Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options

Executive summary* of the report from the 3rd AFNET/EHRA consensus conference

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Summary

There are exciting new developments in several areas of atrial fibrillation (AF) management that carry the hope of improving outcomes in AF patients. This paper is an executive summary that summarises the proceedings from the 3rd AFNET/EHRA consensus conference on atrial fibrillation, held in Sophia Antipolis from November 7th to 9th 2010, shortly after the release of the new ESC guidelines on AF. The conference was jointly organised by the German Atrial Fibrillation competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). This executive summary report covers four sections: 1. Risk factors and risk markers for AF, 2. Pathophysiological classification of AF, 3. Relevance of monitored AF duration for AF-related outcomes, and 4. Perspectives and needs for implementing better antithrombotic therapy.

Keywords

Acquired coagulation disorders, vitamin K-dependent factors, stroke / prevention, thrombin, atrial fibrillation

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Introduction

Atrial fibrillation (AF) is one of the major common and chronic disorders in modern cardiology. Due to its loss of heart rate control, diminished atrial contraction, and especially its propensity to thrombogenesis, AF can cause major cardiovascular complications, including stroke and death. Despite recent advances in AF therapy, including the broader use of anticoagulant therapy, adequate rate control, and newer, safer techniques to maintain sinus rhythm, mortality and morbidity in AF patients remains unacceptably high.

There are exciting new developments in several areas of AF management that carry the hope of improving outcomes in AF patients. This paper is an executive summary that summarises the proceedings from the 3rd AFNET/EHRA consensus conference on atrial fibrillation (for the prior conference reports, see [1, 2]), held in Sophia Antipolis from November 7th to 9th 2010, shortly after the release of the new European Society of Cardiology (ESC) guidelines on AF (3). The report covers four sections: 1. Risk factors and risk markers for AF, 2. Pathophysiological classification of AF, 3. Relevance of monitored AF duration for AF-related outcomes, and 4. Perspectives and needs for implementing better antithrombotic therapy.

Risk factors and markers for AF

Despite marked and successful efforts to reduce cardiovascular risk factors, the incidence of AF continues to increase in developed countries, indicating that the control of traditional risk factors for cardiovascular disease may not reduce AF to a similar extent.

Many risk factors contribute to AF. Several clinical risk factors are well-established and validated for AF, and their identification requires early intervention and appropriate treatment in order to

prevent disease progression (4–8). Preventing these risk factors may also reduce the risk of developing AF (2, 9). On the other hand, there are emerging, less validated risk factors for AF that have received much less attention and may provide additional leverage to decrease the incidence of AF, which is emerging as the new epidemic.

What increases the risk for incident AF?

►Table 1 gives a list of risk factors and risk markers for incident AF. These are split into "established" and "less validated", emerging risk factors and markers. Among the established risk factors, the best validated risk factors that lead to the development of AF include **age**, **hypertension**, **diabetes mellitus, and heart failure**.

Age is one of the key risk factors for AF (10–14). On the contrary, if AF occurs at young age, **genetic factors** play a major role (heritable AF, see below).

Another important and well established factor is **hypertension.** Indeed, the higher the blood pressure, the greater the risk of incident AF, although the lower end of blood pressures may also associate with AF ("J-shaped curve") (15–17).

Other factors such as **heart failure** are less well defined or used in a broad sense (10–13, 18). Also included are patients with heart failure and preserved left ventricular function and patients with **coronary artery disease**, the latter mainly when they present with left ventricular dysfunction. The underlying pathophysiological link and the common pathway for hypertension or heart failure to lead to AF is atrial pressure and/or volume overload as well as diastolic ventricular dysfunction which may lead to atrial dilatation, fibrosis, and electrical remodelling that finally provides the stimulus and the substrate for the development of AF. Of note, atrial refractory periods and action potential durations are prolonged in heart failure, suggesting that electrical remodelling is less relevant in these patients.

In a similar way, **valvular heart disease** leads to pressure and/or volume overload of the atria, especially the left atrium in left-sided disease, and has been associated with the development of AF (10, 11, 13).

Male gender is associated with incident AF (10, 11, 13). This contrasts with the consistent observation that **female** gender is a risk factor for stroke in patients with established AF. These contrasting associations are difficult to explain, and additional mechanistic and epidemiological studies are needed to understand these relations.

