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# Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference

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## Abstract

Despite marked progress in the management of atrial fibrillation (AF), detecting AF remains difficult and AF-related complications cause unacceptable morbidity and mortality even on optimal current therapy. This document summarizes the key outcomes of the 8th AFNET/EHRA Consensus Conference of the Atrial Fibrillation NETWORK (AFNET) and the European Heart Rhythm Association (EHRA). Eighty-three international experts met in Hamburg for 2 days in October 2021. Results of the interdisciplinary, hybrid discussions in breakout groups and the plenary based on recently published and unpublished observations are summarized in this consensus paper to support improved care for patients with AF by guiding prevention, individualized management, and research strategies. The main outcomes are (i) new evidence supports a simple, scalable, and pragmatic population-based AF screening pathway; (ii) rhythm management is evolving from therapy aimed at improving symptoms to an integrated domain in the prevention of AF-related outcomes, especially in patients with recently diagnosed AF; (iii) improved characterization of atrial cardiomyopathy may help to identify patients in need for therapy; (iv) standardized assessment of cognitive function in patients with AF could lead to improvement in patient outcomes; and (v) artificial intelligence (AI) can support all of the above aims, but requires advanced interdisciplinary knowledge and collaboration as well as a better medico-legal framework. Implementation of new evidence-based approaches to AF screening and rhythm management can improve outcomes in patients with AF. Additional benefits are possible with further efforts to identify and target atrial cardiomyopathy and cognitive impairment, which can be facilitated by AI.

## Keywords

Atrial fibrillation • Artificial intelligence • Heart failure • Atrial cardiomyopathy • Cognitive function • Dementia • Outcomes • Quality of care • Cost • Research • Rhythm management • Catheter ablation • Anticoagulation • Bleeding • Research priorities • Technology • Stroke • Integrated care • Screening • AFNET • EHRA • Guidelines • Consensus statement

## Introduction

Despite marked progress in the detection and management of patients with atrial fibrillation (AF), the arrhythmia remains undetected in a large proportion of patients, particularly in the elderly. Atrial fibrillation confers an important public health burden, causing high mortality and morbidity, impacting affected

patients and their families, and incurring high costs to healthcare systems.<sup>1,2</sup>

Implanted devices, and more recently, wearables, as well as other consumer electronics, enable long-term continuous monitoring of biosignals, providing the ability to detect rare arrhythmias including AF. Initial results from continuous rhythm recording over years have provided insights into the natural history of AF and generated

evidence on AF burden-related outcomes. It appears intuitive that more and longer atrial arrhythmias should be associated with higher complication rates, but a clear biological gradient supporting this assumption with data is missing.<sup>3</sup> Defined screening populations as well as modes of screening and analysis are required to render AF screening beneficial and cost-effective.<sup>4,5</sup>

New data show that early rhythm control therapy, initiated after a recent clinical diagnosis of AF, can improve cardiovascular outcomes and mortality in patients with AF and cardiovascular risk factors.<sup>4</sup> These findings will change the concept and practice of rhythm management. Rhythm management should preferably include a resolute attempt at rhythm control in patients with new AF, but also comprise rate control to prepare patients for recurrences of AF. There has also been increasing focus on cognitive function assessment in patients with AF for early detection and prevention of cognitive impairment and its negative impact on treatment compliance.<sup>6</sup> These new data call for better integration of AF screening and early rhythm control in clinical care.

Translational research suggests a complex concept of atrial cardiomyopathy as a major driver for AF incidence and progression, as well as AF-related complications. Advances have been made in the characterization and quantification of atrial cardiomyopathy from cellular to clinical levels. Atrial dysfunction and the broad spectrum of clinical and risk factors have been used to define populations at risk of AF in primary stroke prevention as well as post-stroke cohorts. Artificial intelligence (AI)-based methods integrating multimodal information and extracting central features have shown promising first results, but legal barriers for its implementation have to be overcome while ensuring fair and secure use of data. To improve estimation of AF-related risk and to guide therapy of the arrhythmia, further translational science and clinical research is needed to better understand the different underlying mechanisms that are reflected by the electrocardiographic (ECG) pattern of AF.

## Methods

The 8th AFNET/European Heart Rhythm Association (EHRA) Consensus Conference brought together 83 international interdisciplinary experts including arrhythmia and heart failure (HF) specialists, patients with AF, an AF patient organization, pharmacologists, translational scientists, general practitioners, neurologists, nurse practitioners, epidemiologists, consultants in public health medicine, clinical trialists, and health economists in Hamburg, Germany, for 2 days of intense discussion in the plenary and in breakout groups. Participants who could not travel for pandemic-related reasons participated remotely. The results of the expert discussion and their potential clinical impact are summarized here.

## Atrial fibrillation screening implementation

### Approaches to screening

The 2020 European Society of Cardiology (ESC) guidelines on AF management recommend opportunistic screening for AF in persons aged  $\geq 65$  years (Class I, Level B) as well as systematic screening for AF in individuals aged  $\geq 75$  years, or at high risk of stroke (Class IIa, Level B).<sup>1</sup> Efforts to reduce the burden of AF complications by an early diagnosis have been made through opportunistic and

systematic screening approaches, but also through interrogation of cardiac implantable devices and consumer devices, e.g. wearables.

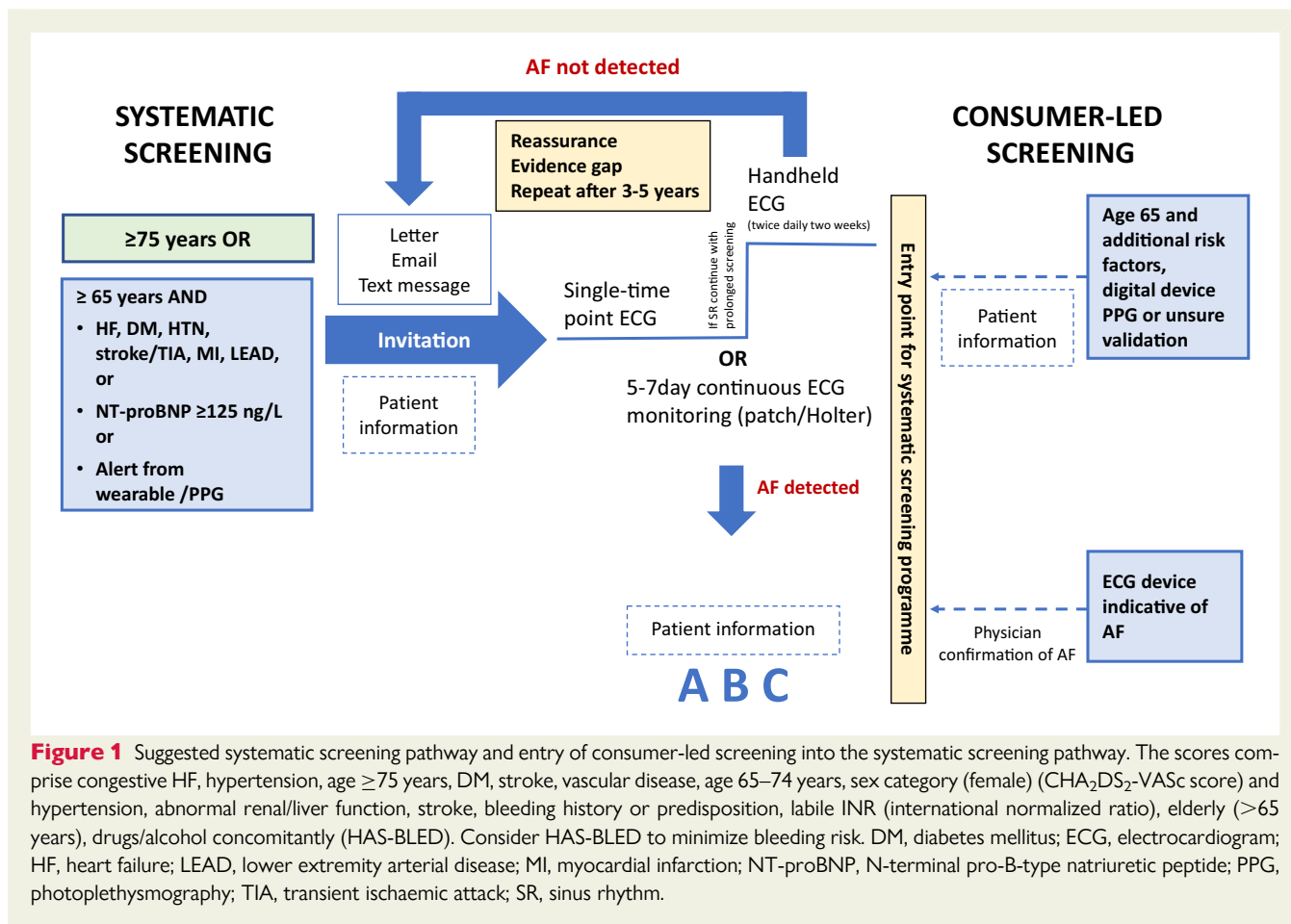
The recommendation for opportunistic screening during medical visits for purposes other than screening was based on a study using pulse palpation carried out in the UK before 2005.<sup>7</sup> New evidence emerged after the publication of the guidelines. The D2AF (*Detecting and Diagnosing Atrial Fibrillation*) study showed that opportunistic screening in primary care did not increase the detection of AF in individuals aged  $>65$  years.<sup>8</sup> In addition, no difference in AF detection was demonstrated when using a single-lead handheld ECG during regularly scheduled office visits in the larger VITAL-AF (*Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics*) study, except for a signal for increased detection in patients aged  $\geq 85$ .<sup>9</sup> Similar observations were made in the randomized MonDAFIS (*Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke*) study comparing systematic ECG monitoring with additional Holter-ECG recording for up to 7 days in hospital and usual care in patients hospitalized with acute ischaemic stroke.<sup>10</sup> These studies illustrate the improvement in AF detection in routine care, i.e. the control arms, during the last decade, possibly because of increased awareness by health professionals and the public attributable to dissemination of the importance of stroke prevention by AF detection and treatment. At the same time, these studies underline the well-known shortcomings of opportunistic AF screening that may miss high-risk parts of the population.

