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STATE OF THE ART REVIEW

Atrial fibrillation and stroke prevention: 25 years of research at EP Europace journal

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Abstract

Stroke prevention in patients with atrial fibrillation (AF) is one pillar of the management of this common arrhythmia. Substantial advances in the epidemiology and associated pathophysiology underlying AF-related stroke and thrombo-embolism are evident. Furthermore, the introduction of the non-vitamin K antagonist oral anticoagulants (also called direct oral anticoagulants) has clearly changed our approach to stroke prevention in AF, such that the default should be to offer oral anticoagulation for stroke prevention, unless the patient is at low risk. A strategy of early rhythm control is also beneficial in reducing strokes in selected patients with recent onset AF, when compared to rate control. Cardiovascular risk factor management, with optimization of comorbidities and attention to lifestyle factors, and the patient's psychological morbidity are also essential. Finally, in selected patients with absolute contraindications to long-term oral anticoagulation, left atrial appendage occlusion or exclusion may be considered. The aim of this state-of-the-art review article is to provide an overview of the current status of AF-related stroke and prevention strategies. A holistic or integrated care approach to AF management is recommended to minimize the risk of stroke in patients with AF, based on the evidence-based Atrial fibrillation Better Care (ABC) pathway, as follows: A: Avoid stroke with Anticoagulation; B: Better patient-centred, symptom-directed decisions on rate or rhythm control; C: Cardiovascular risk factor and comorbidity optimization, including lifestyle changes.

Keywords Atrial fibrillation • Stroke prevention • Rhythm control • Ablation • Anticoagulation • Bleeding risk • Pacemaker

Introduction

In the last decades, substantial progress has been made in relation to stroke prevention in patients with atrial fibrillation (AF). We have seen much progress in understanding the epidemiology and associated pathophysiology underlying AF-related stroke and thrombo-embolism. The introduction of the non-vitamin K antagonist oral anticoagulants (NOACs, also called direct oral anticoagulants, DOACs) has changed the landscape of stroke prevention in AF, such that the default should be to offer oral anticoagulation for stroke prevention, unless the patient is at low risk. Also, in selected patients with recent onset AF, a strategy of early rhythm control is beneficial in reducing strokes, compared to rate control. In addition, the importance of comorbidity and lifestyle management is increasingly recognized. Finally, in selected patients with absolute contraindications to long-term oral anticoagulation, the data for left atrial appendage occlusion (LAAO) or exclusion are increasingly compelling.

The aim of this state-of-the-art review article is to provide an overview of the current status of AF-related stroke and prevention strategies. Stroke prevention in patients with AF can be optimized with adherence to a holistic or integrated care approach to AF management, based on the evidence-based Atrial fibrillation Better Care (ABC) pathway, summarized as follows:[1] A: Avoid stroke with Anticoagulation; B:

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Better patient-centred, symptom-directed decisions on rate or rhythm control; C: Cardiovascular risk factor and comorbidity optimization, including lifestyle changes.

Epidemiology and pathophysiology: a brief overview in relation to stroke

Epidemiology

Atrial fibrillation is the commonest cardiac arrhythmia globally, which is estimated to affect more than 46.3 million individual worldwide in 2016; indeed, due to the ageing population and increasing prevalence of cardiovascular risk factors, the prevalence of AF is expected to rise in the next 30–50 years.[2,3] The Framingham Heart Study has shown that the prevalence of AF increased three-fold over the last 50 years.[4]

By 2050–60, the prevalence of AF is expected to reach 6–16 million in USA[5,6] and ∼14 million in Europe.[7,8] Although limited epidemiological data on AF are available in the Asia-Pacific region, given the increasing age and size of populations in this region, the burden of AF is expected to be even greater than in North America and Europe. It was estimated that by 2050, there will be ∼49 million men and 23 million women with AF in Asia.[9] In the USA, the lifetime risk of AF was estimated as 36% and 30% in White males and females, respectively, and 21% and 22% in Black males and females, respectively.[10] In Europe, the lifetime risk estimates of AF also reached about one in three in White individuals. Recent studies in Taiwan have revealed that the lifetime risk of AF was 16.9% and 14.6% in males and females, respectively.[10]

Hence, AF has become a worldwide public health problem and imposed major burden to the healthcare system. Indeed, recent analysis of the Global Burden of Diseases study 2019 indicated that the global disease burden of AF in term of incidences and mortality has increased by ∼1.1-fold and ∼1.4-fold from 1990 to 2019.[11]

One of the most important causes of increasing mortality and morbidity of AF is the occurrence of arterial thrombo-embolism and ischaemic stroke, as AF increases the risk of ischaemic stroke by five-fold, and is attributed as the aetiology in up to 25–30% of patients presented with acute ischaemic stroke. Moreover, stroke associated with AF is characterized by large and multiple infarcts involving different vascular territories.[12]

Nevertheless, there is a wide variability in stroke risk ranging from 0.5% per year to 9.3% per year between different AF patient populations.[13] Therefore, assessment of stroke risk in AF patients is needed to determine the need for therapies, mainly oral anticoagulation to stroke prevention. Current clinical guidelines recommend the use of validated AF stroke risk scores, such as Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female) (CHA_2DS_2-VASc) score that comprising multiple clinical variables for risk stratification for the use of anticoagulation for stroke prevention in AF patients.[14]

The CHA_2DS_2-VASc score only includes the more common and validated clinical stroke risk factors, which have been extensively reviewed.[15] Amonge these, the inclusion of female sex (Sc criterion) was considered more as a risk modifier rather than a risk factor *per se*. Indeed, the stroke risk in AF females patients was found to be age-dependent,[16] and females with AF who are age ≥65 or report another non-sex stroke risk factor, have a higher stroke risk than males with the same non-sex stroke risk factors, hence being female is additive in terms of thromboembolic risk.[17,18] This is important given the relative under-treatment of females,[19] and should strokes occur in female AF patients, they tend to be more severe and disabling. The CHA_2DS_2-VASc score remains the best validated commonly used simple clinical stroke risk score,[20] and the few validations of the CHA_2DS_2-VASc score without the Sc criterion (i.e. CHA_2DS_2-VA) have methodological issues.[18]

All simple clinical risk scores such as $CHADS_2$ and CHA_2DS_2-VASc score have many limitations, as they are reductionist in nature and mere simplifications to aid decision-making. More complex clinical risk scores are evident [e.g. GARFIELD-AF (Global Anticoagulant Registry in the Field-Atrial Fibrillation), ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)], as well as those adding biomarkers (e.g. ABC stroke score), but even then their c-indexes (a statistical measure of prediction) largely remain <0.7.[21,22] Biomarkers (urine, blood, or imaging) always improve risk stratification compared to scores based on clinical factors, but many such biomarkers are non-specific, reflecting a sick patient or sick heart.[22,23] Some scores were also derived from clinical trial cohorts, and the performance of these scores in real-world clinical practice is variable and where statistical significance is evident, this does necessarily not translate to practical application.[24,25]

Clinical risk scores in use are based on 'static' risk assessment, i.e. assessing the impact of a baseline risk on events occurring many years later, but in reality, the risk of stroke is dynamic, changing with ageing and incident comorbidities.[26] There are increasing publications on the use of machine learning (ML) to account for the dynamic nature of the changing multi-morbidity risk factors, and when compared to clinical risk scores, or multi-morbid index, ML can further improve the stroke risk prediction in AF with c-indexes ∼0.9.[27]

Pathophysiology

In recent decades, there has been an increased understanding of the underlying pathogenesis of stroke in patients AF as summarized in detail elsewhere.[12,28] In brief, hypercoagulability, atrial cardiomyopathy with endothelial damages, and reduced blood flow in the dilated atria as well as the left atrial appendage (LAA) without active contraction contribute to the pathological thrombus formation in the left atrium and thus systemic thrombo-embolism and stroke. Moreover, it has been increasingly recognized the role of atrial cardiomyopathies, due to a complex interplay of structural, architectural, contractile, and electrophysiological abnormalities, in contributing to the progression of AF as well as to the increased thrombo-embolic risk. Indeed, many different well-known risk factors for AF including aging, gender, smoking, alcohol consumption, obesity, diabetes, hypertension, left ventricular hypertrophy, valvular heart diseases, heart failure (HF), and myocardial infarction (MI) that cause atrial cardiomyopathy are also clinical variables that associated with stroke risk in AF.[12]

Recently, the 4S-AF classification scheme comprised of four domains [stroke risk (St), symptoms (Sy), severity of AF burden (Sb), and substrate (Su)] has been proposed to provide a comprehensive characterization, evaluation, and assessment of patients with AF.[14] In the future, assessments of atrial structure and function using different imaging modalities should provide better insights into the possible thrombogenic mechanisms in individual patient and thus improve the risk prediction for stroke beyond current clinical stroke risk scores.[29]

Integrated care for atrial fibrillation

AF is the commonest sustained cardiac arrhythmia and is managed across the whole spectrum of healthcare professionals, ranging from general practitioners to internal medicine specialists to cardiologists.

While stroke prevention is central to the management of AF, this is only one pillar of the holistic or integrated care approach to AF management. This is important as there still remains a residual risk of adverse outcomes in AF patients despite oral anticoagulation, and while mortality in anticoagulated AF patients remains still high, only 1 in 10 deaths are related to stroke, while 7 in 10 are cardiovascular.[30]

Hence, we need a streamlined approach to ensure the pillars of AF care are delivered irrespective of which healthcare professional is managing the patient. Also, patients and their family or carers need to understand the priorities of management in a simple and practical manner. Hence, AF management guidelines have moved towards a more holistic or integrated care approach to management of AF.[31]

First, we need to confirm the diagnosis of the arrhythmia, followed by characterization and evaluation. As mentioned above, such

characterization is based on the 4S-AF scheme,[14] i.e. Stroke risk assessment (with the CHA_2DS_2-VASc score); Symptom severity [using the European Heart Rhythm Association (EHRA) score]; Severity of burden (whether spontaneously terminating or permanent); and Substrate (age, structural heart disease, comorbidities).

Following this, we treat the patient according to the ABC pathway.[1] Adherence with such an approach has been shown in various studies including a clinical trial to be associated with improved clinical outcomes, including reductions in all-cause mortality, cardiovascular mortality, stroke, and major bleeding, as well as hospitalizations (*Figure 1*).[32]

The evidence-based ABC pathway has been tested in numerous retrospective and prospective cohorts from different regions of the world,[32] as well as *post hoc* analysis from adjudicated outcomes from clinical trials[33,34] and the Mobile Atrial Fibrillation Application (mAFA)-II clinical trial. The latter was a prospective cluster randomized trial which showed a significant reduction in the primary outcome with the ABC pathway intervention using a mHealth App, compared to usual care:[35] rates of the composite outcome of 'ischaemic stroke/systemic thrombo-embolism, death, and re-hospitalization' were lower with the mAFA intervention compared with usual care [1.9% vs. 6.0%; hazard ratio (HR): 0.39; 95% confidence interval (CI) 0.22–0.67; $P < 0.001$]. Rates of re-hospitalization were also lower with the mAFA intervention (1.2% vs. 4.5%; HR: 0.32; 95% CI: 0.17–0.60; $P < 0.001$). Notwithstanding the composite primary outcome, a *post hoc* win ratio analysis also shows the benefit of the mAFA intervention using the ABC pathway.[36]

Ongoing clinical trials are testing the impact of implementation of the ABC pathway in Europe [atrial fibrillation integrated approach in frail, multimorbidity and polymedicated older people (AFFIRMO)[37]] and in rural China [MIRACLE-AF (A New Model of Integrated Care of Older Patients With Atrial Fibrillation in Rural China); NCT04622514].

Avoid stroke and anticoagulation

Oral anticoagulation

Oral anticoagulant (OAC) therapy is the cornerstone of effective prevention of stroke and systemic embolism in patients with AF. Currently available OAC agents include vitamin K antagonists (VKAs) and NOACs also referred to as DOACs.

Vitamin K antagonists

The VKA family includes warfarin, acenocoumarol, phenprocoumon, phenindione, and fluindione.[38] Overall, warfarin is the most frequently prescribed VKA in clinical practice, notwithstanding certain geographical variations such as, e.g. a widespread use of acenocoumarol in Spain and Germany or fluindione in France.[39,40]

The anticoagulant effect of VKAs is achieved indirectly, via inhibition of the vitamin K epoxide reductase complex subunit 1 resulting in altered functionality of vitamin K-dependent coagulation factors II, VII, IX, and X (and anticoagulant proteins C, S, and Z).[41] Optimal anticoagulant effect of VKAs is usually achieved within 3–5 days of treatment initiation, depending on the individual patient pharmacogenetics, comorbidity, and co-medication.[41]

In addition to a slow onset and offset of their anticoagulant effect, VKAs have a narrow therapeutic interval and numerous drug–drug and drug–food interactions, requiring regular laboratory monitoring of anticoagulation effect and dose adjustments.[14] Whereas the international normalized ratio (INR) value reflects instantaneous VKA anticoagulant effect intensity, the time in therapeutic range (TTR) reflects the quality of VKA management in a time interval and correlates well with thrombo-embolic and haemorrhagic event rates (an INR of 2–3 and TTR of >70% are recommended for adequate VKA therapy in patients with AF). In patients with AF, VKA therapy (mostly warfarin) reduced the risk of stroke by 64% and all-cause mortality by 26% compared with control or placebo.[42]

Non-vitamin K antagonist or direct oral anticoagulants

Oral direct inhibitors of coagulation Factor II (dabigatran) or activated factor X (rivaroxaban, apixaban, and edoxaban) have a rapid onset and offset of action, stable dose-related anticoagulant effect with less drug–drug interactions than VKAs and are used in fixed doses without routine laboratory monitoring of anticoagulant effect or food restrictions.[43]

In a meta-analysis[44] of the respective landmark trials comparing the use of a NOAC vs. warfarin for the prevention of stroke and systemic embolism in patients with AF,[45–48] the use of a NOAC was associated with statistically significant 19% reduction of the risk of stroke or systemic embolism (including a 51% reduction of haemorrhagic stroke risk and comparable ischaemic stroke risk reduction), a non-significant 14% reduction of the major bleeding risk [with significant 52% reduction in intracranial haemorrhage (ICH), and 25% increase in gastrointestinal (GI) bleeding], and a significant 10% reduction in all-cause mortality compared with warfarin. Whereas the impressive reduction of the ICH risk was consistent among all four NOACs, the risk of GI bleeding was significantly greater with dabigatran 150 mg twice daily,[45] rivaroxaban 20 mg once daily,[46] and edoxaban 60 mg once daily[48] compared with warfarin. The effectiveness and safety of NOACs relative to VKAs has been broadly confirmed in numerous post-marketing observational studies.[49]

Non-adherence and non-persistence to OAC treatment increase the risk of both ischaemic and haemorrhagic complications and all-cause mortality.[50] Although the persistence with any NOAC has been shown to be significantly higher than with VKAs [odds ratio (OR) 1.44, 95% CI 1.12–1.86], there is a considerable need for further improvement (in a recent meta-analysis of adherence and persistence to NOAC therapy among patients with AF, e.g. the overall proportion of patients with good adherence was 66%, and the proportion of persistence was 69%),[51] and multiple patient-related, physicians-related, and healthcare system-related factors can influence individual adherence and persistence to OAC therapy.[50]

Despite a clear guidance on dose reduction criteria provided in the product information for each of the NOACs (*Table 1*), inappropriate under- or over-dosing is still not uncommon in clinical practice, especially for the elderly or other high-risk patients with AF.[52] In a recent meta-analysis, inappropriate under-dosing has been shown to be associate with increased all-cause mortality (HR = 1.28, 95% CI 1.10–1.49; $P = 0.006$) and no effect on major bleeding (HR = 1.04, 95% CI 0.90–1.19; $P = 0.625$), while inappropriate overdosing was associated with significantly increased risk of major bleeding (HR = 1.41, 95% CI 1.07–1.85; $P = 0.013$).[52] Hence, prescriber adherence to NOAC dosing guidelines is of key importance for achieving optimal clinical outcomes for patients with AF.

Whereas routine laboratory monitoring of NOAC anticoagulant effect intensity is not needed, initial assessment (and then a regular reassessment) of renal function is mandatory in patients with AF taking a NOAC, since all four NOACs are to some extent eliminated by the kidneys (dabigatran 80%, edoxaban 50%, rivaroxaban 35%, and apixaban 27%).[43]

Based on the high-quality randomized clinical trial (RCT)-based evidence and advantages of NOACs for long-term use, NOACs are recommended in preference to VKAs for stroke prevention in all NOAC-eligible patients with AF (Class I, level of evidence (LoE) A).[14,53]

(In)eligibility for non-vitamin K antagonist or direct oral anticoagulants

Pregnant women and patients with a prosthetic mechanical heart valve, moderate-to-severe mitral valve stenosis, or end-stage chronic kidney disease or on dialysis were not included in the landmark NOAC trials in AF.[45–48]

Pregnancy

NOACs are contraindicated in pregnant women, and proper contraceptive measures need to be undertaken in childbearing women before initiation of NOAC therapy.[43]

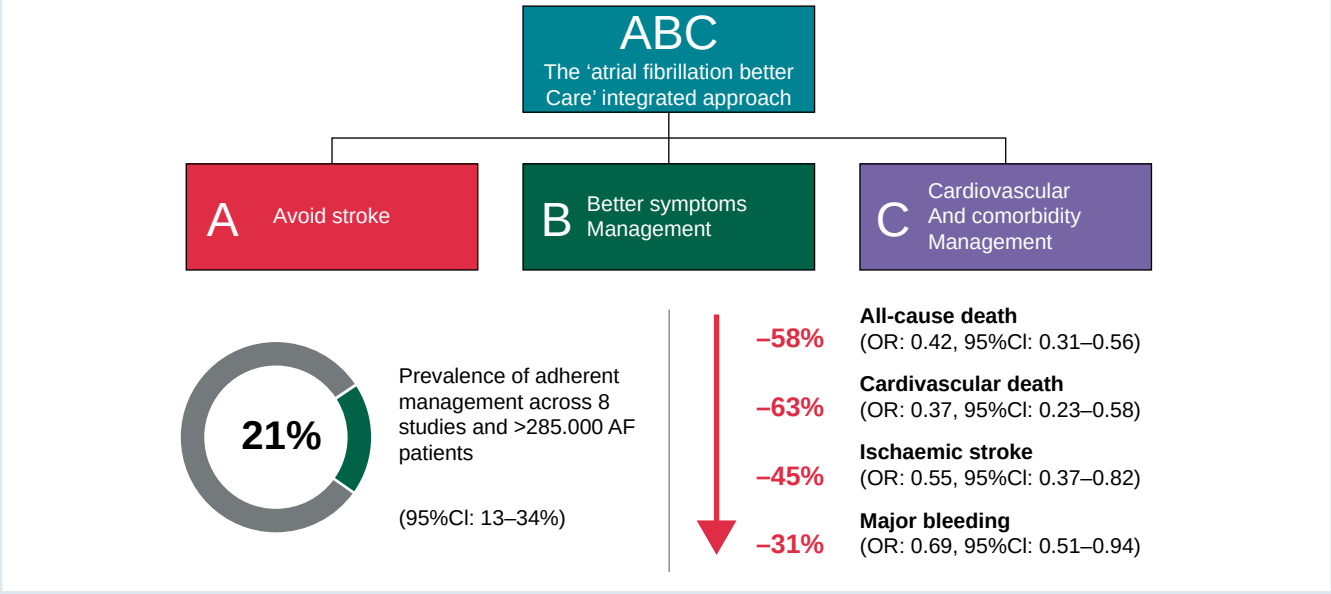

Figure 1 The ABC pathway.[32] A: Avoid stroke with Anticoagulation, where the default is stroke prevention unless the patient is at low risk; B: Better symptom control, with patient-centred, symptom-directed decisions on rate or rhythm control; and C: Cardiovascular risk factor and comorbidity optimization, including attention to lifestyle changes, patient's psychological morbidity, and consideration of patient values and preferences.

