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ESC GUIDELINES

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

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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1 Epidemiology

1.1 Prevalence and incidence of atrial fibrillation

The estimated prevalence of atrial fibrillation (AF) in adults currently ranges between 2% and 4% (globally, 46.3 million individuals had prevalent AF/atrial flutter in 2016).[1] A 2.3-fold rise[2] is expected in the coming decades,[3,4] largely owing to extended longevity of the general population and intensifying search for undiagnosed AF.[5] Although increasing age is a prominent risk factor for AF development, a congruent increase in the burden of other comorbidities including hypertension, diabetes mellitus (DM), heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD),[6] obesity, and obstructive sleep apnoea (OSA) plays an important role.[7–11] Modifiable risk factors including excessive alcohol consumption, smoking, sedentary lifestyles, and extreme exercise have also been proposed as potential contributors to the development and progression of AF (*Supplementary Table 1*).[12,13]

The age-adjusted incidence, prevalence, and lifetime risk of AF are lower in women compared with men and in non-white (i.e. Asian, African American, and Hispanic) ethnic cohorts compared with white populations.[5,14–19] The 2019 Update of the Heart Disease and Stroke Statistics also reported age- and sex-adjusted variations in the incidence, prevalence, and lifetime risk of AF in different ethnic groups.[1]

1.2 Risk factors for atrial fibrillation

The lifetime risk of AF has been previously estimated to be approximately 1 in 4 individuals,[20,21] whereas more recent studies reported an increase to 1 in 3 individuals of European ancestry at an index age of 55 years.[22,23]

The lifetime risk of AF depends on age, and is influenced by genetic and (sub)clinical factors (*Supplementary Table 1*).[1,24,25] The observed impact of clinical risk factor burden and multiple comorbidity on the lifetime risk of AF (significantly increasing from 23.4% among individuals with an optimal clinical risk factor profile to 33.4% and 38.4% in those with borderline and elevated clinical risk factors)[22] suggests that an early intervention and control of modifiable risk factors could reduce the incidence of AF.

Supplementary Table 1 Risk factors for incident AF

Risk factors for incident AF			
Demographic factors	Age[1, 24, 26]	**Cardiovascular conditions / diseases**	HF[1, 24, 26-29]
	Male sex[1, 24, 26]		Valvular disease[1, 26, 27, 30, 31]
	Caucasian ethnicity[1, 24]		CAD[1, 26, 29, 32]
	Lower socioeconomic status[24]		Congenital heart disease[1, 33]
Health behaviours	Smoking/tobacco use[1, 24, 26]	**Subclinical atherosclerosis**	Coronary artery calcification[1, 26, 34]
	Alcohol intake[1, 24]		Carotid IMT and carotid plaque[1, 26, 35]
	Physical inactivity[1, 24]	**Disorders of heart rhythm**	PR interval prolongation[1, 26, 36]
	Vigorous exercise[37–40]		Sick sinus syndrome[1, 41]
	Competitive or athlete-level endurance sports[26, 42]		Wolff-Parkinson White[1, 43]
	Caffeine[44-46]	**Genetic factors**	Family history of AF[1, 26, 47-50]
Health factors and other risk factors	Hypertension[1, 24, 26]		AF susceptible loci identified by GWAS[1, 26, 51]
	Systolic blood pressure[24 a]		Short QT syndrome[1]
	Diastolic blood pressure[24 b]	**Inflammation**	C-reactive protein[24, 26]
	Total cholesterol[1, 24 c]		Fibrinogen[24]
	Low-density lipoprotein cholesterol[24 d]		Thyroid dysfunction[1, 24, 26, 52f]
	High-density lipoprotein cholesterol[24]		Autoimmunity[24]
	Triglycerides[24]		Other biomarkers[1, 26]
	Diabetes mellitus[1, 7, 24, 26]	**Other**	Air pollution[1, 53]
	Pre-diabetes[7]		Sepsis[1, 54]
	Renal dysfunction/CKD[1, 24, 26, 55, 56]		Psychological factors: in men[57], in women[58]
	Obesity[1, 24, 26, 59, 60]		
	Body mass index[1, 24, 26]		
	Height[24, 26 e]		
	Weight[24]		
	Sleep apnoea[1, 26, 61, 62]		
	Chronic obstructive pulmonary disease[63]		

AF = atrial fibrillation; CAD = coronary artery disease; CKD = chronic kidney disease; GWAS = genome-wide association studies; HF = heart failure; IMT = intima-media thickness.

[a]For every 10 - 22 mmHg increase in systolic blood pressure or systolic blood pressure ≥160 mmHg.

[b]For every 10 - 11 mmHg increase in diastolic blood pressure or diastolic blood pressure ≥95 - 100 mmHg.

[c]For every 10 - 50 mg/dL (0.2 - 1.3 mmol/L) increase in total cholesterol or total cholesterol ≥220 - 280 mg/dL (5.7 - 7.2 mmol/L).

[d]For every 10 - 40 mg/dL (0.2 - 1.0 mmol/L) increase in low-density lipoprotein cholesterol or low-density lipoprotein cholesterol ≥150 mg/dL (≥3.9 mmol/L).

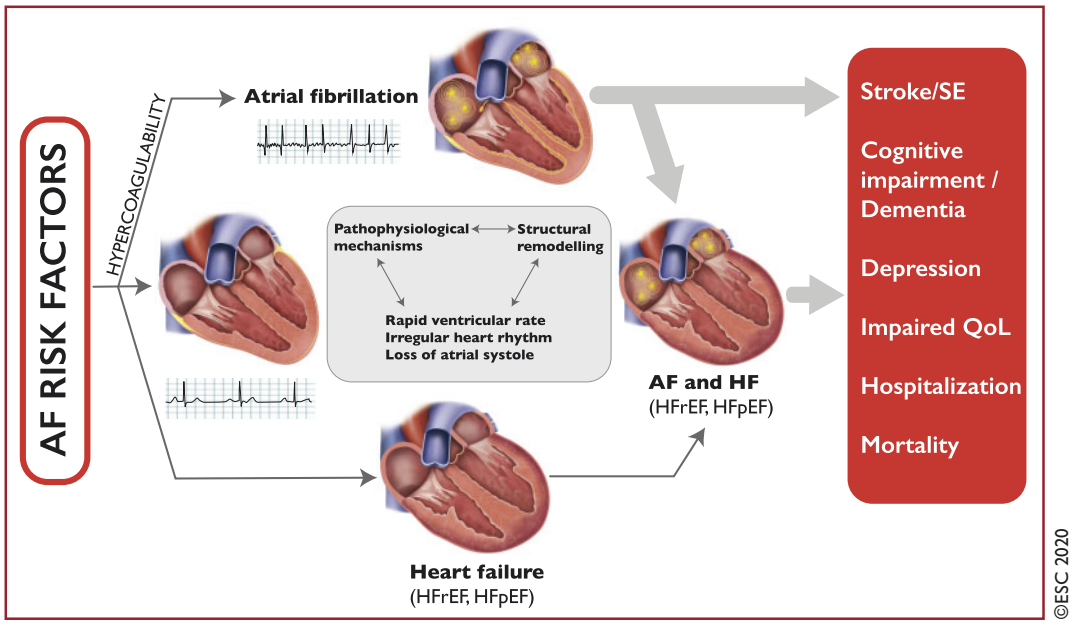
[e]For every 1 - 10 cm increase in height or height ≥173 cm.

[f]For every 1.0 mU/L decrease in thyroid-stimulating hormone or thyroid-stimulating hormone >0.10 - 0.45 mU/L.

Supplementary Table 2 **Predictive scores for new-onset AF**

Score	Database/Cohort	Subjects (n)	C index (95% CI)	Variables
FHS score[64] (10-year risk)	FHS 100% white, 55% female, 61 years (45–95 years)	4764 (457 cases)	0.78 (0.76 - 0.80)	Age, sex, significant murmur, HF, SBP, hypertension treatment, body mass index, PR interval
CHARGE-AF score[65] (5-year risk)	ARIC, CHS, FHS 81% white, 19% Black, 57% female, 65 years (46–94 years)	18 556 (1771 cases)	0.77 (0.75 - 0.78)	Age, ethnicity, height, weight, SBP/diastolic blood pressure, current smoking, hypertension treatment, diabetes, history of myocardial infarction, HF
ARIC score (10-year risk)	ARIC 73% white, 27% Black, 55% female, 45–64 years	14 546 (515 cases)	0.78 (N/A)	Age, ethnicity, height, smoking status, SBP, hypertension treatment, pericardial murmur, left ventricular hypertrophy, left atrial enlargement, diabetes, CAD, HF
WHS score[66] (10-year risk)	100% white, 100% female, median 53 years (IQR 49 - 59)	19 940 (616 cases)	0.72 (0.68 - 0.75)	Age, weight, height, SBP, alcohol use, smoking
MHS[67] (10-year risk)	MHS (Israeli) 54% female, 63 years	145 182 (2791 cases)	0.75 (0.74 - 0.76)	Age, sex, body mass index, history of myocardial infarction, history of PAD, hypertension treatment, SBP, COPD, autoimmune/inflammatory disease (female), age to HF
JMC score[68] (7-year risk)	JMC 100% Japanese, 35% female 52 years	65 984 (349 cases)	0.77 (SE 0.02)	Age, waist circumference, diastolic blood pressure, alcohol consumption, heart rate, cardiac murmur
C_2HEST score[69]	CYID 100% Asian, 43% female, 47 years	471 446 (921 cases)	0.75 (0.73 - 0.77)	CAD/COPD, hypertension, elderly, systolic HF, thyroid disease
C_2HEST score[70] (1-year risk)	French nationwide cohort	240 459 (14 095 cases)	0.734 (0.732 - 0.736)	CAD/COPD, hypertension, elderly, systolic HF, thyroid disease
Shandong score[71]	Shandong 100% Chinese, 33% female, 57 years (45 - 85 years)	33 186 (134 cases)	0.77 (NA)	Age, sex, CAD, hypertension

ARIC = Atherosclerosis Risk in Communities Study; C_2HEST score [C_2: CAD/COPD (1 point each); H: hypertension (1 point); E: elderly (age ≥ 75 years, 2 points); S: systolic HF (2 points); and T: thyroid disease (hyperthyroidism, 1 point)]; CAD = coronary artery disease; CHARGE-AF = Cohorts for Aging and Research in Genomic Epidemiology-Atrial Fibrillation; CHS = Cardiovascular Health Study; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CYID = Chinese Yunnan Insurance Database; FHS = Framingham Heart Study; HF = heart failure; IQR = interquartile range; JMC = Japanese Medical Check; MHS = Maccabi Healthcare Services; NA = not applicable; PAD = peripheral artery disease; SBP = systolic blood pressure; SE = standard error; WHS = Women's Health Study.



Supplementary Figure 1 Pathophysiology of AF. Various factors cause complex atrial alterations, including stretch-induced fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodelling, ischaemia, ion-channel dysfunction, and calcium instability. All enhance ectopy and conduction disturbances, increase atrial propensity to develop/maintain AF, and facilitate the AF-associated hypercoagulable state. Hypocontractility reduces local endothelial shear stress, which increases expression of plasminogen activator inhibitor, and ischaemia-induced inflammation enhances the expression of endothelial adhesion molecules or promotes shedding of endothelial cells, resulting in tissue factor exposure to the blood stream. AF in itself aggravates many of these mechanisms, which may explain its progressive nature. AF = atrial fibrillation; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; SE = systemic embolism; QoL = quality of life.