Systematic ECG screening could improve AF detection by including patients who do not seek medical help, as demonstrated in two large recent randomized clinical trials.<sup>11,12</sup> In the population-based, randomized STROKESTOP study, AF screening using ECG recordings from a portable device, taken twice daily for 2 weeks, was used in individuals aged 75–76 years. This intervention resulted in a reduction of the combined outcome of mortality, stroke, and severe bleeding compared with a control group.<sup>11</sup> In the LOOP study, AF screening in the intervention group was conducted using an implantable cardiac device, which continuously monitored heart rhythm for 3 years. In case of AF detection for  $>6$  min, oral anticoagulant (OAC) therapy was initiated. Despite a three-fold increase in AF detection and OAC initiation, the LOOP study did not show a significant decrease in the outcome of stroke and systemic embolism compared with the control group.<sup>12</sup>

With many consumer devices integrating algorithms for detecting AF readily available, consumer-led screening is a growing trend that health-care systems need to respond to. While the conceptual ability of AF detection using consumer electronics, e.g. smartwatches, has been shown,<sup>13–15</sup> substantial challenges remain, including access to the technology, usability in elderly populations and in populations with relevant risk factors, data privacy, legal, data transfer issues, AF diagnosis validation, and, importantly, sound information on when to initiate treatment in the light of the potential for over-diagnosis of arrhythmias without clinical implications. Once the therapeutic implications of detecting short, rare atrial arrhythmias are understood<sup>16,17</sup> and the usability and reliability in elderly populations has been improved, consumer electronics may be a suitable way to enhance AF screening.

## Evidence-based implementation of systematic screening for atrial fibrillation

To enable the implementation of systematic screening for AF, the participants of the 8th AFNET EHRA consensus conference propose



a simple, scalable, and pragmatic AF screening pathway suitable for different healthcare systems. Such a pathway may improve timely diagnosis of AF and subsequently prevent AF-related complications. At the same time, such efforts can improve research on AF screening by providing systematic evaluation of screening strategies and devices. The consensus conference experts recommend systematic screening for all individuals aged  $\geq 75$  years, and that systematic screening may be considered for individuals aged 65–74 years with additional risk factors [e.g. HF, hypertension, diabetes, previous stroke/TIA, myocardial infarction (MI), lower extremity artery disease], elevation of natriuretic peptides [N-terminal pro B-type natriuretic peptide (NT-proBNP)  $\geq 125$  ng/L], or a positive alert by a digital device using photoplethysmography (PPG, Figure 1). Individuals considered for screening could be invited by the healthcare institution responsible for the screening initiative by letter, email, phone call, or text message based on local availability and practice. Ideally, the invitation should include information on the potential benefits and harms of AF screening in the participants' own language using simple wording.

The ECG screening procedure should be adapted to available healthcare resources. In case of in-person screening, a single time point screen using, for example, a rhythm strip or 12-lead ECG, could be used to diagnose AF.<sup>1</sup> If this does not show AF, 2-week twice-daily handheld ECG monitoring should be performed. Alternatively, a 5–7 day (up to 14 days) continuous ECG patch or

Holter recording could be performed.<sup>18</sup> In continuous monitoring, an AF episode lasting  $\geq 30$  s is diagnostic according to current guidelines.<sup>1</sup> As evidence showing the benefits of screening grows (affect-eu.eu),<sup>19</sup> discussions with regulatory authorities should be initiated to ensure reimbursement for AF screening and define the ensuing diagnostic and therapeutic work-up.

Following AF detection, a medical assessment by a medical team experienced in AF management, in an in-person or remote setting, is required to confirm the diagnosis of AF and to evaluate prognosis. The assessment will evaluate patient information, confirmation of the CHA<sub>2</sub>DS<sub>2</sub>-VASC [congestive HF, hypertension, age  $\geq 75$  years, diabetes mellitus (DM), stroke, vascular disease, age 65–74 years, sex category (female)] stroke risk score, and detection of additional concomitant cardiovascular conditions and risk factors. Subsequently, a comprehensive AF management incorporating all elements of the guideline-recommended approach (avoiding stroke, better rhythm and rate management, treatment of concomitant cardiovascular conditions), considering diagnosis and therapy of concomitant cardiovascular diseases as well as risk factors, can be initiated.<sup>1</sup> Individuals without detected arrhythmias should be reassured. In these individuals, a timeframe for repeated screening/monitoring need to be established in different categories of pre-detection risk. The value of repeated screening and the ideal time point for follow-up (FU) using single time point ECGs are still unclear and should be investigated in future trials.<sup>20–22</sup>

Digital approaches to AF screening were rapidly developed in response to the COVID-19 pandemic and may become the preferred pathway. Systematic AF screening can be achieved using entirely digital technology: Electronic medical records or the population registry (if available) can be used to identify participants eligible for screening based on age. A letter with a link (e.g. a QR code) to an online questionnaire can be sent to confirm whether individuals are willing to participate in the screening programme. Individuals aged 65–74 years would also be invited to answer questions about comorbidities (with the help of their general practitioner if needed, *Figure 1*). Thereafter, a screening device, e.g. an ECG patch or a PPG-based pulse device, can be posted to participants for a recording and returned to the healthcare provider to complete the digital pathway. Alternatively, the pathway could make use of a device already accessible to the participant. If AF is detected and confirmed in the recording, participants are invited for an appointment with a healthcare professional to implement therapy as recommended according to the A–B–C {Atrial fibrillation Better Care [includes A (avoid stroke), B (better symptom control/better rhythm management), and C (cardiovascular risk factors and comorbid conditions management)]} pathway,<sup>1</sup> which could also potentially take place as a digital appointment.

## Consumer-led atrial fibrillation screening

For individuals who have screened themselves for AF using their own devices, i.e. consumer-led screening, false positive findings by the device may be more frequent than in systematic screening. The rate of false positives depends on the specifications of the device, its algorithm, and the pre-test probability in the individual. Therefore, confirmation needs to be done, taking into account individual risk and unrecognized symptoms. The large-scale Apple,<sup>13</sup> Huawei,<sup>23</sup> and Fitbit (NCT04380415) Heart Studies have illustrated the potential of fast, nationwide recruitment of screening participants and demonstrated low rates of false positives among participants who completed the screening. The vast majority of participants were younger than 50 years old and drop-out rates were high. The studies also showed that consumer-led AF screening leads to increased use of healthcare resources in the short term. First, arrhythmias require review and verification by a health professional. Secondly, other arrhythmia findings will trigger additional contacts with the healthcare system for verification. Thirdly, consumer-based AF screening will also be conducted by individuals without stroke risk factors. There is a lack of evidence on the implications and the benefits of screening in patients who are not at risk of stroke, and in young populations. The magnitude of the resources involved is not known and should be estimated during the evaluation of consumer-led ECG AF screening. Although the resources may be substantial, it can also be advantageous as consumer-led AF screening could be an entry point into a more systematic screening programme for patients at cardiovascular risk. Consumer-led screening engages people and gets them involved in managing and learning about AF and their health, being more adherent, focusing on prevention, and thereby has the potential to reinforce the concept of shared decision-making. Further evidence to determine the effectiveness of consumer-led AF screening would be of benefit.<sup>24</sup>

The clinical implications of AF detected by consumer-led screening are not known and dedicated studies, including outcome studies of consumer-screening led interventions, are needed. In consumer-led screening, a diagnosis of AF can be made if the individual used a device with ECG recording, and confirmation was provided by a physician after inspection of the rhythm strip.<sup>1</sup> Digital devices can monitor the rhythm for variable durations depending on the technology used and patient adherence. Therefore, calculated AF burden will differ depending on the device used.<sup>13–15</sup> A structured AF management and initiation of therapy should be considered on an individual basis. Recent data indicate that untreated opportunistic screening-detected AF has a similar stroke risk to clinically detected AF.<sup>21,25</sup> Reassuringly, anticoagulation used in the LOOP study did not show an increased risk of bleeding in patients with atrial arrhythmias detected by an implantable loop recorder, but the stroke rate was lower than expected based on AF diagnosis and stroke risk.<sup>12</sup>

## Knowledge gaps and hurdles

There are still important knowledge gaps, e.g. the ideal timing of repeat screening and the threshold of AF burden related to an increased stroke risk which should lead to the initiation of oral anticoagulation (and other AF therapies) in patients at risk if AF is picked up by long-term monitoring, e.g. using implanted devices. It is also unclear whether picking up irregular pulses by PPG signals could lead to a more direct recommendation of anticoagulation in patients at risk, in the future. For digital AF screening, digital health literacy, inclusiveness of minorities, and equality in access,<sup>26–28</sup> digital pathways to enable participation, outreach initiatives, overcoming geographic distances,<sup>29</sup> awareness of AF, and education are key. Financial coverage needs to be secured, with regard to screening, the ensuing additional visits and investigations, and the subsequent treatment. Today, it remains a privilege to advance digital AF screening when in most regions of the world, even an ECG is not broadly available and pulse palpation has to be considered as an alternative.

## The growing role of rhythm management

### The paradigm of rhythm management

Recent controlled trials and observational analyses demonstrated safety of rhythm control therapy.<sup>4,30–35</sup> Combined with the effectiveness of early rhythm control,<sup>4</sup> these findings suggest a wider use of rhythm control therapy to improve symptoms and quality of life, and provide an additional avenue to prevent outcomes such as stroke and cardiovascular death.<sup>4,36,37</sup> While other mechanisms are still possible,<sup>32,36–38</sup> recent data clearly support the hypothesis that these clinical effects are mediated by the lower arrhythmia burden achieved by systematic rhythm management.<sup>4,36,37</sup> Therefore, it is timely to consider a new approach in the management of patients with clinically detected AF. This group proposes that this approach should encompass initiation of oral anticoagulation based on stroke risk, diagnosis and treatment of concomitant cardiovascular conditions and risk factors, as well as rhythm management. Goals of rhythm management include reduction of adverse outcomes (stroke, HF, hospitalization, cardiovascular mortality),<sup>4,35</sup> symptom improvement, and improvement in quality of life.