Table 1 Dosing of NOAC for stroke prevention in AF[43]

NOAC agent	Standard dose	Reduced dose	Dose reduction criteria
Apixaban	5 mg twice daily	2.5 mg twice daily	If two of three fulfilled: • body weight ≤ 60 kg, • age ≥ 80 years, • serum creatinine > 133 mmol/L (1.5 mg/dL). A single criterion: CrCl 15–29 mL/min
Dabigatran	150 mg twice daily, 110 mg twice daily	Not applicable	No pre-specified dose reduction criteria in the RE-LY trial. Per SmPC: 110 mg twice daily if age > 80 years, concomitant verapamil, increased risk of GI bleeding
Edoxaban	60 mg once daily	30 mg once daily	If one of three fulfilled: • body weight ≤ 60 kg or • CrCl 15–49 mL/min or • concomitant therapy with a strong P-Gp inhibitor
Rivaroxaban	20 mg once daily	15 mg once daily	A CrCl of 15–49 mL/min

NOAC, non-vitamin K antagonist oral anticoagulant; GI, gastrointestinal; CrCl, creatinine clearance; P-Gp, P-Glycoprotein; SmPC, Summary of Product Characteristic; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy.

Patients with prosthetic mechanical heart valves

Available evidence does not support the use of NOACs in patients with prosthetic mechanical heart valves (*Table 2*). The RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) trial[54] mostly included patients early after a prosthetic heart valve implantation (when the risk of early post-operative thrombotic and bleeding complications is the highest), enrolled patients with prosthetic heart valve in the mitral or aortic position (the former being more thrombogenic than the latter) and used dabigatran, which may be a poor alternative to VKAs in patients with mechanical heart valves since the tested dabigatran dosing regimens were insufficient to inhibit persistently high local mechanical valve-related thrombin levels, while further increase in the dabigatran dose would be associated with unacceptably high bleeding event rates.[57]

Although the major lessons from the RE-ALIGN trial [i.e. (i) avoid including patients too early after mechanic valve implantation, (ii) enrol patients with less thrombogenic valves in the aortic position, and (iii) use a factor Xa inhibitor and not dabigatran] were acknowledged in the design of subsequent PROACT Xa trial,[55] apixaban was less effective than warfarin and did not reach non-inferiority in the prevention of

Table 2 RCTs comparing a NOAC vs. warfarin in patients with mechanical prosthetic heart valves

RCT	Study design	Study cohort	Main findings
RE-ALIGN[54]	A Phase II dose-validation RCT comparing dabigatran at initial dose of 150, 220, or 300 mg twice daily (based on kidney function) and then adjusted to obtain a trough plasma level of ≥ 50 ng/mL vs. dose-adjusted warfarin with target INR 2.0–3.0 or 2.5–3.5	Patients who underwent aortic or mitral valve replacement within the last 7 days (79% of patients) or ≥3 months earlier. $n = 252$ (terminated prematurely).	Increased rates of thromboembolic and bleeding complications with dabigatran, in comparison to warfarin, thus showing no benefit and an excess risk. Death or TE: HR 1.94 (95% CI, 0.64–5.86). Major bleeding: HR 1.76 (95% CI, 0.37–8.46).
PROACT Xa[55]	A prospective, randomized, open-label trial with blinded end-point adjudication, comparing apixaban 5 mg twice daily vs. warfarin (target INR 2.0–3.0). The primary efficacy end point was the composite of valve thrombosis or valve-related thromboembolism. The primary safety end point was major bleeding defined as any episode of internal or external bleeding that caused death, hospitalization, or permanent injury or necessitated transfusion, pericardiocentesis, or reoperation.	Patients with an On-X aortic valve implanted at least 3 months before enrolment. $n = 863$ (terminated owing to an excess of thromboembolic events in the apixaban group).	Apixaban was less effective than warfarin and did not reach non-inferiority in the prevention of valve thrombosis or thromboembolism in patients with an On-X mechanical aortic valve. Major bleeding rates were 3.6%/patient-year with apixaban and 4.5%/patient-year with warfarin.
RIWA[56]	A proof-of-concept, open-label, RCT assessing the incidence of thromboembolic and bleeding events of the rivaroxaban-based strategy (15 mg twice daily) in comparison to dose-adjusted warfarin.	$n = 44$ patients with a prosthetic mechanical heart valve. A 90-day follow-up.	Rivaroxaban 15 mg twice daily had TE and bleeding events similar to warfarin in patients with mechanical heart valves.

RCT, randomized controlled trial; INR, international normalized ratio; TE, thromboembolic event; HR, hazard ratio; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; RIWA, Rivaroxaban vs. Warfarin in Patients With Metallic Prosthesis.

valve thrombosis or thrombo-embolism in patients with a less thrombogenic On-X mechanical aortic valve (*Table 2*). Results of the small, proof-of-concept RIWA (Rivaroxaban vs. Warfarin in Patients With Metallic Prosthesis (RIWA) trial[56] are promising, but a larger RCT is needed to evaluate the use of rivaroxaban in patients with mechanical prosthetic heart valves.

Patients with moderate-to-severe mitral stenosis

Whereas the retrospective observational data on the use of NOACs in patients with moderate-to-severe mitral stenosis were encouraging,[58] in the recent INVICTUS (Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) RCT of $n = 4531$ patients with AF and rheumatic heart disease (mostly mitral valve stenosis, in 85% of patients),[59] VKA therapy was associated with a lower rate of a composite of cardiovascular events or death than rivaroxaban therapy, without a higher rate of bleeding.

The ongoing non-inferiority open-label RCT, DAVID-MS (DAbigatran for Stroke PreVention in Atrial Fibrillation In MoDerate or Severe Mitral Stenosis)[60] will enrol 686 patients with moderate or severe mitral stenosis in Hong Kong or China and randomize them to dabigatran (110 or 150 mg twice daily) or dose-adjusted VKA (target INR 2.0–3.0) for the prevention of the primary outcome of stroke or systemic embolism. Currently, the use of NOAC is not recommended in patients with AF and moderate-to-severe mitral valve stenosis.[14,53]

Patients with antiphospholipid syndrome

A recent systematic review and meta-analysis of four RCTs addressing the use of NOACs in patients with anti-phospholipid syndromes[61] showed that the use of NOACs was associated with increased risk of subsequent arterial thrombotic events (OR 5.43; 95% CI, 1.87–15.75; $P < 0.001$, $I^2 = 0\%$), especially stroke, and comparable risks of subsequent VTE (OR 1.20; 95% CI, 0.31–4.55; $P = 0.79$, $I^2 = 0\%$) or major bleeding (OR 1.02; 95% CI, 0.42–2.47; $P = 0.97$; $I^2 = 0\%$) compared with VKAs. Hence, patients with anti-phospholipid syndromes should be treated with VKAs in preference to NOACs.[43]

Patients with end-stage CKD or on dialysis

Based on the lack of high-quality data resulting from the exclusion criteria in respective landmark trials of NOAC in AF, dabigatran (either 150 mg or 110 mg twice daily) use is not approved in patients with a creatinine clearance (CrCl) of <30 mL/min or on dialysis in Europe (dabigatran 75 mg twice daily is approved in patients with CrCl 15–29 mL/min in the USA), while the use of rivaroxaban, apixaban, and edoxaban is not approved in patients with a CrCl of <15 mL/min or on dialysis in Europe, and apixaban is approved in patients on dialysis in the USA.[43] Indeed, the USA,[53] but not European,[14] AF guidelines provide a Class IIb recommendation that, in patients with AF and CrCl <15 mL/min or on dialysis, it might be reasonable to prescribe warfarin (INR 2.0–3.0) or apixaban for oral anticoagulation.

Results of the two small, largely under-powered RCTs (i.e. the RENAL-AF study,[62] comparing apixaban 5 mg twice daily vs. adjusted-dose warfarin with target INR 2.0–3.0, which was stopped early because of slow enrolment after only 154 patients and AXADIA (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease) study,[63] comparing apixaban 2.5 mg twice daily vs. adjusted-dose phenprocoumon with target INR 2.0–3.0, which enrolled 97 patients) showed similarly high rates of thrombo-embolic and bleeding events with apixaban and VKAs, suggesting that patients

with AF on haemodialysis remain at high risk of cardiovascular events despite OAC. However, both RCTs provide reassuring pharmacokinetic evidence that apixaban in the tested doses does not accumulate in patients with AF on dialysis.

A small three-arm Valkyrie pilot trial[64] ($n = 132$) compared rivaroxaban 10 mg once daily (with and without 2000 μg menaquinone-7 three times weekly) with VKA therapy (target INR 2.0–3.0) in patients with AF on dialysis. Compared with VKA, rivaroxaban (with or without menaquinone-7) reduced ischaemic event rate without increasing bleeding with no difference in mortality. Similar to the RENAL-AF trial, the TTR in patients on VKA was sub-optimal.

The ongoing larger RCTs of patients with AF and on dialysis will compare VKA therapy vs. no OAC [the AVKDIAL (Oral Anticoagulation in Haemodialysis Patients) (NCT02886962) and DANWARD (Danish Warfarin-Dialysis Study) (NCT03862859) trial], apixaban 2.5 mg twice daily vs. no OAC [the SACK (Stroke Prophylaxis With Apixaban in CKD5 Patients With Atrial Fibrillation) (NCT05679024) trial], and apixaban 5 mg twice daily (2.5 mg twice daily for selected patients), warfarin, and no OAC [the SAFE-D (Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis) (NCT03987711) trial], thus better informing the net clinical effect of OAC in these high-risk patients and specific OAC choice(s).

Patients with bioprosthetic heart valves

Only a small proportion of patients with bioprosthetic heart valves were enrolled in the landmark NOAC trials, 191 patients in the ENGAGE-AF (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation) (0.9% of the total study population)[65] and 120 patients in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (0.7%).[66] The effects of respective NOAC in these small subgroups were consistent to the main trial findings.

Subsequent dedicated trials (*Table 3*) in patients with AF undergoing surgical mitral or aortic valve replacement with a bioprosthetic valve showed non-inferiority of respective NOAC in comparison to VKAs for the pre-specified composite endpoint. A meta-analysis including data form the RIVER trial, a small Brazilian study of dabigatran vs. VKAs ($n = 27$), and subgroup analyses from ENGAGE-AF and ARISTOTLE trials, showed comparable rates of major bleeding (HR 0.61, 95% CI 0.34–1.09) or stroke or systemic embolism (HR 0.47, 95% CI 0.17–1.29) with NOAC vs. VKA, but the point estimates favoured NOACs.[70]

In patients with a long-term indication for OAC, current European Guidelines recommend OAC monotherapy for patients with surgical bioprosthetic valves (Class I, LoE C), with a Class IIa LoE B recommendation to consider NOAC after 3 months in patients with AF,[14,71] and NOAC can be considered in preference to VKA in AF patients undergoing bioprosthetic mitral valve replacement (Class IIb).[71] The US Guidelines recommend either a NOAC or VKA in patients with a bioprosthetic valve implanted >3 months prior (Class I, LoE A) and VKA in patients with new-onset AF <3 months after bioprosthetic valve implantation (Class IIa, LoE B).[72] For patients with an indication for OAC and undergoing Transcatheter Aortic Valve Implantation (TAVI), lifelong OAC is recommended (Class I, LoE B) with no preference expressed for NOAC or VKA, consistent with the results of ENVISAGE-TAVI AF (Edoxaban versus Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation) and ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events After Trans-Aortic Valve Implantation for Aortic Stenosis) Stratum 1 trials.[71,72]

Ongoing research

A new family of OAC agents, direct inhibitors of factor XIa asundexian and milvexian, has recently entered the phase III of a comprehensive drug development programme for thromboprophylaxis across the spectrum of indications, including stroke prevention in AF.[73] These next-generation OAC agents are expected to better preserve haemostasis, while exerting at least comparable efficacy and better safety in comparison to the current standard of care in patients with AF, as represented by the direct factor Xa inhibitor apixaban used as the comparator in the ongoing Phase III trials (i.e. NCT05643573 with asundexian and NCT05757869 with milvexian).

Bleeding risk

The risk of bleeding in patients with AF reflects the interaction of modifiable and non-modifiable bleeding risks. Various bleeding risk factors are recognized, and the more common ones have been used to formulate bleeding risk stratification scores, which have been recently reviewed.[74] The HAS-BLED score remains the best validated commonly used simple clinical bleeding risk score.[20]

The appropriate use of structured bleeding risk assessment tools is to draw attention to the modifiable bleeding risk factors for mitigation and to identify the high bleeding risk patients for early review and follow-up. This is supported by the bleeding risk analysis from the mAFA trial, where the usual care clusters had a 1-year major bleeding rate of 4.3%, while the mAFA intervention clusters using the HAS-BLED score as part of the ABC pathway reported a major bleeding rate of 2.1% at 1 year. OAC use declined in usual care, from 58.8% to 34.4% at 1 year, while in the intervention arm, OAC use increased from 53.4% to 70.2%.

Intracranial haemorrhage represents the most severe form of OAC-related bleeding, which is more evident in Asians.[75] The decision whether to restart OAC after an ICH requires difficult management decision-making,[76] although if an OAC is started, a NOAC is the preferred option.

Left atrial appendage occlusion

Rationale for left atrial appendage occlusion

There are several situations where an alternative to OAC in patients with AF may be desirable. Firstly, the use of OAC is not without risk, and patients are exposed to higher rates of bleeding while taking these medications. Therefore, there are certain situations whereby this may be deemed an inappropriate treatment option by physicians and patients alike (e.g. recent ICH, intractable recurrent GI bleeding, end-stage renal failure).[77] In addition, some patients may suffer from resistant stroke that occurs despite appropriate guideline-directed anticoagulation therapy. The commonly used strategy of switching or implementing higher doses of OAC in such patients is not supported by trial evidence. There is also an issue of compliance which may be suboptimal with these medications. In the landmark studies of DOACs, discontinuation rates were between 21% and 27%.[45–48] This may be more significant with the use of VKA, especially in younger patients where lifelong treatment and monitoring may be viewed as imposing significant lifestyle restrictions. For such patients, there is a need for a non-pharmacological solution to stroke prevention.

Observational studies in patients with non-valvular AF suggest the LAA is the site for the great majority (~90%) of thrombus formation.[78,79] The benefit of LAA ligation during cardiac surgeries has been shown by several cohort studies,[80] and recently published randomized controlled trial data have proven the efficacy of this intervention.[81] However, as most patients with AF do not require cardiac surgery, this method provides limited clinical impact for the majority. Consequently, percutaneous LAAO was introduced as a potential solution to address some of these issues in the early 2000s.[82]

Clinical data supporting left atrial appendage occlusion

Three randomized trials, two controlled against dose-adjusted warfarin and one against DOACs,[83–85] along with several meta-analyses[86–88]

Table 3 RCTs comparing a NOAC vs. VKAs in patients with AF and bioprosthetic heart valves

RCT	Study design	Study cohort	Main findings
RIVER[67]	A randomized trial comparing rivaroxaban 20 mg once daily with dose-adjusted warfarin (target INR 2.0–3.0). The primary outcome was a composite of death, major cardiovascular events (stroke, TIA, SE, valve thrombosis, or hospitalization for HF), or major bleeding at 12 months.	$n = 1005$ patients with AF and a bioprosthetic mitral valve surgically implanted at least 48 h before enrolment.	In patients with AF and a bioprosthetic mitral valve, rivaroxaban was non-inferior to warfarin with respect to the mean time until the primary outcome of death, major cardiovascular events, or major bleeding at 12 months. Death or TE: HR 0.65 (95% CI, 0.35–1.20). Major bleeding: HR 0.54 (95% CI, 0.21–1.35)
ATLANTIS (Stratum 1)[68]	An international, randomized, open-label, superiority trial comparing apixaban 5 mg twice daily (2.5 mg twice daily if impaired renal function or concomitant antiplatelet therapy) to VKAs. The primary endpoint was the composite of death, MI, stroke or TIA, SE, intracardiac or bioprosthesis thrombosis, DVT or PE, and life-threatening, disabling, or major bleeding over 1-year follow-up. The primary safety endpoint was major, disabling, or life-threatening bleeding.	$n = 1500$ patients with TAVI ($n = 451$ patients with AF).	After TAVI, apixaban was not superior to the standard of care (that is, VKA in the Stratum 1). Death or TE: HR 1.02 (95% CI, 0.68–1.05). Major bleeding: HR 0.92 (95% CI, 0.52–1.60).
ENVISAGE-TAVI AF[69]	A multi-centre, prospective, randomized, open-label, adjudicator-masked trial comparing edoxaban 60 mg once daily (30 mg once daily if CrCl 15–50 mL/min, body weight ≤ 60 kg, or concomitant P-glycoprotein inhibitor medication) with VKAs. The primary efficacy outcome was a composite of adverse events consisting of death from any cause, MI, ischaemic stroke, SE, valve thrombosis, or major bleeding. The primary safety outcome was major bleeding.	$n = 1426$ patients with AF as the indication for OAC after successful TAVR.	In patients with AF who underwent successful TAVR, edoxaban was non-inferior to VKAs for a composite primary outcome of adverse clinical events. The incidence of major bleeding was higher with edoxaban than with VKAs. Death or TE: HR 1.02 (95% CI, 0.76–1.39). Major bleeding: HR 1.40 (95% CI, 1.03–1.91).

INR, international normalized ratio; TIA, transient ischaemic attack; SE, systemic embolism; HF, heart failure; AF, atrial fibrillation; TE, thromboembolic event; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; DVT, deep venous thrombosis; PE, pulmonary embolism; TAVI, transcatheter aortic valve implantation; CrCl, creatinine clearance; TAVR, transcatheter aortic valve replacement; RCT, randomized clinical trial; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; OAC, oral anticoagulant.

have shown that LAAO treatment has compared well with OAC, both with warfarin and with DOAC therapy. There appears to be possibly a small signal of excess of ischaemic strokes with LAAO, but this is more than offset by a substantial reduction in non-procedure–related bleeding and mortality. As such, LAAO may result in net clinical benefit.[89]

In addition to the trial data, several registries have reported on the clinical value of LAAO therapy for a variety of indications[90–94] including patients for whom there is no other safe pharmacological alternatives.[91,93] This particular group of patients were excluded in the OAC vs. LAAO clinical trials. Thus far, there are no prospective controlled studies that have evaluated LAAO in patients with an absolute contraindication to anticoagulation. Current evidence is derived from registries and cohort studies. The EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the Watchman Left Atrial Appendage Closure Technology) study was a prospective observational registry of LAAO involving a total of 1025 patients, where 72% had a documented contraindication to anticoagulation.[36] At 2-year follow-up, the rates of stroke and major non-procedural bleeding were reduced by 83% and 46% compared to predicted rates based on the CHA_2DS_2-VASc and HAS-BLED scores, respectively. The ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study enrolled AF patients who were ineligible for warfarin.[37] The authors cited that haemorrhagic tendency was the most common (93%) reason for warfarin ineligibility and found that the rate of ischaemic stroke was 1.7% per year with LAAO compared to the expected 7.3% per year based on the $CHADS_2$ score. More recently, a prospective study of 1088 patients, where 83% had contraindications to anticoagulation, found that LAAO with the Amulet device was associated with a 67% reduction in ischaemic stroke rates compared to predicted risk by CHA_2DS_2-VASc score.[38]

Only a single study has specifically investigated the use of LAAO in AF patients with resistant stroke despite OAC therapy. Data from the ACP multi-centre registry showed that LAAO was associated with a 65% risk reduction in annual rates of stroke or transient ischaemic attack (TIA) and a 100% risk reduction in annual rates of major bleeding, compared to predicted rates based on the CHA_2DS_2-VASc and the HAS-BLED scores, respectively.[28]

At present, there are no studies with direct comparison of LAAO to standard medical therapy in patients with resistant stroke. With regards to compliance, an observational study by Zhai *et al.*[95] which included 338 (total $n = 658$; 51.4%) patients with non-compliance suggested that LAAO may be feasible for this indication due to low rates of procedural complications.[39]

Is left atrial appendage occlusion the only option for patients with contraindications to oral anticoagulation?

