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REVIEW

Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options—a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference

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While management of atrial fibrillation (AF) patients is improved by guideline-conform application of anticoagulant therapy, rate control, rhythm control, and therapy of accompanying heart disease, the morbidity and mortality associated with AF remain unacceptably high. This paper describes the proceedings of the 3rd Atrial Fibrillation NETwork (AFNET)/European Heart Rhythm Association (EHRA) consensus conference that convened over 60 scientists and representatives from industry to jointly discuss emerging therapeutic and diagnostic improvements to achieve better management of AF patients. The paper covers four chapters: (i) risk factors and risk markers for AF;

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(ii) pathophysiological classification of AF; (iii) relevance of monitored AF duration for AF-related outcomes; and (iv) perspectives and needs for implementing better antithrombotic therapy. Relevant published literature for each section is covered, and suggestions for the improvement of management in each area are put forward. Combined, the propositions formulate a perspective to implement comprehensive management in AF.

Keywords atrial fibrillation • management • outcomes • antithrombotic therapy • rate control • rhythm control • risk factors • early therapy

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 ischaemic stroke and systemic thromboembolism, heart failure, impaired quality of life, and frequent prolonged hospitalizations. Furthermore, mortality rates are doubled in patients with AF, with acute coronary syndromes and other vascular complications being frequent. Despite recent advances in AF therapy, including the broader use of anticoagulant therapy, adequate rate control, and newer, safer techniques to maintain sinus rhythm, which may prospectively help to prevent adverse outcomes in AF patients, mortality and morbidity in AF patients remains unacceptably high.

To discuss and propose the next steps and the perspectives to improve AF management, the German Atrial Fibrillation Competence NETwork (AFNET, www.kompetenznetz-vorhofflimmern.de) and the European Heart Rhythm Association (EHRA, www.escardio.org/ehra) convened over 60 experts from university and industry settings for the 3rd AFNET/EHRA consensus conference on AF (for reference to the 1st and 2nd conference, see Kirchhof *et al.*[1,2]). The conference was held in the European Heart House, the headquarters of the European Society of Cardiology (ESC) in Sophia Antipolis from 7 to 9 November 2010, shortly after the release of the new ESC guidelines on AF.[3]

The participants of this conference discussed several aspects of AF management. For this report, these were grouped into four main sections:

(1) risk factors and risk markers for AF,
(2) pathophysiological classification of AF,
(3) relevance of monitored AF duration for AF-related outcomes,
(4) perspectives and needs for implementing better antithrombotic therapy.

Risk factors and markers for atrial fibrillation

The past few decades have seen an immense effort to reduce the population-wide impact of atherosclerosis and cardiovascular disease, e.g. by the use of statin therapy, control of hypertension, and attempts to reduce smoking. Despite reduced risk for arteriosclerosis and coronary artery disease, the incidence of AF continues to increase, 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—presumably with some additive or cumulative effects that increase the individual risk of developing AF, although many interrelated interactions are likely.[4] Arterial hypertension and congestive heart failure, including heart failure with impaired or preserved left ventricular systolic function,[5–8] as well as myocardial infarction, valvular heart disease and diabetes mellitus, all contribute to development of AF.[9] These risk factors are well established and validated for AF, and as such, identification of these risk factors requires early intervention and appropriate treatment to prevent disease progression. Preventing these risk factors may also reduce the risk of developing AF.[2,10] On the other hand, there are emerging 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 atrial fibrillation?

Table 1 gives a list of risk factors for incident AF. These are split into 'established' and 'emerging' risk factors. 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.[9,12,59,70,71] Depending on the type of study, duration of follow-up and age at start of follow-up, hazard ratios range between 1.1 and 5.9 per decade of age. Age-related fibrosis,[72] intracellular age-related changes, or accumulation of accompanying disorders that occur with increasing frequency with older age may explain this association. 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.[19,23,24] Interestingly, a systolic blood pressure as low as 130 mmHg and a high pulse pressure amplitude may also increase the risk of AF.[23] This may imply that pre-clinical hypertension may commonly underlie AF, and suggests that tighter blood pressure control may be prudent in our efforts to prevent AF. On the other hand, the association between blood pressure and AF may be J-shaped, as has been proposed for other cardiovascular events.[24] Lower blood pressures were associated with an increased risk for AF, possibly, in part, due to severe illness like sepsis or end-stage heart failure.

