Comprehensive risk reduction
Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options - a report from the 3rd AFNET/EHRA consensus conference

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AFNET: Atrial Fibrillation Competence NETwork
EHRA: European Heart Rhythm Association

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Atrial fibrillation (AF) is one of the major common and chronic disorders in modern cardiology.

There are exciting new developments in several areas of AF management that carry the hope of improving outcomes in AF patients.

This pocket guide summarizes the proceedings from the 3rd AFNET/EHRA consensus conference on AF held in Sophia Antipolis from November 7th to 9th 2010.
I. Risk factors and markers for AF

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. Preventing these risk factors may also reduce the risk of developing AF. 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?

Established risk factors

**Age** is one of the key risk factors for AF. On the contrary, if AF occurs at young age, genetic factors play a major role. **Hypertension** is another risk factor. The greater the risk of incident AF, although the lower end of blood pressures may also associate with AF. Other factors such as **heart failure** are less well defined and used in a broad sense. 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. **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.

**Male gender** is associated with incident AF. Metabolic factors such as **diabetes mellitus** and **hyperthyroidism** have been recognized as independent risk factors for AF.
Less well-established risk factors and markers for incident 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 progression of AF to more permanent forms. Chronic kidney disease also appears to be a valid marker of increased risk for AF. 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.

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. 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.

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. Genetic factors are associated with AF, especially when AF occurs in young patients.
<table>
<thead>
<tr>
<th>Validated risk factors</th>
<th>Published HR range</th>
<th>Validated risk factors</th>
<th>Published HR range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 / year - 5.9</td>
<td>Heart Failure</td>
<td>1.4 - 7.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.5 - 2.7</td>
<td>Diabetes</td>
<td>1.4 - 2.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.1 - 2.2</td>
<td>Coronary artery disease (often history of myocardial infarction)</td>
<td>1.4 - 3.6</td>
</tr>
<tr>
<td>Valve disease</td>
<td>1.8 - 3.2</td>
<td>Genetic factors: Family history or genomic associations</td>
<td>1.1 - 1.9</td>
</tr>
<tr>
<td>Obesity/BMI</td>
<td>1.03 (per BMI) - 2.0</td>
<td>Smoking</td>
<td>1.3 - 1.5</td>
</tr>
<tr>
<td>Blood pressure/pulse pressure</td>
<td>1.1 - 2.2</td>
<td>Coffee</td>
<td>?</td>
</tr>
<tr>
<td>Height</td>
<td>1.03 (per 10 cm) - 16.5</td>
<td>PR interval</td>
<td>1.1 - 2.7</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>2.2 - 3.0</td>
<td>Murmur</td>
<td>1.9 - 2.4</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>1.9 - 3.1</td>
<td>ANP or BNP</td>
<td>1.2 - 4.0</td>
</tr>
<tr>
<td>Alcohol consumption (often excessive)</td>
<td>1.3 - 1.5</td>
<td>CRP (and IL1 / TNF-alpha)</td>
<td>0.9 - 2.2</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.4 - 1.9</td>
<td>Birth weight</td>
<td>1.7</td>
</tr>
<tr>
<td>Excessive endurance sports</td>
<td>1.7 - 22.8</td>
<td>Troponin T</td>
<td>1.2</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>1.5 - 2.0</td>
<td>Preclinical atherosclerosis</td>
<td>1.6 - 2.1</td>
</tr>
<tr>
<td>Psychological determinants</td>
<td></td>
<td>Psychological determinants</td>
<td>?</td>
</tr>
</tbody>
</table>
II. A pathophysiologically orientated classification AF to guide therapy

**Inherited AF.** It is best characterized 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 cardio-myopathies, and other, rare familial forms of AF occur without other signs of heart disease.

**Polygenic forms.** A family history of AF is one of the risk factors for incident AF, outside of clear familial clustering. In addition to these genetic factors, epigenetic modifiers and other modifiers of concomitant conditions may also contribute to “polygenic” 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.

