A roadmap to improve the quality of atrial fibrillation management

Kirchhof, Paulus; Breithardt, Günter; Bax, Jeroen; Benninger, Gerlinde; Blomstrom-Lundqvist, Carina; Boriani, Giuseppe; Brandes, Axel; Brown, Helen; Brueckmann, Martina; Calkins, Hugh; Christoffels, Vincent; Crijns, Harry; Dobrev, Dobromir; Ellinor, Patrick; Fabritz, Larissa; Fetsch, Thomas; Freedman, S Ben; Gerth, Andrea; Goette, Andreas; Guasch, Eduard

DOI:
10.1093/europace/euv304

A roadmap to improve the quality of atrial fibrillation management:

Proceedings from the 5th AFNET/EHRA consensus conference

Paulus Kirchhof[1,2,3], Günter Breithardt[2,3], Jeroen Bax[4], Gerlinde Benninger[3], Carina Blomstrom-Lundqvist[5], Giuseppe Boriani[6], Axel Brandes[7], Helen Brown[8], Martina Brueckmann[9,10], Hugh Calkins[11], Melanie Calvert[1], Vincent Christoffels[13], Harry Crijns[14], Dobromir Dobrev[15], Patrick Ellinor[16], Larissa Fabritz[1,2], Thomas Fetsch[17], S. Ben Freedman[18], Andrea Gerth[19,3], Andreas Goette[20,3], Eduard Guasch[21], Guido Hack[22], Laurent Haegeli[23], Stephane Hatem[24], Karl Georg Haeusler[26,3], Hein Heidbüchel[27], Jutta Heinrich-Nols[9], Francoise Hidden-Lucet[25], Gerd Hindricks[28], Steen Juul-Möller[29], Stefan Kääb[19, 30], Lukas Kappenberger[31], Stefanie Kespohl[32], Dipak Kotecha[1], Deirdre A. Lane[1], Angelika Leute[3], Thorsten Lewalter[33,3], Ralf Meyer[34], Lluis Mont[21], Felix Münzel[35], Michael Nabauer[19,3], Jens C. Nielsen[36], Michael Oeff[37,3], Jonas Oldgren[5, 38], Ali Oto[39], Jonathan P. Piccini[40], Art Pilmeyer[41], Tatjana Potpara[42], Ursula Ravens[43,3], Holger Reinecke[2], Thomas Rostock[44,3], Joerg Rustige[29], Irina Savelieva[12], Renate Schnabel[45], Ulrich Schotten[14,3], Lars Schwichtenberg[32], Moritz F. Sinner[19], Gerhard Steinbeck[46,3], Monika Stoll[47,48], Luigi Tavazzi[49], Sakis Themistoclakis[50], Hung Fat Tse[51], Isabelle C. Van Gelder[52], Panagiotis E. Vardas[53], Timo Varpula[54], Alphons Vincent[34], David Werring[55], Stephan Willems[45], André Ziegler[56], Gregory Y.H. Lip[1], A. John Camm[12]

1. University of Birmingham, Birmingham, UK
2. Department of Cardiovascular Medicine, University Hospital Münster, Münster, Germany
3. Atrial Fibrillation Network (AFNET), Germany
4. Leiden University Medical Center, Leiden, The Netherlands
5. Department of Cardiology, Institution of Medical Sciences, Uppsala University, Uppsala, Sweden
6. DIMES Department, University of Bologna, Bologna, Italy
7. Odense University Hospital, Odense, Denmark
8. Meda Pharma SAS, Paris, France
9. Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
10. Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany
11. The Johns Hopkins Hospital, Baltimore, MD, USA
12. St. George's Hospital Medical School, London, UK
13. University of Amsterdam, Amsterdam, The Netherlands
14. University Hospital Maastricht, Maastricht, The Netherlands
15. University Duisburg-Essen, Essen, Germany
16. Harvard University, Boston, USA

17. CRI - The Clinical Research Institute, Munich, Germany
18. University of Sydney, Sydney, Australia
19. Ludwig-Maximilians-University, Munich, Germany
20. St. Vincenz Krankenhaus, Paderborn, Germany
21. Hospital Clinic, Universitat de Barcelona, Barcelona, Catalonia, Spain
22. Bristol-Myers Squibb GmbH & Co. KGaA , Munich, Germany
23. University Hospital, Zurich, Switzerland
24. Institute of Cardiometabolism and Nutrition, INSERM UMR S 1166, Paris, France
25. Hopital Pitié-Salpêtrière AP HP, Paris, France
26. Charité – Universitätsmedizin Berlin, Berlin, Germany
27. Hasselt University and Heart Center, Hasselt, Belgium
28. University Hospital Leipzig, Leipzig, Germany
29. Cardiome Pharma Corp., Vancouver, Canada
30. DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
31. University of Lausanne, Lausanne, Switzerland
32. Bayer HealthCare AG, Berlin, Germany
33. Isar Heart Center, Isarclinic Munich, Munich, Germany
34. Medtronic International Trading Sàrl, Tolochenaz, Switzerland
35. Daiichi Sankyo Europe GmbH, Munich, Germany
36. Aarhus University Hospital, Aarhus, Denmark
37. Städtisches Klinikum Brandenburg, Brandenburg, Germany
38. Uppsala Clinical Research Center, Uppsala, Sweden
39. Department of Cardiology, Memorial Ankara Hospital, Ankara, Turkey
40. Duke University Medical Center, Durham, North Carolina, USA
41. Boston Scientific, St. Paul, MN, USA
42. School of Medicine, University of Belgrade, Clinical Centre of Serbia, Belgrade, Serbia
43. TU Dresden, Dresden, Germany
44. Universitätsmedizin Mainz, Mainz, Germany
45. University Heart Center Hamburg, Germany
46. Zentrum für Kardiologie am Klinikum Starnberg, Starnberg, Germany
47. Institute of Human Genetics, Genetic Epidemiology, University of Muenster, Germany
48. CARIM Research School for Cardiovascular Diseases, University of Maastricht, Maastricht, The Netherlands
49. Ettore Sansavini Health Science Foundation, Cotignola, Italy