Table 1 Factors for incident atrial fibrillation, progression atrial fibrillation[a], and associated events

Validated risk factors, concomitant cardiovascular conditions	Hazard ratio
Age	
Benjamin *et al.* M/F per 10 years[9]	2.1/2.2
Furberg *et al.* per 7 years[11]	1.03
Psaty *et al.*[12]	1.1
Verdecchia *et al.* per 10 years[13]	1.8 PAF
	2.9 CAF
DeVos *et al.*[14]	1.6[a]
Schnabel *et al.*[15]	2.3
Gami *et al.*[16]	2.0
Aviles *et al.*[17]	1.4
Marcus *et al.*[18]	1.1/1.1
Chamberlain *et al.*[19]	2.1–5.9
Male gender	
Benjamin *et al.* M/F per 10 years[9]	1.5
Furberg *et al.* per 7 years[11]	–
Schnabel *et al.*[15]	1.9
Gami *et al.*[16]	2.7
Gammage *et al.*[20]	2.4
Aviles *et al.*[17]	1.7
Marcus *et al.*[18]	1.6/1.7
Chamberlain *et al.*[19]	1.9
Validated risk factors, concomitant cardiovascular conditions	**Hazard Ratio**
Hypertension	
Benjamin *et al.*[9]	1.5/1.4
Furberg *et al.*[11]	1.4
Krahn *et al.*[21]	1.4
Psaty *et al.*[12]	1.1
DeVos *et al.*[14]	1.5[a]
Schnabel *et al.*[15]	1.2
Treated hypertension	1.8
Rosengren *et al.*[22]	1.7
Treated hypertension	2.1
Gammage *et al.*[20]	1.4
Aviles *et al.*[17]	1.3
Conen *et al.*[23]	
Syst 130–140/140–160/>160	1.4/1.7/2.2
Diast 85–90/90–95/>95	1.3/1.5/1.5
Thomas *et al.*[24] Achieved blood pressure: syst	
<120 and>140: J shaped curve	2/2
Marcus *et al.*[18]	1.5
	2.1
Chamberlain *et al.*[19]	1.4/2.2
Valvular heart disease	
Benjamin *et al.*[9]	1.8/3.4
Furberg *et al.*[11]	3.2
Krahn *et al.*[21]	3.2
Psaty *et al.*[12]	2.2
Heart failure	
Benjamin *et al.*[9]	4.5/5.9
Furberg *et al.*[11]	2.8

