Dynamic risk assessment to improve quality of care in patients with atrial fibrillation

Fabritz, Larissa; Crijns, Harry J G M; Guasch, Eduard; Goette, Andreas; Häusler, Karl Georg; Kotecha, Dipak; Lewalter, Thorsten; Meyer, Christian; Potpara, Tatjana S; Rienstra, Michiel

Published in:
Europace

DOI:
10.1093/europace/euaa279

ESC European Society of Cardiology

Europace (2021) **23**, 329–344
doi:10.1093/europace/euaa279

EHRA CONSENSUS STATEMENT

Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: the 7th AFNET/EHRA Consensus Conference

**Larissa Fabritz[1,2], Harry J.G.M Crijns[3], Eduard Guasch[4], Andreas Goette[5,6], Karl Georg Häusler[7], Dipak Kotecha[1], Thorsten Lewalter[6,8], Christian Meyer[9], Tatjana S. Potpara[10], Michiel Rienstra[11], Renate B. Schnabel[6,9], Stephan Willems[6,12], Guenter Breithardt[6,12,13], A. John Camm[14], Anthony Chan[15], Winnie Chua[1], Mirko de Melis[16], Christina Dimopoulou[17], Dobromir Dobrev[18], Christina Easter[1], Lars Eckardt[6,13], Doreen Haase[6], Stephane Hatem[19], Jeff S. Healey[20], Jordi Heijman[2], Stefan H. Hohnloser[21], Thomas Huebner[22], Bushra Saeed Ilyas[15], Aaron Isaacs[3], Ingo Kutschka[6,23], Christophe Leclercq[24], Gregory Y.H. Lip[25], Elena Andreassi Marinelli[26], Jose L. Merino[27], Lluís Mont[28], Michael Nabauer[6,29], Jonas Oldgren[30], Helmut Pürerfellner[31], Ursula Ravens[6,32], Irina Savelieva[33], Moritz F. Sinner[29], Alice Sitch[1], Rüdiger Smolnik[26], Jan Steffel[34], Kenneth Stein[35], Monika Stoll[3], Emma Svennberg[36], Dierk Thomas[6,37], Isabelle C. Van Gelder[38], Burcu Vardar[39], Reza Wakili[6,40], Mattias Wieloch[43], Stef Zeemering[38], Paul D. Ziegler[16], Hein Heidbuchel[45], Gerhard Hindricks[44], Ulrich Schotten[3,6,38], and Paulus Kirchhof[1,6,9]*

[1]Institute of Cardiovascular Sciences, University of Birmingham, UK; [2]Department of Cardiology, University Hospital Birmingham, UK; [3]School for Cardiovascular Diseases, Maastricht University Medical Centre, the Netherlands; [4]Hospital Clinic, IDIBAPS, CIBERCV, University of Barcelona, Spain; [5]Medical Clinic II, St. Vincenz Krankenhaus, Paderborn, Germany; [6]Atrial Fibrillation NETwork (AFNET), Münster, Germany; [7]Department of Neurology, University Hospital Würzburg, Germany; [8]Internistisches Klinikum München Süd, Germany; [9]University Heart Center, University Hospital Hamburg-Eppendorf, Germany; [10]School of Medicine, University of Belgrade, Clinical Centre of Serbia, Serbia; [11]University Medical Center Groningen, the Netherlands; [12]Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany; [13]Department of Cardiovascular Medicine, University Hospital Münster, Germany; [14]St George's Hospital Medical School, University of London, UK; [15]Pfizer; [16]Medtronic; [17]European Society of Cardiology; [18]Department of Cardiology, University Hospital Essen, Germany; [19]Department of Cardiology, Sorbonne Universités, Faculté de médecine UPMC, Assistance Publique—Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France; [20]Population Health Research Institute Hamilton, Canada; [21]Department of Cardiology, Goethe-University of Frankfurt, Germany; [22]Preventicus, Germany; [23]Klinik für Thorax-, Herz- und Gefäßchirurgie, University Hospital Göttingen, Germany; [24]Univ Rennes, CHU Rennes, INSERM, LTSI—UMR 1099, F-35000 Rennes, France; [25]Liverpool Centre for Cardiovascular Science, University of Liverpool, UK; [26]Daiichi Sankyo Europe; [27]Arrhythmia & Robotic EP Unit, La Paz University Hospital, Spain; [28]Hospital Clinic, Universitat de Barcelona, Barcelona, Catalonia, Spain; [29]Medizinische Klinik und Poliklinik I, University Hospital Munich, Germany; [30]Department of Medical Sciences, Uppsala Clinical Research Center, Uppsala University, Sweden; [31]Department für Rhythmologie und Elektrophysiologie, Ordensklinikum Linz, Austria; [32]Institut für Experimentelle Kardiovaskuläre Medizin, Universitätsherzzentrum Freiburg, Bad Krozingen, Germany; [33]St. George's University of London, UK; [34]University Heart Center Zurich, Switzerland; [35]Boston Scientific, USA; [36]Division of Cardiovascular Medicine, Department of Clinical Sciences, Karolinska Institutet, Danderyd's Hospital Stockholm, Sweden; [37]Department of Internal Medicine III—Cardiology, Angiology and Pneumonology, Medical University Hospital Heidelberg, Germany; [38]Department of Cardiology, University Medical Center Groningen, University of Groningen, the Netherlands; [39]Bayer Healthcare, Belgium; [40]Department of Cardiology, University Hospital Essen, Germany; [41]Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, the Netherlands; [42]Institute of Pharmacology, University Hospital Essen, Germany; [43]Sanofi, Paris, France; [44]Department of Electrophysiology, Heart Center Leipzig, University of Leipzig, Germany; and [45]Department of Cardiology, Antwerp University, University Hospital, Belgium

Received 18 November 2019; editorial decision 15 April 2020; accepted after revision 28 November 2020; online publish-ahead-of-print 29 December 2020

* Corresponding author. Tel: +49 40 741052438. *E-mail address*: p.kirchhof@uke.de

Aims The risk of developing atrial fibrillation (AF) and its complications continues to increase, despite good progress in preventing AF-related strokes.

Methods and results This article summarizes the outcomes of the 7th Consensus Conference of the Atrial Fibrillation NETwork (AFNET) and the European Heart Rhythm Association (EHRA) held in Lisbon in March 2019. Sixty-five international AF specialists met to present new data and find consensus on pressing issues in AF prevention, management and future research to improve care for patients with AF and prevent AF-related complications. This article is the main outcome of an interactive, iterative discussion between breakout specialist groups and the meeting plenary. AF patients have dynamic risk profiles requiring repeated assessment and risk-based therapy stratification to optimize quality of care. Interrogation of deeply phenotyped datasets with outcomes will lead to a better understanding of the cardiac and systemic effects of AF, interacting with comorbidities and predisposing factors, enabling stratified therapy. New proposals include an algorithm for the acute management of patients with AF and heart failure, a call for a refined, data-driven assessment of stroke risk, suggestions for anticoagulation use in special populations, and a call for rhythm control therapy selection based on risk of AF recurrence.

Conclusion The remaining morbidity and mortality in patients with AF needs better characterization. Likely drivers of the remaining AF-related problems are AF burden, potentially treatable by rhythm control therapy, and concomitant conditions, potentially treatable by treating these conditions. Identifying the drivers of AF-related complications holds promise for stratified therapy.

Keywords Atrial fibrillation • Big data • Lifestyle • Heart failure • Atrial cardiomyopathy • Cognitive function • Outcomes • Quality of care • Research • Rate control • Rhythm control • Catheter ablation • Anticoagulation • Bleeding • Research priorities • Technology • Stroke • Integrated care • Screening • AFNET • EHRA • Consensus statement

Introduction

Even on optimal anticoagulation, patients with atrial fibrillation (AF) are at high risk of cardiovascular death, often due to heart failure and sudden death, and survivors suffer from diminished quality of life and frequent, unplanned AF-related hospitalizations. Most AF patients are multimorbid with several concomitant chronic cardiovascular and non-cardiovascular conditions, such as atherosclerosis and ensuing coronary and other artery disease, valvular heart disease, hypertension, diabetes, obesity, or metabolic syndrome. Comorbidities interact with AF, worsen the disease course of patients with AF, aggravate atrial damage and atrial cardiomyopathy, and evolve into complex interactions due to their natural variations and/or disease management. Both AF and concomitant conditions threaten healthy survival in patients with AF. Important knowledge gaps can still render our management efforts futile, costly, or risky. Understanding the drivers of these severe complications has the potential to guide stratified therapy in patients with AF. At the same time, containing the emerging AF epidemic by preventing the development of AF in ageing populations remains a priority and an unresolved challenge for all developed nations.[1,2]

To advance the science and management of patients with AF, sixty-five international experts from academia and industry attended the 7th Consensus Conference of the Atrial Fibrillation NETwork (AFNET) and the European Heart Rhythm Association (EHRA) in Lisbon, prior to the EHRA 2019 congress, in March 2019. Two days of discussions were initiated by state-of-the-art overview presentations on different aspects of AF diagnosis and management. All participants then discussed specific topics in break-out sessions and presented their thoughts to the conference plenary in an iterative process, distilling a consensus that was captured on paper and formed the basis of this publication.