2. Clinical presentation of atrial fibrillation

Supplementary Box 1. Clinical presentation of AF

Clinical presentation and symptoms

- Palpitations, dyspnoea, and fatigue are the most frequent AF-related symptoms, but patients may also complain of chest tightness/pain, dizziness, syncope, disordered sleep, etc..[72–76] Patients with paroxysmal AF report more symptoms (80%) than those with permanent AF (51%), the latter more frequently reporting dyspnoea, fatigue, and effort intolerance.[77] Importantly, symptoms may be related to undertreated concomitant conditions (e.g. hypertension or HF).[78]
- Palpitations independently correlate with a lower risk of cardiovascular events and mortality compared with other symptoms,[79] whereas asymptomatic AF has been associated with a less favourable prognosis.

Stroke and systemic embolism

- Of all patients with an ischaemic stroke, 20–30% would have AF.[80–84] In a pooled analysis of AF RCTs, the incidence of systemic embolism was lower than that of cerebral embolism (0.24 vs. 1.92/100 person-years), comprising 12% of all clinical thromboembolic events, but portending a comparable risk of death as ischaemic stroke (around 60% of systemic embolism involved the lower extremities, 30% the visceral-mesenteric system, and only 11% the upper extremities).[85]

LV dysfunction and HF

- Prevalent HF was reported in 33%, 44%, and 56% of patients with paroxysmal, persistent, and permanent AF, respectively;[86] the incidence of HFrEF or HFpEF LVEF was twofold higher in AF than non-AF patients.[28] AF has been more often related to HFpEF than to HFrEF,[28] but the elevated levels of natriuretic peptide frequently encountered in AF may actually reflect the coexistence of HFpEF.[87] In all recently published HF registries, the epidemiological data about AF in HFmEF suggest that HFmEF is between HFrEF and HFpEF.[88,89]

Hospitalization, QoL, and functional status

- A significant increase in rates of AF-related hospitalization has been reported worldwide.[90,91]
- Reportedly, age was not associated with daily activity scores.[92] Factors associated with worse QoL were new-onset AF, higher heart rate, OSA, symptomatic HF,[93] hypertension, COPD,[94] overweight,[95] and CAD.[92] Reduced QoL was associated with higher risks for hospitalization[73].

- Validation studies showed moderate correlations of the EHRA symptom scale with various AF-specific[73,96] or generalized QoL scales.[97] The well-validated Medical Outcomes Study 36-item Short-Form health survey (SF-36) and EuroQoL-5D (EQ-5D) generalized QoL scales enable comparisons among different conditions and conversion of QoL changes to cost-effectiveness measured by quality-adjusted life years. The true advantage of AF-specific scales requires validation in more RCTs.

Cognitive impairment and dementia

- Observational data suggest that OAC could lower the risk of dementia. NOACs were associated with a reduced risk compared with warfarin in some,[98–101] but not all, studies.[102] It is unclear whether NOACs would reduce the incidence of AF-related cognitive decline, but ongoing RCTs (BRAIN-AF [NCT02387229] and CAF[103]), should provide further insight into this important question. The protective effect of statins[104] and rhythm control therapies also requires confirmation.[105,106]

Mortality

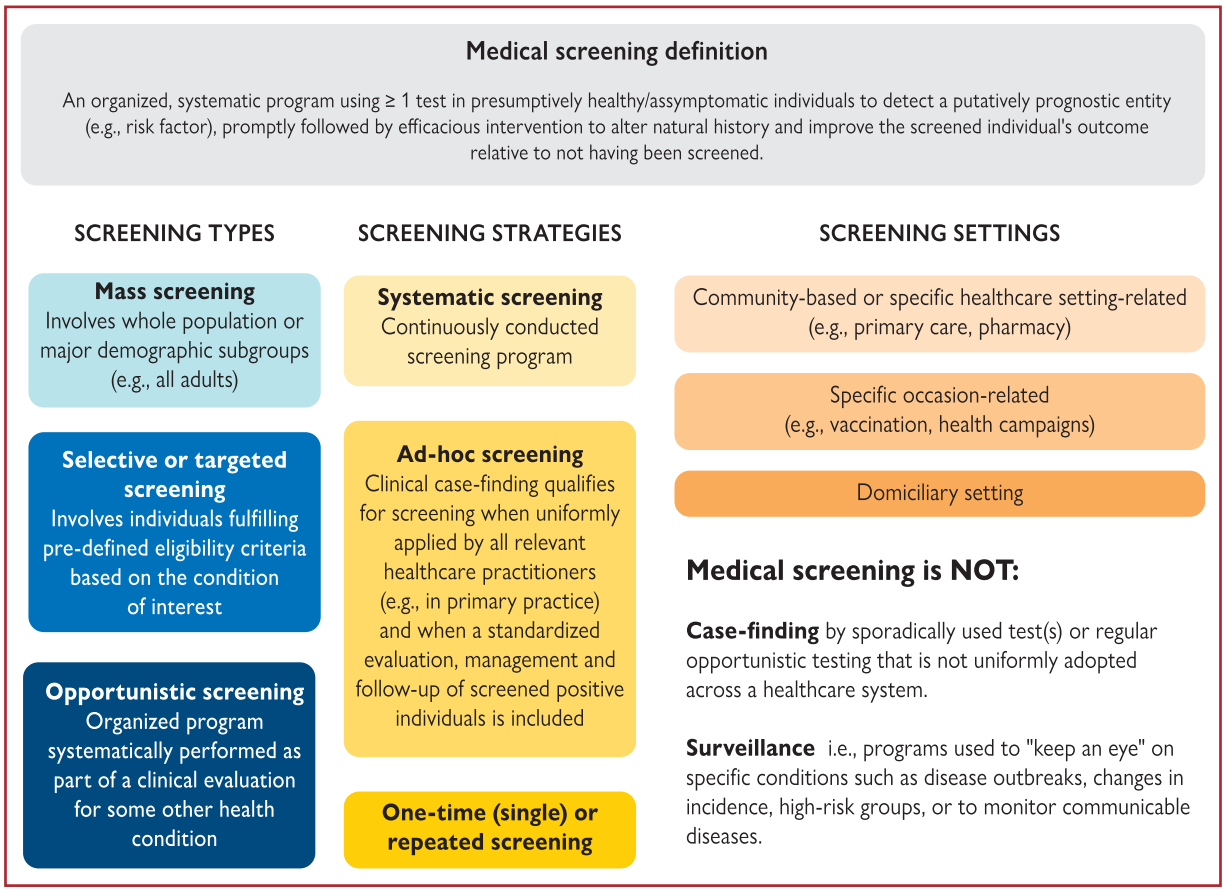
- Comorbidity-adjusted mortality risk was lower in African-American and Hispanic patients compared with white patients with AF,[107] but the difference in all-cause death in AF versus non-AF patients was higher in these ethnic groups.[108] In a Swedish cohort, low educational level or unmarried/divorced men had a higher risk of all-cause death than their more educated or married counterparts.[109] Thirty-day death after first-diagnosed AF was higher than in the following months in another observational study.[110]

AF = atrial fibrillation; BRAIN-AF = Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation; CAF = Cognitive Decline and Dementia in Patients with Nonvalvular Atrial Fibrillation; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; EHRA = European Heart Rhythm Association; EQ-5D-5L = 5-level EQ5D version; HF = heart failure; HFmEF = heart failure with mid-range ejection fraction; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; NOAC = non-Vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; OSA = obstructive sleep apnoea; QoL = quality of life; RCT = randomized controlled trial.

3. Classification of atrial fibrillation

Supplementary Table 3 Clinical types of AF.[111]

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



Supplementary Figure 2 Medical screening: definition, screening types, strategies, and setting.[112]

4 Diagnostic assessment in atrial fibrillation

Supplementary Table 4 QoL and symptom questionnaires

Questionnaire	DescriptionQoL/Symptoms – evaluated in registries	Used in RCT ablation and AAD trials	Advantages	Disadvantages
SF-36 (Short Form Health Survey)[113,114]	QoL. Physical and mental components: 8 equally weighted scores (0 - 100); vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health	Forleo,[115] DiBiase[116] Wilber,[117] Jais[118] Wazni,[119] Walfridsson[120] Singh,[121] AFFIRM[122] Carlsson,[123] Grönefeldt[124] Hagens,[125] Kochhäuser[126] Blomstrom-Lundqvist,[127] Malmborg[128]	Validated in several disease states	Value for cost benefit trials unknown
EQ-5D (EuroQol Five Dimensions Questionnaire)	QoL. Five health-state measures: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Replies in 3 or 5 level scales. Overall health status evaluated by a visual analogue scale (EQ-VAS). EuroHeart Survey[129]	Morillo,[130] Walfridsson,[120] Mortsel[131]	Validated in several diseases, quality-adjusted life-years for cost-utility analysis	

Continued

Supplementary Table 4 *Continued*

Questionnaire	DescriptionQoL/Symptoms – evaluated in registries	Used in RCT ablation and AAD trials	Advantages	Disadvantages
AF specific questionnaire				
AFEQT (AF effect on Quality of Life Survey)[132]	20 items: 4 on AF-related symptoms, 8 on daily function, 6 on AF treatment. 7-point Likert scale. ORBIT-AF,[73] ORBIT-AF[133]		Simple, correlates with EHRA class, compared with AFSS	Limited validation
AF-Qo (Quality of Life Questionnaire for Patients with AF)[134]	18 items on psychological, physical, sexual activity. 5-point Likert scale.	Mont[135]	Simple, validated vs. SF-36	Limited validation
SCL/AF-SC (Arrhythmia-Related Symptom Checklist)	16 items; AF symptom frequency - severity	Wilber,[117] Jais,[118] Singh,[121] AFFIRM,[122] Kochhäuser[126]	Extensively validated, compared with SF-36	Time consuming, applicability?
ASTA (Arrhythmia Specific Questionnaire in Tachycardia and Arrhythmia)[136]	Number of AF episodes, average episode duration over past 3 months. 8 symptoms, 2 disabling symptoms scored 1–4 each	Walfridsson[120]	Simple, validated with symptom checklist, EQ-5D, SF-36	1 validation study
CCS SAF (Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale)[137]	Like EHRA scale. O = asymptomatic, I = AF symptoms minimal effect on patient's QoL, II = AF symptoms minor effect on patient QoL, III = symptoms moderate effect on patient QoL, IV = AF symptoms severe effect on patient QoL		Simple, validated with SF-36 and AFSS	Poor correlation, subjective AF burden; not so specific
AFSS (University of Toronto Atrial Fibrillation Severity Scale)[138]	10 items on frequency, duration, severity. 7-point Likert scale. RECORD-AF[139]	Singh,[121] Vermond,[76] De With[114]	Validated, compared with CCS SAF, and AFEQT	Time consuming, applicability?
MAFSI (Mayo AF Specific Symptom Inventory)[140]	10 items on AF symptoms frequency - severity. 5- point - 3-point Likert scale		Validated in AF ablation trials	Limited external validation; SF-36
EHRA (European Heart Rhythm Association)[96]	EHRA 4 scale: I = no symptoms; II = mild symptoms not affecting daily activity; III = severe symptoms affecting daily activity; and IV = disabling symptoms terminating daily activities. ORBIT-AF,[133] EORP-AF pilot survey,[141] PREFER in AF registry[142]	Blomstrom-Lundqvist,[127] Mortsell,[131] Malmborg[128]	Simple	Limited validation; moderate correlations with AFEQT,[73,96] EQ-5D-5L, PACT-Q[97]
SAS (Specific Activity Scale)	20 items - measures subjective functional capacity, score 0 - 80	Singh[121]		
SSQ, Symptom Severity Score	SSQ 5 AF-related symptoms scored 1 - 5 points	Oral,[143] Mortsell,[131] Malmborg[128]	Simple	Limited validation
AFS/B (Atrial Fibrillation Symptom/Burden)[144]	8 questions on symptoms on daily life. AFS score from 0 - 40. SIX questions relating to AF burden, disease, and healthcare utilization		Simple	Reproducible, correlates with standard QoL measures
AF6 (Atrial fibrillation questionnaire)[145,146]	6 disease-specific questions, scored by a Likert scale 0 - 10 points	Bjorkenheim[147]	Simple	Correlates with SF-36 and AFSS

AAD = antiarrhythmic drug; AE = adverse effects; AF = atrial fibrillation; EORP-AF = EURObservational Research Programme Atrial Fibrillation; ORBIT-AF = Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; QoL = quality of life; RCT = randomized controlled trial; RECORD-AF = Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation; NYHA = New York Heart Association; PREFER in AF = PREvention oF thromboembolic events – European Registry in Atrial Fibrillation.