Continued

Table 1 *Continued*

Validated risk factors, concomitant cardiovascular conditions	Hazard ratio
Krahn *et al.*[21]	3.4
Schnabel *et al.*[15]	3.2
DeVos *et al.*[14] [a]progression to permanent AF	2.2[a]
DeVos *et al.*[14]	7.7
Gammage *et al.*[20]	3.8
Aviles *et al.*[17]	1.4
Tsang *et al.*[8]	2.1
Marcus *et al.*[18]	3.0/2.9
Chamberlain *et al.*[19]	3.0
Diabetes	
Benjamin *et al.*[9]	1.4/1.6
Furberg *et al.*[11]	–
Gammage *et al.*[20]	2
Marcus *et al.*[18]	1.5
	2.1
Chamberlain *et al.*[19]	1.9
Coronary artery disease (MI)	
Benjamin *et al.*[9]	1.4/–
Furberg *et al.*[11]	–
Krahn *et al.*[21]	3.6
Psaty *et al.*[12]	1.4
Gami *et al.*[16] <65 years	2.7
Tsang *et al.*[8]	2.2
Marcus *et al.*[18]	2.2
	3.6
Schnabel *et al.*[15]	1.4
Chamberlain *et al.*[19]	2.2
Associated risk factors, genetic conditions	**Hazard Ratio**
Genetic factors	
Family history	
Fox *et al.*[25]	1.9
Arnar *et al.*[26]	1.8
Marcus *et al.*[18]	1.2
AF susceptible loci identified by GWAS	
Ellinor *et al.*[27] 1q25 lone AF	1.1
Gudbjartsson *et al.*[28] 4q25	1.5
Benjamin *et al.*[29]	1.7
	1.3
Less validated risk factors and risk markers	**Hazard Ratio**
Obesity/BMI	
Krahn *et al.*[21]	1.3
Tsang *et al.*[30] BMI > 30; >35[a]	1.5/1.9[a]
Tedrow *et al.*[31] BMI > 25/>30	1.2/1.7
Frost *et al.*[32] BMI > 30 M/ F	2.3/2.0
Schnabel *et al.*[15]	1.2
Rosengren *et al.*[22] BMI > 27.5	1.7
Gami *et al.*[16] only <65years per 1 kg/m^2	1.1
Wang *et al.*[33] BMI > 30 M/F	1.5/1.5
Dublin *et al.*[34] per unit BMI	1.03

Continued

Table 1 *Continued*

Less validated risk factors and risk markers	Hazard ratio
Marcus *et al.*[18]	–
	–
Chamberlain *et al.*[19] >25/>30	–/1.8
Watanabe *et al.*[35]	1.8
Blood pressure/ pulse pressure	
Psaty*et al.*[12] syst BP per 10	1.1
Mitchell *et al.*[36] per 20 mmHg	1.3
Conen *et al.*[23]	
Syst 130–140/140–160/>160	1.4/1.7/2.2
Diast 85–90/90–95/>95	1.3/1.5/1.5
Height	
Psaty*et al.*[12] per centimetre	1.03
Mont *et al.*[37] >1.77	16.5
Rosengren *et al.*[22] >1.8 m	1.7
Chamberlain *et al.*[19] >1.73	1.9
Sleep apnoea syndrome	
Stevenson *et al.*[38] 2008	3.0
Gami *et al.*[16] only <65 years	3.3
Gami *et al.*[39]	2.2
Subclinical hyperthyroidism	
Sawin *et al.*[40] (relative risk)	3.1
Gammage *et al.*[20]	
Cappola *et al.*[41]	
Heeringa *et al.*[42]	1.9
Alcohol consumption (often excessive)	
Conen *et al.*[43]	1.5
Rosengren *et al.*[22]	1.3
Mukamal *et al.*[44] former	1.3
Kadoma *et al.*	
Chronic kidney disease	
Iguchiet *al.*[45]	
Baber *et al.*[46]	1.9
Asselbergs *et al.*[47] albuminuria	1.5
Go *et al.*[48]	1.9
Horio *et al.*[49]	1.4[a]
Competitive or athlete-level endurance sports	
Mont *et al.*[37]	22.8
Abdulla *et al.*[50] meta-an	5.3
Aizer *et al.*[51] 5–7 days/week	1.7
Molina *et al.*[52]	8.8
Elosua *et al.*[53]	2.9
Chronic obstructive pulmonary disease	
DeVos *et al.*[14] [a]progression to permanent AF	1.5 n.s.
[a]Stroke	2.0
Smoking	
Benjamin *et al.*[9]	–/–
Furberg *et al.*[11]	–
Krahn *et al.*[21]	–
Heeringa *et al.*[54] current/former	1.5/1.5
Rosengren *et al.*[22]	1.3
Schnabel *et al.*[15] current	–
Chamberlain *et al.*[19] current/former	–/–

