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TASK FORCE

Personalized management of atrial fibrillation: Proceedings from the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association consensus conference

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The management of atrial fibrillation (AF) has seen marked changes in past years, with the introduction of new oral anticoagulants, new antiarrhythmic drugs, and the emergence of catheter ablation as a common intervention for rhythm control. Furthermore, new technologies enhance our ability to detect AF. Most clinical management decisions in AF patients can be based on validated parameters that encompass type of presentation, clinical factors, electrocardiogram analysis, and cardiac imaging. Despite these advances, patients with AF are still at increased risk for death, stroke, heart failure, and hospitalizations. During the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association (AFNET/EHRA) consensus conference, we identified the following opportunities to personalize management of AF in a better manner with a view to improve outcomes by integrating atrial morphology and damage, brain imaging, information on genetic predisposition, systemic or local inflammation, and markers for cardiac strain. Each of these promising avenues requires validation in the context of existing risk factors in patients. More importantly, a new taxonomy of AF may be needed based on the pathophysiological type of AF to allow personalized management of AF to come to full fruition. Continued translational research efforts are needed to personalize management of this prevalent disease in a better manner. All the efforts are expected to improve the management of patients with AF based on personalized therapy.

Keywords Atrial fibrillation • Anticoagulation • Rhythm control • Rate control • Genetics • Biomarkers • Imaging • Personalised medicine • Electrocardiogram

Introduction

The management of atrial fibrillation (AF) is rapidly changing in many aspects: Until 2010, only vitamin K antagonists were available for effective prevention of AF-related strokes, but, based on large clinical trials,[1–3] three new, fixed-dose oral anticoagulants have been recently approved in Europe and in North America, and others are in late phase clinical development.[4] Rhythm control therapy has also developed rapidly, with better catheter ablation technologies and improved understanding of which patients are likely to benefit from this procedure.[5,6] Similarly, the role of new antiarrhythmic drugs in clinical practice has been defined in a better manner.[7–11] These developments will reshape the role of rhythm control therapy in the future. In addition, the technology for monitoring heart rhythm, and detecting arrhythmias, has increased considerably.[12–14] Recent genetic and pathophysiological studies have also added to our understanding of how, and in whom, AF may develop.[15–19] This pathophysiological insight still needs to be connected in a better manner with the management of patients with AF.

These developments are much needed, as patients with AF continue to be at high risk for cardiovascular complications, including ischaemic stroke which may occur even in the presence of adequate anticoagulation, frequent hospitalizations, and heart failure.[20] Furthermore, the death rate found in AF patients remains high even on optimal management,[1–3,8,21] especially cardiovascular death and sudden cardiac death.[22–24]

These new treatment options have spurred updates and/or rewrites of clinical AF management guidelines in the USA (where two updates were published in 2011[25,26]), in Canada (where a new set of guidelines was published in 2012[27]), and in Europe (where a focused update was released in 2012[28]), all with overlapping recommendations.[29]

Further improvements in management of AF patients are likely to require a personalized management targeted at individual pathophysiology, clinical risk, and predisposition. Such a personalized AF management approach requires careful case-by-case assessment of the causes and consequences of AF, based on information which can be collected through history taking, risk scores, the electrocardiogram (ECG), imaging of heart and brain, and analysis of blood and DNA (*Figure 1*). The current and future possibilities for personalized AF management were discussed in detail during the fourth Atrial Fibrillation competence NETwork/European Heart Rhythm Association (AFNET/EHRA) consensus conference. Here, we report the outcome of this conference, highlighting current knowledge of different factors which could facilitate personalized AF therapy, and providing suggestions on how new information on such factors can be integrated to personalize management of AF in a better manner.

The document covers five domains which could be useful to personalize AF management, namely:

- Clinical presentation and risk factors
- ECG as a tool
- Imaging of the brain
- Imaging of the heart
- Blood-based biomarkers.

Clinical presentation and risk factors: the current approach to 'personalise' atrial fibrillation management

The care of each patient with AF will depend upon how the patient presents, the medical history and treatment, and the presence or absence of an identifiable precipitant. Further refinements of the management plan will be based on ECG, cardiac and brain imaging, and laboratory findings to ensure optimal therapy based on individual needs (*Figure 2*).

Patient presentation

The presentation of the patient markedly influences acute and chronic management. An important step is to determine whether restoration of sinus rhythm is urgent or not. Myocardial ischaemia,