**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. It is a consequence of several patho-physiological processes.

**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.
<table>
<thead>
<tr>
<th>AF type</th>
<th>Pathophysiological mechanism</th>
<th>Diagnostic characteristics</th>
<th>Proposed ‘specific’ therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritable AF</td>
<td>Patients with AF and inheritable cardiomyopathies (short QT, Brugada, LQTS, or hypertrophic cardiomyopathy, among others).</td>
<td>Gene-defect-related ECG-abnormalities, echo-diagnosis of inherited cardiomyopathy, family history, genetic testing.</td>
<td>Therapy of underlying cardiomyopathy. Pharmacological reversal of the genetic defect (possibly, but not necessarily targeting the ion channel carrying the gene defect).</td>
</tr>
<tr>
<td>Inheritable AF</td>
<td>Currently under study. Manifestation as AF at young age (&lt;65 years) with or without familial clustering.</td>
<td>AF of early onset, often with some familial aggregation of AF, no evident specific underlying cardiovascular disease causing the arrhythmia.</td>
<td>Not yet identified.</td>
</tr>
<tr>
<td>Polygenic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal AF</td>
<td>Localised triggers, in most cases originating from the pulmonary vein(s).</td>
<td>Pattern of frequent, but short-lasting episodes of AF with distinguishable P waves (coarse AF), atrial ectopy, and/or atrial tachycardia deteriorating in AF. AF mainly due to one or a few re-entrant drivers is also considered to be part of this type of AF.</td>
<td>Isolation of the pulmonary vein(s), extended/repeated ablation procedures might be required.</td>
</tr>
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</table>
Atrial Fibrillation Competence NETwork/European Heart Rhythm Association classification of atrial fibrillation by aetiology and suggested ‘type-specific’ therapy (Cont.)

<table>
<thead>
<tr>
<th>AF type</th>
<th>Pathophysiological mechanism</th>
<th>Diagnostic characteristics</th>
<th>Proposed ‘specific’ therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex AF</td>
<td>AF that is maintained by functional multiple reentrant wavelets. Complex AF is common and promoted by shortening of atrial refractoriness (e.g. tachycardia-induced atrial remodelling or enhanced parasympathetic tone) or localised conduction disturbances due to atrial fibrosis induced by structural heart disease. Complex AF is also the “final common pathway”.</td>
<td>Long-lasting episodes, or persistent AF with non-distinguishable P waves (fine AF). The following therapeutic measures aim at quantification of the degree of substrate complexity: Frequency and amplitude of P waves (primarily reflecting right atrial electrophysiological properties). Frequency and amplitude of local wall movements recorded by tissue velocity imaging (electroechocardiography). Incidence of complex fractionated atrial electrograms (CFAE). Non-invasive imaging: Atrial enlargement, scarring, and potentially atrial fibrosis as reflected by MRI.</td>
<td>Therapy depending on grading of the substrate complexity: Low complexity: AADs or PVI. Moderate complexity: AADs and/or extended/repeated ablation procedures. High complexity: rate control (AAD and ablation ineffective). In these patients, both primary prevention of AF in patients with structural heart disease, and possibly also secondary prevention of AF by upstream therapy should be considered (unless contra-indicated).</td>
</tr>
</tbody>
</table>
III. “Silent” AF and the significance of AF detected by long-term monitoring devices

AF is a chronically progressive disease that will eventually be picked up by palpating the pulse, followed by an ECG to establish diagnosis. The need for more accurate and extended diagnostic periods may be met by implanted devices which could theoretically provide continuous information on atrial rhythm or by long-term external recording devices.

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.

There was consensus to propose a stepwise approach to document AHRE (Figure 1).
Approach to patients with atrial high-rate episodes detected by implanted devices (AHRE: atrial high rate episode)

(Figure 1)

AHRE detected by an implanted device

AF known?

Yes

AF documented?