5 Technology tools supporting management of atrial fibrillation

Supplementary Table 5 **Studies on decision tools and applications available for healthcare professionals**

Author, year, country(ies)	Study population	Study design	Target of study	Intervention(s)/ tool	Comparator	Outcomes measured	Results	Other important information
Thomson et al. 2007 UK[148] **DARTS-II**	109 pts, mean age 73 years, 44.3% women	RCT	Antithrombotic treatment	CDSS applied as a shared-decision-making tool	Evidence-based paper guidelines	Decision conflicts	Lower decision conflict with CDSS	Patients in CDSS group less likely to start warfarin
Rosier et al. 2016, France[149] **AKENATON**	60 patients	Retrospective analysis	Automatic classification of AF alerts remotely received from permanent pacemakers	AI automatically implemented to filter AF alerts based on their medical significance	-	Adequate classification of remote AF alerts	98% adequate classification of AF alerts	84% reduction in the workload of remote monitoring of AF alerts
Eckman et al. 2016 USA & UK[150] **AFDST**	1493 patients, mean age 70 years, women 44%	RCT	Antithrombotic therapy	AFDST	Control practices	Proportion of patients with antithrombotic therapy that was discordant from AFDST recommendation	Rate of discordant therapy decreased significantly over 1 year	In non-stratified analyses, the intervention did not result in significant improvements in discordant antithrombotic therapy
Eckman et al. 2018 USA[151] **AFSDM**	76 patients, mean age 65.7 years, women 35%	Observational	Shared decision-making	AFSDM	-	Improvement in decision conflicts with implementation of AFSDM	Decisional conflicts decreased significantly	AFSDM significantly improved multiple measures of decision-making quality, leading to improved medication adherence and patient satisfaction
Karlsson et al. 2018, Sweden[152] **CDS-AF**	13 379	RCT	Stroke prevention	CDS for stroke prevention	Control group	Adherence to guidelines for stroke prevention	CDS increased guideline adherence for OAC in patients with AF	Moderate benefits of the CDS were encountered

AF = atrial fibrillation; AFDST = Atrial fibrillation Decision Support tool; AFSDM = Atrial fibrillation shared decision-making tool; AI = artificial intelligence; CDS = clinical decision support; CDS-AF = Clinical Decision Support for Atrial Fibrillation; CDSS = computerized decision support system; DARTS = Decision Analysis in Routine Treatment Study; OAC = oral anticoagulant; RCT = randomized controlled trial.

Supplementary Table 6 Decision tools and applications available for healthcare professionals

Target	Decision tools or Apps
Information on AF	ESC/CATCH-ME Healthcare Professional App,[153] mAFA[154]
Evaluation of AF symptoms	ESC/CATCH-ME Healthcare Professional App,[153] mAFA[154]
Clinical decision support	ESC/CATCH-ME Healthcare Professional App,[153] DARTS II,[148] IMPACT-AF,[155] mAFA[154]
Evaluation of stroke risk	AKENATON,[149] AFSDM,[150,151] CDS-AF,[152] mAFA[154]
Monitoring of therapy adherence and effectiveness	AFSDM,[150,151] CDS-AF,[152] mAFA[154]

AF = atrial fibrillation; AFSDM = Atrial Fibrillation Shared Decision Making; App = application; CATCH-ME = Characterising AF by Translating its Causes into Health Modifiers in the Elderly; CDS-AF = Clinical Decision Support for Atrial Fibrillation; DARTS = Decision Analysis in Routine Treatment Study; ESC = European Society of Cardiology; IMPACT-AF = Integrated Management Program Advancing Community Treatment of Atrial Fibrillation; mAFA = mobile AF App.

6 Advantages of integrated management of atrial fibrillation patients

Supplementary Table 7 Studies investigating integrated management of AF compared with usual care

Author, year, country	Study design, population, and setting	Intervention	Comparator	Outcomes measured and results
Cox et al., 2020,[156] Canada **IMPACT-AF**	RCT: 1133 patients, mean age 72 years; 432 (39.1%) women Primary care stratified by urban vs. rural practice setting 12-month follow-up	CDSS, incorporating guideline-based physician monitoring system and optional patient self-monitoring system (n=590)	Usual care (n=543)	Efficacy: composite of unplanned emergency department visit or cardiovascular hospitalization 20.0% vs. 23.9% (CDSS vs. usual care) HR 1.06 (95% CI 0.77 - 1.47); *P*=0.71 Safety: ISTH major bleeding 1.3% vs. 1.3% (CDSS vs. usual care) HR 1.04 (95% CI 0.38 - 2.88); *P*=0.94
Wijtvliet et al., 2019,[157] The Netherlands	RCT: 1375 patients, mean age 64 years; 460 (34%) women Nurse-led care vs. usual-care	Specialized nurses using a CDSS, in consultation with the cardiologist (n=671)	Usual care (n=683)	Primary endpoint: composite of cardiovascular death and cardiovascular hospital admissions 9.7% per year vs. 11.6% per year (nurse-led vs. usual care) HR 0.85 (95% CI 0.69−1.04); *P*=0.12
Vinereanu et al., 2017,[158] Argentina, Brazil, China, India, Romania **IMPACT-AF**	Cluster RCT: 2281 patients, mean age 70 years; 1079 (47.3%) women Follow-up 12 months Research institutes or university hospitals	Patient and HCP education, with regular monitoring and feedback to HCPs (n=1184)	Usual care (n=1092)	Change in proportion of patients on OAC at 1-year Intervention: 68% to 80% Usual care: 64% to 67% OR 3.28 (95% CI 1.67−6.44) for OAC use between groups
Carter et al., 2016[159] Canada	Before-and-after study: 433 patients, newly diagnosed AF, mean age 64 years; 44% women Follow-up minimum 12-months Emergency department (before-phase) Tertiary hospital (after-phase)	"After" phase (November 2011-September 2013): nurse-run, physician-supervised AF clinic (n=185); group education session on symptoms, investigations, and AF treatments	"Before" phase (January 2009-October 2011): usual-care pathway for AF management (n=228)	Composite of death, cardiovascular hospitalization, and AF-related emergency department visits: 17.3% vs. 26.2% (intervention vs. usual care) OR 0.71 (95% CI 0.59 - 1.00); *P*=0.049

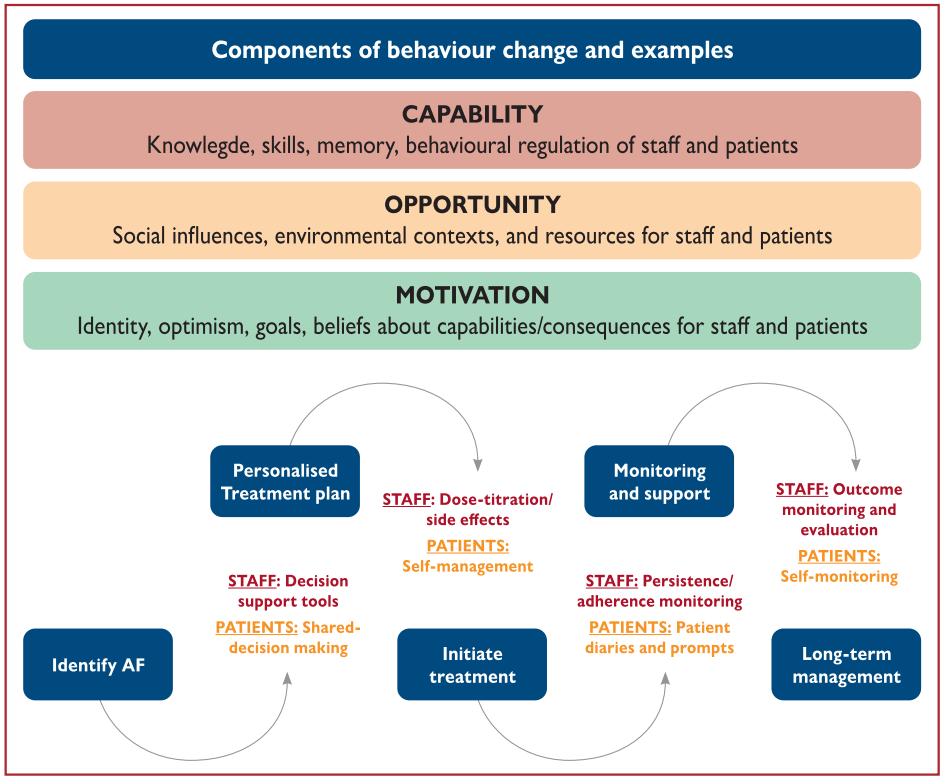
Continued

Supplementary Table 7 *Continued*

Author, year, country	Study design, population, and setting	Intervention	Comparator	Outcomes measured and results
Stewart et al. 2015,[160] Australia **SAFETY**	RCT: 335 patients, mean age 72 years, 161 (48.1%) women Mean follow-up: 30 months Hospitalized with AF	Home visit, Holter monitoring (7–14 days post-discharge) by cardiac nurse, prolonged follow-up, MDT support as needed (n=168)	Usual care (n=167)	Coprimary outcomes: death or unplanned readmission 76% vs. 82% (intervention vs. usual care) HR 0.97 (95% CI 0.76 - 1.23); *P*=0.85
Hendriks et al. 2012,[161] The Netherlands	RCT: 712 patients, mean age 67 years, 294 (41.3%) women Mean follow-up: 22 months Outpatient clinic at 1 hospital	Nurse-led AF (n=356) including decision support software based on clinical guidelines and supervised by a cardiologist	Usual care (n=356) Cardiologist only	Primary endpoint: Composite of cardiovascular hospitalization or cardiovascular death 14.3% vs. 20.8% (nurse-led vs. usual care) HR 0.65 (95% CI 0.45–0.93); *P*=0.017 Adjusted HR 0.63 (95% CI 0.44–0.90)