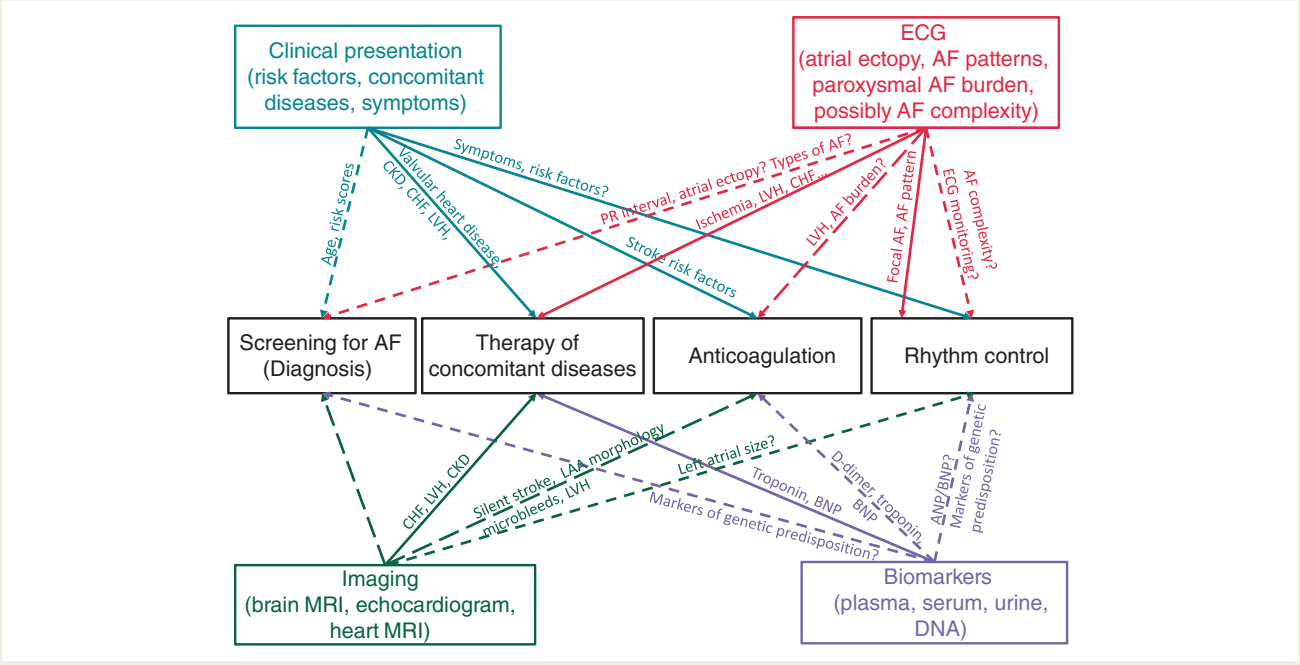

Figure 1 Different types of information, gained from clinical assessment (upper left, turquoise), ECG (upper right, red), blood-based biomarkers (lower right, purple), and imaging (lower left, green) which may be useful to personalize AF management. The black boxes in the middle portion of the diagram illustrate different management domains which may be informed by different measures.

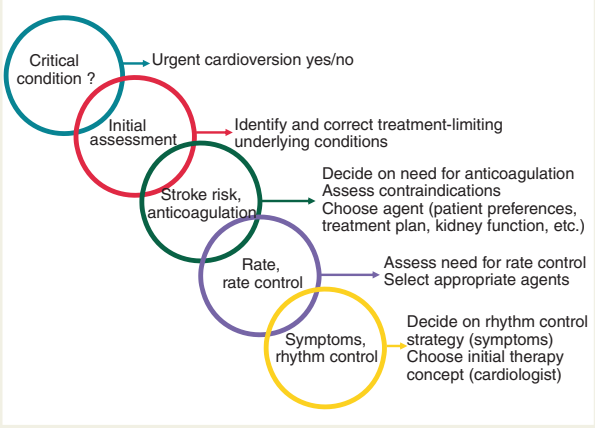

Figure 2 Current approach to stepwise decision making in patients with AF.

haemodynamic instability, or presence of an accessory bypass tract with rapid conduction call for rapid restoration of sinus rhythm and guide the choice of rate control agents. Electrical cardioversion is the most effective method to quickly restore sinus rhythm. Pharmacological conversion has the advantage of simple administration and can be effective in patients with recent-onset AF, especially lasting $<$48 h. Most patients will present in a stable clinical condition, where more time can and should be spent to assess the clinical situation comprehensively. Also, at this stage, blood cell count, electrolytes, serum creatinine, and thyroid stimulating hormone are often analysed. The ECG that led to the diagnosis of AF will be studied for QT interval, heart rate, PR interval if in sinus rhythm, QRS duration, signs of left ventricular hypertrophy (LVH), ischaemia or infarction, and evidence for electrical and other cardiomyopathies. An echocardiogram should be performed to assess LV and valvular function. Uncontrolled hypertension, ischaemia, acute respiratory decompensation, or thyrotoxicosis should be addressed prior to restoring sinus rhythm. Most patients do not need imaging of the coronary arteries. Such tests, similar to all diagnostic procedures, should only be used when management decisions depend on the results.

Anticoagulant therapy

A set of simple clinical risk factors, e.g. summarized in the CHA_2DS_2-VASc score, is used to decide on anticoagulation therapy. Patients with none of these risk factors do not require long-term anticoagulation. All others are at risk for stroke, and those with a previous stroke, age $\geq$75 years, or two or more stroke risk factors should receive long-term oral anticoagulation.[29] Many patients carrying only one of the CHA2DS2VASc factors are also likely to benefit from anticoagulation,[28,30] which will generally convey a net clinical benefit.[31–33] Patients in AF of $>$24–48 h or uncertain duration are in need of immediate initiation of anticoagulation. In patients who present with a stroke, consulting a neurologist is advised particularly to determine when anticoagulation can be started safely,[34] a decision which should consider findings of brain imaging indicating individual risk of bleeding. The decision to anticoagulate must be reassessed during follow-up, but most patients will benefit from long-term anticoagulation.[29] Nevertheless, oral anticoagulation can cause bleeding, whose most feared form is intracerebral haemorrhage. Apart from intracranial haemorrhages, most bleeds can be managed. Although tools to

predict overall bleeding risk exist (e.g. HAS-BLED), we cannot predict intracerebral haemorrhage: Bleeding scores (and stroke risk scores) are associated to some extent with intracranial bleeding as well.[35] While suboptimal international normalised ratio (INR) control increases the risk for intracerebral haemorrhage, most events occur during therapeutic INR levels.[36] The perception of frailty, which is not easily clinically quantifiable,[37] is often cited as a reason for withholding anticoagulation.[38] It is not known whether the balance of strokes and bleeding is really different in frail patients or in those with multiple bleeding risk factors. A prior intracerebral bleed is possibly the best indicator for an individual risk for such events. More research is needed to determine whether individual factors predispose some patients to intracranial haemorrhages sufficiently to justify personalized anticoagulation.

While new oral anticoagulants appear preferable to vitamin K antagonists in patients at increased perceived risk for bleeding,[29,30] clinical conditions, e.g. chronic kidney disease or the presence of valvular AF, may limit their use.

