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SPECIAL ARTICLE

Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'

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Atrial fibrillation (AF) causes important mortality and morbidity on a population-level. So far, we do not have the means to prevent AF or AF-related complications adequately. Therefore, over 70 experts on atrial fibrillation convened for the 2nd AFNET/EHRA consensus conference to suggest directions for research to improve management of AF patients (Appendix 1). The group defined three main areas in need for research in AF: 1. better understanding of the mechanisms of AF; 2. Improving rhythm control monitoring and management; and 3. comprehensive cardiovascular risk management in AF patients. The group put forward the hypothesis that successful therapy of AF and its associated complications will require comprehensive therapy. This applies e.g. to the "old" debate of "rate versus rhythm control", since rhythm control is generally added to underlying (continued) rate control therapy, but also to the emerging debate of "anti-arrhythmic drugs versus catheter ablation", of which both may be needed in most patients to maintain sinus rhythm, but also to therapy of conditions that predispose to AF and contribute to cardiovascular complications such as stroke, cognitive decline, heart failure, and acute coronary syndromes. We call for research initiatives aiming at a better understanding of the different causes of AF and its complications, and at development and validation of mechanism-based therapies. The future of AF therapy may require a combination of management of underlying and concomitant conditions, early and comprehensive rhythm control therapy, adequate control of ventricular rate and cardiac function, and continuous therapy to prevent AF-associated complications (e.g. antithrombotic therapy). The reasons for these suggestions are detailed in this paper.

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Introduction

Atrial fibrillation (AF) is found in 1% of the population at present, and the number of affected individuals is expected to double or triple within the next two to three decades following an increased AF incidence and ageing of European populations.[1–4] Atrial fibrillation doubles mortality and causes marked morbidity[5–12] on a population level, even after adjustment for confounders.[2,13]

Unfortunately, we do not have the means to prevent this 'burden of AF',[14–19] apart from antithrombotic therapy to prevent strokes, small improvements in exercise capacity,[19] prevention of cardiovascular hospitalizations,[20] and effects found in *post hoc* analyses.[21] Research to improve management of AF patients is therefore urgently needed.

With this in mind, the German Atrial Fibrillation competence NETwork (AFNET, www.kompetenznetz-vorhofflimmern.de) and the European Heart Rhythm Association (EHRA, http://www.escardio.org/communities/EHRA/Pages/welcome.aspx) organized the 2nd AFNET-EHRA consensus conference on 'research perspectives in atrial fibrillation' (see Appendix for participants). This paper summarizes the conclusions of the conference grouped in three major sections (Supplementary material online, *Table S1*). A longer version of this paper is available.[22] We hope that this publication will stimulate research, improve the management of patients with AF, and eventually contribute to reducing the burden of AF in the community.

Table 1 Clinical variables advocated for outcomes atrial fibrillation trials, modified from[49]

1	Death
2	Stroke and cerebral bleeds
3	Quality of life
4	Rhythm
5	Left ventricular function
6	Health economics
7	Additional important outcome variables: cardiovascular complications, e.g. acute coronary syndrome or decompensated heart failure

Table 2 Novel therapeutic goals

8	Silent stroke (including asymptomatic intracerebral bleeds) and cognitive function
9	Social functioning and disease-related quality of life
10	Progression to more sustained forms of AF
11	Left ventricular function
12	Left atrial function

This table adds potentially useful novel therapeutic goals to the list of previously advocated outcomes in AF trials that may help quantify a subtle, but in the long-term potentially relevant, effect of AF therapy.

Understanding the mechanisms of atrial fibrillation

Different pathophysiological mechanisms can cause and maintain atrial fibrillation

It is tempting to speculate that we would be able to prevent AF-related complications better (*Tables 1* and *2*) if we understood its causes well enough[23] (*Figure 1*). We therefore propose to define different forms of AF that might require different types of treatment (*Table 3*).

Focal atrial fibrillation

Focal activity in the pulmonary veins initiates AF in many patients with paroxysmal, often 'lone' AF.[24,25] Although some experimental studies have attempted to identify arrhythmogenic mechanisms in the pulmonary veins and adjacent myocardium,[26–29] the prominent role of the pulmonary veins in AF remains poorly understood. A better understanding of the mechanisms initiating 'focal' AF may help develop safer and better ablation strategies (see below) and other therapeutic modalities.