It is important to bear in mind that there are other alternatives, apart from LAAO, in patients who may be deemed unsuitable for anticoagulation with warfarin.

In a pre-specified analysis of 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, the investigators demonstrated that NOAC therapy with apixaban was tolerated in patients who previously failed treatment with warfarin due to poor anticoagulation control (42%), patient refusal (37%), and bleeding on VKA (8%).[96] The benefits of apixaban are confirmed in the long-term follow-up from this trial.[97] Moreover, for patients who are unable to tolerate even the shortest period of anticoagulation, the implantation of most LAAO devices requires long-term antiplatelet therapy, which contributes to similar bleeding risks compared with OAC.[98]

The observational data have also allowed the assessment of LAAO treatment against treatment with DOAC therapy.[99] Network meta-analysis of observational and trial data suggests that whilst LAAO may be marginally less effective than DOAC therapy at preventing ischaemic stroke, it is highly effective at reducing major and life-threatening bleeding. This advantage continues for the whole duration of treatment, suggesting that, as time passes post-implantation, this may become an increasingly important benefit when compared to lifelong DOAC therapy.[100,101]

Importance of shared decision-making with the patient

From a patient perspective, it is important to highlight that there are other factors involved beyond mere efficacy and safety when ultimately deciding on the optimal treatment option. This includes long-term quality of life, overall satisfaction, and perceived inconvenience from potential side effects or complications. As part of our holistic care for these patients, it is therefore imperative to facilitate a shared decision-making process. In fact, this has been required for financial reimbursement of LAAO in USA, as per the Centers for Medicare & Medicaid Services. In this setting, there is a case to respect patient autonomy, regardless of how *unwise* this decision may seem. Furthermore, the chance to avoid anticoagulation as afforded by LAAO may be desired by certain patients according to lifestyle preferences (e.g. participation in high-risk contact sports). Several shared decision-making tools have previously been evaluated for stroke prevention in AF, although their role in LAAO remains to be determined.

Among those patients who may seem suitable for OAC, there are some who refuse treatment (medication averse) with an OAC[102,103] and many who fail to adhere to or persist with OAC therapy, including DOAC treatment even after a previous ischaemic stroke attributable to AF.[104] In this regard, patients may be willing to be exposed to a greater initial risk if this is balanced by an improvement in quality of life and subsequent reduction in bleeding events. Furthermore, patients may have high levels of anxiety post-stroke,[105] especially in those with AF who were already on anticoagulation therapy before these events and are discharged on the same treatment. In such patients with resistant stroke, there may be a role for LAA occlusion[106] and even combination therapy for LAAO and OAC,[107,108] although this warrants further investigation.

Ongoing trials studying left atrial appendage occlusion

There are now large-scale ongoing trials comparing LAAO therapy with DOACs. Other trials are specifically enrolling patients for whom OAC is contraindicated or difficult, such as those with previous intracerebral haemorrhage, advanced chronic kidney disease, or patients for whom previous treatment with anticoagulation has failed to offer protection against ischaemic stroke. The Dutch COMPARE-LAAO (Comparing Effectiveness and Safety of Left Atrial Appendage Occlusion for Non-valvular Atrial Fibrillation Patients at High Stroke Risk Unable to Use Oral Anticoagulation Therapy) RCT (NCT04676880) intends to study whether LAAO is superior to optimal medical therapy for patients contraindicated to the use of OAC. The ASAP TOO (Assessment of the WATCHMAN™ Device in Patients Unsuitable for Oral Anticoagulation) trial (NCT02928497), which was aiming to obtain a similar proof of concept, terminated prematurely owing to low enrolment in countries that already have reimbursement for LAAO. The STROKECLOSE (Prevention of stroke by left atrial appandage closure in atrial fibrilation stroke patients with interacerebral hemorrhage) trial (NCT02830152) is randomizing patients with a previous intracranial haemorrhage to LAAO or optimal medical therapy according to the treating physician but is also facing slow enrolment for similar reasons.

Left atrial appendage occlusion: the Guidelines' view

AF guidelines for the application of LAAO treatment have been offered by the European Society of Cardiology[14,109] and other professional societies.[110–113] Several professional societies too have published consensus documents that expand on the detail available in society guidelines.[114,115] All these documents adhere to the principle that when an OAC can be used, it should take precedence over an Left atrial appendage *closure* (LAAC) implantation. However, it is important to take a shared decision-making approach, in which the patient is counselled about relevant bleeding risks with OAC and procedural complications with LAAO. The present advice from the European Heart Rhythm Association illustrates this in detail.[116]

Better symptom management

Rate vs. rhythm control on stroke

There are two primary clinical approaches to the management of AF, as follows:

(1) *Rate control:* slowing the ventricular rate to a level which is physiologically appropriate. Advantages of the rate control approach include ease simplicity avoiding the potential toxicity of anti-arrhythmic drugs or the risks and discomfort associated with electrical cardioversion or invasive left atrial ablation for recurrences of AF.
(2) *Rhythm control:* restoration and long-term maintenance of sinus rhythm; anti-arrhythmic drugs (ion channel blockers) are predominantly used, but occasionally autonomic manipulation, e.g. with beta blockers may prove valuable.

Rate control remains an essential component of therapy even if the primary strategy is rhythm control (e.g. in the case of a recurrent arrhythmia). Of the two prime treatment strategies for AF, rhythm control is intuitively more attractive as it offers physiological rate control, normal atrial activation and contraction, the correct sequence of atrioventricular (AV) activation, regular ventricular rhythm, and normal intracardiac haemodynamics and AV valve function. Thus, restoration and effective maintenance of sinus rhythm and normal atrial function has been inferred to reduce AF-related risk of stroke by eliminating some of the Virchow's triad elements that promote thrombosis within the atria (stasis, endothelial abnormality, and increased thrombogenic blood factors).

Despite these theoretical prerequisites, the 'traditional' rhythm control strategy using anti-arrhythmic drugs has not proven superior to rate control in the pivotal RCTs (*Table 4*)[117–123] because of the limited

Table 4 Studies of rate vs. rhythm control in atrial fibrillation: outcome of stroke and thromboembolism

Study	*n*	Follow-up, years	Inclusion criteria/stroke risk factors	Primary endpoint	Difference in primary endpoint RhyC vs. RC	Stroke/TE	Anticoagulation requirements
PIAF[124]	252	1	Persistent AF, 85% with (moderate) risk factors	Symptom improvement	Symptoms improved in 70 vs. 76 patients RhyC vs. RC, $P = 0.317$	Not reported	All patients received OAC during the entire study period (INR 2–3)
STAF[121]	100	1.6	Persistent AF	Composite of ACM, cardiovascular events, CPR, TE	5.54%/yr vs. 6.09%/yr RhyC vs. RC ($P = 0.99$), 18/19 primary events occurred during AF ($P = 0.049$)	3.1%/yr vs. 0.6%/yr RhyC vs. RC RhyC: 2/5 ischaemic strokes occurred on INR <2, 3/5 on stable INR > 2 RC: 1 stroke and 1 TE occurred on INR > 2 bleeding: 5.8%/yr	OAC prescribed according to the ACCP guidelines (1998) Patents 65–75 years without clinical risk factors received aspirin 325 mg. Continuation of OAC > 4 weeks post-cardioversion—at the discretion of the treating physician
HOT CAFÉ[122]	205	1.7	First episode of persistent AF	Composite of ACM, TE, bleeding	OR, 1.98 (CI, 0.28–22.3), $P > 0.71$	3 ischaemic strokes (2.9%; 2/3 occurred on day 3 post-cardioversion on stable OAC and TTR and were fatal; 1 stroke occurred during AF recurrence on aspirin) vs. 1 TE (1%) on OAC RhyC vs. RC. No major bleeding	OAC considered according to the ACCP guidelines (1998)
RACE[119]	522	2.3	Persistent AF, post-cardioversion, 91% had one or more risk factors for stroke	Composite of CVM, hospitalizations for CHF, TE, bleeding, PM, AAD adverse effects	22.6% vs. 17.2% RhyC vs. RC (n.s.)	Trend towards more TE in RhyC vs. RC (7.9% vs. 5.5%); in RhyC, 6 strokes after discontinuation of OAC, 23 strokes while INR < 2; 73% had AF at the time of stroke. Bleeding: 9 (3.4%) vs. 12 (4.7%) RhyC vs. RC 20/21 occurred on OAC, 17/20 on INR >3	Only patients in whom OAC was not contraindicated
AFFIRM[117]	4060	3.5	Age ≥ 65 years, hypertension, diabetes, impaired left ventricular systolic function, CHF, or a prior stroke or TIA, PAF, or PersAF	All-cause mortality	23.8% vs. 21.3% RhyC vs. RC [HR, 1.15 (CI, 0.99–1.34), $P = 0.08$]	Trend towards more ischaemic strokes in RhyC: 7.1% vs. 5.5%, $P = 0.79$), 79% of strokes in RhyC were due to no OAC or INR <2 ICH: 1.3% vs. 1.1% ($P = 0.73$) RhyC vs. RC *Post hoc* analysis: OAC associated with lower ACM rates [HR 0.50 (CI, 0.37–0.69), $P < 0.00001$] Major bleeding (not CNS): 6.9% vs. 7.7% ($P = 0.44$) RhyC vs. RC	The goal for OAC (warfarin) was INR 2–3. In the RhyC group, continuous OAC was encouraged but could be stopped at the physician's discretion if sinus rhythm had apparently been maintained for at least 4, and preferably 12, consecutive weeks with AADs. In the RC group, continuous anticoagulation was mandated by the protocol

Continued

Table 4 *Continued*

Study	*n*	Follow-up, years	Inclusion criteria/stroke risk factors	Primary endpoint	Difference in primary endpoint RhyC vs. RC	Stroke/TE	Anticoagulation requirements
AF-CHF[118]	1376	3.1	CHF (LVEF ≤ 35%, NYHA Class II–IV), PAF or PersAF	Cardiovascular mortality	27% vs. 25% RhyC vs. RC (HR,1.06 [CI, 0.86–1.30], $P = 0.59$)	3% vs. 4% RhyC vs. RC [HR, 0.74 (CI, 0.40–1.35), $P = 0.32$]; fatal strokes: 9 (1%) vs. 11 2%). *Post hoc* analysis: OAC associated with lower CVM [HR 0.38 (CI 0.23–0.6), $P = 0.0003$] and ACM [HR 0.48 (CI 0.30–0.77), $P = 0.0025$]. Non-CNS major bleeding: 4.4% vs. 3.6% ($P = 0.45$) RhyC vs. RC	OAC was recommended for all patients, but was not part of inclusion criteria. At enrolment, 86% and 90% patients were on OAC in RhyC vs. RC; these increased to 88% and 92% at 1 year
PAF-2[125]	137	1.3	Paroxysmal AF	Prevention of permanent AF	37% vs. 21% RhyC vs. RC, risk reduced by 57%	3 (4%) vs. 1 (1%) RhyC vs. RC	OAC recommended
J-RHYTHM[123]	823	1.6	Paroxysmal AF $CHADS_2$ 0: 43.3% $CHADS_2$ 1: 34.8% $CHADS_2$ 2+: 21.9%	Composite of ACM, stroke, TE, major bleeding, CHF hospitalization, or physical/psychologic disability requiring changes in the treatment strategy	15.3% vs. 22.0% RhyC vs. RC [HR, 0.664 (CI, 0.481–0.917), $P = 0.0128$]	Stroke: 2.1% vs. 2.7%, TE: 0.2% vs. 0.2% RhyC vs. RC. Major bleeding: 0.25% vs. 0.5% RhyC vs. RC	OAC (warfarin, INR 1.6–3) used if one of the risk factors was present (age >65 years, hypertension, diabetes, CHF, stroke/TIA/TE, LAD > 50 mm, FS < 25%, EF < 40% OAC continued irrespective of the rhythm
ORBIT-AF[126]	6988	1	First detected AF or PAF, $CHADS_2 \geq 2$	Composite of death, stroke, non-CNS embolism, and TIA	4.8% vs. 6.86% RhyC vs. RC [HR 0.90 (CI 0.77–1.06), $P = 0.2032$] Increased CV hospitalizations in RhyC [HR, 1.24 (CI 1.10–1.39), $P = 0.0003$]	First stroke, non-CNS embolism, or TIA: 1.14% vs. 1.54% RhyC vs. RC [HR, 0.87 (CI 0.66–1.16), $P = 0.3452$]	Warfarin or dabigatran in 72%
RECORD-AF[127]	5171	1	PAF or PersAF. Age ≥ 75 or 70 yr and older with ≥ 1 risk factor (treated hypertension, diabetes, previous stroke/TIA, EF ≤ 40%	Therapeutic success and clinical outcomes	Clinically significant event: 17.2% vs. 18.2% RhyC vs. RC ($P = 0.352$) CVM: 0.9% vs. 2.8% ($P < 0.001$) Increased hospitalizations for arrhythmic events (11.3% vs. 7.3%, $P < 0.001$)	1/7% vs. 2.8% RhyC vs. RC ($P = 0.008$)	Managed by treating physiscians
IMPACT *post hoc*[128]	870, 99 in RhyC	1	Ambulatory AF patients	AF-related ED visits and CV hospitalizations	18.2% vs. 12.1% RhyC vs. RC driven by ED visits; odds ratio for ED visits: 2.16 (CI 1.17–3.98), $P = 0.0141$	0.0% in RC	Managed by GP

Continued

Table 4 *Continued*

Study	*n*	Follow-up, years	Inclusion criteria/stroke risk factors	Primary endpoint	Difference in primary endpoint RhyC vs. RC	Stroke/TE	Anticoagulation requirements
CASTLE-AF subanalysis[129]	210	3.76	PAF, PersAF, CHF EF ≤35% CIED	ACM and CHF hospitalization	38.3% vs. 44.7% RhyC vs. RC [HR, 0.99 (CI 0.62–1.60), $P = 0.976$]	Not reported	Guideline-directed OAC
CABANA[130]	2204	4	PAF, PersAF. Age ≥ 65 yr or at least one risk factor for stroke CHA_2DS_2-VASc 0–1: 17.9% CHA_2DS_2-VASc 2: 25.6% CHA_2DS_2-VASc 3+: 56.5%	Composite of ACM, disabling stroke, serious bleeding, or cardiac arrest	8.0% vs. 9.2% ablation vs. drug therapy [HR, 0.86 (CI, 0.65–1.15), $P = 0.30$]	Disabling stroke: 0.1% vs. 0.7% [HR, 0.42 (CI 0.11–1.62), $P = 0.19$]. Major bleeding: 3.2% vs. 3.3% ablation vs. drug therapy [HR, 0.98 (CI 0.62–1.56), $P = 0.93$]	OAC according to 2011 guidelines, risk stratification by CHA_2DS_2-VASc
CASTLE-AF[131]	363	3.1	PAF, PersAF, CHF EF ≤35% CIED	ACM and CHF hospitalization	28.5% vs. 44.6% ablation vs. drug therapy [HR, 0.62 (CI, 0.43–0.87), $P = 0.007$]	Cerebrovascular accidents in the ablation group vs. drug therapy: (2.8%) vs. 11 (6%) HR, 0.46 (CI 0.16–1.33), $P = 0.15$	Guideline-directed OAC
CAMTAF and ARC-HF[132]	102	7.8	PersAF, CHF CAMTAF: EF < 50% ARC-AF: EF ≤35%. Mean EF: 31 ± 11%	ACM	Intention-to-treat: ACM and ACM/CV hospitalization did not differ [HR 0.89 (CI 0.44–1.77), $P = 0.731$ and HR, 0.80 (CI 0.43–1.47), $P = 0.467$, respectively] On-treatment, both reduced by 57% and 52%, respectively, in the ablation group	1 (1%) stroke in the ablation group	OAC according to AF guidelines
EAST-AFNET 4[133]	798	5.1	CHF, NYHA Class ≥ II or EF <50%	Composite of CVM, stroke, or hospitalization for worsening of CHF or for acute coronary syndrome	5.7% vs. 7.9% early rhythm control vs. usual care [HR, 0.74 (CI 0.56–0.97), $P = 0.003$]	0.4% vs. 1% early rhythm control vs. usual care [HR, 0.46 (CI 0.20–1.05), $P = 0.07$]	OAC according to AF guidelines
Inter-mountain Atrial Fibrillation Registry[134]	37 908	2.9	$CHADS_2$ 0: 35.7–38.7% $CHADS_2$ 1: 24.9–26.6% $CHADS_2$ 2: 16.5–18.2% $CHADS_2 \geq 3$: 19.5–19.9%	Long-term stroke rates	NA	Ablation: 1.4%, medical therapy: 3.5% in the matched controls without AF: 1.4%, ($P = 0.0001$ for trend)	VKA continuous use recommended if $CHADS_2 > 2$

EF, ejection fraction; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female); OAC, oral anticoagulant; AF, atrial fibrillation; INR, international normalized ratio; TE, thromboembolic event; HR, hazard ratio; CI, confidence interval; OR, odds ratio; TTR, therapeutic range; PM, pacemaker; n.s., not significant; ICH, intracranial haemorrhage; TIA, transient ischaemic attack; LVEF, left ventricular EF; CHF, congestive heart failure; CV, cardiovascular; ED, emergency department; CIED, cardiac implanted electrical device; CASTLE-AF, Catheter Ablation for Atrial Fibrillation with Heart Failure; EAST-AFNET 4, Early Treatment of Atrial Fibrillation for Stroke Prevention *Trial*; NA, Not Available; RhyC, Rhythm Control; RC, Rate Control; ACM, All-Cause Mortality; ACCP, American College of Chest Physicians; CPR, Cardiopulmonary Resuscitation; CVM, Cardiovascular Mortality; AAD, anti-arrhythmic drugs; PAF, Paroxysmal Atrial Fibrillation; PersAF, Persistent Atrial Fibrillation; NYHA, New York Heart Association; LAD, Left Atrial Diameter; FS, Fractional Shortening; EF, Ejection Fraction; CNS, Central Nervous System.

choice of drugs, their relatively low efficacy, increased and often poorly predicted risk of pro-arrhythmia, as well as untargeted side effects, particularly in older patients with concomitant heart disease who represent the largest proportion of those at risk of AF-related stroke. Later non-randomized data from AF registries and subgroup analyses have also revealed no consistent clinically significant differences, apart from incidental individual endpoints, in outcome between the two treatment strategies (*Table 4*).[126–129]

Anti-arrhythmic drugs

A significant shortcoming of earlier studies was insufficient oral anticoagulation limited to VKA and imperfect TTR maintenance which may have compromised the potentially beneficial effect of effective rhythm control. There have been no uniformed mandatory protocols for anticoagulation, and in many trials, the decision whether to prescribe an anticoagulant and for how long was left at the discretion of a treating physician. Other downsides was inability to achieve a clear difference with respect to rhythm and rate status in the two arms as a significant proportion of patients in the rhythm control arm failed to maintain sinus rhythm, and many patients in the rate control arm were in sinus rhythm at the end of the study [e.g. in the Atrial Fibrillation Follow up Investigation of Rhythm Management (AFFIRM), 42.9%, 38.5%, and 34.6% at 1, 3, and 5 years, respectively][117] and a significant cross-over between the arms [e.g. in Atrial Fibrillation in Congestive Heart Failure (AF-CHF), 21% of patients crossed over from rhythm to rate control, primarily because of the inability to maintain sinus rhythm].[118]

The major studies were AFFIRM trial,[117] RAte Control vs. Electrical Cardioversion (RACE),[119] and AF-CHF trial.[118] The largest of the trials, AFFIRM, compared two treatment strategies in 4060 patients with paroxysmal or persistent AF and one or more risk factors associated with a high risk of stroke and death (age ≥ 65 years, hypertension, diabetes, impaired left ventricular systolic function, congestive HF, or a prior stroke or TIA).[117] The primary endpoint was all cause mortality, whilst the combined secondary endpoint consisted of death, disabling stroke or anoxic encephalopathy, major bleed, or cardiac arrest. During 3.5-year follow-up, 77 ischaemic strokes occurred in the rate control arm and 80 in the rhythm control arm (5.5% vs. 7.1%, $P = 0.79$). Most strokes in both arms occurred in patients who were either not taking warfarin or who had a sub-therapeutic INR. In the rhythm control arm, 22% of strokes occurred in patients whose INR was < 2, and more than one-half (57%) occurred in patients not taking warfarin. These stroke outcomes should be also considered in the context of the likely recurrence of AF, including asymptomatic, in patients with strong risk factors for stroke.