Rate control

Almost all patients are in need of rate control therapy. The acute decision is based on symptoms and on ventricular rate (as determined by the ECG). At resting heart rates >100–110 beats per minute, rate control therapy is required. The choice of rate controlling agent will depend on symptoms and patient factors.[39] In the rare situation when the ventricular rate is not rapid, concomitant atrioventricular (AV) node disease or the use of medication which slows AV nodal or His Purkinje system conduction should be sought.

Restoration and maintenance of sinus rhythm

If cardioversion has not already been performed, rhythm control should be considered in patients who are currently symptomatic.[29,39,40] Symptom assessment will need further review over time as symptoms will vary, and simple scores (e.g. EHRA score) have been proposed for this assessment.[39,41] Depending on the degree of symptoms and patient preference, an initial attempt to control symptoms by rate control is warranted.[29,39] In recent-onset and tolerated AF, spontaneous conversion can be awaited. Sinus rhythm can be restored by pharmacological cardioversion[9,42–44] or by electrical cardioversion,[44,45] which again can be facilitated by pretreatment with an antiarrhythmic drug.[10] In addition, the long-term plan with respect to antiarrhythmic drug treatment will influence the choice of antiarrhythmic drug used acutely. Choosing an antiarrhythmic drug critically relies on knowledge about the presence of structural heart disease, especially heart failure, LV dysfunction or hypertrophy, and coronary artery disease.[29] Furthermore, a detailed analysis of the ECG will guide this decision (e.g. QT interval, QRS duration, and others[46,47]). Prior to administering an antiarrhythmic drug, effective rate control should usually be in place. In addition, patients should avoid vigorous exercise during a recurrence of AF. This is more important for antiarrhythmic drugs which have little intrinsic rate controlling properties (especially flecainide). Infrequent tolerated recurrences of AF can be managed with a 'pill-in-the-pocket' treatment.[28,42] In patients with paroxysmal AF and without structural heart disease, catheter ablation can be considered as an early treatment option.[5,28,48]

Our consensus is that all AF patients should be seen by a cardiologist to review management.[24,49,50] Emerging data suggest that nurse-led AF management centres could help implement and adapt personalized AF management based on clinical information in a better manner.[51,52]

The electrocardiogram as a tool to personalize atrial fibrillation management

An ECG is required for diagnosing AF. The ECG is a non-invasive, well-standardized, and cost-effective diagnostic tool which provides ample information not only about the heart rhythm but also about the presence of concomitant heart disease.

The electrocardiogram during sinus rhythm

The ECG may show signs of concomitant heart disease, such as LVH, conduction disease (AV block), possible heart failure (e.g. bundle branch block), myocardial ischaemia (ST-T segment changes), or inherited cardiomyopathies including channelopathies. Such disease states may guide the selection of antiarrhythmic drugs (e.g. quinidine in Brugada syndrome or sodium channel blockers in patients with long QT3), and even affect decisions related to anticoagulation (e.g. hypertrophic cardiomyopathy). Safety information such as rate during AF, or QT interval, is often used in clinical practice to decide on rate control and rhythm control drugs. Information on atrial activation, found within the signal-averaged 'high resolution' P-wave, has been used to predict progression of paroxysmal to persistent AF[53] and is also associated with incident and recurrent AF.[54–57] Owing to the limited and conflicting data on the predictive performance and utility of signal-averaged ECG, their use in clinical practice is not established.

Atrial fibrillation patterns and 'silent atrial fibrillation'

Different patterns of AF (paroxysmal vs. persistent and other chronic forms) generally carry a similar risk for subsequent stroke.[41,58,59] Indeed, it is recommended that healthcare providers actively search for an irregular rhythm in all persons over 65 years of age to detect 'silent' AF which would be an indication for oral anticoagulation.[29] In the future, personal, easy-to-use and/or miniaturized ECG monitors are likely to advance detection of asymptomatic AF episodes, allowing for earlier initiation of anticoagulation therapy.[12–14,60,61] Even patients who only present with frequent atrial ectopy seem to have an increased risk of subsequent AF and stroke.[62,63] In population-based samples, a long PR interval in sinus rhythm identifies patients at increased risk for AF and ischaemic stroke.[15,64] Prolonged ECG monitoring to detect 'silent AF' could be useful in patients at risk for AF-related stroke who have frequent atrial ectopy and/or a prolonged PR interval, but that would need prospective validation.

Electrocardiogram monitoring may also help to identify the best candidates for catheter ablation. Patients with paroxysmal AF are compared with those in persistent AF.[5] Of patients with paroxysmal AF, those with frequent but short-lasting episodes of AF or repetitive atrial ectopy ('focally induced AF', see *Table 1* and[65]) are regarded as optimal ablation candidates. In the future, assessment of activation patterns during AF may further help to personalize the decision for or against catheter ablation of AF.

Long-term rhythm monitoring and atrial fibrillation burden

Technological advances allow heart rhythm monitoring for an extended time, and provide semi-automated means to detect 'atrial high rate episodes' which often correspond to paroxysms of AF. Patients presenting with such atrial high rate episodes as detected by pacemakers are at increased risk for stroke[12] and should be considered as candidates for anticoagulation once the presence of AF has been verified (see *Figure 2*[66]). Ongoing trials such as IMPACT (NCT00559988[67]), possibly CRYSTAL-AF (NCT00924638[68]), and others, will inform whether patients with atrial high rate episodes or paroxysmal AF with a low burden have a similar stroke risk as other AF patients. Future trials may determine whether such patients benefit from early initiation of anticoagulation. At present, anticoagulation should not be stopped based on apparent rhythm, unless compelling reasons prevail.

While patient-operated ECG monitors have been used extensively to detect asymptomatic 'rhythm outcomes' in AF trials,[10,41,69–72] ongoing trials such as EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial, www.easttrial.org, NCT01288352[21]) use personal ECG monitors to adapt rhythm control interventions earlier than usual. Such trials are expected to determine whether systematic ECG monitoring can be used to personalize rhythm control therapy.