Metabolic factors such as **diabetes mellitus and hyperthyroidism** have been recognised as independent risk factors for AF (10–11, 13).

Less well-established risk factors and markers for incident AF

There is a range of less well established risk factors that associate with AF. Deciphering the functional consequences of genetic changes associated with AF in the population and epigenetic analyses can teach us more about risk factors for AF.

Subclinical hyperthyroidism is considered as a modifying factor for the development of AF.

Obesity has recently been revisited as a less well-validated risk factor for the development of AF in population-based studies. Even high birth weight associates with AF in women above 45 years of age. **Tall stature** also increases the risk of developing AF.

Newer markers of increased risk for AF include the **sleep apnea syndrome** which appears to be associated with obesity. In addition, **chronic obstructive pulmonary disease** has been associated with

Table 1: Factors for incident AF, progression AF, and associated events. For a list of the publications reporting the hazard ratios, and the size and type of populations studied, please refer to the full publication of this report. Very high hazard ratios (HRs) are usually derived from small, hypothesis-generating, often initial reports. Age, gender, and the genetic risk factors are not modifiable. References are given in (46).

Validated risk factors	Published HR range
Age	1.03 / year – 5.9
Male gender	1.5– 2.7
Hypertension	1.1 – 2.2
Valve disease	1.8 – 3.2
Heart failure	1.4 – 7.7
Diabetes	1.4 – 2.1
Coronary artery disease (often history of myocardial infarction)	1.4 – 3.6
Genetic factors: Family history or genomic associations	1.1 – 1.9
Less validated risk factors and risk markers	
Obesity/BMI	1.03 (per BMI) – 2.0
Blood pressure/ pulse pressure	1.1 – 2.2
Height	1.03 (per 10 cm) – 16.5
Sleep apnea syndrome	2.2 – 3.0
Subclinical hyperthyroidism	1.9 – 3.1
Alcohol consnumption (often excessive)	1.3 – 1.5
Chronic kidney disease	1.4 – 1.9
Excessive endurance sports	1.7 – 22.8
Chronic obstructive lung disease	1.5 – 2.0
Smoking	1.3 – 1.5
Coffee	?
PR interval	1.1 – 2.7
Murmur	1.9 – 2.4
ANP or BNP	1.2 – 4.0
CRP (and IL1 / TNF-alpha)	0.9 – 2.2
Birth weight	1.7
Troponin T	1.2
Prelinical atherosclerosis	1.6 – 2.1
Psychological determinants	?

progression of AF to more permanent forms. **Chronic kidney disease** also appears to be a valid marker of increased risk for AF.

Environmental factors such as **alcohol consumption** and **smoking** are well-established risk markers for AF.

While moderate **exercise** may protect against AF and can clearly help to reduce metabolic risk factors for AF, high-level endurance training is associated with an increased risk of AF in athletes.

Biomarkers for AF

Analysis of patient serum, assessment of cardiac size and function by imaging including electrocardiogaphy, and genetic analyses all provide biomarkers which may be helpful to refine assessment of AF risk. Although validation in large patient sets is pending, it is conceivable that serum biomarkers may help to assess AF risk.

Natriuretic peptides (ANP and BNP) are emerging as new serum risk factors with differential value. **C-reactive protein and interleukin-6** have been associated with AF. For either of these markers, the results are somewhat conflicting.

Echocardiographic estimators of **left atrial size** may provide an "integral" of the degree of left atrial structural changes over time, and thereby relate to incident AF or to AF-related complications, including death. Technical issues related to the adequate assessment of left atrial volume and biological variations in left atrial volume render it difficult to compare data directly across studies. Transesophageal echocardiography may furthermore provide information on stroke risk beyond traditional stroke risk factors.

Delayed-enhancement of magnetic resonance imaging can detect transmural radio frequency-induced lesions in the atria. Indeed, large areas of delayed enhancement in the left atrium may predict recurrent AF after catheter ablation. Technicalities of magnetic resonance-based imaging of atrial fibrosis and scar render reproducibility of these findings challenging, and visualisation of scars is likely limited to transmural lesions.