It prioritizes sinus rhythm maintenance, but retains rate control and AV-nodal therapy (ablate and pace) plus possibly cardiac resynchronization as an option when rhythm control is difficult to achieve.<sup>39</sup>

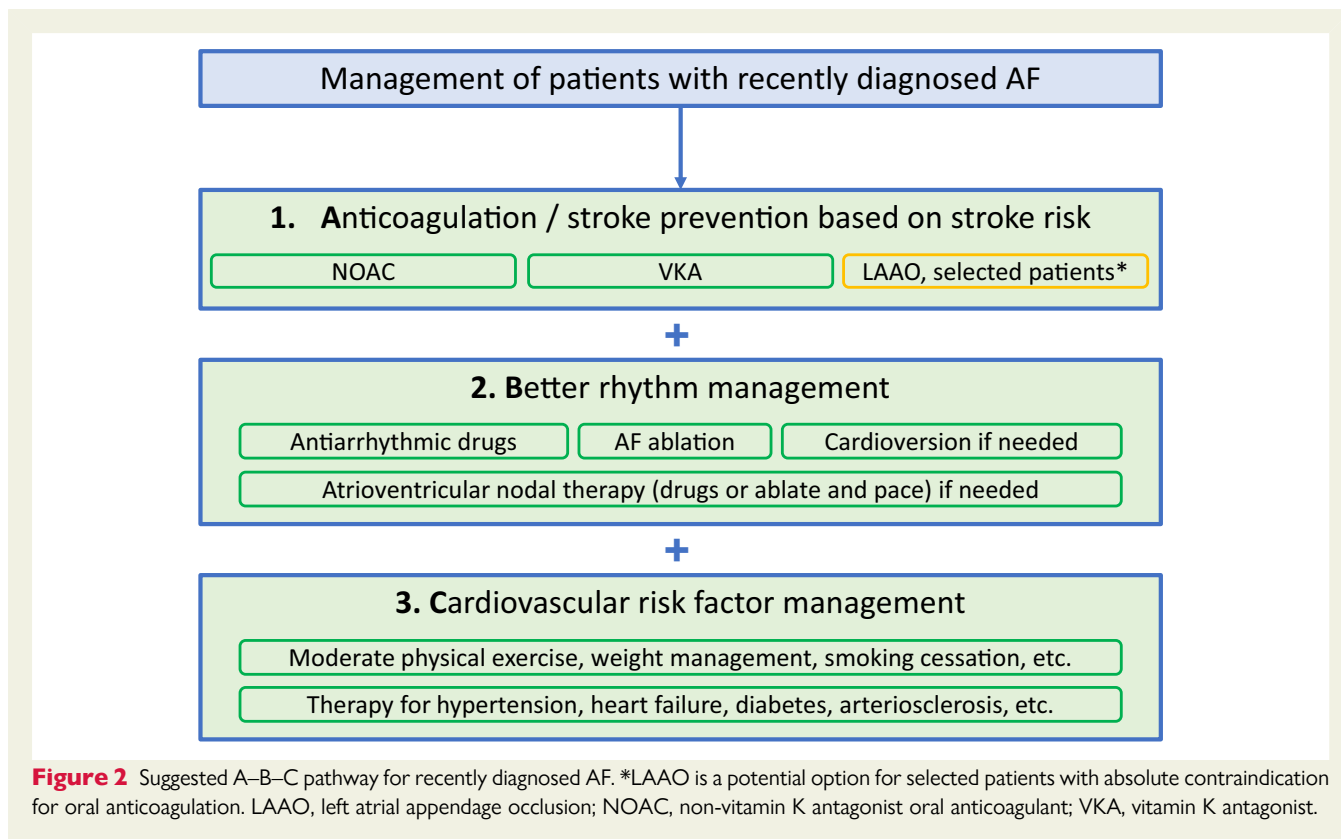
Rhythm management includes (i) rhythm and rate-controlling drugs, (ii) AF ablation, (iii) cardioversion, and/or (iv) AV-nodal therapy. Successful management requires determination of therapy safety for rhythm or rate control. Several randomized controlled trials underpin the safety of rhythm control therapy in elderly AF patients with concomitant cardiovascular diseases, including AF-CHF (Atrial Fibrillation and Congestive Heart Failure),<sup>33</sup> CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation),<sup>34</sup> ATHENA (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),<sup>35</sup> and EAST-AFNET 4 (Early Rhythm-Control Therapy in Patients with Atrial Fibrillation).<sup>4</sup> This is substantiated by analyses of electronic health records and observational data sets that do not show adverse safety signals.<sup>31,32</sup> Thus, the safety of rhythm management has improved compared with the strategy tested in AFFIRM.<sup>40</sup> Additional analyses of large health data sets are underway and may provide further information on the safety of early rhythm control therapy.

Successful rhythm management in selected patients should be embedded in an overall AF management strategy comprising proper anticoagulation ('A') and treatment of concomitant cardiovascular conditions and risk factors ('C'). Reflecting on the new evidence available today, the meaning of 'B' in the A–B–C acronym for AF management could potentially be adapted to *Better rhythm management in selected patients* (Figure 2).

### Attempt at restoration of sinus rhythm

Many patients are suitable for a trial of sinus rhythm restoration to reduce risk of cardiovascular events.<sup>4,35</sup> Although the results of the EAST-AFNET 4 trial were not yet available, the potential of widely used rhythm management was already recognized in the 2020 ESC AF guidelines.<sup>1</sup> The main recommendation on rhythm focuses on AF-related symptoms, but according to the 2020 ESC AF guidelines, rhythm management using antiarrhythmic drugs (AAD) and AF ablation are reasonable. Both usual care and systematic, early rhythm control equally improve symptoms,<sup>4,35</sup> but cardiovascular complications are lower in patients randomized to early rhythm control,<sup>4,35</sup> including in asymptomatic patients.<sup>36</sup> In addition, the improved AF-related symptoms lead to better quality of life. However, it is important to manage expectations when starting rhythm management: While it is very likely that a reduced AF burden mediates the beneficial effects of rhythm management, successful rhythm management does not require complete freedom from recurrent AF and will often call for repeated intervention or adaptation of therapy.

A few patients will not be suitable for continued efforts to maintain sinus rhythm, and occasionally not even for an initial trial of restoration of sinus rhythm. Clinical examples are 'legacy' patients who have a very long history of AF without symptoms and in whom there is less evidence for clinical benefit of rhythm management, patients with severe atrial cardiomyopathy and atrial enlargement, patients with a recent stroke, patients who decide against rhythm management, end-of-life palliative patients, and very old patients in whom limited data are available. The decision to initiate rhythm management in such patients will need clinical acumen and shared decision-making.



**Figure 2** Suggested A–B–C pathway for recently diagnosed AF. \*LAAO is a potential option for selected patients with absolute contraindication for oral anticoagulation. LAAO, left atrial appendage occlusion; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

## Lifelong rhythm management

When rhythm management is initiated, the concept of chronic disease management needs to be communicated and the treatment options presented (Figure 3). It is important to set out realistic treatment goals from the start.

Rhythm control starting with AAD can prevent AF-related outcomes as shown in ATHENA and EAST-AFNET 4.<sup>4,35</sup> Rhythm management is a lifelong part of AF management and will typically require different treatment choices at different time points. These can include referral to AF ablation when AAD do not work,<sup>41</sup> repeat AF ablation,<sup>30,42</sup> or treatment with AAD after AF ablation.<sup>43</sup> Atrial fibrillation ablation and antiarrhythmic drugs appear to have synergistic effects.<sup>43–45</sup> Cardioversion is an important component of rhythm management although not a rhythm maintenance strategy *per se*, but typically a bridge to either AAD or AF ablation to achieve longer-term rhythm management. AV-nodal-directed therapies such as beta-blockers, verapamil/diltiazem, digitalis, or pacemakers have an important role in patients with chronic forms of AF and/or a high arrhythmia burden. But, based on the new evidence, an attempt at sinus rhythm restoration should be considered for many patients.

## Potential of atrial fibrillation ablation therapy

Early rhythm management is effective in patients with AF and HF.<sup>37</sup> Recent clinical trials suggest a possible preference for AF ablation in patients with HF.<sup>34,46</sup> In patients with strong AF-related symptoms and in those in whom an optimal reduction of AF burden seems clinically important,<sup>47,48</sup> AF ablation is also preferred, especially if done early in the course of their disease. Atrial fibrillation ablation is also more effective in improving AF-related quality of life and symptoms than antiarrhythmic drug therapy.<sup>49,50</sup> Atrial fibrillation surgery may succeed in selected patients in whom other rhythm management options fail.

