ESC European Society of Cardiology

Europace (2017) **0**, 1–13
doi:10.1093/europace/eux318

EHRA CONSENSUS STATEMENT

Integrating new approaches to atrial fibrillation management: the 6th AFNET/EHRA Consensus Conference

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Received 14 August 2017; editorial decision 11 September 2017; accepted 20 September 2017

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There are major challenges ahead for clinicians treating patients with atrial fibrillation (AF). The population with AF is expected to expand considerably and yet, apart from anticoagulation, therapies used in AF have not been shown to consistently impact on mortality or reduce adverse cardiovascular events. New approaches to AF management, including the use of novel technologies and structured, integrated care, have the potential to enhance clinical phenotyping or result in better treatment selection and stratified therapy. Here, we report the outcomes of the 6th Consensus Conference of the Atrial Fibrillation Network (AFNET) and the European Heart Rhythm Association (EHRA), held at the European Society of Cardiology Heart House in Sophia Antipolis, France, 17–19 January 2017. Sixty-two global specialists in AF and 13 industry partners met to develop innovative solutions based on new approaches to screening and diagnosis, enhancing integration of AF care, developing clinical pathways for treating complex patients, improving stroke prevention strategies, and better patient selection for heart rate and rhythm control. Ultimately, these approaches can lead to better outcomes for patients with AF.

Keywords Atrial fibrillation • Outcomes • Quality of care • Research • Rate control • Rhythm control • Catheter ablation • Anticoagulation • Bleeding • Research priorities • Technology • Stroke • Integrated care • Screening

Introduction

The predicted rise in both incidence and prevalence of atrial fibrillation (AF) presents an important health care challenge for cardiovascular and general clinicians.[1–4] However, it also offers an opportunity to integrate novel approaches and new technologies to improve patient outcomes. The diagnosis of AF encompasses a broad and heterogeneous group of pathologies,[5] and further classification of this condition based on underlying cause or the extent of atrial disease is likely to provide more personalized and effective treatments in the future.[1] The care of patients with AF can also be improved by applying structured and patient-centred management that integrates the expertise of different health care professionals.[6] Beyond better classification and quality of care, the most immediate advancement in AF management is to incorporate practical ideas, tools, and technologies into routine clinical practice. In particular, these approaches have the potential to (i) provide cost-efficient methods of detection and diagnosis, (ii) allow a platform for local integration of AF care, (iii) develop streamlined clinical pathways for treating complex patients, (iv) improve the benefit-to-risk ratio of stroke prevention strategies, (v) apply more personalized control of heart rate to increase patient well-being and function, and (vi) stratify the choice of rhythm control therapy to enhance treatment success in AF patients.

These issues were raised and discussed during the 6th Consensus Conference of the Atrial Fibrillation Network (AFNET) and the European Heart Rhythm Association (EHRA) in Sophia Antipolis, France (17–19 January 2017). Sixty-two specialists in AF attended from 15 member countries of the European Society of Cardiology (ESC), as well as from Australia, Canada, and the USA, in addition to 13 representatives from industry partners. The conference included multidisciplinary workshops on the key themes of the conference, with delegates obtaining consensus opinion within and across workshops with plenary feedback sessions and wide-ranging discussion. In this article, we report on the major outcomes of this conference and present consensus statements on the integration of new approaches to provide maximal benefit to AF patients and their healthcare teams.

Diagnosis and screening

Atrial fibrillation detection in an era of digital evolution

In this workshop, delegates considered the question of what should constitutes a diagnosis of AF, and whether AF detected by screening has the same therapeutic implication as randomized controlled trials where AF has presented clinically.

Electrocardiographic (ECG) demonstration of AF is a prerequisite before treatment for AF is initiated.[1] The easiest ECG methods to diagnose AF are the 12-lead and ambulatory ECG, but different types of medical technology to diagnose AF are now commonplace, including event recorders, real-time telemetry, and implantable loop recorders. The public also have a variety of options to measure heart rate and identify arrhythmias, including sphygmomanometers, handheld devices, smartphones, wearables, and health-related apps. As a consequence of the lower detection threshold, it is of great importance to evaluate the quality of rhythm monitors, their sensitivity, specificity, and cost-effectiveness and to develop strategies to interpret the findings. Furthermore, long-term monitoring of atrial rhythm may identify patients with very rare episodes of AF who have a different risk profile than patients who present with clinical AF, for whom currently available treatments have been evaluated. We defined the terminology of 'self-initiated rhythm monitoring' for those apparently healthy individuals who decide (for whatever reason) to use commercially available rhythm monitors, whereas 'AF detection, diagnosis, or screening' is usually used in patients at risk of AF and its complications.

Self-initiated heart rhythm monitoring

Medical practice is already transitioning from a profession that remedies acute illnesses to one that prevents disease, often in patients who do not feel acutely unwell. In AF, new technologies are now available that direct populations to seek medical advice based on detection from consumer electronics (*Table 1*). The hardware and algorithms used in these devices are highly variable,[17] validation may be less than for medical devices, and reproducibility could be reduced

Table 1 Overview of cardiac rhythm assessment available to the public for detecting AF