Complexity of atrial fibrillation

It has been suggested that patients with AF who show a coarse appearance on the ECG are more likely to maintain sinus rhythm than patients with fine AF. Direct electrographic contact mapping studies in patients undergoing open chest surgery have demonstrated that a progressive structural remodelling process during AF or triggered by structural heart disease itself results in an increased incidence of conduction block and a higher number and smaller size of separate fibrillation waves.[73,74] Enhanced complexity of AF is regarded as an important driver for maintenance of AF in structurally remodelled atria.[75–77] New insight in AF mechanisms and duration might come from advanced signal analysis processing of the ECG during fibrillation. Such a classification of AF based on electrical complexity might influence the decision to restore sinus rhythm based on expected chances to maintain sinus rhythm in the long term.

The complexity of the AF activation pattern may also be indirectly measured by F-wave morphology in the surface ECG. Prior studies used 12-lead ECGs or Holter recordings (see *Table* in Schotten *et al.*[78]). More importantly, they differ largely in the mathematical technique which was used for complexity computation. Both time domain (F-wave analysis, principal component analysis, and sample entropy) and frequency domain (dominant frequency, organization index of power spectrum, and spectral entropy) parameters were used. Also, the clinical setting or the research question investigated varied widely. The diversity of the studied technical approaches and patient populations limits the comparability of these investigations. Clearly, there is an urgent need to standardize measurement techniques, signal processing, and mathematical techniques.[78,79] The prediction performance of the 12-lead ECG can possibly be improved in the future by adding spatial information from body surface potential maps[79–82] or by using transoesophageal ECGs.

In summary, assessing the electrical complexity of AF may help to personalize antiarrhythmic drug therapy and especially the decision for catheter ablation. Possibly, the ablation strategy could also be influenced by ECG analysis in the future. This requires evaluation in clinical trials assessing electrical complexity of AF through intracardiac recordings and/or through surface ECG recordings.

Imaging of the brain for personalized atrial fibrillation management

Brain imaging, particularly magnetic resonance imaging (MRI), has the unique potential to provide information about cerebrovascular disease, including silent brain infarction, white matter hyperintensities, and cerebral microbleeds. This information may help to tailor individual treatment decisions on anticoagulation by improving estimation of the individual risks for intracerebral haemorrhage and (recurrent) ischaemic stroke. Despite the promise of MRI in this context, there is little information on the prognostic value of brain MRI in AF patients. Indeed, outside research studies, brain MRI is often only obtained when a stroke is suspected, limiting the available information in general AF patients.

'Silent' cerebral embolic lesions are abnormalities consistent with cerebral infarction detected by brain imaging without any matching clinical stroke or transient ischaemic attack (TIA). Silent cerebral embolic lesions, also referred to as silent brain infarcts, can be found in 8–28% of the general population by MRI, more often in elderly patients and those with arterial hypertension.[83] They may be cortical or subcortical; subcortical infarcts include those compatible with a previous acute small deep brain infarct or haemorrhage in the territory of a single perforating arteriole, and are termed 'lacunes'.

Atrial fibrillation was an independent risk factor for silent cerebral embolic lesions in the Framingham Offspring study,[84] but available data are not consistent.[83] Generally, it has not been studied how many patients with silent brain infarcts suffer from 'silent', paroxysmal AF.[40] According to small case series using MRI, 32–75% of AF patients have silent brain infarctions,[85,86] most of which are likely to occur secondary to small vessel disease (see below) and may not actually be due to AF. Conversely, such lesions are frequently found by MRI after left atrial catheter ablation for symptomatic AF.[87] Initial data suggest that there may even be a cognitive decline after catheter ablation,[88] however, the clinical significance of these lesions is uncertain.[89]

In the general population, so called 'silent' brain infarcts are likely to cumulatively cause subtle physical and cognitive deficits: they are associated with a two- to four-fold increase of future clinically clinical strokes, worsening of cognitive function, dementia, and death.[90,91] In

the European Atrial Fibrillation Trial (EAFT), stroke patients with additional silent brain infarcts had a non-significant increased risk of further ischaemic strokes.[92] However, the available data cannot currently determine whether optimal treatment of AF may reduce the burden of silent brain infarcts. While there is growing evidence that AF *per se* and AF-related stroke are associated with cognitive decline and dementia,[93–95] there is a need for adequate longitudinal MRI studies to determine the association between silent brain infarcts and or white matter lesions (see below) and cognitive decline in AF patients. Prospective MRI studies may also help to clarify the mechanisms of ablation-related silent ischaemic strokes, and assist in defining the optimal anticoagulant regime during ablation procedures.

White matter hyperintensities

White matter hyperintensities of presumed vascular origin (also termed white matter lesions or white matter changes) are common in elderly populations. They are associated with other forms of cerebrovascular disease and vascular risk factors. White matter hyperintensities are associated with subtle neurological dysfunction, namely gait, incontinence, and cognitive decline.[64] Both periventricular[96] and deep white matter hyperintensities[86] have been associated with AF, even though they may have different pathogenic mechanisms. Atrial fibrillation may theoretically cause white matter hyperintensities, largely by causing emboli to subcortical white matter, but the pathogenesis is complex, probably multifactorial, and poorly understood. The pathological substrate may include myelin loss, axon loss, a mild gliosis, microinfarction, and dilation of perivascular spaces.[97–99] Nevertheless, if cardiac embolism or hypoperfusion contribute to their development, at least some white matter hyperintensities may be preventable by anticoagulation or rhythm control therapy. White matter hyperintensities in MRI correspond to white matter hypoattenuation on computed tomography scans (sometimes termed leukoaraisosis), which are associated with a substantial increased risk of bleeding on oral anticoagulants.[100]