In the RACE I trial which included 522 patients with persistent AF after previous cardioversion, 91% of whom had at least one risk factor for stroke; there has been a trend in favour of rate control with regards to the composite primary end point of cardiovascular death, hospital admission for HF, thrombo-embolic complications, severe bleeding, pacemaker implantation, and severe adverse effects of therapy: 17.26% vs. 22.6% with rate control vs. rhythm control (absolute difference, 5.4%; 90% CI, −11% to 0.4%), thus fulfilling the criterion for non-inferiority (absolute difference, 10% or less) and approaching superiority to rhythm control.[119] Thrombo-embolic events occurred in 35 patients, all of whom had risk factors for stroke, and were more frequent in the rhythm control, with six patients, all in the rhythm-control group, having the thrombo-embolic complications after discontinuation of OAC (five were in sinus rhythm), whilst 23 patients sustained an event while receiving sub-therapeutical anticoagulant therapy (INR < 2). The majority of patients (73%) with thrombo-embolic events had AF at the time of the event. The majority of bleeding events (17 of 20) occurred on INR > 3.

The AF-CHF trial compared rate and rhythm control strategies in 1376 patients with HFrEF (ejection fraction ≤ 35%, New York Heart Association (NYHA) Class II–IV) showed no benefit of rhythm control on top of optimal HF therapy in the primary endpoint of cardiovascular death as well as pre-specified secondary endpoints including total mortality, worsening HF, stroke, and hospitalization.[118] The incidence of stroke was 3% in with rhythm control and 4% with rate control.

Subsequent 'on-treatment' AFFIRM and AF-CHF analyses employing the actual rhythm status have shown that the use of OACs (mainly warfarin) has had a significant beneficial effect on survival and halved the risk of all-cause death [HR, 0.50 (CI, 0.37–0.69), $P < 0.00001$].[135,136] In AF-CHF, OACs were associated with a 62% reduction in risk in the primary endpoint of cardiovascular death [HR, 0.38 (CI, 0.23–0.65), $P = 0.0003$], consonant with proven protective effects in patients with AF and risk factors for stroke.[136]

Ablation

The outcomes of rate vs. rhythm control studies highlighted the significant survival benefit of oral anticoagulation, underscored the need for continuous oral anticoagulation irrespective of the rhythm status, and exposed the problem of sub-therapeutic INR as inadequate anticoagulation. They also revealed significant limitations of pharmacological management of sinus rhythm. Long-term maintenance of sinus rhythm has proven difficult to achieve in patients with persistent AF, and the method is time-consuming and expensive due to the costs of the anti-arrhythmic drugs and the increased need for hospitalization. In short, it has been suggested that if sinus rhythm could be achieved safely and effectively, sinus rhythm would confer a favourable outcome,[135] and a raft of small-size, open label studies of left atrial ablation have consistently demonstrated a greater freedom from AF with ensuant significant improvement in symptoms compared with pharmacological rhythm (and rate) control.[137] The results of pulmonary vein isolation have been excellent in younger patients with recent onset paroxysmal AF and no or little macroscopic left atrial substrate, with very low rates of serious peri-procedural complications, including thrombo-embolic stroke, but when ablation therapies have expanded to encompass less selective patient populations with long-standing persistent forms of AF, more advanced left atrial remodelling, complex underlying heart disease, and risk factors (including those for stroke), and the duration of follow-up has extended to more than 1 year with the associated late attrition of the short-term anti-arrhythmic effect, the difference in outcomes has become less striking, and the ease of attaining the sinus rhythm has eroded. Nonetheless, pulmonary vein isolation with additional substrate modification when feasible is considered a superior strategy when rhythm control is preferred.

However, no randomized study has yet shown an effect on hard endpoints such as cardiovascular death, stroke, or all-cause mortality. The limitations of rhythm control by ablation when applied to the typical patient with AF (older age, complex comorbidities, and risk factors) have been made evident in the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial that compared catheter ablation and drug therapy (88.4% received anti-arrhythmic drugs) for paroxysmal or persistent AF in 2204 patients aged ≥ 65 years or with at least one risk factor for stroke.[130] Over a median follow-up of 48.5 months, the primary composite endpoint of death, cardiac arrest, disabling stroke, or serious bleeding was neutral (HR, 0.86, 95% CI, 0.65–1.1, $P = 0.30$) as was the secondary point of all-cause mortality, despite a nearly halved risk of AF recurrence (HR, 0.52, 95% CI, 0.45–0.60, $P < 0.001$) in the ablation-treated group. There have also been significant reductions in cardiovascular hospitalization rates and greater improvement in symptoms and quality of life compared with medical therapy. Just over the quarter of patients crossed over to the ablation group. The study only reported the incidence of disabling strokes which was low, and the difference was not statistically significant: there were three (0.3%) events in the ablation arm and seven (0.6%) in the drug therapy arm. In the pre-specified treatment received analysis, the primary endpoint was lower in the ablation than drug therapy (HR 0.67, 95% CI, 0.50–0.89, $P = 0.006$).

The guideline recommendations are based on the intention-to-treat analysis and support the use of ablation as a second-line therapy in patients persistent AF and comorbidities with the main indication for symptom relief. In patients with paroxysmal AF or persistent AF without risk factors for recurrence, AF ablation may be considered AF catheter ablation can be used as first-line therapy (class of recommendation IIa and IIb, respectively).[138] AF ablation should be considered in clinically eligible patients with congestive HF and impaired left ventricular systolic function, particularly when tachycardia-induced cardiomyopathy is likely. In the latter setting, improvement in NYHA functional class and left ventricular systolic function owing to established rhythm control by ablation has been evidenced in a series of small randomized clinical studies,[132,139] subgroup analysis of the CABANA trial,[130] and lately, larger RCTs [CASTLE-AF (CASTLE-AF: Catheter Ablation for Atrial Fibrillation with Heart Failure) and, to some extent, Early Rhythm-Control Therapy in Patients with Atrial Fibrillation (EAST-AFNET 4, Early Treatment of Atrial Fibrillation for Stroke Prevention *Trial*)].[131,140] In the CASTLE-AF study in 363 patients with paroxysmal or persistent AF and HF with HFrEF and a cardiac implantable electronic device [implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator (CRT-D)] in whom anti-arrhythmic drug therapy failed or was poorly tolerated, ablation was associated with significantly lower rates of a composite endpoint of all-cause death and hospitalizations for worsening HF (28.5% vs. 44.6%; HR, 0.62; 95% CI, 0.43–0.87; $P = 0.007$) as well as a secondary endpoint of all-cause death (13.4% vs. 25.0%; HR, 0.53; 95% CI, 0.32–0.86; $P = 0.01$).[131] Compared with medical therapy aimed at rhythm and/or rate control, patients in the ablation group were more likely to remain in sinus rhythm and had a greater improvement in left ventricular systolic function. However, in the general AF population, <10% met the criteria of the CASTLE-AF.[141]

Both the 2020 European Society of Cardiology (ESC) Guidelines on AF and 2019 update on American College of Cardiology (ACC)/American Heart Association (AHA)/HRS AF included ablation in selected patients with symptomatic AF and HFrEF (CASTLE-AF criteria) to potentially lower mortality and hospitalization for HF with some difference in the strength of recommendation (IIa[14] vs. IIb class.[142]) The ESC Guidelines also made an emphasis on patient choice when considering ablation in patients with likely tachycardia-induced cardiomyopathy with an intent to lessen or revert left ventricular systolic dysfunction.[14]

However, none of the individual studies or meta-analyses has shown a reduction in thrombo-embolic events, not in the least because of numerically low event rates due to guideline-driven anticoagulation and better treatment of underlying heart disease. Although the guidelines and expert consensus documents allow for discontinuation of oral anticoagulation if rhythm control is achieved, risk of stroke is low, and this is patient preference,[138] ablation does not have an indication for stroke prevention or reduction.

Effect of early rhythm control on stroke and other outcomes, including death, cardiac hospitalization, symptoms, and quality of life

Effect on stroke

One important benefit of rhythm control in AF is the reduction of the risk of stroke, which has been demonstrated in many studies. While some of these studies had the rate of stroke as a separate end point, most incorporated stroke as a part of a composite end point which included other adverse events such as mortality and congestive HF.

A large population-based observational study from Canada enrolled patients older than 65 years with AF and compared the rates of stroke or TIA among patients using rhythm (Class Ia, Ic, and III anti-arrhythmics), vs. rate control (beta blockers, calcium channel blockers, and digoxin) medications.[143] It included 16 325 and 41 193 patients in the rhythm and rate control groups, respectively. Even though the rate of anticoagulation was similar in both groups, the rate of stroke/TIA incidence rate was lower in patients treated with rhythm control in comparison with rate control therapy (1.74 vs. 2.49, per 100 person-years, $P < 0.001$). This was the first large study showing a beneficial relationship between rhythm control and stroke reduction. Another landmark study was the CABANA study, which aimed to determine whether catheter ablation is more effective than conventional medical therapy for improving outcomes in AF.[130] Conventional medical therapy was defined as pharmacological rate or rhythm control, and the primary end point was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. The intention-to-treat analysis showed that there was no significant difference between the study groups in the primary outcome. However, the CABANA study was limited by the large number of patients who crossed over from the medical therapy to the ablation group. When per-protocol analysis was performed, patients who underwent ablation had a lower rate of the composite end point of death, disabling stroke, serious bleeding, or cardiac arrest at 12-month follow-up than those treated with medical therapy, with a corresponding HR was 0.73 (95% CI, 0.54–0.99), confirming the findings of prior studies.

As a result of the two above-mentioned studies and others,[144,145] it became generally accepted that rhythm control is associated with a reduction in the risk of stroke in patients with AF. None of these studies however limited their patients to those who received early rhythm control. It was not until 2020 that the impact of early rhythm control on stroke reduction was fully appreciated when the EAST-AFNET 4 trial was published.[3,133] In this randomized multi-centre study, patients who had AF diagnosed ≤1 year before enrolment were randomized to either early rhythm control or usual care. Early rhythm control included treatment with either anti-arrhythmic drugs or ablation. Usual care consisted of management of symptoms of AF. The study enrolled 2789 patients at 135 centres and was stopped for efficacy during an interim analysis after a median follow-up of 5.1 years per patient. Although not a primary end by itself, stroke occurred in 40/6813 (0.6%) in the early rhythm control group and 62/6856 (0.9%) in the usual care group with a corresponding HR was 0.65 (95% CI, 0.44–0.97).

Hence, the EAST-AFNET 4 study provides some support for early rhythm control to reduce the rate of stroke in selected patients with AF. Important limitations of the EAST study include the lack of data on the quality of adherence to OAC in the trial arms, the intervention group regularly self-recorded electrocardiogram (ECG) twice weekly, which could have improved the overall adherence to treatment, etc. A real-world analysis from the ESC EORP-AF registry found that early rhythm control was associated with a lower rate of major adverse events, but this difference was non-significant on multivariate analysis, being mediated by differences in baseline characteristics and clinical risk profile.[146] Also, early rhythm control was associated with greater healthcare resource utilization, and clinical outcomes were no different to the 'no rhythm control' group who were fully adherent to the ABC pathway.[146]

One of the most important findings of these studies is that the reduction of stroke occurred independent of anticoagulation medications, which were used equally in both rhythm and rate control groups. Collectively, these data provide ample support for rhythm control as a stroke reduction strategy.

Effect on death and cardiac hospitalization

In addition to stroke, the effect of early rhythm control on other adverse outcomes such as mortality and HF has been studied. The primary outcome for the EAST-AFNET 4 trial mentioned above was a composite of death from cardiovascular causes, stroke, or cardiac

hospitalization with worsening of HF or acute coronary syndrome (ACS).[133] The primary outcome event occurred in 3.9 per 100 person-years in the rhythm control group and in 5.0 per 100 person-years in the usual care group (HR, 0.79; 96% CI, 0.66 to 0.94; $P = 0.005$). When each of the different components of the composite end point was looked at separately, death from cardiovascular causes occurred in 67/6915 (1.0%) in the early rhythm control group and 94/6988 (1.3%) in the usual care group (HR 0.72, 95% CI, 0.52–0.98). Similarly, hospitalization with worsening of HF occurred in 139/6620 (2.1%) in the early rhythm control group and 169/6558 (2.6%) in the usual care group (HR 0.81, CI 95%, 0.65–1.02).

Since the publication of EAST-AFNET 4 trial, many subsequent studies were conducted to further define the relationship between early rhythm control and clinical outcomes. Real-world evidence supports the benefits of early rhythm control on clinical outcomes, especially if intervention was early (<3 months[147]) and in younger patients with less structural heart disease. A meta-analysis by Zhu *et al.*[148] analysed eight studies involving 447 202 AF patients, where 23.5% of participants underwent an early rhythm-control strategy. The primary outcome was a composite of death, stroke, admission to hospital for HF, or ACS. Early rhythm-control strategy was found to be superior to rate control and was associated with reductions in the primary composite outcome (HR = 0.88, 95% CI: 0.86–0.89) and secondary outcomes, including stroke or systemic embolism (HR = 0.78, 95% CI: 0.71–0.85), ischaemic stroke (HR = 0.81, 95% CI: 0.69–0.94), cardiovascular death (HR = 0.83, 95% CI: 0.70–0.99), HF hospitalization (HR = 0.90, 95% CI: 0.88–0.92), and ACS (HR = 0.86, 95% CI: 0.76–0.98).

Effect on symptoms, quality of life, and cost effectiveness

In addition to its impact on the outcomes of stroke, death, and cardiac hospitalization, the effect of rhythm control on softer outcomes such as symptoms, quality of life, and cost-effectiveness was also studied. Interestingly, the beneficial effect of rhythm control on these end points was less striking.

In the EAST-AFNET 4 study, quality of life was included as a secondary outcome and assessed using the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale and the 12-Item Short-Form General Health Survey (SF-12). AF-related symptoms and cognitive function were also analysed as secondary outcomes and assessed using the EHRA score, and Montreal Cognitive Assessment, respectively. At follow-up, most patients in both early rhythm control and usual care groups were free from AF-related symptoms, and the changes from baseline in EHRA and EQ-5D scores did not differ significantly between the two groups. Similarly, cognitive function was stable during the follow-up period and similar between both groups.

These findings were corroborated by Nakamaru *et al.*[149] who used an outpatient-based multi-centre AF registry including 2070 patients diagnosed within 5 years. The patients had health-related quality of life data collected at baseline and 1 year after treatment. They used the Atrial Fibrillation Effect on Quality-of-Life-overall summary (AFEQT-OS) score, with higher scores reflecting better quality of life. They also divided the patients into two groups according to AF stage: early and late AF (AF duration ≤1 and >1 year, respectively). After 1 year of treatment, the positive changes in the AFEQT-OS score were similar in patients with rhythm or rate control and were not affected by the AF stage.

All the data discussed above demonstrating better outcomes with early rhythm control may create some concerns about the magnitude of the economic burden associated with early rhythm control in countries with aging populations and high prevalence of AF such as USA and Europe. To that end, a cost effectiveness analysis was conducted in a German sub-study of the EAST-AFNET 4 trial and included 1664 patients randomized to early rhythm control (832 patients) and usual care (832 patients).[150] The outcomes included are cost of hospitalization and medication, as well time to primary outcome and years survived. The study showed that clinical benefits of early rhythm control can be achieved at reasonable additional costs. With a willingness-to-pay value of ≥€55 000 per year without a primary outcome or per additional life year, cost-effectiveness of early rhythm control was thought to be highly probable (≥95% or ≥80%, respectively).

In summary a large body of evidence generated over the past 5 years clearly demonstrated the superiority of early rhythm control in reducing stroke, death, and cardiac hospitalization compared to the usual care of rate and symptoms control. Interestingly, this superiority did not extend to quality of life, where early rhythm control and rate control were not significantly different. This is important because a secondary analysis of the EAST-AFNET 4 trial showed that asymptomatic patients derive the same benefit as symptomatic patients regarding the primary outcome of death from cardiovascular causes, stroke, or cardiac hospitalization.[151] As a result, the decision to establish and maintain sinus rhythm should be made without considering the presence of AF-related symptoms. Finally, most of these studies discussed in this section did not include patients with long-standing AF, a population that may need to be studied separately.