50. Ospedale dell'Angelo, Mestre-Venice, Italy
51. University of Hong Kong, Hong Kong, China
52. University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
53. Heraklion University Hospital, Heraklion, Crete, Greece
54. VTT Technical Research Centre of Finland, Espoo, Finland
55. Stroke Research Group, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, London, UK
56. Roche Diagnostics International Ltd., Rotkreuz, Switzerland

Abstract

At least 30 million people worldwide carry a diagnosis of atrial fibrillation (AF), and many more suffer from undiagnosed, subclinical or "silent" AF. AF-related cardiovascular mortality and morbidity, including cardiovascular deaths, heart failure, stroke, and hospitalizations, remain unacceptably high, even when evidence-based therapies such as anticoagulation and rate control are used. Furthermore, it is still necessary to define how best to prevent AF, largely due to a lack of clinical measures that would allow identification of treatable causes of AF in any given patient. Hence, there are important unmet clinical and research needs in the evaluation and management of AF patients.

The ensuing needs and opportunities for improving the quality of AF care were discussed during the 5th Atrial Fibrillation Network (AFNET)/European Heart Rhythm Association (EHRA) consensus conference in Nice on 22nd and 23rd January 2015. Here, we report the outcome of this conference, with a focus on:

1. Learning from our "neighbours" to improve AF care
2. Patient centred approaches to AF management
3. Structured care of AF patients
4. Improving the quality of AF treatment
5. Personalization of AF management

This report ends with a list of priorities for research in AF patients.

Key words

Atrial fibrillation, outcomes, quality of care, research, rate control, antiarrhythmic drugs, catheter ablation, anticoagulation, cardiovascular risk, bleeding, research priorities

Introduction

At least 30 million people worldwide carry a diagnosis of atrial fibrillation (AF) [1], and many more suffer from undiagnosed or "silent" AF. Oral anticoagulation can prevent the majority of AF-related strokes [2], but does only partially mitigate the burden of AF that affects patients, their families, and society [3]: AF-related cardiovascular mortality and morbidity, including cardiovascular deaths, heart failure, stroke, and hospitalizations, remain unacceptably high. [3, 4] The prevalence of diagnosed AF has increased in Europe in recent years [5, 6], due to better awareness of AF, earlier and systematic diagnosis of AF, and an increase in the conditions that predispose to developing AF. [7] In fact, we have to expect that 2% or even 3% of the populations in Europe and in other parts of the world suffer from atrial fibrillation [1, 8], including those with silent AF [1, 8-10]: Clearly, this alarming increase calls for better ways to prevent AF: We are not able to prevent AF, largely due to a lack of clinical measures that would allow identification of treatable causes of AF in any given patient. Hence, there are important unmet needs in the evaluation and management of AF patients.

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1. Learning from our neighbours.

Health care systems, like political systems, develop and "grow" into different shapes in different jurisdictions. Some developments are well suited for patient-centred care and/or may be more efficient compared to others. Controlled trials comparing different ways to deliver AF patient care [11, 12] and regional differences in AF management highlight opportunities to improve outcomes in AF patients. [13, 14] Systematic comparisons of health care systems are a useful tool to inform change in health care systems. [15] In addition, informal exchange of health care organisation can benefit health care professionals and patients. Despite differences in background risk, complications of AF and treatment strategies, the goals of care remain the same: stroke prevention, reduction in cardiovascular complications and amelioration of symptoms. Universally, these issues can be addressed by thoughtful consideration and administration of anticoagulant therapy, rate control and rhythm control therapy, and appropriate management of concomitant cardiovascular conditions.

Each country has a unique variety of regional or local organizations that deliver health care. In some countries, healthcare plans (e.g. Medicare in the US) are in place for some populations but not for others, whilst in other countries almost universal healthcare coverage provides equal access to specialist and generalist care (e.g. Austria, Belgium, Germany, the Netherlands, Scandinavia, the UK, and others). Private purchase of medications and healthcare services is the only means to access health care in some other areas of the world. In some jurisdictions, health care is organized centrally or even directly by state agencies, in others it is managed by regional authorities or offered by units that compete for patients and payment. In addition, the care of AF patients differs markedly, as reflected by simple indicators such as the responsible health care professional (Table 1).

Observational studies suggest that the prevalence of AF may be higher in Caucasians than in persons of African or Asian ethnicity. [16] Similarly, differences in stroke risk in patients with diagnosed AF have been found, e.g. higher stroke rates in China compared to Europe in patients at similar stroke risk based on scoring systems. [17, 18] Such disparity likely reflects differences in the definition of cardiovascular diseases, access to diagnostic procedures, and differences in the management of cardiovascular diseases including antihypertensive treatment, heart failure management, anticoagulation, [13] or rhythm control interventions.[14] Differences in "customary" treatment patterns and different organisation of health care systems can furthermore explain the variation in use of evidence-based AF therapies such as oral anticoagulants, [19] in the quality of INR control or in the use of catheter ablation. Such differences are not compatible with the principle of equal access to evidence-based AF management for all patients and may lead to increased cost in the long-term.

In summary, the care offered to AF patients is different in different countries and regions, at times resulting in variations in quality of care. There is a huge opportunity to improve AF care by exposing these differences and identifying the factors that drive high quality diagnosis and treatment of AF. International organisations such as the European Society of Cardiology (ESC) should contribute to the identification of these differences, and coordinate the discussions that are needed to improve diagnostic and therapeutic pathways by learning from our neighbours.

We recommend a continued professional dialogue about the optimal infrastructure and type of AF care, based on comparable data on type of AF care, outcomes, and resource use in different health care settings to allow improvement of existing AF services.

We recommend a policy of identifying role models of excellent AF care for wider

implementation.

