarin for prevention of stroke, systemic embolism, myocardial infarction, and vascular death (the annual risk of events was 5.6% vs. 3.9%,  $P=0.0003$ ), with a similar rate of major bleeding.<sup>438</sup> In the ACTIVE-A trial, patients unsuitable for anticoagulation had a lower rate of thrombo-embolic complications when clopidogrel was added to aspirin compared with aspirin alone, but with a significant increase in major bleeding.<sup>439</sup> Aspirin monotherapy was ineffective for stroke prevention compared with no antithrombotic treatment and was

**Table 11** Dose selection criteria for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
<b>Standard dose</b>	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
<b>Lower dose</b>	110 mg b.i.d.			30 mg o.d.
<b>Reduced dose</b>		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d.
<b>Dose-reduction criteria</b>	Dabigatran 110 mg b.i.d. in patients with: <ul style="list-style-type: none"> <li>● Age <math>\geq 80</math> years</li> <li>● Concomitant use of verapamil, or</li> <li>● Increased bleeding risk</li> </ul>	CrCl 15–49 mL/min	At least 2 of 3 criteria: <ul style="list-style-type: none"> <li>● Age <math>\geq 80</math> years,</li> <li>● Body weight <math>\leq 60</math> kg, or</li> <li>● Serum creatinine <math>\geq 1.5</math> mg/dL (133 <math>\mu</math>mol/L)</li> </ul>	If any of the following: <ul style="list-style-type: none"> <li>● CrCl 30–50 mL/min,</li> <li>● Body weight <math>\leq 60</math> kg,</li> <li>● Concomitant use of dronedarone, ciclosporine, erythromycin, or ketoconazole</li> </ul>

b.i.d. = bis in die (twice a day); CrCl = creatinine clearance; o.d. = *omni die* (once daily).

associated with a higher risk of ischaemic stroke in elderly patients.<sup>440</sup>

Overall, antiplatelet monotherapy is ineffective for stroke prevention and is potentially harmful, (especially amongst elderly AF patients),<sup>441,442</sup> whereas DAPT is associated with a bleeding risk similar to OAC therapy. Hence, antiplatelet therapy should not be used for stroke prevention in AF patients.

10.1.4.4 Combination therapy with oral anticoagulant and antiplatelet drugs

The use of antiplatelet therapy remains common in clinical practice, often in patients without an indication (e.g. PAD, CAD, or cerebrovascular disease) beyond AF.<sup>443</sup> There is limited evidence to support the combination therapy solely for stroke prevention in AF, with no effect on reductions in stroke, myocardial infarction, or death, but with a substantial increase in the risk of major bleeding and ICH.<sup>441,442</sup>

10.1.4.5 Left atrial appendage occlusion and exclusion

10.1.4.5.1 Left atrial appendage occlusion devices. Only the Watchman device has been compared with VKA therapy in RCTs [the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy)],<sup>444–446</sup> where LAA occlusion was non-inferior to VKA stroke prevention treatment in AF patients with moderate stroke risk, with a possibility of lower bleeding rates on longer follow-up.<sup>447</sup> The LAA occlusion may also reduce stroke risk in patients with contraindications to OAC.<sup>448,449</sup>

A large European registry reported a high implantation success rate (98%), with an acceptable procedure-related complication rate of 4% at 30 days.<sup>450</sup> Nevertheless, the implantation procedure can cause serious complications (higher event rates have been reported in real-world analyses compared with industry-sponsored studies, possibly identifying some reporting bias) and device-related thrombosis may not be a benign finding.<sup>451–454</sup> Antithrombotic management after LAA occlusion has never been evaluated in a randomized

manner and is based on historical studies, at least including aspirin (Table 12). For patients who do not tolerate any antiplatelet therapy, either an epicardial catheter approach (e.g. Lariat system) or thoracoscopic clipping of the LAA may be an option.<sup>455,456</sup>

Notably, the non-inferiority of LAA occlusion to VKA treatment was mostly driven by the prevention of haemorrhagic stroke, with a trend for more ischaemic strokes. The limitations of LAA occlusion as a strategy to reduce the risk of stroke associated with AF also include the consideration that AF acts as a risk marker of stroke. Withholding OAC after LAA occlusion is likely to result in under-treating the overall risk of stroke related to atrial cardiomyopathy.

10.1.4.5.2 Surgical left atrial appendage occlusion or exclusion. Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available.<sup>457–459</sup> Residual LAA flow or incomplete LAA occlusion may be associated with an increased risk of stroke.<sup>460</sup> In most studies, LAA occlusion/exclusion was performed during other open heart surgery, and in more recent years in combination with surgical ablation of AF<sup>459,461</sup> or as an isolated thoracoscopic procedure. A large RCT in patients with an associated cardiac surgical procedure is ongoing.<sup>462</sup>

The most common justification for LAA occlusion/exclusion in clinical practice is a perceived high bleeding risk or, less often, contraindications for OAC.<sup>450</sup> However, LAA occluders have not been randomly tested in such populations. Most patients who some years ago would be considered unsuitable for OAC therapy with VKA now seem to do relatively well on NOAC,<sup>433,463,464</sup> and LAA occluders have not been compared with NOAC therapy in patients at risk for bleeding, or with surgical LAA occlusion/exclusion. Long-term aspirin is a common strategy in these patients,<sup>465</sup> and one may question whether a NOAC would not be a better strategy if aspirin is tolerated. There is the need for adequately powered trials to define the best indications of LAA occlusion/exclusion compared with NOAC therapy in patients with relative or absolute contraindications for anticoagulation, in those suffering from an ischaemic stroke on anti-coagulant therapy, and for assessment of the appropriate antithrombotic therapy after LAA occlusion.

**Table 12 Antithrombotic therapy after left atrial appendage occlusion**

Device/patient	Aspirin	OAC	Clopidogrel	Comments
Watchman/low bleeding risk	75 - 325 mg/day indefinitely	Start warfarin after procedure (target INR 2 - 3) until 45 days or continue until adequate LAA sealing is confirmed <sup>a</sup> by TOE. NOAC is a possible alternative	Start 75 mg/day when OAC stopped, continue until 6 months after the procedure	Some centres do not withhold OAC at the time of procedure (no data to support/deny this approach)
Watchman/high bleeding risk	75 - 325 mg/day indefinitely	None	75 mg/day for 1 - 6 months while ensuring adequate LAA sealing <sup>a</sup>	Clopidogrel often given for shorter time in very high-risk situations
ACP/Amulet	75 - 325 mg/day indefinitely	None	75 mg/day for 1 - 6 months while ensuring adequate LAA sealing <sup>a</sup>	Clopidogrel may replace long-term aspirin if better tolerated

ACP = Amplatzer™ Cardiac Plug; INR = international normalized ratio; LAA = left atrial appendage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TOE = transoesophageal echocardiography.

Note: Load aspirin or clopidogrel before procedure if untreated. Heparin with activated clotting time >250 seconds before or immediately after trans-septal punctures for all patients, followed by LMWH when warfarin needed.

<sup>a</sup>Less than 5 mm leak.

#### 10.1.4.6 Long-term oral anticoagulation per atrial fibrillation burden

Although the risk of ischaemic stroke/systemic embolism is higher with non-paroxysmal vs. paroxysmal AF, and AF progression is associated with an excess of adverse outcomes,<sup>169,466</sup> the clinically determined temporal pattern of AF should not affect the decision regarding long-term OAC, which is driven by the presence of stroke risk factors.<sup>156</sup> Management of patients with AHRE/subclinical AF is reviewed in *section 16*. Stroke risk in AHRE patients may be lower than in patients with diagnosed AF,<sup>467</sup> and strokes often occur without a clear temporal relationship with AHRE/subclinical AF,<sup>179,226</sup> underscoring its role as a risk marker rather than a stroke risk factor.<sup>4,172</sup> Whether AHRE and subclinical AF have the same therapeutic requirements as clinical AF<sup>7</sup> is presently unclear, and the net clinical benefit of OAC for AHRE/subclinical AF >24 h is currently being studied in several RCTs.<sup>4</sup>

Notably, patients with subclinical AF/AHRE may develop atrial tachyarrhythmias lasting more than 24 h<sup>468</sup> or clinical AF; hence careful monitoring of these patients is recommended, even considering remote monitoring, especially with longer AHRE and higher risk profile.<sup>469</sup> Given the dynamic nature of AF as well as stroke risk, a recorded duration in one monitoring period would not necessarily be the same in the next.

#### 10.1.4.7 Long-term oral anticoagulation per symptom control strategy

Symptom control focuses on patient-centred and symptom-directed approaches to rate or rhythm control. Again, symptom control strategy should not affect the decision regarding long-term OAC, which is driven by the presence of stroke risk factors, and not the estimated success in maintaining sinus rhythm.

### 10.1.5 Management of anticoagulation-related bleeding risk

#### 10.1.5.1 Strategies to minimize the risk of bleeding

Ensuring good quality of VKA treatment (TTR >70%) and selecting the appropriate dose of a NOAC (as per the dose reduction criteria specified on the respective drug label) are important considerations to minimize bleeding risk. As discussed in *section 10.1.2*, attention to modifiable bleeding risk factors should be made at every patient contact, and formal bleeding risk assessment is needed to help identify high-risk patients who should be followed up or reviewed earlier (e.g. 4 weeks rather than 4–6 months).<sup>407</sup> Concomitant regular administration of antiplatelet drugs or non-steroidal anti-inflammatory drug (NSAID) should be avoided in anticoagulated patients. Bleeding risk is dynamic, and attention to the change in bleeding risk profile is a stronger predictor of major bleeding events, especially in the first 3 months.<sup>389</sup>

#### 10.1.5.2 High-risk groups

Certain high-risk AF populations have been under-represented in RCTs, including the extreme elderly ( $\geq 90$  years), those with cognitive impairment/dementia, recent bleeding or previous ICH, end-stage renal failure, liver impairment, cancer, and so on. Observational data suggest that such patients are at high risk for ischaemic stroke and death, and many would benefit from OAC.

Patients with liver function abnormalities may be at higher risk of bleeding on VKA, possibly less so on NOACs. Observational data in

cirrhotic patients suggest that ischaemic stroke reduction may outweigh bleeding risk.<sup>470–472</sup>

In patients with a recent bleeding event, attention should be directed towards addressing the predisposing pathology (e.g. bleeding ulcer or polyp in a patient with gastrointestinal bleeding), and the reintroduction of OAC as soon as feasible, as part of a multidisciplinary team decision. Consideration should be made for drugs such as apixaban or dabigatran 110 mg b.i.d., which are not associated with an excess of gastrointestinal bleeding compared with warfarin. Where OAC is not reintroduced, there is a higher risk of stroke and death compared with restarting OAC, although the risk of re-bleeding may be higher.<sup>473</sup> Similarly, thromboprophylaxis in cancer may require a multidisciplinary team decision balancing stroke reduction against serious bleeding, which may be dependent on cancer type, site(s), staging, anti-cancer therapy and so on.

Thromboprophylaxis in specific high-risk groups is discussed in detail throughout *section 11*.

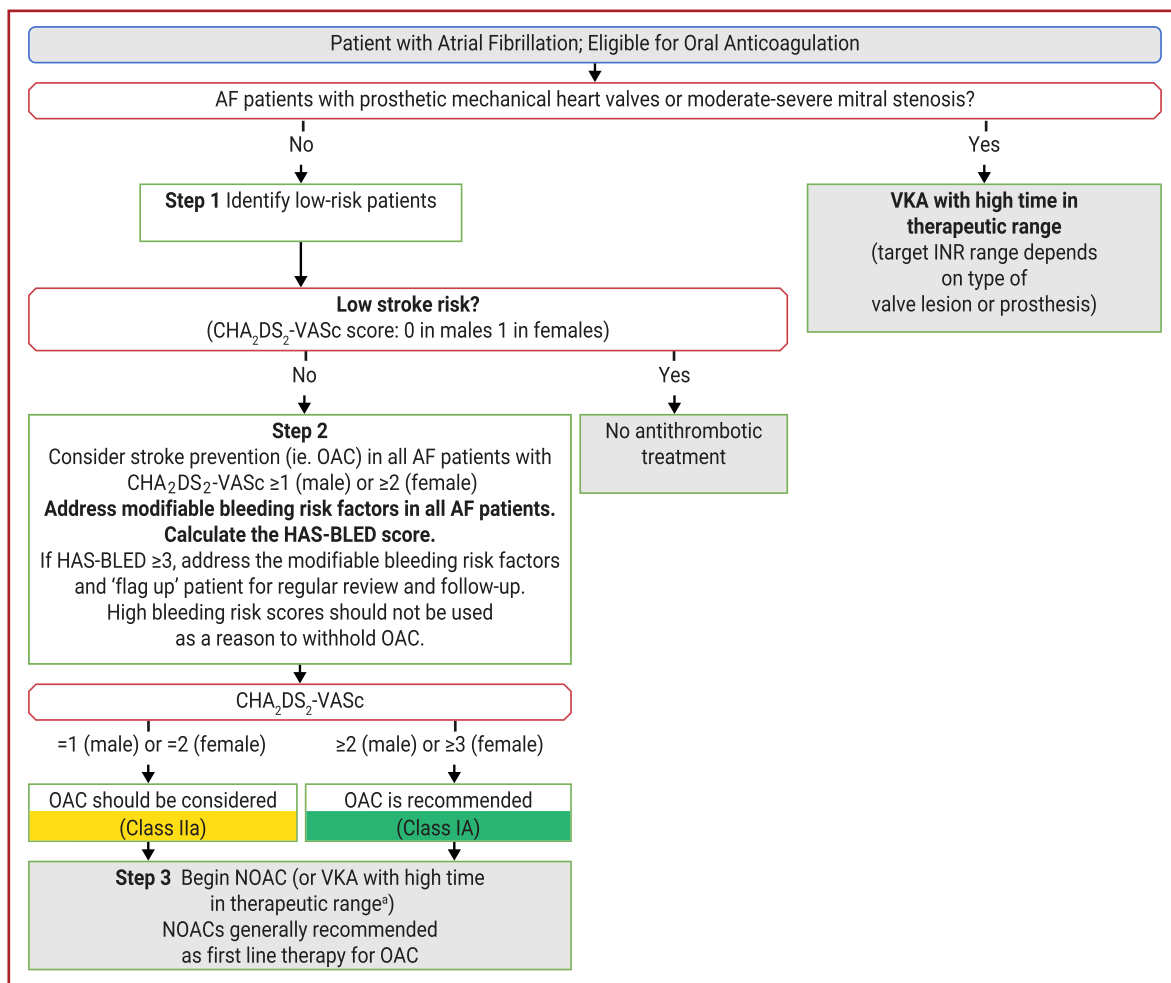
### 10.1.6 Decision making to avoid stroke

In observational population cohorts, both stroke and death are relevant endpoints, as some deaths could be due to fatal strokes (given that endpoints are not adjudicated in population cohorts, and cerebral imaging or post-mortems are not mandated). As OAC significantly reduces stroke (by 64%) and all-cause mortality (by 26%) compared with control or placebo,<sup>412</sup> the endpoints of stroke and/or mortality are relevant in relation to decision making for thromboprophylaxis.

The threshold for initiating OAC for stroke prevention, balancing ischaemic stroke reduction against the risk of ICH and associated QoL, has been estimated to be 1.7%/year for warfarin and 0.9%/year for a NOAC (dabigatran data were used for the modelling analysis).<sup>474</sup> The threshold for warfarin may be even lower, if good-quality anticoagulation control is achieved, with average TTR >70%.<sup>475</sup>

Given the limitations of clinical risk scores, the dynamic nature of stroke risk, the greater risk of stroke and death among AF patients with  $\geq 1$  non-sex stroke risk factor, and the positive net clinical benefit of OAC among such patients, we recommend a risk-factor-based approach to stroke prevention rather than undue focus on (artificially defined) 'high-risk' patients. As the default is to offer stroke prevention unless the patient is low risk, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score should be applied in a reductionist manner, to decide on OAC or not.<sup>476</sup>

Thus, the first step in decision making ('A' Anticoagulation/Avoid stroke) is to identify low-risk patients who do not need antithrombotic therapy. Step 2 is to offer stroke prevention (i.e. OAC) to those with  $\geq 1$  non-sex stroke risk factors (the strength of evidence differs, with multiple clinical trials for patients with  $\geq 2$  stroke risk factors, and subgroups from trials/observational data on patients with 1 non-sex stroke risk factor). Step 3 is the choice of OAC—a NOAC (given their relative effectiveness, safety and convenience, these drugs are generally first choice as OAC for stroke prevention in AF) or VKA (with good TTR at >70%). This 'AF 3-step' patient pathway<sup>182,477</sup> for stroke risk stratification and treatment decision making is shown in *Figure 12*.



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**Figure 12** ‘A’ - Anticoagulation/Avoid stroke: The ‘AF 3-step’ pathway. AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; SAME-TT<sub>2</sub>R<sub>2</sub> = Sex (female), Age (<60 years), Medical history, Treatment (interacting drug(s)), Tobacco use, Race (non-Caucasian) (score); TTR = time in therapeutic range; VKA = vitamin K antagonist.  
<sup>a</sup>If a VKA being considered, calculate SAME-TT<sub>2</sub>R<sub>2</sub> score: if score 0–2, may consider VKA treatment (e.g. warfarin) or NOAC; if score >2, should arrange regular review/frequent INR checks/ counselling for VKA users to help good anticoagulation control, or reconsider the use of NOAC instead; TTR ideally >70%.

**Recommendations for the prevention of thrombo-embolic events in AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis). <sup>423,424</sup>	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA <sub>2</sub> DS <sub>2</sub> -VASc clinical stroke risk score to initially identify patients at ‘low stroke risk’ (CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy. <sup>334,388</sup>	I	A
OAC is recommended for stroke prevention in AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 in men or ≥3 in women. <sup>412</sup>	I	A
OAC should be considered for stroke prevention in AF patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences. <sup>338,378,380</sup>	IIa	B
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up. <sup>388,395,404,406</sup>	I	B

Continued

For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score $\geq 3$ ) for early and more frequent clinical review and follow-up. <sup>388,395,404,406</sup>	IIa	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors. <sup>c389,478,479</sup>	I	B
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation. <sup>385–387</sup>	IIa	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR $\geq 70\%$ . <sup>414</sup>	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR $<70\%$ ), recommended options are:	I	B
• Switching to a NOAC but ensuring good adherence and persistence with therapy <sup>415,416</sup> ; or	IIa	B
• Efforts to improve TTR (e.g. education/counselling and more frequent INR checks). <sup>480</sup>	IIa	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF. <sup>440,441,480,481</sup>	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis. <sup>160</sup>	III	B
<b>Recommendations for occlusion or exclusion of the LAA</b>		
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause). <sup>448,449,481,482</sup>	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery. <sup>459,483</sup>	IIb	C

AF = atrial fibrillation; BP = blood pressure; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist.

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

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

<sup>c</sup>Including uncontrolled BP; labile INRs (in a patient taking VKA); alcohol excess; concomitant use of NSAIDs or aspirin in an anticoagulated patient; bleeding tendency or predisposition (e.g. treat gastric ulcer, optimize renal or liver function, etc.).

## 10.2 'B' – Better symptom control

### 10.2.1 Rate control

Rate control is an integral part of AF management, and is often sufficient to improve AF-related symptoms. Very little robust evidence exists to inform the best type and intensity of rate control treatment.<sup>484–486</sup>

#### 10.2.1.1 Target/optimal ventricular rate range

The optimal heart-rate target in AF patients is unclear. In the RACE (Race Control Efficacy in Permanent Atrial Fibrillation) II RCT of permanent AF patients, there was no difference in a composite of clinical events, New York Heart Association (NYHA) class, or hospitalizations between the strict [target heart rate  $<80$  beats per minute (bpm) at rest and  $<110$  bpm during moderate exercise] and lenient (heart-rate target  $<110$  bpm) arm,<sup>487,488</sup> similar to an analysis from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE trials.<sup>489</sup> Therefore, lenient rate control is an acceptable initial approach, regardless of HF status (with the exception of tachycardia-induced cardiomyopathy), unless symptoms call for stricter rate control (Figure 13).

#### 10.2.1.2 Drugs

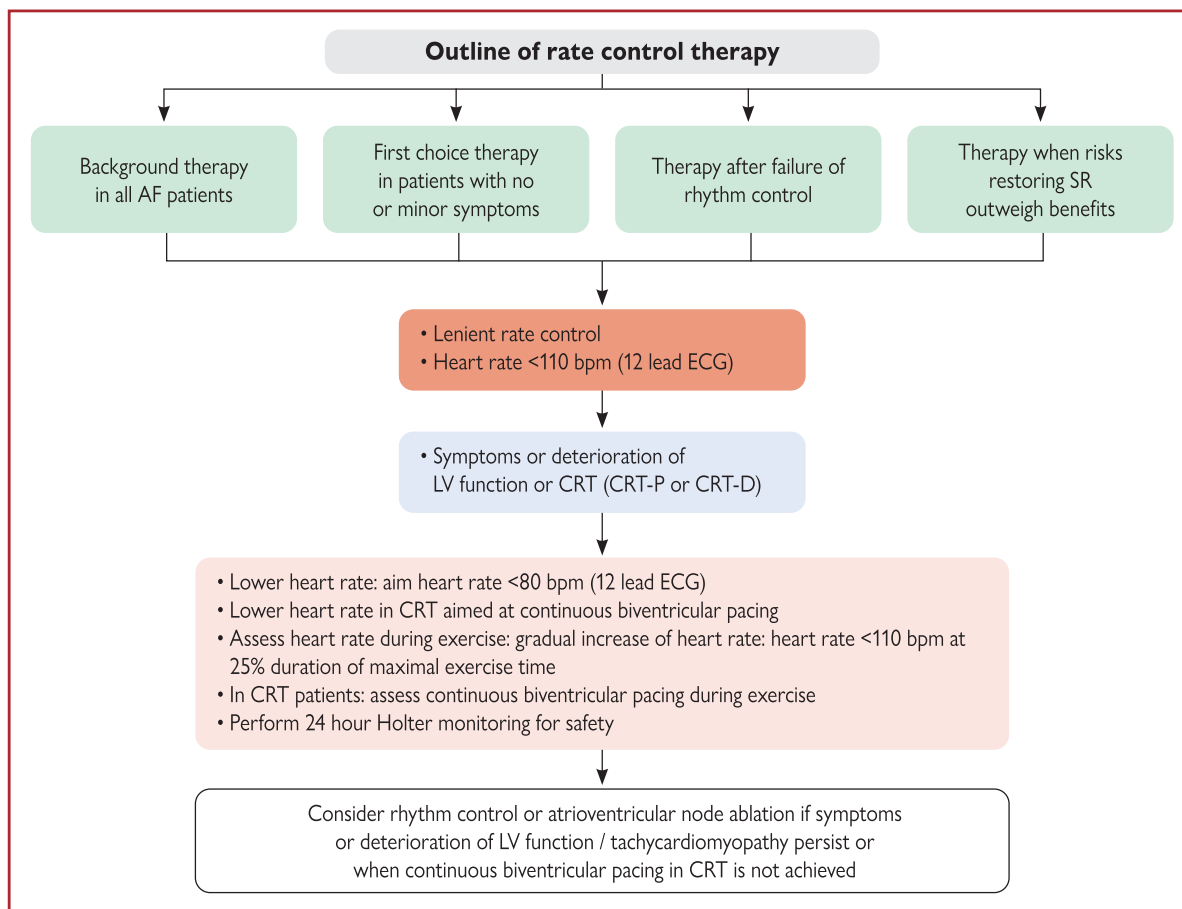
Pharmacological rate control can be achieved with beta-blockers, digoxin, diltiazem, and verapamil, or combination therapy (Table 13).

Some antiarrhythmic drugs (AADs) also have rate-limiting properties (e.g. amiodarone, dronedarone, sotalol) but generally they should be used only for rhythm control. The choice of rate control drugs depends on symptoms, comorbidities, and potential side-effects (Table 13).

**Beta-blockers** are often first-line rate-controlling agents, largely based on better acute rate control. Interestingly, the prognostic benefit of beta-blockers seen in HF with reduced ejection fraction (HFrEF) patients with sinus rhythm has been questioned in patients with AF.<sup>491</sup>

**Non-dihydropyridine calcium channel blockers (NDCC)** verapamil and diltiazem provide reasonable rate control<sup>492</sup> and can improve AF-related symptoms<sup>486</sup> compared with beta-blockers. In one small trial of patients with preserved LVEF, NDCC preserved exercise capacity and reduced B-type natriuretic peptide.<sup>493,494</sup>

**Digoxin** and digitoxin are not effective in patients with increased sympathetic drive. Observational studies have associated digoxin use with excess mortality in AF patients.<sup>495–497</sup> This finding was likely due to selection and prescription biases rather than harm caused by digoxin,<sup>498–501</sup> particularly as digoxin is commonly prescribed to sicker patients.<sup>502</sup> Lower doses of digoxin may be associated with



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**Figure 13** Outline of rate control therapy.<sup>490</sup> AF = atrial fibrillation; AVN = atrioventricular node; bpm = beats per minute; BV = biventricular; CRT = cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ECG = electrocardiogram; LV = left ventricular; SR = sinus rhythm.

better prognosis.<sup>502</sup> An ongoing RCT is addressing digoxin use in patients with HFrEF.<sup>503</sup>

**Amiodarone** can be useful as a last resort when heart rate cannot be controlled with combination therapy in patients who do not qualify for non-pharmacological rate control, i.e. atrioventricular node ablation and pacing, notwithstanding the extracardiac adverse effects of the drug<sup>504</sup> (Table 13).

#### 10.2.1.3 Acute rate control

In acute settings, physicians should always evaluate underlying causes, such as infection or anaemia. Beta-blockers and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at high sympathetic tone.<sup>507–511</sup> The choice of drug (Table 13 and Figure 14) and target heart rate will depend on the patient characteristics, symptoms, LVEF value, and haemodynamics, but a lenient initial heart-rate approach seems acceptable (Figure 13). Combination therapy may be required. In patients with HFrEF, beta-blockers, digitalis, or their combination should be used.<sup>512,513</sup> In critically ill patients and those with severely impaired LV systolic function, i.v. amiodarone can be used.<sup>504,514,515</sup> In unstable patients, urgent cardioversion should be considered (section 11.1).

#### 10.2.1.4 Atrioventricular node ablation and pacing

Ablation of the atrioventricular node and pacemaker implantation can control ventricular rate when medication fails. The procedure is relatively simple and has a low complication rate and low long-term mortality risk,<sup>516,517</sup> especially when the pacemaker is implanted a few weeks before the atrioventricular node ablation and the initial pacing rate after ablation is set at 70–90 bpm.<sup>518,519</sup> The procedure does not worsen LV function<sup>520</sup> and may even improve LVEF in selected patients.<sup>521–523</sup> Most studies have included older patients with limited life expectancy. For younger patients, ablation of the atrioventricular node should only be considered if there is urgent need for rate control and all other pharmacological and non-pharmacological treatment options have been carefully considered. The choice of pacing therapy (right ventricular or biventricular pacing) will depend on patient characteristics.<sup>524,525</sup> His-bundle pacing after atrioventricular node ablation may evolve as an attractive alternative pacing mode,<sup>526</sup> as currently tested in ongoing clinical trials (NCT02805465, NCT02700425).

In severely symptomatic patients with permanent AF and at least one hospitalization for HF, atrioventricular node ablation combined with cardiac resynchronization therapy (CRT) may be preferred. In a small RCT, the primary composite outcome (death

**Table 13** Drugs for rate control in AF<sup>a</sup>

	Intravenous administration	Usual oral maintenance dose	Contraindicated
<b>Beta-blockers<sup>b</sup></b>			
Metoprolol tartrate	2.5 - 5 mg i.v. bolus; up to 4 doses	25 - 100 mg <i>b.i.d.</i>	In case of asthma use beta-1-blockers Contraindicated in acute HF and history of severe bronchospasm
Metoprolol XL (succinate)	N/A	50 - 400 mg <i>o.d.</i>	
Bisoprolol	N/A	1.25 - 20 mg <i>o.d.</i>	
Atenolol <sup>c</sup>	N/A	25 - 100 mg <i>o.d.</i>	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50 - 300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min; followed by 10 - 40 µg/kg/min <sup>505</sup>	N/A	
Nebivolol	N/A	2.5 - 10 mg <i>o.d.</i>	
Carvedilol	N/A	3.125 - 50 mg <i>b.i.d.</i>	
<b>Non-dihydropyridine calcium channel antagonists</b>			
Verapamil	2.5 - 10 mg i.v. bolus over 5 min	40 mg <i>b.i.d.</i> to 480 mg (extended release) <i>o.d.</i>	Contraindicated in HFrEF Adapt doses in hepatic and renal impairment
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 - 15 mg/h	60 mg <i>t.i.d.</i> to 360 mg (extended release) <i>o.d.</i>	
<b>Digitalis glycosides</b>			
Digoxin	0.5 mg i.v. bolus (0.75 - 1.5 mg over 24 hours in divided doses)	0.0625 - 0.25 mg <i>o.d.</i>	High plasma levels associated with increased mortality Check renal function before starting and adapt dose in CKD patients
Digitoxin	0.4 - 0.6 mg	0.05 - 0.1 mg <i>o.d.</i>	
<b>Other</b>			
Amiodarone	300 mg i.v. diluted in 250 mL 5% dextrose over 30 - 60 min (preferably via central venous cannula), followed by 900 - 1200 mg i.v. over 24 hours diluted in 500 - 1000 mL via a central venous cannula	200 mg <i>o.d.</i> after loading 3 × 200 mg daily over 4 weeks, then 200 mg daily <sup>536 d</sup> (reduce other rate controlling drugs according to heart rate)	In case of thyroid disease, only if no other options

AF = atrial fibrillation; *b.i.d.* = *bis in die* (twice a day); CKD = chronic kidney disease; HF = heart failure; HFrEF = HF with reduced ejection fraction; *i.v.* = intravenous; *min* = minutes; *N/A* = not available or not widely available; *o.d.* = *omni die* (once daily); *t.i.d.* = *ter in die* (three times a day).

<sup>a</sup>All rate control drugs are contraindicated in Wolff-Parkinson-White syndrome, also *i.v.* amiodarone.