Cerebral microbleeds

T2*-gradient echo and susceptibility-weighted MR imaging allows detection of cerebral microbleeds: small, rounded, homogeneous, hypointense lesions, not seen with conventional spin echo sequences.[101] Cerebral microbleeds correspond to small collections of blood-breakdown products adjacent to small vessels,[102] providing direct evidence of cerebral blood leakage from pathologically fragile small vessels which are then 'sealed off', thus not causing obvious clinical symptoms. Cerebral microbleeds are associated with intracerebral haemorrhage, especially in patients receiving anticoagulants.[103] Around 10–20% of stroke-free AF patients may have cerebral microbleeds,[104,105] and up to 30% of AF patients with a prior stroke show such lesions. The majority of these AF patients are still likely to benefit from anticoagulation, but cerebral microbleeds may identify a subgroup at higher risk of intracerebral haemorrhage. A recent systematic review found that while overall stroke risk seems doubled in patients with microbleeds, the risk for intracerebral haemorrhage increased up to eight-fold, potentially tipping the balance away from net clinical benefit for anticoagulation in some patients.[106] However, whether these results can be generalized to other populations, and whether such patients would fare better on alternative stroke prevention strategies, e.g. new oral anticoagulants or left atrial appendage closure,[107,108] should be studied further.[109] Further data are also needed to determine whether cerebral microbleeds are relevant for future stroke risk in the large population of patients without recent clinical ischaemic stroke or TIA.

Taken together, the available data suggest promise for brain MRI to help tailor individual treatment decisions on anticoagulation in AF patients in specific situations. However, large prospective studies using serial MRI measurements in AF patients are needed to support this assumption. The present knowledge does not support the unselected or serial use of MRI to guide stroke prevention in AF patients.

Imaging of the heart for personalized atrial fibrillation management

M-mode and two-dimensional echocardiography (2D-echo) are the most useful techniques to analyse cardiac structures to exclude structural heart disease and to measure atrial size.[110] In recent years, technological developments in echocardiography such as 3D imaging and new cardiac imaging techniques (mainly MRI) have been proposed to inform stroke prevention and rhythm control therapy in AF patients in a better manner.

Refining stroke risk by imaging

Valvular heart disease and hypertrophic cardiomyopathy

The presence of structural heart disease increases stroke risk: AF patients with mitral valve stenosis or those after mitral valve surgery have an extremely high stroke risk, as well as hypertrophic cardiomyopathy.[111,112] These entities are therefore defined as 'valvular AF' and 'AF with hypertrophic cardiomyopathy' in current guidelines.[27,28,39] Mitral valve stenosis is best assessed by 3D-echo, whereas 2D-echo and MRI provide the most accurate information in hypertrophic cardiomyopathy.

Left ventricular hypertrophy

In general populations, LVH has been associated with an increased risk of stroke in the Framingham and Copenhagen cohorts.[113,114] Furthermore, regression of LVH on imaging reduces stroke risk.[115,116] In the general population, LVH can be considered as an integral estimate for duration and severity of hypertension, possibly explaining these associations in part: in patients with AF, LVH increases stroke risk, but not as an independent predictor.[117] One small case-controlled study ($n = 165$) showed that LV mass is associated with left atrial thrombus.[118] In summary, LVH is often viewed as a useful indicator for stroke risk, illustrated by its use as an inclusion criterion in recent trials such as EAST (www.easttrial.org, NCT01288352[20]), however, large datasets to validate this perception are lacking.

Left ventricular dysfunction

Reduced systolic LV function is associated with stroke in AF patients.[119] This is reflected in current stroke risk scores. While there is no good evidence for this, it seems likely that more severe LV dysfunction is associated with a higher stroke risk. While most information is available from heart failure patients with reduced left ventricular function (HFrEF[120]), stroke risk may also be increased

in patients with newly diagnosed heart failure,[121] and in those suffering from heart failure and preserved ejection fraction (HFpEF,[122,123]). Left ventricular function is traditionally expressed as LV ejection fraction, which can be assessed by all imaging techniques, including echocardiography, (ECG-gated) nuclear imaging, MRI, and computed tomography. The most accurate technique for assessment of LV ejection fraction is currently MRI.[124] However, newer techniques are being developed for assessment of LV function, particularly strain imaging with echocardiography[125] or MRI[124] which permits quantification of active deformation in the LV.

Enlargement of the left atrium and left atrial appendage morphology is associated with a higher risk for stroke and death in epidemiological studies.[126,127] An enlarged left atrium has been used as an enrolment criterion, e.g. in the ATHENA trial.[8] Left atrial enlargement can be measured in M-mode, two-dimensionally, or as volume.[110,128,129] For more accurate assessment of left atrial size, volumes are preferred over dimensions. The imaging techniques of choice for left atrial volumes are 3D-echo and MRI; 3D echocardiographic measurements have better agreement with MRI (which is considered the gold standard) than 2D measurements, whereas reproducibility of left atrial volume measurements by MRI are superior over echocardiography.[130] In AF patients, an enlarged left atrium is associated with stroke risk, but is not an independent predictor on multivariate analysis.[117,119] The morphology of the left atrium can also be adequately assessed with 3D imaging using echocardiography or MRI. One study suggested that a 'chicken wing' morphology of the left atrial appendage is associated with fewer strokes compared with cactus, windsock, or cauliflower shapes.[131] This finding requires confirmation. Overall, the independent contribution of left atrial size and appendage morphology to stroke risk seems rather small.

Left atrial spontaneous contrast and left atrial appendage thrombi are related to stroke and can be assessed with echocardiography, MRI, and computed tomography. Left atrial function may also be related to stroke risk and can be assessed from echocardiography by pulsed-wave Doppler imaging assessing the velocity, but more precise assessment of left atrial function may be derived from 3D-echo or left atrial strain imaging.[132] Left atrial appendage function is also important in the risk of stroke and can be derived from transoesophageal echocardiography assessing left atrial appendage emptying velocity.