Method	Usage	Sensitivity/ specificity[a] (%)	Examples	References
Pulse wave-based methods to detect irregularity				
Pulse palpation (or heart auscultation)	Physical measure to detect pulse irregularity that can be used by medical professionals and the public	94/72	AF awareness campaign by British Heart Foundation	7
Photoplethysmography	Devices that use a light shining on skin and a photographic sensor. As well as pulse irregularity, can also detect pulse volume and include advanced algorithms to exclude ectopic beats. Sensitive to motion and may require more than one recording	97–100/92–94	Finger probe, smartphones, smart watches, and fitness bands.	8,9
Oscillometry	Devices that measure blood pressure and define the pulse waveform. Principally use irregularity and advanced algorithms to detect AF	92–100/90–97	Microlife BPA 200 (Plus) Omron M6 (comfort) Microlife WatchBP	10–13
ECG hand-held devices usually providing a single lead ECG				
On-device diagnostic algorithm	Devices that collect and some display a single-lead ECG rhythm strip in real time, can make a rhythm diagnosis on the device, and/or transmit to a website for physician or technologist reading. Use both rhythm irregularity and P-wave recognition (variable algorithms)	94–98/76–97	AliveCor (Kardia) heart monitor MyDiagnostick Omron HCG-801	12–15
Transmitted data devices	Devices that have no inbuilt diagnostics but transmit data to a website for either physician or technologist reading or a diagnostic algorithm	94–96/90–95	Merlin ECG event recorder Omron HCG-801 Zenicor EKG	12,16

[a]Mostly compared with 12-lead ECG interpretation by a cardiologist, based on published research studies in ideal situations. Note that some algorithms for AF detection are not publicly available and some commercially available devices have modified the algorithms that were tested in these studies.

in the hands of the consumer. This raises the problem of false positives, which may lead to anxiety for patients and costly additional testing with ECG recorders and echocardiography. Conversely, consumer devices can be helpful to highlight the possibility of paroxysmal AF and the need for further investigation (*Figure 1*).

As ECG-diagnosed AF is the preferred method to decide on treatment[1] (an enrolment criterion for all controlled trials of AF interventions), patients with potential AF detected on devices that do not provide an interpretable ECG rhythm strip should undergo further assessment of cardiovascular and stroke risk, with additional rhythm monitoring as clinically required. This can also apply to technology in use by medical professionals, for example atrial high-rate episodes (AHREs) detected on pacemakers.[18] The physician should decide the stringency of ECG-based rhythm diagnosis based on these factors. Although there are no data available to assist this decision as yet, it seems reasonable to only initiate further rhythm monitoring if the finding of AF would alter management, such as preventing thromboembolism or reducing the risk of other adverse outcomes.

Criteria for atrial fibrillation diagnosis and the impact of screening

Inclusion criteria regarding documentation of AF have varied in recent clinical trials. Although most trials required two ECGs with documentation of AF on separate days,[19–22] one recent trial required a history of AF of any duration recorded by any electrical tracing within the last 12 months[23] and another required symptomatic episodes with resting, ambulatory or trans-telephonic ECG within the last 4 weeks.[24] Such differences in the recording and documentation of AF may have an influence on the composition and generalizability of patient cohorts. The setting in which patients are selected for inclusion may also determine characteristics, including age and the risk of stroke or adverse cardiovascular events.[25,26] The yield from screening for AF will also depend on the underlying risk of incident AF[27] and the type of AF. For example, the probability that AF is detected by a short recording in patients with paroxysmal AF depends on the underlying burden. Thus, a screening programme that uses a single time point of detection will favour identification of persistent AF, while intermittent short recordings will identify additional patients with paroxysmal AF and a relatively high AF burden.[28,29] Conversely, devices capable of continuous atrial rhythm monitoring will identify many more people with short-duration AF episodes and low AF burden of relatively unknown clinical significance.

The impact of atrial fibrillation detection and stroke risk

A major question, as yet unanswered, is whether different modes of detection of AF and the resulting AF pattern and burden

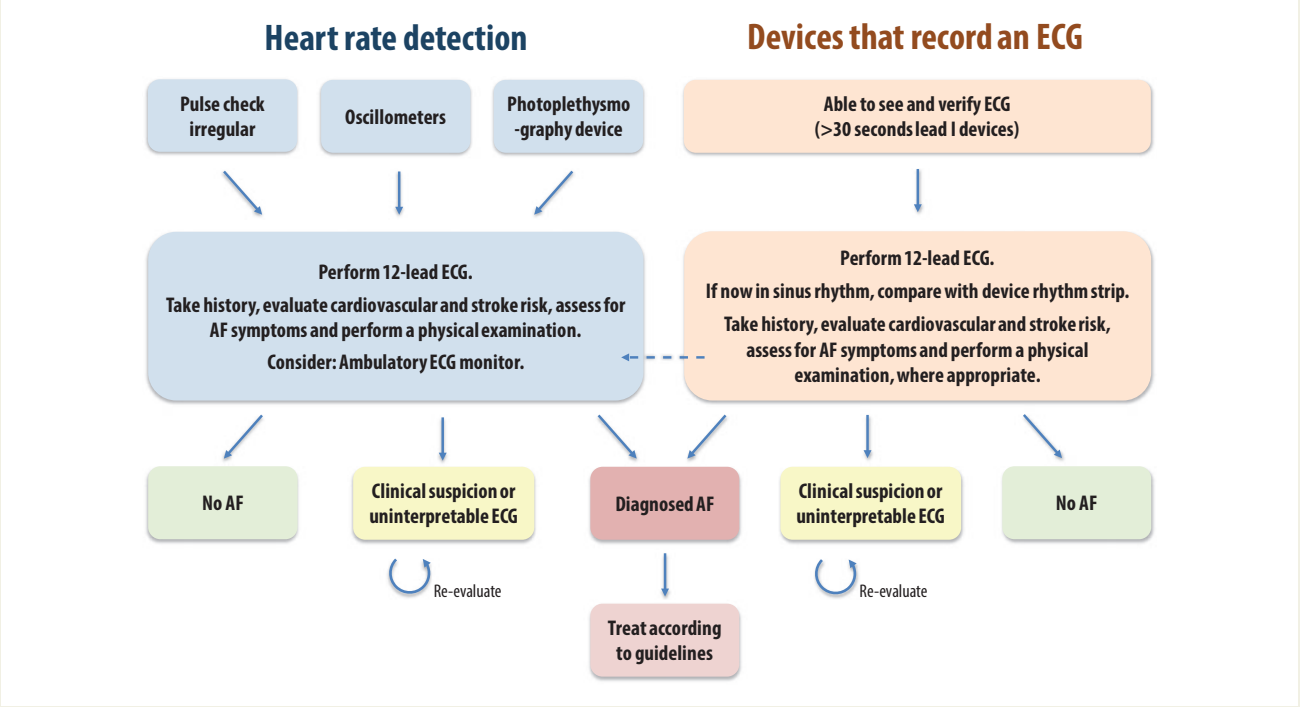

Figure 1 Clinical methods to deal with self-initiated rhythm monitoring by the general public.