2. Patient centred approaches to atrial fibrillation management

Shared decision making with informed patients. Shared decision making and active involvement of patients in chronic care is a principle that should guide most relations between patients and physicians. It seems very suitable for the management of AF. Recent clinical guidelines have stressed the importance of integrating patient preferences into AF management. [20-23] This reflects a broader move in society to educate and inform patients and communities, thus empowering them to contribute actively to decisions about their care. The 2012 ESC AF guidelines have already emphasized the need for shared decision making in the management of AF. [24]

As stated by Seaburg *et al* [25], "*the goal of shared decision making [in the management of patients with AF] is to increase the likelihood that patients will receive the care that they need in a manner consistent with the best available research evidence and their values and preferences*". It requires a change away from traditional "paternalistic" models of treatment decisions to a model integrating medical facts into an open discussion with the patient who contributes his or her own values and preferences. As a result, patients will be appropriately informed about their disease, its potential progression and complications, and the various treatment options. AF seems ideally suited to shared decision making given the range of alternative diagnostic and treatment options that are available. This is particularly true when there is clinical equipoise relating to a decision affecting the patient in markedly different ways, such as the choice between antiarrhythmic drugs or catheter ablation for initial rhythm control of AF. The main aim is to empower the patients to be appropriately informed about all aspects of their health, wellness and disease state,

ultimately improving the outcome of care. Active participation of patients is needed to make life style changes that will improve outcomes and quality of life in AF patients (Table 2A) and to ensure adherence to therapy. However, it is important to gauge the patient's desire for their degree of involvement in treatment decisions as some patients may prefer the doctor to make treatment recommendations while other prefer shared decision-making**.**

Patient reported outcomes. Patient reported outcomes (PRO) are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else". [26] PROs include assessment of health-related quality of life and symptoms. PROs may be used in a number of applications [27] to provide the patient voice within AF care. In a routine clinical setting, quality of life or symptom questionnaires may be used to provide a standardized estimation of a patient´s well-being to health-care providers. Although most instruments have been validated as paper questionnaires, completed by the patient or with the help of a health care professional, they are suitable for digital, semi-automated or remote assessment of patients. [28] In the future these data may be used at an individual level to identify patients with deteriorating symptoms or aggregated to provide a quality measure, Although the use of PRO instruments in AF patients is in its infancy, these data are likely to evolve further and may develop into a quality measure in the future. [29-31]

Shared decision making in the care of AF patients. Once AF is diagnosed, individual assessment should identify the modifiable risk factors (e.g., arterial hypertension, diabetes mellitus, alcohol consumption, obesity, smoking, sleep apnoea

and concomitant cardiovascular diseases) which are found in approximately 60% of populations with AF. [32] Such precipitating factors may be modified by changes in lifestyle [33, 34], while an inherited predisposition to AF cannot be modified. Since AF is a heterogeneous disease with respect to its aetiology, pathophysiology, mechanisms, clinical presentation, natural history [35, 36] and outcomes, patients are entitled to comprehensive information on the causes, manifestations, and complications of AF. The concept of different types of AF reflecting the main pathophysiological drivers of the arrhythmia seems suitable for this conversation [7] and needs to be supplemented by information on the complex interaction of disease-related factors in the shared decision making process. Patients with AF need adequate and understandable information about the main complications, such as stroke, cognitive impairment, heart failure and sudden death. They should recognize signs of stroke (new-onset neurological deficit) and heart failure (shortness of breath) and the need for immediate medical attention when such symptoms develop or quickly worsen. Information technology can provide such information in a tailored way via interactive electronic educational material (e.g. www.afibmatters.org or http://www.atrial-fibrillation-network.eu/en/home or www.afassociation.org.uk). This will require time and a willingness to explain the information in a language that the patient understands. These resources seems well invested to enable the patient to understand and execute the agreed management plan.

We recommend the involvement of all AF patients in the major decisions about their care, and to enhance the publicly available information on AF, its complications, and the therapeutic options.

3. Structured care of AF patients

Evidence-based management of AF patients. Many aspects of AF management are informed by clear evidence, which is reflected in largely overlapping (but with some worrying differences) international guidelines on treatment of underlying cardiovascular conditions, anticoagulation, rate control, and rhythm control. [20, 21] There are multiple treatment modalities, but also many causes of AF, drivers of AF-related complications, and reasons for impaired patient well-being. The profile and treatment needs of AF patients change over time, and frequently require in-patient hospital care when managed in current approaches. [37, 38] Hence, adequate management of AF patients is complex. It requires a structured approach. [39, 40] Such AF care should ensure that evidence-based therapy is offered to all AF patients, and that follow up and repeated evaluation are sufficient to maintain adherence to agreed management principles. Integrated, multidisciplinary care of AF patients, supported by information technology and patient education, can help to avoid AF-related complications and hospital stays according to recent randomized trials, thereby reducing the burden of AF to patients and decreasing the cost of care. [41] The organization of care will differ locally (see section 1) and local solutions will need to be developed to define a good model of care.

We suggest the development of structured, patient-centred care plans for all AF patients, based on structured initial evaluation and guided by risk profiling and symptom assessment (Table 2). [39] *Interdisciplinary, dedicated AF services which also incorporate lifestyle interventions are likely to facilitate such a structured, risk-based, patient-centred care model.* [41]

We recommend the development of integrated and structured approaches to AF care led by interdisciplinary teams to improve the quality of AF care.

3. Improving the quality of AF treatment

Patients are entitled to high quality care that is safe, effective, and accessible. While the medical literature has traditionally focussed on the best way of caring for patients, it is important to define minimal standards of good care for AF patients. Such standards would ideally be developed and endorsed with wide input from global stakeholders.

We recommend that quality standards are defined and monitored in AF care. EHRA, AFNET and similar organisations in other parts of the world should play a central role in the further definition and dissemination of such criteria, and in linking these to outcomes. The following sections (4.1 - 4.4) outline quality criteria, which are summarized in Table 3.1-3.3.