Electrical remodelling in atrial fibrillation

Rapid atrial activation provokes both a shortening of the atrial action potential and refractory period and impaired rate adaptation.[30,31] This prevents cell death due to intracellular calcium overload, but promotes functional re-entry. 'Reversal' of this electrical remodelling is a main effect of ion channel-blocking drugs. Such 'antiarrhythmic drugs' prolong the atrial refractory period and can terminate persistent AF,[32–34] facilitate cardioversion,[35,36] or prevent recurrent AF after cardioversion.[37]

Altered intracellular calcium handling in atrial fibrillation

Cumulative evidence points to the role of abnormal intracellular Ca^{2+} handling for electrical remodelling, triggered activity, focal drivers, and multiple re-entrant mechanisms of AF.[38] In short term, cellular Ca^{2+} overload in AF is counterbalanced by electrical remodelling and inactivation of L-type Ca^{2+} channels. Over time, however, adaptive mechanisms alter the functional state of multiple Ca^{2+} handling proteins, and profoundly alter gene transcription, protein expression, and protein regulation. We propose that a sound understanding of the molecular mechanisms of abnormal Ca^{2+} handling in AF may open new strategies for treatment.

Structural changes

Increased atrial pressure and volume[39] related to structural heart disease,[40] arterial hypertension, or ageing,[41,42] and certain genetic alterations[43,44] result in a steady process of ultrastructural changes in the heart. This process may occur as a result of AF[45] or independently of AF.[41,42] Activation of fibroblasts, enhanced collagen deposition, and fibrosis dissociate muscle bundles, cause heterogeneous conduction, and facilitate AF by more heterogeneous and smaller activation waves. This 'type' of AF may occur independent of electrical remodelling.[46,47]

Atrial fibrillation in inherited cardiomyopathies

Many patients with inherited cardiomyopathies[48] develop AF. The genetic abnormalities in these patients range from defects in ion

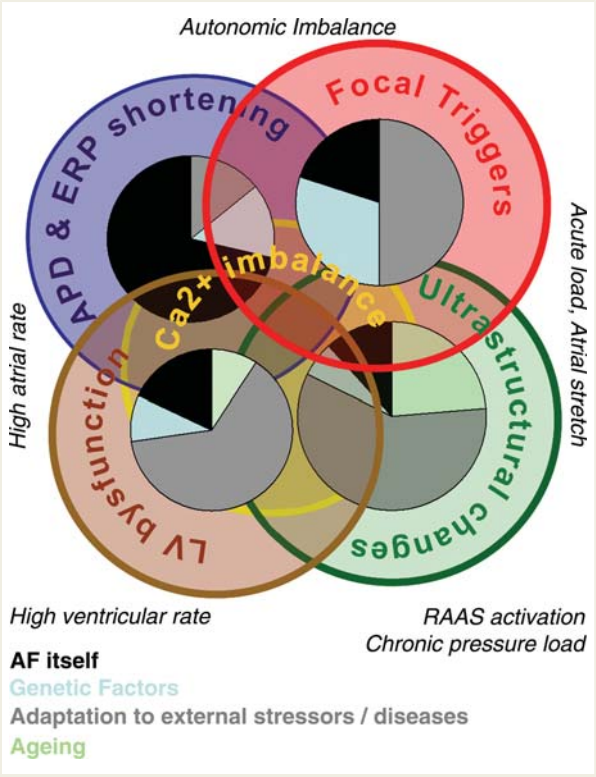

Figure 1 Interdependence of mechanisms that contribute to the initiation and maintenance of atrial fibrillation (AF). Each circle represents a relevant factor that may initiate or perpetuate AF. The pie chart within each circle gives educated guesses as to how often this pathophysiological mechanism will be due to AF itself (black pie piece), genetic predispositions (light blue), a response of the atria to stressors such as hypertension, diabetes, or valvular heart disease (grey), and ageing (light blue). It has to be emphasized that these proportions are educated guesses to illustrate the interdependence of different causes, and not based on real data. Some of the main pathophysiological mechanisms also correspond to a 'type' of AF (compare *Table 3*). In an individual patient (but also in most experimental models), AF will be due to a 'blend' of these different factors as indicated by the overlap between the circles. There may be additional mechanisms, and their interaction will be different in different patients.

channels to polymorphisms in genes involved in early cardiac development (Supplementary material online, *Table S2*). Factors that precipitate AF in these conditions warrant further research, especially as subclinical cardiomyopathy changes may contribute to a relevant portion of unexplained ('lone') AF.

Atrial fibrillation requires a translational research approach

The complex interaction of different mechanisms that initiate and perpetuate AF demands translational interdisciplinary research to allow progress in the understanding of AF. Such research should combine molecular, cellular, organ, and *in vivo* experiments and measurements in patients in order to translate research concepts into clinically applicable diagnostic tools and therapeutic options. Another component of translational research in AF may be the testing of potentially relevant pathophysiological changes 'in silico', i.e. by integrated functional computer modelling.