identified have an implication on stroke risk and the need for anticoagulation. Screening programmes initiated within the health care system will tend to target those patients who have previously unidentified, mostly asymptomatic AF. On the contrary, AF detected by consumer devices will more often identify paroxysmal symptomatic AF which may, when detected or treated early during the course of disease, have a different risk of stroke and systemic embolism.[17,30–32]

The risk of stroke in a screened population can be enriched by requiring additional risk factors such as age and others, and the decision to anticoagulate will require consideration of the net clinical benefit of anticoagulation, taking into account the risk of stroke, major bleeding, and residual cardiovascular risk. Subclinical AF detected on implanted devices is also associated with elevated stroke risk.[32,33] In contrast, AHRE detected by implanted devices may not have the same prognostic impact for stroke as AF detected by ECG recordings, due to the low frequency, short duration of AHRE episodes, and the uncertainty with respect to their nature (AF or other arrhythmias). The stroke risk associated with AHREs is usually lower than for clinically detected AF, and absolute stroke rates with AHRE are often close to 1%, despite the presence of stroke risk factors.[18,34,35]

In summary, medical technologies provide exciting new options to diagnose and screen for AF (from the patient, health care, and societal perspectives). However, it is uncertain whether detection of atrial arrhythmias using these methods has the same implication as using conventional 12-lead ECG, or indeed those who present clinically with AF, particularly with regard to stroke risk and prevention. More studies are needed to investigate the potentially different AF disease states that are uncovered by the use of more advanced and continuous rhythm monitors.

Integrated care of atrial fibrillation patients

In this workshop, delegates were asked to consider how to develop integrated care models in AF, the challenges limiting dissemination, and how novel approaches could support further integration.

Definition of integrated care

Based on the World Health Organization definition of integrated care,[36] we defined this approach in AF as 'a coordinated patient-centred approach by interdisciplinary specialists to improve AF outcomes'. Integrated care enables treatment of AF patients in all five domains of management: acute stabilization, detection and management of underlying cardiovascular co-morbidities and risk factors, appropriate oral anticoagulation for stroke prevention, and treatment with rate and/or rhythm control therapy.[37,38] Electronic decision aids can be helpful for both the patient and the care provider, guiding the management team in clinical decision support, offering education, and measuring the effectiveness of treatment. *Figure 2* illustrates the concept of integrated, patient-centred AF care. A core team, for example an AF nurse and a cardiologist (or other physician who specializes in AF care), is supported by appropriate technology, and this team communicates with the patient and forms an intermediary with other health care professionals to co-ordinate optimal AF management.

Eligible patients and entry/exit criteria for integrated care

Ideally patients with newly diagnosed AF should have at least one appointment with the core team in an integrated care service, based

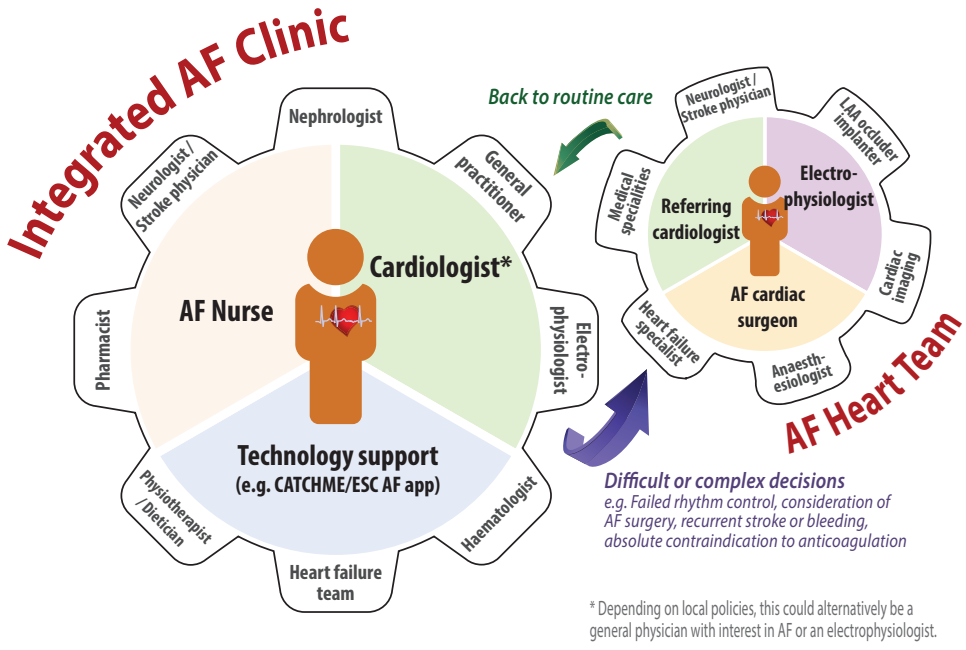

Figure 2 Integrated AF care and the AF Heart Team. An example of some of the members contributing to comprehensive and integrated AF care, and a rhythm control AF Heart Team.