Generating evidence for best care of patients with AF

Call for integrated clinical AF trials and AF biobanks

The care of patients with AF has markedly and rapidly improved in the last decades. Important advances have been achieved by thorough scientific evaluation of novel therapies and management concepts. To address the remaining challenges, interdisciplinary international efforts will need to be continued and broadened. We therefore highly encourage all clinicians and patients to participate in clinical trials and to contribute to systematic collection of clinical data and clinical samples, e.g. blood samples and surgical waste tissue, into standardized biobanks. Such biorepositories need infrastructural support, e.g. from public funders. All patients should have the right to be offered participation in clinical research projects, and the research community has a mandate to explain the need for clinical research in AF to all patients, their families, patient representatives, funders and other stakeholders in health care, and the general public. We can only improve clinical care by thorough evaluation of our diagnostic and management approaches. The resources invested into this activity will enhance and enable an affordable and effective future of care for patients with AF. Concerns regarding scientific reward for

Table 1 Advantages and disadvantages of statistical methods for clinical AF research

	Advantages	Disadvantages/limitations
Classical statistical methods Regression analysis[22] C-statistics[23] Forward/backward selection models[24,25] Cox regression[26] Polygenic risk scores[27] Effect size estimates, confidence intervals and tests	Easily understandable Commonly used in medical research Well established Good understanding of their strengths and limitations Multiple testing corrections[28] Easily implemented using statistical software *A priori* knowledge can be implemented Possibility of combining multiple datasets using meta-analysis (hypothesis generating)	Linear models do not account for the complexity of data and interdependencies Power limitations (large datasets required); penalty of multiple testing Overfitting[21,29] Overreliance on *P*-values Currently not useful for combining different layers of data
Machine learning[30–32] Support vector machines Random forests Neural networks and other self-learning 'artificial intelligence' methods	Data-driven analysis—able to detect non-obvious and unexpected structures in the data Provides an opportunity to identify novel classifiers, useful in prediction models	Methods will detect any association between combinations of variables (and 'irregularity') Validity of the information is less defined, methods are rapidly evolving and thus changing Data-driven analysis—uncertainty of what the methods are within the machine learning environment, i.e. 'black box' Computationally intensive when training the model Requires many replications Translation of classifiers into clinical and meaningful interpretations is difficult Reproducibility is limited Combining multiple studies is difficult

contributing data to large, combined databases, difficulties in assessing the expected benefit of large, merged datasets against the potential risks of sharing potentially re-identifiable data, growing concerns regarding data privacy in the scientific space, and funding for harmonization of deeply phenotyped combined databases are some of the barriers that urgently need to be overcome to accelerate research and harvest the potential patient benefits of combining existing datasets.

Best practice and novel approaches for exploring and analysing large datasets in AF research

Access to large health datasets opens new opportunities for clinical and translational AF research, ranging from discovery of new mechanisms to improvement of quality of care. Handling and analysing such datasets[3,4] calls for multidisciplinary, iterative cooperation, and requires a specific set of skills and competences. Classical statistical methods are well suited to objectively assess the efficacy and safety of therapeutic intervention. Additionally, the development of prediction models using regression and/or automated algorithms has become an important tool for subclassification of patients. Advancing clinical classifications of patients with AF will be essential to build personalized therapies for AF, including the application of novel methods that quantify interactions between multiple factors and comorbidities. There are over 350 published prediction models for cardiovascular diseases, including AF.[5] Validated iterative processes involving *a priori* clinical knowledge[6] and exploration of discovery datasets are tested tools to develop such models. Sample sizes for clinical prediction models need to be considered carefully.[7,8] Clinical prediction models must always be validated in different datasets,[9,10] and associations that suggest new mechanisms require testing in interventional trials. We encourage the publication of analysis plans and further prospective studies, and the use of tools (e.g. PROBAST) for assessment of risk of bias of prognostic models.[11,12] Additional complex and unsupervised data analysis techniques, variously called machine learning, artificial intelligence, neural networks, etc., have been employed for AF research, e.g. for identification of patients with AF based on biomarkers and electrocardiogram (ECG) analysis.[13,14] As with other analytical techniques, these have specific advantages and limitations (see *Table 1* for a broad comparison). Classical statistics have matured over decades and are readily applied to most clinical questions. Limitations exist relating to the combination of multilayer information and handling of complex datasets with multiple interdependencies. There is an urgent need for new mathematical tools that can combine and analyse complex data consisting of genomic, transcriptomic and proteomic data, clinical features, imaging, and outcomes in patients with AF.[15] The most relevant advantage of machine learning algorithms lie in their ability to identify unforeseen and complex classifiers for disease states. Risk prediction can be refined using automated analysis of extensive routine clinical data, as

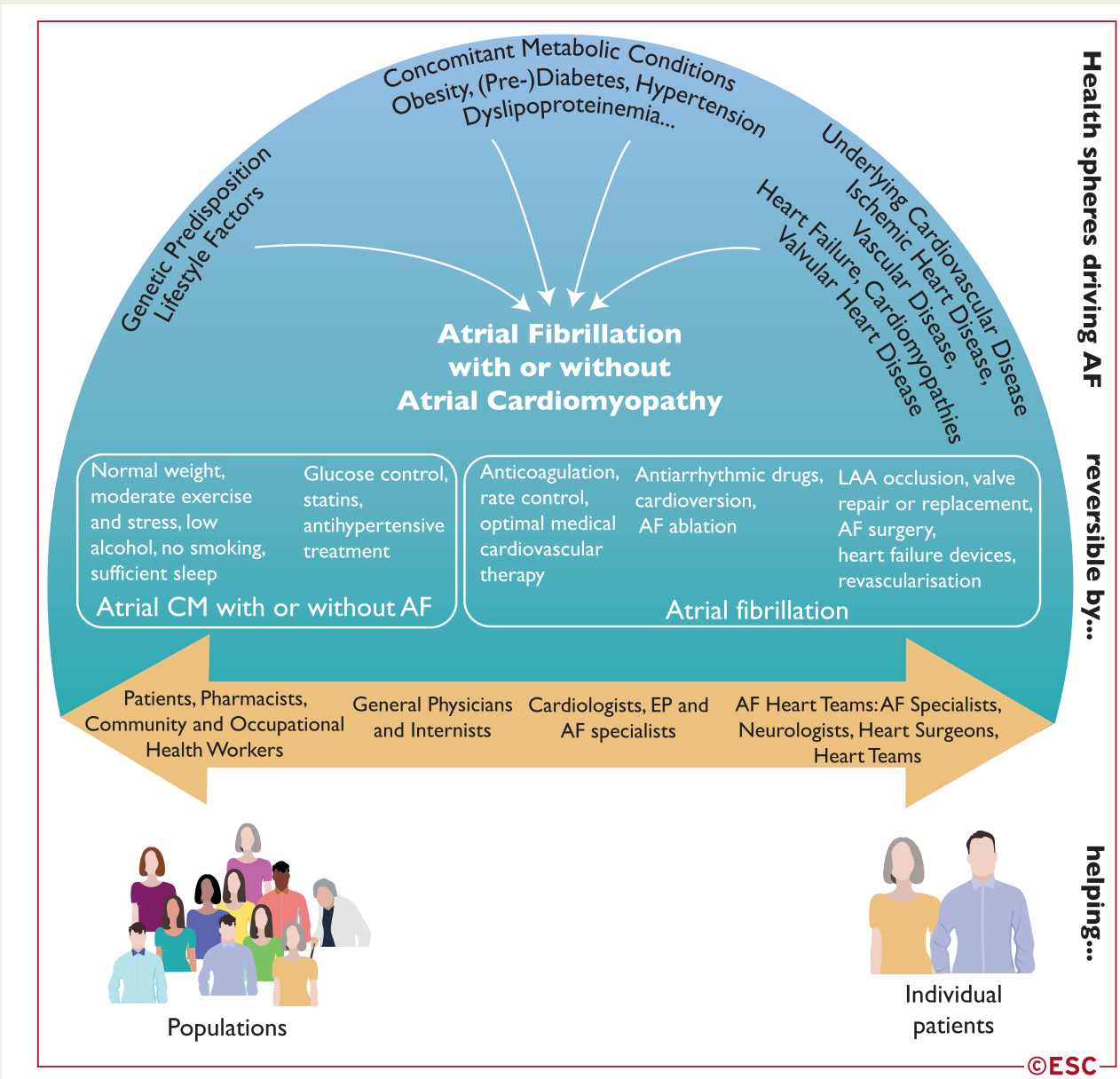

Figure 1 Spectrum of interventions targeting cardiovascular conditions and atrial cardiomyopathy and their effect on AF and AF-related adverse outcomes in patients. Different teams of healthcare professionals, with different competences, skills, and knowledge, need to be involved depending on the desired intervention. The disease and the treatment response become more complex and demand more specialist team care towards the right of the picture. AF, atrial fibrillation; CM, cardiomyopathy; EP, electrophysiologists; LAA, left atrial appendage.

illustrated e.g. in intensive care settings[16] and for predicting heart failure.[17] Imaging data have already been curated and annotated on a large scale, enabling discovery of new imaging markers.[18] These examples illustrate that machine learning is powerful to analyse imaging as well as ECG markers for present or future AF.[13,14,19,20] Such approaches may also be useful to improve risk prediction in patients with AF, e.g. to estimate risk of AF recurrence or to create a more precise estimate of stroke risk. But even the most sophisticated interrogations of complex datasets can only identify associations. Regardless of the initial analysis methodology, validation in independent datasets and mechanistic validation of such associations using interventional experiments or trials are required before robust conclusions can be drawn.[21]

Capturing and changing dynamic risk factors for AF

Lifestyle changes

The causal interaction between genomic predisposition, lifestyle factors, cardiovascular disease, and AF is complex. A continuum exists

from pre-disease states to asymptomatic cardiovascular diseases to severe, clinically obvious manifestations, with important clinical and therapeutic implications (*Figure 1*). Lifestyle changes can reduce AF burden,[33–35] although the effect may be modest compared to antiarrhythmic drug therapy or AF ablation.[36] Several simple healthy lifestyle choices[37] should be encouraged at the population level: regular moderate exercise, moderate food intake, abstention from smoking, and moderation or abstinence in intake of alcohol, have clear beneficial effects on cardiovascular health, thereby reducing the risk of cardiovascular death, stroke, and other complications of AF (see next paragraph).[37] Clinical practitioners have an important role in supporting healthy lifestyles, as periods of acute illness provide an opportunity for life changes. Hence, guidance on healthy lifestyles should be offered to all patients at high risk of AF to enable these benefits (*Figure 1*). Interventions aimed at modifying lifestyle can reduce cardiovascular disease burden and AF risk as part of integrated care,[38] but often require multidisciplinary interventions, as illustrated by complex interventions in overweight or obese patients with AF.[34,35] Interventions to achieve these beneficial changes are challenging to design and implement, and require systematic evaluation e.g. in cluster-randomized trials. Controlled trials of lifestyle interventions and integrated care have yielded mixed results.[39–42] Trials that account for differences in the comparator/baseline management and carefully designed, effective interventions are needed to inform integrated approaches to AF care. The risks of interventions encouraging healthy lifestyles seem minimal, and there is evidence of an association of healthy lifestyle with longevity. Complex, costly management programmes will, however, have to demonstrate cost effectiveness. The resource demand for integrated care can be mitigated by involving patients and their social circles. Identifying predominant mechanisms of AF (*Table 2*) may be useful to select specific interventions suitable for defined patient groups (stratified prevention[37]). However, it still has to be demonstrated to what extent patients with different mechanisms of AF differ in their responses to the various therapeutic options. Targeted lifestyle intervention programmes may focus on patients and patient groups with the highest potential benefit and will often require psychological counselling, motivational programmes, feedback from healthcare professionals or care teams, and technological support. This intervention will require careful phenotyping, and in the view of this group, will need repeated time-based assessment of dynamic risk, including access to information collected by consumer devices.