Improving non-invasive diagnostic tools to assess substrates for atrial fibrillation

New diagnostic tools could help to differentiate various types of AF non-invasively (*Table 3*). The group felt that a better characterization of 'treatable' causes of AF may help to individualize therapy in AF patients. Thorough validation of these diagnostic techniques is needed.

Graded therapy atrial fibrillation?

We suggest 'graded therapy' of AF-causing processes based on the 'type' of AF, e.g. upstream therapy in patients with ultrastructural changes, sodium channel blockers and ablation in patients with focal events, action potential-prolonging drugs after cardioversion, and rate control in the presence of a very severe substrate. Whether 'graded therapy' can improve therapy requires testing.

Basis for research:

(i) Among the known factors that contribute to AF are focal triggers, AF-induced electrical remodelling, localized re-entrant drivers, and ultra-structural 'remodelling' in the atria, altered intracellular Ca^{2+} handling, as well as an inherited predisposition.
(ii) It is likely that a variable combination of the above-mentioned factors causes AF in a given patient.
(iii) In many patients, several of these mechanisms are active before AF occurs.
(iv) Many AF-promoting processes are caused by atrial damage unrelated to AF *per se*, but are then aggravated by AF itself.
(v) Successful therapy of AF likely requires identification of all AF-causing factors, and 'graded' therapy of all relevant pathological processes.

Research perspectives. The following research perspectives appear relevant in the near future:

(i) What causes the first episode of AF?
(ii) What causes progression of AF in the majority, but not in all patients?
(iii) How do genetic factors, and interactions between the heart and the autonomic nervous system, predispose to AF?
(iv) Can subclinical dysfunction of the structures involved in genetic alterations, subtle ultrastructural changes, and/or minimal alterations in Ca^{2+} handling and electrical atrial function contribute to the initiation of AF?
(v) Can an early and 'graded' therapy prevent AF more effectively in specific patients if clinical tools were available to assess the different factors predisposing to AF (see also next section)?

Table 3 Suggested classification of different types of atrial fibrillation

Type of AF	Clinical examples	Clinical or ECG finding that may identify this type of AF
Focal AF	'Lone AF' AF mainly caused by focal triggers, often in the pulmonary veins Typical ablation patients	Frequent atrial ectopy (spontaneous, multiple P-wave morphologies usually present)
Inheritable AF	AF in patients with inherited cardiomyopathies Requires inheritability The cause of AF may vary depending on the genetic defect (see Supplementary material online, *Table S2*) AF can be the only clinical sign of cardiomyopathy	ECG signs of cardiomyopathies (QT interval changes, abnormal hypertrophy, etc.)
'Multiple wavelet AF'		
AF due to shortening of AERP	Tachycardia-induced AF Early AF recurrences after cardioversion	Invasive assessment or fast Fourier transformation of signal-averaged ECG or echocardiographic analysis of atrial rate during AF
AF due to abnormal conduction patterns	Markedly hypertensive patients without marked enlargement of the atria	Prolonged P-wave duration on ECG or signal-averaged ECG or by other techniques
AF due to enlargement and 'electrical fragmentation' of the atria	Severe mitral valve disease and enlarged atria; multiple wavelets may be due to increased atrial size more than other factors	Increased left atrial size, P sinistro-atriale (double-notched P-wave)
AF due to one or a few re-entrant driver or drivers	'Focal' AF or re-entrant 'left atrial flutters after pulmonary vein isolation	'Coarse' AF, AF with distinguishable F-waves in the ECG. This AF type probably requires invasive diagnosis at present
AF in the elderly	Ultrastructural and structural alterations are a prominent cause	Advanced age

The disparate AF pathophysiologies suggest that the different forms of AF may require different treatment (see 'graded therapy'). AERP, atrial effective refractory period.