in either the primary or secondary care setting. This will include a diagnostic assessment, discussion of treatment options, initiation of appropriate therapy according to guidelines, and tailored education and empowerment of the patient and caregiver.[1] Thereafter, stable and adequately managed patients can be followed up by supported self-management in the community. Criteria for another visit with the integrated AF team might include worsening of symptoms, hospitalization, stroke or bleeding complications, unstable situations (e.g. haemodynamic compromise or acute symptomatic arrhythmia recurrence), or suboptimal management. Conversely, empowered and educated patients who are clinically stable on fully established, guideline-based treatment with appropriate general practice support could take on their own management without further routine visits. Integrated AF care will take different shapes in different health care environments and will have to answer to challenges, including the extra time for patient interaction, the availability of treatment options to all patients, and the provision of technology support. Funding and reimbursement of integrated care is also dependent on local factors (particularly the provision of hospital and out-of-hospital specialist care), although integrated AF care may be a cost-effective solution to implement good AF management.[39]

Technology tools to ensure the success of integrated care

Although electronic health portals are now available in many countries, the availability of tools that apply to AF specifically is limited. Furthermore, electronic patient records are often owned by health care providers (e.g. hospitals or general practices) and not by patients. As part of the 2016 AF Guidelines, the ESC in collaboration with the CATCH ME consortium have developed smartphone and tablet apps for patients and health care professionals (freely available from Google Play, Amazon, and Apple Appstores).[40] The patient app offers information and education about AF, encourages active self-management, and also allows transfer of information to health care professionals. The health care professional app includes a patient register, in which risk factors, co-morbidities, and treatments can be prefilled by patients, and is designed as an interactive management tool incorporating the new ESC AF Guidelines. Other apps and websites are also available, for example educational aids available in numerous languages by cardiovascular and AF-specific charities such as the British Heart Foundation (https://www.bhf.org.uk/heart-health/conditions/atrial-fibrillation), the Atrial Fibrillation Association (www.heartrhythmalliance.org), and 'AFib Matters' by EHRA (http://www.afibmatters.org).

The Atrial Fibrillation Heart Team for complex management decisions

In this workshop, delegates were asked to propose practical measures and requirements for setting up local AF Heart Teams to support advanced AF management.

Patient selection

The AF Heart Team is proposed as a means to improve the care of selected and complex cases by providing specialist multidisciplinary input.[1] It is an adjunct to integrated AF care that provides a

comprehensive consideration of therapeutic options to patients who would benefit from such an approach (*Figure 2*). It is important to highlight that the AF Heart Team, while having an important role to support complex decision-making processes for difficult to manage patients with AF, is not required for the vast majority of AF management decisions. Complex AF patients are characterized by failure of first- and second-line therapies in the presence of severe AF-related symptoms, a high event rate, and often several coexisting co-morbidities. The two main areas where AF Heart Teams will be useful are:

(1) Complex rhythm control therapy, for example failure of catheter ablation to control symptomatic AF, consideration of AF surgery, or other situations that make rhythm control therapy difficult.
(2) Complex stroke prevention, for example patients with a relevant contraindication to anticoagulation or the need for left atrial appendage (LAA) exclusion, ligation, or clipping.

As different treatment modalities are evolving rapidly, the AF Heart Team offers such patients expertise from several specialities, with the ultimate goal of optimizing the use of available resources and improving the quality of care.[41]

Set-up and process

The constitution of this team depends on the local infrastructure. An interventional electrophysiologist would preferably be the leader of such a team, which also includes a 'fixed core' consisting of a general or referring cardiologist and a cardiac surgeon for a rhythm control AF Heart Team, and anticoagulation and stroke specialists for a stroke prevention AF Heart Team. Other specialists are invited as needed, such as anaesthesiologists and experts in cardiac imaging, among others (*Figure 2*). Once a patient has been discussed within the AF Heart Team and a strategy has been proposed, one member of the team should take responsibility for the proposed management and interact with the patient and referring physician. An AF Heart Team is preferably implemented by defining membership and responsibilities in advance. The team should meet—at least initially—on a regular basis, and close cooperation with other local heart teams will be useful. It is important to critically review and optimize locally available care pathways and design advanced treatment pathways, with the AF Heart Team defining referral pathways for internal and external caregivers (e.g. general practitioners and other local hospitals). The AF Heart Team should be an important driver of improving the quality and efficiency of care, including review of care pathways, and collation and reporting of data on local outcome and complications rates.

Stroke prevention

In this workshop, delegates were asked to consider the remaining barriers to stroke prevention, including the use of biomarkers to improve patient selection for anticoagulation, the available evidence for the safety of discontinuing anticoagulation after transient AF or AF ablation, how clinicians should manage anticoagulation after serious bleeding, and the role of LAA occluders in current clinical management.