Cardiovascular comorbidities and risk factors

Treatment of cardiovascular comorbidities, changing harmful lifestyles that promote them, and potentially treatment of pre-symptomatic disease states and borderline conditions (*Figure 1*), can reduce cardiovascular risk, for example, treatment of hypertension and hypercholesterolaemia using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins, particularly when they are used in combination in an integrated therapeutic approach.[36] Some 'borderline conditions' comprise a group of intermediate conditions, a lifestyle-cardiovascular disease continuum lying between an unhealthy lifestyle and a definite disease. For example, obstructive sleep apnoea has a strong association with unhealthy lifestyle (i.e. obesity, lack of activity, and smoking). Drugs targeting metabolic dysfunction such as metformin (NCT03603912) and liraglutide (NCT03856632) are currently being tested in AF populations. Whether SGLT2 inhibitors have similar effects on AF as they have on heart failure should be tested. Unlike pharmacological interventions, reducing unhealthy lifestyle has the potential to be applied at a population level (where most persons are not affected y AF). However, the effect of treating cardiovascular comorbidities ('upstream therapy') on rhythm control appears less pronounced than that of ion channel blockers or AF ablation,[36] and may not be detectable at all for single interventions (sartans, statins).[106,107] It is important to select patients who are most likely to benefit (stratified prevention), as has been successfully demonstrated by offering exercise and weight reduction programmes to small cohorts of extremely obese patients with good effects on recurrent AF.[33,35] However, large-scale, long-term interventions could also be rolled-out in the hope that they will have long-term effects at the population level.[108] In contrast, while antiarrhythmic drugs or AF ablation (*Figure 1*) are comparably very effective in selected symptomatic AF patients, these interventions may have a more limited impact on overall AF burden in the population unless they are offered routinely which will require demonstration of a prognostic effect of rhythm control therapy.[109,110]

Atrial cardiomyopathies: interrogation using multidimensional research

The concept of atrial cardiomyopathy was introduced as 'fibrotic cardiomyopathy'[111] and comprehensively defined by an EHRA/HRS/APHRS/SOLAECE consensus document as 'Any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations'.[112] At present, many knowledge gaps exist with regard to the underlying pathophysiology[113] and the quantitative impact of different conditions—comorbidities, hereditary factors, or AF itself—to the development of atrial cardiomyopathy. Specific treatments, including therapies that were shown not to be effective in unselected patients with AF ('AF all comers'),[107] may still be effective in specific patient subgroups. A detailed characterization of different patient groups who all present with AF but with different atrial, cardiac, and systemic pathologies is starting to be undertaken. To identify such patient groups, atrial tissue components such as endothelial cells, cardiomyocytes, their cell–cell contacts, fibroblasts and fibrocytes, smooth muscle cells, immune cells, progenitor cells, adipocytes, nerve cells, and their respective extracellular matrix need to be characterized. Their interactions with atrial electrical and mechanical function as well as with prothrombotic signalling need to be established.[114–126] Cardiac imaging using ultrasound, computed tomography, or magnetic resonance imaging may help to define these tissue characteristics in patients. While imaging of the myocardium is feasible in the ventricular myocardium,[127] there are still important limitations related to the spatial resolution of the thin—though less mobile—atrial myocardium. In addition, genomic information and blood biomarkers[13,128–131] reflecting cardiac and systemic disease states may help to stratify patients, e.g. for targeted therapeutic

Table 2 Selected lifestyle risk factors associated with atrial fibrillation (AF), underlying conditions and the main mechanisms that are expected to lead to AF in populations exposed to each unhealthy lifestyle

	Obesity	Sleep-apnoea	High-level physical exercise	Physical inactivity	Unhealthy nutrition	Smoking	Alcohol consumption	Mental stress
Experimental	Multiple experimental models[33,43–47]	Several experimental models in rats and pigs[48–50]	Exercise produces higher vulnerability to AF and atrial fibrosis in rats[51–53]	More atrial fibrosis and inducible AF in sedentary vs. intermittent aerobic exercise in aged rats[54]	High-fat diet linked to AF in mice[55,56] and rats[57]	Nicotine induced AF in dogs[58] and rat hearts[59]	Binge-drinking increases AF inducibility in animal models[60,61]	Not available, but potential overlap with high level physical exercise experimental studies.
Epidemiological and clinical observational cohort studies	Several large epidemiological surveys,[34,62,63] including patients undergoing AF ablation[64]	Meta-analyses show that OSA increases AF risk[65] and that CPAP reduces recurrences[66]	Numerous studies in athletes and population studies[67–71]	Multiple epidemiological reports[72,73]	Results from Framingham cohort suggest no association of dietary factors to AF risk[74]	Smoking increases risk two-fold in the ARIC[75] Meta-analysis and non-randomized cessation studies[76,77] Exposure to tobacco smoke in childhood increases AF risk in adulthood[78]	Alcohol acutely causes tachycardia[79] Moderate to severe chronic intake increases risk for AF[80–83]	Long working hours and job strain are associated with AF.[84,85] Negative emotions can trigger AF episodes[86]
Interventional trials	RCTs in targeted weight loss in pAF patients[35] and multi-intervention trials in persistent AF patients[36]	Only 1 RCT showing that CPAP does not reduce AF burden[87]	Not available	With weight loss programmes in patients with pAF and post-ablation[36] Reduced AF burden in AF patients with moderate training in a clinical trial[88]	Olive oil reduces AF risk in *post hoc* analyses of large RCT[89] Controversial data on PUFA suppl[90]	Multiintervention trial recommends quitting tobacco in persistent AF patients[36]	Alcohol withdrawal reduces recurrent AF in heavy drinkers[91] and also seems to be effective in conjunction with other lifestyle changes[92]	Yoga may improve quality of life in patients with pAF[93]
Predominant mechanisms	Adipose tissue infiltration, atrial fibrosis, inflammation, oxidative stress, hypertension, atrial dilatation[33,94,95]	Apnoea events induce acute changes in autonomic tone balance[48] and left atrial size[49] Chronic OSA promotes atrial ischaemia, hypoperfusion, and atrial fibrosis[49,50]	Atrial fibrosis/ dilation, autonomic/ion channel imbalance[51,52,69,96]	Physical inactivity increases the burden of cardiovascular risk factors[97]	Depends on specific nutritional element. For example potential direct electrophysiological effects on n3-PUFA[98]or of vitamin D[99]	Atrial fibrosis,[58] and slowing of conduction,[59] acute electrophysiological changes,[100] possibly hypoxia and oxidative stress, vasoconstriction, hypertension	Acute: shortening of atrial refractory period and slowing conduction[101,102]; hypokalaemia; changes in autonomic tone[92] Chronic: atrial fibrosis and dilation[103,104]	Large body of evidence showing that sympathetic and parasympathetic stimulation alters atrial electrophysiology, triggering AF. In addition, mental stress can alter atrial electrophysiology[105]

Colours indicate the quality of underlying evidence in a 'traffic light' coding, with green best, yellow intermediate, red worst.
ACC, American College of Cardiology; ARIC, Atherosclerosis Risk in Communities study; CPAP, continuous positive airway pressure; EP, electrophysiological; OSA, obstructive sleep apnoea; pAF, paroxysmal atrial fibrillation; PUFA, polyunsaturated fatty acid; RCT, randomized controlled clinical trial.