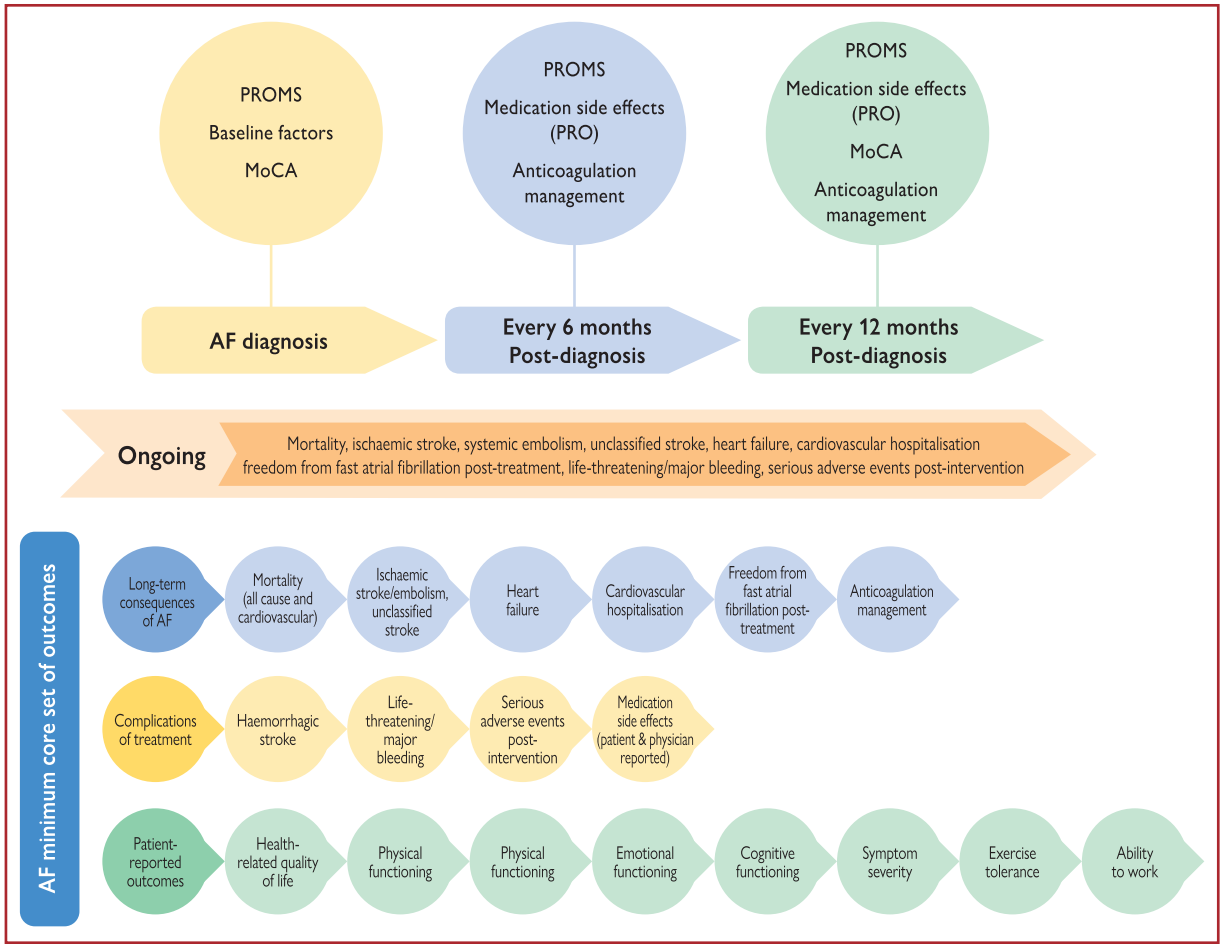
AF = atrial fibrillation; CDSS = Clinical Decision Support System; CI = confidence interval; HCP = healthcare professional; HR = hazard ratio; IMPACT-AF = Integrated Management Program Advancing Community Treatment of Atrial Fibrillation; ISTH = International Society on Thrombosis and Haemostasis; MDT = multidisciplinary team; *n* = number of patients with available data; OAC = oral anticoagulant; OR = odds ratio; RCT = randomized controlled trial; SAFETY = Standard versus Atrial Fibrillation-specific Management Strategy

7 Measures (or approaches) for implementation of integrated management



Supplementary Figure 3 Capability Opportunity Motivation and Behaviour (COM-B) model applied to the development of a comprehensive, integrated, intervention strategy for the management of AF patients. To design comprehensive, integrated, intervention strategies for AF management, Michie et al's Behaviour Change Wheel[162] and associated theory could be used to facilitate structured identification of behaviour-change approaches required to implement the current evidence. In tailoring and implementing AF-management pathways, consideration should be given to contextual issues of capability, opportunity, and motivation for both staff and patients. AF = atrial fibrillation.

8 Patient-reported outcomes



Supplementary Figure 4 AF minimum core set of outcomes and timeline for collection.[382] AF = atrial fibrillation; MoCA = Montreal Cognitive Assessment; PRO = patient-reported outcome; PROMS = patient-reported outcome measures. (See full text, Seligman WH et al., 2020; Eur. Heart J.)

9 Anticoagulation/avoid stroke

Supplementary Table 8 Clinical trial data with NOACs.

Non-inferiority RCT assessing safety and efficacy of NOACs vs. warfarin[111]	RE-LY[163]			ROCKET AF[164]		ARISTOTLE[165]		ENGAGE AF-TIMI 48[166]		
	Warfarin *n* = 6022 Event rate, %/year	Dabigatran 150 *n* = 6076 Event rate, %/year (RR vs. warfarin)	Dabigatran 110 *n* = 6015 Event rate, %/year (RR vs. warfarin)	Warfarin *n* = 7133 Event rate, %/year	Rivaroxaban *n* = 7131 Event rate, %/year (HR vs. warfarin)	Warfarin *n* = 9081 Event rate, %/year	Apixaban *n* = 9120 Event rate, %/year (HR vs. warfarin)	Warfarin *n* = 7036 Event rate, %/year	Edoxaban 60 *n* = 7035 Event rate, %/year (HR vs. warfarin)	Edoxaban 30 *n* = 7034 Event rate, %/year (HR vs. warfarin)
Stroke/systemic embolism	1.72	1.12 (0.65, 0.52–0.81; *P* for non-inferiority and superiority <0.001)	1.54 (0.89, 0.73–1.09; *P* for non-inferiority <0.001)	2.40	2.1 (0.88, 0.75–1.03; *P* for non-inferiority <0.001, P for superiority = 0.12)	1.60	1.27 (0.79, 0.66–0.95; *P*<0.001 for non-inferiority, *P* = 0.01 for superiority)	1.80	1.57 (0.87, 0.73–1.04; *P*<0.001 for non-inferiority, *P* = 0.08 for superiority)	2.04 (1.13, 0.96–1.34; *P* = 0.005 for non-inferiority, *P* = 0.10 for superiority)
Ischaemic stroke	1.22	0.93 (0.76, 0.59–0.97; *P* = 0.03)	1.34 (1.10, 0.88–1.37; *P* = 0.42)	1.42	1.34 (0.94; 0.75–1.17; *P* = 0.581)	1.05	0.97 (0.92, 0.74–1.13; *P* = 0.42)	1.25	1.25 (1.00, 0.83–1.19; *P* = 0.97)	1.77 (1.41, 1.19–1.67; *P*<0.001)
Haemorrhagic stroke	0.38	0.10 (0.26, 0.14–0.49; *P*<0.001)	0.12 (0.31, 0.17–0.56; *P*<0.001)	0.44	0.26 (0.59; 0.37–0.93; *P* = 0.024)	0.47	0.24 (0.51, 0.35–0.75; *P*<0.001)	0.47	0.26 (0.54, 0.38–0.77; *P*<0.001)	0.16 (0.33, 0.22–0.50; *P*<0.001)
Major bleeding	3.61	3.40 (0.94, 0.82–1.08; *P* = 0.41)	2.92 (0.80, 0.70–0.93; *P* = 0.003)	3.45	3.60 (1.04; 0.90-2.30; *P* = 0.58)	3.09	2.13 (0.69, 0.60–0.80; *P*<0.001)	3.43	2.75 (0.80, 0.71–0.91; *P*<0.001)	1.61 (0.47, 0.41–0.55; P<0.001)
Intracranial bleeding	0.77	0.32 (0.42, 0.29–0.61; *P*<0.001)	0.23 (0.29 0.19–0.45; *P*<0.001)	0.74	0.49 (0.67; 0.47–0.93; *P* = 0.02)	0.8	0.33 (0.42, 0.30–0.58; *P*<0.001)	0.85	0.39 (0.47, 0.34–0.63; *P*<0.001)	0.26 (0.30, 0.21–0.43; *P*<0.001)
Gastrointestinal major bleeding	1.09	1.60 (1.48, 1.19–1.86; *P*<0.001)	1.13 (1.04, 0.82–1.33; *P* = 0.74)	1.24	2.00 (1.61; 1.30 - 1.99; *P*<0.001)	0.86	0.76 (0.89, 0.70–1.15; *P* = 0.37)	1.23	1.51 (1.23, 1.02–1.50; *P* = 0.03)	0.82 (0.67, 0.53–0.83; *P*<0.001)
Myocardial infarction	0.64	0.81 (1.27, 0.94 - 1.71; *P* = 0.12)	0.82 (1.29, 0.96 - 1.75; *P* = 0.09)	1.12	0.91 (0.81; 0.63–1.06; *P* = 0.12)	0.61	0.53 (0.88, 0.66–1.17; *P* = 0.37)	0.75	0.70 (0.94, 0.74–1.19; *P* = 0.60)	0.89 (1.19, 0.95–1.49; *P* = 0.13)
Death from any cause	4.13	3.64 (0.88, 0.77–1.00; *P* = 0.051)	3.75 (0.91, 0.80–1.03; *P* = 0.13)	2.21	1.87 (0.85; 0.70–1.02; *P* = 0.07)	3.94	3.52 (0.89, 0.80–0.99; *P* = 0.047)	4.35	3.99 (0.92, 0.83–1.01; P = 0.08)	3.80 (0.87, 0.79–0.96; *P* = 0.006)

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 18 = Effective aNticoaGulation with factor XA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48; HR = hazard ratio; NOAC = non-vitamin K antagonist oral anticoagulant; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-Term Anticoagulation 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; RR = relative risk.

Supplementary Table 9 **Clinical pharmacology of NOACs.**

		Dabigatran[163,167,168]	Rivaroxaban[164,169-171]	Apixaban[169]	Edoxaban[166,169,172-174]
Mechanism		Oral direct reversible competitive thrombin antagonist	Oral direct reversible competitive factor Xa antagonist	Oral direct reversible competitive factor Xa antagonist	Oral direct reversible competitive factor Xa antagonist
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (~25%)	Yes (~25%)	No (<4%)
Metabolism		Glucuronic acid conjugation	CYP3A4, CYP2J2	CYP3A4/5, CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2J2	CYP3A4/5
Bioavailability (%)		3–7%	15 mg/20 mg: 66% without food, 80–100% with food	50%	62%
Prodrug		Yes	No	No	No
Time to peak levels (h)		3	2–4	3	1–2
Elimination half-life (h)		12–17	5–9 (young)	12	10-14
Plasma protein binding (%)			11–13 (elderly)		
Clearance non-renal/ renal of absorbed dose (%)		35%	95%	87%	55%
Dialysability (%)		50–60% (in part dialysable)	N.A. (in part dialysable)	14% (in part dialysable)	N.A. (in part dialysable)
Clearance non-renal/ renal of absorbed dose (%)		20%/80%	65%/35%	73%/27%	50%/50%
Liver metabolism: CYP3A4 involved		No	Yes (hepatic elimination 18%)	Yes [elimination, moderate contribution (25%)]	Minimal (<4% of elimination)
Absorption with food		No effect	Plus 39% more	No effect	6–22% more; minimal effect on exposure
Absorption with H2B/ PPI/Al-Mg hydroxide		Decreased AUC (-12 to 30%) not clinically relevant	No effect	No effect	No effect
Asian ethnicity		Plus 25%	No effect	No effect	No effect
eGFR category	>95 mL/min	2x 150 mg	20 mg	2 x 5 mg/2 x 2.5 mg (see dose reduction below)	60 mg (use with caution in 'supranormal' renal function)
	50-94 mL/min				60 mg (see dose reduction below)
	30-49 mL/min	2 x 150 mg/2 x 110 mg (high bleeding risk)	15 mg		30 mg (see dose reduction below)
	15-29 mL/min	Do not use	15 mg (use with caution)	2 x 2.5 mg (use with caution)	30 mg (use with caution)
	Dialysis	Do not use	Do not use	Do not use	Do not use
Child-Pugh category	A	No dose reduction required	No dose reduction required	No dose reduction required	No dose reduction required
	B	Use with caution	Do not use	Use with caution	Use with caution
	C	Do not use	Do not use	Do not use	Do not use

Supplementary Table 9 **Continued**

	Dabigatran[163,167,168]	Rivaroxaban[164,169-171]	Apixaban[169]	Edoxaban[166,169,172-174]
Dose reduction in selected patients	Age ≥80 years	Rivaroxaban 15 mg once daily if CrCl 30-49 mL/min	Apixaban 2.5 mg twice daily. if at least 2 of age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L)	Edoxaban 60 mg reduced to 30 mg once daily, and edoxaban 30 mg reduced to 15 mg once daily, if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)[a]				
Expected range of plasma levels at peak for standard dose (ng/mL)	64–443	184–343	69–321	91–321
Expected range of plasma levels at trough for standard dose (ng/mL)	31–225	12–137	34–230	31–230
Expected impact of NOACs on routine coagulation tests[a]				
PT	↑	↑↑(↑)	(↑)	↑(↑)
aPTT	↑↑(↑)	↑	(↑)	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	-	-	-

ACT = activated clotting time; aPTT = activated thromboplastin time; AUC = area under the curve; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; NOAC = non-vitamin K antagonist oral anticoagulant; PT = prothrombin time; TT = thrombin time.