Electrocardiogram (ECG)-based parameters such as long (within the normal range) or prolonged PR interval clearly relate to AF in the population, possibly related to atrial structural remodelling and delayed intra-atrial conduction. Similarly, longer P wave duration also associates with the risk for developing AF. Furthermore, the observation of an episode of AF after cardiac surgery may identify patients at high subsequent risk of developing AF.

Genetic factors are associated with AF, especially when AF occurs in young patients. In a small number of patients, genetically conferred cardiomyopathies can be identified as a cause of AF, e.g. long QT syndrome, Brugada syndrome, short QT syndrome, or hypertrophic cardiomyopathy (19). On the population level, several single nucleotide polymorphisms (SNP) close to the PITX2 gene strongly associate with early-onset AF. Other, weaker associations are found on chromosome 1q25 and on chromosome 16. The molecular mechanisms conferring genetically mediated AF have recently been investigated. These data provide first suggestions that genetic biomarkers may in the future help to assess AF risk.

Areas of further research

A clear separation between risk markers and risk factors is not always possible since not all biological causes of AF are well understood, and their interaction remains elusive for most parts. Future research will hopefully give us more insight into risk factors and markers that predispose us to AF and its associated complications. With the notable exception of the Framingham cohort study and population-wide genomic analyses, almost all biomarkers for AF require validation in other patient series that allow sufficient control of confounding factors. The vast majority of patients experience AF as a chronically progressive disease. The available data suggest that these factors overlap largely with factors that lead to the development of AF (see above). There is a clear and unmet need to identify and characterise factors associated with progression of AF, and the relative contribution of established risk factors for progression, first occurrence, or first recurrence of AF. Also, there is a clear need to investigate and quantitate the impact of the known risk factors on "early AF" and silent AF and to better characterise their interrelation.

A pathophysiologically orientated classification of atrial fibrillation to guide therapy

Currently, AF is classified by duration (paroxysmal, persistent, long-standing persistent, permanent) and by the extent of AF-causing symptoms (EHRA score I-IV, or CCS-SAF score 0-IV) (3, 20–21). The symptom classification helps to guide therapeutic decisions, especially on rhythm control therapy. A classification of AF types based on the underlying pathophysiology, in contrast, could help to better select therapies for specific AF patients based on the type of underlying cause and/or the degree of atrial damage. Thereby, the guideline-supported recommendation to treat underlying conditions would be substantiated (3, 20). Therefore, to better guide therapy, the group proposes a classification of AF types based on the presumed AF-causing mechanisms, the validity of which requires further clinical studies (see ►Suppl. Table 1 available online at www.thrombosis-online.com).

Inherited AF

This type of AF is best characterised by AF with familial clustering, often of early onset. Early onset has been defined by a diagnosis of AF before the age of 65 years.

Monogenic forms

AF is a common finding in patients with inherited, monogenic cardiomyopathies, and other, rare familial forms of AF occur without other signs of heart disease. Many of these patients suffer from

genetically conferred cardiomyopathies. It may be of clinical value to look for subtle ECG abnormalities such as a slightly prolonged or shortened QT interval, QRS amplitudes within the upper range of normal, or slight changes of the right precordial ST segments in patients with early-onset AF.

Polygenic forms

A family history of AF is one of the risk factors for incident AF, outside of clear familial clustering (see ▶Suppl. Table 2 available online at www.thrombosis-online.com). In the past years, several population- and genome-wide association studies have identified small genetic changes (SNPs) that are associated with AF. The strongest association with AF and stroke is found on chromosome 4q25, close to the PITX2 gene (see above). In addition to these genetic factors, epigenetic modifiers and other modifiers of concomitant conditions may also contribute to "polygenic" AF. There is an overlap between polygenic forms of AF and complex AF.

Focal AF

In the absence of severe cardiac disease, the initial event that conveys AF is often atrial ectopy from the pulmonary veins. Many short episodes of AF are a good clinical indicator for this pathophysiology. There is a continuum from atrial ectopy, atrial "runs" and short lasting atrial tachycardias to self-terminating atrial fibrillation. Focal AF, and a similar form caused by re-entrant drivers, may best be managed by eliminating the focal cause of AF.