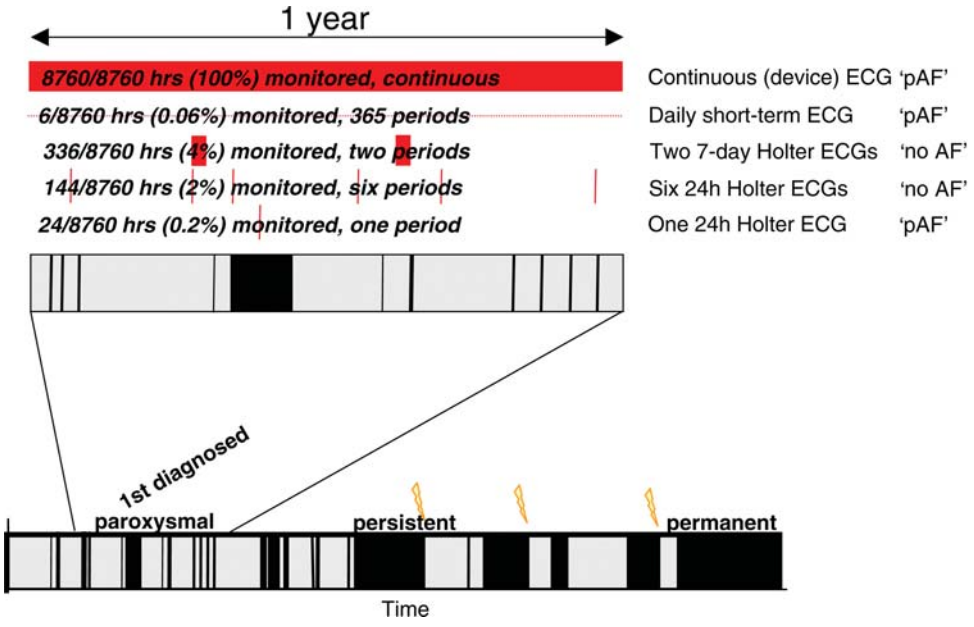

Figure 2 Efficacy of detecting paroxysmal atrial fibrillation (AF) and of assessing AF burden using a standard 24 h Holter ECG, two 7-day (144 h) Holter ECGs telemetric short-term ECG, and continuous (e.g. implantable) ECG monitoring devices in a 1 year period. The black bar on the bottom shows the biological sequence of periods of AF (black) and periods of sinus rhythm (grey). Monitored times are shown in red in each line. Longer ECG monitoring intervals will result better detection of silent AF.

Improving rhythm control and management

2a. Rhythm control monitoring

Does atrial fibrillation duration relate to outcomes?

Any arrhythmia that has the ECG criteria of AF and lasts for 30 s or longer is defined as AF.[4,25,49,50] Given the prevalence of asymptomatic AF epsiodes,[49–52] the risk of complications in paroxysmal AF,[50,53,54] and the technology used in published trials, this definition of AF is reasonable for clinical practice and as a starting point for further research.

Modern techniques for long-term ECG monitoring increase the sensitivity of detecting short AF episodes (*Figure 2*, Supplementary material online, *Table S3*).[50,51] Pacemaker monitoring of atrial rhythm suggests that only AF durations >5 min[55] or even longer[56–58] associate with cardiovascular complications. Further research is needed to better delineate the relevance of very short AF episodes for complications and quality of life. The unpredictable distribution of AF recurrences[49,50] renders such research cumbersome. Screening for asymptomatic AF in high-risk populations may allow identification of patients at risk for AF-related complications, such as stroke. Such patients may be candidates for antithrombitc therapy, or for early interventions to prevent recurrent AF.[59] These are important research areas that need clinical exploration.

2b. Rhythm control management

Antiarrhythmic drug therapy

Antiarrhythmic drug therapy will remain an important part of any rhythm control therapy.

Novel antiarrhythmic drugs

Existing antiarrhythmic ion channel blocking drugs approximately double sinus rhythm rates in controlled trials. Several novel antiarrhythmic agents are in late stages of clinical development.[20,60–62] These drugs should be monitored for their efficacy and safety using prospective registries. Other types of antiarrhythmic agents may become available based on novel targets such as connexins or newly identified ion channels.

In whom and when can antiarrhythmic drug therapy be discontinued?

Pathophysiological considerations such as the reversal of electrical remodelling after several weeks of sinus rhythm suggest that antiarrhythmic drug therapy can be confined to periods 'at high risk for AF recurrence'.[63,64] This can markedly reduce exposure to antiarrhythmic drugs.[65] In some patients, however, cessation of drug therapy may have unwanted effects.[66] Controlled trials on the effects of antiarrhythmic drug discontinuation could help determine the clinical applicability of these concepts.

Ablation in the left atrium for atrial fibrillation

Atrial fibrillation ablation is very effective in patients with 'lone' or 'focal', paroxysmal AF but can usually not 'cure' the arrhythmia (70–85% success rate and 1–3% severe complications[25,67]).

Improving feasibility and safety of pulmonary vein isolation

The pulmonary veins often do not remain isolated,[25,68,69] and linear left atrial lesions may not provide continuous conduction block.[70] Ongoing trials will test whether complete isolation of pulmonary veins is needed for AF suppression. In parallel with improved efficacy and durability of pulmonary vein isolation, the safety of the procedure requires improvement[25,67] (Supplementary material online, *Table S4*). Prospective registries with independent steering bodies and consecutive enrolment prior to the ablation procedure are needed to address complication rates of AF ablation in 'real life'.