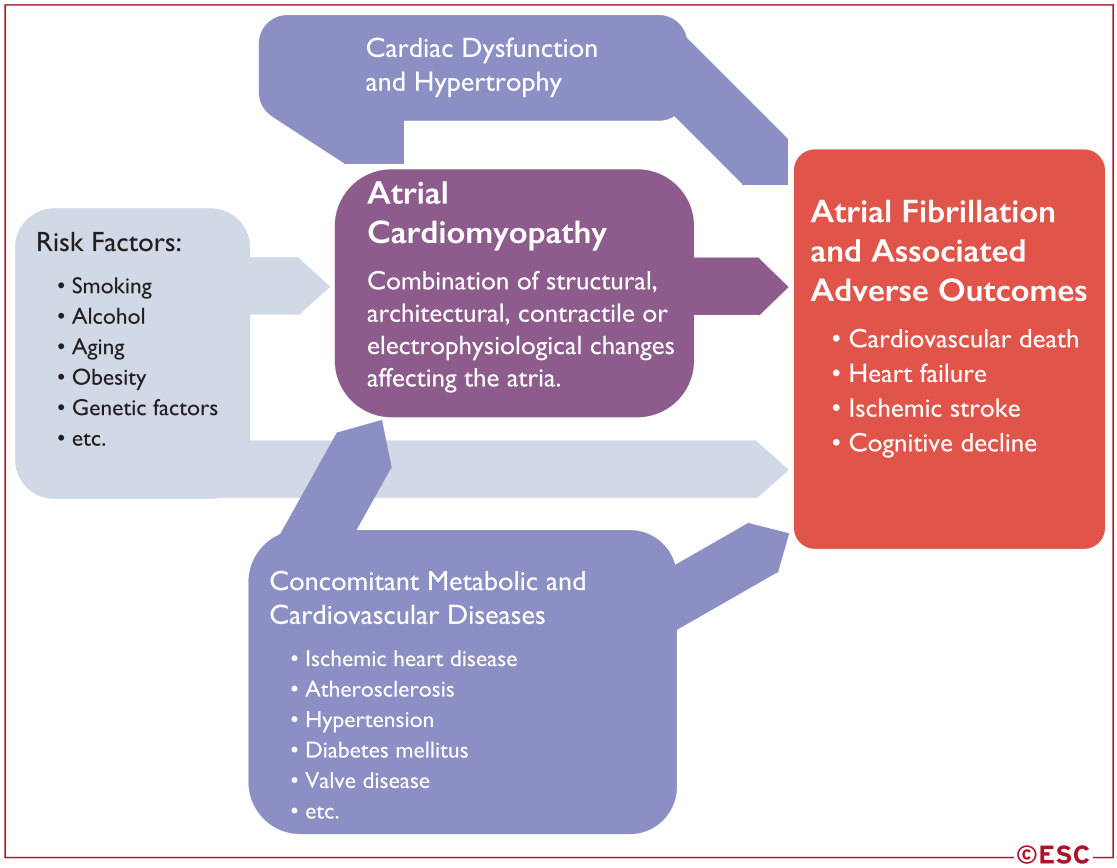

Figure 2 Atrial cardiomyopathy as generator and accelerator of atrial fibrillation (AF)-associated adverse outcomes. In addition to the systemic drivers of atrial cardiomyopathy, other, atrial-specific drivers are likely to further enhance the degree and differentiation of atrial cardiomyopathy in different patients.

reversal of atrial remodelling (*Table 2*, *Figure 1*, see next text section). *Figure 2* illustrates potential interactions of atrial cardiomyopathy. It is conceivable that immunomodulatory therapies, transthyretin stabilizers, or antidiabetic treatments could be effective in patients with specific atrial cardiomyopathies.

Interactions between heart failure and atrial fibrillation—clinical challenges and therapeutic implications

Heart failure and AF are both common conditions in clinical practice with shared pathophysiology and reciprocal causation. Attributing the prognosis and symptoms to both conditions is particularly challenging in patients with AF and heart failure with preserved ejection fraction (HFpEF).[133] Plasma biomarker profiles illustrate clear differences between patients in AF and heart failure with preserved or with reduced ejection fraction.[134] Therefore, biomarkers could provide an opportunity to identify patients with AF who might benefit from specific management strategies.

Both AF and HFpEF can be caused by a *primary myocardial process* (e.g. genetic cardiomyopathies, amyloid, sarcoid, or inflammatory cardiomyopathies), or *secondary causes* (e. g. hypertension, diabetes, obesity, obstructive sleep apnoea, or chronic obstructive lung disease with elevated right heart pressure), both leading to atrial cardiomyopathy.[135] In addition, once AF and HFpEF manifest, a 'vicious circle' is likely to contribute further to cardiac damage and morbidity.[136] Observational data suggest that there are differences in comorbidities and outcomes according to whether the index condition is AF or HFpEF.[137,138] This group of experts expects that patients in whom AF precedes HFpEF will develop AF-related ventricular filling defects, while patients in whom HFpEF precedes AF are more likely to experience AF due to increased left atrial load.

Some patients with AF and severe heart failure experience rapid and almost complete reversal of symptoms upon cardioversion. In others, AF remains asymptomatic for a long time before they develop heart failure. Between these two extremes, patients with risk factors for HFpEF (and hence an increased propensity to AF) may only develop manifest symptoms due to HFpEF when AF is present, and patients with AF may develop symptoms only when they develop HFpEF. Based on this observation, we propose that *the first overtly presenting condition* in patients with AF and HFpEF may stratify patients

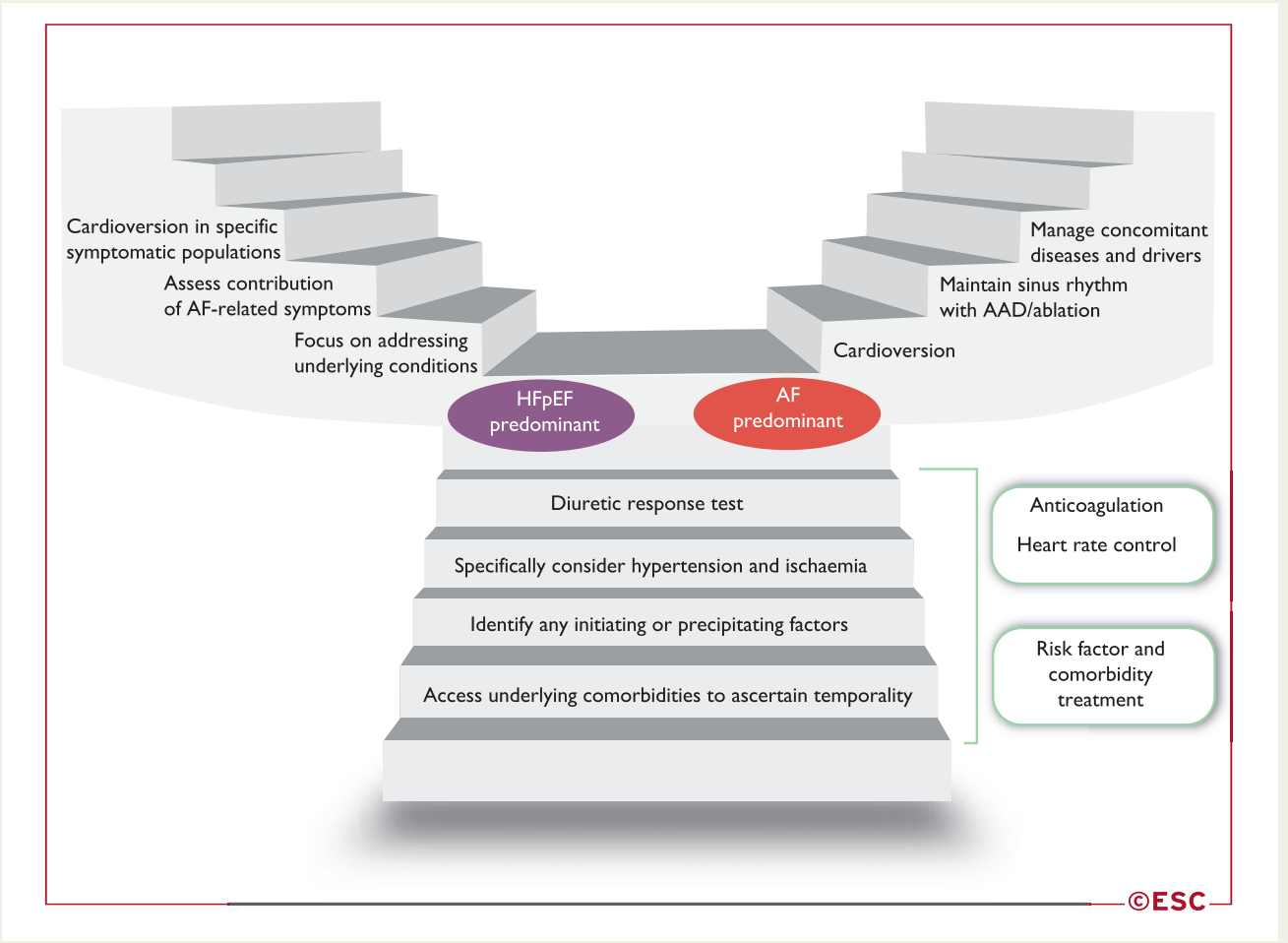

Figure 3 Acute management of patients presenting with AF and HFpEF. This proposal for a sequence of acute interventions is based on expert consensus. This approach is expected to improve patient wellbeing and reduce incidence of adverse events. AAD, antiarrhythmic drugs; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction. The lower staircase is a common to both HFpEF and AF management, the upper staircases illustrates separate management priorities. The approach may be adjusted in patients with early AF.

with primary and secondary causes, possibly enabling differential therapy (*Figure 3*): We propose to assess the initial *response to diuretics and a 'diagnostic cardioversion'* to determine if symptoms improve by restoration of sinus rhythm. This information can define the further management pathway including more aggressive rhythm control management. Those who respond well to diuretics may have HFpEF as their predominant condition, while in those who respond well to rate control and cardioversion, AF may be the main driver of symptoms. The HFpEF-dominant patients would potentially benefit more from identification and treatment of underlying risk factors. The AF-dominant patients may benefit from antiarrhythmic drugs, cardioversion, or ablation to improve symptoms, disease substrate, and possibly even prognosis.[139] (*Figure 3*), as recently demonstrated for patients with early AF.[132] In all patients, oral anticoagulation (OAC) for prevention of stroke and thromboembolism, adequate rate control, and heart failure management should be recommended.[140] The optimal ventricular rate of AF in HFpEF is poorly defined, but treatment should follow current guidelines, acknowledging that bradycardia, tachycardia, and irregularity of RR intervals may adversely affect function of non-compliant ventricles. Similar therapeutic attempts to define patient benefits may be useful for patients with AF and reduced ejection fraction. Further research, particularly into different approaches to rate control and into the role of rhythm control therapy in symptomatic patients with HFpEF and AF, are clearly needed to help resolve the high morbidity in this population.