Continued

Table 1 *Continued*

Less validated risk factors and risk markers	Hazard ratio
Coffee	
Mattioli *et al.*[55]	
Conen *et al.*[56]	
PR interval	
Cheng *et al.*[57] per 20 ms	1.1
Schnabel *et al.*[15]	1.2
Cheng *et al.*[57] [a]all mort >210 ms	1.4
Chamberlain *et al.*[19] > 200 ms	2.7
Murmur	
Schnabel *et al.*[15]	2.4
Chamberlain *et al.*[19]	1.9
Biomarkers haemodynamic stress	
ANP	
Schnabel *et al.*[58]	1.5
Latini, Masson. *J Int Med* 2010 ANP[a]1st re AF	1.2
Smith *et al.*[59]	1.6
BNP	
Schnabel *et al.*[58]	1.6
Latini *et al.*[60] BNP[a]1st re AF	1.2
Smith *et al.*[59]	no
Patton *et al.*[61] 1st vs. 5th Qu	4.0
Biomarkers of inflammation (C-reactive protein, IL6, TNF-alfa a.o.)[a]	
Issac *et al.*[62] (review)	
Schnabel *et al.*[63] (osteoprotegrin)	
Schnabel *et al.*[58] (C-reactive protein)	1.3
Conen *et al.*[64] (multimarker sc. 3)	1.3
Masson *et al.*[65] rec AF[a]	1.6
Aviles *et al.*[17] C-reactive proteinCHS 1st vs. 4th Q	No
Smith *et al.*[59] 2010	1.3
Marrott *et al.*[66] 1st vs. 5th Qu	1.2
Genetically elev C-reactive protein	2.2
	0.9
Newer, less established risk factors or markers	**Hazard Ratio**
Birth weight	
Conen *et al.*[67] >4 kg	1.7
Biomarkers of cardiac damage	
Latini *et al.*[60] TNT[a]	1.2[a]
Pre-clinical atherosclerosis	
Heeringa *et al.*[68] carot int med M/F	1.6/2.1
Furberg *et al.*[11]	–
Psaty *et al.*[12]	–
Psychological determinants	
Mattioli *et al.*[55]	
Eaker *et al.*[69]	

[a]No longer associated with incident AF after adjustment for left atrial diameter.
–: No significant association.
ARIC: atherosclerosis risk in communities; CAF: chronic atrial fibrillation; CHS: cardiovascular heath Study; EHS: Euro Heart Survey; F: female; Fram: Framingham Study; GWAS: genome wide association study; M: male; MI: myocardial infarction; PAF: paroxysmal atrial fibrillation; PHS: physical health study; Q: quartile; Qu: quintile; TNT: cardiac troponin T; WHS: women's health study.

Other factors such as *heart failure* are less well defined or used in a broad sense.[9,12,59,70,73] Also included are patients with heart failure and preserved left ventricular function[6,8] and patients with *coronary artery disease*, the latter mainly when they present with left ventricular dysfunction.[8,15,16,18,19] 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[8,9,11,12,33,37,70] which may lead to atrial dilatation, fibrosis, and electrical remodelling that finally provides the stimulus and the substrate for the development of AF.

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.[9,12,70]

Male gender has often been associated with incident AF.[9,11,15–18,20,59] Notably, few females have been included in trials but some data suggest that females are older and suffer from more concomitant cardiovascular disease when included.[74] This contrasts with the consistent observation that female gender is a risk factor for stroke in patients with established AF.[75,76] These contrasting associations are difficult to explain: Whether male gender pre-disposes to AF, whether AF is more often symptomatic and hence earlier diagnosed in males, or whether males accrue more (possibly less well validated) risk factors for AF, or whether females are less likely to seek medical attention when suffering from AF can only be answered by additional epidemiological data. Despite a higher burden of risk factors, blacks appear to be at less risk of developing AF.

Metabolic factors such as *diabetes mellitus and hyperthyroidism* have been recognized as independent risk factors for AF.[8,9,11,18–20,37,70,77] More recently, the metabolic syndrome has been recognized as a less well-established risk factor, although this term may also describe the summation of several risk factors.[35] However, even in this setting, whether some modifying genetic factors account for the genesis of AF in individual cases, is unknown.