Yes

Initiate AF management including antithrombotic therapy

No

Consider patient characteristics and possibly AHRE duration as the basics for management, such as institution of antithrombotic therapy. The threshold to institute therapy may be lower in patients at high stroke risk than in patients at lower risk for stroke.

No

Verify presence of AF to establish diagnosis

Attempt to document AF by resting and Holter ECG monitoring

No

Review electrograms of device during episodes

Yes

Continue AF management

Consider review of AHRE to relate symptoms to AHRE and to adapt rate and rhythm control therapy

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IV. Improving stroke prevention by antithrombotic therapy

Oral anticoagulation clearly prevents approximately 2/3 of all strokes in AF patients, 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.

**Detecting an increased risk for intracranial bleeds.** Most bleeding risk factors overlap with stroke risk factors, and the CHADS2 score is one of the best bleeding risk predictors.

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 on cerebral magnetic resonance imaging may identify patients at high bleeding risk.

**Information needed for the clinical use of newer anticoagulants.** Vitamin K antagonists are widely used, 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 utilization of vitamin K antagonists. The experience is lacking at present for the newer anticoagulants. Therefore, there is a need to educate physicians, including general physicians, and patients about these new compounds, ideally before they are used.
Patient groups likely to benefit (upper part) or not to benefit (lower part) from therapy with new anticoagulants, including a switch from existing therapy with vitamin K antagonists to one of the newer substances

<table>
<thead>
<tr>
<th>Patients who are likely to benefit from new anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients with poor TTR (time in therapeutic range) and INR control due to:</td>
</tr>
<tr>
<td>innate/genetics for warfarin metabolism,</td>
</tr>
<tr>
<td>inadequate access to monitoring, poor monitoring quality, and/or inability to self-monitor.</td>
</tr>
<tr>
<td>• Patients requiring medication interacting with vitamin K antagonists.</td>
</tr>
<tr>
<td>• Patients who have decided against anticoagulation with vitamin K antagonists despite adequate education.</td>
</tr>
<tr>
<td>• Patients at low risk of gastrointestinal bleeding (dabigatran) and patients without severe renal dysfunction.</td>
</tr>
<tr>
<td>• Patients who suffered an ischaemic stroke on warfarin with adequate INR.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients potentially less suitable for novel anticoagulants in the early phase after market introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fragile patients, especially those requiring polypharmacotherapy and with several concomitant diseases may be at increased risk of accumulating the newer oral anticoagulants or at increased risk for rare unwanted reactions.</td>
</tr>
<tr>
<td>• Patients with markedly decreased moderately impaired renal function (MDRD IV–V). The pharmacology suggests that patients with renal function MDRD stage II–III may be suitable for some of the factor Xa antagonists, and MDRD II–III patients showed most benefit on therapy with dabigatran in the RELY study.</td>
</tr>
<tr>
<td>• Patients with history of gastrointestinal bleeding.</td>
</tr>
<tr>
<td>• Patients with poor TTR due to non-adherence may benefit from the regular reinforcement of therapy by monitoring needed for vitamin K antagonists therapy.</td>
</tr>
<tr>
<td>• Patients at risk of progressing towards severe renal failure, e.g. patients with severe heart failure.</td>
</tr>
<tr>
<td>• Patients with coronary artery disease with a high likelihood of requiring percutaneous revascularization until more data on combination therapy (vitamin K antagonists plus dual antiplatelet therapy) are available.</td>
</tr>
</tbody>
</table>
Patient values and preferences in AF management. Patients need information on AF, but the degree and type of information demanded differs between patients.

Interventional stroke prevention in AF patients. In patients deemed unsuitable for vitamin K antagonist 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.

Stroke prevention beyond anticoagulant therapy. It is likely that a comprehensive approach to AF management can help to improve outcomes in patients with AF on top of optimal anticoagulation. This concept of will be tested in future controlled trials.
Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options - a report from the 3rd AFNET/EHRA consensus conference

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