Advancing ablation for atrial fibrillation beyond pulmonary vein isolation

Different additional ablation techniques have been advocated in patients in whom pulmonary vein isolation is not sufficient to maintain sinus rhythm. Despite small studies from single centres,[71–74] no technique is well-established.[25] There is an urgent need to evaluate the safety and efficacy of these techniques in controlled, multi-centre settings.

Do we understand what we ablate in the left atrium?

Experimental studies suggest that focal drivers of AF or stable or unstable re-entry circuits may reside in different critical regions of the atria including the pulmonary veins,[75] Bachmann's bundle,[76] the ligament of Marshall,[77–80] or the inferior septal right atrium.[81] The original surgical MAZE procedure did not intentionally isolate the pulmonary veins.[82] 'Standard' pulmonary vein isolation will destroy some parasympathetic ganglia.[83] Extrapolating from these examples, it is possible that the lesions used to isolate the pulmonary veins might also eliminate regions critical to other AF-maintaining mechanisms. Identifying critical regions for AF may be important for improvement of AF ablation, as has been shown in patients who present with left atrial flutters or focal left atrial tachycardias after pulmonary vein isolation for AF.

'Upstream therapy' interventions for primary prevention of atrial fibrillation

Blockade of the renin–angiotensin system can prevent AF in patients with structural heart disease,[46,84,85] patients with preserved systolic left ventricular function at risk for AF,[86] and patients with AF undergoing cardioversion,[87] but not in patients with 'lone' AF and well-controlled blood pressure (GISSI-AF[88]). The results of the ACTIVE-I[89] and ANTIPAF[90] trials on sartans in 'lone' AF will become available soon. Other 'upstream' therapies are less validated in controlled trials and require systematic testing.

Early initiation of rhythm control therapy

Atrial fibrillation is a chronically progressing arrhythmia in the vast majority of patients.[2,13,49,91] Early initiation of rhythm control therapy, i.e. in patients with a first documented AF episode, should be tested in controlled trials. Long-term follow-up would be necessary for such studies to detect a delay in AF progression.

Combining interventional and pharmacological treatments to improve rhythm control therapy

It is time to perform large, prospective, multi-centre trials of a comprehensive rhythm control strategy compared with standard care for AF patients. Several trials are either in their planning

phase or already under way. Such trials should apply long-term follow-up for relevant outcomes for AF (*Tables 1* and *2*).[49,50] Given the fact that AF is initiated and maintained by multiple mechanisms, a 'multimodal' antiarrhythmic therapy strategy will be needed in such trials.

Starting points for research:

(i) Any arrhythmia that fulfils conventional criteria of AF on an ECG and lasts longer than 30 s is defined as AF, which is reasonable when applied to standard ECG monitoring tools (short-term ECG) as it carries prognostic information in large outcome studies and surveys.
(ii) Improvement of symptoms and quality of life is at present the only accepted indication for maintenance of sinus rhythm in AF patients.
(iii) Catheter-based isolation of the pulmonary veins is an effective technique to prevent recurrent AF in patients with 'lone', paroxysmal AF. Pulmonary vein isolation should be attempted during the first ablation procedure.
(iv) Solid scientific data to perform more than pulmonary vein isolation routinely during the first ablation procedure is lacking. The optimal type of additional ablation is also not known.
(v) That maintenance of sinus rhythm can positively affect cardiovascular events in AF patients is supported by the recent report of the ATHENA trial[20] and by retrospective and *post hoc* analyses. This is also a persistent clinical perception despite the negative outcome of six trials using antiarrhythmic drugs to maintain sinus rhythm (PIAF, AFFIRM, RACE, STAF, HOT-CAFE, AF-CHF).[14–19]

Research perspectives:

(i) What are the distribution, duration, and frequency of episodes and the patterns of recurrence in AF patients? What is the impact of AF patterns on AF progression and outcome when standardized long-term ECG monitoring is applied?
(ii) What is the minimal AF duration that has a prognostic impact using modern, long-term ECG monitoring tools (pacemakers, ECG garments, or implanted devices)?
(iii) Does 'AF burden', measured as the number or duration of AF episodes, relate to complications of AF?
(iv) Can antiarrhythmic drug therapy be improved by developing safer and more effective antiarrhythmic agents and drug regimens that encompass defined therapy durations?
(v) Can AF ablation targeting the pulmonary veins be made safer and more standardized so that a widespread use of this intervention is possible in patients with 'focal AF'? This is one of the most important tasks at present and needs to be evaluated in large, prospective trials.
(vi) What are the mechanisms of recurrent AF after pulmonary vein isolation? Which therapy is adequate to treat recurrent AF after ablation?
(vii) Do 'extensive ablation' strategies involving either linear lesions, ablation of continuous fractionated electrograms, ablation of ganglionated plexus, or wide antrum pulmonary vein isolation encompassing larger parts of the left atrium result in different outcomes than repeat pulmonary vein isolation alone? This should be addressed in controlled, multi-centre trials.
(viii) Can cardiovascular outcomes be prevented by a combined treatment of concomitant diseases and targeted rhythm control interventions when compared with conventional care, or will such a therapy cause harm?
(ix) Could an early initiation of rhythm control therapy (drugs, ablation, and 'upstream therapy') result in a slower progression of AF and can, in the long term, AF-related complications be prevented by such a therapy?