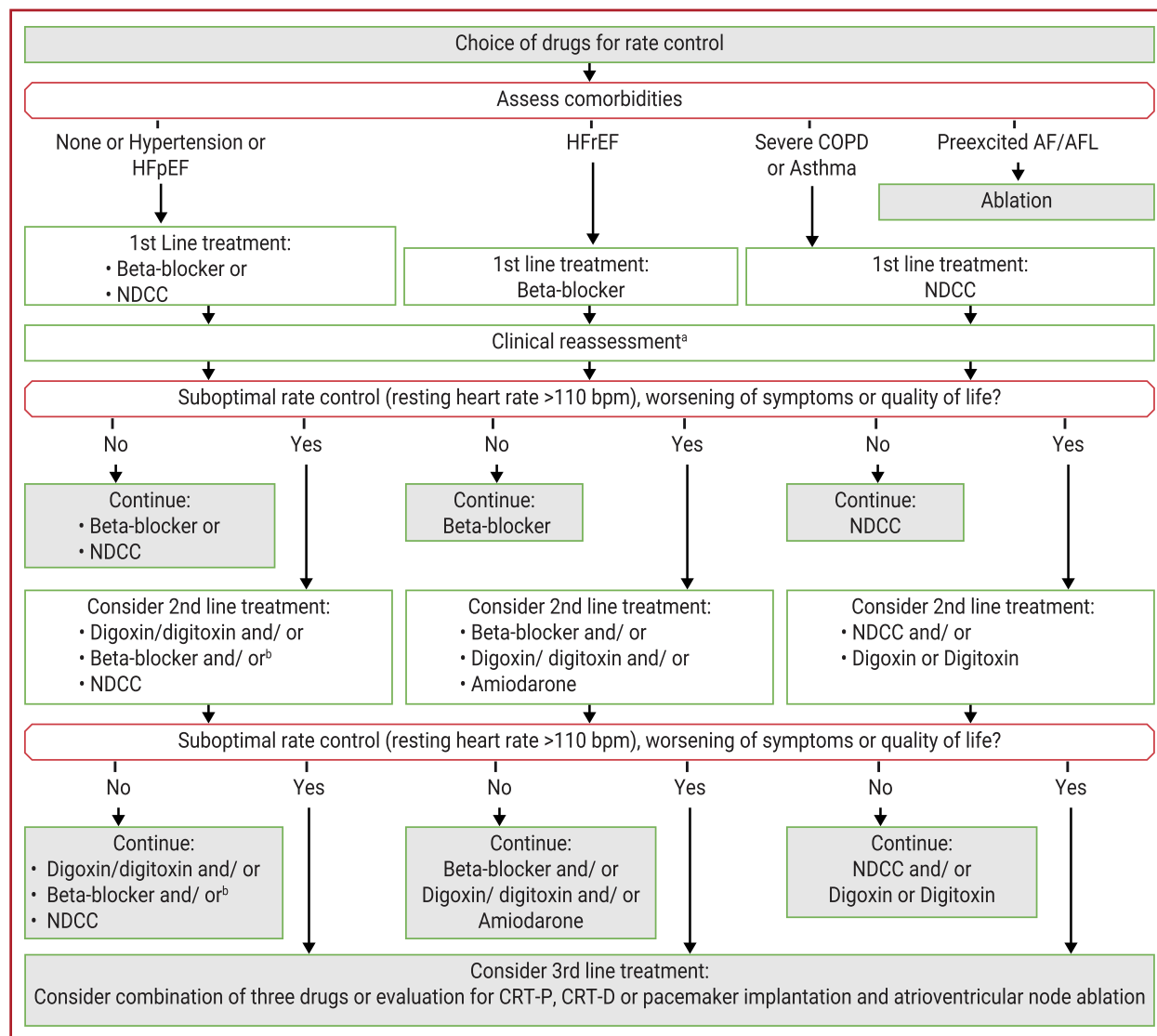
<sup>b</sup>Other beta-blockers are available but not recommended as specific rate control therapy in AF and therefore not mentioned here (e.g. propranolol and labetalol).

<sup>c</sup>No data on atenolol; should not be used in HFrEF.

<sup>d</sup>Loading regimen may vary; *i.v.* dosage should be considered when calculating total load.

or hospitalization for HF, or worsening HF) was significantly less common in the ablation + CRT group vs. the drug arm ( $P=0.013$ ), and ablation + CRT patients showed a 36% decrease in symptoms

and physical limitations at 1-year follow-up ( $P=0.004$ ).<sup>527</sup> Emerging evidence suggest that His-bundle pacing could be an alternative in these patients.<sup>528</sup>



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**Figure 14** Choice of rate control drugs.<sup>490</sup> AF = atrial fibrillation; AFL = atrial flutter; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; HFpEF = heart failure with preserved ejection fraction; HFREF = heart failure with reduced ejection fraction; NDCC = Non-dihydropyridine calcium channel blocker. <sup>a</sup>Clinical reassessment should be focused on evaluation of resting heart rate, AF/AFL-related symptoms and quality of life. In case suboptimal rate control (resting heart rate >110 bpm), worsening of symptoms or quality of life consider 2nd line and, if necessary, 3rd line treatment options. <sup>b</sup>Careful institution of beta-blocker and NDCC, 24-hour Holter to check for bradycardia.

### Recommendations for ventricular rate control in patients with AF<sup>a</sup>

Recommendations	Class <sup>b</sup>	Level <sup>c</sup>
Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF $\geq$ 40%. <sup>492,507,511,529</sup>	I	B
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF<40%. <sup>486,491,502,512,530–532</sup>	I	B
Combination therapy comprising different rate controlling drugs <sup>d</sup> should be considered if a single drug does not achieve the target heart rate. <sup>533,534</sup>	IIa	B
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. <sup>488</sup>	IIa	B
Atrioventricular node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, and not eligible for rhythm control by LA ablation, accepting that these patients will become pacemaker dependent. <sup>516,523,535,536</sup>	IIa	B
In patients with haemodynamic instability or severely depressed LVEF, intravenous amiodarone may be considered for acute control of heart rate. <sup>504,514,515</sup>	IIb	B

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AF = atrial fibrillation; bpm = beats per minute; ECG = electrocardiogram; LA = left atrial; LVEF = left ventricular ejection fraction.

<sup>a</sup>See section 11 for ventricular rate control in various concomitant conditions and AF populations

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

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

<sup>d</sup>Combining beta-blocker with verapamil or diltiazem should be performed with careful monitoring of heart rate by 24-h ECG to check for bradycardia.<sup>488</sup>



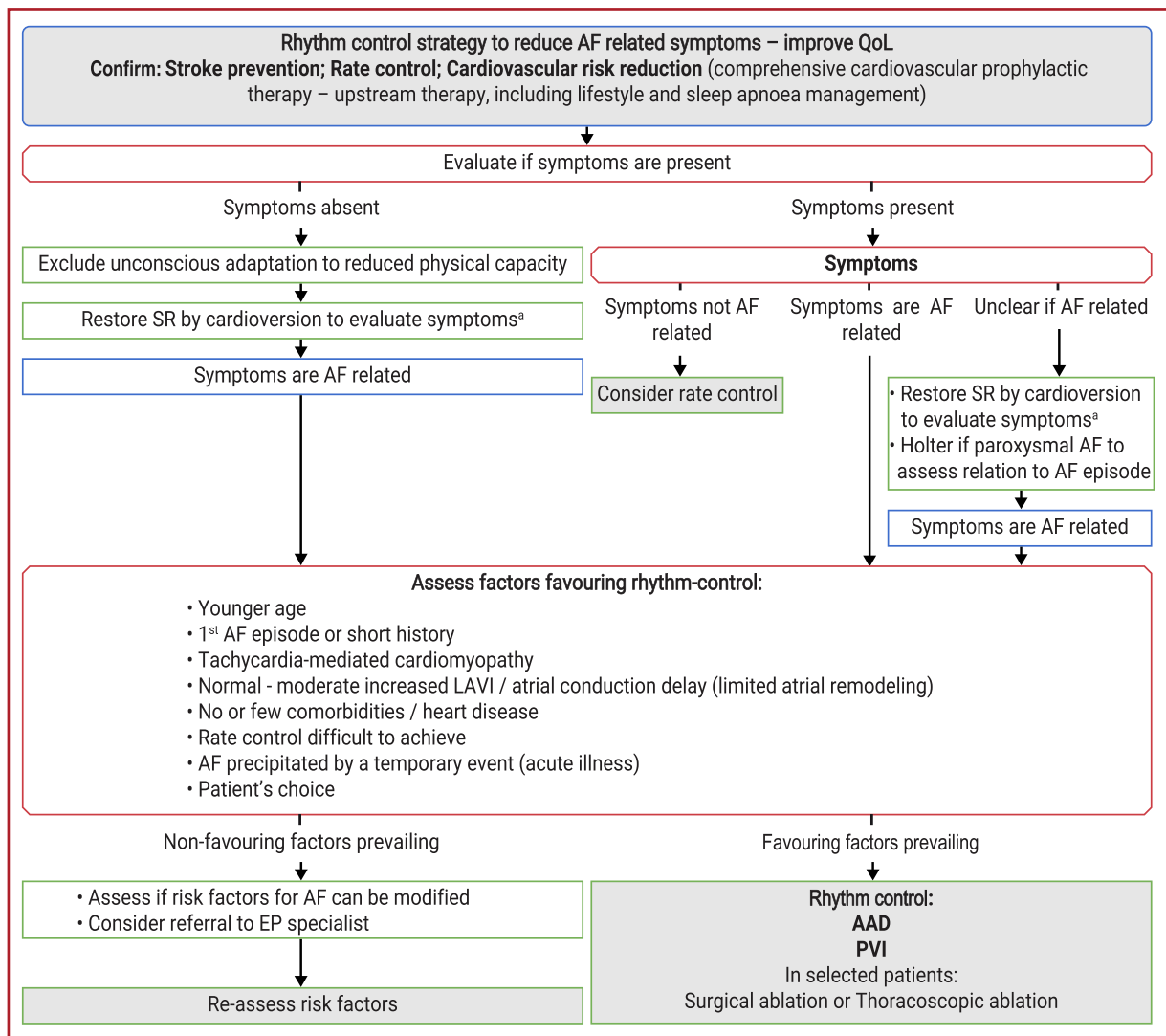
### 10.2.2 Rhythm control

The 'rhythm control strategy' refers to attempts to restore and maintain sinus rhythm, and may engage a combination of treatment approaches, including cardioversion,<sup>164,234</sup> antiarrhythmic medication,<sup>233,537,538</sup> and catheter ablation,<sup>539–541</sup> along with an adequate rate control, anticoagulation therapy (section 10.2.2.6) and comprehensive cardiovascular prophylactic therapy (upstream therapy, including lifestyle and sleep apnoea management) (Figure 15).

#### 10.2.2.1 Indications for rhythm control

Based on the currently available evidence from RCTs, the primary indication for rhythm control is to reduce AF-related symptoms and improve QoL (Figure 15). In case of uncertainty, an attempt to restore sinus rhythm in order to evaluate the response to therapy may be a rational first step. Factors that may favour an attempt at rhythm control should be considered<sup>542,543</sup> (Figure 15).

As AF progression is associated with a decrease in QoL<sup>544</sup> and, with time, becomes irreversible or less amenable to treatment,<sup>176</sup> rhythm control may be a relevant choice, although currently there is no substantial evidence that this may result in a different outcome. Reportedly, rates of AF progression were significantly lower with rhythm control than rate control.<sup>545</sup> Older age, persistent AF, and previous stroke/TIA independently predicted AF progression,<sup>545</sup> which may be considered when deciding the treatment strategy. For many patients, an early intervention to prevent AF progression may be worth considering,<sup>546</sup> including optimal risk-factor management.<sup>245</sup> Ongoing trials in patients with newly diagnosed symptomatic AF will assess whether early rhythm control interventions such as AF catheter ablation offer an opportunity to halt the progressive patho-anatomical changes associated with AF.<sup>547</sup> However, there is evidence that, at least in some patients, a successful rhythm control strategy with AF catheter ablation may not affect atrial substrate



**Figure 15** Rhythm control strategy. AAD = antiarrhythmic drug; AF = atrial fibrillation; CMP = cardiomyopathy; CV = cardioversion; LAVI = left atrial volume index; PAF = paroxysmal atrial fibrillation; PVI = pulmonary vein isolation; QoL = quality of life; SR = sinus rhythm. <sup>a</sup>Consider cardioversion to confirm that the absence of symptoms is not due to unconscious adaptation to reduced physical and/or mental capacity.

development.<sup>548</sup> Important evidence regarding the effect of early rhythm control therapy on clinical outcomes are expected in 2020 from the ongoing EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial) trial.<sup>549</sup>

General recommendations regarding active informed patient involvement in shared decision making (section 9) also apply for rhythm control strategies. The same principles should be applied in female and male AF patients when considering rhythm control therapy.<sup>550</sup>

### Recommendations for rhythm control

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF. <sup>551–553</sup>	I	A

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AF = atrial fibrillation; QoL = quality of life.

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

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

#### 10.2.2.2 Cardioversion

**10.2.2.2.1 Immediate cardioversion/elective cardioversion.** Acute rhythm control can be performed as an emergency cardioversion in a haemodynamically unstable AF patient or in a non-emergency situation. Synchronized direct current electrical cardioversion is the preferred choice in haemodynamically compromised AF patients as it is more effective than pharmacological cardioversion and results in immediate restoration of sinus rhythm.<sup>554,555</sup> In stable patients, either pharmacological cardioversion or electrical cardioversion can be attempted; pharmacological cardioversion is less effective but does not require sedation. Of note, pre-treatment with AADs can improve the efficacy of elective electrical cardioversion.<sup>556</sup> A RCT showed maximum fixed-energy electrical cardioversion was more effective than an energy-escalation strategy.<sup>557</sup>

In a RCT, a wait-and-watch approach with rate control medication only and cardioversion when needed within 48 h of symptom onset was as safe as and non-inferior to immediate cardioversion of paroxysmal AF, which often resolves spontaneously within 24 h.<sup>558</sup>

Elective cardioversion refers to the situation when cardioversion can be planned beyond the nearest hours. Observational data<sup>243</sup> showed that cardioversion did not result in improved AF-related QoL or halted AF progression, but many of these patients did not receive adjunctive rhythm control therapies.<sup>243</sup> Other studies reported significant QoL improvement in patients who maintain sinus rhythm after electrical cardioversion and the only variable independently associated with a moderate to large effect size was sinus rhythm at 3 months.<sup>232</sup>

Factors associated with an increased risk for AF recurrence after elective cardioversion include older age, female sex, previous cardioversion, chronic obstructive pulmonary disease (COPD), renal impairment, structural heart disease, larger LA volume index, and HF.<sup>164,559,560</sup> Treatment of potentially modifiable conditions should be considered before cardioversion to facilitate maintenance of sinus rhythm (Figure 15).<sup>245</sup> In case of AF recurrence after cardioversion in patients with persistent AF, an early re-cardioversion may prolong subsequent duration of sinus rhythm.<sup>561</sup>

Non-emergency cardioversion is contraindicated in the presence of known LA thrombus. Peri-procedural thrombo-embolic risk should be evaluated and peri-procedural and long-term OAC use considered irrespective of cardioversion mode (i.e. pharmacological cardioversion or electrical cardioversion) (section 10.2.2.6). A flow-chart for decision making on cardioversion is shown in Figure 16.

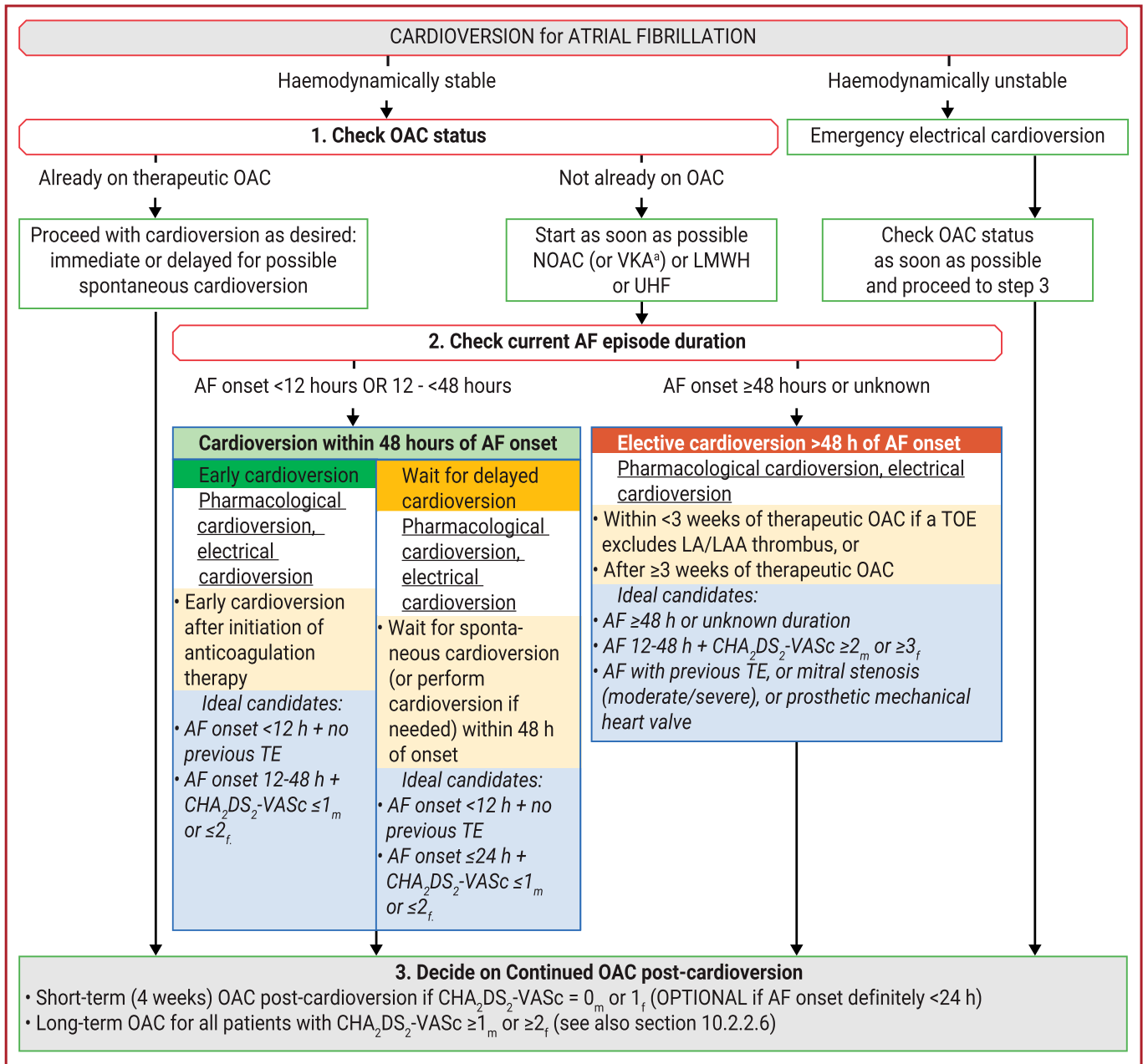
**10.2.2.2.2 Electrical cardioversion.** Electrical cardioversion can be performed safely in sedated patients treated with i.v. midazolam and/or propofol or etomidate.<sup>562</sup> BP monitoring and oximetry during the procedure should be used routinely. Skin burns may occasionally be observed. Intravenous atropine or isoproterenol, or temporary transcutaneous pacing, should be available in case of post-cardioversion bradycardia. Biphasic defibrillators are standard because of their superior efficacy compared with monophasic defibrillators.<sup>563,564</sup> Anterior–posterior electrode positions restore sinus rhythm more effectively,<sup>554,555</sup> while other reports suggest that specific electrical pad positioning is not critically important for successful cardioversion.<sup>565</sup>

**10.2.2.2.3 Pharmacological cardioversion (including ‘pill in the pocket’).** Pharmacological cardioversion to sinus rhythm is an elective procedure indicated in haemodynamically stable patients. Its true efficacy is biased by the spontaneous restoration of sinus rhythm within 48 h of hospitalization in 76–83% of patients with recent onset AF (10–18% within first 3 h, 55–66% within 24 h, and 69% within 48 h).<sup>566–568</sup> Therefore, a ‘wait-and-watch’ strategy (usually for <24 h) may be considered in patients with recent-onset AF as a non-inferior alternative to early cardioversion.<sup>558</sup>

The choice of a specific drug is based on the type and severity of associated heart disease (Table 14), and pharmacological cardioversion is more effective in recent onset AF. Flecainide (and other class Ic agents), indicated in patients without significant LV hypertrophy (LVH), LV systolic dysfunction, or ischaemic heart disease, results in prompt (3–5 h) and safe<sup>569</sup> restoration of sinus rhythm in >50% of patients,<sup>570–574</sup> while i.v. amiodarone, mainly indicated in HF patients, has a limited and delayed effect but can slow heart rate within 12 h.<sup>570,575–577</sup> Intravenous vernakalant is the most rapidly cardioverting drug, including patients with mild HF and ischaemic heart disease, and is more effective than amiodarone<sup>578–583</sup> or flecainide.<sup>584</sup> Dofetilide is not used in Europe and is rarely used outside Europe. Ibutilide is effective to convert atrial flutter (AFL) to sinus rhythm.<sup>585</sup>

In selected outpatients with rare paroxysmal AF episodes, a self-administered oral dose of flecainide or propafenone is slightly less effective than in-hospital pharmacological cardioversion but may be preferred (permitting an earlier conversion), provided that the drug safety and efficacy has previously been established in the hospital setting.<sup>586</sup> An atrioventricular node-blocking drug should be instituted in patients treated with class Ic AADs (especially flecainide) to avoid transformation to AFL with 1:1 conduction.<sup>587</sup>

**10.2.2.2.4 Follow-up after cardioversion.** The goals of follow-up after cardioversion are shown in Table 15. When assessing the efficacy of a rhythm control strategy, it is important to balance symptoms and AAD side-effects. Patients should be reviewed after cardioversion to detect whether an alternative rhythm control strategy including AF catheter ablation, or a rate control approach is needed instead of current treatment.



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**Figure 16** Flowchart for decision making on cardioversion of AF depending on clinical presentation, AF onset, oral anticoagulation intake, and risk factors for stroke. AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); cardioversion = cardioversion; ECV = electrical cardioversion; h = hour; LA = left atrium; LAA = left atrial appendage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TE = thromboembolism; TOE = transoesophageal echocardiography; UHF = unfractionated heparin; VKA = vitamin K antagonist.

**Table 14** Antiarrhythmic drugs used for restoration of sinus rhythm

Antiarrhythmic drugs for restoration of sinus rhythm (pharmacological cardioversion)				Acute success rate and expected time to sinus rhythm	Contraindications/precautions/comments
Drug	Administration route	Initial dose for cardioversion	Further dosing for cardioversion		
<b>Flecainide<sup>a</sup></b>	Oral <sup>b</sup> i.v.	200–300 mg 2 mg/kg over 10 min	-	Overall: 59–78% (51% at 3 h, 72% at 8 h)	<ul style="list-style-type: none"> <li>Should not be used in ischaemic heart disease and/or significant structural heart disease</li> <li>May induce hypotension, AFL with 1:1 conduction (in 3.5–5.0% of patients)</li> <li>Flecainide may induce mild QRS complex widening</li> <li>Do NOT use for pharmacological cardioversion of AFL</li> </ul>
<b>Propafenone<sup>a</sup></b>	Oral <sup>b</sup> i.v.	450–600 mg 1.5–2 mg/kg over 10 min	-	Oral: 45–55% at 3 h, 69–78% at 8 h; i.v.: 43–89% Up to 6 h	
<b>Vernakalant<sup>c</sup></b>	i.v.	3 mg/kg over 10 min	2 mg/kg over 10 min (10–15 min after the initial dose)	<1 h (50% conversion within 10 min)	
<b>Amiodarone<sup>a</sup></b>	i.v.	5–7 mg/kg over 1–2 h	50 mg/h (maximum 1.2 g for 24 h)	44% (8–12 h to several days)	
<b>Ibutilide<sup>c</sup></b>	i.v.	1 mg over 10 min 0.01 mg/kg if body weight <60 kg	1 mg over 10 min (10–20 min after the initial dose)	31–51% (AF) 63–73% (AFL) ≈1 h	<ul style="list-style-type: none"> <li>Effective for conversion of AFL</li> <li>Should not be used in patients with prolonged QT, severe LVH, or low LVEF</li> <li>Should be used in the setting of a cardiac care unit as it may cause QT prolongation, polymorphic ventricular tachycardia (torsades de pointes)</li> <li>ECG monitoring for at least 4 hours after administration to detect a proarrhythmic event</li> </ul>

AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; AFL = atrial flutter; *b.i.d.* = bis in die (twice a day); CrCl = creatinine clearance; CYP2D6 = cytochrome P450 2D6; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; HCM = hypertrophic cardiomyopathy; HF = heart failure; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = LV hypertrophy; NYHA = New York Heart Association; QRS = QRS interval; QT = QT interval; SA = sinoatrial; SBP = systolic blood pressure; VKA = vitamin K antagonist.

<sup>a</sup>Most frequently used for cardioversion of AF, available in most countries.

<sup>b</sup>May be self-administered by selected outpatients as a 'pill-in-the-pocket' treatment strategy.

<sup>c</sup>Not available in some countries.

For more details regarding pharmacokinetic or pharmacodynamic properties refer to EHRA AADs—clinical use and clinical decision making: a consensus document.<sup>568</sup>

**Table 15** Goals of follow-up after cardioversion of AF

Goals
Early recognition of AF recurrence by ECG recording after cardioversion
Evaluation of the efficacy of rhythm control by symptom assessment
Monitoring of risk for proarrhythmia by regular control of PR, QRS, and QTc intervals in patients on Class I or III AADs
Evaluation of balance between symptoms and side-effects of therapy considering QoL and symptoms
Evaluation of AF-related morbidities and AAD-related side-effects on concomitant cardiovascular conditions and LV function
Optimization of conditions for maintenance of sinus rhythm including cardiovascular risk management (BP control, HF treatment, increasing cardiorespiratory fitness, and other measures, see <a href="#">section 11</a> ).

AAD = antiarrhythmic drug; AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram; HF = heart failure; LV = left ventricular; PR = PR interval; QoL = quality of life; QRS = QRS interval; QTc = corrected QT interval.

### Recommendations for cardioversion

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
For pharmacological cardioversion of recent-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or flecainide or propafenone (excluding patients with severe structural heart disease) is recommended. <sup>569,573,579,582,588–590</sup>	I	A
Intravenous amiodarone is recommended for cardioversion of AF in patients with HF or structural heart disease, if delayed cardioversion is consistent with clinical situation. <sup>515,591,592</sup>	I	A
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent AF as part of rhythm control therapy. <sup>232,233,593,594</sup>	I	B
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thromboembolic risk. <sup>595</sup>	I	B
Pre-treatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to facilitate the success of electrical cardioversion. <sup>556,596–599</sup>	IIa	B
In selected patients with infrequent and recent-onset AF and no significant structural or ischaemic heart disease, a single self-administered oral dose of flecainide or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment. <sup>574,586,600,601</sup>	IIa	B
For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc (>500 ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.	III	C

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ACS = acute coronary syndrome; AF = atrial fibrillation; HF = heart failure; ms = milliseconds; i.v. = intravenous; QTc = corrected QT interval. Note: For cardioversion in various specific conditions and AF populations see [section 11](#).

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

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

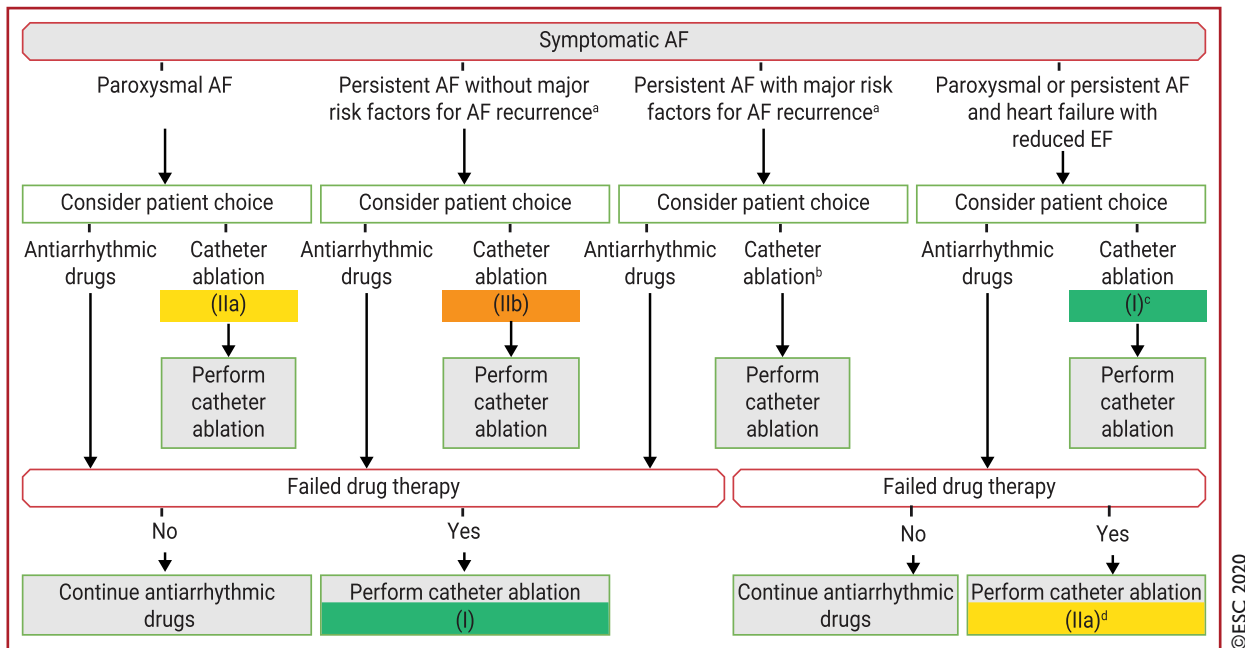
### 10.2.2.3 Atrial fibrillation catheter ablation

AF catheter ablation is a well-established treatment for the prevention of AF recurrences.<sup>1,602–604</sup> When performed by appropriately trained operators, AF catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement.<sup>165,235–242,246,247,605–618</sup> It is advised to discuss the efficacy and complication rates of AF catheter ablation and AADs with the patient once rhythm control as long-term management has been selected.

**10.2.2.3.1 Indications.** In the following section, indications for AF catheter ablation are presented for paroxysmal and persistent AF in patients with and without risk factors for post-ablation AF recurrence. Differentiation of persistent and long-standing persistent AF was omitted because the latter only expresses the duration of persistent AF above an arbitrary and artificial cut-off at 12 months' duration. The significance of such a cut-off as a single measure has never been substantially proven.