[a]Ranges indicate the P5/95 percentiles for dabigatran, rivaroxaban, and apixaban, and the interquartile ranges for edoxaban.

10 Procedure-related complications in catheter ablation of atrial fibrillation

Supplementary Table 10 **Procedure-related complications in catheter ablation of AF**

Complication	Incidence	Time of presentation	Symptoms and signs	Diagnostic testing	Management options
Procedure-related death	<0.1 - 0.4%				
Life-threatening					
Cardiovascular					
Cardiac perforation/ tamponade	0.5 - 1.3%	Early/late	Chest pain, dizziness, syncope, hypotension	Echocardiography	Pericardiocentesis; surgical drainage
Coronary artery stenosis/ occlusion	0 - 0.07%		Chest pain, shortness of breath	Coronary angiography	Percutaneous transluminal coronary angioplasty
Pericarditis	0 - 3.1%	Early	Chest pain, fever	Anamnesis, ECG, sedimentation rate, echocardiography	Non-steroid anti-inflammatory, colchicine, steroids
Stiff left atrial syndrome	<1.5%	Early	Dyspnoea, congestive heart failure	Echocardiography, cardiac catheterisation	Diuretics
Significant bradycardia	0.1 - 0.4%	Early	Dyspnoea, exercise intolerance, dizziness, syncope	Anamnesis, ECG	Pacemaker implantation
Mitral valve damage	<0.1%	Early	Acute dyspnoea, tachypnoea; none	Echocardiography	Gentle catheter manipulation; surgical extraction
Coronary air embolism	<1%0.1 - 0.2%	Early	Chest pain, hypotension	Nothing or coronary angiography	Supportive care (fluid, oxygen, head down tilt, hyperbaric oxygen)
Neurological					
Asymptomatic cerebral embolism	2 - 10.5%	Early	None	Brain MRI	None
Radiation injury	<0.1%	Both	Skin injury, malignancy, genetic abnormalities	None	Supportive care (rarely skin graft)
Stroke	0.1 - 0.6%	Both	Neurological symptoms	Brain CT/MRI; cerebral angiography	Thrombolytic therapy, angioplasty
Transient ischemic attack	0.2 - 0.4%	Early	Neurological symptoms	Brain CT/MRI; cerebral angiography	Anticoagulation
Permanent phrenic nerve injury	0 - 0.4%	Both	Shortness of breath	Chest X-ray, sniff test	Supportive care
Gastrointestinal					
Oesophageal injury	0.1 - 20%	Early	Dysphagia	Endoscopy	Proton-pump inhibitors
Gastric hypomotility/ pyloric spam disorders	0 - 23.8%	Early	Early satiety, nausea, bloating	Endoscopy, barium swallow, gastric emptying study	Metoclopramide; possibly, i.v. erythromycin
Oesophageal fistula or perforation	0 - 0.15%	Late	Fever, chest pain, dysphagia, neurological symptoms, haematemesis	Chest CT/MRI; avoid endoscopy with air insufflation	Surgical repair, covered stents, clinical support (enteral nutrition, antibiotics)
Vascular/peripheral					
Hematoma or bleeding requiring evacuation or transfusion	0.4 - 3.9%	Early	Groin pain at site of vascular access, local swelling	Vascular ultrasound, CT scan	Conservative treatment, transfusion, percutaneous repair, surgical repair
Arteriovenous fistula	0.4 - 1.1%	Early	Groin pain and swelling at site of vascular access	Vascular ultrasound, CT scan	Conservative treatment, transfusion, percutaneous repair, surgical repair

Continued

Supplementary Table 10 *Continued*

Complication	Incidence	Time of presentation	Symptoms and signs	Diagnostic testing	Management options
Pseudoaneurysm	0.2 - 1%	Early	Groin pain and swelling at site of vascular access	Vascular ultrasound, CT scan	Conservative treatment, transfusion, percutaneous repair, surgical repair
Pulmonary					
Pulmonary vein stenosis/ occlusion	0 - 1.1%	Both	Persistent cough, atypical chest pain, haemoptysis, shortness of breath	Chest CT/MRI, ventilation/ perfusion lung scan	Angioplasty, stent; surgery

CT = computed tomomgraphy; ECG = electrocardiogram; i.v. = intravenous; MRI = magnetic resonance imaging;

Supplementary Table 11 **Risk scores for prediction of recurrence after AF ablation**[383]

	Age	Sex	LA size	AF type	eGFR	EF	CAD	HT	Diabetes/ metabolic syndrome	ERAF	Smoking	BMI	Drugs failed	Prolonged QRS duration
CHA_2DS_2-VASc[175]	X	X				X	X	X	X					
Apple[176]	X		X	X	X	X								
DR-FLASH[177]	X	X	X	X	X			X	X					
MB-LATER[178]		X	X	X						X				X
ATLAS[179]	X	X	X	X							X			
CAAP-AF[180]	X	X	X	X			X						X	
BASE-AF2[181]			X	X						X	X	X		
ALARMEc[182]			X	X	X	X			X					

AF = atrial fibrillation; ALARMEc = Atrial fibrillation type, Left Atrium size, Renal insufficiency, Metabolic syndrome, cardiomyopathy (risk score); BASE-AF = Body mass index > 28 kg/m^2 (1), Atrial dilatation > 40 mm (1), current Smoking (1), Early recurrence (E), duration of AF history > 6 years (1) and non-paroxysmal type (1) of AF; BMI = body mass index; CAAP-AF = Presence or absence of CAD, left Atrial diameter, Age, the presence of Persistent or long-standing AF, the number of Antiarrhythmic drugs failed and Female sex (score); CAD = coronary artery disease; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); DR-FLASH = Diabetes mellitus, Renal dysfunction, persistent form of AF, LA diameter >45 mm, Age >65 years, female Sex and Hypertension (score); EF = ejection fraction; eGFR = estimated glomerular filtration rate; ERAF = early recurrent atrial fibrillation; HT = hypertension; LA = left atrium; MB-LATER = Male gender, Bundle branch block, Left Atrium dilatation ≥47 mm, Type of AF (paroxysmal, persistent or long-standing persistent) and Early recurrent AF (score).

11 Risk assessment for recurrence of atrial fibrillation post catheter ablation

Supplementary Box 2. Modifiable risk factors and impact on AF ablation outcome

Hypertension is a strong, independent predictor of AF recurrence after ablation, particularly if uncontrolled.[183–187] Small trials using renal sympathetic denervation suggest that this technique may be useful for sustained BP reduction and reducing recurrences after ablation.[188–193] However, aggressive BP control with pharmacological treatment failed to reduce recurrences after catheter ablation,[194] but the treatment duration in this study was short (0 - 6 months before and ≤3 months after the procedure). Longer periods may be needed for reverse remodelling and outcome improvement.[195,196]

Obesity is increasingly recognised as a risk factor for AF recurrence after ablation.[184,197–205] A meta-analysis of 16 observational studies (n = 5864) revealed a 13% greater post-ablation AF recurrence for every 5-unit increase in body mass index (odds ratio 1.13; 95% confidence interval 1.06 - 1.22).[205] These findings were later supported by large international cohorts.[202,203,205] There is less information on the effect of weight control on improving the results of AF catheter ablation, but observational data suggest that weight and other risk-factor management improve symptoms and arrhythmia-free survival after AF ablation.[206]

OSA is associated with lower arrhythmia-free survival after AF ablation, independently of obesity and LA size.[197,207–215] Patients with OSA have a higher prevalence of non-pulmonary vein triggers and show a more complex substrate.[216,217] However, the effect on ablation outcomes of treating OSA has not been well established, with observational studies reporting conflicting results.[197,207,211,212,214,215,218] RCTs in the context of AF catheter ablation are needed; in electrical cardioversion, no significant benefit was found in patients randomized to positive airway pressure treatment.[219]

AF = atrial fibrillation; BP = blood pressure; LA = left atrial; OSA = obstructive sleep apnoea; RCT = randomized controlled trial.

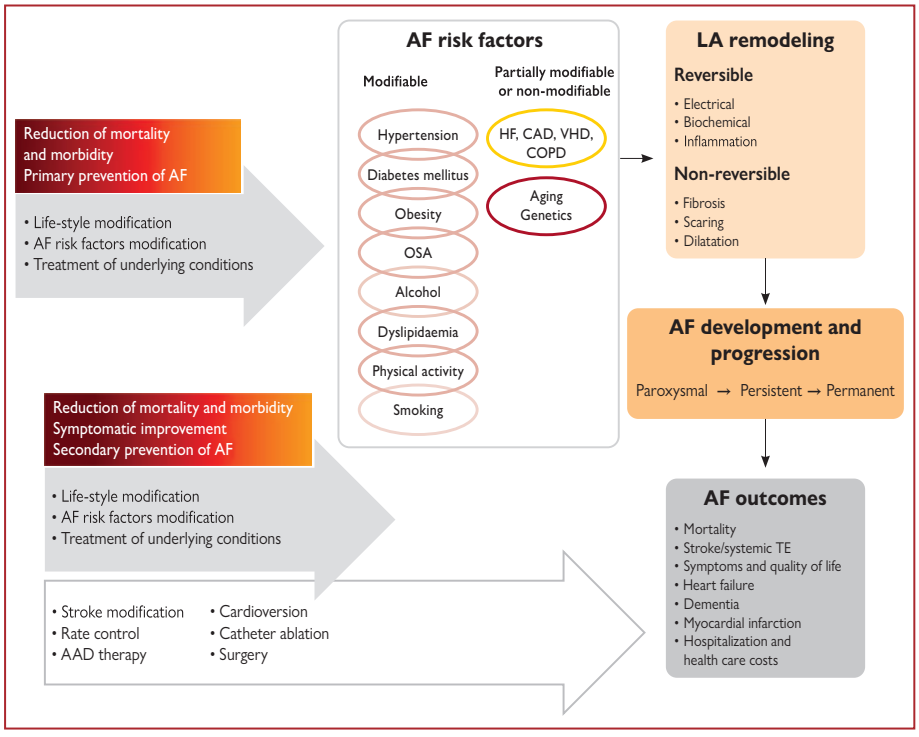
12 Long-term antiarrhythmic drug therapy for rhythm control

Supplementary Box 3. New investigational AADs

- Classic AADs are imperfect, as they mainly affect pure electrophysiological properties and not the arrhythmia-vulnerable parameters.
- New drugs are continuously developing in parallel with increasing knowledge, but a huge gap exists between currently available AADs and contemporary practical expectations.[220] Some atrial-specific targeted molecules can directly interfere with vulnerable components of AF with increased safety as they are deprived of proarrhythmic ventricular effects.
- Drugs blocking the potassium ultra-rapid current (I_{KUR}) gave disappointing results because of paradoxical shortening of APD and downregulation in AF patients.[221,222] TASK-1, a member of the two-pore-domain potassium current, is abundant in human atria but not in the ventricles, and is up-regulated in AF.[223,224] Several classic AADs (amiodarone, dronedarone, carvedilol) are non-selective TASK-1 blockers, but TASK-1 currents are reduced (and not increased) in AF patients with HF,[223] thus limiting this approach for AF patients with structurally remodelled atria.
- Unlike sinus rhythm, there is a receptor-independent 'constitutive' acetylcholine ($I_{K,Ach}$) current component, causing a re-entry-promoting atrial refractoriness shortening in AF.[220,225–227] However, targeting this current is still of unproven clinical efficacy.
- Calcium handling is importantly perturbed in AF patients.[228–230] Among other effects, the small-conductance calcium-dependent potassium channels (SK channels) are activated, contributing to AF-related APD shortening[231] and triggered activity in AF. Several molecules were synthetized to modulate the calcium sensor of SK channels or to block the pore of the SK channels.[232] Other molecules interfere with intracellular calcium dynamics targeting Ca^{2+}-calmodulin–dependent protein kinase activity[233] or ryanodine receptors.[221]
- Some specific non-coding microRNAs are involved in atrial fibrosis and electrical remodelling in AF and represent attractive targets for new AAD therapies.[234] New mechanistic discoveries are expected to drive the development of antiarrhythmic approaches traditionally not considered effective in arrhythmias. Recent work identified the contribution of the inflammatory signalling (NLRP3 inflammasome) system to electrical and structural atrial remodelling which promotes AF induction, maintenance, and progression.[235]

AAD = antiarrhythmic drug; AF = atrial fibrillation; APD = action potential duration; HF = heart failure; TASK 1 = member of two-pore domain potassium current; RNA = ribonucleic acid.