Biomarkers to refine risk scores

Current clinical risk scores have only a modest predictive ability to define stroke and bleeding risk in individual patients and do not differentiate the severity of component risk factors. This leads to uncertainties of the benefit of stroke prevention treatment, most obvious when considering initiation of oral anticoagulation in patients at the lower end of the risk spectrum by clinical risk scores or in patients with bleeding complications on oral anticoagulation.[1] The digital era facilitates the calculation of risk based on continuous variables and more complex risk calculators on smartphones, computers, or with integration into electronic health records. Several biomarkers are linked with underlying pathophysiology and clinical outcomes, including markers of myocardial injury (troponins), cardiac stress and dysfunction [natriuretic peptides, growth differentiation factor (GDF) 15], myocardial fibrosis (galectin-3 and fibroblast growth factors), renal dysfunction (creatinine and cystatin C), inflammation (C-reactive protein and cytokines), and coagulation activity (D-dimer).[42] Risk scores combining clinical characteristics and biomarkers have recently been developed, validated (generally in anticoagulated populations), and compared with established clinical risk scores (such as CHA_2DS_2-VASc[43]). These biomarker risk scores include, among others, the ATRIA stroke risk score [The AnTicoagulation and Risk factors In Atrial Fibrillation; includes glomerular filtration rate (GFR)][44,45] and the ABC stroke score (Age, Biomarkers, Clinical history; includes troponin and NT-proBNP).[46,47] Biomarker-based risk scores for prediction of major bleeding in AF include ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; GFR < 60 mL/min and categorical cut-offs for haemoglobin or haematocrit)[48] and the ABC bleeding score (Age, Biomarkers, Clinical history; haemoglobin, troponin, and GDF-15 or GFR).[49] Two recent scores also include the estimation of composite outcomes using a multi-biomarker approach,[50,51] allowing clinicians to refine their assessment of balance between stroke and bleeding risk and thus potentially the net clinical benefit of stroke prevention therapies. This approach can avoid the overestimation of bleeding risk that can lead to inappropriate withholding of anticoagulation from suitable patients but is limited by the delay and practical difficulty of relying on biomarkers. The major evidence gaps for this approach at present are the cost-effectiveness and incremental precision of such scores, and the lack of prospective randomized trials to evaluate the use of risk scores on cardiovascular outcomes in AF patients. Properly validated and well-calibrated risk scores delivered by technology solutions may in the future prove useful to support more personalized approaches to anticoagulant therapy.

Safety of discontinuing anticoagulation in specific patient groups

Atrial fibrillation ablation is increasingly being used to treat symptomatic AF patients, with 1 year success rates of around 60–80% for paroxysmal AF and 50–70% for persistent AF.[52–55] Despite these reductions in recurrent AF, it is unclear whether ablation reduces the associated risk of stroke. Between 2% and 5% of patients per year will experience late recurrences of AF, and this seems to continue up to 5 years post-ablation and beyond.[54,56] The minimum amount of AF required to increase the risk of stroke is unknown, and the risk stratification schemes such as CHA_2DS_2-VASc do not take account

of AF burden, implying that even one episode of AF may carry the same stroke risk as recurrent or persistent AF. In the TRENDS study (Temporal Relationship of Atrial Tachyarrhythmias, Cerebrovascular Events, and Systemic Emboli Based on Stored Device Data), the risk of stroke increased two-fold in those patients with an atrial tachycardia/AF burden of >5.5 h in any 30 days window.[57] In the ASSERT trial (ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial), atrial arrhythmias detected within 90 days of pacemaker implant increased the risk of stroke, although the increase was smaller than for conventionally detected AF.[34] Further analysis of ASSERT showed that subclinical AF with a duration >24 h (but not less) was associated with increased risk of subsequent stroke or embolism (hazard ratio 3.24, 95% confidence interval 1.51–6.95).[32]

However, the absolute risk of stroke may still fall below the perceived threshold for anticoagulant treatment. In the ASSERT trial, the annualized risk of stroke reported for patients with brief occurrences of AF were only 0.28%, 0.70%, and 0.97% for patients with $CHADS_2$ scores of 1, 2 and >2, respectively.[38] Observational cohort studies have suggested a reduced risk of stroke after catheter ablation[58,59]; however, propensity matching cannot entirely account for patient selection bias.[60] Current guidelines recommend that even patients with 'successful' ablation should be treated with OAC according to underlying stroke risk.[1] These recommendations reflect the fact that recurrence is common post-AF ablation, recurrent AF is often asymptomatic, and patients accumulate stroke risk factors as they age. Further trials, such as OCEAN (Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial; NCT02168829) need to report their outcomes before this 'safety-first' practice can change. Similarly, the role of new digital technologies that can obtain frequent (or even continuous) rhythm monitoring needs to be studied in the context of stroke rates, also considering the low risk of major complications from contemporary oral anticoagulation.

Another important area where anticoagulation is often discontinued is 'reversible' or 'transient' AF, terms used to describe bouts of AF related to the postoperative state or an acute illness (e.g. sepsis or metabolic disturbances).[61,62] Although some patients may have truly self-limiting AF, many are at longer-term risk of AF recurrence (and therefore stroke).[63,64] This uncertainty has led to major variation in practice, with some advocating short-term anticoagulation (e.g. 3–6 months), followed by careful monitoring for recurrent AF and others recommending long-term anticoagulation for those with an elevated CHA_2DS_2-VASc score. Importantly, such patients were not specifically evaluated in the pivotal anticoagulation trials, and so further research is vital to address this major gap in evidence.

Anticoagulation after serious bleeding

Anticoagulants increase the risk of bleeding, and after minor bleeding events with a clear precipitating cause, oral anticoagulation should often be reinitiated once bleeding has been controlled.[1] More severe or life-threatening bleeding [e.g. intracranial haemorrhage (ICH)] requires cessation or even therapeutic 'reversal' of anticoagulation, with careful consideration about the risks and benefits of resumption. There is wide variation in clinical practice for whether or not to restart anticoagulation after ICH,[65] and patients who are reinitiated on anticoagulation seem to have better outcomes than those who are not.[66,67] Patients at highest risk of recurrent bleeding are often those at highest risk of thrombo-embolic stroke.[1] The risk of recurrent ICH can be stratified by ICH location (deep vs. lobar) and markers of small vessel disease. Cerebral amyloid angiopathy is associated with a high annual bleeding risk of around 10%.[68] Advances in cerebral imaging,[69] biomarkers and technology for AF screening all have the potential to clarify stroke and bleeding risk in individual patients.