4.1 Timely diagnosis of atrial fibrillation

Many people, especially those who are older and have concomitant cardiovascular conditions, suffer from undiagnosed, "silent" AF. The prognosis of untreated asymptomatic atrial fibrillation is characterized by a high risk of stroke and death which can be reduced by appropriate oral anticoagulation. [42] Screening for unknown AF and initiation of anticoagulation has the potential to prevent strokes in patients with undiagnosed AF, but has so far mainly been evaluated in physician offices, where pulse palpation followed by 12-lead ECG recording seem cost effective for AF screening.[43, 44] A recent systematic review [45] demonstrated that unknown AF would be detected in 1.4% of the population aged ≥65 on a single screening whether in a clinical or community setting. Pulse palpation is universally available to an educated population. Novel technologies which allow easy cardiac rhythm assessment by lay persons and patients, either by pulse irregularity (oscillometry [46] or smart phone

camera [47]) or by analysis of an ECG rhythm strip [48-51], are now readily available and offer better, less costly methods for more effective and more broadly-based AF screening. A number of studies have explored population or clinic screening using hand-held single-lead ECG devices. [48-50] An economic analysis showed that if an AF screen with these devices at a single time point was extended to the population aged 65-84 years, it would be cost-effective for stroke prevention. [49] Community pilot screening studies suggest that the criteria for widespread screening over age 65 are now met, [52] but the precise implementation method would need to fit with the country-specific health care system.

Silent AF first presenting with ischaemic stroke accounts for at least 10% of all ischaemic strokes. [53-56], and widespread screening could substantially reduce this figure. A systematic review found that an additional 11.5% of survivors will have paroxysmal AF which remains undetected by current ECG monitoring practices, but may be detected by prolonged non-invasive or invasive ECG monitoring, although the available studies are heterogeneous. [57] More recently, two randomised trials of either 30 day external monitors [10] or 1- 3 years of implantable cardiac monitors [58] demonstrated an even higher detection rate of AF, albeit in a subgroup of stroke survivors with "cryptogenic" stroke. Some form of prolonged monitoring after ischaemic stroke should now become the standard of care [59], and offered by a high quality AF service. Ongoing randomized multicentre studies such as MonDAFIS (NCT02204267) will determine whether the detection of "silent" AF after acute ischemic stroke will change long term management in stroke survivors.

We recommend the establishment of more widespread screening programmes for persistent and paroxysmal AF in those over age 65, and in populations at risk, particularly survivors of ischaemic stroke.

4.2 Defining and improving the quality of stroke prevention

The majority of ischaemic strokes in AF patients are caused by AF, and a substantial proportion of those "cardio-embolic" strokes can be prevented by oral anticoagulation. Aspirin is not effective in preventing strokes in AF. Nonetheless, underuse or premature termination of therapy with oral anticoagulants is still common. [60-65] Although non-vitamin K antagonist oral anticoagulants (NOAC) are easy to handle and offer the promise of improved efficacy and safety compared to vitamin K antagonist (VKA) treatment [2, 66], there is still a substantial underuse of oral anticoagulation in AF patients in the "NOAC era". [67, 68] While anticoagulation therapy needs to be paused when patients actively bleed, absolute contraindications to long-term anticoagulant treatment in AF patients are rare, e.g. severe bleeding *without treatable underlying cause in critical organs*. The bleeding risk of anticoagulant use in elderly patients, in patients with cognitive dysfunction, or in those with frequent falls or frailty is often overestimated and should usually not preclude the use of anticoagulants. [69, 70]

Oral anticoagulants need to be taken consistently. The best evidence for this stems from analyses of the time of patients treated with VKA within and below the therapeutic range [71], but it seems reasonable to suggest that regular intake of relatively short half-life NOACs is even more important for successful stroke prevention. [65, 72] Although adherence to therapy is currently not measured systematically in clinical practice, the outcomes of recent observational data-sets replicate the findings in phase III trials of NOACs . [66, 73] Dedicated interventions to enhance adherence to therapy are currently being evaluated e.g. AEGEAN (NCT01184350). [74, 75] Permanent withdrawal of anticoagulation therapy is associated with cardiovascular complications. Re-initiation of anticoagulation after a bleeding event is often possible and clinically justified. Difficult decisions, including the discontinuation of anticoagulation, should

be taken by multidisciplinary teams involving AF, anticoagulation, stroke specialists as well as the patients to adequately balance the risks and benefits of continued anticoagulation.

Limited reimbursement of NOACs is an important driver of inequality in care of patients with AF. [68] This group advocates access to NOACs for all AF patients in need for oral anticoagulation as an initial therapy option. [66, 73, 76, 77] When this is not deemed feasible, clinical estimates for the likelihood to achieve good anticoagulation with VKA could be considered to identify patients who can be treated with VKA. [73, 78]

We recommend the following steps to improve stroke prevention in AF patients

1. *All AF patients in need of oral anticoagulation should have access to NOAC therapy, or to VKA therapy, if NOACs therapy is not feasible.*
2. *We recommend a structured follow-up for all anticoagulated AF patients to remind the patient of the need for AF treatment and to increase adherence and persistence to therapy.* [40, 79]
3. *AF patients who suffer a stroke should be acutely managed in specialized stroke units.* [80]

4.3 What is effective rate control?

The goal of rate control therapy of AF is to reduce patient symptoms and prevent a tachycardia-related reduction in myocardial function. While these treatment goals can be achieved with a lenient rate control approach in some patients [81], others may require stricter rate control, such as those with heart failure or persistent symptoms. [21, 22] The effectiveness of rate control therapy should be assessed at regular intervals in AF patients as part of integrated AF management. Adjustments to rate control

medication seem necessary in many patients [60, 82], and all AF patients need systematic follow-up to allow such adjustments over time. Such assessment will require analysis of a conventional 12-lead ECG, Holter consideration of patient symptoms and preferences, and repeated assessment of left ventricular function (especially when symptoms worsen). The optimal therapy for achieving rate control requires further research. [83, 84] Until the results of such research are available, it will be difficult to define quality indicators for effective rate control therapy in addition to the simple statement that resting heart rate should be < 110 bpm. In patients who remain symptomatic on such a lenient rate control therapy, it may be worthwhile to control rate during exercise, and/or to aim for a lower resting heart rate.