## Practical implications to improve rhythm management

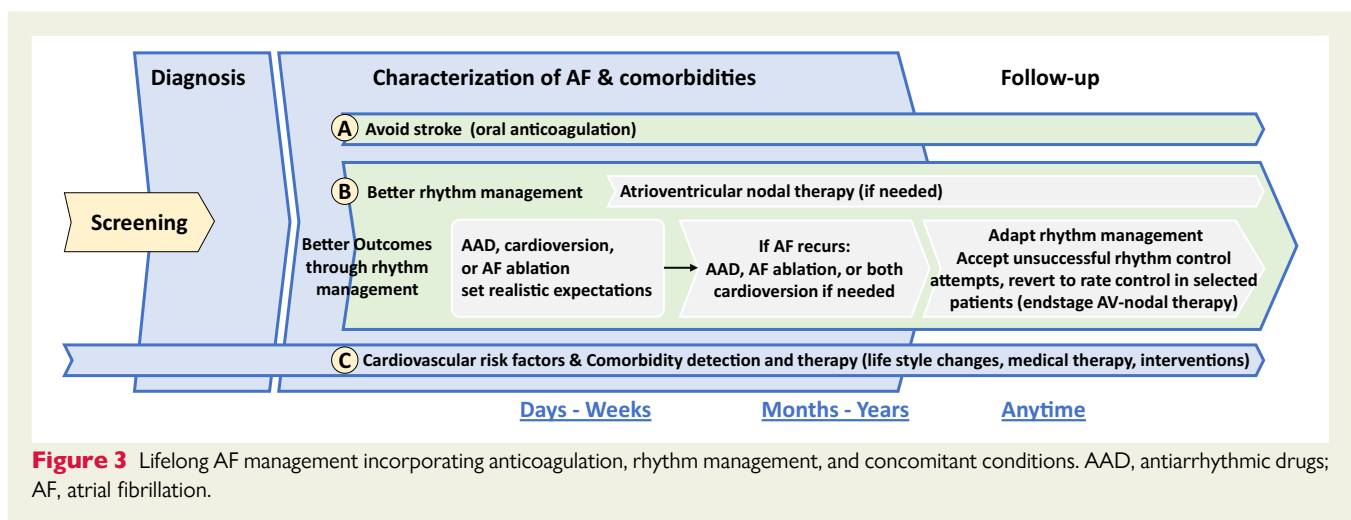
In view of recent data, many newly diagnosed patients with AF should have access to early rhythm management. This recommendation has

major implications for training and resource provision. Rhythm management will need to be led not only by electrophysiologists, but also general cardiologists, HF specialists, and other healthcare professionals whose patients have AF. Nurse-led AF clinics may also play a role in improving access to and FU for rhythm management. Educating patients on the importance of rhythm management will be crucial. Practical next steps should include the following:

- (1) Healthcare professionals' knowledge on prescribing and managing AAD will need to be updated and learned based on the principles laid out in AF guidelines. European Heart Rhythm Association and similar professional organizations are well placed to create new rhythm management training programmes.
- (2) Access to catheter ablation will need to be improved. This calls for simple, standardized procedures that can be delivered more widely and locally to the patient by well-trained teams. More complex procedures required for repeat ablations are probably better concentrated in specialized centres.
- (3) Access to cardioversion will need to be improved. This procedure can be done under sedation by general cardiologists, emergency physicians, and internists, as well as in specialized centres. Apart from direct current cardioversion, newer drugs such as vernakalant allow more effective rapid pharmacological cardioversion.<sup>51</sup>

## Knowledge gaps and research opportunities

The tipping point at which rigorous rhythm management can improve outcomes still needs to be defined. Early rhythm control supports the hypothesis that the observed clinical effects are mediated by the lower arrhythmia burden achieved by rhythm management, but the exact mechanisms remain unclear. Furthermore, the identification of patients suitable for antiarrhythmic medication or direct ablation therapy needs to be optimized. Selective, more effective, and safer AAD may allow a tailored treatment of AF patients but requires further research. Left atrial appendage removal should be a routine part of open-heart surgery in patients with AF<sup>52</sup> and the role of concomitant AF ablation at the time of cardiac surgery needs to be defined.





## Assessment and treatment of cognitive impairment in atrial fibrillation

Atrial fibrillation may lead to cognitive impairment or dementia as a result of clinically overt and/or silent stroke. However, several pathways that are independent of stroke may also be implicated,<sup>53,54</sup> including AF-induced systemic inflammation, chronic brain hypoperfusion,<sup>55</sup> and side effects of AF-specific medication.<sup>56</sup> Thus, AF significantly contributes directly to the burden of cognitive impairment and dementia for patients, and indirectly to their caregivers and society.<sup>6,57</sup> It is likely that an integrated AF management which considers the assessment of cognitive function can reduce the risk of dementia.<sup>1</sup> However, the potential protective role of AF treatment options for maintenance of cognitive function is not well established because the available data are derived from population-based observational studies. Fortunately, several randomized trials are ongoing (*Table 1*). In the absence of specific recommendations in the 2020 guidelines of the ESC,<sup>1</sup> the lack of awareness regarding the impact of AF on cognitive function among physicians may be a key hurdle in clinical practice. Involvement of the patient, their family/caregiver(s), and primary care physician is needed. Conversely, screening for AF seems reasonable in patients presenting with dementia (*Figure 4*), as AF and dementia share risk factors like hypertension and diabetes, and therefore undetected AF may lead to further cognitive decline.

### Specific aspects of management in patients with cognitive dysfunction

Cognitive dysfunction is defined as a reduction in one or more cognitive abilities, such as memory, awareness, judgement, and mental acuity, across the adult lifespan. Multiple significant cognitive impairments in memory plus one or more other cognitive defects are characteristic of dementia. As shown in *Figure 4*, a *Mini-Mental State Examination* (MMSE) or *Montreal Cognitive Assessment* (MoCA) test provide robust signals suggesting the presence of cognitive impairment. Such a finding should trigger a detailed cognitive assessment using an established and validated battery of tests. Furthermore, assessment by a neurologist and brain imaging using magnetic resonance imaging (MRI) can often identify the (most probable) aetiology for cognitive impairment and guide selection of disease-specific treatment.

There is clear evidence showing that anticoagulation therapy prevents strokes in patients with AF and stroke risk factors.<sup>1</sup> Some data suggest that effective anticoagulation can preserve cognitive function in patients with AF.<sup>58</sup> Unfortunately, cognitive dysfunction and dementia are among the factors leading to discontinuation of anticoagulation, thereby enhancing the risk of stroke and death.<sup>59,60</sup> Moreover, cognitive dysfunction was associated with a shorter time in therapeutic range in patients treated with vitamin K antagonists.<sup>58</sup>

Evidence from the EAST-AFNET 4 trial shows that early rhythm management is associated with a lower risk of stroke,<sup>4</sup> but there is no clear evidence that early rhythm management affects cognitive function 2 years after randomization.<sup>36</sup> In a large retrospective cohort study using propensity score matching, AF patients who

underwent catheter ablation had a reduced risk of stroke and dementia compared with non-ablation patients.<sup>61</sup> In a population-based nationwide Korean cohort, catheter ablation was associated with a lower incidence and risk of dementia compared with AF patients who were medically managed.<sup>62</sup> Despite potential residual confounding and bias, this could be attributed to the greater reduction of AF burden achieved by AF ablation compared with antiarrhythmic drug therapy.<sup>30</sup> However, AF ablation also causes clinically silent white matter lesions as detected in studies using MRI.<sup>63–66</sup> Whether or not ablation-related MRI-detected acute ischaemic brain lesions worsen cognitive function has not been demonstrated so far.<sup>54</sup> A recent analysis of over 300 patients undergoing AF ablation and high-resolution brain MRI did not find an effect of MRI-detected lesions on cognitive function 3 months after AF ablation.<sup>67</sup> Thus, even though it is clearly desirable that ablation-induced brain lesions are minimized, rhythm management could be considered for appropriately anticoagulated AF patients with cognitive dysfunction, given the possible reductions in stroke risk and progression to dementia (*Figure 4*).<sup>68</sup>

Identification and treatment of cardiovascular risk factors can reduce dementia.<sup>69</sup> Increasing evidence points towards the importance of lifestyle modification in AF patients,<sup>70</sup> although more data on cognitive decline and incident dementia are needed. For example, AF patients who start or continue regular exercise after the diagnosis of AF were observed to have a lower risk of dementia than persistent non-exercisers.<sup>71</sup>

### Practical and research implications for cognitive dysfunction in patients with atrial fibrillation

Experts suggest that even a moderate suspicion for cognitive impairment should lead to formal cognitive function assessment in AF patients.<sup>72</sup> In addition, patients with cognitive dysfunction/dementia should be assessed for the presence of AF, as AF has to be regarded as an independent risk factor of cognitive impairment. The presence of cognitive impairment should trigger a stepwise and interdisciplinary diagnostic pathway, aiming for optimal (non-)medical treatment to avoid the progression of cognitive dysfunction.<sup>73–76</sup>

### Knowledge gaps and research opportunities

Further prospective studies addressing the interplay of cognitive (dys-)function and AF and its treatment are urgently needed, despite emerging evidence that anticoagulation is associated with a lower risk of dementia in AF patients.<sup>77,78</sup> On the contrary, it is not known if rhythm management or therapy of concomitant conditions can reduce cognitive decline. Therefore, randomized controlled trials evaluating management strategies for AF should also evaluate the course of cognitive function. In addition, the FU duration of such interventional trials should also be adapted to adequately address cognitive decline in patients with AF. Ideally, brain imaging would be obtained to detect structural brain damage associated with cognitive decline.