Complex AF

This form of AF identifies the "typical" AF patient, often at advanced age who usually has pre-existing left atrial damage and/or enlargement. "Complex AF" is a consequence of several pathophysiological processes, including (but not limited to) AF-induced electrical remodelling, structural changes in the atria, pressure and volume overload secondary to external conditions such as ventricular cardiac dysfunction or arterial hypertension, subtle genetic predisposition, and age (19). Within this group of patients, the degree of "complexity" is highly variable. In the future, it is worth to investigate whether the degree of complexity might serve as a relevant predictor for successful rhythm control, allowing "graded rhythm control therapy" (22).

Postoperative AF

Post-operative AF is an intriguing subform of AF. One in five to one in three patients undergoing cardiac surgery suffer from post-operative AF. As enhanced sympathetic tone and inflammation are the most relevant factors predisposing to postoperative AF, beta-blockers and anti-inflammatory compounds can be effective in its prevention. In any case, the transient nature of AF has to be considered in the decision making process (e.g. transient use of antiarrhythmic drugs or anticoagulation therapy), while emerging data also show that patients with post-operative AF are at higher risk of developing spontaneous AF later in life.

"Silent" AF and the significance of atrial fibrillation detected by long-term monitoring devices

AF is a chronically progressive disease (23, 24) that will eventually be picked up by palpating the pulse, followed by an ECG to establish diagnosis (3). Indeed, prolonged monitoring, usually by prolonged Holter ECG recordings for seven days, may detect AF in one in 20 or even one in 10 patients admitted with acute stroke and being in sinus rhythm at the time of admission. The need for more accurate and extended diagnostic periods may also be met by implanted devices which could theoretically provide continuous information on atrial rhythm or by long-term external recording devices (23, 25, 26). Whether short atrial high-rate episodes (AHRE) recorded by an implanted device from an intracardiac lead have the same clinical implications and prognostic impact in patients without ECG-documented AF as AF documented by ECG is not clear. The available data suggest that these patients are at increased risk for stroke and also put forward the concept that patients who spend more time in AF are at higher risk for complications than patients who spend less time in AF (27). There is a clear need to unify the definitions of AHRE across device manufacturers, and to investigate the impact of short AHRE episodes (less than 5 minutes duration) on outcomes and stroke risk estimation. The currently accepted "minimal duration" of AHRE episodes, 5–6 minutes, is based on technicalities related to the adequate diagnosis of true AHREs and their distinction from artifacts and other arrhythmias, rather than on biological processes (27–29). Implantable subcutaneous devices can provide continuous cardiac rhythm monitoring in patients that do not require pacemakers or defibrillators (30).

There was consensus to propose a stepwise approach to document AHRE (▶Fig. 1). To establish the diagnosis from intracardiac recordings or implanted devices, criteria may differ from established criteria to diagnose AF in the surface ECG (3). Indeed, prevention of AF initiated immediately after early detection could help to reduce strokes in patients with AF on anticoagulant therapy. This will be tested in the EAST (Early Treatment of Atrial Fibrillation Stroke Prevention Trial) trial (ISRCTN04708680, NCT01288352).