Imaging to guide rhythm control therapy

Structural heart disease, such as hypertensive cardiomyopathy, LV systolic dysfunction, or valvular heart disease, is associated with higher rates of recurrent AF. Personalized management of AF calls for careful assessment and treatment of accompanying diseases to improve overall risk (see above) and rhythm control maintenance.

An enlarged left atrium may predict recurrent AF after cardioversion and after catheter ablation.[133–135] Left atrial size regresses when sinus rhythm is successfully restored and maintained,[136–138] possibly visualizing decreased left atrial wall stress which also translates to reduced atrial natriuretic peptide (ANP) levels (see below). Of note, similar regressions of left atrial size are also found in hypertensive patients on therapy.[139–141] Possibly comparable with its effect on stroke risk prediction, left atrial size does not show an independent effect on recurrent AF in larger series.[10,128] In summary, left atrial size most probably reflects the effect of chronic haemodynamic stress to the atrium,[65,141–143] comparable to the relation between LVH and arterial hypertension and pressure load.

Reduced left atrial function may be more important in prediction of AF recurrence, and can be measured by echocardiography using 3D imaging or strain measurements. Patients with reverse left atrial remodelling after ablation showed reduced left atrial strain prior to ablation,[144] but larger datasets are needed to assess the value of atrial strain to predict absence of AF after ablation.

Prolongation of atrial activation time, measured as the interval between the onset of the P-wave on the ECG and the time of active contraction of the left atrium on tissue Doppler imaging (P-TDI[145–147]), may help to identify patients at high risk for development of AF, e.g. those in heart failure, but further studies are needed to validate this parameter as an independent predictor of incident or recurrent AF in larger populations. P-tissue Doppler imaging seems an attractive tool to personalize rhythm control therapy as it can be readily assessed using standard echocardiographic equipment.

Persistent delayed enhancement in the left atrium (at times termed 'left atrial fibrosis') is technically difficult to assess due to thin atrial walls. Specialized centres have reported that contrast-enhanced left atrial MRI imaging could allow the quantification of left atrial damage which may relate to recurrent AF after catheter ablation.[148–151] Others have confirmed that MRI can visualize atrial catheter ablation lines,[152,153] and one study even suggested that gaps in prior ablation lines could be seen by MRI.[154] Furthermore, it is likely that atrial damage precedes AF and facilitates its occurrence. Such atrial damage, e.g. detected by MRI, could identify patients at risk for developing AF in the future. While promising, the existing observations clearly require replication by other investigators, including multicentre settings, and application to non-ablated AF patient cohorts and patients at risk for AF. (*Table 1*).

Blood biomarkers for personalized atrial fibrillation management

Clinical AF management already relies on a stratification of patients based on clinical presentation, clinical risk scores, and ECG-based parameters, often supplemented by imaging of the heart (*Figure 1*). More complex clinical scoring systems based on multivariate modelling have been tried and resulted in higher *c* statistics, but appear less practical for everyday use. When used in conjunction with clinical risk markers, blood- or urine-based biomarkers could further personalize AF management in the future. Furthermore, such biomarkers provide an opportunity to validate the activation of signalling pathways which are relevant to AF in patients, where direct access to atrial tissue remains limited. This may, in the future, allow to identify patients who are likely to benefit from specific therapies (*Table 2*).

Blood-based biomarkers to refine anticoagulation therapy

Clinical practice guidelines largely agree that most patients with AF are in need of oral anticoagulation,[27,28] limiting the usefulness of further biomarkers to those patients in whom this general decision is in doubt. Recent guidelines of the European Society of Cardiology have pioneered the paradigm change away from identification of patients at high risk for stroke towards identification of patients

Table 1 AFNET/EHRA classification of clinical types of AF

AF type	Clinical presentation	Possible pathophysiology
Defined types of AF		
Monogenic AF	AF in patients with inherited cardiomyopathies including channelopathies	The arrhythmogenic mechanisms conveying sudden death in these diseases also contribute to the occurrence of atrial fibrillation
Focally induced AF	Patients with repetitive atrial runs and frequent, short episodes of paroxysmal atrial fibrillation. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, and/or atrial tachycardia deteriorating in AF	Localized triggers, in most cases originating from the pulmonary veins, initiate AF. AF due to one or a few re-entrant drivers is also considered to be part of this type of AF
Post-operative AF	Atrial fibrillation occurring after cardiac/pulmonary surgery in patients who were in sinus rhythm before surgery and had no prior history of AF	Acute factors: inflammation, surgical trauma, high sympathetic tone, electrolyte changes, and volume overload, potentially interacting with a chronic predisposition
Complex types of AF[a]		
Valvular AF	Atrial fibrillation manifesting before senescence (e.g. $<$80 years) in patients with mitral stenosis or patients after mitral valve surgery	Left atrial pressure (stenosis) and volume (regurgitation) load contributes to atrial enlargement and structural atrial damage in these patients
AF in the elderly	AF which first manifests at an age $\geq$80 years	Ageing of the atria (possibly including 'accelerated ageing'), interstitial fibrotic infiltration, loss of cardiomyocytes, increased arterial and myocardial stiffness contribute to this type of AF
Polygenic AF	This type of AF is defined by the presence of common gene variants which are associated with early onset AF in the population	Currently under study, possibly including shortening of the left atrial action potential and/or left atrial cardiomyocytes with abnormal automaticity
Unclassified AF	AF which does not fulfil any of the other definitions. These forms of AF may be rather common, illustrating the need for a better classification	Shortening of atrial refractoriness (e.g. tachycardia-induced atrial remodelling or enhanced parasympathetic tone) or localized conduction disturbances due to atrial fibrosis induced by structural heart disease may contribute to this type of AF

This preliminary distinction between different types of AF could provide a step towards a taxonomy of AF. We propose that each patient should be assigned to only one of these types of AF. Modified from Kirchhof *et al.*[210] The table also illustrates the current difficulty in classifying AF and substantiates the need to improve our understanding of the arrhythmia.
[a]Complex types of AF may show overlapping mechanisms of AF.

without relevant stroke risk who may not require anticoagulation.[27,38] Hence, oral anticoagulation is considered the default therapy for almost all patients with AF.[155] Still, there is insufficient information on optimal stroke prevention therapy in patients at relatively low stroke risk, e.g. patients with a CHA_2DS_2VASc score of 1.[28] Other patient groups who may benefit from more personalized anticoagulation management are patients with an increased risk of bleeding complications and patients with an ischaemic stroke on well-managed anticoagulant therapy (1.5% per year in recent trials). Various blood-based biomarkers have been proposed to refine stroke risk estimation.