**Table 1** Current studies on cognitive function and dementia in relation to AF

Trial / Study	Intervention / Treatment	Study Details	Cognition-Related Outcome
<i>Oral anticoagulation</i>			
ARISTA NCT03839355	Apixaban vs. warfarin	N = 280; FU = 24 months Randomized, single blinded <i>Terminated due to low enrolment</i>	Primary Change in cognitive function (using standardized neurocognitive assessment) and new silent cerebral infarcts on MRI
CAF NCT03061006	Dabigatran vs. warfarin	N = 120; FU = 24 months Prospective, randomized, open label, blinded outcome assessment trial	Primary Incident dementia or moderate cognitive decline at 24 months Secondary endpoints: Stroke/TIA, intracranial bleed, changes from baseline scores on MMSE and Hachinski ischaemic scale
GIRAF NCT01994265	Dabigatran vs. warfarin	N = 200; FU = 24 months Prospective, randomized, open, blinded outcome assessment, efficacy study	Neuropsychological evaluation (MoCA + NINDS-CSN-Vascular Cognitive Impairment Harmonization) after 1 year and at the end of follow-up
BRAIN-AF NCT02387229	Rivaroxaban vs. standard care (placebo/ASA)	N = 2280; FU = 5 years Prospective, randomized, double blind, efficacy study	Cognitive decline (MoCA decreased $\geq$ 3 points from baseline) and/or stroke/TIA
ARTESIA neurocognitive sub-study NCT01938248	Apixaban vs. ASA	N = 1000 Prospective, multicentre, double-blind, randomized controlled trial	Change of cognitive function on MoCA
DaRe2THINK NCT04700826	Non-vitamin K oral anticoagulant vs. no therapy in AF at low to intermediate stroke risk	N = 3000; FU = 5 years Nationwide England	Cognitive outcomes are cognitive decline using the UK Biobank cognitive assessment tests yearly and at 10 years, plus a sub-study of N=160 with brain imaging at baseline and 3 years plus Cambridge Neuropsychological Test Automated Battery (CANTAB) cognitive function
OCEAN NCT02168829	Rivaroxaban vs. ASA	N = 1572; FU = up to 3 years Prospective, open label, randomized trial	Secondary Changes on neuropsychological testing (MoCA and MMSE)
NOAH-AFNET 6 NCT02618577	Edoxaban vs. ASA	N = 2686; FU = 24 months Prospective, parallel-group, double-blind, randomized, multicentre trial	Cognitive function (MoCA) at 12 and 24 months
The LOOP study NCT02036450	Internal loop recorder monitoring and oral anticoagulation if AF detected or standard of care	N = 6,004; FU 65 months Prospective, randomized, single blinded	Cognition-related outcome

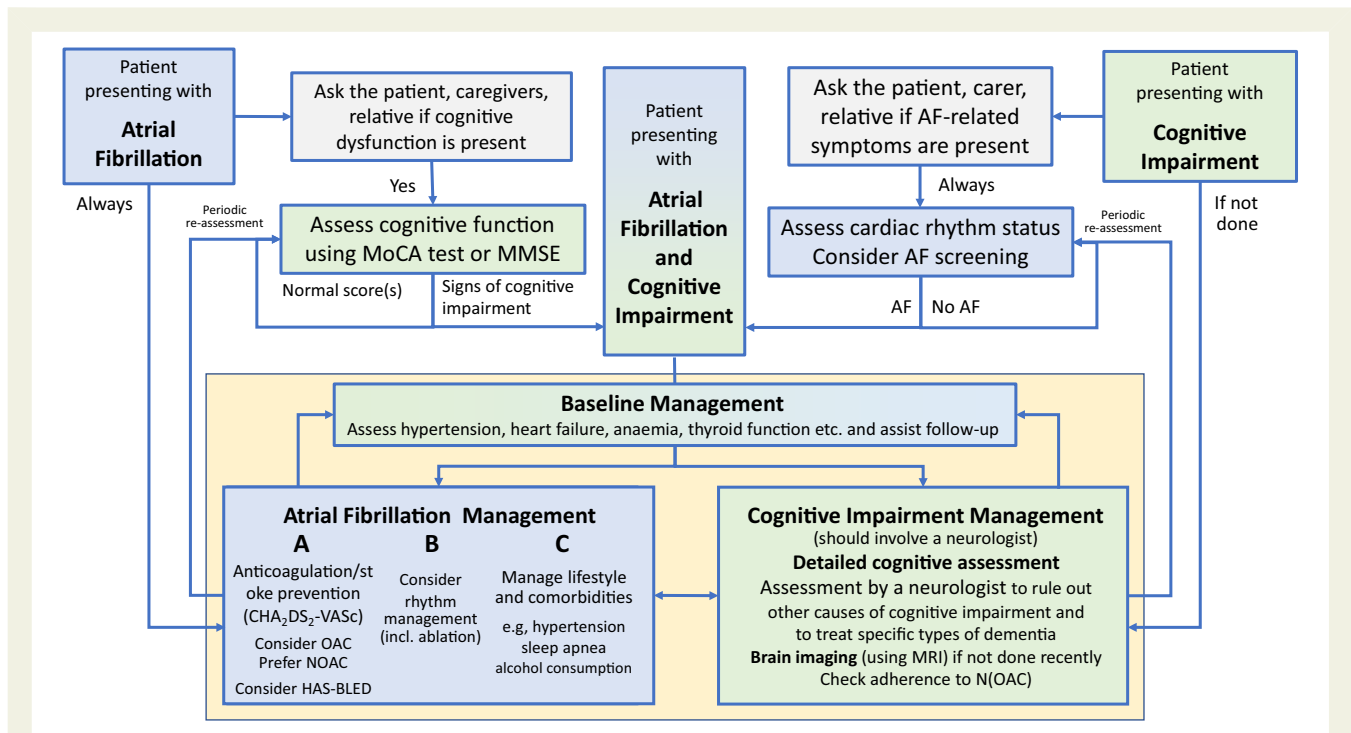
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**Table 1 Continued**

Trial / Study	Intervention / Treatment	Study Details	Cognition-Related Outcome
Rhythm management DIAL-F NCT01816308	AAD vs. AF ablation	N = 888; FU = 24 months	MoCA at baseline and 2 years follow-up
AFCOG NCT04033510	Standard of care intervention for restoring sinus rhythm	Prospective case-control study N = 600; FU = n/a Single cohort study	Differences in cognitive test performance (CANTAB) while in arrhythmia vs. sinus rhythm
Comparison of Brain Perfusion in Rhythm Control and Rate Control of Persistent Atrial Fibrillation NCT02633774	Rhythm control (propafenone) vs. control (apixaban)	N = 200; FU = 12 months Prospective, randomized control trial	Cognitive functions (k-MoCA) and brain perfusion (CT)
EAST-AFNET 4 NCT01288352	Early, comprehensive, rhythm control therapy vs. usual care	N = 2789; FU = 60 months Prospective, randomized, open, blinded outcome assessment trial	MoCA at 24 months after randomization
Other UK SAFER trial	AF screening vs. no screening	N = 126 000; FU = 5 years Cluster randomized trial	Cognitive function
SWISS-AF NCT02105844	Cohort study	N = 2415; FU = 30 months Prospective, observational, multicentre cohort study	Annual neurocognitive function tests (not specified)
PLUG dementia trial NCT03091855	Cohort study	N = 60; FU = 24 months Terminated due to low enrolment	Incident dementia as determined by a neurologist, change in cognitive test (30% decrease in Alzheimer's Disease Assessment Scale/score of <50% or 30% change on the Disability Assessment for Dementia)

Estimated patient enrolment and completion date were taken from trial registration on ClinicalTrials.gov. ARISTA, Apixaban Versus Warfarin in Reducing Rate of Cognitive Decline, Silent Cerebral Infarcts and Cerebral Microbleeds in Patients With Atrial Fibrillation; CAF, Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients With Non-Valvular Atrial Fibrillation. GIRAF, Cognitive Impairment Related to Atrial Fibrillation Prevention Trial; BRAIN-AF, Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation; ARTESA, Apixaban for the Reduction of Thrombo-Embolic Events in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; OCEAN, Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial; DIAL-F, Cognitive Impairment in Atrial Fibrillation; AFCOG, Acute Cognitive Changes During Atrial Fibrillation Episodes; SWISS-AF, Swiss Atrial Fibrillation Cohort Study; PLUG, Dementia Trial and MRI PLUG Dementia Sub-Study.

CANTAB, Cambridge Neuropsychological Test Automated Battery; FU, follow-up; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging.



**Figure 4** Flow chart on three common presentations of AF and cognitive impairment (or dementia): (i) a patient presenting with known AF whose mental state is not the reason for the presentation, (ii) a patient with known cognitive impairment, and (iii) a patient with both, known AF and cognitive impairment. For the patient with known AF, simple tests of cognitive function may confirm the need for detailed assessment to evaluate the cause of cognitive impairment and initiate therapy for reversible causes. Similarly, patients presenting with cognitive impairment should undergo opportunistic screening for AF (pulse palpation eventually followed by an ECG) and, if AF is discovered, it should be assessed and managed initially by a specialist following the A–B–C (Atrial fibrillation Better Care [includes A (avoid stroke), B (better symptom control), C (cardiovascular risk factors and comorbid conditions management)] scheme recommended by the European Society of Cardiology. AF, atrial fibrillation; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant.