Stroke prevention after catheter ablation

Irrespective of stroke risk factors, it is generally recommended to continue OAC for at least 2 months following an AF ablation in all patients.[14,152] The recommendation is primarily based on the knowledge that catheter ablation transiently damages the endothelium, creating a sore surface, a nidus for thrombus formation, with the notion of an increased risk for thrombo-embolism irrespective of traditional risk score calculations.[153]

Beyond this time, the continuation at long-term of OAC therapy is governed primarily by the patient's stroke risk as assessed by the CHA_2DS_2-VASc score and not on the apparent success or failure of the ablation procedure. These recommendations are currently defined as Class I with a level of evidence C, i.e. according to expert opinion, in the ESC AF Guidelines and the 2017 HRS/EHRA/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Society of Electrophysiology and Cardiac Stimulation (SOLAECE) AF ablation consensus document without further specification of any cut-offs for CHA_2DS_2-VASc score.[14,152] A similar recommendation to guide decision-making on continued OAC therapy is given in the 2020 Canadian AF Guidelines, although using a divergent risk score.[154]

Several observational studies and registries have suggested that the risk of stroke after 'successful' AF ablation in a wide variety of patient risk profiles[144,153,155] is low enough to justify discontinuation of OAC beyond the first 3 months post-ablation, even though data on OAC were frequently missing[156] (*Table 5*). Studies have reported that an AF ablation strategy lowers the rate of stroke when compared to a medical approach[158] and that the stroke risk post-AF ablation is similar to that observed in a general population without AF.[134,165,166] In a large Danish National Ablation and Prescription Registry with 4050 first time AF ablation patients followed for 3.4 years, the incidence rates of thrombo-embolism with and without OAC were low 0.56 (95% CI 0.40–0.78) and 0.64 (95% CI 0.46–0.89).[160] The corresponding figures for serious bleedings were 0.99 (95% CI 0.77–1.27) and 0.44 (95% CI 0.29–0.65), respectively. It was concluded that the thrombo-embolic risk was low, and the serious bleeding risk associated with OAC [HR 2.05 (95% CI 1.25–3.35)] seemed to outweigh the benefits of thrombo-embolic risk reduction.[160] Another post-AF ablation registry reported that the incidence rates of thrombo-embolism beyond 3 months post-ablation were low and similar in those with vs. without OAC, regardless of stroke risk; 1.11 vs. 0.69 per 100 patient years ($P = 0.11$), suggesting that it may be safe to discontinue OAC post-ablation under monitoring.[172] A single-centre study reported no thrombo-embolic events late after AF ablation in patients without AF recurrences and who

Table 5 Prospective and retrospective trials on OAC post-AF ablation and risk of stroke and bleeding

Study, public	Study type	Pat no	Group comparisons	Primary outcome	Comment
Oral, *Circulaton* 2006[153]	Single centre FU 25 months	755 AF ablation	522 pts in SR, VKA discontinued in 79% of 256 pts wo stroke risk factors and 68% of 266 pts with ≥1 risk factor	No patients in whom OAC was discontinued had a TE during follow-up TE in 0.9% within 2 weeks of ablation and 6–10 months post-ablation in 2 patients (0.2%)	OAC discontinuation appears safe after successful ablation, in pts wo and with stroke risk factors
Themistoclakis, *JACC* 2010[144]	Prospective multi-centre, cohorts, FU 28 months	3355	OAC Off 2692 pts ON 663pts	Stroke; 0.07% vs. 0.45%, $P = 0.06$ Bleeds; 0.04% vs. 2%, ($P < 0.0001$)	$CHADS_2$ score ≥2; Off 13% vs. ON 37% Favoured discontinued OAC post-ablation
Yagishita, *Circ J* 2011[157]	Single centre, FU 44 months	524 AF ablation	VKA discontinued in 93% of 429 pts wo AF recurrence	No TE in pts wo AF recurrence 3% TE in pts with AF recurrence	Low TE events if SR post-ablation
Hunter, *Heart* 2012[158]	Multi-centre registry, 7 centres vs. EuroHeart Survey vs. hypothetical cohort wo AF FU 3 years	1273 vs. 5333 vs. matched hypothetical cohort	Post-AF ablation pts vs. AAD AF pts vs. general population	Stroke/TIA: 0.5% vs. 2.8% ($P < 0.0001$) vs. 0.4% per patient-year, ns. Stroke OFF OAC vs. expected annual rate: 0.7% vs. 1.9% (CHA_2DS_2-VASc = 2)	AF ablation strategy lower rates of stroke vs. patients treated medically, no different risk vs. general population.
Bunch, *Heart Rhythm* 2013[134]	Prospective AF Study Registry, FU 3 years	37 908	4212 AF ablation pts vs. 16 848 matched AF controls wo ablation vs. 16 848 wo AF	Stroke rate 1.4% in AF pts with ablation vs. 3.5% in AF controls vs. 1.4% control wo AF (P trend 0.0001) at 1 year	Stroke risk post-AF ablation similar to patients wo AF. Ablation favourably affects stroke risk in AF.
Riley, *J Cardiovasc Electrophysiol 2014*[155]	Single centre, FU 12 months	1990 patients	OAC off in 40–65%	Stroke rate/year in patients 'off 'OAC, stratified by $CHADS_2$ score similar; score 0–0.28%; score 1–0.07%; score 2–0.50%; P = NS. 75% with stroke/TIA—documented AF.	Study under-powered for conclusion on stroke events.
Noseworthy, *J Am Heart Assoc.* 2015[159]	National administrative claims database, 12 months	6886	High vs. low stroke risk groups	Stroke 1.4% in CHA_2DS_2-VASc ≥2 pts vs. 0.3% in CHA_2DS_2-VASc 0–1 pts. Cardioembolic risk increased if OAC discontinued in high-risk pts [HR 2.48 (95% CI 1.11–5.52), $P < 0.05$] but not low risk pts.	Rate of OAC discontinuation higher in low vs. high risk (82% vs. 62.5%) at 12 months (CHA_2DS_2-VASc 0–1 vs. ≥2, < 0.001)
Karasoy, *European Heart Journal* 2015[160]	AF ablation & Prescription Registry FU 3.4 years	4050	First time AF ablation pts	Incidence rates of thromboembolism with vs. without OAC 0.56 (95% CI 0.40–0.78) vs. 0.64 (95% CI 0.46–0.89). Serious bleedings w vs. wo OAC 0.99 (95% CI 0.77–1.27) vs. 0.44 (95% CI 0.29–0.65)	Serious bleeding risk associated with OAC [HR 2.05 (95% CI 1.25–3.35)], outweigh benefits of thromboembolic risk reduction.
Zheng, *Journal of Geriatric Cardiology* 2015[161]	Meta-analysis RCT AF ablation trials	13 trials, 1952 pts	1097 AF ablation pts, 855 AAD pts	No difference in ischaemic stroke/TIA in AF ablation patients 0.64% *vs.* AAD patients 0.23% (RD: 0.003, 95% CI: −0.006 to 0.012, $P = 0.470$)	Larger prospective randomized trial warranted.
Nührich, *Clin Res Cardiol* 2015[162]	Registry, FU 489 days	460	Paroxysmal AF 83 high-risk pts (previous stroke) vs. 377 low-risk pts (no stroke)	Thromboembolism more often in high-risk vs. low-risk pts (4.3 vs. 0.3%, $P = 0.05$)	OAC discontinued 38.6% high-risk vs. 66.3% low-risk ($P = 0.0001$) Favours to continue OAC post-ablation in high risk groups

Continued

Table 5 *Continued*

Study, public	Study type	Pat no	Group comparisons	Primary outcome	Comment
Gallo, *J Cardiovasc Med* 2016[163]	Retrospective study 3 AF ablation centres FU 60 months	1500	AFA with VKA vs. AFA wo VKA vs. rate control with VKA	TE not differ between groups (1% vs. 1.4% vs. 2.2%; $P = 0.45$). Bleeding events greater in pts on VKA; AFA 1.8% and rate control 2.4% vs. those without,0%, $P = 0.003$). All TE (4%) occurred in AFA pts with AF relapses ($P < 0.001$).	Routine ECG monitoring essential after OAC discontinuation in pts with high TE risk
Själander, *JAMA Cardiology* 2016[164]	Ablation Registry, 1 year	1585	Ischaemic stroke in pts with a CHA_2DS_2-VASc score ≥ 2 and discontinued vs. continued OAC post-ablation	Patients with a CHA_2DS_2-VASc score ≥ 2. Higher rate of ischaemic stroke, 1.6% vs. 0.3% per year if discontinued vs. continued OAC ($P = 0.046$).	Discontinuation of OAC post-ablation unsafe in high-risk patients
Saliba, *Heart Rhythm* 2017[165]	Database of health maintenance organization,	4741	969 Post-AF ablation pts vs. 3772 matched AF controls wo ablation	Stroke/TIA rate 2.10 vs. 3.26 per 100 person-years in ablation group vs. non-ablation group. HR stroke/TIA 0.61 (95% CI 0.48–0.79) in ablation group vs. non-ablation. Adjusted HRs stroke alone, 0.62 (95% CI 0.47–0.82)	No data available on OAC strategy. Predominantly high-risk AF ablation patients have lower risk of stroke/TIA than patients treated medically.
Srivatsa, *Circ Arrhythm Electrophysiol.* 2018[166]	Retrospective State registry, FU 3.6 yr	8338	4169 AF ablation pts vs. 4169 AF matched Controls	AF ablation lower ischaemic stroke 0.37% vs. 0.59% in controls, HR = 0.68 ($P = 0.04$; CI 0.47–0.97); haemorrhagic stroke 0.11% vs. 0.35%, HR = 0.36 ($P = 0.001$; CI: 0.20–0.64).	No data available on OAC AF ablation patients lower risk of stroke than matched AF controls
Joza, *J Cardiovasc Electrophysiol.* 2018[167]	Population-based cohort, FU 5 years	3667	1240 AF ablation pts vs. 2427 propensity score matched AF pts wo ablation	No difference for stroke (adjusted HR, 0.88; 95% CI, 0.63–1.21) or major bleeds (adjusted HR, 0.88; 95% CI, 0.73–1.06). No evidence that CA decreases stroke rsik or major bleeding when adjusting for OAC use over time	OAC post-ablation 61% vs. 68% at 5 years. Favours to continue OAC post-ablation
Atti, *J Atr Fibrillation* 2018[168]	Meta-analysis	9 observational trials, 3436 patients	CHA_2DS_2-VASc or $CHADS_2$ score ≥ 2. 1815 continued OACs vs. 1621 discontinued OAC post-AF ablation	No difference in risk of cerebrovascular events (RR: 0.85, 95% CI: 0.42–1.70, $P = 0.64$) and systemic thromboembolism (RR: 1.21, 95% CI: 0.66–2.23, $P = 0.54$). Continuation of OACs—increased risk of major bleeding (RR: 6.50, 95% CI: 2.53–16.74, $P = 0.0001$).	Discontinued OAC 3 months after AF ablation appears to be safe
Romero, *J Cardiovasc electrophysiol* 2019[169]	Systematic review, FU 39.6 months	5 studies, 3956 pts	TE events in AF post-ablation pts, on-OAC vs. off-OAC. High vs. low-risk cohorts (CHA_2DS_2-VASc ≥ 2 vs. ≤ 1)	Continued OAC associated with lower risk of TE in high-risk cohort (RR 0.41, 95% CI 0.21–0.82, $P = 0.01$) with 59% RR reduction. ICH higher in ON-OAC group (RR, 5.78; 95% CI, 1.33–25.08; $P = 0.02$). No significant benefit in low-risk cohort ON-OAC	Continued OAC after AF ablation in CHA_2DS_2-VASc $\geq$ 2results in decreased TE risk and a favourable net clinical benefit despite increased ICH. Continued OAC offers no benefit in CHA_2DS_2-VASc ≤ 1

Continued

Table 5 *Continued*

Study, public	Study type	Pat no	Group comparisons	Primary outcome	Comment
Proietti, *JCE* 2019[156]	Meta-analysis, 10 prospective and 6 retrospective cohorts	16 trials, 25 177 patients	13 166 pts off-OAC, 12 011 pts on-OAC.	No difference in TE after AF ablation in pts on-OAC vs. off-OAC (risk ratio, 0.66; CI 0.38, 1.15).	No information on AF recurrence rates in groups. No definitive conclusion on safety of OAC discontinuation after successful SF ablation
Freeman, *Circ Arrhythm Electrophysiol* 2019[170]	ORBIT registry	21 595	1087 AF ablation pts vs. 1087 propensity score matched AF cohort on AAD	Cardiovascular and neurological events—not differ between AF ablation vs. AAD with a CHA_2DS_2 VASc score ≥2/≥ 3 for men/women. 23% OAC discontinued after ablation.	No difference in adjusted rates of all-cause death in pts treated with AF ablation vs. AAD only
Packer, *JAMA* 2019[130]	RCT FU 4 years	2204	1108 AF ablation vs. 1096 drug pts	No difference in disabling stroke 0.1% vs. 0.7% [HR 0.42 (95% CI 0.11–1.62), $P = 0.19$]	OAC as recommended by guidelines. Favours to continue OAC post-ablation
Rong, *Am J Cardiol* 2020[171]	Single centre, FU 29.2 months	796 pts	Discontinued OAC 3 months post-ablation	Incidence of thrombo-embolism 1.62 vs. 0.33 per 100 patient-years in those with vs. without AF recurrence. AF recurrence the only independent predictor of thrombo-embolism [4.837 (1.498 to 15.621), $P = 0.008$].	Discontinued OAC unsafe in AF recurrence pts with high stroke risk—high incidence rate of thromboembolism.
Yang, *Europace* 2020[172]	AF ablation registry, FU 24 months	4512	3149 pts discontinued OAC (Off-OAC group) 3 months post-ablation vs. 1363 On-OAC group	Incidence rates for thromboembolism 0.54 (95% CI 0.39–0.76) vs. 0.86 (95% CI 0.56–1.30) per 100 patient-years for Off-OAC vs. On-OAC groups.	May be safe to discontinue OAC post-ablation under monitoring. AF recurrence, history of stroke, and diabetes mellitus—increased risk.
Kim, *Europace* 2021[173]	Korean National Health Insurance FU 51 days	8145	1629 AF ablation pts, 3258 AF medical therapy pts, 3258 non AF pts propensity scored matched	Incidence rate ratio of ischaemic stroke higher in sustained AF recurrence post-ablation (0.87%) vs. in sinus rhythm (0.24%, $P = 0.017$; log rank $P = 0.003$), and higher in medical therapy (1.09%) group than on-AG group (0.34%).	AF ablation reduces risk of stroke and bleeding to the extent of non-AF population compared to AAD
Pothineni, *J Cardiovasc Electrophysiol* 2021[174]	Single centre, FU 3 year	196 patients	OAC discontinued in 33.7% pts depending on stroke risk, mean 7.4 months post-ablation. 15.8% restarted OAC for AF recurrence.	21.9% reduction in time exposed to OAC. No thromboembolic or major bleeding events	ICM or CIED. Study under-powered for conclusion on stroke events
Maduray, *Clinical and Applied Thrombosis/Hemostasis* 2022[175]	Systematic review and meta-analysis	20 trials, 22 429 patients (13 505 off-OAC)	Continued vs. discontinued OAC post-AF ablation	Stratified CHA_2DS_2-VASc score ≥2 for thromboembolic events favoured OAC continuation (OR 1.86; 95% CI: 1.02–3.40; $P = 0.04$).	Findings support sustained OAC in patients with CHA_2DS_2-VASc score of ≥2.

Continued

Table 5 *Continued*

Study, public	Study type	Pat no	Group comparisons	Primary outcome	Comment
Liang, *J Cardiovasc Electrophysiol.* 2018[176]	Single centre FU 3.5 years	400	First AF ablation persistent AF pts	43.0% free of AF recurrence 43.5% off OAT at FU Cardiovascular events in 0.49/100 patient years, major bleeding in 0.98/100 patient years	Discontinued OAC in closely monitored pts wo AF recurrence—low stroke rate. Older age and CAD only predictors of CVE but not AF recurrence nor CHA_2DS_2-VASc score.

CVE, cardiovascular events; wo, without; TE, thromboembolism, ICH, intracranial haemorrhage, pts, patients; CIED, cardiac-implanted electrical device; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female); RCT, randomized clinical trial; VKA, vitamin K antagonist; AF, atrial fibrillation; TIA, transient ischaemic attack; NS, not significant; HR, hazard ratio; CI, confidence interval; RR, risk ratio; ICM, implantable cardiac monitor; CIED, cardiac implanted electrical device; OAC, oral anticoagulant; OR, odds ratio; SR, Sinus Rhythm; FU, Follow-Up; AAD, Anti-Arrhythmic Drugs.

discontinued warfarin.[157] These findings are consistent with a retrospective three-centres study reporting that all thrombo-embolic events (4%) occurred in patients with AF relapses after ablation ($P < 0.001$), while there was no difference in embolic events between groups with or without OAC.[163] A meta-analysis of 3 436 high-risk patients with $CHADS_2$ or CHA_2DS_2-VASc scores ≥2 found no difference in cerebrovascular events nor systemic thrombo-embolisms between patients continuing OAC vs. discontinuing OAC 3 months post-ablation [risk ratio (RR) 0.9, 95% CI 0.4–1.7, $P = 0.64$ and RR 1.2, 95% CI 0.7–2.2, $P = 0.54$].[168] Given the increased risk of major bleeding among those who continued OAC (RR 6.5, 95% CI 2.5–16.7, $P = 0.0001$), it was concluded that discontinuation of OAC 3 months after AF ablation appears to be safe.[168]

Other more recent national health insurance data reported lower rates of ischaemic stroke post-AF ablation in those remaining in sinus rhythm (0.24%) than in those with sustained AF recurrences (0.87%) to the extent of non-AF patients (0.34%) after 51 months and lower than a matched AF groups with medical therapy (1.09%%).[173]

Although these studies seems to support the perception that the stroke risk after a successful AF ablation is low enough to justify discontinuation of OAC, it is in sharp contrast to other studies advocating a continuation of OAC post-ablation, particularly in high risk groups,[162,164,167] In a population-based cohort of AF patients, there was no difference in stroke (adjusted HR, 0.88; 95% CI, 0.63–1.21) or major bleeds (adjusted HR, 0.88; 95% CI, 0.73–1.06) between post-AF ablation patients vs. matched AF controls adjusting for OAC use over time.[167] Moreover, in a national administrative claims database of 6886 patients, OAC discontinuation 3 months after AF ablation was associated with increased risk of thrombo-embolic events among high-risk (HR 2.48, 95% CI 1.11–5.52, $P < 0.05$) but not lower-risk patients.[159] A meta-analysis of AF ablation randomized trials reported no difference in ischaemic stroke/TIA in AF ablation patients, 0.64%, vs. AAD patients, 0.23% (risk differences: 0.003, 95% CI: −0.006 to 0.012, $P = 0.470$),[161] which is similar to findings in study from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) registry,[170] although data on OAC therapy were lacking. The importance of continued OAC in high stroke risk AF patients was underlined in a single-centre study related to the high incidence of thrombo-embolism in patients with vs. without AF recurrences post-ablation (0.62 vs. 0.33 per 100 patient-years).[171] AF recurrence was the only independent predictor of thrombo-embolism [4.837 (1.498–15.621), $P = 0.008$].[171] In a similar study of persistent AF patients, older age [HR =1.23 (95% CI: 1.09–1.38), $P = 0.001$] and coronary artery disease [HR = 5.36 (95% CI: 1.19–24.08), $P = 0.028$] were the only predictors associated with cardiovascular events post-ablation, while AF recurrence or CHA_2DS_2-VASc score was not.[176]

In a systematic review of five AF ablation studies, continued OAC after AF ablation in high stroke risk patients (CHA_2DS_2-VASc c ≥ 2) was associated with decreased thrombo-embolic events and a favourable net clinical benefit despite increased intracranial bleedings.[169] A more recent meta-analysis including 20 studies with 22 429 patients (13 505 off-OAC) stratified CHA_2DS_2-VASc score ≥2 examining thrombo-embolic events, also favoured OAC continuation (OR 1.86; 95% CI: 1.02–3.40; $P = 0.04$).[175]

Randomized trials to guide clinicians on whether 'successful' AF ablations are sufficiently protective against stroke to permit discontinuation of long-term use of OAC are currently lacking. Two randomized trials addressing the prognostic impact of rhythm control therapies in general AF populations, the ATHENA (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter) trial, comparing dronedarone vs. placebo,[177] and the EAST trial, assessing the efficacy of early rhythm control vs. usual care,[133] both demonstrated a favourable outcome for the rhythm control arm, including a reduction in

stroke rate. This is in contrast to the findings in the CABANA trial, comparing AF ablation vs. anti-arrhythmic drug therapy, which failed to show a significant reduction in primary endpoint and ischaemic stroke by AF ablation, albeit not surprising given the high cross-over rates.[130]

Despite this lack of knowledge, 16% of centres discontinued OAC even in patients at high risk[178] and in another survey a majority based their decision not only on stroke risk factors alone but also considering clinical results and patient preference.[179] When assessing the risk for stroke after AF ablation, other factors apart from conventional stroke risk factors may influence the likelihood of stroke, including the time spent in AF (AF burden) post-ablation, the presence of left atrial fibrosis/cardiomyopathy, secondary effects of extensive left atrial ablation lesions, other disease states, and effect of any therapies that might affect the stroke risk.