Prothrombotic or hypercoagulable state markers are biologically plausible biomarkers for ischaemic stroke risk as they reflect activation of the systemic clotting system.[156] These biomarkers are influenced by the use of oral anticoagulants.[157] In the general population, high D-dimer levels are associated with an increased risk of stroke.[158] In AF patients, high levels of fibrin, D-dimer, and von-Willebrand factor may identify patients at higher risk for stroke, both in non-anticoagulated patients,[159–161] and—albeit at lower absolute levels[162]—in anticoagulated patients.[163,164] It remains to be established, as also seen in left atrial size, whether these parameters really add to carefully collected information on clinical risk factors and anticoagulation control, and whether the effects of different prothrombotic mechanisms could be integrated into a single measure.

Blood markers for cardiac damage or strain may be useful to refine stroke risk: In a recent subanalysis of anticoagulated participants in the RE-LY trial, elevated levels of high-sensitive troponin-T and brain natriuretic peptide (NT-proBNP) increased the risk for stroke and death,[165,166] and may help to identify patients who benefit from oral anticoagulation in historic cohorts.[167] Elevated troponin-T and interleukin-6 are also associated with death and stroke in anticoagulated AF patients.[168] These markers could reflect either 'structural damage' in the atria, or quantify the extent of concomitant cardiac and vascular disease.

Genetic markers for stroke and bleeding

Genetically determined cardiomyopathies can confer a risk for stroke: observational data demonstrate that hypertrophic cardiomyopathy carries a high stroke risk.[111,112] More recently, large genome-wide association studies found that the same genetic markers (e.g. on chromosomes 4q25 and 16q22) are associated with both stroke and AF.[16,169] Furthermore, genetic alterations in the VKORC1 and CYP2C9 genes are associated with lower maintenance doses of warfarin, leading to a higher risk for overdosing and bleeding events.[170] It remains to be tested whether measuring these polymorphisms to guide vitamin K antagonist therapy can improve outcomes, as simple dosing rules may already improve the time in therapeutic range.[171] Apo-E polymorphisms have varying associations with intracerebral haemorrhage, but other genes may be more closely associated with these events,[172] specifically markers for amyloid angiopathy.[173,174] Further genetic analyses specifically targeting

prediction of intracranial haemorrhage on anticoagulants are currently underway.[175]

Increased serum creatinine levels and estimated glomerular filtration rates

Chronic kidney disease, estimated from serum creatinine, is associated with an increased risk for stroke, bleeding, myocardial infarction, and death in epidemiological analyses[176,177] and in AF patients with or without anticoagulation.[176,178,179] While data from one of the large anticoagulation trials have suggested that chronic kidney disease could be a novel risk factor for stroke in anticoagulated AF patients,[179,180] other analyses in cohorts which are closer to real-world practice suggest that chronic kidney disease is not an independent predictor of stroke in AF.[181,182] This is perhaps not surprising in

Table 2 Current stratification (teal) and potential future personalization (red) of AF management

Clinically used stratification	Future perspectives for personalization	Clinical	ECG	Imaging	Blood
Age		X			
	Genetic predisposition for polygenic AF				X
Hypertrophic cardiomyopathy	Signs for inherited cardiomypathies (including electrical cardiomyopathies)	X	X	B	X
AF pattern	Duration of AF ('early AF' vs. later stages)	X	X		
Prior stroke	Silent brain lesions	X		B	
	Cognitive decline (neuropsychological testing, clinical assessment)	X			
History of bleeding	Brain imaging (MRI) for microbleeds	X		B	
Valvular heart disease		X		H	
Left ventricular dysfunction	Markers of cardiac strain (troponins, possibly BNP)	X		H	X
Left ventricular hypertrophy			X	X	X
Hypertension	Current/average blood pressure	X			
Diabetes	(including severity of disease)	X			X
	Chronic kidney disease				X
Haemodynamic instability		X			
EHRA score		X			
P-wave duration, fine vs. coarse AF	P-TDI interval (in sinus rhythm)		X	H	
	AF complexity (during AF)		X		
	Left atrial size			H	
	Left atrial (appendage) morphology			H	
	Left atrial structure (including detection of left atrial enhancement)			H	
	Natriuretic peptides and other markers of cardiac strain				X
	Markers of inflammation, e.g. in patients undergoing open heart surgery				X

Here, we provide a list of the information which is currently used to stratify AF management (first column, teal), and perspectives to personalize management (second column, red) by emerging markers. The four rightmost columns indicate the techniques to assess these markers.
AF, atrial fibrillation; ECG, electrocardiogram; MRI, magnetic resonance imaging; H, heart; B, brain.

light of the complex interaction between reduced kidney function and several of the established stroke risk factors, e.g. age, diabetes, vascular disease, heart failure, or hypertension.