Left atrial appendage occlusion

Exclusion of the LAA is now possible with percutaneous devices, although scientific evidence is mainly based on observational studies and registries, with just two randomized controlled trials of a single device compared with warfarin therapy.[70–72] The Watchman® device has been approved by the Food and Drug Administration (FDA) for patients with AF not related to heart valve disease, at an increased risk of stroke and suitable for warfarin but with an appropriate reason to seek a warfarin alternative. In a composite analysis, the device was associated with less haemorrhagic strokes and cardiovascular/unexplained death than warfarin, but there were more ischaemic strokes in the device group.[73] Unfortunately, there are no direct comparisons of occluder therapy and non-vitamin K antagonist oral anticoagulants, and no comparisons of occluders in patients deemed ineligible for anticoagulation. Left atrial appendage occluders are often used in AF patients who cannot be anticoagulated, a group with no other realistic treatments. Further information is needed about long-term efficacy, adverse events, and comparison with other stroke prevention strategies, such as thoracoscopic LAA exclusion. It is also unclear whether the results from one device can be extrapolated to the many others in development or what the minimal duration of antithrombotic therapy after LAA exclusion should be. Adequately powered controlled trials are urgently needed to inform the best use of these devices, and several such studies are under way.

Rate control therapy

In this workshop, delegates were asked to consider novel approaches to heart rate control, to define the gaps in current evidence, and consider the impact of new technologies on rate control in routine clinical practice.

When and how to use rate control therapy

Rate control is usually the first-line treatment strategy for patients with symptomatic AF[1] but has a relatively poor evidence-base.[74] There are also two major groups of patients in whom rate control is used even when a rhythm control strategy is attempted.[75] First, rate control should be background therapy for nearly all AF patients, because well-controlled heart rates are important during relapses of AF. Secondly, rate control is the therapy of choice to contain symptoms in patients for whom the risks of restoring sinus rhythm outweigh the benefits, or in those in whom advanced rhythm control fails.

The choice of rate-controlling drugs, alone or in combination, depends on symptoms, co-morbidities and potential side effects. Following the RACE II trial (RAte Control Efficacy in permanent atrial

Table 2 Tools to assess the effectiveness of rate control

Technology	Advantages	Limitations	Applicability to type of AF
Pulse palpation	Correlation to symptoms	Difficult to assess Inaccurate (pulse deficit)	All types
Standard 12-lead resting ECG (10 s)	Gold standard for AF diagnosis	No correlation to symptoms	Persistent and permanent
Exercise test	Heart rate dynamics	No validation for moderate exercise	Persistent and permanent
Ambulatory Holter ECG	Day and night heart rate dynamics Correlation with symptoms	Accurate correlation to symptoms needs patient education	All types of AF
External event recorder ±telemonitoring	Day and night heart rate dynamics Correlation with symptoms	Not widely available	All types of AF
Wearable heart rate monitors (smartphones, watches, and bands)	Correlation to symptoms Self-management and empowerment	Patient education essential Potential anxiety for patient Increased workload for physician	All types of AF
Wearable heart rate monitors (pulse detection)	Potential for wide use	Pulse wave only	All types of AF
Diagnostic functions available in implanted cardiac devices (pacemakers, implanted monitors, and defibrillators)	Day and night heart rate dynamics Correlation to symptoms	Cost of remote monitoring or hospital visits	All types of AF in patients with implanted devices

fibrillation II),[76] AF guidelines have adopted a lenient rate control strategy as the first-choice approach, with stricter control reserved for patients with persistent symptoms or deterioration in cardiac function.[1] Even in heart failure and reduced ejection fraction, control of heart rate with beta-blockers was not associated with mortality benefit in the subgroup of patients with AF,[77] in contrast to a marked benefit in women and men with sinus rhythm of all ages.[78] In the case of cardiac resynchronization therapy that necessitates continuous biventricular pacing, effective slowing of intrinsic AF is required to prevent adverse outcomes.[79]

New approaches to monitoring heart rate control

Table 2 lists the major approaches to assessing rate control, including novel methods such as wearable monitors and smartphone applications. Key differences are concerned with cost (to the patient and health care systems), the ability to correlate heart rate with symptoms and patient activity, and the capacity to measure AF burden. There are also multifaceted and contradictory patient effects; the ability to record and transmit an ECG will reassure many and underpin independent patients who 'own' their disease management but can also increase anxiety, generate a focus on numerical heart rate, and potentially lead to incorrect self-management. Each approach has specific limitations due to the type of technology (as discussed in the screening section), which need to be taken into account when clinicians appraise the results.

Gaps in knowledge for rate control

Unfortunately, there are many evidence gaps in rate control that affect clinical management of AF. We identified the key areas in need of further study:

- Optimal heart rate (rest and exercise) with respect to symptoms and outcomes and taking into account other comorbidities such as heart failure.[80]
- Selection of drugs and drug combinations in general, but also in specific patient groups, for example heart failure with preserved[81] or reduced systolic function[82] and pulmonary disease.[83]
- Parameters to assess the success of rate control and their association with prognosis (heart rate, symptoms, B-type natriuretic peptide, and others).
- Measurement of patient benefit, including AF-specific quality of life.[84]
- The role of irregularity (RR interval) vs. absolute heart rate and their correlation with symptoms and the effects of specific drugs on outcomes such as cardiac function.[85]
- Potential role for 'pill-in-the-pocket' approaches to rate control, similar to that used for flecainide and propafenone in rhythm control.

Approaches for rhythm control

In this workshop, delegates were asked to consider new paradigms for improving the success of rhythm control strategies, moving beyond the conventional time-based concept of AF classification.