While the definition of a 'successful' AF ablation procedure relates to the absence of AF recurrences post-ablation, it is complicated by the various definitions used and applied ECG monitoring technique. Freedom from AF for the discontinuation of OAC cannot rely on absence of symptoms alone, as evident by the 12–37% under-estimation of AF recurrences post-ablation[180,181] and reports that almost 50% are asymptomatic AF recurrences.[182] Moreover, short-term freedom from recurrent AF might not predict long-term success, as there is a progressive decline in efficacy.[183–185] Both paroxysmal and persistent AF progress to more persistent forms with higher AF burden with time,[186] and even though AF progression was greatly slowed by rhythm control in registry studies[187] and randomized trials,[188] it was not eliminated.

More persistent AF forms and high AF burden are associated with higher thrombo-embolic risks than paroxysmal.[189] In a retrospective cohort study of paroxysmal AF patients, ≥11% cumulative burden of AF, assessed by 14-day continuous ECG monitoring, was associated with a higher risk of ischaemic stroke while off-OAC even after adjusting for known stroke risk factors.[190]

There is great controversy about what amount of AF leads to increased risk of stroke, and the question is which AF duration cut-off should define an AF recurrence for which OAC should be discontinued or reinitiated. It was recently demonstrated that there is a clinically relevant dose–response relationship between increasing AF burden in paroxysmal AF patients and increasing risks of ischaemic stroke and mortality at 1 and 3 years.[191] The study showed that episodes of AF ≥24 h were associated with a 37% increase in the adjusted risk of ischaemic stroke, while durations < 23 h were not associated with significantly increased risk,[191] in line with the ASSERT (Atrial Fibrillation Reduction Atrial Pacing Trial) trial suggesting that clinically meaningful risk emerges with AF durations >24 h.[192] Another retrospective study including non-anticoagulated patients with implantable cardiovascular devices[193] reported that the stroke risk crossed an actionable threshold defined as >1%/year in patients with a CHA_2DS_2-VASc score of 2 with AF >23.5 h, a CHA_2DS_2-VASc score 3–4 with AF >6 min, and patients with a CHA_2DS_2-VASc score ≥5 even with no AF.

So far, the role of continuous ECG in monitoring post-AF ablation has not been thoroughly discussed in the decision-making process about when to discontinue or reinitiate OAC. The randomized AF ablation trials using continuous ECG monitoring demonstrated that intermittent Holter monitoring post-ablation significantly underestimate both AF recurrences and AF burden.[194–196] Given this knowledge, even regular and prolonged intermittent ECG monitoring for AF burden estimates post-ablation, would at this point in time not be advised in cases with preference to discontinue anticoagulation, even if at low risk.[197]

Even in the absence of AF recurrences or high AF burden post-ablation, one may question a mechanistic link between AF and stroke risk related to the reported lack of clear temporal relationships.[198,199] Some strokes may thus not be caused by AF directly but rather serve as a marker for vascular mechanisms with which AF is frequently associated.[200–203]

Given the continuum of increasing age and frequently change in comorbidities with associated change in thrombo-embolic risk profile, 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.[204] Moreover, the extent of ablation lesions may also render patients more prone to an atrial cardiomyopathy state with a higher risk of stroke.

A strategy of 'pill-in-the-pocket' anticoagulation with NOACs triggered by AF episodes on continuous ECG monitoring devices was tested in two trials enrolling patients with non-permanent AF and low risk for stroke.[205,206] The recurrence of AF defined as a 6 min episodes (total AF burden >6 h/day) or ≥1 h, respectively, triggered re-initiation of NOAC, which decreased OAC utilization by 75% and 94%, respectively. No thrombo-embolic events were observed during the 12 months follow-up, although studies were not powered to assess the safety of subsequent stroke risk.

Even though observational studies reported that the risk of stroke or transient ischeamic attack (TIA) among patients who discontinued OAC after 'successful' AF ablation was as low as 0.7% per year, the studies were limited by a lack of information about stroke risks and medical comorbidities and were all non-randomized with associated limitations. Moreover, given the recent reports of a favourable net clinical benefit of continued OAC post-ablation in AF patients with CHA_2DS_2-VASc scores ≥2, it is currently questionable to discontinue OAC in AF patients with moderate or high stroke risk.

It therefore seems reasonable to advice against discontinuation of OAC after a successful ablation in patients with CHA_2DS_2-VASc score ≥ 2.

Only large RCTs can provide definitive answers on whether OAC can be safely discontinued in different subsets of patients. Although several ongoing trials (*Table 6*) may guide us for a better decision-making regarding OAC on long-term post-ablation, two of the trials rely mainly on the occurrence of silent emboli detected on magnetic resonance imaging.[207,208] Even though silent cerebral emboli may be clinically important given the association between AF and increased risk of dementia[210,211] and future risk of stroke,[212,213] it is yet unclear whether AF ablation can prevent such silent emboli and thereby even clinical strokes in such patients.

Comorbidities and lifestyle changes

Comorbidity, cardiovascular risk factors, and unhealthy lifestyle behaviours may cause alterations in myocardial function and structure, thus facilitating the occurrence of AF which, in turn, may result in additional AF-related electrical and structural remodelling of atrial and ventricular myocardium.[214,215] This multiple factor-related progression of abnormal atrial (and ventricular) substrate translates into poorer outcomes with rhythm control strategies, as well as a greater risk of AF-related morbidity and mortality.[214]

In 2019, there were 0.32 million [95% uncertainty interval (UI) 0.27 to 0.36] deaths from AF globally, and these age-standardized deaths were mostly attributable to high systolic blood pressure (34.0%; 95% UI, 27.3 to 41.0), high body mass index (20.2%; 95% UI, 11.2 to 31.2), alcohol use (7.4%; 95% UI, 5.8 to 9.0), smoking (4.3%; 95% UI, 2.9 to 5.9), and high-sodium diet (4.2%; 95% UI, 0.8 to 10.5).[216] These findings underscore an urgent need for widespread implementation of sustainable strategies and interventions addressing modifiable risk factors in patients with AF.

Indeed, AF rarely comes truly alone. Reportedly, nearly 50% of patients with low risk profile at the time of first-onset AF were subsequently diagnosed with a clinically overt disease (mostly hypertension) in the next few years, most commonly within 6 months after first-

Table 6 Ongoing randomized control trials evaluating strategies for prevention of stroke or silent embolism following AF ablation

Trial Acronym	No. of patients, follow-up	Inclusion criteria	Primary endpoint	Treatment arms
Schrickel, ODIn-AF (NCT02067182)[207]	564, 1 year	Paroxysmal or persistent AF CHA_2DS_2-VASc score ≥ 2 Sinus rhythm and no clinical AF recurrence after 3 months blanking and 3 months observation after ablation (72 h Holter)	New silent cerebral embolism or stroke on MR at 12 months vs. baseline MR	Dabigatran vs. discontinued OAC
Verma, OCEAN trial (NCT02168829)[208]	1572, 3 years	AF, ≥1 stroke risk factor without recurrent AF ≥ 1 year post-ablation on serial 24 h Holter.	Composite stroke, systemic embolism, or silent stroke on brain MR.	Rivaroxaban vs. ASA
Wazni, Am Heart J 2022, OPTION (NCT03795298)[209]	1600, 3 years	AF, AF ablation, CHA_2DS_2-VASc ≥2 men or ≥3 women	Composite stroke, systemic embolism or all-cause death, non-procedural major bleeding or clinically relevant non-major bleeding	WATCHMAN FLX vs. OAC

AF, atrial fibrillation; MR, magnetic resonance imaging; OAC, oral anticoagulation; OCEAN, Optimal Anti-Coagulation for Enhanced-Risk Patients Post-Catheter Ablation for Atrial Fibrillation; ODIn-AF, Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation With Dabigatran After PVI for Atrial Fibrillation; OPTION, Comparison of Anticoagulation With Left Atrial Appendage Closure After AF Ablation; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female); ASA, acetylsalicylic acid.

diagnosed AF,[204] which highlights the importance of periodical risk profile re-assessment in patients with incident AF, as recommended in the latest ESC AF Guidelines.[14]

The risk of major cardiovascular adverse events (MACEs) including morality in patients with AF increases proportionally to increasing burden of comorbidities[217–220] and/or clustering of unhealthy lifestyle behaviours.[221] Patients with AF have a greater risk of multi-morbidity (i.e. the presence ≥ 2 concomitant chronic comorbidities) in comparison to individuals without AF.[218,222] A recent systematic review and meta-analysis of reports from 54 countries revealed a global prevalence of multi-morbidity of 37.2% (95% CI, 34.9–39.4) among adults and 51.0% (95% CI, 44.1–58.0) among individuals ≥ 60 years of age.[223] The prevalence of multi-morbidity in contemporary AF cohorts, however, is nearly 2.5-fold higher, ranging from 80%[219,222,224] to >90%.[225]

Patients with AF may have variable clinical phenotypes regarding concomitant comorbidities and unhealthy lifestyle behaviours. Whereas the risk of MACE was significantly higher in both patients with non-cardiovascular comorbidities and those with cardiovascular risk factors/comorbidities in comparison to low-risk patients, the risk of MACE also was significantly higher in patients with cardiovascular risk factors/comorbidities than in those with non-cardiovascular comorbidities in a large registry-based AF cohort.[220]

The risk of potentially deleterious consequences of the complex circulus vicious resulting in AF substrate development and progression can be effectively reduced by timely identification and optimal management of comorbidities, modifiable cardiovascular risk factors and unhealthy lifestyle in patients with AF, as promoted in recent AF guidelines.[14,226]

In addition to numerous observational studies, increasing number of RCTs has examined the effects of comorbidity/unhealthy lifestyle behaviours management in patients with AF (*Tables 7* and *8*). Notably, most of the earlier RCTs were focused on a single comorbidity or an isolated component of lifestyle behaviours (*Table 7*). Some of these studies reported neutral effect most likely owing to such selective approach not accounting for clinical complexity and clustering of risk factors in participating patients. Indeed, most of the RCT of interventions addressing multiple modifiable risk factors yielded positive findings in terms of reducing AF symptoms, AF burden, or increasing the success of rhythm control strategies (*Table 2*).

Overall, available evidence clearly supports active efforts to identify and address comorbidity, risk factors, and unhealthy lifestyle behaviours in patients with AF, suggesting that multi-disciplinary structured approaches addressing multiple risk factors (rather that selectively focusing on a single risk factors) are more effective in reducing AF burden and improving outcome in AF patients.[300,301] Since patients with AF may first come to attention of physicians of various specialties, simple pathways for integrated holistic care for AF patients, such as the ABC pathway recommended by the ESC AF Gudelines,[14] are essential to their optimal management.

Notably, the long-term adherence to structured multi-disciplinary interventions addressing risk factors may be challenging.[302] More data are needed to inform optimization of the structure and targets of integrated treatment strategies, especially in clinically complex multimorbid patients with AF, in whom the use of artificial intelligence[303] could inform more clinically useful targeted approach(es) instead of a 'treat all' strategy which may not be feasible or sustainable. The ongoing research, including the 2020 EU Horizon AFFIRMO[37] and EHRA-PATHS (Addressing multimorbidity in elderly atrial fibrillation patients through interdisciplinary, patient-centred, systematic care pathways)[304] Research Projects will provide more data regarding the optimization of management of patients with AF in clinical practice.

Special circumstances with regards to stroke prevention in atrial fibrillation

Atrial fibrillation and coronary artery stenting

Antithrombotic therapy to prevent bleeding and ischaemic events is changeling in patients with AF who require antiplatelet therapy for percutaneous coronary intervention (PCI) and/or ACS.[305–308] All published NOAC AF PCI studies [PIONEER-AF (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral

Table 7 Comorbidity and risk factor overview and RCTs focusing on a single comorbidity or unhealthy lifestyle behaviour (positive studies are highlighted in *italics*)

Risk factor	Impact on AF
Hypertension	• The most prevalent comorbidity in AF patients,[227] with prevalence ranging from 49% to 90% in epidemiological studies and registries[228,229] • The presence and burden of hypertension is important risk factor for incident AF[227,230] and AF progression[231,232] • Hypertension increases the risk of major adverse outcomes (e.g. stroke,[233] major bleeding,[234] death[235]) in AF patients,[229] even when on OAC[236] • Among AF patients on OAC, the risk of ischaemic stroke increases for 6–7% per 10 mmHg increase in systolic blood pressure[236]

RCT	Study population	Intervention	Outcomes
SMAC-AF[237]	Patients undergoing ablation for AF: • Aggressive treatment group ($n = 88$) • Standard care ($n = 85$)	Target systolic BP <120 mmHg	**AF recurrence post-ablation** • Aggressive treatment group: 71% • Standard care: 64% (HR 1.12; CI, 0.78–1.62)
Pokushalov et al.[238]	*Patients undergoing PVI with resistant hypertension:* • *14 PVI only ($n = 14$)* • *PVI + RAD ($n = 13$)*	*Renal artery denervation*	***AF freedom post-ablation*** • *PVI only: 69%* • *PVI + RAD: 29%*
ERADICATE-AF[239]	*Patients undergoing PVI with resistant hypertension:* • *PVI alone ($n = 148$)* • *PVI + RAD ($n = 154$)*	*Renal artery denervation*	***AF freedom post-ablation*** • *PVI only: 57%* • *PVI + RAD: 72%* *(HR 0.57; CI, 0.38–0.85)*

Diabetes mellitus	• DM is a risk factor for incident AF,[240] especially asymptomatic AF,[241] and a risk factor for stroke[242] • Aggressive glycaemic control has been associated with reduced risk of AF development and recurrence in observational studies[243,244] • The efficacy and safety of catheter ablation for AF is comparable with that in unselected AF patients, especially in younger patients with well-controlled blood sugar[245] • Blood glucose control may be and important strategy for reducing recurrent AF burden in patients undergoing catheter ablation for AF[246]

RCT	Study population	Intervention	Outcomes
Deshmukh et al.[247]	*Patients with diabetes undergoing ablation for AF:* • *Metformin ($n = 182$)* • *No metformin ($n = 89$)*	*Metformin vs. no metformin*	***AF freedom post-ablation*** • *Metformin: 55%* • *No metformin: 40%* *(aHR 0.66; CI, 0.44–0.98)*

Obesity	• Genetic variants associated with increased BMI correlate well with incidence of AF[248] • Obesity is a risk factor for incident AF (a 4% increase in the risk of AF per 1-unit increase in BMI,[249] 29% risk increase for each 5-unit increase in BMI[250]), including postoperative AF[250] • The risk of AF is associated with epicardial and abdominal fat[251] • Higher BMI and obesity are associated with AF progression and increased AF burden[252–254] • Weight fluctuations can modulate the risk of AF and AF persistence[251,252] • Prospective observational data suggest that, for overweight or obese patients with AF, targeting at least a 10% weight reduction is needed to impact the reduction in AF burden progression and/or a reversal in AF burden.[255–257] Indeed, a modest weigh loss in combination with increased physical activity was ineffective in the prevention of incident AF in patients with diabetes mellitus[258]

RCT	Study population	Intervention	Outcomes
No RCT focusing solely on the weight reduction (see *Table 2* for RCTs exploring a structured intervention)			

Sleep disordered breathing	• Reportedly, SDB is associated with a two-fold increase of AF[259] • Evidence suggests a 'dose-dependent' relationship between severity of SDB and AF incidence, burden, and response to treatment[260,261] • Observational data showed that patients with OSA had a 25% greater risk of recurrent AF after catheter ablation for AF than those without OSA[262] • Several observational or registry-based studies have shown that patients using CPAP for OSA had a 42% lower risk of AF (especially younger, obese, or male patients),[263] lower AF recurrence rate after cardioversion[264] or AF progression[265]

RCT	Study population	Intervention	Outcomes
Hunt et al.[266]	Patients with OSA and AF undergoing PVI • CPAP ($n = 37$) • Standard care ($n = 46$)	CPAP	**AF recurrence post-ablation** • CPAP 57% • Standard care 57% (OR 1.0; CI, 0.4–2.4)
Caples et al.[267]	Patients with OSA and AF undergoing electrical cardioversion • CPAP ($n = 12$) • Standard care ($n = 13$)	CPAP	**AF recurrence after successful electrical cardioversion** AF recurred in 25% of patients in each group

Continued

Table 7 *Continued*

Risk factor			Impact on AF
	Traaen et al.[268] Patients with OSA and non-permanent AF implanted a loop recorder • CPAP ($n = 55$) • Standard care ($n = 54$)	CPAP	**AF burden** No difference between the groups
Physical activity	• Increasing body of evidence suggests that physical inactivity is an independent risk for AF[269–272] • Regular moderate-intensity aerobic exercise may reduce the risk of new-onset AF[269,270,273] and partially offsets the increased risk of AF in obese individuals[271,273] • An inverse relationship between cardiorespiratory fitness and AF burden has been reported in middle aged or elderly people,[274] and higher cardiorespiratory fitness and gaining 1 metabolic equivalent were associated with a 9% decline in AF recurrence after adjustment for body weight and other cardiac risk factors[275] • Athletes could have a five-fold greater risk of AF compared with age-matched controls,[276] and the risk could increase with increasing exercise severity[277] • A single-centre pre- vs. post-study showed that 3 months of yoga training reduced AF-related symptoms and AF burden, and improved several domains of QoL[278] • An RCT comparing high intensity interval training with yoga showed that high intensity exercise adversely affected atrial remodelling in healthy middle-aged sedentary adults, with no significant changes in the yoga arm[278]		
	RCT	**Study population**	**Intervention** / **Outcomes**
	Hegbom et al.[279]	*Patients with permanent AF* • *2-month exercise training programme ($n = 15$)* • *2-month control period with subsequent exercise training programme*	*Exercise training programme consisting of 24 training sessions with aerobic exercise and muscle strengthening* ***Health-related QoL, symptoms*** • *No difference between the study arms at 2 months* • *Pooled study cohort before and after training—a significant improvement in HRQoL, symptoms during exercise testing and exercise capacity after a short-term exercise training programme*
	Osbak et al.[280]	*Patients with permanent AF ($n = 45$)* • *12-week aerobic exercise* • *Control*	*A 12-week aerobic exercise training.* ***Exercise capacity, QoL*** *Significantly increased exercise capacity and 6MWT, decreased resting pulse rate and improved QoL in active patients. Cardiac output and natriuretic peptides were unchanged in both groups*
	Kato et al.[281]	*Patients undergoing ablation for AF* • *Rehab group ($n = 30$)* • *Usual care ($n = 24$)*	*A 30 min 2–3 times weekly moderate intensity, 60 min exercise endurance programme* ***AF recurrence post-ablation*** • *Rehab: 24%* • *Usual care: 26%* *(RR 0.83; CI, 0.33–2.10)*
	Malmo et al.[282]	*Patients with non-permanent AF implanted with a loop recorder to record AF burden* • *Aerobic interval training group ($n = 26$)* • *Control group ($n = 25$)*	*Aerobic interval training* ***Time in AF, symptoms, cardiovascular health, and QoL*** *Reduced time in AF, significant improvement in symptoms, O_2 peak, left atrial and ventricular function, and QoL compared with the control group*
	Skielboe et al.[283]	Patients with non-permanent AF ($n = 75$) • Low-intensity exercise • High-intensity exercise	Comparison of low vs. high intensity exercise in reduction of AF burden **Reduction in AF burden** No significant difference in AF burden reduction. No evidence of an increased risk was found for high-intensity compared with low-intensity exercise
Alcohol	• Excessive alcohol consumption is associated with atrial remodelling and increased risk of incident AF in a dose-dependent manner[284–286] • A curvilinear association between alcohol and the risk of AF has been reported, with no risk for ≤1 drink per day, minimal risk for ≤7 drinks per week, and significant risk increase for >14 drinks per week[287]		
	RCT	**Study population**	**Intervention** / **Outcomes**
	Voskoboinik et al.[288]	*Patients with non-permanent AF drinking ≥ 10 drinks per week* • *Abstinence ($n = 70$)* • *Control ($n = 70$)*	*Abstinence from alcohol* ***Freedom from AF recurrence after a 2-week 'blanking period' and total AF burden during 6 months of follow-up*** • *Recurrent AF: 53% in the abstinence vs. 73% in the control group (HR 0.55; CI, 0.36–0.84).* • *AF burden: 0.5% vs. 1.2% ($P = 0.01$)*
Coffeine	• There may be a week association between coffee drinking and the risk of incident AF, with possible protective effect of low or elevated caffeine doses[289–291] • Nevertheless, >3 cups of coffee were associated with lower probability of spontaneous cardioversion in a cohort of otherwise healthy individuals with first-onset AF[292]		
	RCT	**Study population**	**Intervention** / **Outcomes**
	No RCT focusing on the effects of coffee consumption in AF patients		

Continued

Table 7 *Continued*

Risk factor	Impact on AF		
Cigarette smoking	• Tobacco use has been associated with increased risk of AF,[293–295] and a dose-dependent relationship between smoking and the risk of AF has been observed when active smokers were compared with former smokers[295] • Reportedly, smoking negatively affected the efficacy of catheter ablation for AF and was associated with increased risk of AF recurrence after ablation[296]		
	RCT	**Study population**	**Intervention**	**Outcomes**
		No RCT focusing on the effects of smoking cessation in AF patients		

AF, atrial fibrillation; OAC, oral anticoagulant; RCT, randomized clinical trial; BP, blood pressure; HR, hazard ratio; CI, confidence interval; PVI, pulmonary vein denervation; RAD, renal artery denervation; DM, diabetes mellitus; BMI, body mass index; SDB, sleep disordered breathing; OSA, obstructive sleep apnoea; CPAP, continuous positive airway pressure; QoL, quality of life; HRQoL, health-related QoL.

Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) PCI trial, RE-DUAL (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) PCI trial, AUGUSTUS (Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention) trial, ENTRUST (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) AF PCI trial] used safety parameters as primary endpoints.[305–308] Bleeding endpoints were typically defined as major bleeding or clinically relevant non-major bleeding.[305–308] Secondary efficacy endpoints included all-cause death, cardiovascular death, trial-defined MACE, MI, stroke, and stent thrombosis (ST). In addition to the four randomized controlled trials, several meta-analyses were presented to discuss this in more detail using larger retrospective datasets.[309–313] Overall, regimens of NOACs plus a P2Y12-inhibitor were associated with lower bleeding risk compared with VKAs plus dual antiplatelet therapy. Moreover, regimens that stopped aspirin in the early phase after stenting (<30 days) caused less intracranial bleeding, while preserving efficacy. It was shown that bleeding events immediately after PCI were related to the puncture site and different from organ bleeding during follow-up. Thus, the access site is of importance to reduce the bleeding rates with lowest rate after puncture of the radial artery.[308]

At present, it remains unclear if the use of ticagrelor or prasugrel as more potent P2Y12-inhibitor reduces the ischaemic risks in this setting. Importantly, a recent sub-analysis of the ENTRUST-AF PCI study could demonstrate that in patients with AF who underwent PCI, the edoxaban-based regimen, as compared with VKA-based regimen, provides consistent safety and similar efficacy for ischaemic events in patients with AF regardless of their clinical presentation with ACS or chronic coronary syndrome (CCS).[311] Furthermore, it was shown that the CHA_2DS_2-VASc score above 4 was helpful to predict the occurrence of ST in AF patients after PCI and stenting.[314] Interestingly, the pattern of AF was also identified in a substudy to have an impact on outcome and ACS during follow-up.[314] This finding is in line with other studies showing that patients with low AF burden (first manifestation; new-onset AF) or paroxysmal AF had more frequent ACS during follow-up than patients with non-paroxysmal AF.[314–316] This finding may need further investigation to validate these results.

Overall, the 2020 ESC guidelines on diagnosis and management of AF recommend early cessation (≤1 week) of aspirin and continuation of DAT with a NOAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 12 months in AF patients with ACS.[14,317] The NOAC practical guide also suggests to stop clopidogrel after 6 months in patients with CCS and to continue with monotherapy using a NOAC.[318] Nevertheless, the molecular interaction among endothelium, stent struts, and platelet activation in patients with irregular blood flow due to AF warrants further investigation. Biomarkers might be helpful to identify certain subcohorts.[319]

The elderly, frail, and multi-morbid

In AF, older age has always represented an important and prominent clinical factor. Indeed, both prevalence and incidence progressively rise with age,[14] influencing significantly the clinical management.[320,321] In particular, older age has been described consistently as a significant barrier to the prescription of OAC drugs, linked to the perceived high risk of bleeding and bleeding-predisposing factors (i.e. risk of falls, ability to comply with drugs prescription, dementia).[320] Moreover, older age is described frequently as a significant predictor of OAC non-adherence in clinical practice.[322] Recent analyses coming from the

Table 8 RCTs of interventions addressing multiple risk factors

Study	Cohort size (*n*)	Intervention	Follow-up	Main findings
Abed *et al.*[297]	150	Participation in a physician-led multiple risk factor modification clinic managing weight loss, OSA, hypertension, tobacco, alcohol, and glycaemic control.	15 months	Intervention groups had lower AF symptom burden scores (11.8 vs. 2.6 points; $P < 0.001$) and fewer AF episodes (2.5 vs. no change; $P = 0.01$) and total duration (692-min decline vs. 419-min increase; $P = 0.002$).
Rienstra *et al.*[298] RACE 3	245	Risk factor–driven upstream therapy with MRAs, statins, ACE inhibitors or ARBs, and cardiac rehabilitation (physical activity, dietary restrictions, counselling) in patients with early persistent AF and heart failure.	1 year	Sinus rhythm at 1 year after cardioversion by 7-day Holter monitoring occurred in 75% of the intervention and 63% of the conventional group (OR, 1.765; $P = 0.021$).
Gessler *et al.*[299] SORT-AF	133	Weight-loss, dietary changes, a 6-month exercise programme in symptomatic non-permanent AF patients with a BMI 30–40 kg/m^2 implanted with a loop recorder and undergoing catheter ablation for AF.	1 year	AF burden reduction • Intervention group: 21.55 ± 36.03% to 3.70 ± 12.54% • Control: 22.4 ± 36.78% to 4.21 ± 11.28% Between group difference: 0.005% (−0.04 to 0.05).

OSA, obstructive sleep apnoea; AF, atrial fibrillation; MRA, mineralocorticoid receptor antagonist; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; RCT, randomized controlled trial; OR, odds ratio.

USA, focusing on patients ≥65 years old with high thrombo-embolic risk, indeed revealed the fact that despite a significant OAC uptake over time, there is still a substantial under prescription, particularly in oldest-old and in patients with chronic conditions.[323,324]

In the last years, despite these data still underlining the importance of 'chronological' age, there has been a progressive interest in studying and understanding the relationship between some 'geriatric' syndromes and AF, such as multi-morbidity, polypharmacy, and frailty, which all appeared to influence significantly clinical management and risk of adverse outcomes.[225,325–328] The presence of all these syndromes/phenomena entails the so-called 'clinical complexity', which substantially affects all clinical aspects regarding the management and the natural history of AF patients.[219]

In *Table 9*, we summarize the main results from some of the larger studies published regarding the influence of geriatric syndromes on OAC prescription.

Multi-morbidity, intended as the presence of several different chronic clinical conditions, appears to be a strong determinant and barrier to OAC prescription. An increasing burden of multi-morbidity expressed by the Charlson Comorbidity Index (CCI) was found inversely associated with OAC prescription, as well as 'high' multi-morbidity was associated with a lower likelihood of being prescribed with OAC.[218] In another study, a very high burden of comorbidities (≥6) was associated with a 30% lower likelihood of being prescribed with OAC, while a progressively higher number of comorbidities was inversely associated with the chance of a patient of being prescribed with NOACs.[329] Few data are available regarding the differential effectiveness and safety of OAC in AF patients with multi-morbidity, also appearing significantly more challenging. Indeed, in a series of sub-analyses stemming from NOACs Phase III trials, multi-morbidity does not seem to affect the effectiveness of both apixaban and edoxaban compared to warfarin, but some differences appear in safety outcomes,[337,338] with apixaban appearing more favourable in terms of major bleeding risk in patients with a low burden of comorbidities[337] and edoxaban being more favourable in terms of GI bleeding risk in patients with a high burden of comorbidities.[338] On the contrary, in two very large claim-based and propensity score-matched analyses exploring the interaction between NOACs, VKAs, and multi-morbidity, all data strongly underline how apixaban seems to have a better effectiveness and safety profile compared to warfarin, dabigatran, and rivaroxaban in multi-morbid AF patients.[339,340]

Polypharmacy is also a significant barrier to OAC prescription, despite the high risk of events associated with its presence in AF patients[325] (*Table 9*). In a UK nationwide study from a primary care setting in AF patients with cognitive impairment, polypharmacy represented a strong predictor of OAC non-prescription even in a large multi-variate analysis including several different clinical characteristics.[332]

Data regarding effectiveness and safety of OAC according to polypharmacy are controversial. In general, all NOACs are considered more favourable than warfarin even in patients reporting polypharmacy,[341–343] notwithstanding while some studies suggest no difference between the various NOACs,[344] others show conflicting data regarding possible differences between the various drugs.[341,345]

Regarding frailty, the evidence appears slightly more conflicting regarding the impact on OAC prescription (*Table 9*). While in some studies, frailty was reported as significantly associated with OAC under-prescription,[334,336] or VKAs preferential prescription,[333,336] in others a progressively higher degree of frailty was associated with a higher likelihood of being prescribed with OAC.[335] A recent extensive

Table 9 Relationship between multi-morbidity, polypharmacy and frailty with OAC prescription in AF

Study	Year	Location	Patients	Epidemiology, *n* (%)	OAC prescription, *n* (%)	Impact on OAC prescription
Multi-morbidity						
Proietti *et al.*[218]	2019	Italy	24 040	CCI 0–3 19,745 (82.1) CCI ≥4 4295 (17.9)	9646 (40.1) at baseline	Continuous CCI was inversely associated with OAC prescription at baseline (OR 0.91, 95% CI 0.89–0.92), as well as CCI ≥4 (OR 0.65, 95% CI 0.60–0.70) compared to CCI 0–3
Dalgaard *et al.*[329]	2020	USA	34 174	0–2 CMs 13 194 (38.6) 3–5 CMs 17 331 (50.7) ≥ 6 CMs 3649 (10.7)	29 239 (85.6) at discharge NOACs 20 480 (59.9)	At discharge compared to patients with 0–2 CMs, those with ≥6 CMs had lower odds of receiving OAC (OR 0.72, 95% CI 0.60–0.86), with a non-significant trend for those with 3–5 CMs (OR 0.93, 95% CI 0.82–1.05) Regarding the prescription of NOACs, a progressively higher number of CMs was inversely associated with the prescription of NOACs vs. VKAs (OR 0.72, 95% CI 0.67–0.78 and OR 0.59, 95% CI 0.50–0.69, respectively for 3–5 CMs and ≥6 CMs compared to 0–2 CMs)
Koziel *et al.*[224]	2021	Balkans	2712	≥2 CMs 2263 (83.4)	1965 (72.4) NOACs 338 (12.5)	Patients with multi-morbidity (≥2 CMs) received less likely OAC than those without (62.1% vs. 74.5%, $P < 0.001$) No difference was found regarding NOACs prescription ($P = 0.107$)
Rasmussen *et al.*[330]	2022	Denmark	48 995	0–1 CMs 18 950 (38.7) 2–3 CMs 20 723 (42.3) 4–5 CMs 7190 (14.7) ≥ 6 CMs 2132 (4.3)	38 068 (77.7) NOACs 20 699 (54.4)	Compared to patients with 0–1 CMs, increasing number of CMs was inversely associated with OAC prescription (2–3 CMs OR 0.79, 95% CI 0.75–0.83; 4–5 CMs OR 0.54, 95% CI 0.51–0.58; ≥ 6 CMs OR 0.38, 95% CI 0.35–0.42)
Polypharmacy						
Mazzone *et al.*[331]	2016	Italy	305	≥5 drugs 84 (27.5)	170 (55.7)	At hospital discharge presence of polypharmacy was associated with a higher risk of OAC non-prescription (OR 2.07, 95% CI 1.10–3.86)
Mongkhon *et al.*[332]	2020	UK	9845	≥5 drugs 2244 (22.8)	3801 (38.6) NOACs 465 (12.0)[a]	In a large multivariate analysis, polypharmacy was inversely associated with OAC prescription (OR 0.62, 95% 0.51–0.75) No impact of polypharmacy was found on NOACs prescription
Koziel *et al.*[224]	2021	Balkans	2712	≥5 drugs 1505 (55.5)	1965 (72.4) NOACs 338 (12.5)	Patients with polypharmacy (≥5 drugs) received less likely OAC than those without (59.9% vs. 82.5%, $P < 0.001$) No difference was found regarding NOACs prescription ($P = 0.865$)
Frailty						
Gugganig *et al.*[333]	2019	Swiss	2369	robust 681 (28.7) pre-frail 1436 (60.7) frail 252 (10.6)	2141 (90.4) VKAs 936 (39.5) NOACs 1205 (50.9)	Frail patients were more likely prescribed with VKAs than pre-frail and robust ones (52.0% vs. 43.1% vs. 27.2%), while NOACs were less likely prescribed (36.1% vs. 48.6% vs. 61.1%)
Campitelli *et al.*[334]	2021	Canada	36 466	robust 5703 (15.6) pre-frail 12 985 (35.6) frail 17 778 (48.8)	18 514 (50.8) NOACs 9328 (50.4)[a]	Adjusted analyses showed that both being pre-frail and frail were inversely associated with OAC prescription (RR 0.97, 95% CI 0.94–1.00 and RR 0.95, 95% CI 0.92–0.98, respectively)
Wilkinson *et al.*[335]	2021	UK	61 177	robust 6443 (10.5) mildly frail 20 352 (33.3)	30 916 (53.1)[b] NOACs 7329 (23.7)[a]	Increasing frailty was found to be associated with a higher likelihood of being prescribed with OAC, compared with being robust (OR 1.84, 95% CI 1.72–1.96, OR 2.34, 95% CI

Continued

Table 9 *Continued*

Study	Year	Location	Patients	Epidemiology, *n* (%)	OAC prescription, *n* (%)	Impact on OAC prescription
				moderately frail 20 315 (33.2) severely frail 14 067 (23.0)		1.18–2.50, OR 2.51, 95% CI 2.33–2.71, respectively for mild, moderate, and severe frailty)
Proietti *et al.*[336]	2022	Europe	10 177	robust 1939 (19.1) pre-frail 6066 (59.6) frail 2172 (21.3)	8676 (85.2) NOACs 3638 (35.7)	Compared to robust patients, frail ones were less likely to receive OAC (OR 0.70, 95% CI 0.55–0.89), while pre-frail were more likely to receive (OR 1.21, 95% CI 1.01–1.44) Compared to no OAC treatment, frail patients were less likely to receive both VKAs (OR 0.73, 95% CI 0.56–0.94) and NOACs (OR 0.54, 95% CI 0.41–0.70) than robust ones

CCI, Charlson comorbidity index; CI, confidence interval; CMs, comorbidities; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulant; OR, odds ratio; RR, risk ratio; VKAs, vitamin K Antagonists; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female); AF, atrial fibrillation.
[a]Among prescribed ones.
[b]Among eligible patients for CHA_2DS_2-VASc ≥2.

systematic review and meta-analysis, while confirming the high prevalence of frailty among AF patients (~40%) and its detrimental impact on the risk of adverse outcomes, was inconclusive regarding the likelihood of OAC prescription according to frailty levels.[327] Indeed, while overall no difference was found in OAC prescription, as well as in NOACs vs. VKAs prescription, comparing the various possible degrees of frailty (robust, pre-frail, and frail), in some subgroups frail patients are significantly less prescribed with OAC than robust ones.[327] Conversely, in population-based studies and in those focusing only on patients with high thrombo-embolic risk, frail patients were more likely to be prescribed with OAC than robust ones.[327]

Regarding the impact of OAC in frail AF patients, which appears to be still debated,[346,347] data seem to be reassuring regarding the beneficial effect of OAC in frail AF patients,[336,348] even though uncertainties remain regarding patients with a very high level of frailty for which in some studies was reported no difference in risk of outcomes between OAC treated and not treated patients.[336] Looking at the potential differences between NOACs and VKAs, while data coming from NOACs Phase III trials seem to underline no major differences in terms of effectiveness (with only small advantages regarding safety),[349] only a few real-life studies are available so far, generally underlying that in frail AF patients dabigatran, rivaroxaban, and apixaban have a beneficial effect on effectiveness outcomes, with apixaban showing the better profile in terms of safety when compared with VKAs.[350–352] Furthermore, data regarding the comparison between the various NOACs seem to indicate that apixaban would be a more favourable clinical profile, particularly regarding the risk of major bleeding and other secondary bleeding outcomes.[350,351]

Atrial high-rate episode on cardiac-implanted electrical device and subclinical atrial fibrillation

Cardiac implanted electrical devices (CIEDs) with an atrial lead or with the capability of rhythm discrimination by means of specific algorithms (i.e. implantable cardiac monitors) allow continuous monitoring of the cardiac rhythm, with an extended ability to appropriately detect any atrial tachyarrhythmias, including AF.[353] The atrial tachyarrhythmias detected by CIED have been reported in the literature as atrial high-rate episodes (AHREs),[353–355] and their characterization and management have been extensively discussed in Guidelines.[14] A key characteristic of AHREs episodes is that they are recorded exclusively through continuous monitoring with CIEDs and include various atrial arrhythmias such as AF, atrial flutter, and atrial tachycardias, often with the transition from regular to irregular rhythm in the same patient, with recordings that can be stored in the device memory, as intra-cavitary electrograms (EGMs).