Biomarkers for prediction of AF and its complications, and to define patient groups

Plasma biomarkers

The ECG remains the most powerful tool to detect AF, and the only one to definitely diagnose AF.[142,143] Circulating biomarkers provide quantifiable measures of clinical or subclinical disease states, can be used to assess dynamic changes in AF risk factors (Capturing and changing dynamic risk factors for AF section), and enable prediction

of AF when long-term monitoring or even an ECG is not feasible (e.g. in community settings[134,143,144]), improving AF detection. Furthermore, biomarkers can help to estimate prognosis once AF has been diagnosed. Biomarkers can also help to guide stratified approaches to prevention and management. Plasma can easily be sampled in many routine care settings and analysed using point-of-care test kits.[145] Natriuretic peptides, in particular B-type natriuretic peptide (BNP) and its pro-hormone fragment (NT-proBNP), are markers of cardiac load and stress, which have consistently been found to predict AF[146] and its complications such as stroke, heart failure and bleeding.[147,148] Several additional markers have been associated with AF in different populations, including inflammatory biomarkers, markers of coagulation, ST2, growth differentiation factor 15, high-sensitivity troponin, cancer antigen-125, galectin-3, and fibroblast growth factor 23 (FGF23).[13,129,149–153] These biomarkers for AF, some of which have been associated with AF-related complications, reflect different major drivers of AF such as atrial fibrosis, metabolic dysfunction, inflammation, and genomic predisposition, reviewed in.[4] A recent review article[154] and the protocol of a large, harmonized analysis of biomarkers in different cohorts[128] provide more detailed overviews of biomarkers in AF. NT-proBNP predominates amongst biomarker profiles for AF, including in patients with heart failure with reduced or preserved ejection fraction.[133] The clinical utility of BNP or NT-proBNP to improve earlier detection of AF is currently evaluated in the STROKESTOP 2 study,[155] while the randomized ABC AF study is prospectively evaluating biomarker-based risk scores for tailored treatment with oral anticoagulants and other treatments to prevent stroke and death in AF (NCT03753490).

Promising biomarkers for AF detection have emerged from numerous approaches, including multiplexing techniques. As an example, in addition to natriuretic peptides, FGF23, a marker that has been previously proposed as identifying patients with incident AF,[156] was recently identified in an analysis comprising 92 biomarkers in 638 unselected patients with and without AF.[146] FGF23 is a secreted hormone by the bone-cell regulating phosphate homeostasis, and has been related to left ventricular hypertrophy and atrial fibrosis and will need to be further validated as a biomarker for AF. Taking blood samples during clinical studies for biomarker quantification is strongly encouraged to enable identification and validation of new markers and to facilitate exploratory, hypothesis-free research into stratifiers for AF.

Genomic markers for AF

AF has a strong heritable trait. Common genetic markers underlying this heritability have been identified using genome-wide association studies (GWAS). The most recent GWAS found 97 individual genetic biomarkers for AF, explaining 42% of the predicted heritability.[157] By far the strongest cluster of signals is located on chromosome 4q25, closest to the PITX2 gene locus and not far from the locus for ENPEP.[157] For risk stratification purposes, single genetic loci confer only a small effect size and insufficient discriminatory potential, but may provide complementary information to clinical variables. The identified genetic variants implicate genes enriched within cardiac development, electrophysiology, contractile and structural pathways. AF genetic risk can explain ~20% of the heritability of cardioembolic stroke, but not atherosclerotic strokes.[158] Several genetic signals have been combined into polygenic risk scores[158–161] that improve AF prediction. A more liberal, computationally intensive and innovative combination of hundreds of genetic markers with below genome-wide significance into comprehensive polygenic risk scores enables identification of individuals at clinically relevant high risk for AF with an odds ratio of ≥3.0 in ≥6% of patients.[162] It still remains to be tested if these polygenic risk scores can improve risk stratification and prognosis beyond known clinical characteristics and biomarkers, both at the cohort and individual patient levels.

So far, there is a limited number of small-sized biomarker and genetics studies investigating AF post-cardioversion, post-ablation, post-surgery, or under antiarrhythmic drug therapy. To generate large datasets that can be used to produce valid prediction models for AF (*Table 1*), deeply phenotyped cohorts with data specific to the clinical question and outcome are needed. These should include blood samples, risk factor information, imaging, rhythm monitoring, and electrophysiological data. Such deep-phenotyping data should be used to define distinct clinically useful sub-types of AF to impact treatment. Ideally, these data should be collected in a common format according to standardized definitions and operating procedures.[4,128] Collaborative structures to leverage existing and future information/datasets and knowledge are required for future biomarker research in AF. International funding, e.g. provided by the European Union, the Leducq Foundation, and increasingly through collaborative programmes of different National Research funders, is critical for such research.

Clinical risk assessment in patients with atrial fibrillation—a reappraisal

Tailored therapy for the individual patient with AF should be based on best available risk prediction models with the aim to reduce risks as broadly as possible, in addition to alleviating symptoms of AF. Underuse of effective preventive therapies, not only oral anticoagulants, is still common, in part due to lack of quantitative clarity on benefits and risks. Appropriate use of such interventions can lead to substantial cost reduction by avoiding the complications of AF itself and AF treatments side effects. Interventions can slow down or prevent comorbid conditions and are highly desirable for patients, healthcare systems, and society. A general challenge for health economic analyses of such efforts is their dependence on healthcare system organization. A cost-effective intervention in one healthcare system can be very expensive or even ineffective in another. Despite these challenges, the ability to deliver these goals rests on integrated, shared care, enabling personalized AF management.

Dynamic and continuous risk estimates: opportunities for research and refinement

Current risk scores categorize risk predictors despite the fact that some predictors are best considered as a continuous risk marker.[163] This has recently been shown for age.[163] Quantifiable risk factors also include blood pressure; severity of metabolic dysfunction in diabetes (e.g. quantified by HbA1c and treatment[164]); severity of sleep

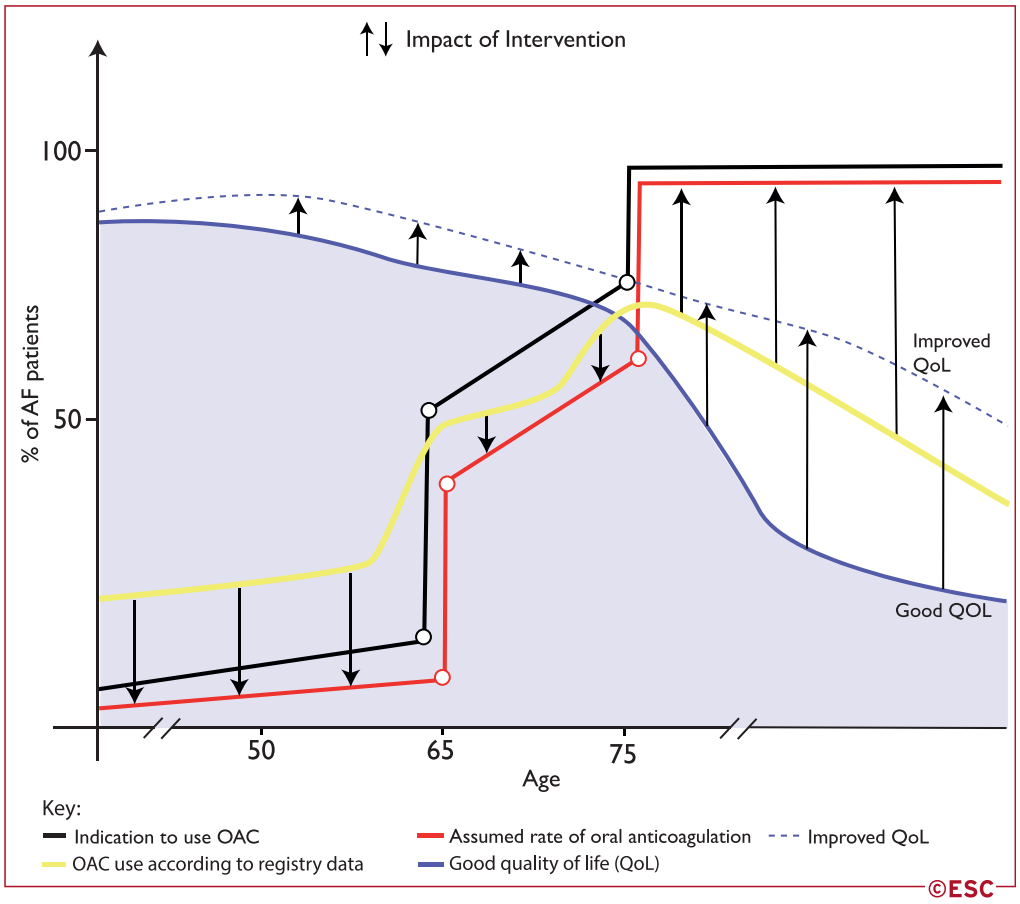

Figure 4 Dynamic stroke risk assessment and treatment of modifiable risk factors can improve quality of life in patients with AF. Potential clinical implications of dynamic assessment of risk factors for atrial fibrillation (AF) on the assumed rate of oral anticoagulation (OAC, red line) and good quality of life (QoL, blue line, dashed blue line). Modifiable risk factors include: blood pressure, blood glucose or HbA1c levels, AF burden, renal function, disordered breathing during sleep, physical activity, body weight, alcohol consumption, smoking (see *Table 2*). The black line represents the assumed indication to use oral anticoagulation (OAC) according to CHA_2DS_2-VASc in AF patients, the yellow line roughly represents registry data on OAC use, and the red line represents the assumed window-of opportunity-effect on the indication to use OAC according to CHA_2DS_2-VASc. Controlling risk factors in younger AF patients may also have implications on QoL, if there is a potential to reduce the impact of AF on stroke, dementia, and heart failure later in life. This effect (arrows) of an early intervention regarding AF-related risk factors on QoL (blue line to dashed black line) and OAC rate (yellow line to red line) is assumed and warrants formal testing.

apnoea or ventricular dysfunction in heart failure[165]; severity and subtype of stroke and AF burden. In addition, modifiable risk factors not incorporated into the CHA_2DS_2-VASc score can refine risk assessment, e. g. ventricular hypertrophy, left atrial size, severity of kidney disease, or obstructive sleep apnoea, while other factors (e.g. sex) may have a modifying role interacting with other risk factors, including lifestyle factors (*Table 2*). The increasing availability of multimarker panels for biomarkers (*Table 1*), bio-monitoring of activity, heart rate, and physiological parameters using consumer devices, and other digital tools to collect patient information, will facilitate more detailed characterization of individual risks based on dynamic risk factors and/or risk factor patterns. The utility of dynamic risk markers and multi-factor risk models in clinical practice which may improve relevant clinical endpoints and/or quality of life by guiding treatment decisions should be prospectively evaluated and included in health economics analyses (*Figure 4*). Clearly, validation of risk factor models in interventional trials is desirable.