4.4 Improving quality of rhythm control therapy

Defining quality in AF ablation. The evidence underpinning the use of catheter ablation to maintain sinus rhythm in symptomatic AF patients has mainly been generated in recognized regional, national, or international centres of electrophysiological excellence. As AF ablation is being offered to more patients, and hence AF ablation services are established in more and more centres, recruiting and training of electrophysiologists and maintaining a high quality of AF ablation procedures develops into a key issue. It is recognized that there is a need to define and measure quality, both in terms of AF ablation operators and institutions offering AF ablation. Catheter ablation of AF, especially isolation of the pulmonary veins, is now a standardized procedure that has become part of routine clinical care. [24, 85, 86]. Thus, a set of variables to define both a qualified operator and a quality AF ablation centre is proposed (Table 3.3). Using these criteria, systematic assessment of the AF ablation operators and of AF ablation centres can be undertaken to ensure their quality, and to

study the validity and the clinical usefulness of these criteria. This process should be led by professional organisations such as EHRA or Heart Rhythm Society (HRS).

Hybrid rhythm control therapy. It is well recognized that catheter ablation will not completely eliminate AF in many patients. [87, 88] It is in this context that we discuss the concept of "hybrid therapy" for AF (ablation plus antiarrhythmic drugs). Hybrid therapy, defined as the use of antiarrhythmic drug therapy more than 3 months following an ablation to reduce symptoms and/or episodes of AF, is a common therapeutic concept in AF patients. [89, 90] While it is common practice to stop antiarrhythmic drugs a few weeks or months after restoration of sinus rhythm by catheter ablation [91] or cardioversion [92], the result is an excess in AF recurrences compared to continued antiarrhythmic drug therapy [91, 92] Hence, some patients may be advised and/or may prefer to continue antiarrhythmic drug therapy after ablation of AF, especially when the therapy is well tolerated, integrating patient preferences, the perceived risk of recurrence, and the risk of therapy. [93]

Repeat ablation or antiarrhythmic drug therapy after AF ablation? Many patients who undergo an initial AF ablation will continue to experience symptomatic AF once antiarrhythmic drugs have been discontinued. [85, 89] Decisions to perform a repeat ablation should only be done once recurrence of AF has been documented and follow the same process used to decide on the initial AF ablation. This process involves shared decision making based on a consideration of safety and efficacy of repeat ablation, discussion of all treatment options including antiarrhythmic drug therapy and acceptance of AF ("rate control only"), and should integrate patient preferences. Hereby, the patient has a better appreciation of what the procedure

involves, and the electrophysiologist has more knowledge about the procedural details, including risk and the potential extent of re-ablation. Atrial tachycardias may be better amenable to re-ablation than AF. Some patients will prefer a trial of antiarrhythmic drugs rather than repeat ablation.

We recommend systematic collection of information on centre and operator quality, based on simple quality indicators and procedural complications (Table 3.3), from all AF ablation centres.

We recommend further research into the best rhythm control therapy in patients with recurrent AF after AF ablation.

5. Beyond the present state of the art: Personalized AF management

A broad range of different cellular and molecular mechanisms underlie AF and are modified by environmental factors. [94-96] Thus, the manifestation, progression and outcome of disease will vary between these subtypes of AF, consistent with clinical observations.[7] Furthermore, the clinical differentiation between "paroxysmal" and "persistent" AF may be poor, suggesting that this differentiation is not reflecting different biology. [97] Clinical conditions that are associated with AF and AF-related complications may vary substantially by AF aetiology, but will overlap. To investigate the development of mechanism-oriented therapy of AF, prior consensus conferences suggested a pathophysiological classification of AF types. [7] The precise identification of AF mechanisms would ideally involve assessment of atrial tissue. As this is inherently difficult to obtain, blood (or possibly imaging) markers that correlate with atrial pathophysiology, could indicate whether major molecular mechanisms of AF are present in a given patient. Cardiac imaging modalities such as echocardiography, CT, or magnetic resonance imaging give a relatively detailed view of atrial size and to some

extent of atrial structure. They usually require specialised equipment and expertise for interpretation, and have been discussed in a recent review [7]. The existing biomarkers for AF were therefore reviewed with a view to utilising them for the classification of AF patients into different types.

Unfortunately, many biomarkers that have been evaluated in AF patients identify abnormal cardiac or inflammatory states, rather than reflecting atrial pathology.

Natriuretic peptides, in particular B-type natriuretic peptide (BNP), cannot differentiate between underlying or concomitant cardiovascular conditions and comorbidities. Elevated BNP is associated with incident AF, and BNP is correlated with disease burden, e.g. frequency and duration of AF episodes and overall cardiac abnormality.[98] Its predictive ability for new onset AF in community cohorts is strong, but improvement in C-statistic and reclassification remain modest. [99, 100] N-terminal pro-BNP is also strongly and independently associated with stroke and mortality in patients with AF. [101]

C-reactive protein may be considered for general cardiovascular risk assessment when treatment decisions based on conventional risk scoring are uncertain. [102] Although modification of C-reactive protein concentrations, e.g. by statin treatment may alter AF risk [103] , Mendelian randomization, i.e. a correlation of genetic determinants of CRP levels and their association with AF, suggests that it is unlikely that C-reactive protein *per se* causes AF. [104] Consequently, the power of CRP to identify patients with AF is low. [99, 100]

Similarly, markers of impaired kidney and bone marrow function such as *glomerular filtration rate, cystatin C, or low hemoglobin* have been associated with many aspects of AF pathophysiology. [105] They represent aging, general health status and comorbid conditions that affect AF incidence and prognosis rather than intrinsic AF

mechanisms. While the combination of these markers of disease can slightly improve the prediction of incident AF [99, 100] , or complications of therapy (e.g. bleeding on anticoagulants), the value of such general biomarkers for personalized management of AF needs to be established. It seems unlikely that these markers can discriminate different subtypes of AF in the near future.