13 'C' – Cardiovascular risk factors and concomitant diseases – detection and management



Supplementary Figure 5 Role of risk factors and underlying conditions in the management of AF. AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LA = left atrium; OSA = obstructive sleep apnoea; TE = thromboembolism.

14 Cryptogenic stroke/embolic stroke with undetermined source

Supplementary Box 4. Cryptogenic stroke and ESUS

About one in four ischaemic strokes remains of undetermined source (i.e. cannot be attributed to definite cardiac embolism, large-artery atherosclerotic disease, or small-artery disease) and are termed cryptogenic strokes.[236]

ESUS is a subcategory of cryptogenic stroke. Approximately one in six ischaemic strokes may qualify as ESUS, after a standardized diagnostic pathway (including brain imaging, echocardiography, cardiac rhythm monitoring for ≥24 h, and imaging of the arteries supplying the affected brain area) shows that the stroke is not lacunar, there is no significant (≥50%) stenosis in the arteries supplying the area of ischaemia or a major-risk cardioembolic source such as AF, sustained AFL, intra-cardiac thrombus, prosthetic cardiac valve, cardiac tumours, mitral stenosis, recent (<4 weeks) myocardial infarction, LVEF <30%, valvular vegetations or infective endocarditis, and no other specific cause of stroke is identified (e.g. arteritis, dissection, migraine, vasospasm, drug misuse).[237,238]

Clinical characteristics of ischaemic strokes of uncertain aetiology often resemble embolic strokes, and trials such as EMBRACE[239], CRYSTAL AF,[80] and FIND-AF[240] showed that AF can be detected in many cases of cryptogenic stroke, depending on the duration of monitoring. These findings have important treatment implications, as stroke patients diagnosed with AF should be offered stroke prevention using OAC therapy.

Many patients have paroxysmal, often asymptomatic, AF that may not be captured during routine post-stroke assessment. Indeed, AF detection rates depend on the mode and duration of post-stroke monitoring (i.e. 'look harder, look longer, and use more sophisticated monitoring tools'). For example, sequential, multiphase, post-stroke cardiac monitoring starting from admission 12-lead ECG in the emergency room, over in-hospital monitoring to post-discharge ambulatory monitoring, yielded 23.7% newly diagnosed cases of AF.[241]

The NAVIGATE ESUS[242] and RE-SPECT ESUS[243] RCTs investigated the use of a NOAC (rivaroxaban 15 mg o.d and dabigatran 150 mg or 110 mg b.i.d., respectively) vs. aspirin 100 mg daily in ESUS patients without documented AF between 7 days and 6 months post stroke (NAVIGATE ESUS) or ≤3 months after acute presentation (RE-SPECT ESUS). Neither NOAC was superior to aspirin in the reduction of recurrent ischaemic stroke, but rivaroxaban was associated with significantly higher rates of major bleeding (1.8% vs. 0.7%, HR 2.72, 95% CI 1.68 - 4.39; $P<0.001$), and dabigatran use was associated with higher rates of clinically relevant non-major bleeding (1.6% vs. 0.9%). These RCTs showed that the use of NOACs for prevention of recurrent ischaemic stroke in patients with ESUS without documented AF is not justified.

Subgroup analyses of those two RCTs suggested that certain subgroups (i.e. ≥75 years' old or with impaired renal function[243] or with enlarged LA[244]) 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 (the ATTICUS[245] and ARCADIA [NCT03192215] trials).

AF = atrial fibrillation; AFL = atrial flutter; ARCADIA = AtRial Cardiopathy *and* Antithrombotic Drugs in Prevention After Cryptogenic Stroke; ATTICUS = Apixaban for Treatment of Embolic Stroke of Undetermined Source; b.i.d. = *bis in die* (twice a day); CI = confidence interval; CRYSTAL AF = CRYptogenic STroke And underLying Atrial Fibrillation; ECG = electrocardiogram; EMBRACE = 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event; ESUS = embolic stroke of undetermined source; ESUS = embolic stroke of undetermined source; FIND-AF = Finding Atrial Fibrillation in Stroke; HR = hazard ratio; LA = left atrium; NAVIGATE ESUS = New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial vs. ASA to Prevent Embolism in Embolic Stroke of Undetermined Source; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d = *omni die* (once daily); RCT = randomized controlled trial; RE-SPECT ESUS = Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source; RCT = randomized controlled trial.

15 Management of patients with atrial fibrillation post-intracranial haemorrhage

Supplementary Box 5. Management of patients with AF after ICH

- Spontaneous ICH is responsible for 1 in 10 strokes. However, about 50% of patients were taking an antithrombotic drug at the time of ICH.[246]
- ICH survivors with AF are at risk of ischaemic stroke, but also of recurrent ICH. Whereas the risk of ischaemic stroke depends on the presence of associated clinical stroke risk factors and can be assessed using the CHA_2DS_2-VASc score, the risk of recurrent ICH is highly variable (1.3 - 7.4% in observational studies[247]) and multifactorial.
- Observational studies show that in selected AF patients who survived ICH, ischaemic stroke and mortality rates were significantly lower on OAC use[247,249] not necessarily increasing the risk of haemorrhagic events including recurrent ICH.[250]
- Notably, in patients with a traumatic ICH, OAC (re)initiation was associated with a reduction in subsequent ischaemic stroke and mortality without an increase in recurrent ICH.[251] In contrast, OAC use in AF patients with a non-traumatic ICH can be associated with increased ICH recurrence rates, especially if cerebral imaging shows evidence of cerebral microbleeds.[252]
- A meta-analysis of seven observational studies of AF patients who survived an ICH (n = 2452) showed that in those subsequently not taking any antithrombotic treatment, the rates of ischaemic stroke were higher than the rates of recurrent ICH,[253] as shown below.

Follow-up 6 weeks to 1 year after index ICH	Ischaemic stroke		Recurrent ICH	
	Event rate	95% CI	Event rate	95% CI
No antithrombotic therapy	6.1	4.9 - 7.6	4.2	3.2 - 5.5
Antiplatelet therapy	9.5	7.3 - 12.0	3.7	2.5 - 5.4
VKA	3.2	2.0 - 4.9	4.6	3.1 - 6.6
No VKA (antiplatelets or no antithrombotic therapy)	7.3	6.2 - 8.5	4.0	3.2 - 5.0
	Rate ratio	**95% CI**	**Rate ratio**	**95% CI**
VKA versus no antithrombotic therapy	0.47	0.29 - 0.77	0.93	0.45 - 1.90
Antiplatelet versus no antithrombotic therapy	1.06	0.72 - 1.54	0.77	0.47 - 1.25
VKA versus antiplatelet therapy	–	–	1.34	0.79 - 2.30

- Another systematic review and meta-analysis also showed that restarting OAC was associated with a significantly reduced risk of stroke/systemic embolism (pooled rate ratio 0.34, 95% CI 0.25 - 0.45) with no increase in the risk of recurrent ICH (pooled rate ratio 1.01, 95% CI 0.58 - 1.77).[254]
- There are no high-quality RCT data to inform optimal timing of OAC (re)start after ICH. Haematoma expansion, common in acute ICH, is aggravated by anticoagulation, which should be reversed and avoided in acute ICH (<24 - 48 h). A modelling analysis estimated that the overall risk of stroke and ICH was the lowest when OAC was (re)started 10 weeks after acute ICH, and a period of ≥4 weeks was suggested.[255]
- Notably, there are no large-scale RCTs providing information on whether long-term OAC is beneficial in ICH survivors with AF. Several ongoing RCTs will investigate the use of antithrombotic therapies after ICH in patients with AF: APACHE-AF,[256] RESTART[257] PRESTIGE-AF (NCT03996772), NASPAF-ICH (NCT02998905), STATICH (NCT03186729), SoSTART (NCT03153150), and A3ICH (NCT03243175).

AF = atrial fibrillation; APACHE-AF = Apixaban versus antiPlatelet drugs or no antithrombotic drugs after Anticoagulation-associated intraCerebral HaEmorrhage in patients with Atrial Fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CI = confidence interval; CT = computed tomography; ICH = intracranial haemorrhage; MRI = magnetic resonance imaging; OAC = oral anticoagulant; PRESTIGE-AF = PREvention of Stroke in Intracerebral haemorrhage survivors with Atrial Fibrillation; RCT = randomized controlled trial; RESTART = Restart or Stop Antithrombotics Randomized Trial; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

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

Supplementary Table 12 **Main characteristics and results of the PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS and ENTRUST-AF PCI trials**