Context and success of rhythm control

Rhythm control therapy is very effective in some patients, whereas others experience early, frustrating therapy failures despite concerted efforts to restore and maintain sinus rhythm.[1,86–89] Technical failure can contribute to recurrent AF (e.g. due to reconnection of isolated pulmonary veins[90]) or deterioration of associated conditions and should be reduced by structured and high-quality care.[6] Combining therapy modalities, making use of all rhythm control treatment options (antiarrhythmic drugs, catheter ablation and AF

Table 3 Clinical factors associated with atrial damage and a predisposition to AF

Coexisting risk factors	Drivers for AF
Heart failure/disease	Monogenic AF
Hypertension	Polygenic AF risk
Age	Atrial electrical foci
Diabetes mellitus	Inflammation (postoperative or inflammatory disease)
Stroke or transient ischaemic attack	Valvular heart disease
Kidney disease	Atrial ageing
Obesity	AF indicators
Sleep apnoea	Atrial high-rate episodes
Sedentary lifestyle, alcohol, smoking, and habitual vigorous exercise	Atrial runs or premature atrial complexes
AF-related symptoms	Atrial cardiomyopathies
Dyspnoea, lethargy, and palpitations	Biomarkers

surgery[1,91]) and involving patients in the care process[37,92] can help to manage expectations and maintain patient satisfaction. In the future, personalized implementation of different rhythm control therapy modalities may improve this situation.[5,93]

In addition, there is a growing realization that rhythm control interventions only target part of the relevant disease processes driving recurrent AF.[94] A variety of clinical conditions such as obesity, lack of exercise, hypertension, heart failure, and sleep apnoea have been associated with recurrent AF as well as with newly diagnosed AF.[95–99] Atrial damage caused by such factors can promote recurrent AF (*Table 3*). Atrial myocardium is affected by several cardiac and non-cardiac diseases or abnormalities.[100] Of note, atrial cells (cardiomyocytes, fibroblasts, endothelial cells, and neurons) react extensively to pathological stimuli,[100] and therefore atrial cardiomyopathies can contribute to arrhythmia occurrence.[101,102] These markers for atrial damage can be found by careful analysis of electrical atrial function[103,104] and/or by assessment of atrial structure and function.[105,106] Integrated AF care tackling these underlying conditions may have an important role in successful rhythm control therapy.[107]

Role of imaging to support rhythm control

AF development and the recurrence of AF following rhythm control are significantly related to left atrial (LA) substrate, including the extent of dilatation and fibrosis and the severity of dysfunction. These three parameters can be assessed and quantified using non-invasive imaging techniques, in addition to defining the pulmonary vein anatomy to support successful AF ablation (*Figure 3*). LA size is preferably measured as a volume using 3D imaging techniques, including 3D echocardiography, computed tomography (CT), or cardiac magnetic resonance (CMR) imaging. Due to differences between these imaging techniques and changes during the cardiac cycle, systematic use of the same technique and care with timing of volume assessment are required during follow-up.

In general, despite these limitations, LA dilatation has been associated with the development of AF and recurrence of AF after catheter ablation.[108] The extent of LA fibrosis is related to LA size, although small atria can still exhibit fibrosis and larger atria may not.[109] In a multicentre observational study, extensive LA fibrosis on CMR was associated with an AF recurrence rate of 51% almost 1 year after first catheter ablation compared to 15% in patients with the least fibrosis.[110] Echocardiography can also indirectly assess LA fibrosis, including integrated backscatter techniques and the time interval between the onset of the P-wave and atrial contraction measured with tissue Doppler imaging (TDI); both techniques are predictive of AF recurrence.[109,111,112]

The atria provide an important contribution to the performance of the heart[101,113] and serve as a volume reservoir to regulate ventricular filling and a booster pump in late diastole. Left atrial function is typically assessed by echocardiography using transmitral and pulmonary vein Doppler, TDI (active LA contraction reflected by the atrial velocity, *a'*) and volume-based measures.[114] Much of the information on LA function can also be derived from CMR and CT, but for practical reasons, echocardiography is mostly used in the clinical setting. Active deformation of the LA during the cardiac cycle can be assessed with strain imaging from 2D speckle-tracking echocardiography, with LA global strain identified as another important predictor of AF recurrence after catheter ablation.[115]

Atrial cardiomyopathy

A recent expert consensus described the concept of an atrial cardiomyopathy as 'any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations'.[105] Histopathological alterations reflecting such atrial cardiomyopathies are often not specific to the damaging factor and may also vary substantially over time.[116,117] Importantly, atrial cardiomyopathies with pathological or mechanical atrial alterations may exist in the absence of atrial arrhythmia or AF. Thus, these alterations may contribute to a 'pre-AF state' (*Figure 4*), which could include electrical irritability, structural changes and neurohormonal activation. Characterization of atrial pathology and imaging techniques, in particular, are of utmost importance, consistent with the observation that recurrent AF after catheter ablation seems to be higher in patients with signs of atrial cardiomyopathy.[118] Blood biomarkers (natriuretic peptides, galectin-3, and others[6]) or imaging of subtle cardiac dysfunction (e.g. cardiac strain) may be able to