Less well-established risk factors for incident atrial fibrillation

There is a range of less well-established risk factors that are associated with incident AF or with AF-related complications such as stroke, heart failure, or death. Deciphering the functional consequences of genetic changes associated with AF in the population[78,79] and epigenetic analyses can teach us more about risk factors for AF.[80] Identifying genetic 'biomarkers' that promote the development of subclinical disease might open new pathways for risk stratification and prevention of AF (see below).

Traditionally, *subclinical hyperthyroidism* [normal peripheral thyroid hormone levels but suppressed thyroid stimulating hormone (TSH)] has been considered as a modifying factor for the development of AF, but recent data suggest that even in a pre-subclinical setting (a newly defined term in this context), the incidence of AF is increased, i.e. when TSH remains in the lower level of normal or T4 increases within the normal range.[20,40–42]

Obesity has recently been revisited as a less well-validated risk factor for the development of AF in population-based studies[15,16,18,19,21,30–34] (*Table 1*). High body mass index also associates with increased left atrial volume.[81] One study suggests that high birth weight already associates with AF in women >45 years of age.[67] *Increased epicardial fat* also has been associated with increased AF persistence independent of other risk factors.[82,83] *Tall stature* also increases the risk of developing AF.[22,37]

Newer markers of increased risk for AF include the *sleep apnea syndrome* which appears to be associated with obesity.[16] In addition, *chronic obstructive pulmonary disease*[14] 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.[45,48]

Environmental factors such as *excessive alcohol consumption*,[22,43,44] possibly also moderate alcohol consumption[84] and *smoking*[9,11,21] are well-established risk markers for AF. Recent data confirm the deleterious effects of smoking on incident AF in contemporary cohorts.[15,19,22,85] Many of these factors are components of the so-called metabolic syndrome, and may share biological causes and AF-related effects.

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,[52,86–88] possibly associated with training-related hypertrophy, diastolic dysfunction, atrial dilatation, and fibrosis as has been demonstrated in trained rats.[89]

Biomarkers for atrial fibrillation

Analysis of patient serum, assessment of cardiac size and function by imaging including electrocardiography, and genetic analyses all provide biomarkers that 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 are emerging as new serum risk factors. In a population-based sample of middle-aged people, these biomarkers had incremental value for the prediction of incident AF.[58,64,90–93] Notably, atrial natriuretic peptide (ANP) might be a better predictor for AF than brain natriuretic peptide (BNP),[59] although other studies have shown the opposite.[61] Preliminary data suggest that higher levels of natriuretic peptides (and of C-reactive protein, see below) may also increase the risk for stroke in AF patients.

C-reactive protein and interleukin-6

Analysis of myocardial biopsies demonstrates infiltration by inflammatory cells in patients with AF.[47,62,94] Likewise, (high-sensitivity) C-reactive protein or interleukin-6[17,47,59,95,96] is associated with AF. Overall, the association of serum biomarkers with AF is not uniformly found.[17,65,90]

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.[97,98] Left atrial size or volume and left ventricular mass may predict AF, and left atrial volume even relates to death.[13,99,100] In addition, abnormal ventricular relaxation and diastolic dysfunction were predictors of first diagnosed non-valvular AF among elderly men and women,[8] and large size and anatomy of the atrial appendages may also relate to AF and its complications.[101,102]

Detailed imaging of atrial function

Left atrial size and volumes can be assessed routinely with M-mode echocardiography. 2D echocardiography is more precise, but also

more operator-dependent.[103] Three-dimensional imaging techniques (echocardiography, computed tomography, and cardiac magnetic resonance imaging) provide the most accurate information on the exact atrial size, shape, and volume.[104,105] From 3D echocardiography and cardiac magnetic resonance imaging,[106] the total atrial emptying fraction, active atrial emptying fraction (active contraction), passive atrial emptying fraction (conduit function), and atrial expansion index (reservoir function) can be assessed.[107,108] Moreover, the left atrial velocities and active deformation (strain) can also be assessed with sophisticated echocardiography,[109] and left atrial synchronicity can also be derived.[110,111] Despite the availability of these modalities, there is still a lack of data showing correlations between such parameters and incident AF as well as of complications of AF. In addition, whether improvements of these parameters are associated with better outcome needs to be assessed. Transoesophageal echocardiography may furthermore provide information on stroke risk beyond traditional stroke risk factors.[112]