	PIONEER AF-PCI[258]			RE-DUAL PCI[259]			AUGUSTUS[260]				ENTRUST-AF PCI[261]	
Year of publication	2016			2017			2019				2019	
Cohort size (n)	2124			2725			4614				1506	
Randomization window after index event	72 h			120 h			14 days				5 days	
Treatment strategy	Riv 15 mg daily + a $P2Y_{12}$ inhibitor vs Riv iv 2.5 mg bid + DAPT vs VKA + DAPT			Dab 110 mg bid + a $P2Y_{12}$ inhibitor vs Dab 150 mg bid + a $P2Y_{12}$ inhibitor vs VKA + DAPT			Api 5 mg bid + DAPT vs Api 5 mg bid + a $P2Y_{12}$ inhibitor vs VKA + DAPT vs VKA + a $P2Y_{12}$ inhibitor				Edo 60 mg daily + a $P2Y_{12}$ inhibitor vs VKA + DAPT	
Clinical setting (%)												
Elective PCI	61.5			49.5			38.8				48.0	
Primary PCI	38.5			50.5			37.3				52.0	
Medically managed ACS	0.0			0.0			23.9				0.0	
$P2Y_{12}$ inhibitor (%)												
Clopidogrel	94.4			87.9			92.6				92.0	
Ticagrelor	4.3			12.1			6.2				7.0	
Prasugrel	1.3			0.0			1.2				0.5	
TAT regimen duration (months)	1, 6 or 12			1 (BMS) or 3 (DES)			6				1 - 12	
DAPT regimen	OAC + aspirin			OAC+ a $P2Y_{12}$ inhibitor			OAC+ a $P2Y_{12}$ inhibitor				OAC+ a $P2Y_{12}$ inhibitor	
Follow up(months)	12			14			6				12	
Safety endpoint	Composite of TIMI major bleeding or minor bleeding			Major or CRNM ISTH bleeding			Major or CRNM ISTH bleeding				Major or CRNM ISTH bleeding	
Event, n (%)	**Riv 15 mg**	**Riv 2.5 mg**	**TAT**	**Dab 110 mg**	**Dab 150 mg**	**TAT**	**Api vs. VKA**		**ASA vs. placebo**		**Edo**	**TAT**
Trial defined safety endpoint	109 (16.8)	117 (18.0)	167 (26.7)	151 (15.4)	154 (20.2)	264 (26.9)	241 (10.5)	332 (14.7)	367 (16.1)	204 (9.0)	128 (17.0)	152 (20.1)
TIMI major and minor bleeding	109 (16.8)	117 (18.0)	167 (26.7)	29 (3.0)	27 (3.5)	69 (7.0)	96 (4.2)	132 (5.8)	146 (6.4)	80 (3.5)	NR	NR
ISTH major or CRNM bleeding	117 (16.8)	122 (17.3)	239 (17.0)	151 (15.4)	154 (20.2)	264 (26.9)	241 (10.5)	332 (14.7)	367 (16.1)	204 (9.0)	128 (17.0)	152 (20.1)
ISTH major bleeding	27 (3.9)	25 (3.5)	48 (6.9)	49 (5.0)	43 (5.6)	90 (9.2)	69 (3.0)	104 (4.6)	108 (4.7)	65 (2.9)	45 (6.0)	48 (6.4)
ISTH CRNM bleeding	90 (12.9)	97 (13.7)	130 (18.7)	102 (10.4)	111 (14.6)	174 (17.7)	180 (7.9)	246 (10.9)	275 (12.1)	148 (6.5)	97 (12.9)	114 (15.1)
Intracranial haemorrhage	NR	NR	NR	3 (0.3)	1 (0.1)	10 (1.0)	5 (0.2)	13 (0.6)	8 (0.4)	10 (0.4)	4 (0.5)	9 (1.2)

Continued

Supplementary Table 12 *Continued*

	PIONEER AF-PCI[258]			RE-DUAL PCI[259]			AUGUSTUS[260]				ENTRUST-AF PCI[261]	
MACE definition	Composite of CV death, MI, or stroke; and ST			Composite of all-cause death or ischemic event (including stroke, MI, SE, or unplanned revascularization)			Composite of all-cause death or ischemic event (including stroke, MI, ST definite/probable, or urgent revascularization)				Composite of CV death or ischemic event (including stroke, MI, ST definite, SE)	
Event, n (%)	**Riv 15 mg**	**Riv 2.5 mg**	**TAT**	**Dab 110 mg**	**Dab 150 mg**	**TAT**	**Api vs. VKA**		**ASA vs. Placebo**		**Edo**	**TAT**
Trial defined MACE[a]	41 (6.5)	36 (5.6)	36 (6.0)	149 (15.2)	90 (11.8)	131 (13.4)	154 (6.7)	163 (7.1)	149 (6.5)	168 (7.3)	49 (7)	46 (6)
All-cause death	NR	NR	NR	55 (5.6)	30 (3.9)	48 (4.9)	77 (3.3)	74 (3.2)	72 (3.1)	79 (3.4)	46 (6.1)	37 (4.9)
CV deaths	15 (2.4)	14 (2.2)	11 (1.9)	NR	NR	NR	57 (2.5)	54 (2.3)	53 (2.3)	58 (2.5)	17 (2.3)	16 (2.1)
MI	19 (3.0)	17 (2.7)	21 (3.5)	44 (4.5)	26 (3.4)	29 (3.0)	72 (3.1)	80 (3.5)	68 (2.9)	84 (3.6)	29 (3.9)	23 (3.0)
Stent thrombosis	5 (0.8)	6 (0.9)	4 (0.7)	15 (1.5)	7 (0.9)	8 (0.8)	14 (0.6)	18 (0.8)	11 (0.5)	21 (0.9)	8 (1.1)	6 (0.8)
Stroke	8 (1.3)	10 (1.5)	7 (1.2)	17 (1.7)	9 (1.2)	13 (1.3)	13 (0.6)	26 (1.1)	20 (0.9)	19 (0.8)	10 (1.3)	12 (1.6)

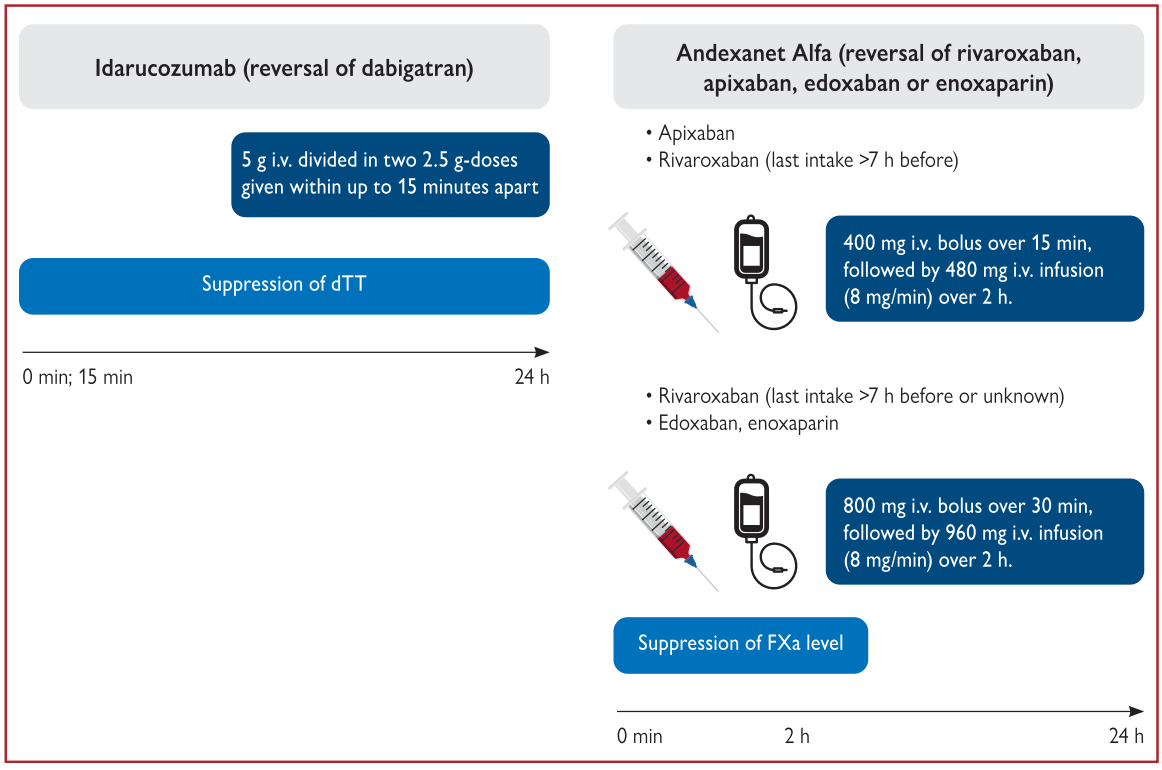
ACS = acute coronary syndrome; Api = apixaban; ASA = aspirin; BMS = bare-metal stent; CRNM = clinically relevant non-major; CV = cardiovascular; Dab = dabigatran; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; Edo = edoxaban; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ISTH = International Society on Thrombosis and Haemostasis; MACE = major adverse cardiac event; MI = myocardial infarction; NR = nor reported; OAC = oral anticoagulation; 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; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; Riv = rivaroxaban; SE = systemic embolism; ST = stent thrombosis; TAT = triple antithrombotic therapy; TIMI = Thrombolysis In Myocardial Infarction; VKA = vitamin K antagonist.

17 Active bleeding on anticoagulant therapy – management and reversal drugs

Supplementary Table 13 Antidotes for NOACs

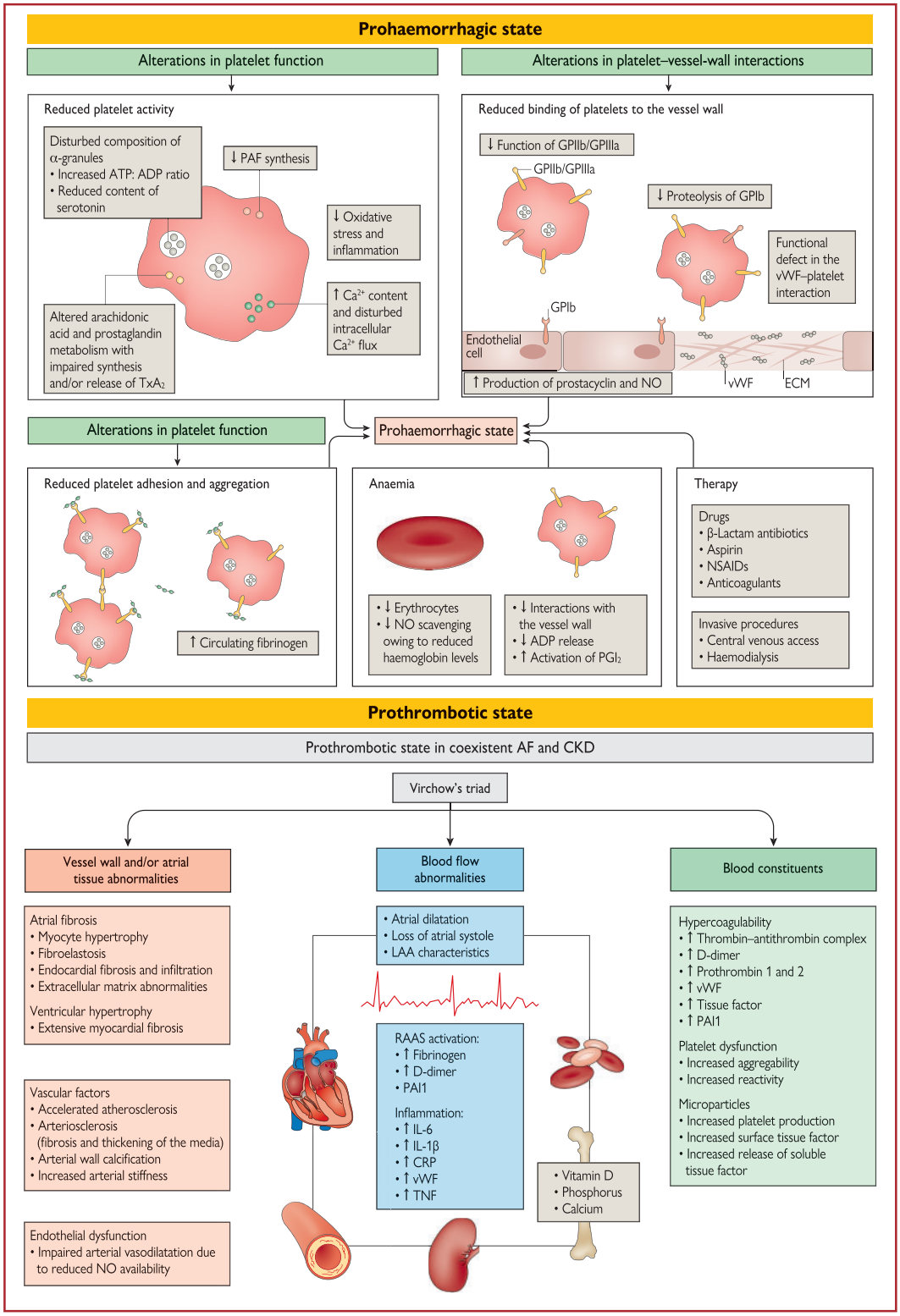
Antidote	Description	Landmark study	Inclusion criteria	Main results
Idarucizumab	Monoclonal antibody fragment that binds dabigatran, resulting in a rapid reversal of its anticoagulant effect	REVERSE-AD[262] (*n* = 503)	Uncontrolled bleeding (mostly GI or ICH) Urgent surgery	Idarucizumab stopped bleeding in a median time of 2.5 h and haemostasis was achieved in median time 1.6 h in 93.4% of patients. In a post-hoc analysis of GI bleeding (137 patients), complete reversal of dabigatran occurred in 97.5%, and bleeding cessation within 24 h in 68.7% of patients.[263]
Andexanet alfa	Catalytically inactive recombinant modified human factor Xa protein that can bind to factor Xa inhibitors[264]	ANNEXA-4[265] (*n* = 352)	Acute major bleeding (mostly ICH [64%] or GI) within 18 h after intake of a factor Xa inhibitor	Anti-factor Xa activity was reduced by 92% in patients on rivaroxaban or apixaban. Effective haemostasis at 12 h was achieved in 82% of patients.
Ciraparantag	Synthetic drug that binds and inhibits the direct factor Xa inhibitors, dabigatran and heparin	Investigational	A double-blind, placebo-controlled phase 1 trial in 80 healthy volunteers revealed full reversal of anticoagulation within 10 - 30 min after a single dose (100 - 300 mg) of ciraparantag with minor non dose-limiting adverse events.[266]	
		If proven to be effective ciraparantag would potentially provide broader reversal of anticoagulation than either idarucizumab or andexanet.		