A careful analysis of EGM tracings is recommended for diagnostic confirmation of the arrhythmia, excluding artefacts or noise.[14,353] AHREs have been variably defined or specified but are currently defined by most as episodes of at least 5 min of atrial tachyarrhythmias with an atrial rate ≥ 175 b.p.m. and three criteria have to be fulfilled for a diagnosis of AHRE: no history of prior AF, *lack of* symptoms attributable to AF, and absence of AF on a 12-lead ECG recording. The term subclinical AF identifies AHRE confirmed to be an atrial tachyarrhythmia by visually adjudicated intra-cardiac EGMs. *However,* although not completely identical, the terms AHRE and subclinical AF are often used interchangeably in the literature.[14] The term 'AF burden' has been often used to indicate the overall time spent in AF during a specified period of time (usually 24 h).[356,357]

The prevalence of AHREs among patients implanted with CIEDs is variable, depending on underlying heart disease, periods of observation, clinical profile, co-morbidities, and a previous history of atrial tachyarrhythmias. In the ASSERT study, subclinical atrial tachyarrhythmias with at least 6 min duration were detected within 3 months in around 10% of patients implanted with a CIED. During a follow-up period of 2.5 years, additional subclinical atrial tachyarrhythmias occurred in around 25% of patients, and around 16% of those who had subclinical atrial tachyarrhythmias developed a symptomatic 'clinical' AF.[202] An analysis of all the data from the literature reveal that AHREs with a duration >5–6 min are common in patients implanted with CIEDs, with an incidence ranging between 10% and 68%,[353,357] recently estimated in a meta-analysis to be around 28%, but with substantial heterogeneity among the different reports in the literature.[356]

In practice, the key questions on AHRE and subclinical AF are related to the threshold of detected AF duration or of daily AF burden which is significantly associated with stroke/systemic embolism and the risk/benefit ratio of OACs in this specific setting.[358] As known, OACs are

strongly recommended by consensus guidelines[359,360] in patients presenting clinical AF when the CHA_2DS_2-VASc excludes a low-risk profile, irrespectively of symptoms,[14,361] but according to current knowledge, the favourable risk/benefit ratio of anticoagulants in clinical AF cannot be directly transferred to AHREs.

The association between AHRE/subclinical AF of variable time duration and stroke/systemic thrombo-embolism has been evaluated by several observational studies.[362–364]

As shown, the risk of stroke/thrombo-embolism associated with AHRE is not negligible, and in a recent meta-analysis that excluded patients with prior clinical AF, patients with AHREs showed a 2.13-fold higher risk of thrombo-embolic events.[365] Since this risk is actually lower than the 4.8-fold increase in the risk of stroke reported for clinical AF, two randomized controlled trials [ARTESiA and NOAH-AFNET6 (Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes)—*Figure 2*] are ongoing to evaluate anticoagulants in terms of risk-benefit ratio in this specific setting.[362,363] Currently, AHRE episodes < 5 min in duration are not considered to be associated with a substantial risk of stroke.[353,362]

AF burden and AHRE duration show a dynamic pattern, with a tendency to progression along with time and transition from burdens in the range of minutes or a few hours to 12–23 h and even more than 23 h, particularly in patients with a higher risk for stroke.[366] AHREs with a duration > 23–24 h are associated with a significantly increased risk of stroke,[192] and therefore in these cases, long-term anticoagulation becomes an important clinical consideration.[14,367,368]

Currently, while waiting for evidence-based recommendations, patient-tailored decision-making on the need for anticoagulation is required in patients with AHREs/subclinical AF, particularly in frail patients,[369] taking into account that CIED-detected AHREs may occur with a marked temporal dissociation with regard to stroke events, thus suggesting that they may be actually a marker, rather than a risk factor for stroke.[370] Indeed, there is an important heterogeneity in the perception of the thrombo-embolic risk associated with AHREs of different durations with variable thresholds of AHRE/AF burden used as a cut-off to start an OAC.[371]

As suggested by the guidelines, in patients with AHREs, there is a need for individualized decision-making, taking into account risk stratification for previous stroke, stroke risk factors using CHA_2DS_2-VASc in combination with the amount of detected AF burden associated comorbidities, and predicted risk of bleeding, thus leading to a prediction of the expected risk-benefit ratio of treatment with anticoagulants.[14] The result should be an integrated assessment with AHRE having a variable role, from an 'innocent bystander' to an important and evolutive finding, associated with a substantial risk of stroke/thrombo-embolism (*Figure 3*). Use of OACs, preferentially NOACs, may be justified in selected patients, such as patients with longer durations of AHRE/subclinical AF (in the range of several hours or ≥24 h), and with an estimated high/very high individual risk of stroke, accounting for a favourable anticipated net clinical benefit, to be shared with the patient, after appropriate information and considering patient's preferences (*Figure 4*).[14]

Hence, it is appropriate to perform a tighter clinical follow-up, also using remote monitoring of the CIED,[372] targeted to detect the development of clinical AF, to monitor the evolution of AHRE/AF burden and specifically the transition to AHRE lasting more than 24 h, as well as the onset or worsening of HF, or any clinical change that might suggest an important worsening in clinical conditions.[373–377]

Digital health

In the last years, there has been a great expansion of applications and trials of digital health solutions, particularly related to the mobile health (mHealth) field.[378] Use of mHealth solutions has been applied both to AF screening strategies and to clinical management and monitoring.[378,379]

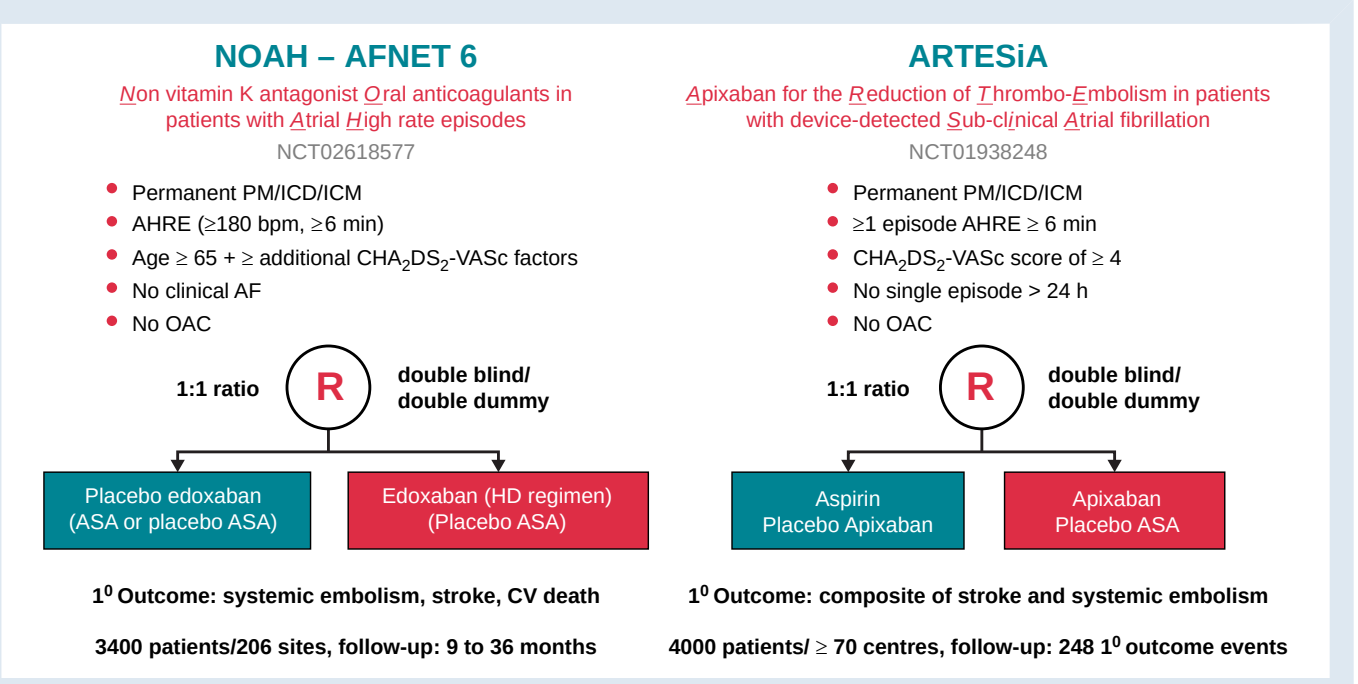

Figure 2 ARTESiA and NOAH-AFNET 6 randomized controlled clinical trials. PM, pacemaker; ICD, implantable cardioverter defibrillator; ICM, implantable cardiac monitor, AHRE, atrial high rate episodes; AF, atrial fibrillation; OAC, oral anticoagulation; R, randomization; ASA, aspirin; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female).

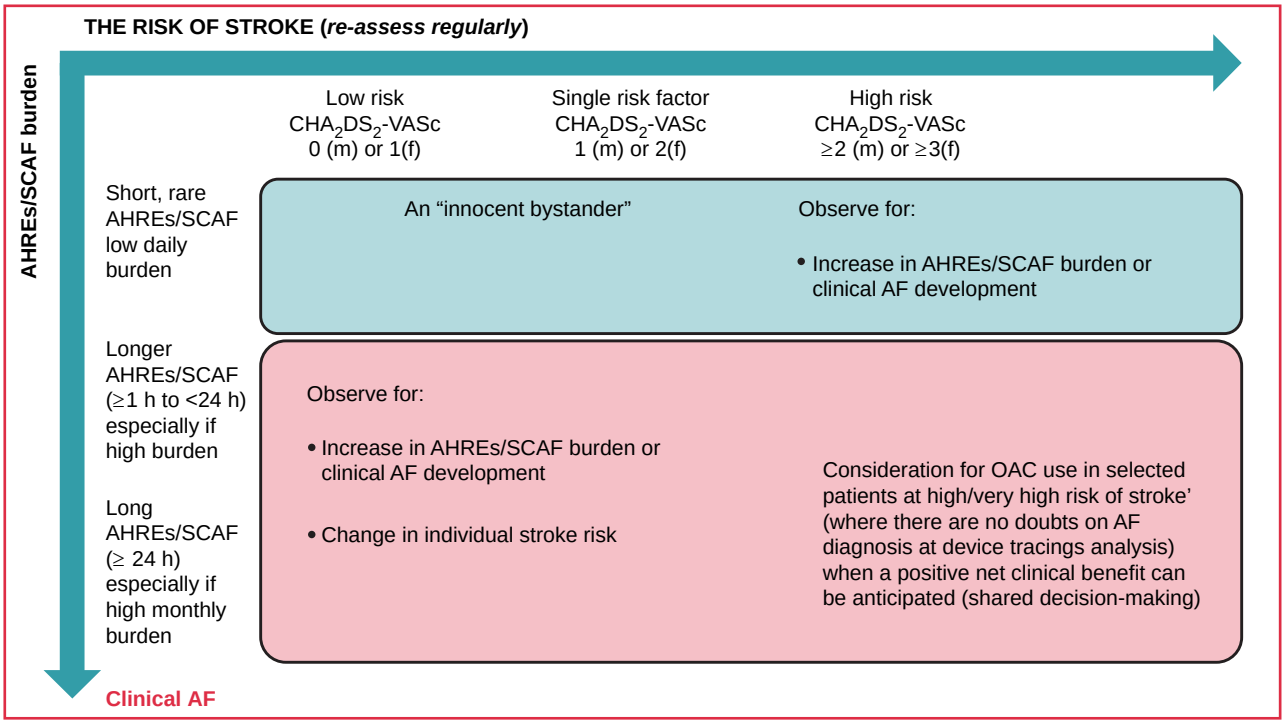

Figure 3 Proposed approach to patients with CIED-detected AHREs according to the 2020 ESC Guidelines[14] (with permission). AF, atrial fibrillation; AHRE, atrial high-rate episode; OAC, oral anticoagulant; SCAF, subclinical atrial fibrillation; CIED, cardiac-implanted electrical device; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female).

In the recent years, the field of AF screening strategies has seen a big development. The evidence that large proportion of AF patients can present with an asymptomatic status and that no major difference exists in terms of baseline thrombo-embolic risk and risk of major adverse events over long-term observation[361] clearly highlighted the need for structured screening programmes to identify asymptomatic AF patients. Indeed, several data underlined how screening strategies have a significant yield of AF diagnosis, irrespective of the screening method and that very often these patients with asymptomatic AF have a high risk of stroke and thrombo-embolic events and are deemed to be prescribed with OAC drugs.[379,380] In this context, the use of simple and widespread digital technology solutions using photoplethysmography (PPG) appeared to be promising tools to be used in implementing large-scale screening programmes.

Several studies have been performed to verify whether the use of digital mHealth solutions would be feasible tools to identify asymptomatic AF patients (*Table 10*). In the Huawei Heart Study, Guo *et al.*[384] demonstrated that a programme using a wristband/wristwatch device was able, in the context of a structured screening programme, to identify 87% of patients with AF among those flagged with an irregular heart rhythm, with >90% positive predictive value (PPV). Similar data were showed by the Apple Heart Study, published in 2019, with ~84% of PPV. More recently, Rizas *et al.*[390] demonstrated that the use of PPG through a smartphone camera to identify asymptomatic AF patients granted more than twice the likelihood (OR 2.12, 95% CI 1.19–3.76) of identifying AF patients eligible to receive OAC than common usual care.

The main issue of using digital mHealth tools and screening strategies is the ability of reducing the risk of stroke in the long-term observation. General evidence provided by an analysis of available studies underlines that despite substantial data indicating that screening would be likely to obtain a significant risk reduction in stroke and other adverse outcomes, solid proof is still lacking due to several methodological issues.[379] Several studies, including the Heartline study which will enrol ≥65 years old subjects and will evaluate if the use of a PPG-based smartwatch AF detection in conjunction with an engagement/adherence module, will elucidate the actual ability of screening programmes to reduce risk of stroke.[379,391]

Furthermore, search for AF after an ischaemic stroke was traditionally based on use of Holter recordings, also of prolonged duration,[392] or on implantable loop recorders,[392,393] but more recently also digital tools such as smartwatches and smartphones (also called 'wearables'), usually proposed with a direct-to-consumer approach,[394,395] are currently implemented in daily practice. However, even if a wider use of digital tools is emerging, some issues related to organization of care, data management, digital literacy, and reimbursement are still open,[396–400] and more studies are needed.

Going over the issue of screening, which still remains crucial in the clinical management of AF, use of digital tools, i.e. web- or mobile-based applications seems to be useful also in the improvement of engagement, quality of life, and clinical management of AF patients.[401] For example, in the second phase of the mAFA II, the use of a mobile-based app used to deliver the 'ABC' pathway reduced the risk of a composite outcome of ischaemic stroke/systemic thrombo-embolism/all-cause death and hospitalization [HR 0.39, 95% CI 0.22–0.67] over 1-year follow-up observation.[384] Current ongoing programmes, particularly the 'AFFIRMO' Programme, will provide more evidence about the implementation of AF clinical management and reduction of ischaemic stroke and other adverse outcomes risk through the use of digital health tools.[37]

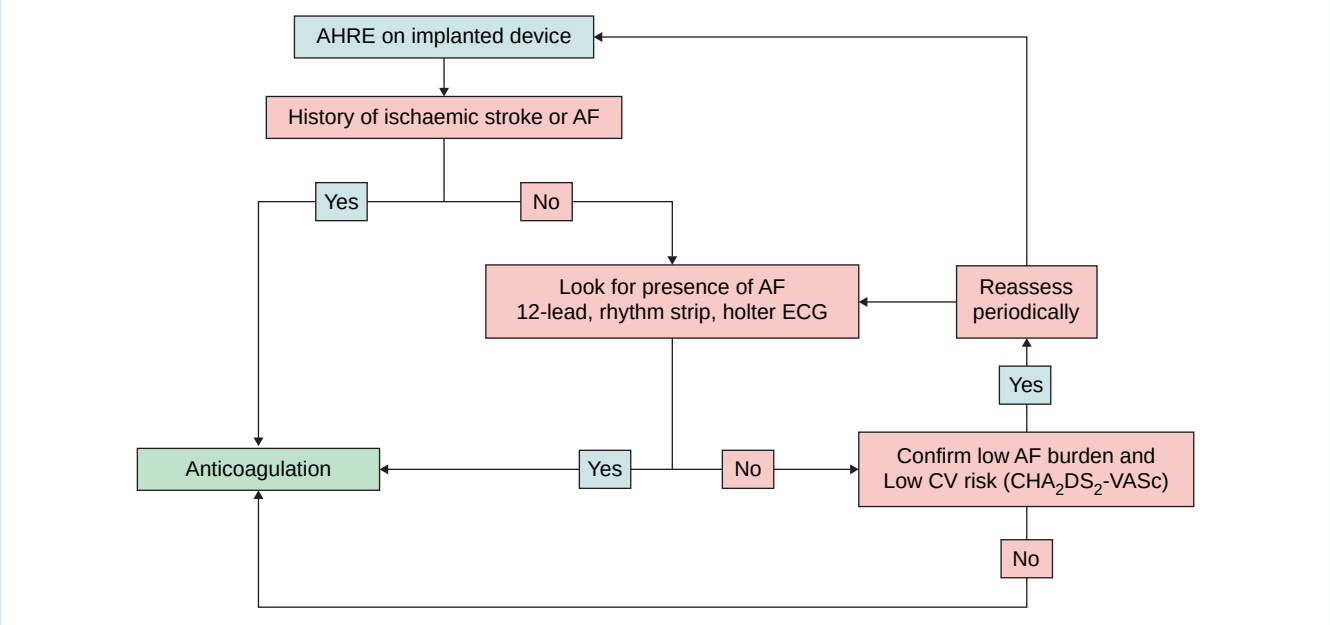

Figure 4 Decision process for considering anticoagulation for patient with AHREs. ECG, electrocardiogram; AF, atrial fibrillation; CV, cardiovascular risk; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65_74 years, Sex category (female).

Table 10 Studies involving digital health solutions for AF screening

Study	Year	Design	*n*	Age	Study cohort	Country	Type of device	Monitoring time	% AF
Nemati *et al.*[381]	2016	RSA	36	NA	Hospitalized	USA	Wristwatch	3.5–8.5 min	33
Yan *et al.*[382]	2018	PSA	217	70.3	Hospitalized	China	Smartphone camera	20 s × 3	34.6
Brasier *et al.*[383]	2019	PSA	592	78	Hospitalized	Germany/ Switzerland	Smartphone camera	5 min	41.9
Guo *et al.*[384]	2019	PSA	187 912	34.7	Outpatient	China	Wristband/ Wristwatch	60 s every 10 min for 14 days	87
Perez *et al.*[385]	2019	mPSA	419 297	41	General	USA	Wristwatch	3 min	0.52
Verbrugge *et al.*[386]	2019	PSA	12 328	49	General	Belgium	Smartphone camera	7 days	0.01
Zhang *et al.*[387]	2019	PSA	361	50	Outpatient	China	Wristband/ Wristwatch	45 s every 10 min for 14 days	8.6
Chen *et al.*[388]	2020	PR	401	NA	Hospitalized/ Outpatient	China	Wristband	3 min	37
Lubitz *et al.*[389]	2022	PSA	1057	NA	General ≥22 years	USA	Wristband	122 days	32.2
Rizas *et al.*[390]	2022	RCT	5551	NA	General ≥65 years	Germany	Smartphone camera	6 min	1.33

AF, atrial fibrillation; mPSA, multi-centre prospective single arm; NA, not available; PSA, prospective single arm; RCT, randomized clinical trial.

Conclusions

As this state-of-the-art review illustrates, substantial advances in the field of stroke prevention in AF are evident over the last years. Advances in our understanding of the epidemiology and pathophysiology of stroke risk as well as refinements in stroke risk stratification are evident. While oral anticoagulation remains the mainstay, particularly with the NOACs, the emerging role of LAAO for selected patients with absolute contraindications to long-term anticoagulation is clear. In addition, the impact of early rhythm control in reducing stroke risk when used in selected patients with recent onset AF is supported by clinical trial evidence. Finally, a holistic or integrated care management

approach based on the ABC pathway is fully supported by clinical trial evidence as well as retrospective and prospective cohorts, to be associated with improved clinical outcomes.

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Data availability

No new data were generated or analysed in support of this research.

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