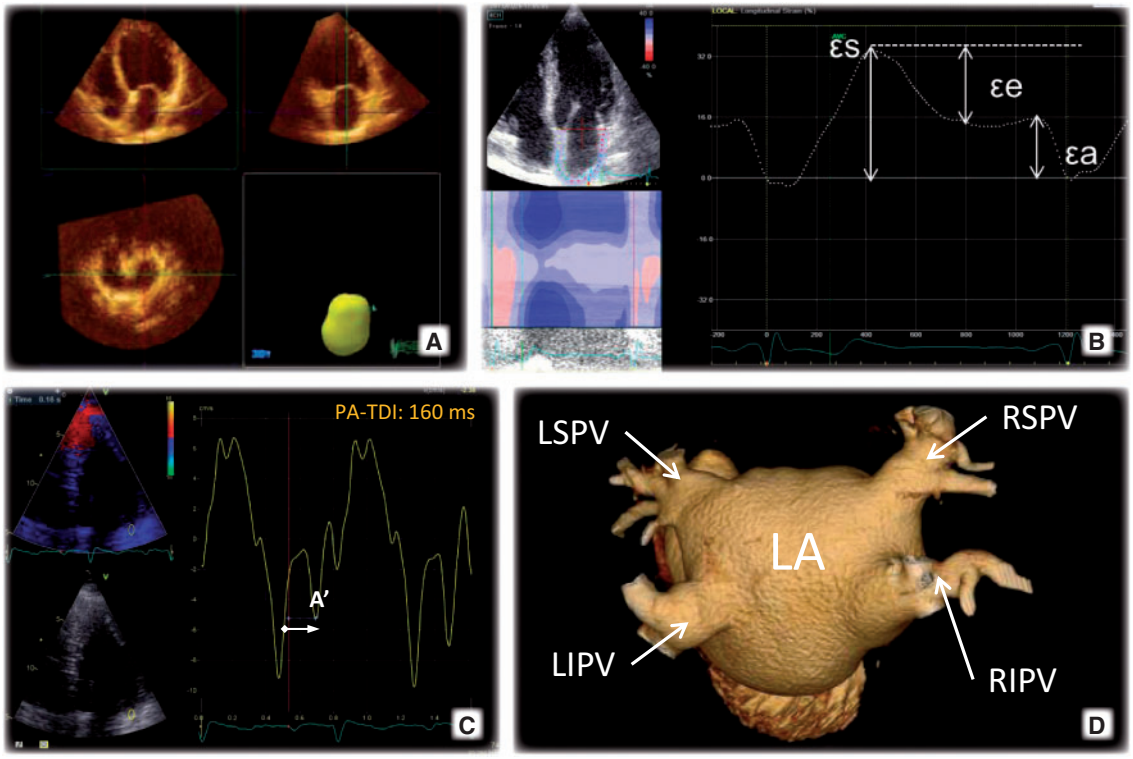

Figure 3 Multi-modality imaging to support rhythm control of AF. Assessment of left atrial volume (*A*) (real-time 3D transthoracic echocardiography), function (*B*) (2D speckle-tracking echocardiography, from which the longitudinal strain of the LA can be measured and the reservoir (εs), conduit (εe), and booster pump (εa) functions derived), fibrosis (*C*) (time interval between the onset of the P-wave and active atrial contraction measured with tissue Doppler imaging, PA-TDI), and pulmonary vein anatomy (*D*) (computed tomography). LA, left atrium; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

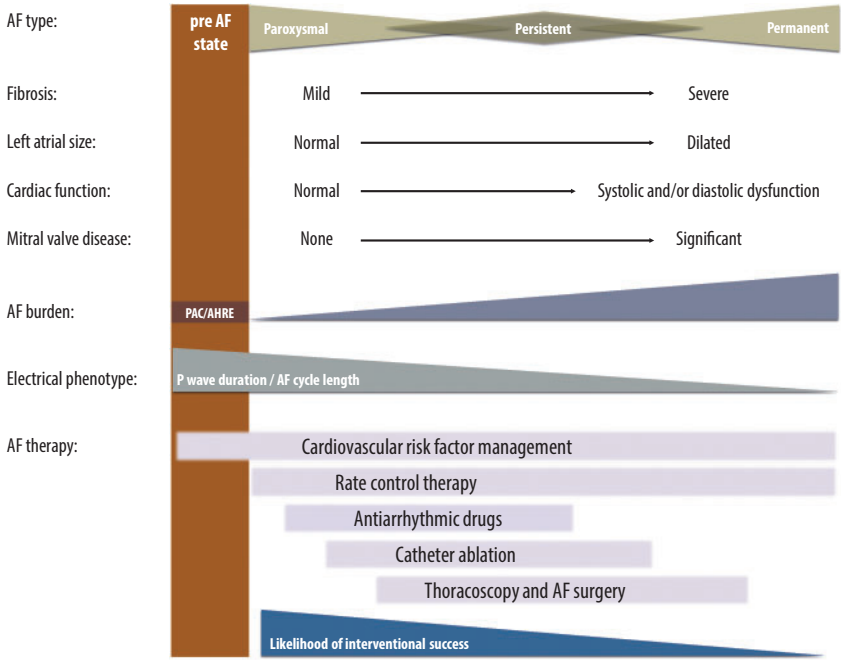

Figure 4 Pre-AF, atrial cardiomyopathy, and the spectrum of AF management. AHRE, atrial high rate episodes; PAC, premature atrial complex.

detect drivers or markers of atrial cardiomyopathic damage. The ultimate goal of these markers is to define different types of AF that are characterized by a specific pathophysiology which may warrant early aggressive intervention or will respond favourably to stratified therapy. This group feels that assessing and reversing the major factors damaging the atria in clinical practice would be an important step to underpin a more systematic approach to rhythm control therapy in AF patients. Providing this new approach is shown to be clinically effective, it would support the development of personalized rhythm control therapy and afford a pathway for improvement in clinical outcomes and patient well-being.

Conclusions

The 6th Consensus Conference of AFNET and the EHRA outlined a vision for future management that incorporates new approaches and novel technologies to improve outcomes for patients with AF. With large increases in the burden of AF expected in coming decades, better diagnosis, integration of care, patient involvement and stratification of treatment selection by a multidisciplinary AF team could help to offset the impact of AF on health care services.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

We wish to thank all participants of the 6th AFNET/EHRA consensus conference and especially the staff of AFNET, the EHRA, and the ESC for excellent organization of the conference.

Conflict of interest: a detailed list of disclosures of financial relations is provided in the Supplementary material online, Appendix.

Funding

The 6th AFNET/EHRA consensus conference was co-financed by AFNET and EHRA, and received additional financial support from the CATCH ME consortium (EU Horizon 2020 grant number 633196). Industry participants paid an attendance fee for the conference and provided an industry perspective during the discussions at the meeting but had no involvement in the writing process.

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