A number of risk factors for AF recurrence after AF ablation have been identified, including LA size, AF duration, patient age, renal dysfunction, and substrate visualization by means of MRI.<sup>619–625</sup> Recent systematic reviews on prediction models for AF recurrence after catheter ablation showed the potential benefits of risk predictions, but a more robust evaluation of such models is desirable.<sup>167,626</sup> The model variables can be measured before ablation; therefore models could be used pre-procedurally to predict the likelihood of recurrence.<sup>627–635</sup> However, no single score has been presently identified as consistently superior to others. Thus, at present, for an improved and more balanced indication for ablation in patients with persistent AF and risk factors for recurrence, the most intensely evaluated risk predictors (including duration of AF) should be considered, and adjusted to the individual patient's situation including their preferences. Notably, patients must also be explicitly informed about the importance of treating modifiable risk factors to reduce risk of recurrent AF.<sup>621,636–652</sup>

The indications for AF catheter ablation are summarized in [Figure 17](#). AF catheter ablation is effective in maintaining sinus rhythm in patients with paroxysmal and persistent AF.<sup>165,235–242,605–616</sup> The main clinical benefit of AF catheter ablation is the reduction of arrhythmia-related symptoms.<sup>246,247,603,604,607,617,653,654</sup> This has been confirmed in a recent RCT showing that the improvement in QoL was significantly higher in the ablation vs. medical therapy group,



**Figure 17** Indications for catheter ablation of symptomatic AF. The arrows from AAD to ablation indicate failed drug therapy. AAD = antiarrhythmic drug; AF = atrial fibrillation; EF = ejection fraction; LA = left atrial. <sup>a</sup>Significantly enlarged LA volume, advanced age, long AF duration, renal dysfunction, and other cardiovascular risk factors. <sup>b</sup>In rare individual circumstances, catheter ablation may be carefully considered as first-line therapy. <sup>c</sup>Recommended to reverse LV dysfunction when tachycardiomyopathy is highly probably. <sup>d</sup>To improve survival and reduce hospitalization.

as was the associated reduction in AF burden.<sup>246</sup> Symptom improvement has also been confirmed in the recent large CABANA (Catheter Ablation vs. ANtiarrhythmic Drug Therapy for Atrial Fibrillation) RCT,<sup>655</sup> but the trial showed that the strategy of AF catheter ablation did not significantly reduce the primary composite outcome of death, disabling stroke, serious bleeding, or cardiac arrest compared with medical therapy.<sup>617</sup> As no RCT has yet demonstrated a significant reduction in all-cause mortality, stroke, or major bleeding with AF catheter ablation in the 'general' AF population, the indications for the procedure have not been broadened beyond symptom relief,<sup>617</sup> and AF catheter ablation is generally not indicated in asymptomatic patients. Further important evidence regarding the impact of ablation on major cardiovascular events is expected from the EAST trial.<sup>656</sup>

In selected patients with HF and reduced LVEF, two RCTs have shown a reduction in all-cause mortality and hospitalizations with AF catheter ablation,<sup>611,657</sup> although combined mortality and HF hospitalization was a primary endpoint only in the CASTLE-AF (Catheter Ablation vs. Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation) trial.<sup>657</sup> The generalizability of the trial has recently been evaluated in a large HF patient population.<sup>658</sup> This analysis showed that only a small number of patients met the trial inclusion criteria (<10%) and patients who met the CASTLE-AF inclusion criteria had a significant benefit from treatment as demonstrated in the trial.<sup>658</sup> The smaller AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) RCT, which included patients with more advanced HFrEF, did not show benefits gained by AF catheter ablation at 1-year follow-up,<sup>659</sup> whereas a recent CABANA subgroup analysis supported the benefits of AF catheter ablation in patients with HFrEF, showing a significant

reduction in the study primary endpoint (death, stroke, bleeding, cardiac arrest) and reduced mortality in the ablation group.<sup>617,660</sup> Overall, AF catheter ablation in patients with HFrEF results in higher rates of preserved sinus rhythm and greater improvement in LVEF, exercise performance, and QoL compared with AAD and rate control.<sup>611,657,661–671</sup> Accordingly, ablation should be considered in patients with HFrEF who have been selected for rhythm control treatment to improve QoL and LV function, and to reduce HF hospitalization and, potentially, mortality.

When AF-mediated tachycardia-induced cardiomyopathy (i.e. ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction, partially or completely reversed after treatment of the causative arrhythmia) is highly suspected, AF catheter ablation is recommended to restore LV function.<sup>672–676</sup>

Ablation is recommended, in general, as a second-line therapy after failure (or intolerance) of class I or class III AADs. This recommendation is based on the results of multiple RCTs showing superiority of AF catheter ablation vs. AADs regarding freedom from recurrent arrhythmia or improvement in symptoms, exercise capacity, and QoL after medication failure.<sup>235–239,246,247,605–607,609,611,613–617</sup>

Clinical trials considering AF catheter ablation before any AAD suggest that AF catheter ablation is more effective in maintaining sinus rhythm, with comparable complication rates in experienced centres.<sup>240–242,614</sup> The 5-year follow-up in the MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial showed a significantly lower AF burden in the ablation arm that did not, however, translate into improved QoL compared with AAD treatment,<sup>615</sup> whereas the CAPTAF (Catheter Ablation compared with Pharmacological

Therapy for Atrial Fibrillation) study showed that, in AF patients mostly naive to class I and III AADs, the greater improvement in QoL in the ablation arm was directly associated with greater reduction in AF burden compared with the AAD arm.<sup>246</sup> Based on these studies and patient preferences, AF catheter ablation should be considered before a trial of AAD in patients with paroxysmal AF episodes (class IIa), or may be considered in patients with persistent AF without risk factors for recurrence (class IIb).

**10.2.2.3.2 Techniques and technologies.** The cornerstone of AF catheter ablation is the complete isolation of pulmonary veins by linear lesions around their antrum, either using point-by-point radiofrequency ablation or single-shot ablation devices.<sup>235,237,239,607–609,612,613,654,677–686</sup> Unfortunately, persistent pulmonary vein electrical isolation is difficult to achieve (pulmonary vein reconnection rates of >70% are reported<sup>683,687–697</sup>, but could be significantly lower with the newer generation of catheters<sup>698–700</sup>).

Particularly in persistent and long-standing persistent AF, more extensive ablation has been advocated. This may include linear lesions in the atria, isolation of the LAA or of the superior vena cava, ablation of complex fractionated electrograms, rotors, non-pulmonary foci, or ganglionated plexi, fibrosis-guided voltage and/or MRI-mapping, or ablation of high dominant frequency sites.<sup>701–710</sup> However, additional benefit vs. pulmonary vein isolation (PVI) alone, justifying its use during the first procedure, is yet to be confirmed.<sup>677,680,711–730</sup> A RCT-based data suggest improved outcome with targeting extrapulmonary (particularly the LAA) foci and selective ablation of low-voltage areas as adjunct to PVI.<sup>708,725</sup> In patients with documented cavotricuspid isthmus (CTI)-dependent flutter undergoing AF catheter ablation, right isthmus ablation may be considered.<sup>731–734</sup> In case of non-CTI-dependent atrial tachycardia, the ablation technique depends on the underlying mechanism and tachycardia focus or circuit.<sup>1,614</sup>

Several RCTs and observational studies have compared point-by-point radiofrequency and cryoballoon ablation, mostly in the first procedure for paroxysmal AF.<sup>612,681,735–755</sup> They reported broadly similar arrhythmia-free survival and overall complications with either technique, with slightly shorter procedure duration but longer

fluoroscopy time with cryoballoon ablation.<sup>612,681,735–755</sup> However, some studies showed reduced hospitalization and lower complication rates with cryoballoon ablation.<sup>746,756,757</sup> The choice of energy source may depend on centre availability, operator preference/experience, and patient preference. Alternative catheter designs and energy sources have been developed in an attempt to simplify the ablation procedure and improve outcomes,<sup>613,755,758–761</sup> but further evidence is required before changing current recommendations.

**10.2.2.3.3 Complications.** Prospective, registry-based data show that approximately 4–14% of patients undergoing AF catheter ablation experience complications, 2–3% of which are potentially life-threatening.<sup>602–604,762–765</sup> In the recent CABANA trial, mostly including experienced high-volume centres, complications occurred in the lower range of these rates.<sup>617</sup> Complications occur mostly within the first 24 h after the procedure, but some may appear 1–2 months after ablation.<sup>1,602–604</sup> (Table 16 and Supplementary Table 10). Peri-procedural death is rare (<0.2%) and usually related to cardiac tamponade.<sup>603,604,766–770</sup>

**10.2.2.3.4 AF catheter ablation outcome and impact of modifiable risk factors.** Multiple RCTs have compared AADs with AF catheter ablation using different technologies/energy sources, either as ‘first-line’ therapy or after AAD failure, showing superiority of AF catheter ablation in arrhythmia-free survival.<sup>165,235–242,605–616</sup> However, many patients require several procedures and late recurrences are not infrequent.<sup>248,639,772–780</sup>

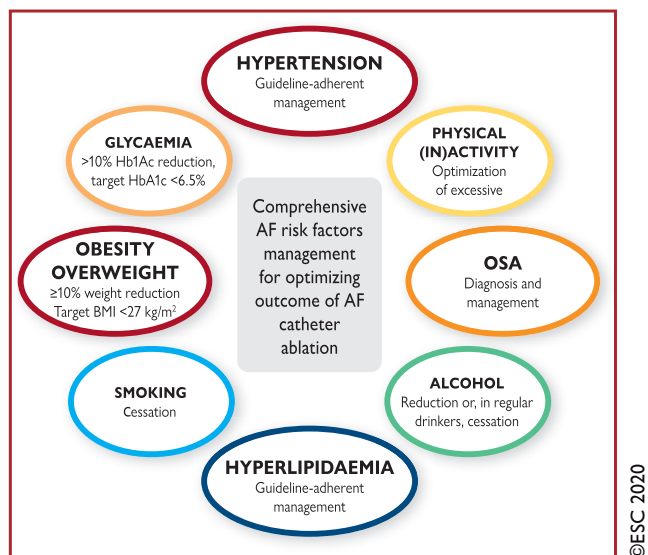
Key outcomes include QoL, HF, stroke, and mortality.<sup>539–541,608,781,782</sup> Compared with AADs, AF catheter ablation was associated with significant and sustained improvement in QoL scores in several RCTs and meta-analyses.<sup>1,235,239–242,246,247,539–541,783,784</sup> To date, there is no RCT sufficiently large to properly evaluate a reduction in stroke by catheter ablation.

Several factors, including AF type and duration,<sup>235–237,239,607,609,612,613,654,680,682,785</sup> and the presence of comorbidities such as hypertension,<sup>621,639–641</sup> obesity,<sup>638,639,643,646,772,786–791</sup> metabolic syndrome,<sup>792–794</sup> and sleep apnoea<sup>643–645,647–652</sup> may influence the outcome of catheter

**Table 16 Procedure-related complications in catheter ablation and thoracoscopic ablation of AF<sup>771</sup>**

Complication severity	Complication type	Complication rate	
		Catheter ablation	Thoracoscopic ablation
Life-threatening complications	Periprocedural death	<0.1%	<0.1%
	Oesophageal perforation/fistula	<0.5%	N/A
	Periprocedural thromboembolic event	<1.0%	<1.5%
	Cardiac tamponade	≈1%	<1.0%
Severe complications	Pulmonary vein stenosis	<1.0%	N/A
	Persistent phrenic nerve palsy	<1.0%	N/A
	Vascular complications	2–4%	N/A
	Conversion to sternotomy	N/A	<1.7%
	Pneumothorax	N/A	<6.5%
Moderate or minor complications	Various	1–2%	1–3%
Complications of unknown significance	Asymptomatic cerebral embolism	5–15%	N/A

NA = not available.



**Figure 18** Risk factors for AF contributing to the development of an abnormal substrate translating into poorer outcomes with rhythm control strategies. AF = atrial fibrillation; BMI = body mass index; CPAP = continuous positive airway pressure; HbA<sub>1c</sub> = haemoglobin A1c; OSA = obstructive sleep apnoea. Several AF risk factors may contribute to the development of LA substrates and thus affect the outcome of AF catheter ablation, predisposing to a higher recurrence rate. Aggressive control of modifiable risk factors may reduce recurrence rate.

ablation (Figure 18 and Supplementary Box 2). Prospective cohort studies suggest that aggressive control of modifiable risk factors may improve arrhythmia-free survival after catheter ablation.<sup>636</sup>

**10.2.2.3.5 Follow-up after atrial fibrillation ablation.** AF catheter ablation is a complex procedure that may be associated with a range of specific post-procedural complications (section 10.2.2.3.3)<sup>603,604,766–770</sup>. Although mostly rare, potentially catastrophic complications may initially present with non-specific symptoms and signs to which managing physicians should be attuned. Key issues in follow-up are shown in Table 17.

**10.2.2.3.6 Risk assessment for recurrence of atrial fibrillation post catheter ablation.** Recurrence of AF after catheter ablation is driven by the complex interaction of various factors. These include increasing AF duration, age, and LA size,<sup>619–624</sup> and structural factors such as the abundance of epicardial fat tissue<sup>807–810</sup> and the presence of atrial substrate as evident from electrical or morphological markers.<sup>811</sup> A number of risk-prediction scores have been evaluated (for detailed description see Supplementary Table 11 and Supplementary Box 2). Whereas these scores only moderately predict AF recurrence, one of the strongest predictors is early recurrent AF, indicating the need for further refinement of these scoring systems.<sup>629</sup>

**Table 17** Key issues in follow-up after AF catheter ablation

Key issues
<p><b>Recognition and management of complications</b></p> <ul style="list-style-type: none"> <li>Patients must be fully informed about the clinical signs and symptoms of rare but potentially dangerous ablation-related complications that may occur after hospital discharge (e.g. atrio-oesophageal fistula, pulmonary vein stenosis).</li> </ul>
<p><b>Follow-up monitoring:</b></p> <p>Useful to assess procedural success and correlate symptom status with rhythm.<sup>795,796</sup> Recurrences beyond the first month post-ablation are generally predictive of late recurrences,<sup>797,798</sup> but recurrent symptoms may be due to ectopic beats or other non-sustained arrhythmia<sup>640,799,800</sup>; conversely the presence of asymptomatic AF after ablation is well described.<sup>801–803</sup></p> <p>Monitoring may be performed with intermittent ECG, Holter, Patch recordings, external or implanted loop recorder, or smart phone monitor (although the latter has not been validated for such use). Patients should be first reviewed at a minimum of 3 months and annually thereafter.<sup>1</sup></p>
<p><b>Management of antiarrhythmic medication and treatment of AF recurrences</b></p> <ol style="list-style-type: none"> <li>Continuing AAD treatment for 6 weeks to 3 months may reduce early AF recurrences, rehospitalizations and cardioversions during this period.<sup>797,804</sup> Clinical practice regarding routine AAD treatment after ablation varies and there is no convincing evidence that such treatment is routinely needed.</li> <li>Subsequently, AADs may be weaned, ceased, or continued according to symptoms and rhythm status. Recent findings suggest that in AAD-treated patients remaining free of AF at the end of the blanking period, AAD continuation beyond the blanking period reduces arrhythmia recurrences.<sup>805</sup></li> </ol>
<p><b>Management of anticoagulation therapy</b></p> <ol style="list-style-type: none"> <li>In general, OAC therapy is continued for 2 months following ablation in all patients.<sup>1,806</sup> Beyond this time, a decision to continue OAC is determined primarily by the presence of CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke risk factors rather than the rhythm status (section 10.2.2.6).</li> </ol>

AAD = antiarrhythmic drug; AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); ECG=electrocardiogram; OAC = oral anticoagulant.



**Recommendations for rhythm control/catheter ablation of AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>General recommendations</b>		
For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient. <sup>235–237,239,607,609,612,613,636,638,652,654,680,682,785,789</sup>	I	B
Repeated PVI procedures should be considered in patients with AF recurrence provided the patient’s symptoms were improved after the initial PVI. <sup>812–814</sup>	IIa	B
<b>AF catheter ablation after failure of drug therapy</b>		
AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with <sup>235–238,247,605–609,612,613,615–617,654,677,678,680,682,685,758,779,780,815</sup> .	I	
• Paroxysmal AF, or		A
• Persistent AF without major risk factors for AF recurrence, or		A
• Persistent AF with major risk factors for AF recurrence.		B
AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF. <sup>246</sup>	IIa	B
<b>First-line therapy</b>		
AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic:		
• Paroxysmal AF episodes, <sup>240–242,614,615</sup> or	IIa	B
• Persistent AF without major risk factors for AF recurrence. <sup>253–255,264,598–601,609,610,633,636,641,724,745,746,832</sup>	IIb	C
as an alternative to AAD class I or III, considering patient choice, benefit, and risk.		
AF catheter ablation:		
• Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status. <sup>666,675,676</sup>	I	B
• Should be considered in selected AF patients with HF with reduced LVEF to improve survival and reduce HF hospitalization. <sup>612,659,662–666,668–671,817–826</sup>	IIa	B
AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation. <sup>816–818</sup>	IIa	C
<b>Techniques and technologies</b>		
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures. <sup>235–237,239,606,608–610,613,614,678,679,681,683,684,686,713,731,759,780</sup>	I	A
If patient has history of CTI-dependent AFL or if typical AFL is induced at the time of AF ablation, delivery of a CTI lesion may be considered. <sup>731–733,819–821</sup>	IIb	B
Use of additional ablation lesions beyond PVI (low voltage areas, lines, fragmented activity, ectopic foci, rotors, and others) may be considered but is not well established. <sup>677,680,708,711–730</sup>	IIb	B
<b>Lifestyle modification and other strategies to improve outcomes of ablation</b>		
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation. <sup>636,638,639,643,646,772,786–791</sup>	I	B
Strict control of risk factors and avoidance of triggers are recommended as part of a rhythm control strategy. <sup>636,637</sup>	I	B

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; CTI = cavotricuspid isthmus; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.

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

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

**10.2.2.4 Surgery for atrial fibrillation**

With development of the maze procedure for surgical cure from AF, Cox *et al.* opened up a new window of therapeutic opportunities for AF patients.<sup>822</sup> The classical cut-and-sew maze procedure underwent several modifications and various device-based surgical ablation procedures have been developed.<sup>823,824</sup> More than 200 publications documented the application of these techniques and technologies in various clinical scenarios.<sup>825</sup> Most studies are retrospective and/or

observational, but some RCTs and meta-analyses have also been published.<sup>771,826–828</sup> While the effects of surgical ablation on rhythm outcome (i.e. restoration of sinus rhythm/freedom from AF) have been clearly demonstrated, the effects on endpoints such as QoL, hospitalization, stroke, and mortality are not well established.<sup>461,827,829,830</sup> The only RCT with longer follow-up has shown a significant reduction in stroke risk at 5 years and a greater likelihood of maintaining sinus rhythm although the trial was underpowered for

stroke risk assessment.<sup>828</sup> The largest registry published, from the Polish National Health Service, describes better survival when ablation is performed concomitant to mitral or coronary surgery.<sup>831,832</sup> Close cooperation between cardiac surgeons and electrophysiologists (heart team) for proper patient selection and postoperative management, especially for handling of arrhythmia recurrences, seems advisable for high-standard quality care.

**10.2.2.4.1 Concomitant surgery for atrial fibrillation: indications, outcome, complications.** Most trials of concomitant AF ablation have been based mainly on patients undergoing mitral valve repair or replacement. While surgical PVI has been shown to be effective for maintaining sinus rhythm,<sup>833</sup> the most effective ablation treatment for AF isolates the pulmonary veins and the LA posterior wall, creates ablation lines that impede electrical impulses around the most important structures (mitral and tricuspid annuli, venae cavae and appendages), and excludes the LAA. Most evidence supports bipolar radiofrequency clamps and cryotherapy to perform a maze.<sup>834</sup> For non-paroxysmal AF, a biatrial lesion pattern is more effective than left-sided only, performed by sternotomy or minimally invasive techniques.<sup>826</sup>

In general, the same preoperative risk factors for AF recurrence after concomitant AF surgery as for AF catheter ablation have been identified. These include LA size, patient age, AF duration, HF/reduced LVEF, and renal dysfunction.<sup>379,636,835–841</sup> The significant positive effects of concomitant surgical ablation on freedom from atrial arrhythmias is clearly documented. Most RCTs with 1-year follow-up show no effect on QoL, stroke, and mortality,<sup>842–845</sup> but some reported reduced event rates.<sup>828,830,846</sup>

Surgical AF ablation concomitant to other cardiac surgery significantly increases the need for pacemaker implantation with biatrial (but not left-sided) lesions,<sup>827</sup> being reported from 6.8% to 21.5%, while other complications are not increased.<sup>827–830,846,847</sup>

**10.2.2.4.2 Stand-alone surgery for atrial fibrillation: indications, outcome, complications.** Thoracoscopic radiofrequency ablation targets the pulmonary veins, LA posterior wall, and LAA closure in AF patients with no structural heart disease. Freedom from AF after the procedure is well documented, but only a few studies have reported improved QoL.<sup>844,845,848–850</sup> A recent meta-analysis of three RCTs showed a significantly higher freedom from atrial tachyarrhythmia and less need for repeat ablations after thoracoscopic ablation compared with AF catheter ablation for paroxysmal or persistent AF.<sup>851</sup> The FAST trial randomized patients who were prone to AF catheter-ablation failure (i.e. failed previous ablation or LA dilatation and hypertension) and reported common but substantially lower recurrence after thoracoscopic compared with AF catheter ablation (56% vs. 87%) at long-term follow-up (mean 7 years).<sup>849</sup> Hospitalization was longer and complication rates of surgical ablation were higher compared with catheter ablation<sup>771</sup> (Table 16). A systematic safety analysis of thoracoscopic ablation showed a 30-day complication rate of 11.3%, mainly self-limiting, whereas it was significantly lower (3.6%) in a multicentre registry.<sup>456</sup> In RCTs, thoracoscopic ablation proved more effective in rhythm control than catheter ablation; however, surgical ablation is more invasive, with higher complication rates and longer hospitalization.<sup>461,852</sup> Because of this risk-benefit ratio of surgical vs. catheter

ablation, it seems reasonable to consider thoracoscopic surgery preferentially in patients with previous failed catheter ablation or with a high risk of catheter-ablation failure. There are no convincing data on the effects on stroke of surgical ablation as a stand-alone procedure or in combination with LAA occlusion or exclusion. Hence, OAC therapy should be continued after the procedure regardless of rhythm outcome in AF patients with stroke risk factors.

#### 10.2.2.5 Hybrid surgical/catheter ablation procedures

Hybrid AF procedures combine a minimally invasive epicardial non-sternotomy ablation not using cardiopulmonary bypass with a percutaneous endocardial approach. They can be performed as a single intervention or sequentially, when the endocardial catheter mapping and, if needed, additional ablations are done within 6 months after the epicardial procedure.<sup>853</sup> There are no studies comparing these two hybrid strategies.

A systematic review on rhythm outcome and complications with a hybrid procedure or AF catheter ablation in patients with persistent or long-standing persistent AF showed that at 12 months or longer, a hybrid procedure achieved a significantly higher rate of freedom from atrial arrhythmias with and without the use of AAD compared with AF catheter ablation. Although the overall complication rate was low for both strategies, hybrid ablations had more complications (13.8% vs. 5.9%).<sup>854</sup> The difference in outcome could be explained by a long-lasting isolation of the pulmonary veins after bipolar radiofrequency clamping of the pulmonary veins, epicardial clipping of the LAA, and the add-on possibility of an endocardial touch-up.<sup>855,856</sup>

### Recommendations for surgical ablation of AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Concomitant AF ablation should be considered in patients undergoing cardiac surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (left atrial dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors). <sup>461,843,857–859</sup>	<b>IIa</b>	<b>A</b>
Thoracoscopic—including hybrid surgical ablation—procedures should be considered in patients who have symptomatic paroxysmal or persistent AF refractory to AAD therapy and have failed percutaneous AF ablation, or with evident risk factors for catheter failure, to maintain long-term sinus rhythm. The decision must be supported by an experienced team of electrophysiologists and surgeons. <sup>860,861</sup>	<b>IIa</b>	<b>B</b>
Thoracoscopic—including hybrid surgical ablation—procedures may be considered in patients with persistent AF with risk factors for recurrence, who remain symptomatic during AF despite at least one failed AAD and who prefer further rhythm control therapy.	<b>IIb</b>	<b>C</b>

AAD = antiarrhythmic drug; AF = atrial fibrillation.

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

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

### 10.2.2.6 Peri-procedural stroke risk management in patients undergoing rhythm control interventions

**10.2.2.6.1 Management of stroke risk and oral anticoagulant therapy in atrial fibrillation patients undergoing cardioversion.** Patients undergoing cardioversion of AF are at increased risk of stroke and thrombo-embolism, especially in the absence of OAC and if AF has been present for  $\geq 12$  h.<sup>860–862</sup> The exact duration of an AF episode before cardioversion may be difficult to ascertain, as many patients develop AF asymptotically, seeking help only when symptoms or complications occur. If there is uncertainty over the exact onset of AF (i.e. unknown duration of AF), peri-cardioversion anticoagulation is managed as for AF of  $>12$  h to 24 h. Mechanisms of the increased propensity to peri-cardioversion thrombo-embolism include the presence of pre-existing thrombus (especially if not anticoagulated), change in the atrial mechanical function with restoration of sinus rhythm, atrial stunning post-cardioversion, and a transient prothrombotic state.<sup>863</sup>

No RCT has evaluated anticoagulation vs. no anticoagulation in AF patients undergoing cardioversion with a definite duration of AF  $<48$  h. Observational data suggest that the risk of stroke/thrombo-embolism is very low (0–0.2%) in patients with a definite AF duration of  $<12$  h and a very low stroke risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc 0 in men, 1 in women),<sup>860,864,865</sup> in whom the benefit of 4-week anticoagulation after cardioversion is undefined and the prescription of anticoagulants can be optional, based on an individualized approach.

Peri-cardioversion anticoagulation with a VKA results in a significant decrease of stroke and thrombo-embolism,<sup>863</sup> but achieving the necessary therapeutic anticoagulation (INR 2.0–3.0) for a minimum of 3 weeks before cardioversion may be difficult. This 3-week period is arbitrary, based on the time presumably needed for endothelialization or resolution of pre-existing AF thrombus. To shorten this time, TOE-guided cardioversion was introduced. If there is no atrial thrombus on TOE, cardioversion is performed after administration of heparin, and OAC is continued post-cardioversion.<sup>866,867</sup>

As NOACs act rapidly, cardioversion can be scheduled 3 weeks after NOAC initiation, provided that patients are counselled about the need for compliance to NOAC therapy<sup>868–870</sup>; NOACs have at least comparable efficacy and safety to warfarin in AF patients undergoing cardioversion.<sup>871–874</sup> A review of the three largest prospective trials ( $n = 5203$  patients) showed that the composite primary outcome (stroke/systemic embolism, myocardial infarction, or cardiovascular death) was significantly reduced with NOACs compared with VKA.<sup>873</sup>

Long-term OAC therapy after cardioversion should not be based on successful restoration of sinus rhythm, but on the stroke risk profile (using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score), balanced against bleeding risk (e.g. HAS-BLED score).

For patients in whom a thrombus is identified on TOE, effective anticoagulation for at least 3 weeks before reassessment for cardioversion is recommended. A repeat TOE to ensure thrombus resolution should be considered before cardioversion.<sup>875</sup> Antithrombotic management for these patients is challenging and decided on an individual basis based on the efficacy (or inefficacy) of previous treatments.

### Recommendations for stroke risk management peri-cardioversion

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety to warfarin. <sup>868–873</sup>	I	A
For cardioversion of AF/AFL, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion. <sup>866–870</sup>	I	B
TOE is recommended to exclude cardiac thrombus as an alternative to 3-week pre-procedural anticoagulation when early cardioversion is planned. <sup>866,868–870,875</sup>	I	B
In patients at risk of stroke, it is recommended that OAC therapy is continued long term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion, the apparent maintenance of sinus rhythm, or characterization of AF as a 'first-diagnosed episode'. <sup>412,872,876</sup>	I	B
When thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks before cardioversion of AF. <sup>875</sup>	I	B
It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.	I	C
Effective anticoagulation should be initiated as soon as possible before every cardioversion of AF or AFL. <sup>866–870</sup>	IIa	B
Early cardioversion can be performed without TOE in patients with an AF duration of $<48$ h. <sup>866</sup>	IIa	B
In patients with AF duration of $>24$ h undergoing cardioversion, therapeutic anticoagulation should be continued for at least 4 weeks, even after successful cardioversion to sinus rhythm (beyond 4 weeks, the decision about long-term OAC treatment is determined by the presence of stroke risk factors). <sup>860,861</sup>	IIa	B
When thrombus is identified on TOE, a repeat TOE to ensure thrombus resolution should be considered before cardioversion. <sup>875</sup>	IIa	C
In patients with a definite duration of AF $\leq 24$ h and a very low stroke risk (CHA <sub>2</sub> DS <sub>2</sub> -VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted. <sup>871,876</sup>	IIb	C

AF = atrial fibrillation; AFL = atrial flutter; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TOE = transoesophageal echocardiography.

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

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

10.2.2.6.2 Management of stroke risk and oral anticoagulant therapy in atrial fibrillation patients undergoing atrial fibrillation catheter ablation. Although there is some variability in the peri-procedural OAC management in patients undergoing AF ablation, more recently operators have moved towards a strategy of performing the ablation under uninterrupted VKA or NOAC treatment, provided the INR is within therapeutic range. In non-anticoagulated patients, initiating therapeutic anticoagulation 3–4 weeks before ablation may be considered.<sup>1</sup>

In a meta-analysis of 12 studies,<sup>877</sup> uninterrupted anticoagulation using NOACs vs. VKAs for AF catheter ablation was associated with low rates of stroke/TIA (NOACs, 0.08%; VKA, 0.16%) and similar rates of silent cerebral embolic events (8.0% vs 9.6%). However, major bleeding was significantly reduced with uninterrupted NOACs (0.9%) compared with VKAs (2%).

In the largest RCT comparing peri-procedural NOAC vs. warfarin [the RE-CIRCUIT trial (Randomized Evaluation of dabigatran etexilate Compared to warfarin in pulmonary vein ablation: assessment of different peri-procedural anticoagulation strategies)],<sup>878</sup> the incidence of major bleeding events during and up to 8 weeks after ablation was significantly lower with dabigatran vs. warfarin (1.6% vs. 6.9%). Other RCTs (VENTURE-AF with rivaroxaban,<sup>879</sup> AXAFA-AF NET 5 with apixaban,<sup>880</sup> and ELIMINATE-AF with edoxaban<sup>881</sup>) also showed similar event rates under uninterrupted NOACs vs. VKAs. Overall, uninterrupted peri-procedural NOACs were associated with a low incidence of stroke/TIA and a significant reduction in major bleeding compared with uninterrupted VKAs in patients undergoing AF catheter ablation. In contrast, heparin bridging increases the bleeding risk and should be avoided.

Frequently, the term 'uninterrupted' is used in clinical practice for the description of regimens where one or two NOAC doses are omitted before ablation, whereas in the RCTs comparing uninterrupted NOACs vs. warfarin, NOAC administration before ablation was truly uninterrupted.<sup>869,878</sup> Hence, there is no reason to recommend omitting one or two NOAC doses before ablation. After the procedure, administration of the first dose the evening after ablation or the next morning (if this corresponds to the timing of the next

dose according to the patient's previous OAC regimen) appears to be safe.<sup>878,881</sup>

10.2.2.6.3 Postoperative anticoagulation after surgery for atrial fibrillation. Owing to endothelial damage during ablation, OAC is advisable in all patients after AF surgery, starting as soon as possible (balancing the risk of postoperative bleeding). There are no RCT data regarding interruption of OAC over the long term. Non-randomized studies with longer follow-up have shown better long-term freedom from stroke in patients with persistent sinus rhythm, but not in those with AF despite LAA exclusion.<sup>824</sup> Therefore, long-term OAC is recommended in all patients at risk of stroke despite a successful maze surgery and appendage closure.