## Atrial (cardio)myopathies: definition, risk factors, and progression

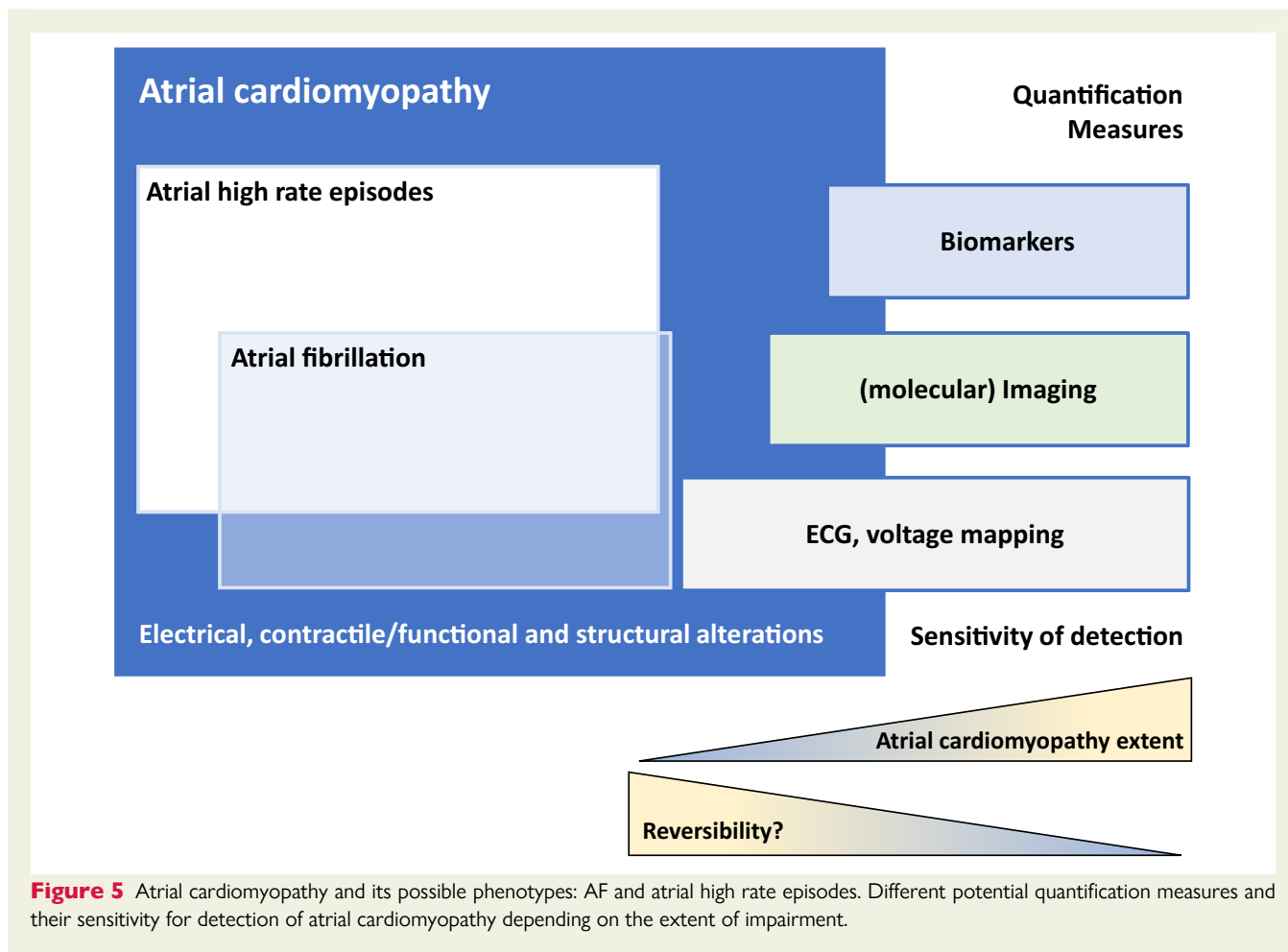
### Defining the concept

The earliest systematic characterisation of atrial (cardio)myopathy dates back to 1972.<sup>79</sup> In line with the 2017 EHRA/HRS/APHRS/SOLAECE expert consensus,<sup>80</sup> we consider atrial cardiomyopathy as an extension of the pathophysiological concept of AF initiation and perpetuation that comprises triggers, substrate, and modifying factors together with the genetic architecture. Atrial cardiomyopathy affects all cellular components of the atria and manifests in three main ways, where each component can be present alone or in combination with the others: electrical, contractile/functional, and structural alterations. We acknowledge that detecting all potential manifestations of atrial cardiomyopathy is not feasible yet, mainly because our diagnostic abilities of atrial imaging or electrical mapping are limited. Furthermore, the underlying pathophysiological processes are not completely known.<sup>81</sup> For application in clinical care, atrial cardiomyopathy needs to be quantifiable and uniform definitions are a prerequisite. Several ways of measurement are possible and refined methods will improve detection. To date, it has been

observed that detection increases with advanced impairment (Figure 5). Specific and sensitive non-invasive measures are not available to validate the clinical relevance of the concept of atrial cardiomyopathy. Indication-specific characterizations have to be developed, e.g. voltage mapping in invasive electrophysiology, combinations of electrocardiographic, imaging, and blood biomarker-based definitions (also see Table 2). The latter has been used as a provisional surrogate of atrial cardiomyopathy in the ARCADIA (*AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke*) trial.<sup>116</sup> In addition to clinical characteristics and imaging, circulating biomolecules reflecting general cardiovascular and atrial disease processes can help to detect and characterize atrial cardiomyopathy, e.g. natriuretic peptide, bone morphogenic protein 10, or fibroblast growth factor 23.<sup>104,117–119</sup> Such definitions require prospective confirmation in relation to interventions and hard clinical outcomes.

### Atrial cardiomyopathy disease progression

Although atrial cardiomyopathy is not precisely defined, nor the different stages of diseases are described in detail, the prevailing idea is that atrial cardiomyopathy progresses: electrical manifestations are



**Figure 5** Atrial cardiomyopathy and its possible phenotypes: AF and atrial high rate episodes. Different potential quantification measures and their sensitivity for detection of atrial cardiomyopathy depending on the extent of impairment.

**Table 2** Quantification measures of atrial cardiomyopathy

Measurement method	Parameters	References
X-ray	Dilated atrium	
Surface electrocardiogramme	Prolonged P-waves, abnormal P-waves, P-wave terminal force in ECG lead V1, sinoatrial node dysfunction, atrial ectopy	82–86
ECGi, electrocardiographic imaging	Abnormal activation, prolonged activation time, slowing of conduction velocity	87,88
Echocardiogramme	Dilated atrium, reduced contractility, reservoir function, conduit function, emptying fraction, left atrial strain imaging	89–95
CT scan	Abnormal atrial function, fatty infiltration, morphology: atrial sphericity, left atrial appendage shape	96
MRI	Dilated atrium, decreased contractility, abnormal morphology: sphericity, fibrosis (late gadolinium enhancement)	97–103
Blood biomarkers	Natriuretic peptides—atrial dilatation, myocyte stretch Fibroblast growth factor—fibrosis Bone morphogenic protein-10—atrial remodelling Fatty acid binding protein 3—atrial metabolic disturbance C-reactive protein, Interleukin-6—inflammation Factor VIII, von Willebrand factor, Fibrinopeptide A—pre-thrombotic state, hypercoagulability	104–107
Electrophysiological 3-D mapping	Low voltage in sinus rhythm, prolonged atrial activation time, decreased conduction velocity	108–114
Biopsy	Fibrosis, fatty infiltration, collagen accumulation, amyloid depositions, endocardial remodelling, vascular rarefaction, molecular imaging	115

Summary of potential methods used to quantify atrial cardiomyopathy.

ion channel remodelling that affects action potential duration and the development of low-voltage areas in the left atrium, causing AF to evolve from self-limiting to more persistent AF types. Contractile/functional manifestations include increased atrial size and loss of contractile function, as well as deterioration of conduit and reservoir functions of the atria.<sup>120</sup> Progression of structural manifestations is characterized by cardiomyocyte hypertrophy, atrial fibrosis, fatty infiltration,<sup>121</sup> atrial dilatation, and amyloid depositions.<sup>122</sup> It can be assumed that early stages of atrial cardiomyopathy may be largely reversible, but with this progression of disease, these manifestations will become more permanent and less reversible. This idea aligns with the recent findings of EAST-AFNET4<sup>4</sup> which showed that early rhythm management in AF, i.e. within the first year of diagnosis, is beneficial for reducing the risk of common cardiovascular outcomes and in patients with detectable ventricular dysfunction.<sup>37</sup>

Atrial MRI has been proposed as a tool to quantify atrial cardiomyopathy and to assess the risk of recurrent AF after catheter ablation. Initial MRI studies (Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation, DECAAF I) have demonstrated the correlation between the amount of fibrosis and AF recurrence.<sup>123</sup> The multicentre results of Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF II) and Isolation of Pulmonary Veins With the Aid of Magnetic Resonance Imaging (ALICIA)<sup>124</sup> trials could not demonstrate that this increased risk is modifiable by AF ablation. It remains unclear to what extent currently available MRI algorithms detect atrial cardiomyopathy that is related to low-voltage areas.<sup>125–127</sup> In DECAAF II, the attempt to show the benefit of a fibrosis-guided individualized ablation strategy failed.

In addition, the extent of atrial cardiomyopathy has been related to the risk for cerebrovascular events.<sup>128,129</sup> Signals for atrial cardiomyopathy could potentially be detected in community settings based on quantification of circulating cardiovascular biomolecules. Whether the concept of atrial cardiomyopathy will be adopted in clinical practice depends on its impact on patient management and whether the following central knowledge gaps can be sufficiently addressed.

## Atrial cardiomyopathy and atrial fibrillation

Quantifying atrial cardiomyopathy and AF in patients may increase understanding of the temporal disconnect between AF and stroke.<sup>130</sup> It seems likely that structural remodelling is influenced by the presence of cardiovascular risk factors and diseases as atrial remodelling occurs before the development of clinically detected AF.<sup>131</sup> The atrial cardiomyopathy is aggravated by AF episodes and by concomitant cardiovascular conditions and risk factors. The concept of atrial cardiomyopathy may also be of value for patient communication and education to emphasize the importance of continuous risk factor and lifestyle management together with long-term use of medical therapies or FU visits because of the presence of atrial cardiomyopathy. It helps to avoid the notion that with the temporal freedom of AF, further preventive management may no longer be necessary.

A favourable clinical outcome currently is most likely achieved by optimal AF treatment (see earlier sections).

## Potential practical implications

- Atrial cardiomyopathy is a valuable emerging concept to explain the nature of AF and its management to patients.
- The interactions between atrial cardiomyopathy and AF require quantification in patients, initially in research settings.
- Better tools to objectively quantify atrial cardiomyopathy are needed. Electrocardiographic and electroanatomical mapping, modern imaging modalities, circulating biomolecules, and innovative combined analytical methods may become useful to provide such quantification.
- Further potential clinical applications are provided in *Table 3*.

## Knowledge gaps and research opportunities

To investigate the central atrial cardiomyopathy hypothesis, we need basic, translational, and clinical research to more precisely define atrial cardiomyopathy, its risk factors, and progression. Clinically available accurate quantification of atrial cardiomyopathy is required to translate the concept of atrial cardiomyopathy into clinically meaningful management strategies. Furthermore, practical definitions of atrial cardiomyopathy are required for clinical trials and need to be tested for meaningful outcomes including hard endpoints.