Common genetic variants. Genetic variation is fairly stable over a life course, independent of environmental changes and may help to define AF subtypes. In rare monogenic AF, a single mutation determines the disease phenotype (e.g. long QT syndrome or an inherited cardiomyopathy, but also in familial AF [106, 107]). Common genetic polymorphisms correlate with the risk of AF development and risk of stroke, and predispose to recurrences of AF on antiarrhythmic drugs [108] or ablation success. [109] About a third of all AF patients carry common gene variants that predispose to AF. [110, 111] In general, every single nucleotide polymorphism (SNP) only carries a small relative risk, but they can be combined to generate more precise information. [111, 112] Genetically determined subtypes of AF in the community have not yet been formulated. Future in-depth analysis of genetic information collected in large consortia will provide additional information on the genetic underpinnings of AF, including very many SNPs. Furthermore, the molecular mechanisms conveying AF risk in carriers of the AF-related genetic variants may unveil novel “atrial specific” disease pathways and biomarkers, including altered epigenetic or microRNA related pathways. [113-118] The practical consequences of these findings need to be determined and tested in controlled trials.

The search for atrial-specific biomarkers. The increasingly broad availability of

novel “big data” technologies will provide access to blood and tissue for largely unbiased “omics” interrogation. Omics data including genome transcriptome, proteome and metabolome information will reveal intermediate phenotypes and disease patterns in AF. These analyses have the potential to identify promising new AF biomarkers. The information derived from different clinical and molecular sources then needs to be combined to identify new biomarkers or marker signatures of clinical relevance.[119]

Novel biomarkers will need to be able to identify a group of AF patients (or populations at risk for AF) who respond well to a given therapy and/or who show a distinct course of disease, e.g. in terms of AF progression or for complications of AF. Subsequently, proof of concept and prospective controlled testing need to demonstrate feasibility and cost effectiveness.

The overall success of future biomarker studies will rely crucially on two interrelated issues: the establishment of distinct AF phenotypes and rigorous validation of biomarkers e.g, as recently suggested by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) investigators. [120] Current biomarker studies are limited by the crude AF phenotype definition that impairs specific associations. On the other hand, biomarkers and biomarker signatures may largely enhance the differentiation of AF subtypes and their optimal management. Existing and emerging biomarkers and AF subtypes will then need rigorous validation and prospective testing.

ECG parameters. The ECG is a widely available diagnostic test in many health care settings. Furthermore, emerging technology will give patients and citizens unsupervised access to ECG recordings. Several ECG parameters can be used to detect

patients at risk for AF. The PR interval has a clear genetic trait [121, 122] and a prolonged PR interval is associated with an increased the risk of prevalent AF in populations. [123-125] Direct electrocardiographic contact mapping studies in patients undergoing open-chest surgery have indeed demonstrated that a progressive structural remodeling process is reflected in more complex atrial activation patterns [126, 127] which may promote recurrent AF [128-130]. The complexity of the AF activation pattern may be indirectly measured by time domain (F-wave analysis, principal component analysis, sample entropy) and frequency domain (dominant frequency, organization index of power spectrum, spectral entropy) parameters. [131] Such quantifiable parameters of "AF complexity" have been evaluated as markers for recurrent AF in patients receiving rhythm control therapy (cardioversion, antiarrhythmic drug therapy, or catheter ablation). [132, 133] Sufficiently powered studies using standardized technology are needed to determine the clinical value of ECG analyses during AF to differentiate different types of AF. [132]

We recommend performing properly powered genomic, genetic and biochemical analyses in controlled trials.

We recommend using existing large biosample collections to identify atrial-specific biomarkers.

We recommend research into clinical parameters that can differentiate different "aetiologic types" of AF.

6. Research priorities in the next five years

Based on the challenges in understanding and eliminating the inequalities and barriers that prevent optimal care of AF described above, we have outlined the priority research needs:

1. Prospective studies evaluating the prognostic value of modern rhythm control therapy are fortunately underway and should be completed as soon as possible.
2. Prospective studies are needed to determine the most effective strategy for AF detection in populations and in patients at risk for AF and stroke, including the methods of detection, implementation and cost effectiveness.
3. Evaluation of integrated and structured care approaches compared to current care models has immense potential to improve quality of AF patient care and is essential to make these useful in clinical practice.
4. Definition of the optimal patient reported outcomes to capture AF-related symptoms and patients' experiences of AF, and the development and adoption of methods to ensure optimal PRO assessment and reporting from AF trials.
5. Evaluation of new parameters (e.g. blood biomarkers, ECG parameters, etc.) to refine anticoagulation decisions in patients with an intermediate or low risk for stroke.
6. Strategies to minimize interruption or discontinuation of anticoagulant therapy should be systematically evaluated, including different in-person or remote follow-up patterns and interventions geared at empowering patients.
7. Interdisciplinary therapeutic strategies for "therapy failures" on oral anticoagulation, e.g. patients with an ischaemic stroke on adequate anticoagulation or those with severe bleeds, should be developed and evaluated.
8. Controlled trials of anticoagulation strategies in AF patients with advanced kidney disease (MDRD stages IV-V) are urgently needed.

9. We recommend high quality research projects on the research on timing of recommencing oral anticoagulants after bleeding. [134]

10. The best use of left atrial appendage occlusion devices in clinical practice is not well established.[135] Evaluation of this technology in patient groups with the potentially highest benefit and optimization of post-interventional antithrombotic treatment is needed.

11. Controlled studies on heart rate control comparing beta adrenoceptor-blockers, digoxin, and non-dihydropyridine calcium channel blockers as well as heart rate targets and their effects on quality of life, cardiac function, and cardiovascular outcomes are urgently needed.