### Recommendations for postoperative anticoagulation after AF surgery

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Long-term OAC therapy is recommended in patients after AF surgery and appendage closure, based on the patient's thrombo-embolic risk assessed with the CHA <sub>2</sub> DS <sub>2</sub> -VASc score.	I	C

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AF = atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); OAC = oral anticoagulant.

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

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

### 10.2.2.7 Long-term antiarrhythmic drug therapy for rhythm control

10.2.2.7.1 *Antiarrhythmic drugs.* The aim of AAD therapy is to improve AF-related symptoms.<sup>484,882,883</sup> 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 are shown in Tables 18 and 19.

Compared with no therapy, AAD therapy approximately doubles sinus rhythm maintenance,<sup>883</sup> but it is difficult to draw firm

### Recommendations for stroke risk management peri-catheter ablation

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and:	I	C
<ul style="list-style-type: none"> <li>● Preferably, therapeutic OAC for at least 3 weeks before ablation, or</li> <li>● Alternatively, the use of TOE to exclude LA thrombus before ablation.</li> </ul>	IIa	C
For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended. <sup>878,879,881</sup>	I	A
After AF catheter ablation, it is recommended that:	I	C
<ul style="list-style-type: none"> <li>● Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and</li> <li>● Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.</li> </ul>	I	C

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AF = atrial fibrillation; LA = left atrial; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant therapy; TOE=transoesophageal echocardiography.

<sup>a</sup>Class of recommendation

<sup>b</sup>Level of evidence

conclusions from existing trials on their comparative efficacy.<sup>884</sup> In general, AAD therapy is less effective than AF catheter ablation,<sup>114,611,615</sup> but previously ineffective AADs can be continued after PVI, to reduce recurrent AF.<sup>805</sup> A shorter duration of AAD therapy would likely reduce the risk of side-effects<sup>883,885</sup> but late recurrences may occur.<sup>595</sup> Short-term AAD therapy is also used to prevent early AF recurrences after catheter ablation,<sup>886</sup> although the benefit is still debated<sup>797,887</sup>; this strategy may be reasonable in patients deemed at increased risk of AAD side-effects or in those with a low perceived risk of recurrent AF. Concomitant management of underlying

cardiovascular conditions is pivotal to reduce AF symptom burden and facilitate the maintenance of sinus rhythm.<sup>245,636,888,889</sup>

10.2.2.7.1 *Available antiarrhythmic drugs.* Several AADs have been shown to reduce AF recurrences (Table 20).<sup>890</sup> Class Ia (quinidine and disopyramide) and sotalol have been associated with increased overall mortality.<sup>884</sup> Again, safety should dictate both the initiation and continuation of AADs.

A flow chart for use of AADs for long-term rhythm control, depending on the underlying disease, is given in Figure 19.

10.2.2.7.2 *Non-antiarrhythmic drugs with antiarrhythmic properties (upstream therapy).* Either resulting from, or being a marker of, structural atrial remodelling, AF is closely related to atrial cardiomyopathy. Drugs that affect the atrial-remodelling process could prevent new-onset AF acting as non-conventional AADs (i.e. upstream therapy) (Table 21).

Recently, the RACE 3 study<sup>245</sup> confirmed the importance of assessing underlying conditions and targeted upstream therapy for intense risk-factor control in AF patients with mild or moderate HF in optimizing rhythm control. The results showed that targeted therapy of underlying conditions improves maintenance of sinus rhythm in patients with persistent AF.

A list of new investigational antiarrhythmic drugs is provided in Supplementary Box 3.

**Table 18 Principles of antiarrhythmic drug therapy<sup>143</sup>**

Principles
AAD therapy aims to reduce AF-related symptoms
Efficacy of AADs to maintain sinus rhythm is modest
Clinically successful AAD therapy may reduce rather than eliminate AF recurrences
If one AAD ‘fails’, a clinically acceptable response may be achieved by another drug
Drug-induced proarrhythmia or extracardiac side-effects are frequent
Safety rather than efficacy considerations should primarily guide the choice of AAD

AAD = antiarrhythmic drug; AF = atrial fibrillation.

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**Table 19 Rules to initiate antiarrhythmic drugs for long-term rhythm control in AF**

Consideration	Criteria
Indication for AAD	<ul style="list-style-type: none"> <li>● <b>Is the patient symptomatic?</b></li> <li>● Are AF symptoms severe enough (EHRA class) to justify AAD use?</li> <li>● Are there associated conditions predicting poor tolerance of AF episodes?</li> </ul>
When to start AAD	<ul style="list-style-type: none"> <li>● <b>Usually not for the first episode, but it may enhance efficacy of cardioversion</b></li> </ul>
How to choose among AADs	<ul style="list-style-type: none"> <li>● <b>Minimize proarrhythmic risk and organ toxicity</b></li> </ul> Evaluate for: <ul style="list-style-type: none"> <li>● basal ECG abnormalities (QRS duration, PR, QTc) and possible interference with AAD</li> <li>● impact on LV function</li> <li>● important pharmacokinetic and pharmacodynamic interactions (i.e. antithrombotic drugs)</li> </ul> <ul style="list-style-type: none"> <li>● <b>Risk factors for proarrhythmia may be dynamic and change over time</b></li> </ul>
How to minimize proarrhythmic risk	<ul style="list-style-type: none"> <li>● <b>Evaluate ECG after the treatment, as indicated in these Guidelines</b></li> <li>● Evaluate periodically for organ toxicity (amiodarone)</li> <li>● Long-term Holter monitoring and exercise test in selected cases</li> <li>● Avoid AAD combinations</li> </ul>
How to verify efficacy	<ul style="list-style-type: none"> <li>● <b>Estimate AF burden under therapy (ask patient for noting episodes)</b></li> <li>● If the patient is already on AAD and it was effective but was stopped because of intolerance, choose preferably from the same class</li> </ul>
Adjuvant interventions and hybrid therapy	<ul style="list-style-type: none"> <li>● <b>In patients with atrioventricular conduction abnormalities and/or sinus node dysfunction, pacemaker implantation should be considered if AAD therapy is deemed necessary</b></li> <li>● Short-term AAD therapy could prevent early recurrences after AF ablation</li> </ul>

AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; LV = left ventricular; PR = PR interval; QRS = QRS interval; QTc = corrected QT interval.

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**Table 20** Antiarrhythmic drugs used for long-term maintenance of sinus rhythm in AF patients<sup>890</sup>

Drug	Administration route	Dose	Contraindications/precautions/comments
Amiodarone <sup>233,506,891–896</sup>	Oral	3 × 200 mg daily over 4 weeks, then 200 mg daily <sup>506</sup>	<ul style="list-style-type: none"> <li>● The most effective AAD<sup>890,897</sup></li> <li>● RCTs showed lower AF recurrence compared with sotalol and dronedarone<sup>884</sup></li> <li>● Also reduces ventricular rate (for 10–12 bpm), safe in patients with HF<sup>898–900</sup></li> <li>● Concomitant use with other QT-prolonging drugs with caution</li> <li>● Concomitant use with VKAs or digitalis (their dose should be reduced)</li> <li>● Increased risk of myopathy when used with statins</li> <li>● Requires regular surveillance for liver, lung, and thyroid toxicity</li> <li>● Has atrioventricular nodal-slowing properties, but should not be used as first intention for rate control</li> <li>● QT prolongation is common but rarely associated with torsades de pointes (&lt;0.5%)<sup>901</sup></li> <li>● Torsades de pointes occurs infrequently during treatment with amiodarone (the proarrhythmia caution requires QT-interval and TU-wave monitoring)<sup>902</sup></li> <li>● Should be discontinued in case of excessive QT prolongation (&gt;500 ms)</li> <li>● ECG at baseline, after 4 weeks</li> <li>● Contraindicated in manifest hyperthyroidism</li> <li>● Numerous and frequent extracardiac side-effects may warrant discontinuation of amiodarone, thus making it a second-line treatment when other choices are possible<sup>903–907</sup></li> </ul>
Flecainide Flecainide slow release <sup>896,908,909</sup>	Oral	100–200 mg b.i.d., or 200 mg once daily (flecainide slow release)	<ul style="list-style-type: none"> <li>● Effective in preventing recurrence of AF<sup>891,908,910</sup></li> <li>● Should not be used in patients with CrCl &lt;35 mL/min/1.73 m<sup>2</sup> and significant liver disease</li> <li>● Both are contraindicated in patients with ischaemic heart disease or reduced LVEF<sup>911–913</sup></li> <li>● Should be discontinued in case of QRS widening &gt;25% above baseline and patients with left bundle-branch block or any other conduction block &gt;120 ms</li> <li>● Caution when sinoatrial/atrioventricular conduction disturbances present<sup>a</sup></li> <li>● CYP2D6 inhibitors increase concentration</li> <li>● May increase AFL cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate.<sup>914</sup> This risk can be reduced by concomitant administration of an atrioventricular nodal-blocking drug such as a beta-blocker or NDCC</li> <li>● In patients properly screened for propensity to proarrhythmias, both flecainide and propafenone are associated with a low proarrhythmic risk<sup>915</sup></li> <li>● ECG at baseline, after 1–2 weeks</li> </ul>
Propafenone Propafenone slow release <sup>895,896,916–922</sup>	Oral	150–300 mg three times daily, or 225–425 mg b.i.d. (propafenone slow release)	<ul style="list-style-type: none"> <li>● Should not be used in patients with significant renal or liver disease, ischaemic heart disease, reduced LV systolic function, or asthma</li> <li>● Should be discontinued in case of QRS widening &gt;25% above baseline and in patients left bundle-branch block and any other conduction block &gt;120 ms</li> <li>● Caution when sinoatrial/atrioventricular conduction disturbances present<sup>a</sup></li> <li>● Increases concentration of warfarin/acenocoumarin and digoxin when used in combination</li> <li>● May increase AFL cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate</li> <li>● ECG at baseline and after 1–2 weeks</li> </ul>

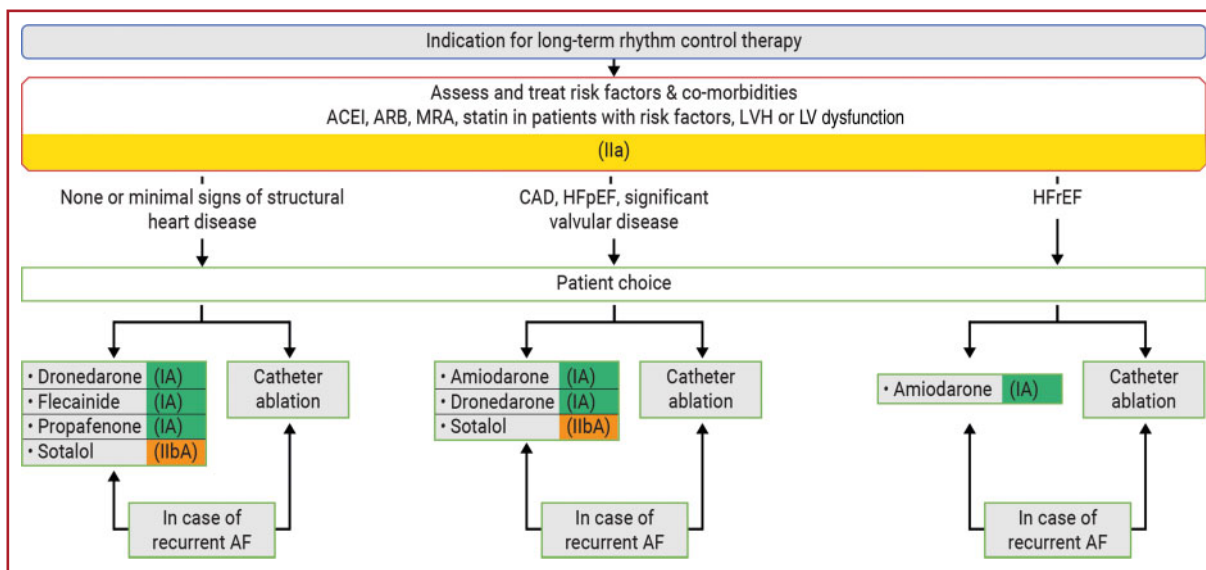
Continued

**Table 20** Continued

Drug	Administration route	Dose	Contraindications/precautions/comments
Dronedaron <sup>923–927</sup>	Oral	400 mg b.i.d.	<ul style="list-style-type: none"> <li>• Less effective than amiodarone in rhythm control but has very few extracardiac side-effects<sup>925,928–930</sup></li> <li>• Reduces cardiovascular hospitalizations and death in patients with paroxysmal or persistent AF or AFL and cardiovascular comorbidity<sup>923,931</sup></li> <li>• Associated with increased mortality in patients with recent decompensated HF<sup>927</sup> or permanent AF<sup>932</sup></li> <li>• Dronedaron has the most solid safety data and may thus be a preferable first choice,<sup>933,934</sup> however not indicated in patients with HF and permanent AF<sup>935,936</sup></li> <li>• Should not be used in NYHA class III or IV or unstable HF, in combination with QT-prolonging drugs or with strong CYP3A4 inhibitors (e.g. verapamil, diltiazem) and in patients with CrCl &lt;30 mL/min</li> <li>• Concomitant use with dabigatran is contraindicated</li> <li>• Combination with digoxin may significantly increase digoxin serum concentration</li> <li>• When used with digitalis or beta-blockers their doses should be reduced</li> <li>• Should be discontinued in case of excessive QT prolongation (&gt;500 ms or &gt;60 ms increase)</li> <li>• A modest increase in serum creatinine is common and reflects drug-induced reduction in CrCl rather than a decline in renal function<sup>937</sup></li> <li>• Has atrioventricular nodal-slowng properties</li> <li>• ECG at baseline and after 4 weeks</li> </ul>
Sotalol (d,l racemic mixture) <sup>233,891,894,895,920,938–940</sup>	Oral	80 - 160 mg b.i.d.	<ul style="list-style-type: none"> <li>• Only class III effects if dosing &gt;160 mg daily</li> <li>• Considering its safety and efficacy and potential drug alternatives, sotalol should be used with a caution</li> <li>• Should not be used in patients with HFrEF, significant LVH, prolonged QT, asthma, hypokalaemia, or CrCl &lt;30 mL/min</li> <li>• Dose-related torsades de pointes may occur in &gt;2% of patients<sup>941</sup></li> <li>• Should be discontinued in case of excessive QT prolongation (&gt;500 ms or &gt;60 ms increase)</li> <li>• Should not be used if CrCl &lt;50 mL/min</li> <li>• The potassium channel-blocking effect increases with increasing dose and, consequently, the risk of ventricular proarrhythmia (torsades de pointes) increases</li> <li>• Observational data and a recent meta-analysis revealed a correlation with an increased all-cause mortality<sup>890,897,934</sup>, whereas a nationwide registry analysis and two RCTs found no evidence for increased safety concerns with sotalol<sup>233,933,942,943</sup></li> <li>• ECG at baseline, after 1 day and after 1 - 2 weeks</li> </ul>
Disopyramide <sup>944–946</sup>	Oral	100 - 400 mg two or t.i.d. (maximum 800 mg/24 h)	<ul style="list-style-type: none"> <li>• Associated with significantly increased mortality<sup>890,947</sup>, and rarely used for rhythm control in AF.<sup>948,949</sup> Should not be used in patients with a structural heart disease. Rarely used for rhythm control in AF patients, due to increased mortality and frequent intolerance to side-effects</li> <li>• May be useful in 'vagal' AF occurring in athletes or during sleep<sup>901</sup></li> <li>• Reduces LV outflow obstruction and symptoms in patients with HCM<sup>950</sup></li> </ul>

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; b.i.d. = *bis in die* (twice a day); bpm = beats per minute; CrCl = creatinine clearance; CYP2D6 = cytochrome P450 2D6; CYP3A4 = cytochrome 3A4; ECG=electrocardiogram; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFrEF = HF with reduced ejection fraction; LV = left ventricular; LVEF = LV ejection fraction; LVH = LV hypertrophy; NDCC = non-dihydropyridinecalcium-channel blocker; NYHA = New York Heart Association; QRS = QRS interval; QT = QT interval; RCT=randomized controlled trial; SBP = systolic blood pressure; t.i.d. = *ter in die* (three times a day); VKA = vitamin K antagonist.

<sup>a</sup>Caution is needed when using any AAD in patients with conduction-system disease (e.g. sinoatrial or atrioventricular node disease).



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**Figure 19** Long-term rhythm control therapy. ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CAD=coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVH = left ventricular hypertrophy; MRA=mineralocorticoid receptor antagonist.

**Table 21** Non-antiarrhythmic drugs with antiarrhythmic properties (upstream therapy)

Drugs	Comment
<b>ACEi, ARBs</b>	<p>Activated renin-angiotensin-aldosterone system is up-regulated in AF.<sup>951,952</sup> ACEi and ARBs showed encouraging results in preventing AF in preclinical studies.<sup>953</sup></p> <p>As suggested by retrospective analyses and studies where AF was a prespecified secondary endpoint, ACEi/ARBs could prevent new-onset AF in patients with LV dysfunction, LVH, or hypertension.<sup>954–961</sup></p> <p>As initial treatment, ACEi and ARBs seem to be superior to other antihypertensive regimens,<sup>962</sup> but ARBs did not reduce AF burden in patients without structural heart disease.<sup>963</sup> Despite several positive small-scale prospective studies and retrospective analyses, larger RCTs have shown controversial results and failed to confirm the role of ACEi or ARBs in secondary (post-cardioversion) prevention of AF.<sup>964</sup> The multifactorial pathways for AF promotion and study design could explain these negative results and should not discourage the use of ACEi or ARB to AAD in patients with structural heart disease.</p>
<b>MRA</b>	<p>Aldosterone is implicated in inducibility and perpetuation of AF.<sup>965–967</sup> Evidence from RCTs showed that MRAs reduced new-onset atrial arrhythmias in patients with HFrEF in parallel with improvement of other cardiovascular outcomes.<sup>968,969</sup></p> <p>Recently, the positive impact of MRAs was also shown in patients with HFpEF<sup>970</sup> irrespective of baseline AF status. Regarding other renin-angiotensin-aldosterone system inhibitors, the role of MRAs as upstream therapy in rhythm control strategy for patients with HF and AF has not been clarified. As AF is a marker of HF severity, the beneficial antiarrhythmic effect could be driven indirectly, through improvement of HF. A recent meta-analysis showed that MRAs significantly reduced new-onset AF and recurrent AF, but not postoperative AF.<sup>971</sup></p>
<b>Beta-blockers</b>	<p>Several small studies suggested a lower AF recurrence rate with beta-blockers, with a comparable efficacy with sotalol.<sup>939,972,973</sup> However, most evidence pleads against a significant role of beta-blockers in preventing AF.<sup>890</sup> The observed beneficial effect could also result from transformation of clinically manifested AF to silent AF, because of the rate control with beta-blockers.</p>
<b>Statins</b>	<p>Statins are attractive candidates for upstream therapy, as the role of inflammation in AF is well established. However, in an adequately designed RCT,<sup>974</sup> statins failed to show a beneficial effect, and their preventive effect was not confirmed in other settings.<sup>975,976</sup> Specific patient groups in whom statins could induce reverse remodelling are not identified yet, but findings from the CARAF registry suggested that AF patients already on beta-blockers could benefit from statin therapy.<sup>977</sup> Polyunsaturated fatty acids also failed to show convincing benefit in preventing AF.<sup>978–982</sup></p>

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AAD = antiarrhythmic drug; ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB=angiotensin receptor blocker; CARAF = Canadian Registry of Atrial Fibrillation; HF = heart failure; HFrEF = HF with reduced ejection fraction; HFpEF = HF with preserved ejection fraction; LV = left ventricular; LVH = LV hypertrophy; MRA = mineralocorticoid receptor antagonist; RCT = randomized controlled trial.



## Recommendations for long-term antiarrhythmic drugs

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible. <sup>233,570,884,942,983,985</sup>	I	A
Dronedaron is recommended for long-term rhythm control in AF patients with: <ul style="list-style-type: none"> <li>• Normal or mildly impaired (but stable) LV function, or</li> <li>• HFpEF, ischaemic, or VHD.<sup>884,923,925,985</sup></li> </ul>	I	A
Flecainide or propafenone is recommended for long-term rhythm control in AF patients with normal LV function and without structural heart disease, including significant LVH and myocardial ischaemia. <sup>594,884,910,942,983,984</sup>	I	A
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended. <sup>884,942</sup>	I	B
In AF patients treated with flecainide for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered.	IIa	C
Sotalol may be considered for long-term rhythm control in patients with normal LV function or with ischaemic heart disease if close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is provided. <sup>233,983</sup>	IIb	A
AAD therapy is not recommended in patients with permanent AF under rate control and in patients with advanced conduction disturbances unless antibradycardia pacing is provided.	III	C

AAD = antiarrhythmic drug; AF = atrial fibrillation; CrCl = Creatinine clearance; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVH = LV hypertrophy; VHD = Valvular heart disease.

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

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

10.2.2.7.3 *Assessment and long-term monitoring of the risk of proarrhythmia with antiarrhythmic drugs.* A variety of clinical, echocardiographic, and ECG criteria have been associated with a higher risk of proarrhythmia.<sup>986–989</sup> Increasing age, female sex, impaired renal and/or liver function, and known CAD have been variously identified as associated with higher risk.<sup>890,990–992</sup> Concomitant AAD use, hypokalaemia, or family history of sudden death have also been implicated.<sup>990</sup> Proarrhythmic events tend to cluster shortly after drug initiation, especially if a loading dose or a change in usual dosage is prescribed.<sup>568</sup> For quinidine, the risk is idiosyncratic independent of dosage. Impaired LV function and LVH are echocardiographic markers of increased proarrhythmic risk. Sotalol has a proarrhythmic risk even in the absence of structural heart disease. On the 12-lead ECG, prolonged corrected QT interval (QTc), widened QRS, and prolonged PR interval have all been associated with proarrhythmia.<sup>993–995</sup> Significant ion-channel mutations have been detected in only a minority of cases of drug-induced torsade.<sup>996</sup> Periodic ECG analysis for proarrhythmia signs has been used successfully in recent AAD trials<sup>594,997</sup>. Specifically, ECG monitoring was used systematically on days 1–3 in patients receiving flecainide, propafenone, or sotalol to identify those at risk of proarrhythmia<sup>233,594,998</sup>. The role of routine use of exercise stress testing in patients commencing 1C drugs who had no evidence of structural heart disease is still debatable<sup>915,999</sup>.

## 10.3 'C' – Cardiovascular risk factors and concomitant diseases: detection and management

Cardiovascular risk-factor burden and comorbidities, including lifestyle factors and borderline conditions, significantly affect the lifetime risk for AF development (*Supplementary Figure 5*). The continuum of

unhealthy lifestyle, risk factor(s), and cardiovascular disease can contribute to atrial remodelling/cardiomyopathy and development of AF that commonly results from a combined effect of multiple interacting factors (often without specific threshold values).

The 'C' component of the ABC pathway includes identification and management of concomitant diseases, cardiometabolic risk factors, and unhealthy lifestyle factors. Management of risk factors and cardiovascular disease complements stroke prevention and reduces AF burden and symptom severity. In a recent RCT, for example, targeted therapy of underlying conditions significantly improved maintenance of sinus rhythm in patients with persistent AF and HF.<sup>245</sup>

Whereas strategies on comprehensive risk-factor modification and interventions targeting underlying conditions have shown reduction of AF burden and recurrence, studies addressing isolated management of specific conditions alone (e.g. hypertension) yielded inconsistent findings,<sup>1000</sup> likely because the condition was not a sole contributor to AF.

### 10.3.1 Lifestyle interventions

#### 10.3.1.1 Obesity and weight loss

Obesity increases the risk for AF progressively according to body mass index.<sup>366,1001–1005</sup> It may also increase the risk for ischaemic stroke, thrombo-embolism, and death in AF patients,<sup>366</sup> notwithstanding an obesity paradox in AF patients, especially regarding all-cause and cardiovascular death, with an inverse relationship between overweight/obesity and better cardiovascular prognosis in long-term follow-up.<sup>1006</sup>

Intense weight reduction with comprehensive management of concomitant cardiovascular risk factors resulted in fewer AF recurrences and symptoms than general advice in obese patients with AF.<sup>636,888,889</sup> Achieving a healthy weight may reduce blood pressure (BP), dyslipidaemia, and risk of developing type 2 diabetes mellitus,

thus improving the cardiovascular risk profile.<sup>1007</sup> Obesity may increase AF recurrence rates after AF catheter ablation (with OSA as a potential confounder).<sup>638,643,789,1008</sup> It has also been linked to a higher radiation dose and complication rate during AF ablation,<sup>1009,1010</sup> whereas symptom improvement after AF catheter ablation seems comparable in obese and normal-weight patients.<sup>1008</sup> Given the potential to reduce AF episodes by weight reduction, AF catheter ablation should be offered to obese patients in conjunction with lifestyle modifications for weight reduction (Figure 18).

#### 10.3.1.2 Alcohol and caffeine use

Alcohol excess is a risk factor for incident AF<sup>1011–1014</sup> and bleeding<sup>395</sup> in anticoagulated patients (mediated by poor adherence, liver disease, variceal bleeding, and risk of major trauma), and high alcohol intake may be associated with thrombo-embolism or death.<sup>1015</sup> In a recent RCT, alcohol abstinence reduced arrhythmia recurrence in regular drinkers with AF.<sup>1016</sup>

By contrast, it is unlikely that caffeine consumption causes or contributes to AF.<sup>47</sup> Habitual caffeine consumption might be associated with lower risk of AF, but caffeine intake may increase symptoms of palpitations unrelated to AF.

#### 10.3.1.3 Physical activity

Many studies have demonstrated beneficial effects of moderate exercise/physical activity on cardiovascular health.<sup>1017–1019</sup> Nevertheless, the incidence of AF appears to be increased among elite athletes, and multiple small studies reported a relationship between AF and vigorous physical activity, mainly related to long-term or endurance sport participation.<sup>1020–1023</sup> A non-linear relationship between physical activity and AF seems likely. Based on these data, patients should be encouraged to undertake moderate-intensity exercise and remain physically active to prevent AF incidence or recurrence, but maybe avoid chronic excessive endurance exercise (such as marathons and long-distance triathlons, etc.), especially if aged >50 years. Owing to few randomized patients and outcomes, the effect of exercise-based cardiac rehabilitation on mortality or serious adverse events is uncertain.<sup>1024</sup>

### 10.3.2 Specific cardiovascular risk factors/comorbidities

#### 10.3.2.1 Hypertension

Hypertension is the most common aetiological factor associated with the development of AF, and patients with hypertension have a 1.7-fold higher risk of developing AF compared with normotensives.<sup>26,1025</sup>

Hypertension also adds to the complications of AF, particularly stroke, HF, and bleeding risk. AF patients with a longer hypertension duration or uncontrolled systolic BP (SBP) levels should be categorized as 'high-risk', and strict BP control in addition to OAC is important to reduce the risk of ischaemic stroke and ICH.

Given the importance of hypertension as a precipitating factor for AF, which should be regarded as a manifestation of hypertension target-organ damage, treatment of hypertension consistent with current BP guidelines<sup>1026</sup> is mandatory in AF patients, aiming to achieve BP<sub>≤</sub>130/80 mmHg to reduce adverse outcomes.<sup>338,1027,1028</sup> A recent randomized trial in patients with paroxysmal AF and hypertension reported fewer recurrences in patients undergoing renal denervation in addition to PVI compared with patients undergoing PVI only.<sup>1029</sup> Sotalol should not be used in the presence of hypertensive LVH or

renal impairment, owing to the risk of proarrhythmia. There is some evidence of angiotensin converting enzyme or angiotensin receptor blocker use to improve outcomes in AF or reduce progression of the arrhythmia.<sup>26,1025</sup> Other lifestyle changes, including obesity management, alcohol reduction, and attention to OSA, may also help in patients with AF and hypertension.

#### 10.3.2.2 Heart failure

The interactions between AF and HF and the optimal management of patients with both AF and HF are discussed in section 11.6.

#### 10.3.2.3 Coronary artery disease

The interactions between AF and CAD and the optimal management of patients with both AF and CAD are discussed in section 11.3.

#### 10.3.2.4 Diabetes mellitus

In addition to shared risk factors (e.g. hypertension and obesity),<sup>1004,1030</sup> diabetes is an independent risk factor for AF, especially in young patients.<sup>1031</sup> Silent AF episodes are favoured by concurrent autonomic dysfunction,<sup>1032</sup> thus suggesting an opportunity for routine screening for AF in diabetes mellitus patients. The prevalence of AF is at least two-fold higher in patients with diabetes compared with people without diabetes,<sup>1033</sup> and AF incidence rises with increasing severity of microvascular complications (retinopathy, renal disease).<sup>1034</sup> Both type 1 and type 2 diabetes mellitus are the risk factors for stroke.<sup>342,1035</sup>

Intensive glycaemic control does not affect the rate of new-onset AF,<sup>1036</sup> but metformin and pioglitazone could be associated with lower long-term risk of AF in patients with diabetes,<sup>1037</sup> while this was not confirmed for rosiglitazone.<sup>1038</sup> Currently there is no evidence that glucagon-like peptide-1 agonists, sodium glucose co-transporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors affect the development of AF.<sup>1039</sup>

Previous meta-analyses showed no significant interaction between diabetes mellitus and NOAC effects in AF patients,<sup>423,1040</sup> but vascular mortality was lower in patients with diabetes treated with NOACs than in those on warfarin.<sup>1040</sup> Bleeding risk reduction with NOACs was similar in diabetic and non-diabetic patients except for apixaban, where a lower reduction in haemorrhagic complications was reported in the AF patients with diabetes compared with AF patients without diabetes.<sup>1041</sup> Regarding potential side-effects of OAC, there is no evidence that bleeding risk is increased in patients with diabetes and retinopathy.<sup>341</sup>

Optimal glycaemic control in 12 months before AF catheter ablation was associated with significant reduction in recurrent AF after ablation.<sup>1042</sup>

#### 10.3.2.5 Sleep apnoea

The most common form of sleep-disordered breathing, OSA, is highly prevalent in patients with AF, HF, and hypertension, and is associated with increased risk of mortality or major cardiovascular events.<sup>1043</sup> In a prospective analysis, approximately 50% of AF patients had OSA compared with 32% of controls.<sup>1044</sup> The mechanisms facilitating AF include intermittent nocturnal hypoxemia/hypercapnia, intrathoracic pressure shifts, sympathovagal imbalance, oxidative stress, inflammation, and neurohumoral activation.<sup>1045</sup> OSA has been shown to reduce success rates of AADs, electrical cardioversion, and catheter ablation in AF.<sup>1045</sup>

Continuous positive airway pressure (CPAP) is the therapy of choice for OSA, and may ameliorate OSA effects on AF recurrences.<sup>1046,1047</sup> Observational studies and meta-analyses showed that appropriate CPAP treatment of OSA may improve rhythm control in AF patients.<sup>648,649,1047–1051</sup>

It seems reasonable to test for OSA before the initiation of rhythm control therapy in symptomatic AF patients, with the aim to reduce symptomatic AF recurrences (Figure 18). In the ARREST-AF (Aggressive Risk Factor Reduction Study – Implication for AF) and LEGACY (Long-term Effect of Goal-directed weight management on an Atrial fibrillation Cohort: a 5-Year follow-up study) studies, an aggressive risk-factor reduction programme focusing on weight management, hyperlipidaemia, OSA, hypertension, diabetes, smoking cessation, and alcohol-intake reduction significantly reduced AF burden after PVI.<sup>636,1052</sup> However, it remains unclear how and when to test for OSA and implement OSA management in the standard work-up of AF patients.

**Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients. <sup>888</sup>	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity. <sup>245,636,887,889,1016,1052</sup>	I	B
Opportunistic screening for AF is recommended in hypertensive patients. <sup>26,172,222</sup>	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding. <sup>26,1035</sup>	I	B
In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms. <sup>898,899,1011</sup>	IIa	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for OAC therapy. <sup>324,1012,1014,1016</sup>	IIa	B
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF. <sup>1027–1033,1063</sup>	IIa	C
Opportunistic screening for AF should be considered in patients with OSA. <sup>172</sup>	IIa	C
Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms. <sup>650,651,1057–1061,1064,1065</sup>	IIb	C

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AF = atrial fibrillation; BP = blood pressure; OAC = oral anticoagulant; OSA = obstructive sleep apnoea.

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

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

**11 The ABC pathway in specific clinical settings/conditions/patient populations**

In this section, the management of AF in patient populations with specific conditions is described. The principles of the ABC pathway apply in these settings as well. Additionally, specific considerations are given for each of these special conditions and populations.

**11.1 Atrial fibrillation with haemodynamic instability**

Acute haemodynamic instability (i.e. syncope, acute pulmonary oedema, ongoing myocardial ischaemia, symptomatic hypotension, or cardiogenic shock) in AF patients presenting with a rapid ventricular rate requires prompt intervention. In severely compromised patients, emergency electrical cardioversion should be attempted without delay, and anticoagulation should be started as soon as possible.

In critically ill patients and those with severely impaired LV systolic function, AF is often precipitated/exacerbated by increased sympathetic tone, inotropes, and vasopressors, and rhythm control is often unsuccessful. It is important to identify and correct precipitating factors and secondary causes and optimize background treatment. Owing to their rate-controlling effect during exertion and increased sympathetic tone, rather than only at rest, beta-blockers are preferred over digitalis glycosides for ventricular rate control in AF.<sup>490</sup> Beta-blockers and NDCC antagonists may exert a negative inotropic effect (the latter are contraindicated in HFrEF). Digoxin is often unsuccessful due to the increased sympathetic tone in these patients.

As conventional therapy is often ineffective or not well-tolerated,<sup>490</sup> electrical cardioversion should always be considered, even as initial therapy, whereas intravenous amiodarone may be instituted for rate control (or potential cardioversion to sinus rhythm), with or without electrical cardioversion.<sup>504,514,515</sup> Intravenous administration of amiodarone may lead to a further decrease in BP.

**Recommendations for management of AF with haemodynamic instability**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Emergency electrical cardioversion is recommended in AF patients with acute or worsening haemodynamic instability. <sup>1053,1054</sup>	I	B
In AF patients with haemodynamic instability, amiodarone may be considered for acute control of heart rate. <sup>503,511,512</sup>	IIb	B

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AF = atrial fibrillation.

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

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

**11.2 First-diagnosed (new-onset) atrial fibrillation**

First-diagnosed or new-onset AF is a working diagnosis in a patient without a history of AF, until the pattern of AF can be defined more

precisely. Although the clinical profile and outcome of patients with first-diagnosed AF in AF registries were less favourable than those with paroxysmal AF, rather resembling permanent AF,<sup>1055,1056</sup> OAC prescription rates were the lowest in patients with first-diagnosed AF.<sup>1057</sup> In patients with first-diagnosed AF, the ABC pathway should resemble all steps outlined in the *Central Illustration*.

### 11.3 Acute coronary syndromes, percutaneous coronary intervention, and chronic coronary syndromes in patients with atrial fibrillation

The incidence of AF in acute coronary syndromes (ACS) ranges from 2–23%,<sup>1058</sup> the risk of new-onset AF is increased by 60–77%<sup>1059</sup> in myocardial infarction patients, and AF per se may be associated with an increased risk of ST-segment elevation myocardial infarction (STEMI) or non-STEMI ACS.<sup>381,1060–1063</sup> Overall, 10–15% of AF patients undergo PCI for CAD.<sup>1064</sup> In observational studies, patients with AF and ACS were less likely to receive appropriate antithrombotic therapy<sup>1065</sup> and more likely to experience adverse outcomes<sup>1066</sup> than ACS patients without AF.

Peri-procedural management of patients with an ACS or undergoing PCI is detailed in the respective ESC Guidelines on myocardial revascularization<sup>1067</sup> and chronic coronary syndromes (CCS).<sup>1068</sup>

#### Post-procedural management of atrial fibrillation patients with acute coronary syndrome and/or percutaneous coronary intervention

In AF patients having an ACS or undergoing PCI, concomitant risks of ischaemic stroke/systemic embolism, coronary ischaemic events, and antithrombotic treatment-related bleeding need to be carefully balanced when considering the use and duration of combined antithrombotic therapy.<sup>1069</sup> Overall, dual antithrombotic therapy including OAC (preferably NOAC) and a P2Y<sub>12</sub> inhibitor (preferably clopidogrel) is associated with significantly less major bleeding (and ICH) than triple therapy. However, available evidence suggests that at least a short course of triple therapy (e.g. ≤1 week) would be desirable in some AF patients after a recent ACS or undergoing PCI, especially in those at increased risk of ischaemic events<sup>1070,1071</sup> (*Figure 20*).

#### Box 1 About post-procedural management of patients with AF and ACS and/or PCI

Shorter courses of triple therapy (OAC + DAPT) may be safe in post-ACS/PCI patients requiring OAC.<sup>1076</sup> Observational data<sup>1077</sup> and the WOEST trial with warfarin (a safety RCT, underpowered for ischaemic outcomes)<sup>1078</sup> suggested better safety and similar efficacy with dual (OAC + clopidogrel) vs. triple therapy.

##### RCTs of NOACs in AF patients after a recent ACS/PCI

Four RCTs compared dual therapy with a P2Y<sub>12</sub> inhibitor (mostly clopidogrel) plus a NOAC—dabigatran 110 mg or 150 mg b.i.d. (RE-DUAL PCI),<sup>1079</sup> rivaroxaban 15 mg o.d. (PIONEER AF-PCI),<sup>1080</sup> apixaban 5 mg b.i.d. (AUGUSTUS),<sup>1081</sup> or edoxaban 60 mg o.d. (ENTRUST-AF PCI)<sup>1082</sup> —vs. triple therapy with a VKA in AF

patients with a recent ACS or undergoing PCI. The two-by-two factorial AUGUSTUS trial design enabled the comparison of aspirin vs. placebo (see *Supplementary Table 12* for detailed information about these studies). All four trials had a primary safety endpoint (i.e. bleeding) and were underpowered to assess ischaemic outcomes.

Despite some heterogeneity among these trials, all have consistently:

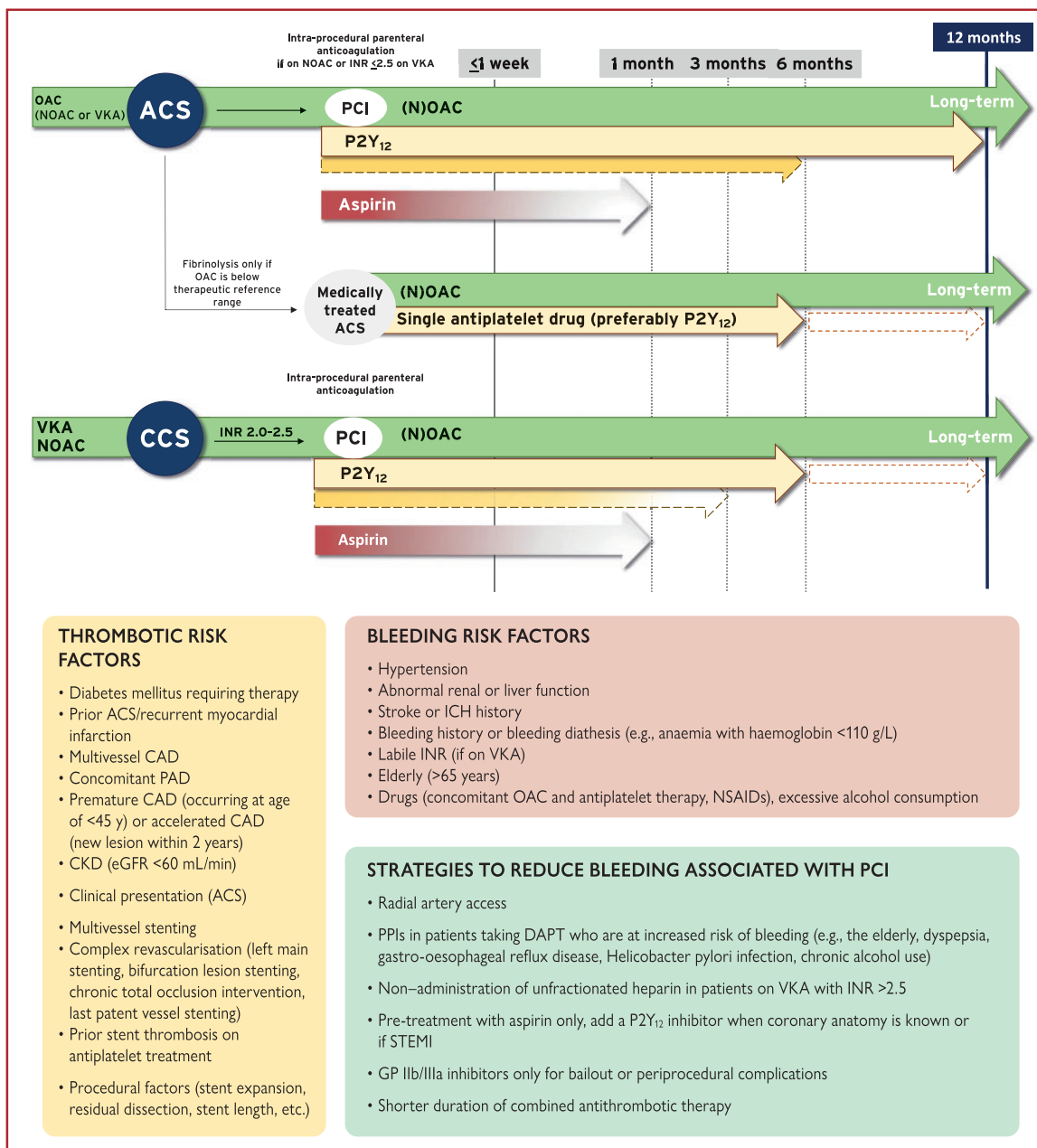
- Included a proportion of patients with an ACS/PCI (37–52%); nevertheless, the highest risk patients (e.g. previous stent thrombosis or a complex PCI with stent-in-stent placement) were largely under-represented;
- Used triple therapy during PCI and until randomization (1–14 days post PCI);
- Most commonly used the P2Y<sub>12</sub> inhibitor clopidogrel (overall, >90%); and
- Reported a significant reduction of major/clinically significant bleeding, comparable rates of ischaemic stroke, similar or non-significantly higher rates of myocardial infarction and stent thrombosis, and a neutral effect on trial-defined major adverse cardiovascular events and all-cause mortality with dual (NOAC + P2Y<sub>12</sub>) vs. triple (VKA + P2Y<sub>12</sub> + aspirin) therapy.

In AUGUSTUS,<sup>1081</sup> both placebo (vs. aspirin) and apixaban (vs. VKA) regimens were associated with significant reduction in bleeding, and apixaban (vs. VKA) was associated with significantly lower rates of stroke, death, or hospitalization.

##### Meta-analyses of RCTs

- **Bleeding outcomes:** Meta-analyses<sup>1070,1071,1083,1084</sup> consistently showed a significant reduction in major bleeding with dual vs. triple and NOAC- vs. VKA-based therapies (NOAC-based treatments were also associated with a significant reduction in ICH).
- **Ischaemic events:** Stroke rates were similar across all treatment arms, but the rates of myocardial infarction and stent thrombosis were numerically higher with dual vs. triple therapy. In two meta-analyses<sup>1070,1071</sup> stent thrombosis was statistically significantly increased on dual (i.e. no aspirin) vs. triple therapy. Also, the risk of myocardial infarction or stent thrombosis was slightly higher with dabigatran 110 mg but not dabigatran 150 mg.
- The trial-defined major adverse cardiovascular events and mortality rates were similar in all treatment arms, suggesting that the benefit from major bleeding and ICH reduction is counterbalanced by a higher risk for coronary (mainly stent-related) ischaemic events with dual therapy.

ACS = acute coronary syndromes; AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); DAPT = dual antiplatelet therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ICH = intracranial haemorrhage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d. = *omni die* (once daily); PCI = percutaneous coronary intervention; PIONEER AF-PCI = (OPen-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention); RCT = randomized controlled trial; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; VKA = vitamin K antagonist; WOEST = What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting.



**Figure 20** Post-procedural management of patients with AF and ACS/PCI (full-outlined arrows represent a default strategy; graded/dashed arrows show treatment modifications depending on individual patient’s ischaemic and bleeding risks).

Pretreatment with a P2Y<sub>12</sub> inhibitor is recommended in STEMI patients or when coronary anatomy is known; it should be withheld in non-STEMI ACS until the time of coronary angiography in case of an early invasive strategy within 24 hours. Observational studies indicate that PCI on uninterrupted VKAs is generally safe compared with OAC interruption and heparin-bridging therapy,<sup>1073</sup> particularly with radial artery access; in contrast, studies on NOACs are conflicting, predominantly discouraging a PCI on fully uninterrupted NOAC therapy.<sup>1074,1075</sup> If urgent PCI is needed, administration of a parenteral anticoagulant (UFH, LMWH, or bivalirudin) is suggested, with temporary withdrawal of NOAC at least for the initial post-procedural period (e.g. 24 h) depending on the patient’s thrombotic and bleeding risk profile. Where thrombolysis is being considered in a patient with STEMI, the initial step should be to assess the anticoagulation status (e.g. INR in a patient taking VKA; with a NOAC, assessing, for example, activated partial thromboplastin time on dabigatran or anti-factor Xa activity on factor Xa inhibitors). Thrombolytic therapy may be associated with an increased risk of bleeding in systemically anticoagulated patients, especially if parenteral heparin and antiplatelet drugs are coadministered. A balance between the potential benefit (e.g. large anterior myocardial infarction) and harm (e.g. ICH) is needed, as well as the reassessment of urgent transfer to a PCI centre. If the supposedly anticoagulated patient does not have evidence of a therapeutic anticoagulation effect (e.g. INR <2.0 on warfarin; or no NOAC anticoagulant effect detected), systemic thrombolysis may be considered if no access to primary PCI is possible.

ACS = acute coronary syndromes; ASA = acetylsalicylic acid; CAD = coronary artery disease; CCS = chronic coronary syndromes; CKD = chronic kidney disease; DAPT = dual antithrombotic therapy; eGFR = estimated glomerular filtration rate; ICH = intracranial haemorrhage; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Whichever initial treatment plan was chosen, dual therapy with OAC and an antiplatelet drug (preferably clopidogrel) is recommended for the first 12 months after PCI for ACS, or 6 months after PCI in patients with CCS.<sup>1067</sup> Thereafter, OAC monotherapy is to be continued (irrespective of the stent type) provided that there were no recurrent ischaemic events in the interim. In 1-year event-free (i.e. 'stable') AF patients with CAD and no PCI, OAC monotherapy is also recommended.<sup>1072</sup>

Use of prasugrel or ticagrelor has been associated with a greater risk of major bleeding compared with clopidogrel<sup>1085–1089</sup> and should be avoided in ACS patients with AF. In the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial, 12% of patients received ticagrelor with dabigatran, but experience with ticagrelor or prasugrel was minimal in PIONEER-AF (OPen-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo

Percutaneous Coronary Intervention), AUGUSTUS, and ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention). In patients at potential risk of gastrointestinal bleeding, concomitant use of proton-pump inhibitors is reasonable.<sup>1084</sup>

In AF patients treated with surgical coronary revascularization, OAC should be resumed as soon as bleeding is controlled, possibly in combination with clopidogrel, and triple therapy should be avoided.

Poor ventricular rate control during AF may exacerbate symptoms of myocardial ischaemia and precipitate or worsen HF. Appropriate treatment may include a beta-blocker or rate-limiting calcium antagonist. In haemodynamic instability, acute cardioversion may be indicated. Vernakalant, flecainide, and propafenone should not be used for rhythm control in patients with known CAD (section 10.2.2.2).

In all AF patients with an ACS/CCS, optimized management of risk factors is needed, and cardiovascular prevention strategies such as good BP control,<sup>338</sup> lipid management, and other cardiovascular prevention interventions<sup>1007</sup> should be implemented as needed, once the acute presentation is stabilized.

### Recommendations for patients with AF and an ACS, PCI, or CCS<sup>1068</sup>

General recommendations for patients with AF and an indication for concomitant antiplatelet therapy	Class <sup>a</sup>	Level <sup>b</sup>
In AF patients eligible for NOACs, it is recommended to use a NOAC <sup>c</sup> in preference to a VKA in combination with antiplatelet therapy. <sup>1079,1081</sup>	I	A
In patients at high bleeding risk (HAS-BLED $\geq 3$ ), rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk. <sup>1080</sup>	IIa	B
In patients at high bleeding risk (HAS-BLED $\geq 3$ ), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk. <sup>1079</sup>	IIa	B
In AF patients with an indication for a VKA in combination with antiplatelet therapy, the VKA dosing should be carefully regulated with a target INR of 2.0–2.5 and TTR >70%. <sup>1094,1095,1104,1105</sup>	IIa	B
<b>Recommendations for AF patients with ACS</b>		
In AF patients with ACS undergoing an uncomplicated PCI, early cessation ( $\leq 1$ week) of aspirin and continuation of dual therapy with an OAC and a P2Y <sub>12</sub> inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis <sup>d</sup> is low or if concerns about bleeding risk <sup>e</sup> prevail over concerns about risk of stent thrombosis, <sup>d</sup> irrespective of the type of stent used. <sup>1090,1092–1095</sup>	I	B
Triple therapy with aspirin, clopidogrel, and an OAC <sup>f</sup> for longer than 1 week after an ACS should be considered when risk of stent thrombosis <sup>d</sup> outweighs the bleeding risk, <sup>e</sup> with the total duration ( $\leq 1$ month) decided according to assessment of these risks, and the treatment plan should be clearly specified at hospital discharge.	IIa	C
<b>Recommendations in AF patients with a CCS undergoing PCI</b>		
After uncomplicated PCI, early cessation ( $\leq 1$ week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis <sup>d</sup> is low or if concerns about bleeding risk <sup>e</sup> prevail over concerns about risk of stent thrombosis, <sup>d</sup> irrespective of the type of stent used. <sup>1076,1078–1081</sup>	I	B
Triple therapy with aspirin, clopidogrel, and an OAC <sup>f</sup> for longer than 1 week should be considered when risk of stent thrombosis <sup>d</sup> outweighs the bleeding risk, <sup>e</sup> with the total duration ( $\leq 1$ month) decided according to assessment of these risks, and the treatment plan should be clearly specified at hospital discharge.	IIa	C

ACS = acute coronary syndrome; AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); CCS = chronic coronary syndrome; CKD = chronic kidney disease; DAPT = Dual antiplatelet therapy; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; o.d. = *omni die* (once daily); OAC = oral anticoagulant; PCI = percutaneous coronary intervention; TTR = time in therapeutic range; VKA = vitamin K antagonist.

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

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

<sup>c</sup>See summary of product characteristics for reduced doses or contraindications for each NOAC in patients with CKD, body weight <60 kg, age >75–80 years, and/or drug interactions.

<sup>d</sup>Risk of stent thrombosis encompasses: (i) risk of thrombosis occurring, and (ii) risk of death should stent thrombosis occur, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for CCS patients include: stenting of left main stem or last remaining patent artery; suboptimal stent deployment; stent length >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

<sup>e</sup>Bleeding risk in AF patients may be assessed using the HAS-BLED score (section 10.1.2), which draws attention to modifiable bleeding risk factors; those at high risk (score  $\geq 3$ ) can have more frequent or early review and follow-up. Bleeding risk is highly dynamic and does not remain static, and relying on modifiable bleeding risk factors alone is an inferior strategy to evaluate bleeding risk.<sup>389</sup>

<sup>f</sup>When dabigatran is used in triple therapy, dabigatran 110 mg b.i.d. may be used instead of 150 mg b.i.d., but the evidence is insufficient.

## 11.4 Acute stroke or intracranial haemorrhage in patients with atrial fibrillation

### 11.4.1 Patients with atrial fibrillation and acute ischaemic stroke or transient ischaemic attack

Management of acute stroke in AF patients is beyond the scope of this document. In AF patients presenting with acute ischaemic stroke while taking OAC, acute therapy depends on the treatment regimen and intensity of anticoagulation. Patients on VKA with an INR < 1.7 are eligible for thrombolysis according to the neurological indication (if presenting with a clinically relevant neurological deficit within the appropriate time window and ICH is excluded with cerebral imaging). In patients taking NOACs, measurement of activated partial thromboplastin time or thrombin time (for dabigatran), or antifactor Xa levels (for factor Xa inhibitors) will provide information on whether the patient is systemically anticoagulated. Whenever possible, the time when the last NOAC dose was taken should be elucidated (generally, thrombolysis is considered to be safe in patients with last NOAC intake being  $\geq 48$  h, assuming normal renal function).<sup>1090</sup>

If the patient is systemically anticoagulated, thrombolysis should not be performed due to the risk of haemorrhage, and endovascular treatment should be considered. In patients taking dabigatran, systemic thrombolysis may be performed after reversal of the dabigatran action by idarucizumab.<sup>1091</sup>

Secondary prevention of stroke/systemic embolism in patients after acute AF-related ischaemic stroke or TIA includes early

prevention of recurrent ischaemic stroke in the 2 weeks after the index event and long-term prevention thereafter

Whereas infarct size/stroke severity is used clinically to guide timing of OAC initiation,<sup>1090</sup> the usefulness of such an approach in estimating the net benefit of early treatment may be limited. Robust data to inform optimal timing for (re)initiation of OAC after acute stroke are lacking. From the cardiologist perspective, OAC should be (re)initiated as soon as considered possible from the neurological perspective (in most cases within the first 2 weeks). A multidisciplinary approach with involvement of stroke specialists, cardiologists, and patients is considered appropriate.

In AF patients who presented with acute ischaemic stroke despite taking OAC, optimization of OAC therapy is of key importance—if on VKA, optimize TTR (ideally >70%) or switch to a NOAC; if on NOAC, ensure appropriate dosing and good adherence to treatment. Inappropriate NOAC under-dosing using lower or reduced doses of specific NOACs has been associated with increased risk of stroke/systemic embolism, hospitalization, and deaths without appreciable reduction in major bleeding.<sup>1107</sup>

### 11.4.2 Cryptogenic stroke/embolic stroke with undetermined source

Currently available evidence including two recently completed RCTs<sup>1108,1109</sup> does not support *routine* OAC use in patients with acute ischaemic stroke of uncertain aetiology (cryptogenic stroke) or acute embolic stroke of undetermined source in patients *without documented AF* (*Supplementary Box 4*). Of note, subgroup

## Box 2 About acute ischaemic stroke in patients with AF

AF-related ischaemic strokes are often fatal or disabling<sup>106</sup>, with increased risk of early recurrence within 48 h<sup>1092</sup> to 2 weeks,<sup>1092–1095</sup> or haemorrhagic transformation,<sup>1096</sup> especially in the first days after large cardio-embolic lesions and acute recanalization therapy.<sup>1097,1098</sup> Notably, ICH is generally associated with higher mortality and morbidity than recurrent ischaemic stroke.

### Timing of OAC (re)initiation after acute ischaemic stroke

- Early anticoagulation after acute ischaemic stroke might cause parenchymal haemorrhage, with potentially serious clinical consequences<sup>1097,1099</sup>. Using UFH, LMWH, heparinoids, or VKAs <48 h after acute ischaemic stroke was associated with an increased risk of symptomatic ICH, without significant reduction in recurrent ischaemic stroke.<sup>1095</sup>
- Reportedly, the 90-day risk of recurrent ischaemic stroke outweighs the risk of symptomatic ICH in AF patients receiving a NOAC 4–14 days after the acute event<sup>1100–1102</sup> (ischaemic stroke recurrence rates after mild/moderate ischaemic stroke significantly increased with a later NOAC administration,<sup>1101</sup> e.g. >14 days).<sup>1100</sup> In a small RCT, rivaroxaban use within 5 days after mild ischaemic stroke in AF patients was associated with similar event rates compared with VKA.<sup>1103</sup>

As high-quality RCT-derived evidence to inform optimal timing of anticoagulation after acute ischaemic stroke is lacking, OAC use in the early post-stroke period is currently based on expert consensus.<sup>505</sup> Several ongoing RCTs [ELAN (NCT03148457), OPTIMAS (EudraCT, 2018-003859-3), TIMING (NCT02961348), and START (NCT03021928)] are investigating early (<1 week) vs. late NOAC initiation in patients with AF-related ischaemic stroke (first results are not expected before 2021).

### Long-term secondary stroke prevention

- There is no evidence that the addition of aspirin to OAC or supratherapeutic INRs would improve outcomes in secondary stroke prevention.
- Compared with VKAs, NOACs were associated with better efficacy in secondary stroke prevention and better safety regarding ICH in a meta-analysis of landmark NOAC AF trial.<sup>1104</sup>
- Good adherence to OAC treatment is essential for effective secondary stroke prevention.

There is some evidence to support that strokes can induce AF through neurogenic mechanisms<sup>1105,1106</sup>. The first study showed that damage to the insula increases the odds of AF detection after ischaemic stroke and is more prevalent in patients with AF diagnosed after stroke than among those without AF.<sup>1105</sup> The second study explained the reason why AFDAS detected soon after ischaemic stroke is associated with a low risk of ischaemic stroke recurrence.<sup>1106</sup>

AF = atrial fibrillation; ELAN = Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With AF; ICH = intracranial haemorrhage; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; OPTIMAS = Optimal TIMING of Anticoagulation after Stroke; RCT = randomized controlled trial; START = Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in AF; TIMING = TIMING of Oral Anticoagulant Therapy in Acute Ischemic Stroke With AF; UFH = unfractionated heparin; VKA = vitamin K antagonist.

analyses of those two RCTs suggested that certain subgroups (i.e. age  $\geq 75$  years, impaired renal function,<sup>1109</sup> or enlarged LA<sup>1110</sup>) could benefit from OAC, but more data are needed to inform optimal use of NOACs among patients with a cryptogenic stroke. Two ongoing trials will study the use of apixaban in this setting [ATTICUS (Apixaban for treatment of embolic stroke of undetermined source)]<sup>1111</sup> and ARCADIA [(AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) (NCT03192215)].

Efforts to improve detection of AF are needed in such patients (see also [section 8](#)). Clinical risk scores {e.g. C<sub>2</sub>HEST [CAD/COPD (1 point each), Hypertension (1 point), Elderly ( $\geq 75$  years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point) (score)]} have been proposed for identification of 'high-risk' patients for AF diagnosis<sup>1112</sup> and facilitation of prolonged monitoring.

### Recommendations for the search for AF in patients with cryptogenic stroke

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
In patients with acute ischaemic stroke or TIA and without previously known AF, monitoring for AF is recommended using a short-term ECG recording for at least the first 24 h, followed by continuous ECG monitoring for at least 72 h whenever possible. <sup>1113–1116</sup>	I	B
In selected <sup>c</sup> stroke patients without previously known AF, additional ECG monitoring using long-term non-invasive ECG monitors or insertable cardiac monitors should be considered, to detect AF. <sup>1112</sup>	IIa	B

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AF = atrial fibrillation; C<sub>2</sub>HEST = CAD/COPD (1 point each), Hypertension (1 point), Elderly ( $\geq 75$  years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point) (score); ECG=electrocardiogram; LA = left atrial; TIA=transient ischaemic attack.

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

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

<sup>c</sup>Not all stroke patients would benefit from prolonged ECG monitoring; those deemed at risk of developing AF (e.g. elderly, with cardiovascular risk factors or comorbidities, indices of LA remodelling, high C<sub>2</sub>HEST score, etc.) or those with cryptogenic stroke and stroke characteristics suggestive of an embolic stroke should be scheduled for prolonged ECG monitoring.

### 11.4.3 Post-stroke patients without known atrial fibrillation

Detection of previously unknown AF after stroke has important implications for secondary prevention. Several RCTs have established the effectiveness of ECG monitoring for post-stroke AF detection, with numbers needed to screen of 8–14.<sup>1117,1118</sup>

Looking harder and longer and using more sophisticated monitoring may generally improve AF detection. In a meta-analysis<sup>1118</sup>

of 50 post-stroke studies, the proportion of patients with post-stroke AF was 7.7% in the emergency room using admission ECG; 5.1% in the wards using serial ECG, continuous inpatient ECG monitoring/cardiac telemetry, and in-hospital Holter monitoring; 10.7% in the first ambulatory period using ambulatory Holter; and, after discharge, 16.9% using mobile cardiac outpatient telemetry and external or implantable loop recording. The overall post-stroke AF detection after all phases of cardiac monitoring reached 23.7%.<sup>1118</sup>

In patients with ischaemic stroke/TIA, monitoring for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 h, also considering a tiered longer ECG monitoring approach<sup>1113</sup> and insertion of an intracardiac monitor in case of cryptogenic stroke.<sup>1114,1119</sup> Post-stroke ECG monitoring is likely cost-effective<sup>1120,1121</sup>; however, RCTs have not been powered to assess the effect of prolonged ECG monitoring and subsequent prescription of OAC on stroke or mortality in patients with detected AF.

### 11.4.4 Management of patients with atrial fibrillation post-intracranial haemorrhage

As ICH is the most feared, often lethal, complication of anticoagulant and antiplatelet therapy, there is a considerable reluctance to (re)initiate OAC in AF patients who survived an ICH, despite their high estimated risk of AF-related ischaemic stroke.