Irrespective of its disputed value as a risk marker for stroke, there is an important interaction between reduced kidney function and elimination of the new oral anticoagulants which illustrates the need to assess kidney function for personalized anticoagulant therapy.[27,33]

Blood-based biomarkers to predict recurrent atrial fibrillation

Many biomarkers, e.g. of inflammation, cardiac load, damage, or kidney function, interact in a complex fashion with clinical risk factors for AF (e.g. diabetes, vascular disease, hypertension, or heart failure) which will affect the time course of AF. Careful validation is required to control for such interactions.

Natriuretic peptide elevation[183,184] may identify patients at risk for incident or recurrent AF[185–187] and relate to recurrent AF after catheter ablation.[188] Natriuretic peptides are mainly produced in atrial tissue. Supraventricular tachycardias (probably including AF) markedly increase ANP and NT-proBNP levels.[189,190] Conversely, ANP and NT-proBNP decrease immediately[191,192] and mid-term[193] after successful rhythm control therapy. In view of the large proportion of undiagnosed AF episodes, it could be speculated—without current proof—that elevated ANP or NT-proBNP levels identify patients with a higher AF burden, in addition to reflecting patients with more severe structural heart disease.

Inflammatory markers

Although the contribution of the atria to the circulating pool of markers of extracellular matrix turnover is bound to be small, an association between these markers and AF persistence or recurrence after ablation has been documented by some small studies.[194–197] The causal role of inflammation in structural atrial damage has been reinforced by experimental studies.[198–200] In one meta-analysis, statins seemed to prevent post-operative AF potentially via their anti-inflammatory effects.[201] Blood markers of inflammation (C-reactive protein[202,203]) and oxidative stress[204,205] may indeed be associated with recurrent AF, especially after cardiac surgery. This is currently tested in the large randomized Statin Therapy In Cardiac Surgery (STICS) trial (NCT 01573143). The effect of statins is much less well-established in other types of AF with different underlying pathophysiology (*Table 2*).

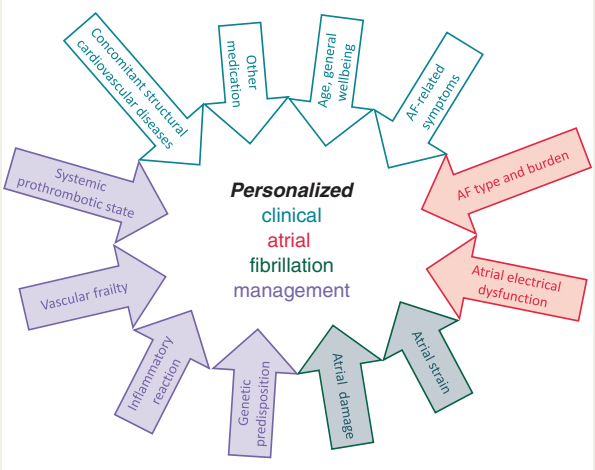

Figure 3 Relevant information on atrial, cardiac, and systemic processes, including genetic predisposition, which can help personalize management of atrial fibrillation in the near future, pending validation of the proposed measurements.

Unsaturated fatty acids

A recent report has linked higher circulating total long-chain n-3 polyunsaturated fatty acids (PUFA) and docosahexaenoic acid levels with a lower risk of incident AF in older subjects,[206] but n-3 PUFA supplementation does not prevent AF in clinical trials,[207–209] suggesting that low PUFA levels and AF are two effects of an unknown cause.

Chronic kidney disease may be associated with incident AF,[210] again reinforcing the usefulness of serum creatinine to personalize AF management, and possibly illustrating the complex and important interaction between chronic kidney disease and structural damage to the heart.

Genetic markers for atrial fibrillation

The discovery of genes involved in familial forms of AF has provided insights on the molecular mechanisms of this arrhythmia and potential biomarkers for identification of individuals at risk of developing AF. One small group of patients with early onset AF suffer from arrhythmogenic cardiomyopathies, often with Mendelian inheritance, such as Brugada syndrome, hypertrophic cardiomyopathy, or long QT syndrome ('monogenic AF',[211] *Table 1*). These patients can be identified by ECG and imaging, and require treatment of the underlying inherited cardiomyopathy.

Gene polymorphisms associated with an increased risk of AF in the population suggest that subtle alterations in developmental factors, cell signalling, extracellular matrix regulation, and ion channel function predispose to AF (e.g. close to the PITX2 gene on chromosome 4q25, and close to the ZFHX3 gene on chromosome 16q22).[212] Indeed, the same genetic variants on chromosome 4q25 identify patients at increased risk for recurrent AF on antiarrhythmic drugs, after catheter ablation, and after open heart surgery in several medium-sized cohorts.[213–216] Further understanding of the physiology which links these genetic predispositions to AF is needed,[18,217,218] but it seems reasonable to assume that assessing a combination of these predisposing genetic alterations could help to inform management of—especially young—patients with AF in the mid-term future, including specific antiarrhythmic drug selection. Recent data furthermore suggest that genetic variants in the ß1 adrenoreceptor influence the drug dose for adequate rate control therapy.[219] While this information provides promising avenues for further research, it remains to be tested whether 'genetic AF recurrence risk' can personalize rhythm control therapy.[215,216]

Summary

Most clinical management decisions in AF patients can be based on validated parameters which encompass type of the presentation, clinical factors, ECG analysis, and cardiac imaging. Emerging markers may allow a more personalized management, e.g. by selecting an

anticoagulant or rhythm control therapy, by integrating emerging information such as atrial morphology and damage, brain imaging, genetic predisposition, systemic or local inflammation, and markers for cardiac strain (*Figure 3*). Each of these promising avenues requires validation in the context of existing risk factors in patients. More importantly, a new taxonomy of AF may be needed based on the pathophysiological type of AF (*Table 1*) to allow personalized management of AF to come to full fruition. It is obvious that continued translational clinical research efforts are needed to personalize management of this prevalent disease in a better manner. All the ongoing efforts are expected to improve the complex management of patients with AF, translating into much needed better outcomes, based on personalized management decisions.

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