12. Prospective studies evaluating the success of hybrid rhythm control therapy combining antiarrhythmic drugs and ablation compared to catheter ablation alone seem warranted. Follow-up after catheter ablation for AF should be standardized to enable comparison of research results. Evaluation of novel markers for different "types" of AF should be integrated into such projects.

13. Databases of existing trials and cohort studies should be used to propose clinical subtypes of AF, e.g. based on imaging, ECG or on blood biomarkers (including genetic markers).

14. Genetic risk variants or genetic risk scores for AF should be examined to see if they can help to identify AF or stroke risk prediction, the subtypes of AF, response to therapies, or clinical outcomes.

15. Since clinical trials of AF represent unique research opportunities, we encourage the systematic collection of AF covariate data and samples to enable future studies on biomarkers and "types of AF".

16. Patients should be actively involved in clinical AF research projects. Patients

can for example advise on patient information sheets, lay summaries and consent forms and help to optimize recruitment strategies, but also contribute to practical design aspects. [136] To ensure effective patient involvement, all parties should be clear of the role of patient involvement. More information can be found (http://www.nets.nihr.ac.uk/ppi; and http://www.invo.org.uk/).

17. Mechanistic research should be conducted to link genetic variants to AF mechanisms, and to reveal novel therapeutic targets.

18. Long-term research funding is critically necessary to address each of these challenges and to ensure the optimal treatment of AF.

Acknowledgments. All participants of the 5th AFNET/EHRA consensus conference, and especially the conference organisers Günter Breithardt, John Camm, Paulus Kirchhof, and Gregory YH Lip want to thank the staff of AFNET and EHRA for excellent organisation of the conference. The 5th AFNET/EHRA consensus conference, like its predecessors, was organized and funded by AFNET and EHRA. Industry participants paid an attendance fee. A full list of the author declarations of interest can be found in an on line appendix.

Table 1: Examples of existing care models for the care of AF patients

Care model	Advantages	Disadvantages
General practitioner	Easy access for patients; possibility to perform initial tests (history, ECG, blood sample)	Limited initial evaluation; limited management options; lower adherence to guidelines[137]
Cardiologist/ AF subspecialist	Experience; comprehensive evaluation; full range of treatment options	Resource demanding; initially expensive
Integrated care of general practitioner and internal medicine specialist	More complete assessment and management of co-morbidities	Limited cardiology-specific evaluation and management options
Integrated care of general practitioner and cardiologist	More tailored management approach using full range of treatment options; distribution of care across healthcare system	Limited cardiology-specific follow-up
Cardiologist led integrated care including nurses, allied professionals/lifestyle specialists	Full assessment and range of treatments; tailored follow-up; structured care	Costs (but possibly cost-effective)
Nurse led integrated care	Patient-centred care approach; efficient and possibly cost-effective[138]	Education, training and monitoring of staff

Table 2A: Life style changes that can improve AF management by either improving outcomes, reducing the risk of complications, rendering recurrent AF less likely, or improving quality of life.

Life style change	**Effect on**	
	Outcomes and complications	**recurrent AF and quality of life**
Regular physical activity	X	not known
Weight reduction	not known	X
Low sodium, low fat diet	X (by reducing blood pressure)	not known
Smoking cessation	X	not known

Table 2B. Structured initial care of AF patients

A. Components of initial care:
ECG – confirmation of AF[139]
Detailed medical history
mEHRA symptom assessment [140]
CHA_2DS_2-VASc stroke risk assessment [141]
Assessment and correction of modifiable bleeding risk factors (e.g. by HASBLED score) [142]
Physical examination including blood pressure and body mass index
Risk factors and comorbidities assessment including heart failure, chronic airways disease, dementia, sleep apnoea, renal disease, diabetes, thyroid disease and coronary artery disease – requires cardiac imaging (usually echocardiogram) and blood sampling [86]
B. Tailored additional evaluation according to the patient:
Additional diagnostic tests
Correction of risk factors
C. Initial management plan
According to ESC guidelines Defined by an AF team representing all relevant expertise Advice on life style changes affecting outcomes and AF
D. Follow-up
Regular, scheduled follow-ups according to the model of care (see Table 1) Assessment of symptoms and patient-reported outcomes (see Section 2, Table 4) Heart rate targets (see Section 4) Adherence and response to treatment Complications of treatment and complications of AF Assessment of quality metric targets (see Tables 3 and 4) Informed decision on adjustment of therapy

Table 3: Quality criteria for management components of atrial fibrillation

Table 3.1: Quality criteria for anticoagulant therapy

Individual risk assessment
▪ Assess stroke risk with CHA_2DS_2-VASc score ▪ Assess bleeding risk and minimize bleeding risk factors - Control blood pressure - Discontinue treatment with non-essential antiplatelet(s)/NSAIDs - Counsel patient to reduce alcohol consumption if excessive ▪ Check renal function and estimate creatinine clearance prior to deciding on anticoagulation therapy
Guideline adherent OAC prescription
▪ CHA_2DS_2-VASc score ≥2, OAC recommended ▪ Documented decision in patients with CHA_2DS_2-VASc score = 1 ▪ If patient is on VKA, achieve high time in therapeutic range (TTR, e.g. > 65%)
Decision-making
Individualized approach to decision making ▪ Gauge and follow patient's desire for involvement in making OAC treatment decision (e.g. following input from patient, doctor, or relative)
Support of anticoagulation therapy
▪ OAC-specific information (verbally, pictorially, written)[40, 146] ▪ Check patient understanding of key elements: dose, frequency, with/without food, bleeding side effects; result of non-adherence (stroke) ▪ check and reinforce knowledge on TIA/stroke alarm symptoms e.g. by "FAST" (face, arm, speech, time) and explain need for emergency transfer to stroke unit when such symptoms occur ▪ Provide written information to reinforce verbal information ▪ All information tailored to the patient's ability to understand and desire for information
Providers of care (see table 2, one option should be available)
▪ Physician, nurse, pharmacist, other healthcare professional, 'expert' patient, combination ▪ Nurse led supported by consultant expertise[40] ▪ Supported with software to aid clinical decisions (algorithms)[144] ▪ Intervention for VKA initiation[145]

Table 3.2 Quality criteria for antiarrhythmic drug therapy in AF patients.