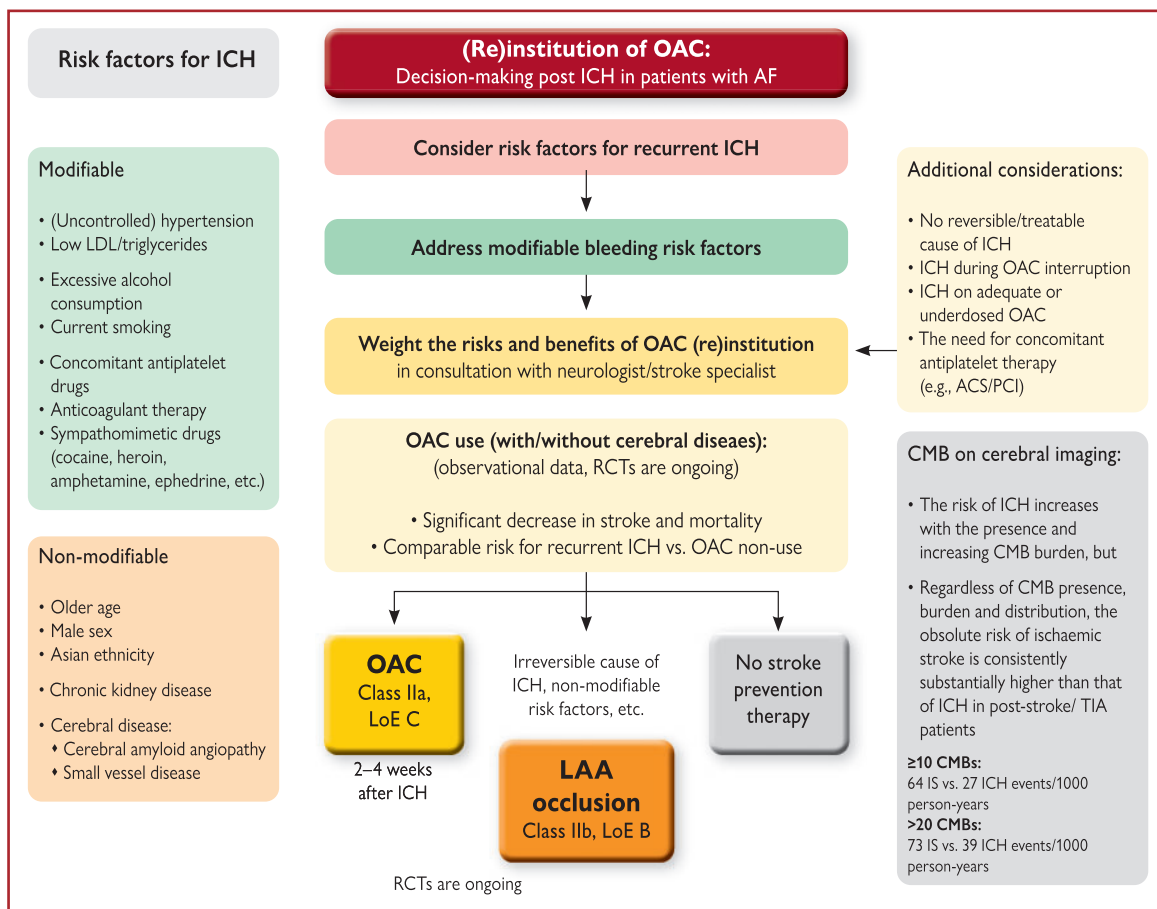
Patients with a history of recent ICH were excluded from RCTs of stroke prevention in AF, but available observational data suggest that many AF patients would benefit from (re)institution of OAC, depending on the cause(s) of ICH and findings on brain CT and MRI ([Supplementary Box 5](#)).

Treatment decision to (re)start OAC in AF patients after an ICH requires multidisciplinary-team input from cardiologists, stroke specialists, neurosurgeons, patients, and their family/carers. After acute spontaneous ICH (which includes epidural, subdural, subarachnoid, or intracerebral haemorrhage), OAC may be considered after careful assessment of risks and benefits, and cerebral imaging may help. The risk of recurrent ICH may be increased in the presence of specific risk factors, shown in [Figure 21](#). Of note, the risk of OAC-related ICH is increased especially in Asian patients.<sup>1122</sup>

Compared with VKAs, the use of NOACs in patients without previous ICH is associated with an approximately 50% lower risk of ICH,<sup>423</sup> whereas the size and outcome of OAC-related ICH is similar with NOACs and VKAs.<sup>1124</sup> Hence, NOACs should be preferred in NOAC-eligible ICH survivors with AF although there is no RCT to prove this.

The optimal timing of anticoagulation after ICH is unknown, but should be delayed beyond the acute phase, probably for at least 4 weeks; in AF patients at very high risk of recurrent ICH, LAA occlusion may be considered. Ongoing RCTs of NOACs and LAA occlusion may inform decision making in the future.





**Figure 21** (Re-) initiation of anticoagulation post-intracranial bleeding.

A pooled analysis of individual patient data from cohort studies (n=20 322 patients; 38 cohorts; >35 225 patient-years) showed that although cerebral microbleeds can inform regarding the risk for ICH in patients with recent ischaemic stroke/TIA treated with antithrombotic therapy, the absolute risk of ischaemic stroke is substantially higher than that of ICH, regardless of the presence, burden, or location of cerebral microbleeds.<sup>505,1123</sup>

IS = ischaemic stroke; ACS = acute coronary syndrome; CMB = cerebral microbleeds; ICH = intracranial haemorrhage; LAA = left atrial appendage; LDL = low-density lipoprotein; LoE = level of evidence; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; TIA = transient ischaemic attack.

Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke	Class <sup>a</sup>	Level <sup>b</sup>
In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients. <sup>1125–1130</sup>	I	A
In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH, or VKAs is not recommended. <sup>1095</sup>	III	B
Recommendations for stroke prevention in AF patients after intracranial haemorrhage		
In AF patients at high risk of ischaemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: <ul style="list-style-type: none"> <li>• A trauma-related ICH</li> <li>• Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits.<sup>c</sup></li> </ul>	IIa	C

AF = atrial fibrillation; ICH = intracranial haemorrhage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TIA = transient ischaemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist.

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

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

<sup>c</sup>A more favourable net benefit is likely with deep ICH or without neuroimaging evidence of cerebral amyloid angiopathy or microbleeds.

## 11.5 Active bleeding on anticoagulant therapy: management and reversal drugs

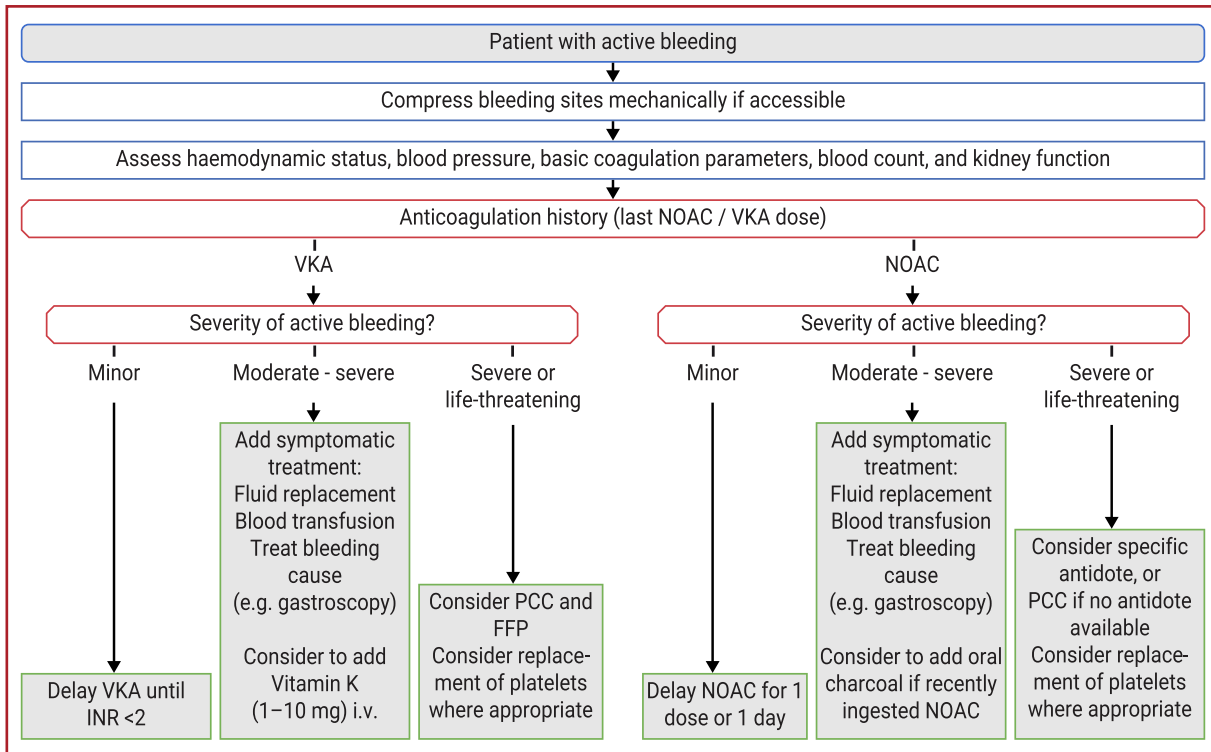
Management of patients with active bleeding while on OAC is shown in Figure 22. General assessment should include detection of the bleeding site, assessment of bleeding severity, and evaluation of the time-point of last OAC intake. Concomitant antithrombotic drugs and other factors influencing bleeding risk (alcohol abuse, renal function) should be explored. Laboratory tests, such as INR, are useful in case of VKA therapy. More specific coagulation tests for NOACs include diluted thrombin time, ecarin clotting time, or ecarin chromogenic assay for dabigatran, and chromogenic anti-factor Xa assay for rivaroxaban, apixaban, and edoxaban.<sup>1131</sup> However, these tests or measurement of NOAC plasma levels are not always readily available in practice and are often unnecessary for bleeding management.<sup>1132</sup> An overview of reversal drugs for NOACs is given in [Supplementary Table 13](#) and [Supplementary Figure 6](#).

Notably, the time of last drug ingestion combined with assessment of renal function, haemoglobin, haematocrit, and platelet count enable appropriate clinical decision making in most of the cases.

Minor bleeding events should be treated with supportive measures such as mechanical compression or minor surgery to achieve haemostasis. Withdrawal of VKAs is not associated with a prompt reduction of anticoagulant effect, while NOACs have a short plasma half-life and haemostasis can be expected within 12–24 h after an omitted dose.

Treatment of moderate bleeding events may require blood transfusions and fluid replacement. If the last intake of NOACs was less than 2–4 h before bleeding assessment, charcoal administration and/or gastric lavage will reduce further exposure. Specific diagnostic and treatment interventions to identify and manage the cause of bleeding (e.g. gastroscopy) should be performed promptly. Dialysis is effective in reducing dabigatran concentration and has been associated with reduction in the duration and/or severity of associated bleeding.<sup>1133</sup>

Severe or life-threatening bleeding requires immediate reversal of the antithrombotic effect of OACs. For VKAs, administration of fresh frozen plasma restores coagulation more rapidly than vitamin K, but prothrombin complex concentrates achieve even faster blood coagulation<sup>1134</sup> and are first-line therapy for VKA reversal.<sup>1135</sup> Specific reversal drugs are available for NOACs: idarucizumab (for dabigatran) and andexanet alfa (for factor Xa inhibitors) effectively reverse the anticoagulation action of NOACs and restore physiological haemostasis.<sup>1136,1137</sup> However, their use is often associated with subsequent non-reinitiation of OAC and increased rates of thrombotic events. These drugs can be effectively applied in case of severe life-threatening bleeding or urgent surgery, but their use is only very rarely necessary in daily clinical practice. Ciraparantag is an investigational synthetic drug that binds and inhibits direct factor Xa inhibitors, dabigatran, and heparin. The use of four-factor prothrombin complex concentrates may be considered as an alternative treatment for reversing the anticoagulant effect of rivaroxaban, apixaban, and edoxaban, although scientific evidence is very limited in this context and is frequently from healthy volunteers.<sup>1138–1140</sup>



**Figure 22** Management of active bleeding in patients receiving anticoagulation (institutions should have an agreed procedure in place).<sup>143</sup> FFP = fresh frozen plasma; INR = international normalized ratio; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation therapy; PCC = prothrombin complex concentrates; VKA = vitamin K antagonist.

### Recommendations for the management of active bleeding on OAC

	Class <sup>a</sup>	Level <sup>b</sup>
In an AF patient with severe active bleeding, it is recommended to: <ul style="list-style-type: none"> <li>Interrupt OAC until the cause of bleeding is identified and active bleeding is resolved; and</li> <li>Promptly perform specific diagnostic and treatment interventions to identify and manage the cause(s) and source(s) of bleeding.</li> </ul>	<b>I</b>	<b>C</b>
Four-factor prothrombin complex concentrates should be considered in AF patients on VKA who develop a severe bleeding complication.	<b>IIa</b>	<b>C</b>

AF = atrial fibrillation; OAC = oral anticoagulant; VKA=vitamin K antagonist.

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

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

### 11.6 Atrial fibrillation and heart failure

Both AF and HF facilitate the occurrence and aggravate the prognosis of each other, and often coexist (see also *sections 4.2* and *5.3*); HF is also a thrombo-embolic risk factor in AF. The efficacy and safety of NOACs do not seem to differ in AF patients with and without HF.<sup>1141,1142</sup>

The management of patients with AF and HF is often challenging (*section 10.2*). The optimal heart-rate target in AF patients with HF remains unclear, but a rate of <100 - 110 bpm is usually recommended.<sup>1143–1145</sup> Pharmacological rate control strategies are different for patients with heart failure with preserved ejection fraction (HFpEF) and HFrEF. Beta-blockers, diltiazem, verapamil, and digoxin are all viable options in HFpEF, while beta-blockers and digoxin can be used in those with HFrEF. Amiodarone may be considered for rate control in both forms of HF, but only in the acute setting. Atrioventricular-node ablation and pacing can control ventricular rate when medication fails (*section 10.2.1*). However, in an observational study, rhythm control strategies showed a lower 1-year all-cause death over rate control in older patients (≥65 years) with HFpEF.<sup>1146</sup>

Haemodynamic instability or worsening of HF may require emergency or immediate electrical cardioversion of AF, whereas pharmacological cardioversion using i.v. amiodarone may be attempted if a delayed cardioversion is consistent with the clinical situation (*section 10.2.2.2*). AF catheter ablation has been shown to improve symptoms, exercise capacity, QoL, and LVEF in AF patients with HF,<sup>661</sup> whereas the recent CASTLE-AF RCT showed a reduction in all-cause mortality and hospitalization for worsening HF after AF catheter ablation in patients with HFrEF<sup>657</sup> (*section 10.2.2.3*).

All patients with HF and AF should receive guideline-adherent HF therapy.<sup>1145</sup> The benefit of beta-blocker therapy in reducing mortality in AF patients with HFrEF has been questioned by some meta-analyses,<sup>491</sup> although this is not a universal finding, especially

with some real-world studies supporting an improved prognosis.<sup>1147,1148</sup>

### 11.7 Atrial fibrillation and valvular heart disease

VHD is independently associated with AF<sup>1149</sup> and more than one-third of patients with AF have some form of VHD.<sup>512</sup>

Among patients with severe VHD, including those undergoing surgical and transcatheter aortic or mitral valve intervention, AF is associated with less favourable clinical outcomes.<sup>1150–1155</sup> Compared to AF patients without VHD, the risk of thrombo-embolism and stroke is increased among AF patients with VHD other than mitral stenosis and mechanical heart prostheses, mostly owing to older age and more frequent comorbidities.<sup>1156,1157</sup> While patients with moderate-to-severe mitral stenosis and mechanical prosthetic heart valves require anticoagulation with VKAs,<sup>1158</sup> there is no evidence that the presence of other VHDs including aortic stenosis/regurgitation, mitral regurgitation, bioprostheses, or valve repair should modify the choice of OAC.<sup>1156,1159</sup> In a meta-analysis of the four pivotal RCTs comparing NOACs with VKAs, the effects of NOACs vs. VKAs in terms of stroke/systemic embolism and bleeding risk in patients with VHD other than mitral stenosis and mechanical prosthetic heart valves were consistent with those in the main RCTs.<sup>1160</sup> In an observational study, NOACs were associated with better outcomes, with reduced rates of ischaemic stroke and major bleeding compared to warfarin in AF patients with mitral stenosis.<sup>1161</sup>

Recently, a functional categorization of VHD in relation to OAC use was introduced, categorizing patients with moderate-severe or rheumatic mitral stenosis as type 1 and all other VHD as type 2.<sup>148,1157,1162</sup> There are gaps in evidence on NOAC use in AF patients with rheumatic mitral valve disease, and during the first 3 months after surgical or transcatheter implantation of a bioprosthesis, and observational data regarding NOACs use after transcatheter aortic valve implantation are conflicting.<sup>1163</sup> An RCT in *non-AF* patients comparing rivaroxaban 10 mg daily with aspirin after transcatheter aortic valve implantation was stopped early due to higher risks of death or thrombo-embolic complications and bleeding in the rivaroxaban arm.<sup>1164</sup>

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

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
NOACs are contraindicated in patients with a prosthetic mechanical valve. <sup>1165</sup>	<b>III</b>	<b>B</b>
Use of NOACs is not recommended in patients with AF and moderate-to-severe mitral stenosis.	<b>III</b>	<b>C</b>

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

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

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

## 11.8 Atrial fibrillation and chronic kidney disease

Independently of AF, CKD is a prothrombotic and prohaemorrhagic condition (*Supplementary Figure 7*),<sup>1166,1167,1168</sup> and AF may accelerate CKD progression. Coexisting in 15–20% of CKD patients,<sup>1169</sup> AF is associated with increased mortality,<sup>1170</sup> whereas CKD may be present in 40–50% of AF patients.<sup>1171</sup> In AF patients, renal function can deteriorate over time,<sup>1172</sup> and worsening CrCl is a better independent predictor of ischaemic stroke/systemic embolism and bleeding than renal impairment per se.<sup>1172</sup> In RCTs of OAC for stroke prevention in AF, renal function was usually estimated using the Cockcroft–Gault formula for CrCl, and a CrCl cut-off of <50 mL/min was used to adapt NOAC dosage.

In patients with mild-to-moderate CKD (CrCl 30–49 mL/min), the safety and efficacy of NOACs vs. warfarin was consistent with patients without CKD in landmark NOAC trials<sup>1173–1176</sup>, hence the same considerations for stroke risk assessment and choice of OAC may apply.

In patients with CrCl 15–29 mL/min, RCT-derived data on the effect of VKA or NOACs are lacking. These patients were essentially excluded from the major RCTs. The evidence for the benefits of OAC in patients with end-stage kidney disease with CrCl ≤15 mL/min or on dialysis is even more limited, and to some extent controversial. There are no RCTs, whereas observational data question the benefit of OAC in this patient population. Data from observational studies suggest possible bleeding risk reduction in patients with end-stage kidney disease taking a NOAC compared with VKA,<sup>435,1177</sup> but there is no solid evidence for a reduction in embolic events with either NOACs or VKAs, as recently shown in a systematic review.<sup>1178</sup> Notably, NOACs have not been approved in Europe for patients with CrCl ≤15 mL/min or on dialysis.

Several RCTs are currently assessing OAC use and comparing NOACs with VKAs in patients with end-stage renal disease (NCT02933697, NCT03987711). The RENAL-AF trial, investigating apixaban vs. warfarin in AF patients on haemodialysis, was terminated early with inconclusive data on relative stroke and bleeding rates.<sup>1179</sup>

There are no RCT data on OAC use in patients with AF after kidney transplantation. The prescription and dosing of NOACs should be guided by the estimated glomerular filtration rate of the transplanted kidney and taking into account potential interactions with concomitant medication.

Particular attention must be given to the dosing of NOACs in patients with CKD (*Supplementary Table 9*).

## 11.9 Atrial fibrillation and peripheral artery disease

Patients with AF often have atherosclerotic vascular disease. With the inclusion of asymptomatic ankle-brachial index ≤0.90 in the definition PAD, the prevalence of vascular disease increased significantly.<sup>1180</sup> In a systematic review and meta-analysis, the presence of PAD was significantly associated with a 1.3- to 2.5-fold increased risk of stroke.<sup>347</sup> Complex aortic plaque in the descending aorta, as identified on TOE, is also a significant vascular stroke risk factor (*section 10.1.1*).

In patients with asymptomatic PAD, the risk of cardiovascular events progressively increases with increasing vascular disease

burden.<sup>470</sup> Therefore, PAD patients should be opportunistically screened for AF. Patients with AF and PAD should be prescribed OAC, unless contraindicated. Those with stable vascular disease (arbitrarily defined as no new vascular event in the past 12 months) should be managed with OAC alone (*section 11.3*), as concomitant use of antiplatelet therapy has not been shown to reduce stroke or other cardiovascular events, but may increase serious bleeds, including ICH.

The principles of rate and rhythm control outlined in *section 10.2* also apply for AF patients with PAD. Special considerations include possibly limited exercise capacity in these patients, owing to intermittent claudication. Beta-blockers may exacerbate PAD symptoms in some patients, in whom NDCC blockers may be more appropriate for rate control.

## 11.10 Atrial fibrillation and endocrine disorders

Electrolyte disturbances and altered glucose and/or hormone levels in endocrine disorders such as thyroid disorders, acromegaly, pheochromocytoma, diseases of adrenal cortex, parathyroid disease, or pancreas dysfunction including diabetes mellitus may contribute to development of AF. Data on management of AF in these settings are limited.<sup>3</sup> Diabetes is discussed in *section 10.3.2.4*. Stroke prevention should follow the same principles as in other AF patients, with risk stratification using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>3,1181</sup> In AF patients with hyperthyroidism, spontaneous conversion of AF often occurs once a euthyroid state is achieved.<sup>1182</sup> Withdrawal of amiodarone is mandatory in hyperthyroidism. AF catheter ablation should be performed under stable electrolytic and metabolic conditions and should not be carried out during active hyperthyroidism.

## 11.11 Atrial fibrillation and gastrointestinal disorders

While gastrointestinal lesions can lead to bleeding events in anticoagulated AF patients, some gastrointestinal conditions such as active inflammatory bowel disease increase the risk of AF and stroke.<sup>1183</sup> Gastrointestinal bleeding is a well-known complication of OAC. Overall, NOAC use is associated with an increased risk of gastrointestinal bleeding,<sup>1184,1185</sup> but in patients treated with apixaban or dabigatran 110 mg the risk is similar to warfarin.<sup>419,421</sup> Bleeding lesions can be identified in more than 50% of cases of major gastrointestinal bleeding.<sup>1186</sup> After correction of the bleeding source, OAC should be restarted, as this strategy has been associated with decreased risks of thrombo-embolism and death.<sup>1187</sup>

Patients treated with dabigatran may experience dyspepsia (about 11% in the RE-LY trial, and 2% discontinued the drug because of gastrointestinal symptoms<sup>419</sup>). After-meal ingestion of dabigatran and/or the addition of proton-pump inhibitors improves symptoms.<sup>1188</sup>

Management of AF patients with liver disease is challenging, owing to increased bleeding risk (associated with decreased hepatic synthetic function in advanced liver disease, thrombocytopenia, and gastrointestinal variceal lesions), as well as increased ischaemic risk<sup>1189,1190</sup>. Patients with hepatic dysfunction were generally excluded from the RCTs,<sup>1191</sup> especially those with abnormal clotting tests, as such patients may be at higher risk of bleeding on VKA, possibly less so on NOACs. Despite the paucity of data, observational

studies did not raise concerns regarding the use of NOACs in advanced hepatic disease.<sup>1192</sup> In a recent study, AF patients with liver fibrosis had no increase in bleeding on NOACs compared with VKAs.<sup>470</sup> Other reassuring data for NOACs come from a large nationwide cohort.<sup>472</sup> A number of patients may be started on a NOAC while having unrecognized significant liver damage and, in cirrhotic patients, ischaemic stroke reduction may outweigh bleeding risk.<sup>471</sup> NOACs are contraindicated in patients within Child-Turcotte-Pugh C hepatic dysfunction, and rivaroxaban is not recommended for patients in the Child-Turcotte-Pugh B or C category.<sup>1193</sup>

### 11.12 Atrial fibrillation and haematological disorders

Anaemia is an independent predictor of OAC-related major bleeding.<sup>393,402</sup> In a population-based AF cohort, anaemia was associated with major bleeding and lower TTR, whereas OAC use in AF patients with moderate or severe anaemia was associated with more major bleeding but no reduction in thrombo-embolic risk.<sup>1194</sup> Thrombocytopenia is also associated with increased bleeding risk. Before and during anticoagulation treatment, both anaemia and thrombocytopenia should be investigated and corrected, if possible. Decision making on OAC use in patients with platelet counts <100/μL requires a multidisciplinary approach including haematologists, balancing thrombotic and bleeding risks and addressing modifiable bleeding risk factors. Some chemotherapeutic drugs may increase the risk of incident AF (e.g. ibrutinib, melphalan, anthracyclines)<sup>1195–1197</sup> or impair platelet function, thus increasing the risk of bleeding (e.g. ibrutinib).<sup>1198,1199</sup>

### 11.13 The elderly and frail with atrial fibrillation

The prevalence of AF increases progressively with age<sup>67,1200–1206</sup>, and age is an independent risk factor for adverse outcomes in AF.<sup>372,1200,1207,1208</sup> Older people are less likely to receive OAC<sup>1209–1216</sup> despite sufficient evidence supporting the use of OAC in this population. Frailty, comorbidities, and increased risk of falls<sup>1217–1219</sup> do not outweigh the benefits of OAC given the small absolute risk of bleeding in anticoagulated elderly patients.<sup>339,390,391,1220–1223</sup> Evidence from RCTs,<sup>441,1224</sup> meta-analyses<sup>423,1225</sup> and large registries<sup>339,433,1209,1226</sup> support the use of OAC in this age group. Antiplatelets are neither more effective nor safer than warfarin and may even be harmful,<sup>433</sup> whereas NOACs appear to have a better overall risk–benefit profile compared with warfarin.<sup>423,433,441,1035,1225,1227–1236</sup> Prescribing a reduced dose of OAC is less effective in preventing AF adverse outcomes.<sup>1107,1211,1237,1238</sup>

Rate control is traditionally the preferred strategy, but evidence informing the choice between rate and rhythm control in the elderly is insufficient.<sup>1239–1242</sup> Limited evidence on other AF treatments supports the use of all rate and rhythm control options, including cardioversion, pacemaker implantation, and AF catheter ablation without any age discrimination. AF catheter ablation may be an effective and safe option in selected older individuals with success rates comparable to younger patients<sup>1243–1255</sup> and acceptable complication rates.<sup>1243,1245–1247,1249–1260</sup> Nevertheless, age was a predictor of complications in AF catheter ablation in some studies<sup>1261–1263</sup> and

longer follow-up studies suggested an age-related increase in multivariable-adjusted risk for AF/AFL recurrence, death, and major adverse cardiac events.<sup>1257</sup>

### 11.14 Patients with cognitive impairment/dementia

Evidence regarding effective prevention of cognitive impairment in AF is derived mainly from observational studies, suggesting that OAC could play a protective role in AF patients with stroke risk factors, not only for stroke prevention but also for prevention of cognitive decline.<sup>1264</sup> The quality of anticoagulation with VKAs (i.e. TTR) seems to play an additional role: low TTR and supratherapeutic INR values were associated with higher risk of dementia.<sup>1265,1266</sup> Limited evidence suggests that NOACs may be superior to VKA for preventing cognitive impairment in some,<sup>1267,1268</sup> but not all, studies.<sup>1269</sup> Recent observational data indicate a protective effect of OAC even in low-risk AF patients who do not need OAC for stroke prevention.<sup>1270</sup> A number of RCTs with cognitive function as an endpoint are ongoing and will provide more insights into the role of anticoagulation (NOACs and VKAs) for prevention of cognitive impairment in AF.<sup>86</sup>

Conversely, cognitive impairment can influence treatment adherence,<sup>1271,1272</sup> thus affecting outcomes in AF patients. After AF catheter ablation, silent brain lesions are detected by MRI, but this has not led to cognitive impairment in the AXAFA–AFNET 5 trial, although underpowered.<sup>880</sup>

### 11.15 Atrial fibrillation and congenital heart disease

Survival of patients with congenital heart disease has increased over time, but robust data on the management of AF are missing and available evidence is derived mainly from observational studies and/or extrapolation from large clinical trials.

In patients with AF (or AFL or intra-atrial re-entrant tachycardia) and congenital heart disease, OAC treatment is recommended for all patients with intracardiac repair, cyanotic congenital heart disease, Fontan palliation, or systemic right ventricle.<sup>1273</sup> Patients with AF and other congenital heart diseases should follow the general risk stratification for OAC use in AF. Notably, NOACs are contraindicated in patients with mechanical heart valves,<sup>1165</sup> whereas they seem safe in those with a valvular bioprosthesis.<sup>1274,1275</sup>

Rate control drugs such as beta-blockers, verapamil, diltiazem, and digitalis can be used with caution due to the risk of bradycardia and hypotension. Rhythm control strategies (i.e. amiodarone) may be effective. In Fontan patients, sodium-channel blockers suppress half of the atrial arrhythmias, but caution is needed for proarrhythmia. When cardioversion is planned, both 3 weeks of anticoagulation and TOE may be considered as thrombi are common in patients with congenital heart disease and atrial tachyarrhythmias.<sup>1276,1277</sup>

In patients with atrial septal defect, closure may be considered before the fourth decade of life to decrease the risk of AF or AFL.<sup>1278</sup> Patients with stroke who underwent closure of the patent foramen ovale may have an increased risk of AF,<sup>1279</sup> but in patients with patent foramen ovale and AF, closure is not recommended for stroke prevention; and OAC use should be decided using the conventional stroke risk assessment tool. In patients with a history of AF, AF surgery or AF catheter ablation should be considered at the time of

closure of the septal defect.<sup>1280–1282</sup> AF catheter ablation of late atrial arrhythmias is likely to be effective after surgical atrial septal defect closure.<sup>1283</sup>

### Recommendations for the management of AF in patients with congenital heart disease

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<ul style="list-style-type: none"> <li>Oral anticoagulation should be considered in all adult patients with intracardiac repair, cyanosis, Fontan palliation, or systemic right ventricle and a history of AF, AFL, or intra-atrial re-entrant tachycardia.<sup>1273</sup></li> <li>In patients with AF and other congenital heart diseases, anticoagulation should be considered in the presence of one or more non-sex stroke risk factor(s).<sup>1273</sup></li> </ul>	IIa	C
Surgery for AF should be considered in patients: <ul style="list-style-type: none"> <li>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).<sup>1280–1282</sup></li> <li>Cox maze surgery should be considered in patients with symptomatic AF and an indication for corrective repair of congenital heart defects. The surgery should be done in experienced centres.<sup>1280–1282</sup></li> </ul>	IIa	C
AF catheter ablation of atrial arrhythmias associated with congenital heart defects may be considered when performed in experienced centres. <sup>1283</sup>	IIb	C
In patients with congenital heart disease, TOE may be considered together with 3-week anticoagulation therapy before cardioversion. <sup>1292,1293</sup>	IIb	C

AF = atrial fibrillation; AFL = atrial flutter; TOE = transoesophageal echocardiography.