Informed decisions to initiate oral anticoagulation

Patients with only one of the 'CHA_2DS_2-VASc' factors

Initiation of OAC in patients who fulfil only one of the 'CHA_2DS_2-VASc' criteria (ca 3–6% of typical AF populations[165–167]) should currently be considered (ESC guidelines IIa indication), but the evidence supporting such therapy is indirect and limited, given the absence of specific randomized trials. In particular, the effect of female sex as a risk factor appears lower in younger patients[168] than in the elderly.[169] Considering additional 'sub-threshold' factors (e.g. age, blood pressure), and severity of the existing risk factor (e.g. left ventricular

Table 3 Selected conditions that can pose clinical challenges and suggestions for when to initiate oral anticoagulation (OAC) based on current evidence. AHRE, atrial high rate episodes OAC, oral anticoagulation; NOAC, non-oral anticoagulants; RCT, randomized clinical trial; VKA, Vitamin-K antagonist.

	Evidence to start OAC from observational studies	Ongoing RCTs	References
Acute ischaemic stroke	Start after 1–14 days in selected patients based on expert consensus	ELAN OPTIMAS TIMING START	171–173
Haemorrhagic stroke/intracranial bleed in patient with known AF and significant stroke risk	Start after 4–8 weeks in selected patients	PRESTIGE-AF APACHE-AF NASPAF-ICH ASPIRE STATICH SoSTART A3ICH ENRICH	171
Detection of AHRE in a patient at significant risk of stroke	No indication for OAC	NOAH-AFNET6 ARTESiA	172,187,188
AF detection in a patient with dementia or cognitive impairment	Start in patients with CHA_2DS_2-VASc ≥2, if compliance can be assured and there are no contraindications		191
AF detection in a patient at high risk of falls	Start in patients with CHA_2DS_2-VASc ≥2 in men and ≥3 in women, if there are no contraindications; address modifiable factors predisposing to falls		
AF detection in a patient with one CHA_2DS_2VA risk factor (outside of sex)	Consider NOAC rather than VKA		168,169,192,193
Embolic stroke of unknown origin (no AF detected)	No indication for OAC	ATTICUS ARCADIA (ESUS with atrial cardiomyopathy)	182,194–196

function, and intensity of diabetes treatment or antihypertensive treatment), and also additional information such as biomarker concentrations (e.g. BNP, troponin, or FGF23), left ventricular hypertrophy, or left atrial size, may help individual decisions. Repeated assessment of dynamic risk factors (*Figure 4*) will have therapeutic implications as the severity of these risk factors changes over time.[170]

AF patients after an acute stroke

The timing of initiation of OAC after an acute ischaemic stroke must weigh recurrent stroke risk vs. risk of secondary haemorrhagic transformation.[171] After a transient ischaemic attack, anticoagulation can probably be initiated immediately after ruling out an intracranial haemorrhage using imaging, while patients with larger strokes and those with haemorrhagic transformation may need a longer interval without anticoagulation (historically a few weeks).[172,173] Several ongoing controlled clinical trials will evaluate the optimal timing of anticoagulation in the first days and weeks after a stroke (*Table 3*). A recent meta-analysis of observational studies, identifying a relevant selection bias, suggests that restarting anticoagulation (but not antiplatelet therapy) 4–8 weeks after intracranial bleeding is associated with less ischaemic stroke without significantly increasing the risk of recurrent intracranial bleeding as compared to not initiating anticoagulants.[174]

Patients with AF due to potentially reversible causes

Many individuals have AF documented for the first-time following surgery or hospitalization for a severe medical illness. It is often unclear if these transient stressors cause AF or if these patients already have asymptomatic AF that happens to be documented for the first time during their hospitalization.[175] Recent analyses suggest that the stroke risk of 'resolved AF', a condition that bears some resemblance to AF diagnosed in an acute condition, is similar to that of other patients with AF,[176–178] potentially pointing to an underlying atrial cardiomyopathy (clinically approximated by enlarged atrial size or elevated BNP).[175] This issue is even more complicated in patients receiving medications that increase the risk of AF, e.g. ibrutinib,[179] who are at an increased bleeding risk due to an underlying oncological conditions. Ongoing research is using ambulatory ECG monitoring to document the rate of recurrent AF in patients following discharge from hospital after surgery or medical illness.[175] A

randomized trial is evaluating long-term OAC in patients with post-operative AF following non-cardiac surgery (NCT040445665).

Patients with very infrequent episodes of AF or atrial high rate episodes

A growing body of evidence suggests that anticoagulation does not prevent strokes in patients without AF with multiple stroke risk factors, while increasing bleeding risk.[180–183] It is unclear whether patients who solely have device-detected atrial arrhythmias (as high rate episodes in implanted pacemakers or loop recorders) or patients with rare atrial arrhythmia episodes detected by continuous monitoring, e.g. via smart watches, would benefit from OAC.[184] Their bleeding risk on anticoagulation is similar to that of other anticoagulated patients (ca 1–2% major bleeds per year in clinical practice[184,185]), while the stroke risk without anticoagulation seems lower than in patients with ECG-diagnosed, more frequent AF. Considering the magnitude of risk factors and the 'burden' (number and duration of episodes) of arrhythmias could help,[186] but more data is needed.[184] Therefore, these patients should be enrolled into controlled clinical trials such as NOAH-AFNET 6 or ARTESiA.[187,188] Similar efforts using consumer electronic devices[189,190] are planned or underway, including large-scale trials.

When participation in these trials is not possible, individual decisions to anticoagulate such patients when they present with many other stroke risk factors, e.g. based on arrhythmia burden and dynamic assessment of stroke risk factors, should be documented as off-label use of oral anticoagulants.

Text box: Measures to improve quality of oral anticoagulation therapy.

(1) Identification and management of bleeding risk factors and their interaction.
(2) Integrated, cross-sector AF care based on shared decision-making.
(3) Empowered patients who understand and 'own' their care.
(4) Patient- and physician-directed educational interventions to enhance the quality of AF management based on current evidence and guidelines.
(5) Providing a simplified effective AF management algorithm to be used at primary/secondary healthcare level in order to facilitate timely initiation of OAC, as exemplified in the 2016 ESC guidelines.

What to do in patients who experience a stroke while on oral anticoagulation?

Suboptimal anticoagulation, including inadequate dosing of novel oral anticoagulants; failure to achieve good INR control in patients treated with vitamin K antagonist; and interruptions and discontinuation of treatment (e.g. after a bleeding event, including discontinuation after 'nuisance bleeds'), remain common and are a major driver of thromboembolic events in anticoagulated patients.[197] Measures to improve quality of OAC therapy are therefore essential for successful treatment.

After a failure of OAC therapy, optimization of OAC by addressing the underlying mechanisms may first be attempted using the same anticoagulant as before the event, or the patient could be switched to another anticoagulant based on the perceived specific drug efficacy, anticipated improvement in adherence, or at patient preference.

Whereas a suboptimal OAC management can be optimized using a range of interventions,[198–200] some less common and often non-modifiable conditions predisposing to apparent OAC failure pose more difficulties, e.g. haematological disorders, cerebrovascular disorders, diffuse telangiectasias and other causes of repeated bleeding. In such cases, a multidisciplinary AF Heart Team approach[172] should be sought that may include consideration of percutaneous left atrial appendage occlusion. Future steps in improvement of OAC therapy include the development of new anticoagulants, possibly with alternative routes of administration. Clearly, controlled trials evaluating additional interventions to prevent strokes in anticoagulated patients with AF are needed to further reduce this stroke risk.

How to preserve cognitive function in patients with AF?

Cognitive decline and dementia are important health outcomes for patients and society. AF is associated with cognitive decline[201,202] and (vascular) dementia[191] independent of shared comorbidities.[203,204] Anticoagulation use has been associated with lower dementia risk,[205] including in patients at low risk of stroke. In addition to AF-related (clinically evident or covert) ischaemic brain lesions,[201] AF-induced chronic hypoperfusion of the brain and systemic inflammation may contribute to cognitive impairment. Whether paroxysmal AF increases the risk of cognitive decline to a similar extent as (long-standing) persistent AF is uncertain. Silent brain lesions are relatively common after AF ablation.[206,207] While an early observational study detected reduced cognitive function after AF ablation in patients not receiving continuous anticoagulation,[209] more recent observational data suggest that AF ablation could slow cognitive decline.[206] Recent data suggesting improved short-term cognitive function after AF ablation despite silent brain lesions are reassuring,[205] but more needs to be done to maintain brain integrity after AF ablation. Large randomized trials will inform about the effects of different AF therapies on cognitive function in AF patients, e.g. EAST–AFNET 4,[132,109]GIRAF (NCT01994265), or BRAIN-AF (NCT02387229).