Preventing atrial fibrillation-related complications

3a. Improving stroke prevention

How do we improve and define existing stroke risk stratification in atrial fibrillation?

The $CHADS_2$ score and related schemes are valuable and accepted in identifying patients at high risk for stroke and patients with a low risk.[92] Unfortunately, many AF patients are classified as 'intermediate risk', e.g. '$CHADS_2 = 1$' patients. The existing classifications therefore need refinement by better definition of existing and delineation of new 'stroke risk factors'.

Stroke events have been declining recently in AF populations.[93] Risk schemes need to recognize the impact of asymptomatic AF on thromboembolism.[49] This indicates a need for trials investigating the value of ECG screening in populations at high cardiovascular risk to initiate antithrombotic therapy upon diagnosis of 'silent' AF.

How to integrate bleeding risk assessment into thromboprophylaxis recommendations?

In the vast majority of AF patients, the risk-benefit ratio between bleeding and stroke is clearly in favour of antithrombotic therapy.[94,95] Bleeding risk assessment is imperfect at present,[96] and factors associated with bleeding largely overlap with stroke factors (Supplementary material online, *Table S5*). Furthermore, aspirin may increase bleeding risk to a similar extent as anticoagulation.[97] Variable INR values can in some patients be alleviated by low-level substitution of vitamin K or by considering a genetic predisposition to warfarin metabolism,[98] drug–drug interactions,[99] and altered drug excretion. These considerations warrant evaluation. To better understand factors associated with bleeding in AF patients, bleeding events should prospectively be collected and counted, e.g. using a modified International Society for Thrombosis and Haemostasis (ISTH) definition of bleeds.[100]

What is the best antithrombotic therapy in specific settings in atrial fibrillation patients?

Atrial fibrillation patients with concomitant coronary artery disease

Published case series in AF patients undergoing stenting support the use of short-term triple antithrombotic therapy,[101,102] but the optimal duration of such treatment remains uncertain. Similarly, a combination of anticoagulation with aspirin in patients with stable atherosclerotic disease is not based on solid data.[103–106] A consensus statement endorsed by three of the

branches of the ESC can be expected. Additional data from clinical trials and registries are needed.

'Bridging' of antithrombotic therapy in atrial fibrillation patients undergoing interventions

Current AF guidelines suggest that anticoagulation can be stopped for 1 week,[4] while other recommendations suggest a 'half-dose' bridging therapy with low-molecular heparin.[107] Some uncertainty also exists for the duration of anticoagulation in low-risk patients after AF ablation.[25,108]

Antithrombotic therapy in atrial fibrillation patients with an acute stroke

Systematic data on early anticoagulant therapy in acute stroke are needed. In this context, intensive monitoring and therapy initiation after a transient ischaemic attack[109] may be reasonable.

When is discontinuation of anticoagulant therapy appropriate?

At present, it appears likely that discontinuation of antithrombotic therapy in patients with AF and a risk for stroke will be confined to small, highly selected patient groups.[110]

Improving safety for and compliance with thromboprophylactic therapy

Discontinuation of anticoagulant therapy often happens in real life and in controlled trials[111] and is, in part, explainable by poor risk-benefit appreciation. Although ximelagatran was not superior in preventing strokes in AF patients when compared with warfarin,[112,113] newer, fix-dose anticoagulants may be helpful to improve 'time spent on adequate anticoagulation'. This area requires further research in 'real-life' conditions.

3b. Cardiovascular risk management in atrial fibrillation patients

Most patients with AF present with concomitant diseases and conditions that promote AF-related complications and can contribute to AF persistence (Supplementary material online, *Table S6*). Understanding the interplay of these factors with occurrence and recurrence of AF and its complications is an urgent issue for the management of AF patients.

Relevance of risk factors for atrial fibrillation progression

It is likely that adequate management of cardiovascular risk factors can prevent AF. One of the most pressing issues in this field is to systematically and prospectively obtain AF outcomes in intervention trials targeting cardiovascular risk. The group proposes ECG substudies in some of the ongoing large hypertension and/or heart failure trials by ECG, 24 h (Holter) ECG, and at times by implantable ECG recorders.