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

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

## 11.16 Atrial fibrillation in inherited cardiomyopathies and primary arrhythmia syndromes

A higher incidence and prevalence of AF have been described in patients with inherited cardiomyopathies and primary arrhythmia syndromes.<sup>1284–1318</sup> Sometimes AF is the presenting or only clinically overt feature,<sup>1319–1323</sup> is often associated with adverse clinical outcomes,<sup>1292,1299,1301,1307,1308,1310,1324–1329</sup> and has important implications:

- The use of AADs may be challenging. In congenital long QT syndrome, many drugs are contraindicated owing to increased risk of QT prolongation and torsade de pointes (<http://www.crediblemeds.org/>); in Brugada syndrome, class I drugs are contraindicated (<http://www.brugadadrugs.org/>). Owing to its long-term

adverse effects, chronic use of amiodarone is problematic in these typically young individuals.

- In patients with an implantable cardioverter defibrillator, AF is a common cause of inappropriate shocks.<sup>1307,1311,1330–1333</sup> Programming a single high-rate ventricular fibrillation zone  $\geq 210$ –220 bpm with long detection time is safe,<sup>1295,1296,1334</sup> and is recommended in patients without documented slow monomorphic ventricular tachycardia. Implantation of an atrial lead may be considered in case of significant bradycardia under beta-blocker treatment.

*Supplementary Table 14* summarizes the main clinical features of AF in patients with inherited cardiac diseases.

Patients with Wolff-Parkinson-White syndrome and AF are at risk of fast ventricular rates resulting from rapid conduction of atrial electrical activity to the ventricles via the accessory pathway, and at increased risk of ventricular fibrillation and sudden death.<sup>1335,1336</sup> Electrical cardioversion should be readily available for haemodynamically compromised patients with pre-excited AF, and atrioventricular node-modulating drugs (e.g. verapamil, beta-blockers, digoxin) should be avoided.<sup>1337,1338</sup> Pharmacological cardioversion can be attempted using ibutilide,<sup>1339</sup> whereas class Ic AADs (procainamide, propafenone, flecainide) should be used with caution owing to their effect on the atrioventricular node.<sup>1340–1343</sup> Amiodarone may not be safe in pre-excited AF as it may enhance pathway conduction.<sup>1343</sup>

## 11.17 Atrial fibrillation during pregnancy

AF is one of the most frequent arrhythmias during pregnancy,<sup>1344</sup> especially in women with congenital heart disease<sup>1345,1346</sup> and in older gravidae,<sup>1344,1347,1348</sup> and is associated with increased risk of death.<sup>1344</sup> Rapid atrioventricular conduction may have serious haemodynamic consequences for mother and foetus.

Pregnancy is associated with a hypercoagulable state and increased thrombo-embolic risk. Given the lack of specific data, the same rules for stroke risk assessment should be used as in non-pregnant women.<sup>1349</sup> Detailed practical recommendations on oral and parenteral anticoagulation regimens depending on the pregnancy trimester, such as low- and high-dose VKA use during the second and third trimesters, timing of low-molecular-weight heparin (LMWH) to unfractionated heparin (UFH) relative delivery, and control of therapeutic effects are given in the recent ESC Pregnancy Guidelines.<sup>1349</sup> Immediate anticoagulation is required in clinically significant mitral stenosis, using LMWH at therapeutic doses in the first and last trimesters, and VKA with the usual INR targets or LMWH for the second trimester. Use of NOACs is prohibited during pregnancy. Vaginal delivery should be advised for most women but is contraindicated while the mother is on VKAs because of the risk of foetal intracranial bleeding.<sup>1349</sup>

Intravenous beta-blockers are recommended for acute rate control. Beta-1 selective blockers (e.g. metoprolol and bisoprolol) are generally safe and are recommended as the first choice.<sup>1349</sup> If beta-blockers fail, digoxin and verapamil should be considered for rate control.

Rhythm control should be considered the preferred strategy during pregnancy. Electrical cardioversion is recommended if there is haemodynamic instability or considerable risk for mother or foetus. It can be performed safely without compromising foetal blood flow<sup>1350</sup> and the consequent risk for foetal arrhythmias or preterm

labour is low.<sup>1351,1352</sup> The fetal heart rate should routinely be controlled after cardioversion.<sup>1353</sup> Cardioversion should generally be preceded by anticoagulation (section 10.2.2.6).<sup>1349</sup> In haemodynamically stable patients without structural heart disease, i.v. ibutilide or flecainide may be considered for termination of AF but experience is limited.<sup>1354,1355</sup> Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail. AF catheter ablation has no role during pregnancy.

**Recommendations for the management of AF during pregnancy**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<i>Acute management</i>		
Immediate electrical cardioversion <sup>c</sup> is recommended in case of haemodynamic instability or pre-excited AF. <sup>1350,1351,1354</sup>	I	C
In pregnant women with HCM, cardioversion <sup>c</sup> should be considered for persistent AF. <sup>882</sup>	Ila	C
Ibutilide or flecainide i.v. may be considered for termination of AF in stable patients with structurally normal hearts. <sup>1355</sup>	Ilb	C
<i>Long-term management (oral administration of drugs)</i>		
Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF. <sup>1349</sup>	I	C
Beta-selective blockers are recommended for rate control in AF. <sup>d</sup>	I	C
Flecainide, <sup>e</sup> propafenone, <sup>e</sup> or sotalol <sup>f</sup> should be considered to prevent AF if atrioventricular nodal-blocking drugs <sup>f</sup> fail.	Ila	C
Digoxin <sup>g</sup> or verapamil <sup>g</sup> should be considered for rate control if beta-blockers fail.	Ila	C

AF = atrial fibrillation; ECG = electrocardiogram; US FDA = United States Food and Drug Administration; i.v. = intravenous; LV = left ventricular; HCM = hypertrophic cardiomyopathy; QTc = corrected QT interval; VKA = vitamin K antagonist.

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

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

<sup>c</sup>Cardioversion of AF should generally be preceded by anticoagulation.

<sup>d</sup>Atenolol has been associated with higher rates of foetal growth retardation and is not recommended.<sup>1356</sup>

<sup>e</sup>Flecainide and propafenone should be combined with atrioventricular nodal-blocking drugs, but structural heart disease, reduced LV function, and bundle branch block should be excluded.

<sup>f</sup>Class III drugs should not be used in prolonged QTc.

<sup>g</sup>Atrioventricular nodal-blocking drugs should not be used in patients with pre-excitation on resting ECG or pre-excited AF.

Note that the former A to X categories of drugs—the classification system for counselling of pregnant women requiring drug therapy—was replaced by the Pregnancy and Lactation Labelling Rule, which provides a descriptive risk summary and detailed information on animal and clinical data, by the US FDA in June 2015.

**11.18 Atrial fibrillation in professional athletes**

Moderate physical activity improves cardiovascular health and prevents AF, whereas intense sports activity increases the risk of

AF.<sup>35,1357</sup> Athletes have an approximate five-fold increased lifetime risk of AF compared with sedentary individuals despite a lower prevalence of conventional AF risk factors.<sup>35,1020</sup> Risk factors for AF in athletes include male sex, middle age, endurance sports, tall stature, and total lifetime exercise dose exceeding 1500–2000 hours.<sup>1020,1358–1361</sup> Endurance sports such as running, cycling, and cross-country skiing<sup>35,1362</sup> carry the highest risk.

In the absence of RCTs, recommendations for AF management in athletes are based largely on evidence in non-athletes, observational data, and expert consensus.<sup>143</sup> The need for anticoagulation is determined by clinical risk factors. Sports with direct bodily contact or prone to trauma should be avoided in patients on OAC. As athletes have a high prevalence of sinus bradycardia and sinus pauses, medical therapy is frequently contraindicated or poorly tolerated.<sup>1021,1363</sup> Digoxin and verapamil are often ineffective for rate control during exertional AF, whereas beta-blockers may not be well tolerated or are sometimes prohibited. Pill-in-the-pocket therapy has been used, but sports activity should be avoided after ingestion of flecainide or propafenone until AF ceases and two half-lives of the drug have elapsed.<sup>586</sup> AF catheter ablation is often preferred by athletes and was similarly efficacious in both the athletic and non-athletic populations in small studies.<sup>1364,1365</sup>

**Recommendations for sports activity in patients with AF**

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended to counsel professional athletes that long-lasting intense sports participation may promote AF, while moderate physical activity is recommended to prevent AF. <sup>35,38,1020,1360,1366–1368</sup>	I	B

AF = atrial fibrillation.

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

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

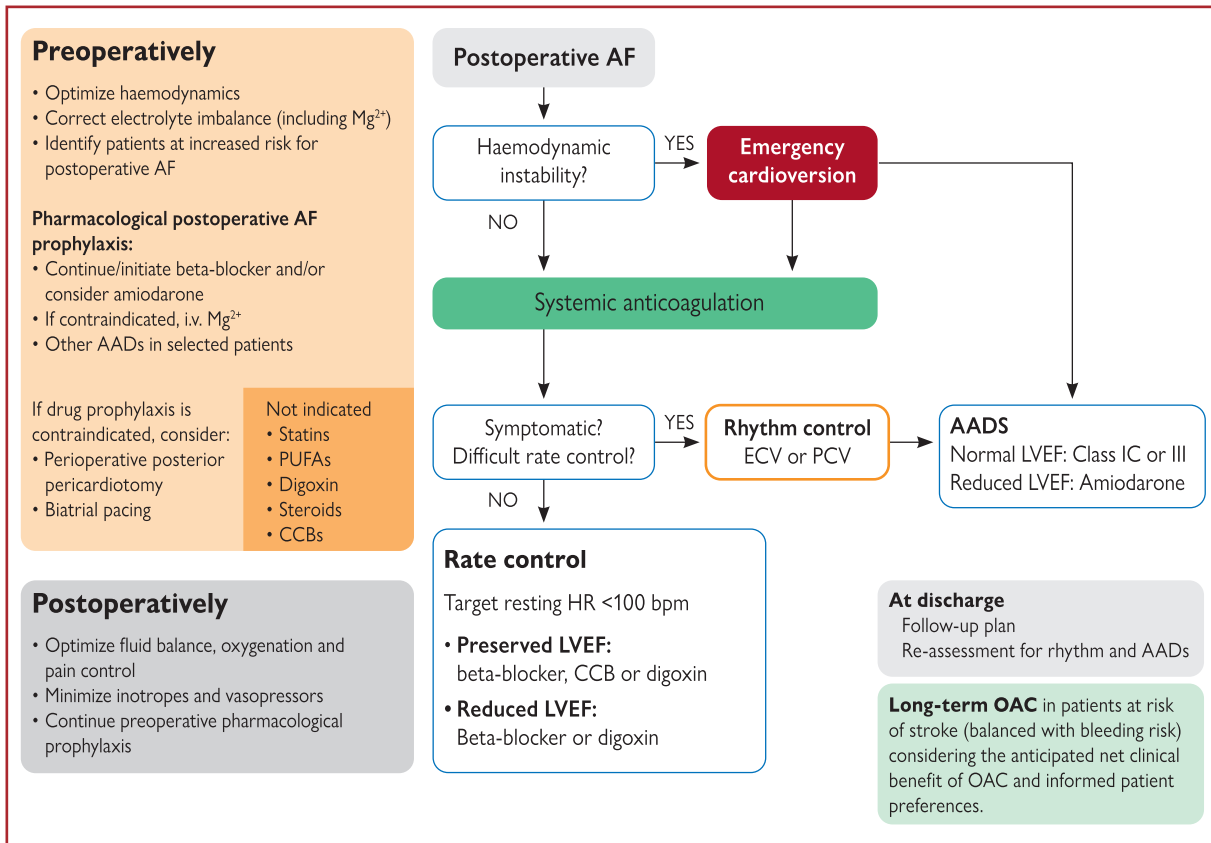
**11.19 Postoperative atrial fibrillation**

Perioperative AF describes the onset of the arrhythmia during an ongoing intervention. This is most relevant in patients undergoing cardiac surgery. While multiple strategies to reduce the incidence of perioperative AF with pretreatment or acute drug treatment have been described, there is lack of evidence from large RCTs. Amiodarone is the most frequently used drug for prevention of perioperative AF.<sup>1369</sup>

Postoperative AF, defined as new-onset AF in the immediate postoperative period, is a clinically relevant problem,<sup>1370,1371</sup> occurring in 20–50% of patients after cardiac surgery,<sup>1372,1373</sup> 10–30% after non-cardiac thoracic surgery,<sup>1374</sup> and in 5–10% after vascular or large colorectal surgery,<sup>1375</sup> with peak incidence between postoperative day 2 and 4.<sup>1376</sup> Intra- and postoperative changes affecting AF triggers and pre-existing atrial substrate may increase atrial vulnerability to AF. Many episodes of postoperative AF are self-terminating and some are asymptomatic, but postoperative AF has been associated with a four- to five-fold risk of recurrent AF in the next 5 years.<sup>1377,1378</sup> It has also been shown to be a risk factor for stroke,

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**Figure 23** Management of postoperative AF. AAD = antiarrhythmic drug; bpm = beats per minute; CCB = calcium channel blocker; ECV = electrical cardioversion; LVEF = left ventricular ejection fraction; Mg<sup>2+</sup> = magnesium; OAC = oral anticoagulation; PCV = pharmacological cardioversion; PUFA=polyunsaturated fatty acid.

myocardial infarction, and death compared with non-postoperative AF patients.<sup>1379,1380</sup>

Other adverse consequences of postoperative AF include haemodynamic instability, prolonged hospital stay, infections, renal complications, bleeding, increased in-hospital death, and greater healthcare costs.<sup>1371,1381,1382</sup> Management of postoperative AF is shown in Figure 23.

### 11.19.1 Prevention of postoperative AF

Preoperative beta-blocker (propranolol, carvedilol plus N-acetyl cysteine) use in cardiac and non-cardiac surgery is associated with a reduced incidence of postoperative AF,<sup>1383–1386</sup> but not major adverse events such as death, stroke, or acute kidney injury.<sup>1387</sup> Notably, in non-cardiac surgery, perioperative metoprolol was associated with increased risk of death in a large RCT.<sup>1388</sup> In a meta-analysis, amiodarone (oral or i.v.), and beta-blockers were equally effective in reducing postoperative AF,<sup>1389</sup> but their combination was better than beta-blockers alone.<sup>1390</sup> Lower cumulative doses of amiodarone (<3000 mg) could be effective, with fewer adverse events.<sup>1391–1393</sup> Data for other interventions such as statins<sup>974, 1394</sup> magnesium,<sup>1395</sup> sotalol,<sup>1385</sup> colchicine,<sup>1396</sup> posterior pericardiotomy,<sup>1397,1398</sup> (bi)atrial pacing,<sup>1385</sup> and corticosteroids<sup>1399</sup> are not robust. Two large RCTs showed no significant effect of i.v. steroids on the incidence of postoperative AF after cardiac surgery,<sup>1400,1401</sup> and colchicine is currently being investigated in the

prevention of postoperative AF [COP-AF (Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery): NCT03310125].

### 11.19.2 Prevention of thrombo-embolic events

In a large meta-analysis, patients with postoperative AF had a 62% higher odds of early and 37% higher risk of long-term stroke compared with those without postoperative AF ( $\geq 1$ -year stroke rates were 2.4% vs. 0.4%, respectively), as well as 44% higher odds of early and 37% higher risk of long-term mortality; long-term stroke risk was substantially higher with non-cardiac than cardiac postoperative AF (HR 2.00; 95% CI 1.70–2.35 for non-cardiac vs. HR 1.20; 95% CI 1.07–1.34 for cardiac postoperative AF; *P* for subgroup difference <0.0001).<sup>1379</sup>

Nevertheless, the evidence on OAC effects in patients with postoperative AF is not very robust.<sup>1382,1402–1407</sup> Observational data<sup>1408</sup> suggest that although coronary artery bypass graft-related postoperative AF might not be equivalent to non-surgery AF regarding the long-term risk of adverse outcomes, OAC use during follow-up was associated with a significantly lower risk of thrombo-embolic events in both postoperative AF and non-surgery AF compared with no OAC.<sup>1408</sup> Reportedly, postoperative AF occurring after non-cardiac surgery was associated with a similar long-term thrombo-embolic risk to non-surgery AF, and OAC therapy was associated with comparably lower risk of thrombo-embolic events and all-cause death in



both groups.<sup>1409</sup> Ongoing RCTs in cardiac [PACES (Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG); NCT04045665] and non-cardiac (ASPIRE-AF; NCT03968393) surgery will inform optimal long-term OAC use among patients developing postoperative AF.

In haemodynamically unstable patients with postoperative AF, emergency electrical cardioversion (or i.v. administration of amiodarone<sup>1385</sup> or vernakalant,<sup>583</sup> if consistent with the clinical situation) is indicated. In a recent RCT of postoperative AF patients after cardiac surgery, neither rate nor rhythm control showed net clinical advantage over each other.<sup>1373</sup> Hence, rate or rhythm control treatment decisions should be based on symptoms, and non-emergency cardioversion should follow the principles of peri-cardioversion anticoagulation outlined in [section 10.2](#).

### Recommendations for postoperative AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Perioperative amiodarone or beta blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery. <sup>1390,1492</sup>	I	A
Long-term OAC therapy to prevent thromboembolic events should be considered in patients at risk for stroke with postoperative AF after non-cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences. <sup>1404,1405,1408,1409</sup>	IIa	B
Long-term OAC therapy to prevent thromboembolic events may be considered in patients at risk for stroke with postoperative AF after cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences. <sup>1404,1405,1408,1409</sup>	IIb	B
Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery. <sup>1410</sup>	III	B

AF = atrial fibrillation; OAC = oral anticoagulant.

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

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

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## 12 Prevention of atrial fibrillation

### 12.1 Primary prevention of atrial fibrillation

Primary prevention of AF refers to the implementation of preventive measures in patients at risk but without previous documentation of AF. This strategy relies on the identification and management of risk factors and comorbidities predisposing to AF, before the development of atrial remodelling and fibrosis.<sup>964,1411</sup> Upstream therapy refers to the use of non-AADs that modify the atrial substrate or target-specific mechanisms of AF to prevent the occurrence or recurrence of the arrhythmia. The key targets of upstream therapy are structural changes in the atria (e.g. fibrosis, hypertrophy, inflammation, oxidative stress), but effects on atrial ion channels, gap junctions, and calcium handling are also evident.<sup>964</sup>

Adequate management of hypertension and HF may prevent AF by reducing atrial stretch, but inhibition of the renin-angiotensin-aldosterone system may exert an additional protective role by suppressing electrical and structural cardiac remodelling.<sup>964,1411,1412</sup> Large RCTs and meta-analyses have yielded equivocal results, either in favour<sup>1413–1416</sup> or against<sup>1417–1421</sup> statin use for primary prevention of AF. Controversial results have also been reported for the effects of fish oils on primary prevention of AF.<sup>1422</sup>

For primary prevention of postoperative AF after cardiac and non-cardiac surgery, see [section 11.19](#).

### 12.2 Secondary prevention of atrial fibrillation

For secondary AF prevention see [section 11.3](#) and [Supplementary section 12](#).

## 13 Sex-related differences in atrial fibrillation

Female patients are generally under-represented in RCTs, including AF trials. Sex-related differences in the epidemiology, pathophysiology, clinical presentation, and prognosis of AF that are consistently reported<sup>19,107,124,1423,1424</sup> may influence the effectiveness of AF treatment, and hence should be considered in a personalized, individual patient-centred approach to AF management in clinical practice.<sup>1425</sup> Understanding the underlying pathophysiological mechanisms and biology may help to improve personalized treatments. Adequate representation of women in future AF trials is recommended, as well as the identification and resolution of sex-specific barriers to implementation of guideline-recommended treatments for AF.

Women presenting with AF are older, have a higher prevalence of hypertension, VHD, and HFpEF, and a lower prevalence of CAD compared with men. Women with AF are more often symptomatic than men with AF, with greater symptom severity.<sup>1423,1426</sup>

Female sex is a stroke risk modifier that increases the risk of AF-associated stroke in the presence of other stroke risk factors.<sup>353</sup> Women with AF have a greater stroke severity and permanent disability than men with AF.<sup>1427</sup> Anticoagulation with warfarin may be less well controlled in women, and they have a greater residual stroke risk even with well-controlled VKAs.<sup>1428</sup> The efficacy and safety of NOACs in landmark RCTs were consistent in both sexes, but women were largely under-represented.<sup>423</sup>

In women with AF, the use of AADs for rhythm control is associated with significantly higher rates of life-threatening adverse events (e.g. acquired long QT syndrome with class Ia or III AADs)<sup>1429,1430</sup> or sinus-node disease/bradyarrhythmia requiring pacemaker implantation<sup>19</sup> compared with male patients. Women with AF are less likely to undergo electrical cardioversion,<sup>1426</sup> and are referred for AF catheter ablation later than men, possibly reflecting AF occurrence later in life among women.<sup>107,1431,1432</sup> The result of PVI may be less favourable in women,<sup>1431,1432</sup> with higher rates of procedure-related complications.<sup>1431</sup> Women are more likely to undergo atrioventricular nodal ablation for AF than men.<sup>124</sup> Sex-specific data on cardiovascular risk management in women with AF are lacking. Principles outlined in [section 11.3](#) apply to women with AF.

### Recommendations pertaining to sex-related differences in AF

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
It is recommended that women and men with AF are equally offered diagnostic assessment and therapies to prevent stroke and other AF-related complications. <sup>423,1433</sup>	I	A
Women with symptomatic paroxysmal or persistent AF should be offered timely access to rhythm control therapies, including AF catheter ablation, when appropriate for medical reasons. <sup>1448,1451</sup>	IIa	B

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AF = atrial fibrillation.

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.

## 14 Implementation of the atrial fibrillation guidelines

Guideline-adherent care (i.e. the implementation of guideline-recommended management to individual AF patients) aims to improve patient outcomes and reduce healthcare costs,<sup>1238,1434,1435</sup> but adherence to guidelines is modest worldwide.<sup>124,1436–1439,1440,1441</sup> Reportedly, the adoption of NOACs as first-line therapy has been associated with increasing guideline-adherent stroke prevention.<sup>1442,1443</sup>

Guideline non-adherence is multifactorial,<sup>1215,1444,1445</sup> including physician/healthcare professional- and healthcare system-related factors.<sup>1446</sup> Integrated AF management may facilitate adherence to guidelines. Various educational interventions<sup>280,284,290,1447,1448</sup> based on guideline-provided recommendations<sup>284</sup> and tailored to close specific knowledge gaps among healthcare professionals and/or AF patients<sup>1446</sup> may facilitate the implementation of guideline-based AF management to improve patient outcomes.<sup>277,1449–1452</sup> Further research is needed to identify the cost-effective intervention type(s) that would more effectively improve patient clinical outcomes, medication adherence, and QoL.

## 15 Quality measures and clinical performance indicators in the management of atrial fibrillation

Measurable service quality has been identified as a cornerstone for optimal AF management and is a mandatory step towards value-based healthcare. Quality and performance indicator sets should provide practitioners and institutions with the tools to measure the quality of care (e.g. adherence to guideline class I recommendations upon discharge/end of visit, complications after procedures, access/waiting list times) and identify opportunities for improvement. They should capture important aspects of care quality, including structure, process, outcome measures, and patient-centredness, while the reporting

burden for hospitals, practices, and practitioners should be kept to a minimum.<sup>658,1453–1455</sup>

A collaborative effort involving the ESC, EHRA, Asia Pacific Heart Rhythm Society, Heart Rhythm Society, and Latin American Heart Rhythm Society was put in place to develop quality indicators for the diagnosis and management of AF; a summary form of these quality indicators is provided in *Table 22*, with the full set published separately.<sup>317</sup> The ESC quality indicators are intended for quality improvement and performance measurement through meaningful surveillance, as well as for integration within registries that specifically aim to identify areas for improvement in clinical practice and are not intended for ranking healthcare professionals/providers or payment incentives.

### Recommendations for quality measures in patients with AF

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
The introduction of tools to measure quality of care and identify opportunities for improved treatment quality and AF patient outcome should be considered by practitioners and institutions. <sup>317</sup>	IIa	B

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AF = atrial fibrillation.

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.

## 16 Epidemiology, clinical implications, and management of atrial high-rate episodes/subclinical atrial fibrillation

The incidence of AHRE/subclinical AF in patients with a pacemaker/implanted device is 30–70%, but it may be lower in the general population.<sup>1458</sup> Very short episodes ( $\leq 10$ –20 s/day) are considered clinically irrelevant, as they are not significantly associated with longer episodes or an increased risk of stroke or systemic embolism.<sup>1459</sup> However, longer episodes of AHRE/subclinical AF (minimum of 5–6 min) are associated with an increased risk of clinical AF,<sup>467,469</sup> ischaemic stroke,<sup>168,467</sup> major adverse cardiovascular events,<sup>1460</sup> and cardiovascular death.<sup>1461</sup>

Overall, the absolute risk of stroke associated with AHRE/subclinical AF may be lower than with clinical AF.<sup>160,168,226,467</sup> The temporal dissociation from acute stroke suggests that AHRE/subclinical AF may represent a marker rather than a risk factor for stroke<sup>4,7,1462</sup> (*Supplementary Box 6*).

Whereas current data were obtained mostly from pacemakers/implantable cardioverter defibrillators or post-stroke patients, AHRE/subclinical AF is increasingly reported in a variety of patients undergoing cardiac monitoring. Clinical AF will reportedly develop in 1 in 5–6 of patients within 2.5 years after diagnosing AHRE/subclinical AF.<sup>168</sup> Notwithstanding that more high-quality evidence is needed to inform optimal management of these patients, more intense

**Table 22 Summary of quality indicators for the diagnosis and management of AF**

<b>Domain: Patient assessment (at baseline and follow-up)</b>
Main quality indicator: CHA <sub>2</sub> DS <sub>2</sub> -VASC cardioembolic risk assessment.
Main quality indicator: bleeding risk assessment using a validated method such as the HAS-BLED score.
Numerator: Number of AF patients who have their respective score documented at the time of diagnosis and at every follow-up appointment.
Denominator: Number of AF patients.
<b>Domain: Anticoagulation</b>
Main quality indicator: inappropriate prescription of anticoagulation to patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 0 for men and 1 for women.
Numerator: number of AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 0 for men and 1 for women, who are inappropriately prescribed anticoagulation.
Denominator: number of AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASC score of 0 for men and 1 for women who do not have other indication for anticoagulation.
Main quality indicator: proportion of patients with a CHA <sub>2</sub> DS <sub>2</sub> -VASC score of $\geq 1$ for men and $\geq 2$ for women who are prescribed anticoagulation.
Numerator: Number of AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASC score of $\geq 1$ for men and $\geq 2$ for women who are prescribed anticoagulation.
Denominator: Number of AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASC score of $\geq 1$ for men and $\geq 2$ for women who are eligible for anticoagulation with no contraindication or refusal.
<b>Domain: rate control</b>
Main quality indicator: inappropriate prescription of AADs <sup>a</sup> to patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned).
Numerator: Number of patients with permanent AF who are prescribed one or more AADs <sup>a</sup> for rhythm control.
Denominator: Number of patients with permanent AF.
<b>Domain: rhythm control</b>
Main quality indicator: inappropriate prescription of class IC AADs to patients with structural heart disease.
Numerator: number of AF patients with structural heart disease who are inappropriately prescribed class IC AADs.
Denominator: number of AF patients with structural heart disease.
Main quality indicator: proportion of patients with symptomatic paroxysmal or persistent AF who are offered AF catheter ablation after failure of/intolerance to one class I or class III AAD.
Numerator: Number of patients with paroxysmal or persistent AF who are offered catheter ablation after the failure of, or intolerance to, at least one class I or class III AAD.
Denominator: Number of patients with paroxysmal or persistent AF with no contraindications (or refusal) to catheter ablation who remain symptomatic on, or intolerant to at least one class I or class III AAD.
<b>Domain: risk factor management</b>
Main quality indicator: Proportion of patients who have their modifiable risk factors identified.
Numerator: number of AF patients who have their modifiable risk factors (e.g. BP, obesity, OSA, alcohol excess, lack of exercise, poor glycaemic control and smoking) identified
Denominator: number of AF patients.
<b>Domain: outcomes</b>
Main quality indicator: ischaemic stroke or TIA.
Main quality indicator: life-threatening or major bleeding events. <sup>b</sup>
Numerator: number of AF patients who have a documented ischaemic or bleeding event
Denominator: number of AF patients or number of patients prescribed an OAC, respectively.

AAD = antiarrhythmic drug; AF = atrial fibrillation; BP = blood pressure; CHA<sub>2</sub>DS<sub>2</sub>-VASC = Congestive heart failure, Hypertension, Age  $\geq 75$  years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly ( $>65$  years), Drugs/alcohol concomitantly; OAC = oral anticoagulant; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.

<sup>a</sup>Flecainide, propafenone, amiodarone, dronedarone, sotalol and disopyramide.

<sup>b</sup>Using the definitions of the International Society of Thrombosis and Haemostasis.<sup>1456,1457</sup>

follow-up and monitoring to detect clinical AF early is prudent (preferably with the support of remote monitoring). Notably, the AHRE/subclinical AF burden is not static but may change on daily basis,<sup>469</sup> hence should be regularly reassessed—the greater the AHRE/subclinical AF burden at diagnosis, the higher the risk of subsequent progression to longer episodes<sup>469</sup> (Figure 24).

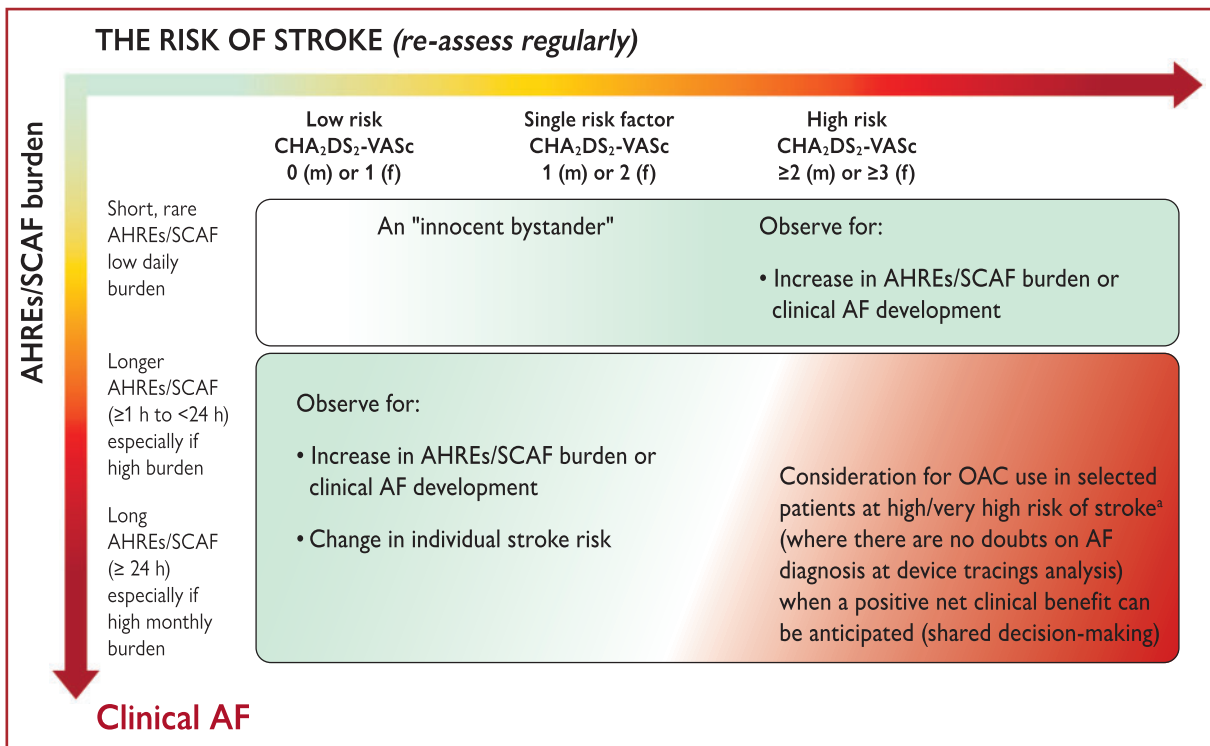
Whereas available evidence is insufficient to justify routine OAC use in patients with AHRE/subclinical AF, modifiable stroke risk factors should be identified and managed in each patient.