Improving rhythm control therapy

Patient selection

Symptomatic AF patients should be offered a rhythm control strategy as part of integrated management. Based on the recent results of the EAST - AFNET 4 trial, patients with early AF will have clinical benefit from systmatic initiation of rhythm control therapy.[132] In others, the modified EHRA score provides a simple tool to estimate symptoms related to AF to aid the decision on rhythm control therapy.[172,210] In view of the high risk of recurrent AF, it is important to explain to the patient that AF is often a chronic condition, and management often requires repeated interventions. Recent controlled trials have shown safety of rhythm control therapy—either AF ablation or antiarrhythmic drug therapy—in patients with comorbidities,[211] and AF ablation

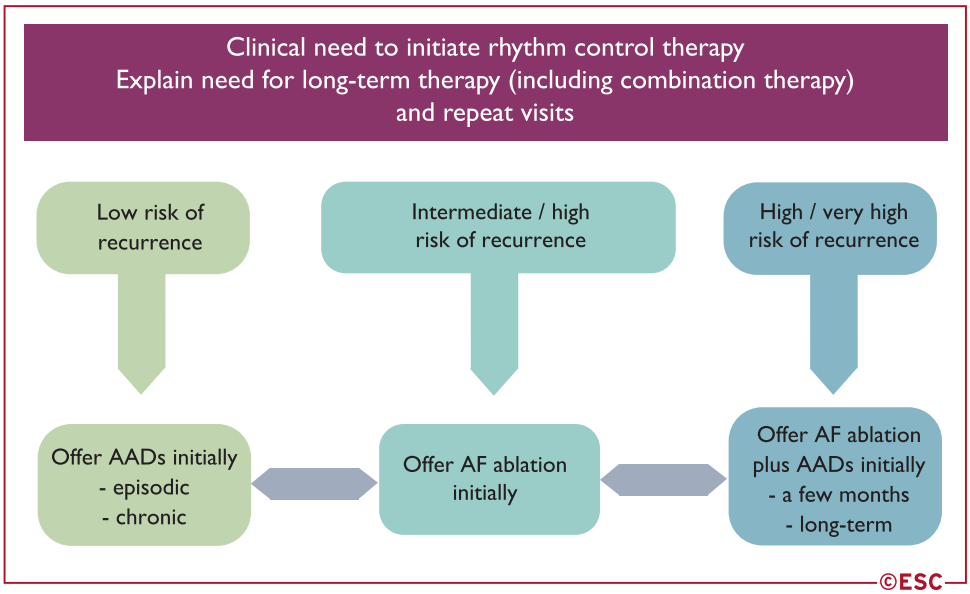

Figure 5 Suggested rhythm therapy management tree. Ongoing research[128,240] will help to define patients at different risk of recurrent AF. AADs, antiarrhythmic drugs.

has further demonstrated an enhanced effect on quality of life and sinus rhythm maintenance when compared to antiarrhythmic drug therapy.[213,214]

Therapy selection

All patients considered for rhythm control therapy should be offered adequate anticoagulation, rate control, lifestyle interventions, and treatment of underlying cardiovascular conditions.[36] Despite good overall effectiveness of rhythm control therapy, AF recurrences are highly variable in individual patients. Symptomatic recurrences of AF are found in 40–70% of patients on antiarrhythmic drug therapy,[212–217] and in 20–50% after catheter ablation.[141,205,212,213,218,219] Interestingly, therapy selection is currently driven by centre-based factors rather than patient factors.[220] Given the lack of safety data, combination therapy with more than one antiarrhythmic drug should be reserved for very specific, rare situations as evidence supporting combining antiarrhythmic drugs with AF ablation seems more suitable for most patients.[221,222] Moreover, optimal ablation strategies improving patient outcomes beyond pulmonary vein isolation need to be determined.

Risk-based therapy selection

Antiarrhythmic drugs are non-invasive and easy to initiate, but also less effective than AF ablation for AF recurrences, while AF ablation combined with antiarrhythmic drugs is more effective than AF ablation alone.[221,222] Patients at low risk of recurrence could therefore be offered initial therapy with antiarrhythmic drugs. Patients at higher risk of recurrence would benefit from AF ablation, and those at highest risk of recurrent AF could benefit from initial combination therapy with AF ablation and antiarrhythmic drugs. Such a combination therapy seems warranted in patients with recurrent AF after AF ablation.[223,224] A risk-based therapy selection would be feasible when validated risk estimators become available (*Figure 5*). In the mid-term future, individualized treatment approaches will be developed based on molecular characterization of AF subtypes in addition to rather than on AF phenotypes and clinical presentation alone.[4]

Monitoring success of rhythm control

On the one hand, monitoring success of rhythm control requires a prompt reaction to symptoms suggestive for AF recurrence to record rhythm during symptoms. On the other hand, there will be an increase in patient-based ECG documentation tools and consumer electronic devices that enable continuous monitoring of physiological parameters to facilitate arrhythmia detection. Due to a significant amount of false positive findings of those devices,[225,226] and reflecting the fact that most arrhythmia episodes are asymptomatic even in patients with symptomatic AF,[225,227] there is a definite need to triage these tracings before an arrhythmia specialist is contacted. In this field of tracing analysis, artificial intelligence (e.g. machine learning) may play an important role in the future. The positive influence of involving arrhythmia nurses as part of an integrated approach to management has been convincingly demonstrated.[40,228]

Access to AF therapy and quality of AF care

Patients with AF are entitled to have access to the high-quality care they need, based on evidence, considering their own values and preferences. Patients and care pathways benefit from seamless cross-disciplinary provision of care. This is a key challenge in view of the high prevalence of AF and considering that some patients require

Table 4 Dimensions impacting on access to AF care

Dimensions impacting access to AF care	
Geography	Regional differences between countries and within countries (e.g. rural vs. urban)
Socio-economic	Differences between healthy lifestyle and prompt AF specialist care availability based on socio-economic disparities and education level, affluent vs. deprived individuals and neighbourhoods, elderly and female patients may encounter more barriers to receive AF therapy
Knowledge of AF	State of the art knowledge of the care giver on available management options for AF is necessary to offer appropriate care, patient knowledge improves adherence to therapy
Reimbursement of AF care	Reimbursement, availability of therapies, and design of healthcare systems may limit referral to specialists or to novel treatments, and also limit network development
Physician preferences	General practitioners, internists, general cardiologists, and AF specialists may have different perspectives on AF care
Cultural issues	Differences in implementation of the varieties of care networks, patient view towards disease and ageing (e.g. active or passive), availability of treatments, unconscious bias, barriers encountered by the elderly and by women

Further details can be found in the abovementioned EHRA report.[228]

subspecialist therapies while others can be followed up in primary care. The variability of care for AF patients across Europe[229] provides opportunities to learn from each other but also suggests that improvement is needed to give all AF patients access to optimal care. This group of experts proposes that quantifying the quality of AF care is a requirement for improving overall care.[3] While models of care will differ regionally, reflecting historical care patterns, cultural preferences, availability of resources, and societal priorities, the creation of AF centres and associated care networks could help to enable equal delivery of good AF care.

Access to AF care and integration of care

A first concern is access to AF care, driven by several factors (*Table 4*). A more detailed discussion of these can be found in a recent report from EHRA.[230] A solution for the disparities of regional access to AF care within a country, as well as improving its quality, is the development of regional, integrated AF care networks to enable integrated care for patients with AF.[40,229,230] These networks should involve individual patients, patient groups, healthcare providers in primary care, general cardiologists and multidisciplinary AF experts. Apart from specific AF treatments as required, almost all patients need ongoing management of their cardiovascular/stroke risk and regular reassessment of optimal stroke prevention therapy. There is a strong need to actively involve primary care physicians and allied professionals, working hand-in-glove with specialists and patients, to enable patient-centred risk assessment and therapy delivery using modern technologies including point-of-care biomarkers, app-based rhythm monitoring and simple clinical risk algorithms. To bring all stakeholders into an integrated care network requires planning that includes insurers and payers, the ministry of health and national, local and regional organizations. The communication between different organizations providing care can be enhanced by knowledgeable, educated, empowered patients and digital tools such as the CATCH ME ESC apps (myAF and AFmanager) and 'AF passport' which help to visualize the state of affairs, rolling action points and goals of treatment.[228,230]

Quantifying the quality of AF care

At present, there is a vacuum regarding the responsible parties for implementation of adequate quality of care and its measurement. Quality of AF care is variable and large differences exist between countries, regions, centres, patients of different sex, age, and comorbidities (e.g. undertreatment in elderly women), and individual healthcare professionals regarding access and reimbursement, care pathways, usage, and outcomes.[227,231–233] These differences influence access to therapy innovations[234] but also affect evidence-based therapies. There is an urgent need to ensure quality and outcome control, especially following catheter ablation. An initial step would be the unbiased collection of information on complications.[232,233,235,236] Ideally, health insurance data or large-scale registries would also collect information on recurrent AF and other health outcomes (e.g. hospitalizations). Local establishment of educational and procedural criteria for operator and centre certification is encouraged. There is an inverse relation between volume per centre or even operator and complications of interventions in AF ablation,[232,233] similar to other fields of medicine.[237,238] However, this is not the sole component of quality of care. Instead, quality of care requires a metric combining patient characteristics to estimate risk, case load (per institution/per operator), measures of cardiovascular outcomes, complications and patient-reported outcome and effectiveness measures, as well as efficacy during standardized follow-up. Initial suggestions have been made,[239,240] and systems are being deployed, e.g. in the UK. Professional organizations can play an important role in defining such metrics. The circuit of measuring quality, identifying deficiencies, improving them and measuring the effect of the improvements needs to be closed. EHRA, AFNET and similar organizations elsewhere should support local experts and provide access to knowledge, tools and define best practices. Cooperation with patient representatives and patient organizations as well as the general public and local/regional leadership will be important to implement programmes supporting quality of care. Above all, AF experts should take the responsibility to build a network of healthcare providers and organize regional AF care. Doing so, they should consider the dimensions of access to care, and the fact that the large majority of patients do not need

advanced AF care, but remain managed by general practitioners, and enrolled in cardiovascular risk factor management programs.[3] It needs the internal and external control systems to improve quality of care. The international consortium for health outcomes measurements (ICHOMS) contains all elements for a robust Quality Assurance Cycle for AF care (https://www.ichom.org/portfolio/atrial-fibrillation/).