ANNEXA = A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors; bpm = beats per minute; GI = gastrointestinal; ICH = intracranial haemorrhage; REVERSE-AD = REVERSal Effects of Idarucizumab on Active Dabigatran.



Supplementary Figure 6 Application of antidotes for reversal of anticoagulant effect of NOACs.[262,265,267] dTT = diluted thrombin time; FXa = Factor Xa; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant.

18 Atrial fibrillation and chronic kidney disease



Supplementary Figure 7 Pathophysiology of prohaemorrhagic and prothrombotic state in CKD.[268] ADP = adenosine diphosphate; AF = atrial fibrillation; ATP = adenosine triphosphate; CKD = chronic kidney disease; CRP = C-reactive protein; ECM = extracellular matrix; GP = glycoprotein; IL = interleukin; NO = nitric oxide; NSAID = non-steroidal anti-inflammatory drug; PAF = platelet activating factor; PAI = plasminogen activator inhibitor; PGI_2 = prostaglandin I_2; RAAS = renin-angiotensin-aldosterone system; TNF = tumour necrosis factor; TxA_2 = thromboxane A_2; vWF = von Willebrand factor.

19 Atrial fibrillation in inherited cardiomyopathies and primary arrhythmia syndromes

Supplementary Table 14 Main clinical features of AF in inherited cardiac diseases

Condition	Prevalence of AF	Contraindicated drugs	Special considerations for treatment			
			Anticoagulation	Rate control	Rhythm control AADs	Ablation
Long QT syndrome	2 - 29%[269,270]	QT-prolonging drugs (amiodarone, sotalol)	According to cardioembolic risk	Beta-blockers	LQTS1: Mexiletine[271] LQTS3: Flecainide[272]	No data
Short QT syndrome	18 - 70%[273–277]		According to cardioembolic risk		Propafenone[278] Quinidine[279,280]	No data
Brugada syndrome	6 - 53%[281–286]	Class IC drugs	According to cardioembolic risk		Quinidine Bepridil	[287–290]
Catecholaminergic polymorphic VT	11 - 37%[291,292]		According to cardioembolic risk	Beta-blockers[293–295]	Flecainide,[295–299] propafenone[300]	[301,302]
Hypertrophic cardiomyopathy	17 - 30%[303–309]	Class I drugs	Always[310,311] (if no contraindication)	Beta-blockers	Rhythm control is preferred; Amiodarone[310,312] Sotalol	[305,313–320]
Arrhythmogenic cardiomyopathy	9 - 30%[321–326]		According to cardioembolic risk	Beta-blockers[327]		No data
Familial dilated cardiomyopathy	25 - 49%[328] LMNA-related[329–332]		According to cardioembolic risk			
Familial ventricular non-compaction	1 - 29%[333–335]		Always (if no contraindication)[336]			[337]
Wolff-Parkinson-White syndrome	Variable (7 - 50%, a presenting arrhythmia in 20%)[43,338]	Digoxin, verapamil, diltiazem, beta-blockers, amiodarone	According to cardioembolic risk	Procainamide, propafenone, or flecainide for acute rate control;	Accessory pathway(s) catheter ablation first, then AADs for AF as needed	As needed

AAD = antiarrhythmic drug; AF = atrial fibrillation; i.v. = intravenous; LMNA = LMNA gene; LQTS = long QT syndrome; VT = ventricular tachycardia.

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

Supplementary Box 6. AHRE/subclinical AF

- The incidence of AHRE/subclinical AF in patients with a CIED depends on clinical profile of the studied population and device-specific detection algorithm.[339,340] Many CIED-implanted patients have sinus node disease and/or ventricular pacing (both are associated with a higher incidence of AF).[341] In patients with cryptogenic stroke, a 21-day mobile cardiac output telemetry revealed AHRE/subclinical AF in 23% of cases.[342]
- Longer AHRE/subclinical AF (≥5 - 6 min) is associated with an increased risk of clinical AF (HR 5.66, 95% CI 4.02 - 7.97; $P<0.001$),[343,344] ischaemic stroke/systemic embolism (HR 2.41, 95% CI 1.78 - 3.26; $P = 0.007$),[344,345] and cardiovascular mortality (HR 2.80, 95% CI 1.24 - 6.31),[346] compared with no AHRE/subclinical AF. In a recent study, developing AHRE/subclinical AF of ≥5 min was associated with a significant risk of MACE, including acute HF, myocardial infarction, cardiac revascularization, cardiovascular death, hospitalization, or ventricular tachycardia/fibrillation (HR 1.79, 95% CI 1.25 - 2.56; $P = 0.002$), and the association was even stronger for AHRE/subclinical AF of ≥24 h (HR 2.39, 95% CI 1.48 - 3.86; $P<0.001$).[347] In another study, duration >24 h was associated with a significantly increased risk of subsequent stroke/systemic embolism, whereas the risk associated with a duration of ≤24 h was similar to that without AHRE/subclinical AF.[348] Additionally, AHRE/subclinical AF-related thromboembolic risk is influenced by the presence of clinical stroke risk factors,[344] which in turn could be significantly associated with increased risk of new-onset clinical AF among patients with AHRE/subclinical AF.[349]

- Whereas thromboembolic risk in patients with CIED is mainly driven by comorbidity burden (i.e. CHA_2DS_2-VASc score),[69] adding AHRE/subclinical AF to clinical risk scores significantly improved discrimination for thromboembolism or death.[350]
- Noteworthy, the observed low rates of stroke in patients with AHRE/subclinical AF (but no clinical AF) could have been at least partly influenced by discretionary use of OAC during the trials.[344] However, a strategy of early initiation and interruption of OAC using VKAs based on remotely detected AHRE/subclinical AF in patients with pacemakers/implantable cardioverter-defibrillators did not prevent thromboembolism and bleeding in an interventional therapy trial.[351] Two randomized trials[352,353] are currently investigating the potential benefits of NOACs over aspirin or no antithrombotic therapy in the specific setting of AHRE/subclinical AF.

AF = atrial fibrillation; AHRE = atrial high-rate episode; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CI = confidence interval; MACE = major adverse cardiac event; CIED = cardiac implantable electronic device; HF = heart failure; HR = hazard ratio; HR = hazard ratio; MACE = major adverse cardiovascular events; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist.

21 Atrial fibrillation and other atrial tachyarrhythmias (atrial flutter and atrial tachycardias)

Supplementary Box 7. AFL (also see the 2019 ESC Supraventricular Tachycardia Guidelines.[355])

AFL is most commonly based on atrial macro re-entrant, but micro re-entry is also possible. It is classified as *CTI-dependent* AFL, which includes typical AFL (common-anticlockwise/reverse-clockwise) and other CTI-dependent AFLs, and *non-CTI-dependent* AFL (or MRAT; also includes RA and LA AFL).[354]

Typical AFL

Although less common than AF, AFL shares many common risk factors with AF[356–358] and is associated with increased risk of HF, stroke, and all-cause death.[359–361]

Compared with matched controls, AF and AFL patients had a significantly higher prevalence of comorbidities, ischaemic stroke, hospitalization for HF, and all-cause death.[360] Event rates in AFL patients were lower than in AF, but higher than in matched controls - e.g. the incidence densities of ischaemic stroke in the AF, AFL, and control cohort were 3.08 (95% CI 3.03 - 3.13), 1.45 (95% CI 1.28 - 1.62), and 0.97 (95% CI 0.92 - 1.03), respectively,[360] consistently increasing with increasing CHA_2DS_2-VASc score value. The 'tipping point' for NOAC use (≥0.9% annual stroke rate)[361] was reached at the score of 2 in the AFL cohort and 1 in the AF cohort.

There may be prognostic differences between solitary AFL and AFL with the subsequent development of AF. Reportedly, the latter had an incidence of stroke similar to AF patients.[362,363] In contrast, stroke rates were significantly lower with solitary AFL,[363] whereby OAC use was associated with a significant reduction in stroke rates with CHA_2DS_2-VASc score values ≥3, with the best net clinical outcome with scores ≥4.[363]

Stroke rates in non-anticoagulated patients with solitary AFL increase in parallel with increasing CHA_2DS_2-VASc score, and 22 - 45% of patients with solitary AFL will develop AF within 2 - 3 years after CTI ablation.[365–367] Hence, stroke prevention in patients with AFL should follow the same principles as in AF patients.

Compared with AF, electrical cardioversion is more effective in AFL and less energy is required.[367,368] When atrial electrodes are in place, AFL can be converted using high-rate stimulation.[369] Amiodarone may not be effective for rapid restoration of sinus rhythm, but it helps in rate control and long-term rhythm control.[370] However, CTI catheter ablation is the most effective rhythm control treatment for AFL,[370,371] resulting in <10% recurrence.[372] Notably, nearly 50% of patients will develop AF over the long-term. When ablation is not considered in AFL patients, AADs (e.g. dofetilide, amiodarone)[370] may be used, but caution is needed for potential proarrhythmia (dofetilide) or serious side-effects (amiodarone).

Atypical AFL /MRAT

RA atypical AFL/MRAT most commonly originates around surgical or ablation scars in the RA, but may occur in patients without a history of such interventions. These AFLs are less amenable to pharmacological therapies and are best treated using catheter ablation.[373,374]

LA atypical AFL/MRAT originates around electrically silent areas of abnormal myocardial tissue caused by surgery, catheter ablation, or progressive atrial fibrosis. Pre-existing LA disease,[375] LA catheter ablation for AF,[376–379] or mitral valve[380] or AF surgery[381] may create substrate for macro re-entry AFL/MRAT. Local segmental pulmonary vein disconnection may cause focal tachycardias, and gaps in the lines for circumferential antral ablation may also create MRAT.

Ablation to treat atypical AFL/MRAT occurring post ablation or surgery for AF should not be performed immediately after the index procedure (thus allowing maturation of index lesions) and should preferably be performed by experienced operators and centres.[354]

AAD = antiarrhythmic drug; AF= atrial fibrillation; AFL = atrial flutter; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CTI = cavotricuspid isthmus; ECV = electrical cardioversion; ESC = European Society of Cardiology; HF = heart failure; i.v. = intravenous; LA = left atrium/atrial; MRAT = macro re-entrant atrial tachycardia; RA = right atrium/atrial; SVT = supraventricular tachycardia.

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