The use of OAC may be considered in selected patients with longer durations of AHRE/subclinical AF ( $\geq 24$  h) and an estimated high individual risk of stroke,<sup>4,1462</sup> accounting for the anticipated net

Six-month incidence of transition to higher AHRE burden <sup>a</sup> (n = 6580, pooled from three prospective studies) <sup>1469</sup>					Stroke rates <sup>b</sup> per AHRE burden and CHA <sub>2</sub> DS <sub>2</sub> -VASc category (n = 21 768 device patients not taking OAC) <sup>1466</sup>			
	Baseline burden					Baseline maximum daily burden		
6-month progression	5 min to <1 h	1 h to <6 h	6 h to <12 h	12 h to <23 h	CHA <sub>2</sub> DS <sub>2</sub> -VASc score	No AF	AF 6 min–23.5 h	AF >23.5 h
Transition to ≥1 h	33.5%				0	0.33%	0.52%	0.86%
Transition to ≥6 h	15.3%	42.2%			1	0.62%	0.32%	0.50%
Transition to ≥12 h	8.9%	27.5%	55.8%		2	0.70%	0.62%	1.52%
Transition to ≥23 h	5.1%	16.0%	40.6%	63.1%	3–4	0.83%	1.28%	1.77%
					≥5	1.79%	2.21%	1.68%

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**Figure 24** Progression of atrial high-rate episode burden (left panel) and stroke rates according to AHRE daily burden and CHA<sub>2</sub>DS<sub>2</sub>-VASc score (right panel). AHRE = atrial high-rate episodes; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); OAC = oral anticoagulant. <sup>a</sup>The higher the burden at diagnosis, the greater the incidence of progression in the next 6 months and thereafter. <sup>b</sup>Stroke rates above the threshold for OAC are shown in red.



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**Figure 25** Proposed management of AHRE/subclinical AF. AF = atrial fibrillation; AHRE = atrial high-rate episode; CKD = chronic kidney disease; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); f = female; LA = left atrium; LoE = level of evidence; m = male; OAC = oral anticoagulant; SCAF = subclinical atrial fibrillation. <sup>a</sup>Highly selected patients (e.g. with previous stroke and/or age ≥75 years, or ≥3 CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors, and additional non-CHA<sub>2</sub>DS<sub>2</sub>-VASc stroke factors such as CKD, elevated blood biomarkers, spontaneous echo contrast in dilated LA, etc); selected patients (e.g. with previous stroke and/or age ≥75 years, or ≥3 CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors, etc).

clinical benefit and informed patient’s preferences (Figures 24 and 25). In the recent trials, OAC was initiated in 76.4% and 56.3% of patients with ≥2 clinical stroke risk factors and insertable cardiac monitor-detected physician-confirmed AF≥6 min, but follow-up bleeding

rates were not reported.<sup>1463,1464</sup> In a large retrospective cohort study using remote monitoring data about daily AF burden, there was large practice variation in OAC initiation. Across increasing AF burden strata (from >6 min to >24 h) the risk of stroke in untreated

patients increased numerically, and the strongest association of OAC with reduction in stroke was observed among patients with device-detected AF episodes of >24 h.<sup>5</sup>

### Recommendations for management of patients with AHRE

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<p>In patients with AHRE/subclinical AF detected by CIED or insertable cardiac monitor, it is recommended to conduct:</p> <ul style="list-style-type: none"> <li>Complete cardiovascular evaluation with ECG recording, clinical risk factors/comorbidity evaluation, and thrombo-embolic risk assessment using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>469</sup></li> <li>Continued patient follow-up and monitoring (preferably with the support of remote monitoring) to detect progression to clinical AF, monitor the AHRE/subclinical AF burden (especially transition to ≥24 h), and detect changes in underlying clinical conditions.<sup>469</sup></li> </ul>	<b>I</b>	<b>B</b>

AF = atrial fibrillation; AHRE = atrial high-rate episode; CIED = cardiac implantable electronic device; ECG = electrocardiogram.

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

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

## 17 Atrial fibrillation and other atrial tachyarrhythmias (atrial flutter and atrial tachycardias)

Although AFL may exist as a solitary atrial arrhythmia, a significant proportion of patients will subsequently develop AF.<sup>1466–1470</sup> Typical AFL may occur in those taking class IC AADs or amiodarone.<sup>1467,1468,1471</sup> The ABC pathway for integrated AF management largely applies to patients with AFL. It is recommended that stroke-prevention strategies in patients with solitary AFL, including periprocedural management of stroke risk, follow the same principles as in patients with AF.<sup>1472</sup>

Rate control should be the first step in symptom management. However, cardioversion to sinus rhythm may be more effective, especially electrical cardioversion or (where feasible) high-rate stimulation.<sup>1473,1474</sup> Of note, the class III AADs dofetilide and ibutilide i.v. are very effective in interrupting AFL, whereas the class Ic drugs flecainide and propafenone<sup>1475–1478</sup> should not be used in the absence of atrioventricular-blocking drugs as they may slow the atrial rate, thus facilitating 1 : 1 atrioventricular conduction with a rapid ventricular rate.<sup>1479,1480</sup> AF catheter ablation of the CTI is the most effective rhythm control treatment for CTI-dependent AFL.<sup>732,1481,1482</sup> When typical AFL develops in AF patients during treatment with class Ic drugs or amiodarone, CTI ablation should be considered to ensure that AADs can be continued for AF rhythm control.<sup>732,1481</sup>

Atypical AFL (i.e. macro re-entrant atrial tachycardia) most commonly occurs in diseased or scarred atrial myocardium. Clinical

management of atypical AFL/macro re-entrant atrial tachycardia broadly follows the principles of typical AFL management, but the use of AADs is often limited by significant structural heart disease, and ablation is more complex.<sup>1336</sup>

Notably, the intervention to treat atrial tachycardias (AFL/macro re-entrant atrial tachycardia) occurring early after AF catheter ablation (or surgery) should be delayed, and initial rate control or the use of AADs should be considered instead, as some of these tachyarrhythmias are transient and cease after maturation of the lesions deployed by the index procedure.<sup>1483–1485</sup> For additional details about AFL, see [Supplementary Box 7](#) and the 2019 ESC Guidelines on supraventricular tachycardias.<sup>1336</sup>

## 18 Key messages

- (1) The diagnosis of AF needs to be confirmed by a conventional 12-lead ECG tracing or rhythm strip showing AF for ≥30 s.
- (2) Structured characterization of AF, including stroke risk, symptom severity, severity of AF burden, and AF substrate, helps improve personalized treatment of AF patients.
- (3) Novel tools and technologies for screening and detection of AF such as (micro-)implants and wearables substantially add to the diagnostic opportunities in patients at risk for AF. However, appropriate management pathways based on such tools are still incompletely defined.
- (4) Integrated holistic management of AF patients is essential to improving their outcomes.
- (5) Patient values need to be considered in treatment decision making and incorporated into the AF management pathways; the structured assessment of PRO measures is an important element to document and measure treatment success.
- (6) The ABC pathway streamlines integrated care of AF patients across healthcare levels and among different specialties.
- (7) Structured, clinical, risk-score-based assessment of individual thrombo-embolic risk, using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, should be performed as the first step in optimal thrombo-embolic risk management in AF patients.
- (8) Patients with AF and risk factors for stroke need to be treated with OAC for stroke prevention. In NOAC-eligible patients, NOACs are preferred over VKAs.
- (9) A formal structured risk-score-based bleeding risk assessment using, for example, the HAS-BLED score, helps to identify non-modifiable and address modifiable bleeding risk factors in AF patients.
- (10) An elevated bleeding risk should not automatically lead to withholding OAC in patients with AF and stroke risk. Instead, modifiable bleeding risk factors should be addressed, and high-risk patients scheduled for a more frequent clinical review and follow-up.
- (11) Rate control is an integral part of AF management and is often sufficient to improve AF-related symptoms.
- (12) The primary indication for rhythm control using cardioversion, AADs, and/or catheter ablation is reduction in AF-related symptoms and improvement of QoL.
- (13) The decision to initiate long-term AAD therapy needs to balance symptom burden, possible adverse drug reactions, particularly drug-induced proarrhythmia or extracardiac side-effects, and patient preferences.

- (14) Catheter ablation is a well-established treatment for prevention of AF recurrences. When performed by appropriately trained operators, catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement.
- (15) Major risk factors for AF recurrence should be assessed and considered in the decision making for interventional therapy.
- (16) In patients with AF and normal LVEF, catheter ablation has not been shown to reduce total mortality or stroke. In patients with AF and tachycardia-induced cardiomyopathy, catheter ablation reverses LV dysfunction in most cases.
- (17) Weight loss, strict control of risk factors, and avoidance of triggers for AF are important strategies to improve outcome of rhythm control.
- (18) Identification and management of risk factors and concomitant diseases is an integral part of the treatment of AF patients.
- (19) In AF patients with ACS undergoing uncomplicated PCI, an early discontinuation of aspirin and switch to dual antithrombotic therapy with OAC and a P2Y<sub>12</sub> inhibitor should be considered.
- (20) Patients with AHRE should be regularly monitored for progression to clinical AF and changes in the individual thrombo-embolic risk (i.e. change in CHA<sub>2</sub>DS<sub>2</sub>-VASc score). In patients with longer AHRE (especially >24 h) and a high CHA<sub>2</sub>DS<sub>2</sub>-VASc score, it is reasonable to consider the use of OAC when a positive net clinical benefit from OAC is anticipated in a shared, informed, treatment decision-making process.

## 19 Gaps in evidence

Whereas some progress has been made since publication of the 2016 ESC AF Guidelines, major gaps identified in those guidelines persist in 2020, calling for more intense research. In 2019, the EHRA published a white paper that covers major gaps in the field of AF in detail.<sup>1486</sup> The following bullet-list gives the most important knowledge gaps:

### □ Major health modifiers causing atrial fibrillation

Mechanisms of AF are not yet fully understood. Improvement in understanding of these mechanisms in individual patients, e.g. patients with cardiac structural remodelling or HF, would allow better selection of treatments including the best rate and rhythm control strategies and OAC.

It is uncertain how educational interventions translate into actual behavioural change (patients and physicians) that leads to improvements in clinical management and outcomes, especially in the multi-morbid AF patient.

### □ Implementation of digital technologies for screening, diagnosis, and risk stratification in the atrial fibrillation patient

New techniques for digital ECG analysis (e.g. machine learning and artificial intelligence) and new technologies (e.g. wearables and injectables) have opened up potentially significant opportunities for the detection and diagnosis of AF. These innovations may help to personalize therapy and risk stratification. Studies are needed to evaluate such opportunities and to define for which groups of patients this is worthwhile.

### □ Type of atrial fibrillation

There is a gap in knowledge regarding classification of AF. Recent data suggest that paroxysmal AF is not one entity. According to the pattern, type of therapy and outcome may differ.<sup>1487</sup> More studies are needed.

### □ How much atrial fibrillation constitutes a mandate for therapy?

The threshold of AF burden at which to initiate OAC therapy needs to be defined more clearly. This knowledge gap has resulted in substantial variation in physician attitudes and practice patterns.<sup>5</sup>

We are still waiting for the results of two ongoing RCTs in subclinical AF patients who are detected with cardiac implantable electronic device (CIED) [(Apixaban for the Reduction of Thrombo-Embolicism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) (NCT 01938248) and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) (NCT 02618577)].

### □ Role of biomarkers in atrial fibrillation management

Although some studies have demonstrated an effective role of biomarkers (including natriuretic peptides and troponin) in AF risk assessment, there is uncertainty over the exact time point of biomarker assessment, optimal cut-offs, and the effect on management decision making based on changes in biomarker levels over time, especially with increasing age and incident comorbidities.

### □ Stroke risk in specific populations

Some studies have tested the effect of biomarkers in predicting risk of AF-related complications, including stroke, in specific populations. However, it is unknown if biomarkers and biomarker-based scores practically help physicians in refining stroke risk, especially in prospective non-anticoagulated cohorts, particularly given the dynamic nature of stroke risk and how many current biomarkers are non-specific for AF or AF-related outcomes.

There is uncertainty of actual stroke risk in AHRE, compared with actual stroke risk in overt AF, in properly matched cohorts in similar settings, and the effect of appropriate management pathways.

The effect of sex in AF patients has been more investigated. Men with AF are less likely to have hypertension or VHD vs. women.<sup>1488</sup> Women often present with atypical symptoms related to AF. Further comparative studies are needed in different settings and ethnic groups on the effect of different stroke risk factors and female sex on stroke and bleeding risks.

### □ Anticoagulant therapy in specific patients

There is a gap in knowledge regarding optimal NOAC dosing in specific groups, including those with mild-to-moderate CKD, with very low/high body mass index, and patients receiving medications with a high risk of metabolic interaction.<sup>1489</sup>

In patients with CrCl ≤25 mL/min, RCT-derived data on the effect of VKA or NOACs is still lacking, due to the exclusion of these patients from the major RCTs. However, two RCTs (NCT02933697, NCT03987711) are currently assessing OAC use and comparing NOACs with VKAs in patients with end-stage renal disease.

### □ Anticoagulation in patients with heart valve diseases

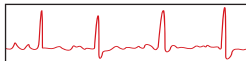
There are gaps in evidence on NOAC use in AF patients with rheumatic mitral valve disease and during the first 3 months after surgical or transcatheter implantation of a bioprosthesis; observational data regarding the use of NOACs after transcatheter aortic valve implantation are conflicting.<sup>1163</sup>

### □ Anticoagulation in atrial fibrillation patients after a bleeding or stroke event

As high-quality RCT-derived evidence to inform optimal timing of anticoagulation after acute ischaemic stroke is lacking, OAC use in the early post-stroke period is currently based on expert consensus. Several ongoing RCTs [ELAN (NCT03148457), OPTIMAS

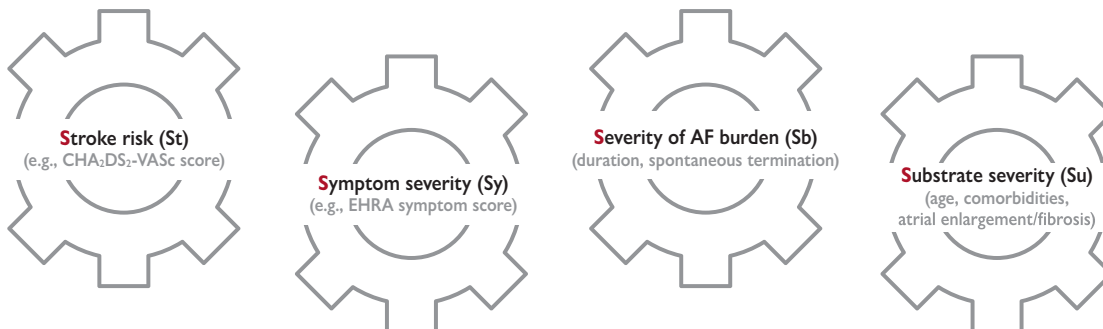
# CC To ABC

## Confirm AF

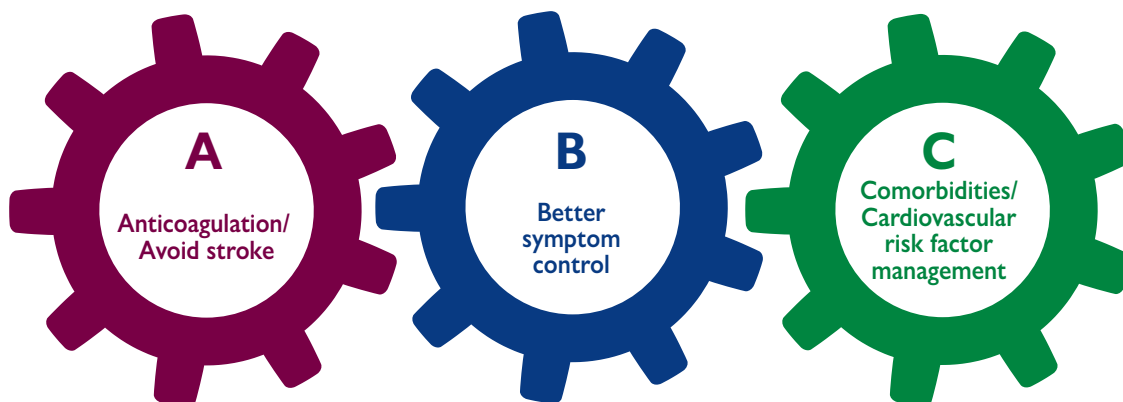


A 12-lead ECG or a rhythm strip showing AF pattern for  $\geq 30$  s

## Characterise AF (the 4S-AF scheme)



## Treat AF: The ABC pathway



1. Identify low-risk patients  
CHA<sub>2</sub>DS<sub>2</sub>-VASc 0(m), 1(f)
2. Offer stroke prevention if  
CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 1$ (m), 2(f)  
Assess bleeding risk, address  
modifiable bleeding risk factors
3. Choose OAC (NOAC or VKA  
with well-managed TTR)

- Assess symptoms,  
QoL and patient's  
preferences
- Optimize rate  
control
- Consider a rhythm  
control strategy  
(CV, AADs, ablation)

- Comorbidities and  
cardiovascular  
risk  
factors
- Lifestyle changes  
(obesity reduction,  
regular exercise,  
reduction of alcohol use,  
etc.)

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**Central Illustration** Management of AF. AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive HF, Hypertension, Age  $\geq 75$  years, diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CV = cardioversion; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist.

(EudraCT, 2018-003859-3), TIMING (NCT02961348), and START (NCT03021928)] will try to assess the differences between the two approaches, including early (<1 week) vs. late NOAC initiation in patients with AF-related ischaemic stroke.

**□ Left atrial appendage occlusion for stroke prevention**

More studies have been conducted in this field. There is clearer evidence of the safety and possible complications of the LAA closure procedure.<sup>450–454</sup> However, there are still knowledge gaps to be addressed: (i) antithrombotic management after LAA occlusion has not been evaluated in a randomized manner; and (ii) the efficacy and safety of LAA closure vs. OAC therapy needs to be assessed in randomized trials.

LAA occluders have not been compared with NOAC therapy in patients at risk for bleeding, or with surgical LAA occlusion/exclusion.

**□ Surgical exclusion of Left atrial appendage**

Only limited RCT data are available<sup>457–459</sup> on surgical exclusion of the LAA. Although a large RCT in patients with an associated cardiac surgical procedure is ongoing,<sup>462</sup> adequately powered RCTs are needed.

There is the need for adequately powered trials to define the best indications for LAA occlusion/exclusion compared with NOAC therapy in patients with relative or absolute contraindications for anticoagulation, in those with an ischaemic stroke on anticoagulant therapy, and for assessment of the appropriate antithrombotic therapy after LAA occlusion.

**□ Atrial fibrillation catheter ablation technique**

The best approach to safely and expeditiously achieve permanent PVI in a single procedure is still one of the knowledge gaps in relation to emerging technologies for catheter ablation of AF. Moreover, it remains unknown if ablating additional targets will improve the outcomes of AF catheter ablation.<sup>1490</sup>

**□ Outcome of atrial fibrillation catheter ablation**

The following issues need to be addressed in further studies:

- The value of early AF ablation to prevent AF progression.
- The optimal outcome measure (AF 30 s, AF burden, etc.) for AF-related outcome.

- How much reduction in AF burden is needed to achieve an effect on hard endpoints, including survival, stroke, and comorbidity.
- The main mechanism of PVI translating into freedom of AF.
- The potential effect of cardiac structure and function on the likelihood of success of AF ablation.

Despite the publication of CABANA and CASTLE-AF, more data are needed on the effect of AF catheter ablation on clinical outcomes, including death, stroke, serious bleeding, AF recurrence, QoL, and cardiac arrest.

The relationship between the degree of atrial dilation/fibrosis and successful ablation of AF needs to be addressed. Additionally, the impact of specific components of structural heart disease, including LA structure/function, LV structure, etc., on the success of AF catheter ablation and the likelihood of recurrence requires further investigation.

**□ Who may benefit less from atrial fibrillation catheter ablation**

There are gaps in knowledge about subgroups of patients who may benefit less from AF catheter ablation, including (i) persistent and long-standing persistent AF; (ii) patients with enlarged atrial size and/or atrial fibrosis; (iii) patients with atypical AFL; and (iv) patients with risk factors for AF recurrence, including obesity or sleep apnoea.

**□ Thoracoscopic ‘stand-alone’ atrial fibrillation surgery**

There are no convincing data on the effects on stroke of surgical ablation as a stand-alone procedure or in combination with LAA occlusion or exclusion on various outcomes including QoL, stroke, and death.

**□ Personalized therapy**

The arrhythmia phenotype may differ among patients. Improved assessment of the pathophysiological process involved in the individual patient by using clinical characteristics, blood biomarkers, and non-invasive substrate determination (echo/MRI/CT) may improve personalized therapy (e.g. selection of rhythm control, yes or no; treatment of risk factors and comorbidities; type of antiarrhythmic drug; atrial ablation; and which type/techniques used for AF).

## 20 ‘What to do’ and ‘what not to do’ messages from the Guidelines

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Recommendations for diagnosis of AF</b>		
ECG documentation is required to establish the diagnosis of AF.	I	B
<ul style="list-style-type: none"> <li>• A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.</li> </ul>		
<b>Recommendations for screening of AF</b>		
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age.	I	B
It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.	I	B
When screening for AF it is recommended that:	I	B
<ul style="list-style-type: none"> <li>• The individuals undergoing screening are informed about the significance and treatment implications of detecting AF.</li> <li>• A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF.</li> <li>• Definite diagnosis of AF in screen-positive cases is established only after the physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.</li> </ul>		

Continued



<b>Recommendations for diagnostic evaluation of patients with AF</b>		
In patients with AF, it is recommended to: <ul style="list-style-type: none"> <li>Evaluate AF-related symptoms (including fatigue, tiredness, exertional shortness of breath, palpitations, and chest pain) and quantify the patient symptom status using the modified EHRA symptom scale before and after initiation of treatment.</li> <li>Evaluate AF-related symptoms before and after cardioversion of persistent AF to aid rhythm control treatment decisions.</li> </ul>	I	C
In patients with AHRE/subclinical AF detected by CIED or insertable cardiac monitor, it is recommended to conduct: <ul style="list-style-type: none"> <li>Complete cardiovascular evaluation with ECG recording, clinical risk factors/comorbidity evaluation, and thrombo-embolic risk assessment using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.</li> <li>Continued patient follow-up and monitoring (preferably with the support of remote monitoring) to detect progression to clinical AF, monitor the AHRE/subclinical AF burden (especially transition to <math>\geq 24</math> h), and detect changes in underlying clinical conditions.</li> </ul>	I	B
<b>Recommendations about integrated AF management</b>		
To optimize shared decision making about specific AF treatment option(s) in consideration, it is recommended that physicians: <ul style="list-style-type: none"> <li>Inform the patient about the advantages/limitations and benefit/risks associated with the treatment option(s) being considered; and</li> <li>Discuss the potential burden of the treatment with the patient and include the patient's perception of treatment burden in the treatment decision.</li> </ul>	I	C
It is recommended to routinely collect PROs to measure treatment success and improve patient care.	I	C
<b>Recommendations for the prevention of thrombo-embolic events in AF</b>		
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA <sub>2</sub> DS <sub>2</sub> -VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy.	I	A
OAC is recommended for stroke prevention in AF patients with CHA <sub>2</sub> DS <sub>2</sub> -VASc score $\geq 2$ in men or $\geq 3$ in women.	I	A
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.	I	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors.	I	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR $\geq 70\%$ .	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR $< 70\%$ ), switching to a NOAC but ensuring good adherence and persistence with therapy is recommended.	I	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.	III	B
<b>Recommendations for stroke risk management peri-cardioversion</b>		
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety as warfarin.	I	A
For cardioversion of AF/AFL, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B
TOE is recommended to exclude cardiac thrombus as an alternative to 3-week pre-procedural anticoagulation when early cardioversion is planned.	I	B
In patients at risk of stroke, it is recommended that OAC therapy is continued long term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion, the apparent maintenance of sinus rhythm, or characterization of AF as a 'first-diagnosed episode'.	I	B
When thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks before cardioversion of AF.	I	B
It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.	I	C
<b>Recommendations for stroke risk management peri-catheter ablation</b>		
In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and, preferably, therapeutic OAC for at least 3 weeks before ablation.	I	C

Continued

For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended.	I	A
After AF catheter ablation, it is recommended that: <ul style="list-style-type: none"> <li>• Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and</li> <li>• Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.</li> </ul>	I	C
<b>Recommendations for postoperative anticoagulation after AF surgery</b>		
Long-term OAC is recommended in patients after AF surgery and appendage closure, based on the patient's thrombo-embolic risk assessed with the CHA <sub>2</sub> DS <sub>2</sub> -VASc score.	I	C
<b>Recommendations for patients with AF and an ACS, PCI, or CCS</b>		
In AF patients eligible for NOACs, it is recommended to use a NOAC in preference to a VKA in combination with antiplatelet therapy.	I	A
In AF patients with ACS undergoing an uncomplicated PCI, early cessation ( $\leq 1$ week) of aspirin and continuation of dual therapy with an OAC and a P2Y <sub>12</sub> inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	I	B
After uncomplicated PCI, early cessation ( $\leq 1$ week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	I	B
<b>Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke</b>		
In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients.	I	A
In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH, or VKAs is not recommended.	III	B
<b>Recommendations for patients with valvular heart disease and AF</b>		
NOACs are contraindicated in patients with a prosthetic mechanical valve.	III	B
Use of NOACs is not recommended in patients with AF and moderate-to-severe mitral stenosis.	III	C
<b>Recommendations for the management of AF during pregnancy</b>		
Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF.	I	C
<b>Recommendations for the management of active bleeding on OAC</b>		
In an AF patient with severe active bleeding, it is recommended to: <ul style="list-style-type: none"> <li>• Interrupt OAC until the cause of bleeding is identified and active bleeding is resolved; and</li> <li>• Promptly perform specific diagnostic and treatment interventions to identify and manage the cause(s) and source(s) of bleeding.</li> </ul>	I	C
<b>Recommendations for ventricular rate control in patients with AF</b>		
Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF $\geq$ 40%.	I	B
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF<40%.	I	B
<b>Recommendations for the management of AF during pregnancy</b>		
Beta-selective blockers are recommended for rate control in AF.	I	C
<b>Recommendations for rhythm control</b>		
Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF.	I	A
<b>Recommendations for cardioversion</b>		
For pharmacological cardioversion of new-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or flecainide or propafenone (excluding patients with severe structural heart disease) is recommended.	I	A
Intravenous amiodarone is recommended for cardioversion of AF in patients with HF or structural heart disease, if delayed cardioversion is consistent with clinical situation.	I	A
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
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thrombo-embolic risk.	I	B

Continued

Emergency electrical cardioversion is recommended in AF patients with acute or worsening haemodynamic instability.	I	B
For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc (>500 ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.	III	C
<b>Recommendations for the management of AF during pregnancy</b>		
Immediate electrical cardioversion is recommended in case of haemodynamic instability or pre-excited AF.	I	C
<b>Recommendations for rhythm control/catheter ablation of AF</b>		
For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient.	I	B
<b>AF catheter ablation after failure of drug therapy</b>		
AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with:	I	
● Paroxysmal AF, or		A
● Persistent AF without major risk factors for AF recurrence, or		A
● Persistent AF with major risk factors for AF recurrence.		B
<b>First-line therapy</b>		
AF catheter ablation is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status.	I	B
<b>Techniques and technologies</b>		
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.	I	A
<b>Lifestyle modification and other strategies to improve outcomes of ablation</b>		
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.	I	B
Strict control of risk factors and avoidance of triggers are recommended as part of a rhythm control strategy.	I	B
<b>Recommendations for long-term antiarrhythmic drugs</b>		
Flecainide or propafenone are recommended for long-term rhythm control in AF patients with normal LV function and without structural heart disease, including significant LVH and myocardial ischaemia.	I	A
Dronedronarone is recommended for long-term rhythm control in AF patients with:	I	A
● Normal or mildly impaired (but stable) LV function, or		
● HFpEF, ischaemic, or VHD.		
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.	I	A
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.	I	B
AAD therapy is not recommended in patients with permanent AF under rate control and in patients with advanced conduction disturbances unless antibradycardia pacing is provided.	III	C
<b>Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF</b>		
Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.	I	B
Opportunistic screening for AF is recommended in hypertensive patients.	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	B
<b>Recommendations for sports activity in patients with AF</b>		
It is recommended to counsel professional athletes that long-lasting intense sports participation may promote AF, while moderate physical activity is recommended to prevent AF.	I	B
<b>Recommendations for postoperative AF</b>		
Perioperative amiodarone or beta blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery.	I	A
Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery.	III	B

Continued

### Recommendations pertaining to sex-related differences in AF

It is recommended that women and men with AF are equally offered diagnostic assessment and therapies to prevent stroke and other AF-related complications.

I

A

AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; AFL = atrial flutter; AHRE = atrial high-rate episodes; BP = blood pressure; CCS = chronic coronary syndrome; CHA<sub>2</sub>DS<sub>2</sub>-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); CIED = cardiac implantable electronic device; CrCl = creatinine clearance; ECG = electrocardiogram; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; i.v. = intravenous; INR = international normalized ratio; LMWH = low-molecular-weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PRO = patient-reported outcome; PVI = pulmonary vein isolation; QoL = quality of life; TIA = transient ischaemic attack; TOE = transoesophageal echocardiography; TTR = time in therapeutic range; UFH = unfractionated heparin; VHD = Valvular heart disease; VKA = vitamin K antagonist.

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## 21 Supplementary data

Supplementary Data with additional Supplementary Figures, Tables, and text complementing the full text are available on the *European Heart Journal* website and via the ESC website at [www.escardio.org/guidelines](http://www.escardio.org/guidelines).

## 22 Appendix

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