Text box: Main outcomes of the 7th AFNET/EHRA Consensus Conference. The recommendations are listed here in the order in which they are discussed in the article, split into five clinical recommendations and five research recommendations.

Clinical recommendations

(1) Assess risk in AF patients dynamically, considering the effects of lifestyle changes and management of concomitant conditions on atrial cardiomyopathy, cardiovascular conditions, and systemic illness (Capturing and changing dynamic risk factors for AF section).
(2) Carefully assess patients presenting with AF and heart failure, aiming to establish the dominant condition (Interactions between heart failure and atrial fibrillation—clinical challenges and therapeutic implications section).
(3) Use all available information to maintain and re-establish OAC in patients at high risk of stroke (Clinical risk assessment in patients with atrial fibrillation—a reappraisal section).
(4) Assess patients for cognitive dysfunction and consider effects of management on this outcome that is important for patients (Clinical risk assessment in patients with atrial fibrillation—a reappraisal section).
(5) Consider a risk-based approach to the choice of rhythm control therapy (Improving rhythm control therapy section).

Research recommendations

(6) Make clinical and translational research accessible to all patients with AF (Generating evidence for best care of patients with AF section).
(7) Combine existing datasets and biobanks to enable identification of the major factors causing AF and its complications (Generating evidence for best care of patients with AF section).
(8) Continue and intensify research efforts aiming to understand the interaction between atrial cardiomyopathy, cardiovascular, and systemic disease states (Capturing and changing dynamic risk factors for AF section).
(9) Integrate information from biomarkers and genomic information with clinical data and outcomes to differentiate groups of patients with AF (Biomarkers for prediction of AF and its complications, and to define patient groups section).
(10) Measure quality of care and take action to improve care for patients with AF (Access to AF therapy and quality of AF care section).

Clinical and research recommendations

In conclusion, multidisciplinary research into AF, from mechanisms to care models is a healthcare priority, and continued research efforts are needed to contain the emerging AF epidemic. To improve care for patients with AF and to reduce AF and its complications by prevention and optimal therapy, this group of experts identified ten ways to improve care of patients with AF. These can be summarized as five approaches to improve management and five research recommendations (*Text Box*). We hope that these proposals will both improve management of patients with AF and initiate much-needed research evaluating new approaches to contain the emerging AF epidemic and its associated morbidity and mortality.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

We wish to thank all participants of the 7th AFNET/EHRA Consensus Conference and the staff of AFNET, EHRA, and ESC for excellent organization of the conference.

Funding

The 7th AFNET/EHRA Consensus Conference was co-financed by AFNET and EHRA, and received additional financial support from the CATCH ME consortium (EU Horizon 2020 grant number 633196). Industry participants paid an attendance fee for the conference and provided an industry perspective during the discussions at the meeting but had no involvement in the writing process.

Conflict of interest: The AFNET/EHRA consensus conference was part-funded by the European Union (CATCH ME) and by participation fees paid by industry participants. A detailed list of disclosures of financial relations is provided in the Supplementary material online, *Appendix*.

References

All the references available in Supplementary material online.

1. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD *et al.* 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–62.
3. Kirchhof P, Breithardt G, Bax J, Benninger G, Blomstrom-Lundqvist C, Boriani G *et al.* A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016;**18**:37–50.
4. Fabritz L, Guasch E, Antoniades C, Bardinet I, Benninger G, Betts TR *et al.* Expert consensus document: defining the major health modifiers causing atrial fibrillation: a roadmap to underpin personalized prevention and treatment. *Nat Rev Cardiol* 2016;**13**:230–7.
13. Chua W, Purmah Y, Cardoso VR, Gkoutos GV, Tull SP, Neculau G *et al.* Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation. *Eur Heart J* 2019.
14. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ *et al.* An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019.
19. Hannun AY, Rajpurkar P, Haghpanahi M, Tison GH, Bourn C, Turakhia PM *et al.* Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med* 2019; **25**: 65–9.
34. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D *et al.* Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014; **64**:2222–31.

35. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME *et al.* Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050–60.
36. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J *et al.*; for the RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987–96.
37. Kirchhof G, Lindner JF, AChenbach S, Berger K, Blankenberg S, Fangerau H *et al.* Stratified prevention: opportunities and limitations. Report on the 1st interdisciplinary cardiovascular workshop in Augsburg. *Clin Res Cardiol* 2018;**107**: 193–200.
38. Kirchhof P The future of atrial fibrillation management: integrated care and stratified therapy. *Lancet* 2017;**390**:1873–1887.
51. Guasch E, Benito B, Qi X, Cifelli C, Naud P, Shi Y *et al.* Atrial fibrillation promotion by endurance exercise: demonstration and mechanistic exploration in an animal model. *J Am Coll Cardiol* 2013;**62**:68–77.
69. Guasch E, Mont L. Diagnosis, pathophysiology, and management of exercise-induced arrhythmias. *Nat Rev Cardiol* 2017;**14**:88–101.
112. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA *et al.* EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–90.
113. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H *et al.* EHRA White Paper: knowledge gaps in arrhythmia management-status 2019. *Europace* 2019;**21**:993–4.
127. Wijesurendra RS, Liu A, Eichhorn C, Ariga R, Levelt E, Clarke WT *et al.* Lone atrial fibrillation is associated with impaired left ventricular energetics that persists despite successful catheter ablation. *Circulation* 2016;**134**:1068–81.
128. Chua W, Easter CL, Guasch E, Sitch A, Casadei B, Crijns H *et al.* Development and external validation of predictive models for prevalent and recurrent atrial fibrillation: a protocol for the analysis of the CATCH ME combined dataset. *BMC Cardiovasc Disord* 2019;**19**:120.
131. Santema BT, Kloosterman M, Van Gelder IC, Mordi I, Lang CC, Lam CSP *et al.* Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. preserved ejection fraction. *Eur Heart J* 2018;**39**: 3867–75.
132. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med.* 2020;**383**:1305–16.
143. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J *et al.* Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation* 2017;**135**:1851–67.
148. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM *et al.* The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–90.
157. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM *et al.* Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet* 2018;**50**:1225–33.
176. McIntyre WF, Um KJ, Cheung CC, Belley-Cote EP, Dingwall O, Devereaux PJ *et al.* Atrial fibrillation detected initially during acute medical illness: a systematic review. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:130–41.
177. Adderley NJ, Nirantharakumar K, Marshall T. Risk of stroke and transient ischaemic attack in patients with a diagnosis of resolved atrial fibrillation: retrospective cohort studies. *BMJ* 2018;**361**:k1717.
185. Bertaglia E, Blank B, Blomstrom-Lundqvist C, Brandes A, Cabanelas N, Dan GA *et al.* Atrial high-rate episodes: prevalence, stroke risk, implications for management, and clinical gaps in evidence. *Europace* 2019;**21**:1459–67.
204. Dietzel J, Haeusler KG, Endres M. Does atrial fibrillation cause cognitive decline and dementia? *Europace* 2018;**20**:408–19.
205. Dagres N, Chao TF, Fenelon G, Aguinaga L, Benhayon D, Benjamin EJ *et al.* European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice? *Europace* 2018;**20**:1399–421.
206. Kirchhof P, Haeusler KG, Blank B, De Bono J, Callans D, Elvan A *et al.* Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J* 2018;**39**:2942–55.
209. Medi C, Evered L, Silbert B, Teh A, Halloran K, Morton J *et al.* Subtle post-procedural cognitive dysfunction following atrial fibrillation ablation. *J Am Coll Cardiol* 2013;**62**:531–9.
211. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P *et al.* The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;**16**: 965–72.
212. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE *et al.*; for the CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**: 1261.
214. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G *et al.* Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA* 2019;**321**:1059–68.
221. Glorioso TJ, Grunwald GK, Ho PM, Maddox TM. Reference effect measures for quantifying, comparing and visualizing variation from random and fixed effects in non-normal multilevel models, with applications to site variation in medical procedure use and outcomes. *BMC Med Res Methodol* 2018;**18**:74.
222. Dretzke J, Chuchu N, Agarwal R, Herd C, El Chua W, Fabritz L *et al.* Predicting recurrent atrial fibrillation after catheter ablation: a systematic review of prognostic models. *Europace* 2020;**22**:748–60.
223. Duytschaever M, Demolder A, Phlips T, Sarkozy A, El Haddad M, Taghji P *et al.* PulmOnary vein isolation With vs. without continued antiarrhythmic Drug trEatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicentre randomized trial. *Eur Heart J* 2018;**39**:1429–37.
224. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB *et al.* Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J* 2014;**35**:3356–64.
226. Bumgarner JM, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K *et al.* Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:2381–8.
230. Heidbuchel H, Dagres N, Antz M, Kuck KH, Lazure P, Murray S *et al.* Major knowledge gaps and system barriers to guideline implementation among European physicians treating patients with atrial fibrillation: a European Society of Cardiology international educational needs assessment. *Europace* 2018;**20**:1919–28.
233. Konig S, Ueberham L, Schuler E, Wiedemann M, Reithmann C, Seyfarth M *et al.* In-hospital mortality of patients with atrial arrhythmias: insights from the German-wide Helios hospital network of 161 502 patients and 34 025 arrhythmia-related procedures. *Eur Heart J* 2018;**39**:3947–57.
234. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K *et al.* In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation* 2013;**128**:2104–12.
235. Prinzen FW, Dagres N, Bollmann A, Arnar DO, Bove S, Camm J *et al.* Innovation in cardiovascular disease in Europe with focus on arrhythmias: current status, opportunities, roadblocks, and the role of multiple stakeholders. *Europace* 2018;**20**:733–8.
236. Bollmann A, Ueberham L, Schuler E, Wiedemann M, Reithmann C, Sause A *et al.* Cardiac tamponade in catheter ablation of atrial fibrillation: german-wide analysis of 21 141 procedures in the Helios atrial fibrillation ablation registry (SAFER). *Europace* 2018;**20**:1944–51.
238. Jha AK. Back to the future: volume as a quality metric. *JAMA* 2015;**314**:214–5.