## Structuring high-quality care

Structured quality of care for AF patients includes both having a structured pathway for delivering optimal quality of care for patients and a structured assessment of quality indicators (*Figure 6*). Quality of care encompasses (i) diagnosis, (ii) referral where needed, (iii) management, and (iv) FU. The main areas of quality assessment for AF diagnosis and management are: patient assessment (baseline and FU), anticoagulation therapy, rhythm management, and patient-reported outcome measures, as recently outlined by an ESC and EHRA-led international task force.<sup>138</sup> In addition to treatment domains and outcomes, patient-reported outcomes are important measures to quantify quality of care.<sup>139</sup>

The entire assessment of each patient should be structured, including detection and management of comorbidities, risk factors and lifestyle changes, anticoagulation and stroke prevention, and rhythm management.<sup>1</sup> The upcoming EU-funded projects EHRA-PATHS<sup>140</sup> (EHRA-PATHS, No. 847770) and AFFIRMO<sup>141</sup> (AFFIRMO, No. 899871) work to develop a framework for how to improve AF management through a holistic, inclusive, and personalized care pathway centred on patients.<sup>142</sup> Continuous FU and regular re-evaluation of the process and the quality indicators of care are needed. This structured approach should be clearly defined, interprofessional, transparent, and easy to implement. Responsibilities need to be clear, taking into account differences between various countries and local health-care organizations. Nurses and general practitioners can have a certain autonomy in this structured approach; however, they should work in coordination with an expert in AF, e.g. a cardiologist.

An important quality measure is adherence to defined, structured care pathways.<sup>143</sup> However, there is a knowledge gap on how to measure and ensure adherence to such pathways, which should be addressed by new research. The quality of care should be regularly evaluated, e.g. yearly, but again, there is a gap of knowledge on the optimal time interval for reassessment.

**Table 3 Potential clinical implications of atrial cardiomyopathy**

- Correlation between MRI-detected fibrosis and AF recurrence, but not ECG phenotype (DECAAF,<sup>132</sup> efficacy of late gadolinium enhancement MRI-guided fibrosis ablation vs. conventional catheter ablation of atrial fibrillation)
- Correlation between atrial fibrosis and difficulty of SR restoration (DECAAF), risk for cerebrovascular events—surrogate (echo contrast) and major adverse cardiovascular events<sup>128,129</sup>)

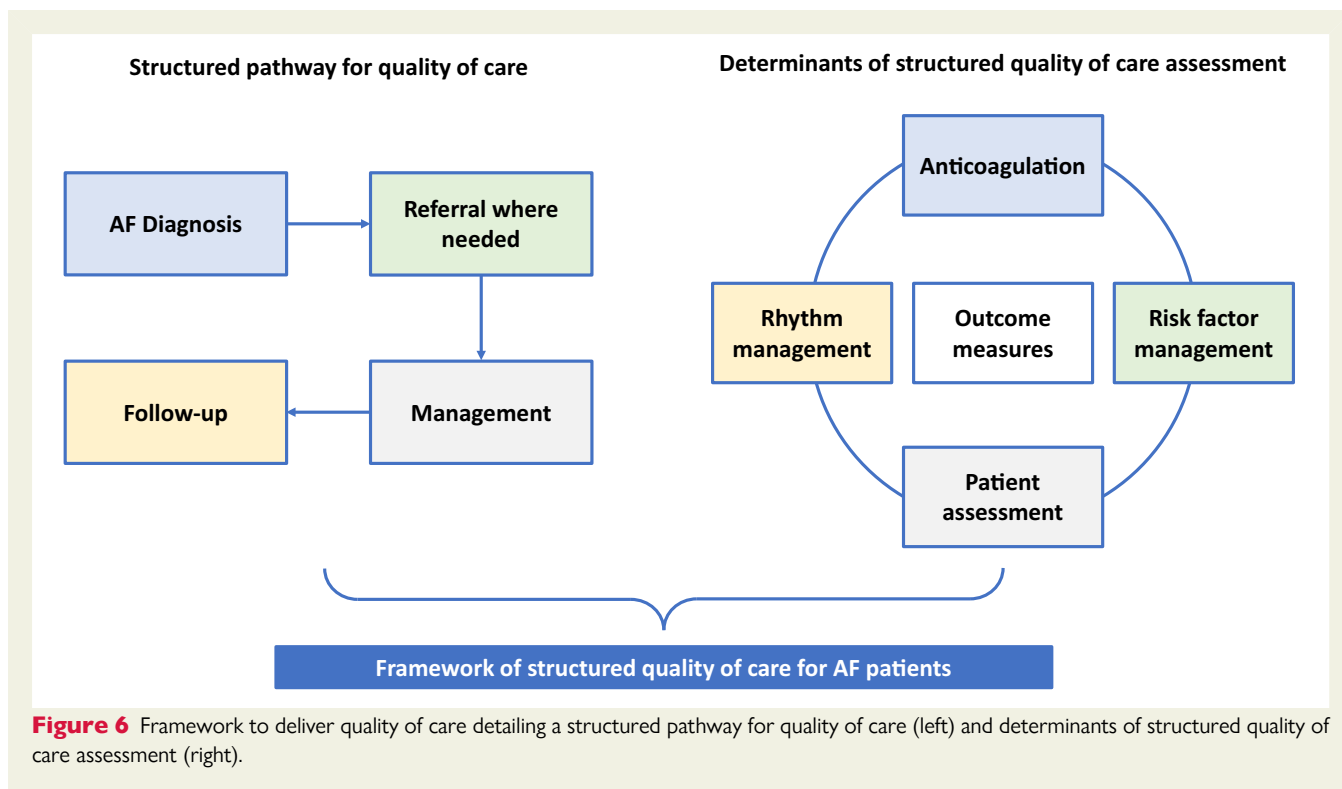
*Progression, slowing progression*

- Recovery of voltage reduction after successful ablation (CAMERA-MRI, Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction<sup>133</sup>)
- Recovery of fibrosis—left atrial reverse remodelling after ablation (Echo, MRI)
- Ventricular fibrosis as marker ablation response (CAMERA-MRI) with regression after restoration of SR<sup>134</sup>
- Benefit of early rhythm management of AF (EAST)<sup>4</sup>
- Benefit of risk factor management, e.g. weight reduction<sup>135</sup> (REVERSE-AF, PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation)
- Benefit of lifestyle changes, e.g. alcohol abstinence
- Benefit of upstream therapy (RACE3, targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation)<sup>136</sup>

Potential future clinical implications

- End-organ damage assessment (e.g. in hypertension)
- Identification of subgroups of AF patients who benefit from therapies not successful in unselected patients, individualized treatment
- Tool for patient communication
- Improved stroke risk assessment, stroke prevention, recurrent stroke prevention (ARCADIA trial)
- OAC indication in borderline risk patients with AF (BRAIN-AF trial)
- Prevention of AF onset and progression
- Inform about the preferential procedural strategy in ablation procedures beyond pulmonary vein isolation
- Better explain the continuation of OAC after ablation (OCEAN trial<sup>137</sup>)

ARCADIA, AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke; CAMERA-MRI, Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction; DECAAF, Delayed-Enhancement MRI-Guided Ablation versus Conventional Catheter Ablation of Atrial Fibrillation; EAST, Early treatment of atrial fibrillation for stroke prevention trial; MRI, magnetic resonance imaging; OAC, oral anticoagulant; OCEAN, Optimal anti-Coagulation for Enhanced-risk patients post-catheter Ablation for atrial fibrillation; RACE3, Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure.



**Figure 6** Framework to deliver quality of care detailing a structured pathway for quality of care (left) and determinants of structured quality of care assessment (right).

In addition to components of care and clinical outcomes, patient-reported outcomes are useful to assess the quality of care.<sup>144–146</sup> These can be measured using scales capturing general health-related quality of life.<sup>138</sup> Several validated tools such as EQ-5D-5L (*European Quality of Life 5 Dimensions 5 Level*)<sup>147,148</sup> or SF-12 (short form survey)<sup>149</sup> are available to measure it. Atrial fibrillation-specific quality-of-life questionnaires are validated, available,<sup>150,151</sup> and recommended by the *International Consortium of Healthcare Outcome Measures* (ICHOM) for AF.<sup>144</sup> Follow-up measurement of quality of life with the same tool is required to compare trends for evaluation and decision-making. Patient-reported experience measures such as patient satisfaction, subjective experiences (e.g. symptom control) or objective experiences (e.g. waiting time to appointment), and treatment burden are indicators to identify the quality of care.<sup>152</sup>

Education should be provided in an appropriate and understandable way for patients and their caregivers and can improve outcomes.<sup>148,153–155</sup> Education of patients and continued medical education is needed to maintain care pathways, to achieve quality indicators, and to implement new technical developments.<sup>156</sup> Knowledge gaps and unmet needs should be identified and addressed.<sup>157,158</sup> An ESC and EHRA-funded project, STEEER-AF [STEEER-AF Project Study (escardio.org)] is currently evaluating the impact of an educational programme for HCPs on outcomes in patients with AF.<sup>159</sup>

Objective information on AF, its consequences, and its management should be available on websites, smartphone apps, or in print for patients and relatives, ideally available in all relevant local languages. Unbiased resources and reliable sources endorsed by scientific societies increase confidence, effectiveness, and trustworthiness.<sup>160</sup> Health and digital literacy should be taken into account to ensure optimal education of patients and relatives and avoid potential adverse effects.<sup>157,161,162</sup> Professional organizations such as EHRA and the ESC have an important role in the generation of such information.

## Practical implications

- Measuring the quality of care in patients with AF is required to improve it.
- Outcomes measures capturing the efficacy and safety of therapy are known and should be measured.
- The quality of care delivery can be estimated by measuring adherence to evidence-based recommendations in guidelines, possibly through audits.
- In addition to these measures, patient-reported outcomes and patient experience are important domains for a comprehensive estimation of quality of care.