Comprehensive cardiovascular risk management in patients with atrial fibrillation

In many individuals, AF may actually represent an additional risk factor urging for more intensive risk management. This may apply to patients with mitral valve disease,[114–117] coronary artery disease,[115,117] hypertrophic cardiomyopathy,[118–120] reduced left ventricular function, and clinically detectable structural heart disease,[121] but also to arterial hypertension, obesity, sleep-apnoea, diabetes mellitus, chronic renal dysfunction, and other vascular disease.[91,117,122–124] Atrial fibrillation patients are at higher risk for cardiovascular events and should hence probably receive intensified risk management by lifestyle interventions and/or drugs.[125–128] This requires adequate clinical testing.

3c. Novel therapeutic goals

Using accepted outcomes in AF patients (*Table 1*),[49,50] studies have been disappointing in terms of demonstrating benefit of rhythm control. There has recently been a shift of concern from symptoms and rhythm to cardiac structure and function, other end organ damage (e.g. in the brain), and quality of life. We suggest potential novel therapeutic goals for evaluating AF therapy (*Table 2*).

Silent stroke, cognitive decline, and hippocampal atrophy are associated with AF,[129] and silent stroke is associated with cognitive decline[129] and a two-fold higher chance for developing dementia.[130] We recommend assessing silent stroke and cognitive decline associated with AF in ongoing rhythm control trials.

Quality of life is markedly impaired in AF patients, and even patients with 'asymptomatic' AF report lower quality of life compared with subjects in sinus rhythm.[129,131] We recommend the development of AF-specific instruments in combination with established methodology. It is noted that other instruments are already developed, e.g. SAGE (standard assessment of global activities in the elderly) which may assess social function in AF patients, possibly with slight adaptations for younger populations,[132–134] and other scores.

Avoidance of AF progression may be a therapeutic goal in itself given the difficulties in managing 'advanced' AF. This requires prospective testing.

Left ventricular function is an accepted surrogate outcome for cardiac complications.[49,50,71,72] Small changes in LV function may be measured by myocardial longitudinal velocities, strain, and the torsion of the left ventricle.[135]

Left atrial function preservation may be a therapeutic goal in AF. Left atrial function can be measured by Doppler (e/a waves) techniques,[136,137] by calculated parameters from left atrial volumes,[131,137] or from left atrial strain.[131,138]

A call for coordinated research

One of the great opportunities and, at the same time, challenges of a comprehensive research program is the possibility to perform studies that are linked, coordinated, and harmonized from the onset. Such coordinated research will facilitate patient recruitment, long-term follow-up, and health-economic analyses. If formal coordination cannot be achieved, a clear and unified definition of outcome parameters[49,50] and a unified scheme for patient characterization and assessment of relevant outcomes should be a minimum requirement for large-controlled trials in AF.

'Translation' of therapeutic concepts into clinical practice

Research to evaluate the 'translation' of new diagnostic and therapeutic recommendations into daily clinical practice is needed. In this regard, the organizing bodies of the 2nd AFNET/EHRA consensus conference have an important obligation. The effectiveness of such translation requires careful evaluation to identify optimal communication tools and incentives to make good therapy available to everyone.

Starting points for research:

(i) Preventing strokes is one of the most important clinical issues in AF patients. The $CHADS_2$ score and similar risk stratification schemes are adequate for the identification of patients at high and at low risk for stroke. Unfortunately, a large number of patients are currently classified as 'intermediate risk' for stroke, leaving physicians without clear guidance on antithrombotic management.
(ii) Prevention of strokes in patients with silent AF, whose first clinical manifestation of the arrhythmia is a stroke or a transient ischaemic attack, is an unresolved clinical problem.
(iii) Clinical risk factors for bleeding and stroke risk overlap to a relevant extent in AF patients.
(iv) An increasing number of AF patients at risk for stroke experience acute coronary syndromes or stent implantation, that, in principle, require combined anticoagulant and antiplatelet therapy. The optimal antithrombotic therapy in such patients is not known.
(v) Despite its proven net benefit on death and stroke, anticoagulation is underused, and when used, anticoagulants often result in patients being inadequately anticoagulated or over-anticoagulated.
(vi) In addition to established outcomes in AF patients, novel therapeutic goals may help identify subtle effects of rhythm control therapy.