Individual assessment
▪ Quantify AF related symptoms (mEHRA score) [147] ▪ Assess the need for rhythm control on the background of adequate rate control ▪ Assess concomitant cardiovascular diseases and prior attempts of rhythm control to inform choice of AAD ▪ Assess 12-lead ECG for signs of conduction or repolarization disturbances ▪ Document baseline QT interval, QTc, QRS duration, and QRS abnormalities ▪ Check baseline blood levels as needed (thyroid and liver function for amiodarone, liver function and creatinine for dronedarone, creatinine and estimated creatinine clearance for sotalol, flecainide, and propafenone)
Guideline adherent prescription and therapy initiation
▪ Choose antiarrhythmic drug according to ESC guidelines ▪ Prescribe effective dose ▪ Monitor ECG during therapy initiation (days 1-3 for flecainide, propafenone, and sotalol, week 1 and 2 for dronedarone, week 1 and 4 for amiodarone) ▪ Monitor blood levels as needed
Dedicated patient education[143]
Provide information on: ▪ The main aims of rhythm control therapy (reducing symptoms) ▪ The possible need for further procedures (cardioversion, catheter ablation) ▪ Possible side effects including proarrhythmia ▪ All information tailored to the patient's ability to understand and desire for information
Once antiarrhythmic drug treatment decision is made
▪ Provide clear information on duration of therapy (pill in the pocket, short-term, long-term) and drug interactions (e.g. anticoagulants) ▪ Check patient understanding of key elements: dose, frequency, with/without food, result of non-adherence (recurrence of AF) ▪ Provide written information to reinforce verbal information

Table 3.3 Quality indicators for AF ablation.[85]

A. Quality indicators for care in AF ablation centres
Structured and documented assessment of indications for AF ablation - Symptoms (mEHRA score) Prior rhythm control attempts - Other therapeutic options (antiarrhythmic drugs, no further rhythm control therapy, combination therapy) - Likelihood of recurrent AF
Required infrastructure for AF ablation centres in addition to the general quality criteria (See Tables 3.1 and 3.2) - Dedicated, adequately equipped electrophysiology laboratory - Minimum number of AF ablation procedures per year (over 50) - Availability of backup open heart surgery capable of managing complications of AF ablation, especially pericardial tamponade - Availability of backup anaesthetic support. - Data base to track complications over time - Regular structured complication conference - Standardized patient follow-up program
B. Quality indicators for AF ablation operators
Adequately trained and qualified electrophysiologists
Operators should perform a minimum of 25 AF ablation procedures per year.
Rate of major complications: defined as complications that prolong hospital stay or require intervention. The rate of cardiac tamponade is an important subset of the complication rate that should be separately monitored.
Although efficacy is also important, this parameter is difficult to define as it depends on the type and complexity of the patient's AF, the extent of post-ablation monitoring, the definition of success, and the duration of follow-up. We encourage operators to track the recurrence rate of AF, rate of re-ablation, and to assess quality of life before and after ablation using dedicated PRO instruments.

Table 4 (on line): Relevant biomarkers that have been evaluated to identify AF patients at risk for complications. Most markers identify general cardiovascular risk and cardiovascular diseases, with the exception of genetic variants that are relatively specific for AF. Biomarkers that are specific for AF or for AF-related complications seem most promising for further evaluation.

Biomarker	Occurrence/Recurrence	Complications		
		Death	Stroke	Bleeding
Cardiovascular stress and cell damage				
Elevated hs-Troponin	↑ [148] ↑ (postoperative) [149, 150]	↑ [151-153]	↑ [151-153]	↑ [152, 153]
Elevated BNP	↑ [99, 100, 154-159] ↑ (postoperative) [160, 161]	↑ [151, 162]	↑ [151, 163-166]	X [151]
Inflammation and oxidative stress				
Elevated CRP	↑ [99, 100, 104, 157, 167-171] ↑ (recurrence after ablation) [171-175] ↑ (recurrence after cardioversion) [176] X (recurrence after cardioversion) [177]	↑ [178]	↑ [179] ↑ (echo markers of thrombus) [180]	
Elevated GDF-15	X [148]	↑ [181]	↑ [181]	↑ [181]
Kidney function				
High creatinine / low eGFR	↑ (recurrence after ablation) [182]	↑ [183]	↑ [183-187]	↑ [183, 184, 186]
Cystatin C	↑ [105, 188, 189] X [190]	↑ [183]	↑ [183]	↑ [183]
Coagulation state				
D-dimer	X [99]	↑ [191-193]	↑ [191, 192, 194-196] ↑ (LAA thrombus) [197]	↑ [192]
Anaemia	↑ [189] ↑ (postoperative) [198]	↑ [199]		↑ [187, 200-203]
Common genetic variation				
Chromosome 4q25 locus, SCN10A, SCN5A, KCNE1	↑ [110, 111, 119, 204-210]		↑ [111, 211-214] X (postoperative) [210] X (Han Chinese) [215]	
ECG parameters				
PR interval	↑			
P-wave and F-wave information	↑ stroke ↑ recurrence after ablation			

↑ = positive association, X = no association ; hs = high-sensitivity.

Figure legends

Figure 1: Roadmap to improve quality of AF services. Shown is a virtuous circle relying on four major pillars to improve the quality of AF services for patients. Shared decision making, quantifiable quality measures, integration of AF services across health care sectors, and the use of stratified approaches to therapy can improve AF service quality. They will require continuous evaluation of quality.

Figure 2: Biomarkers may help to define AF subtypes. They can comprise blood and tissue based markers as well as electrocardiographic or further objectively determined characteristics (e.g. atrial imaging). Both, biomarkers and existing and novel AF phenotypes need rigorous validation.

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