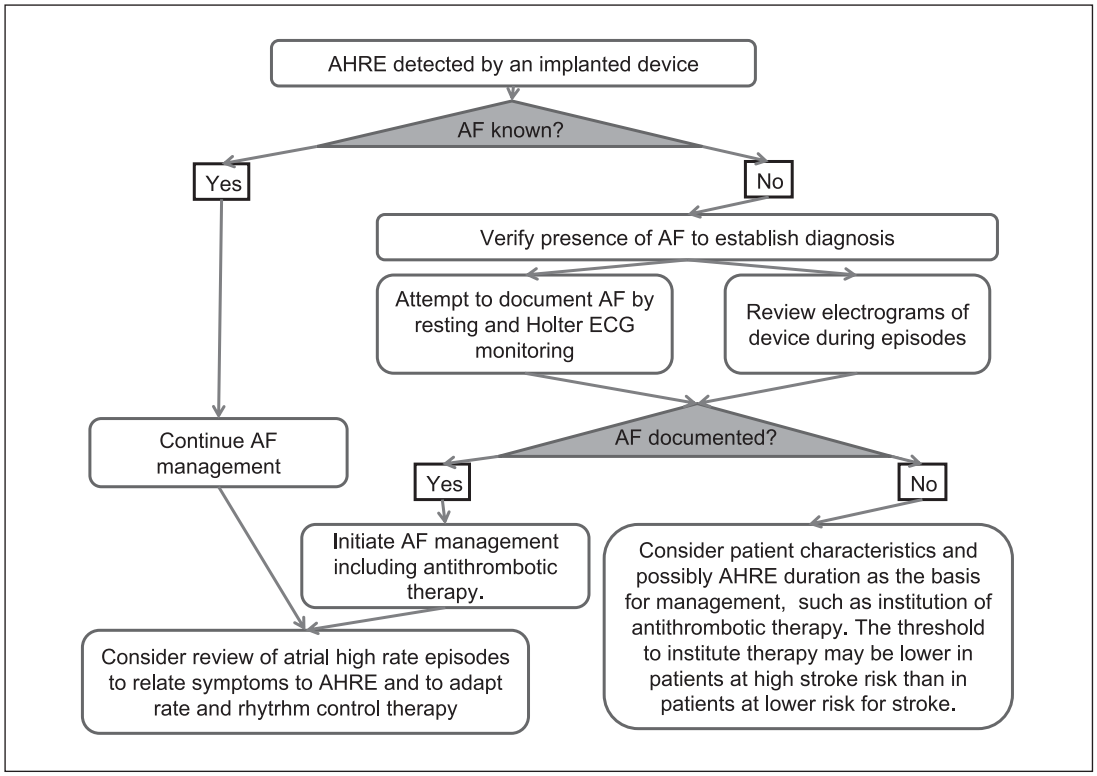

Figure 1: Approach to patients with atrial high-rate episodes (AHRE) detected by implanted devices.

Improving stroke prevention by antithrombotic therapy

Oral anticoagulation clearly prevents approximately 2/3 of all strokes in AF patients (3), and most patients with AF are likely to benefit from anticoagulant therapy. But this effective and potentially life-saving therapy comes at the price of inducing relatively rare but potentially severe bleeding events. While numerically "major bleeds" and strokes may occur in similar frequency in large trials, major bleedings events include clinically relevant and less significant events ranging from the rare but severe intracranial haemorrhage to less relevant smaller gastrointestinal bleeds. Ischemic strokes, in contrast, have usually a lasting medical impact.

Detecting an increased risk for intracranial bleeds

The available data suggest that patients are often willing to accept excess bleeds if this helps to prevent ischaemic strokes. This is in line with the net clinical benefit of oral anticoagulation in most AF patients. Nonetheless, challenges remain in stroke risk assessment, especially in patients at increased risk for bleeding. Unfortunately for the decision models, most bleeding risk factors overlap with stroke risk factors, and the CHADS2 score is one of the best bleeding risk predictors (31–33). Nonetheless, variable INR values, excess consumption of alcohol or drugs, enzymatically detected liver damage and renal dysfunction, incontinence and gait apraxia, as well as certain genetic factors and potentially subclinical lesions (detectable as amyloid angiopathy) on cerebral magnetic resonance imaging may identify patients at high bleeding risk (31, 32, 34–39)

Careful classification of intracranial bleeds

For the acute management of such events as well as for the interpretation in light of anticoagulant therapy, a careful classification of intracranial bleeds is important. This requires differentiation between parenchymal brain haemorrhage, epidural or subdural haematoma, and subarachnoidal haemorrhage (▶Fig. 2). Haemorrhagic transformation of cerebral ischaemia is not considered as a primary bleeding complication.

Information needed for the clinical use of newer anticoagulants

Vitamin K antagonists (VKAs) are widely used throughout Europe and the US, but their effectiveness is limited by their narrow therapeutic range, drug-food and drug-drug interactions, and the difficulty to maintain patients in the therapeutic range. This limits utilisation of VKAs. There is extensive knowledge about VKAs in the medical community and anticoagulated patients are familiar