## Knowledge gaps and research opportunities

The development of evidence-based educational interventions to improve knowledge and skills of healthcare providers needs to be fostered. Objective and easily ascertainable measures are required to ensure adherence to care pathways. The frequency of their re-evaluation needs to be determined. New care pathways should be developed to detect, address, and FU multimorbidity and polypharmacy in the often older and multimorbid patients with AF. Multidisciplinary and patient-centred approaches need to be

designed. Further potential issues and barriers in the guideline-adherent management of AF at the patient and healthcare provider level will need to be identified and addressed.

## Artificial intelligence in the management of atrial fibrillation

Artificial intelligence comprises methods that enable a computer to learn from data with two main subcategories: the supervised and the unsupervised learning methods. In supervised learning, the output or target is defined (e.g. recognition of a sinus rhythm or AF on the ECG). The learning process uses labelled data sets to solve classification and regression problems. In unsupervised learning, there is no prediction of any output or need for labelled data. Instead, raw data are modelled with the goal of identifying patterns and structures, and to cluster similar variables. Nowadays, unsupervised deep neural networks are the most popular method for identification of hidden signatures of diseases. However, it requires large data sets, and generates its own logical process, creating a black box that requires complex explanatory analysis methods.

There has been a massive increase of AI in the field of AF, with 5298 articles on AF and AI indexed in Pubmed since 2016.<sup>163</sup> This trend is driven by two main factors. First, the electrical and imaging signals, which are the two pillars for AF assessment, are well-suited data for machine learning approaches. Secondly, the creation of large data sets, such as the *Computing in Cardiology challenge 2017/PhysioNet*,<sup>164</sup> facilitated the deployment of studies on AI.

Artificial intelligence technologies have been used primarily in studies to improve AF detection, and, to a lesser extent, in studies to predict incident and recurrent AF in patients undergoing rhythm control therapy, or response to drug treatment in multimorbid patients.<sup>165</sup> For example, deep neural networks have been used to detect AF based on ECG and pulse plethysmography signals.<sup>166–168</sup> They improved the performance of AF identification based on such combinations of signals as compared to traditional AF detection algorithms.

Recent studies have implemented explanatory elements and allowed understanding of ECG features which can be used to better detect AF. Both, RR interval irregularity and lack of P-waves contribute to AF detection equally.<sup>169</sup> Artificial intelligence algorithms also can predict impending AF within the next 31 days based on a single standard 12-channel ECG in sinus rhythm using a deep learning convolutional network with an area under the curve of 0.87 for the detection of AF based on ECGs in sinus rhythm.<sup>170</sup> When using multiple ECGs within the same time window, the area under the curve increased to 0.90. The same algorithm was subsequently used to predict incident AF in an independent cohort of elderly patients with a mean FU of 7.4 years.<sup>171</sup> The performance was comparable with the clinical AF risk scores combining clinical information, ECG parameters, and blood pressure measurements. Taken together, these results demonstrate the predictive strength contained in the ECG. Such algorithms might be used to identify patients at risk for AF and in whom monitoring for AF might be initiated. *Table 4* lists the ongoing registered trials using AI for AF care.

Although these algorithms perform well, the deep neural network studies often have not provided sufficient insights into how exactly



**Table 4** Prospective trials on AI-based methods listed currently under clinicaltrials.gov

Intended use of AI method	Study title	No. participants	Country
AI-guided patient selection for AF catheter ablation	AI-PAFA <i>NCT04997824</i>	340	South Korea
AI-based AF detection referring to heart rhythm monitoring with wearable devices	WB-AF <i>NCT04917653</i>	100	Finland
AI-enabled ECG-based screening tool for AF	BEAGLE <i>NCT04208971</i>	1000	USA
Predicting patient-level new onset atrial fibrillation	Re-use of CPRD-GOLD and CPRD-AURUM <sup>172</sup>	140 000	UK
AI-enhanced performance of Apple watch in ablation/ cardioversion patients	AI-AW <i>NCT05045456</i>	200	France
Prevention of stroke and sudden cardiac death by AI-enhanced one-channel ECGs	PRICE <i>NCT04637230</i>	10 000	Germany
Home-based AF screening with handheld one-lead ECG recording	HUATUO-AF <i>NCT04523649</i>	1740	Hong Kong
Correlation between cardiovascular disease and individualized differences	Artificial intelligence with deep learning and genes on cardiovascular disease <i>NCT03877614</i>	5000	Taiwan
Remote monitoring of AF recurrence using mHealth technology	REMOTE-AF <i>NCT05037136</i>	35	UK
Accuracy of cardiac arrhythmias and conduction disorders diagnosis using a smartwatch	Accuracy of cardiac arrhythmias and conduction disorders diagnosis using a smartwatch <i>NCT04437914</i>	110	Brazil
Arrhythmia classification for shockable cardiac rhythms	AI-ECG <i>NCT03662802</i>	25 458	USA
Differentiate stroke subtypes and predict source in acute ischemic stroke	Validation of 3D simulations in embolic stroke <i>NCT05055960</i>	100	UK
Multimodality imaging for diagnosis and outcomes evaluation of multicenter patients with heart failure with preserved ejection fraction and AF	Diagnosis and Outcomes evaluation of Multicenter Patients With HFpEF Using Multimodality Imaging <i>NCT04602338</i>	1000 + 430	China

Estimated patient enrolment and completion date were taken from trial registration on ClinicalTrials.gov. AI-PAFA Trial, Artificial Intelligence Guided Patient Selection for Atrial Fibrillation Catheter Ablation: Randomized Clinical Trial; WB-AF, Portable Measurement Methods Combined With Artificial Intelligence in Detection of Atrial Fibrillation; BEAGLE, Batch Enrollment for AI-Guided Intervention to Lower Neurologic Events in Unrecognized AF; AI-AW, Observational Clinical Investigation of EKG Diagnostic Performance of the Apple Watch Augmented With an AI Algorithm; PRICE, Prevention of Stroke and Sudden Cardiac Death by Recording of 1-Channel Electrocardiograms; HUATUO-AF, Home-Based Solution for Remote Atrial Fibrillation Screening to Prevent Recurrence Stroke; REMOTE-AF, Remote Monitoring of AF Recurrence Using mHealth Technology; AI-ECG, Development of a Novel Convolution Neural Network for Arrhythmia Classification.

the algorithm is working and how a diagnostic decision is taken—leaving uncertainties on independent verification and generalizability, jeopardizing its incorporation into daily clinical practice.

## Knowledge gaps and research opportunities

Artificial intelligence benefits from large, high-quality data sets, where data constitution and access represent a major challenge for both research and clinical translation. First, different data sets are governed by different data protection rules which limit accessibility, especially in Europe. Data sets are owned and controlled by diverse stakeholders (e.g. private companies that might develop and commercialize AI tools; academic institutions that might also develop, compare, and implement them). Strict legal frameworks for data protection

and use (e.g. General Data Protection Regulation and Good Clinical Practice) apply to the use of medical data. For reproducibility, data accessibility is crucial for validation of algorithm-generated predictions. Good data accessibility is also required including scientific transparency in accordance with the International Committee of Medical Journal Editors (ICMJE). In this context, it should be required that all prospective clinical trials and registries using AI are listed in official trial registries.

Unfortunately, the current complexity and disorganization of processes for data sharing and circulation between academic partners within Europe and beyond are a major handicap for progress in AI in medicine. Although the European Union (EU) has been vocal about data strategies (Strategy for Data | Shaping Europe's digital future (europa.eu)) and FAIR (Findability, Accessibility, Interoperability, and Reuse) guiding principles for scientific data

and digital assets management and stewardship, the principles outlined in these strategies often conflict with other European and National regulations, e.g. EU general data protection regulation, at the individual project level. In particular, there is also the fundamental aspect of the medical responsibility when using tools for prediction and aid in medical decisions that needs to be evaluated in context with the updated medical device regulation (MDR).

## Steps to facilitate clinical implementation of artificial intelligence

The results of AI-based investigations and applications will become increasingly available. Beyond formal regulatory approval of such applications by the respective authorities, their performance and use will need to be compared in the context of the current state of art of AF care. Such context is typically generated by the medical community and their professional societies such as the ESC and EHRA. Understanding the methodology and implications of AI-based AF detection methods requires specific knowledge, involving expertise in the fields of informatics, computational networks, biostatistics, legal and medico-legal implications, and medicine. Additional questions need to be addressed, such as the reimbursement of these machine learning derived medical devices which likely requires a health economic analysis comparing costs of current practice with an AI supported pathway. Cardiology societies like ESC and EHRA are encouraged to establish and promote working groups equipped with such expertise to generate informed guidance on the sharing and use of AI-related data and algorithms, devices, and products to their society members and the medical community.

## Summary

During the 8th Joint AFNET/EHRA Consensus Conference, we have clarified current AF screening and management strategies, especially an update on the role of rhythm management, with clear implications for clinical practice. Research gaps in clinical and translational science have been identified and tasks and mandates for the ESC and EHRA suggested.

Main outcomes of the 8th Joint AFNET/EHRA Consensus Conference:

- New evidence supports the implementation of systematic screening for AF to achieve long-term reduction in a combined outcome of mortality, stroke, and severe bleeding.
- Rhythm management, including a consideration of an attempt at rhythm control, should be part of the initial treatment in patients with recently diagnosed AF.
- As AF can be regarded as a risk factor for stroke and cognitive decline, attention should be paid to cognitive function, which is a cornerstone for compliance with AF treatment.
- The concept of atrial cardiomyopathy requires better and objective tools for its quantification and research to align cardiomyopathy and AF.
- Defining and measuring the quality of care in terms of process, patient experience, and outcomes will be important to improve it.
- Artificial intelligence has the potential to unravel the complex pathophysiology leading to atrial cardiomyopathy and AF, early AF

detection, prognosis, and precision treatment, but its role, circumstances of its application, and the optimal methods need to be defined.

## Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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