Research perspectives:

(i) Are there any new risk factors for stroke in 'intermediate risk' patients (clinical parameters, biomarkers, or imaging markers) that can be identified in analysis of data bases from ongoing antithrombotic therapy trials in AF patients and validated in appropriate registries?
(ii) Can existing data bases be used to identify new clinical markers for bleeding risk?
(iii) What is the value of ECG screening in patients who would be candidates for anticoagulant therapy if AF was known?
(iv) What is the value of subsequent initiation of adequate AF management?
(v) Can intensified INR monitoring, genetic testing prior to initiation of vitamin K antagonist therapy, and low-dose supplementation of vitamin K improve efficacy and safety of anticoagulant therapy?
(vi) Can structured delivery of anticoagulant therapy and implementation of anticoagulation recommendations in managed health care settings improve the situation in comparison with standard care?
(vii) Can anticoagulants which are under clinical development improve anticoagulant therapy in AF patients?
(viii) Is dual or 'triple' antithrombotic therapy needed in AF patients undergoing special situations such as stent implantation or for 'bridging' therapy?
(ix) Is AF a 'cardiovascular risk factor' in addition to established cardiovascular risk factors?
(x) Does sinus rhythm carry benefits beyond the 'classical' outcome parameters death, stroke, quality of life, and left ventricular ejection fraction? New therapeutic goals that could measure effects of sinus rhythm maintenance may comprise, among others:
- Cognitive dysfunction as assessed by functional tests
- Silent strokes as assessed by magnetic resonance imaging
- Quality of life as assessed by social functioning
- Left atrial function and size as assessed by novel echocardiographic parameters.

Outlook: from 'rate vs. rhythm' to comprehensive management of atrial fibrillation

Therapy of AF patients is inadequate at present, with a high morbidity and mortality still assigned to AF. Many aspects of the current care for AF patients differentiate between treatment 'strategies' whose combination may, in many patients, achieve better outcomes. This idea applies foremost to the 'old' debate of 'rate vs. rhythm control' since rhythm control is generally added to underlying (continued) rate control therapy, but also applies to therapy of conditions that predispose to AF and contribute to cardiovascular complications including antithrombotic therapy to prevent strokes and prevention of heart failure and acute coronary syndromes ('comprehensive AF management'). The overall final conclusions of this conference are that:

(i) Atrial fibrillation is a rising epidemic and in almost all patients is a slowly progressing, chronic disease. Due to its consequences and complications, AF represents an unresolved population-based clinical problem in the 21st century.
(ii) The causes of AF and its consequences, including complications, are multifaceted.
(iii) Understanding the different pathophysiological processes that cause AF and its complications will help devise mechanism-based therapies.
(iv) Adequate therapy of AF will need to simultaneously address management of underlying and concomitant conditions, early and comprehensive rhythm control therapy, adequate control of ventricular rate and cardiac function, and continuous therapy to prevent AF-associated complications.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Appendix

The 2nd AFNET/EHRA consensus conference was a group exercise. Many of the concepts, observations, and hypotheses were

aired by participants of the conference. The authors of this paper are members of a 'writing group' that complied the main findings of the conference in a style suitable for publication. The organizers of the conference and the members of this 'writing group' would like to explicitly acknowledge the contributions of many other participants of the conference. Therefore, a list of all participants of the conference in alphabetical order is published here: Maurits Allessie; Dietrich Andresen; J.B.; Carina Blomstrom-Lundqvist; Martin Borggrefe; Gianluca Botto; Günter Breithardt; Michele Brignole; Martina Brückmann; Hugh Calkins; A. John Camm; Riccardo Cappato; Francisco G. Cosio; Harry J. Crijns; Hans-Christoph Diener; Dobromir Dobrev; Nils Edvardsson; Michael Ezekowitz; Thomas Fetsch; Robert Hatala; Karl Georg Häusler; Hein Heidbüchel; Andreas Heppel; Gerd Hindricks; Alexander Huemmer; Carsten Israel; Warren M. Jackman; Lars Joensson; Stefan Kääb; Otto Kamp; Lukas Kappenberger; In-Ha Kim; P.K.; Stefan Knecht; Karl-Heinz Kuck; Karl-Heinz Ladwig; Angelika Leute; Thorsten Lewalter; Gregory Y.H. Lip; João Melo; Jay O. Millerhagen; Lluís Mont; Stanley Nattel; Seah Nisam; Michael Oeff; Dieter Paar; Richard L. Page; Ursula Ravens; Ludger Rosin; Patrick Schauerte; Ulrich Schotten; Anna Schülke; Dipen Shah; Gerhard Steinbeck; Christoph Stoeppler; Ruth H. Strasser; Natalie Taylor; Jan G. P. Tijssen; András Treszl; Isabelle C. Van Gelder; Panagiotis E. Vardas; Albert Waldo; Karl Wegscheider; Thomas Weiß; Karl Werdan; Stephan Willems; Stefan N. Willich.

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