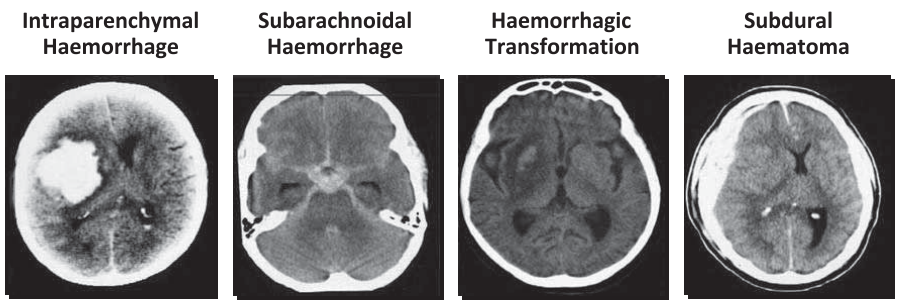

Figure 2: Cerebral computed tomograms of four types of intracranial bleeding (true intracerebral haemorrhage, subdural haematoma, subarachnoidal haematoma, epidural haematoma).

with the oral anticoagulation regimen. Furthermore, experience with combination therapy using novel anticoagulants, specifically "triple therapy", is limited at present. Therefore, there is a need to educate physicians, including general physicians, and patients about these new compounds (see ▶Box).

Monitoring of anticoagulation with the newer anticoagulants will only be needed in special situations (e.g. a patient suffering a stroke on one of the newer substances or emergency). Direct thrombin inhibitors and direct factor Xa inhibitors will have a slight effect on aPTT, while assessment of factor Xa activation will not suffice to detect the anticoagulant effect of these substances. The degree of aPTT elevation does not relate to either efficacy or bleeding risk of these compounds, and such measures should probably not affect drug dose.

Renal dysfunction – a risk marker for stroke in a complicated situation

Patients with severe renal dysfunction are at high risk for stroke and bleeds. It is unlikely that renal dysfunction – unlike other risk factors – would favour bleeds in excess of ischaemic events. Hence, it appears reasonable to consider severe renal dysfunction as an additional risk factor for stroke. In the typical elderly AF patient with renal dysfunction, renal function can deteriorate over time, and may be associated with an increase in bleeding events. Even experience with VKAs in those with renal dysfunction is limited at present, and therefore the choice of oral antithrombotic agents cannot be based on controlled data. There is a clear need to better understand the effects of the new anticoagulants in patients with renal dysfunction.

Patient values and preferences in AF management

Patients need information on AF, but the degree and type of information demanded differs between patients (40). Public campaigns to palpate your pulse, followed by ECG screening, may be suitable ways to communicate to the general public about AF and its associated risk to relevant populations. The advent and commercialisation of new anticoagulants generates a need to inform and educate patients better. Seizing this opportunity could help to achieve earlier and comprehensive management of AF patients. In addition to this general need of information on AF and its complications, there is also a specific need for information on the new anticoagulants, e.g. on the adequate dosing, the lack of need to monitor the drug effect, techniques to eliminate or antagonise the drug in emergencies, and specific interactions with drugs or food.

There was consensus to recommend collaboration between pharmaceutical and medical device companies, ideally coordinated by professional and scientific organisations, to establish and produce generic patient education materials. Such a collaboration could end up in a toolkit for physicians that will help to educate patients, but also (e.g. internet-based) industry-independent information to patients. Patient groups will be helpful in the dissemination of this information.

Important information for physicians on new anticoagulants in comparison to vitamin K antagonists

(This information should be provided by the drug manufacturer.)

- Information on AF and concomitant comorbidities
- Characteristics of the novel anticoagulant (trial data, pharmacokinetics, drug interactions, special precautions)
  - Shorter half life requires attention to adherence
  - Shorter half-life may make periprocedural issues easier, but this has not been formally tested. Attention to haemostasis may help to decide on the time point of operations. For vitamin K antagonists, there are good data for many procedures that continuation of vitamin K antagonist (with keeping the INR in the lower therapeutic range) is better than bridging.
  - Drug-drug interactions including cytochrome p450 isoenzymes
  - Antagonising the drug in emergencies
  - Metabolism and interaction with renal and/or hepatic dysfunction
- Patient preference-threshold for stroke and excess bleeding
- Awareness of patient's knowledge & understanding of antithrombotic therapy
- Importance of maintaining drug use
- Monitor renal function in selected patients (recent illness/renal dysfunction)
- What to do in special situations (surgery, acute coronary syndromes / stents, accidents)

Information for payers

In addition to the medical and general need for information, institutions and decision makers will need information on the cost of new anticoagulants. Such information will need to account for the local practice of anticoagulant therapy and the local potential for delivery of the new therapies. Cost estimates should include cost of the drug, direct and indirect cost of oral anticoagulant therapy, safety profile, and ideally result in a cost-benefit analysis over VKAs in different European countries.

Interventional stroke prevention in AF patients?

In patients deemed unsuitable VKA therapy, often on the basis of bleeding risk, transcatheter closure of the left atrial appendage has been evaluated as an alternative for stroke prevention in AF (41), and a specific device for epicardial suture-based closure of the appendage during open-heart surgery has recently been approved in the US. While technically feasible, this intervention will need to be re-evaluated compared to newer, safer anticoagulants in patients who are considered unsuitable for VKA therapy. The group suggests a trial of such a device in patients with established contraindications to oral anticoagulation, possibly involving one of the newer anticoagulants as comparator therapy.

Appendix

Like its predecessors, the 3rd AFNET/EHRA consensus conference was a group exercise. Many of the concepts, observations, and hypotheses were aired by participants of the conference. The authors of this paper are members of a 'writing group' that compiled the main findings of the conference in a style suitable for publication. The organisers of the conference and the members of this 'writing group' would like to explicitly acknowledge the contributions of many other participants of the conference. Therefore, a list of all participants of the conference in alphabetical order is published here: Maria Aunes-Jansson, Jeroen Bax, Carina Blomstrom-Lundqvist, Maria Borentain, Giuseppe Boriani, Axel Brandes, Stefanie Breitenstein, Günter Breithardt, Martina Brueckmann, A. John Camm, Nilo Cater, Andreas Clemens, Hans Diener, Paul Dorian, Dobromir Dobrev, Sergio Dubner, Nils. G. Edvardsson, Michael Ezekowitz, Leif Friberg, Isabelle C. Van Gelder, Andreas Goette, Michele Gulizia, Laurent Haegeli, Robert Hatala, Hein Heidbuchel, Jenny Horwood, Elaine Hylek, Lukas Kappenberger, Stefan Kaab, Josef Kautzner, Paulus Kirchhof, Angelika Leute, Deirdre Lane, Gregory Y. H. Lip, Trudie Lobban, Ralf Meyer, Jay Millerhagen, Luis Mont, John Morgan, Felix Muenzel, Michael Nabauer, Christoph Baertels, Michael Oeff, Dieter Paar, Juergen Polifka, Ursula Ravens, Ludger Rosin, Ulrich Schotten, W. Stegink, Gerhard Steinbeck, Lukas Szumowski, Panos Vardas, Alphons Vincent, Maureen Walter, Karl Wegscheider, Stephan Willems.

Stroke prevention beyond anticoagulant therapy

Continuous oral anticoagulation is the cornerstone of stroke preventing in AF patients, and relies on adequate delivery of anticoagulant therapy as evidenced by e.g. achieving therapeutic international normalised ratio values. But even on optimal anticoagulant therapy in controlled trials, the residual stroke rate in AF patients remains unacceptably high at approximately 1.5% per year (42–44).

Almost all available studies so far have investigated the effect of anticoagulant therapy in patients with established AF, often long-lasting AF. The long-term impact of "transient" AF (e.g. postoperative AF) and of "silent" AF (3, 22) is much less well studied. Based on this information, it appears unlikely that rhythm control therapy can be sufficient to prevent AF-related strokes. Nonetheless, there is a signal of reduced stroke rates by dronedarone in a non-prespecified post-hoc analysis in the ATHENA trial (45). Hence, rhythm control therapy could well contribute to reduce residual stroke rates in patients on anticoagulation. It is likely that a comprehensive approach to AF management ("early and comprehensive therapy of AF" [22]) can help to improve outcomes in patients with AF on top of optimal anticoagulation. This concept of "comprehensive rhythm control therapy" for reducing relevant outcomes in AF patients will be tested in future controlled trials, including the EAST trial (ISRCTN04708680, NCT01288352).

Note: An extended list of references for the statements in this report is given in the full report on the conference (46).

Conflict of interest

All authors have actively shaped the 3rd AFNET/EHRA consensus conference, and compiled the results of the different discussions at that meeting. All authors have been active in advising different drug manufacturers and device companies, including advice on drugs and devices related to management of atrial fibrillation. The 3rd AFNET/EHRA conference, like its predecessors, was organised and funded by AFNET and EHRA. Industry participants paid an attendance fee.

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