Visualizing atrial scars and fibrosis

Another important measurement is the detection of left atrial fibrosis and scar tissue as assessed by delayed-enhanced magnetic resonance imaging. The technique is relatively sensitive and specific for transmural radio frequency-induced lesions.[113,114] The extent of scar tissue and fibrosis on 3D delayed-enhanced magnetic resonance imaging is inversely related to left atrial performance measured by echocardiographic left atrial strain and strain rate,[115] and large areas of delayed enhancement in the left atrium may predict recurrent AF after catheter ablation.[113] Hyper-enhancement of the left atrial wall was observed after ablation, representing scar tissue, and the extent of scar tissue 3 months after the ablation was related to freedom of AF after ablation.[116–118] Technicalities of magnetic resonance-based imaging of atrial fibrosis and scar render reproducibility of these findings challenging, and visualization of scars is likely limited to transmural lesions.

ECG-based parameters

ECG-based parameters such as long (within the normal range) or prolonged PR interval clearly relate to AF in the population,[15,119] possibly related to atrial structural remodelling and delayed intra-atrial conduction.[15,19,57] Similarly, longer P wave duration also associates with the risk for developing AF.[120–122]

Depressed heart rate variability may pre-dispose survivors of a myocardial infarction to AF.[123] Furthermore, the observation of an episode of AF after cardiac surgery may identify patients at high subsequent risk of developing AF. Similar to the serum biomarkers discussed above, electrocardiogram (ECG) changes may be proxies or 'integrators' of other risk factors, e.g. prolongation of PR interval may be a sign of sodium channelopathies (see 'genetic factors'), but may also reflect damage to atrial conduction.

Genetic factors

Genetic factors are associated with AF, especially of pre-mature onset of AF. In a small number of patients (~5% of AF patients, more in patients with early onset-AF), mutations associated with genetically conferred cardiomyopathies can be identified such as long QT syndrome,[124–129] Brugada syndrome,[130] short QT syndrome,[128,131] atrial septal defects,[132] or hypertophic cardiomyopathy.[133–135] Some of these patients carry a familial predisposition to AF ([25,26,131,136]; see overview in Kirchhof *et al.*[2]). On the population level, several single nucleotide polymorphisms (SNPs) close to the PITX2 gene located on chromosome 4q25 strongly associate with AF,[28,137] especially with early-onset AF.[138] Other, weaker associations are found on chromosome 1q25[27] and on chromosome 16.[29] Association of other polymorphisms with AF, found in smaller cohorts, could often not be replicated, indicating the risk of overreporting of 'false positive' results.[139] The molecular mechanisms conferring AF in such a setting have recently been investigated in genetically modified models for long QT syndrome[140] and in models with reduced PITX2 expression.[78,79]

Open questions

Distinction between risk factors and risk markers

AF risk factors are clinically measurable indicators of a biological process that relates to AF, while risk markers are proxies to an AF-causing process, but do not contribute by themselves to the biology of AF. A clear separation between risk markers and risk factors is not always possible since not all biological causes of AF are well understood (*Table 1*). Moreover, it is not well understood how these risk factors and risk markers interact, i.e. aggravate or mask each other, and whether there are special subgroups where risk factors have a different meaning. Future research will hopefully give us more insight into risk factors and markers that predispose to AF and its associated complications.

Role of biomarkers

With the notable exception of the Framingham cohort study and population-wide genomic analyses, most reports on serum, imaging-based, or genetic biomarkers have been done in small patient cohorts and require validation in other patient series that allow sufficient control of confounding factors.[18,25,26,141] Some of the large antithrombotic trials may provide opportunities to relate AF recurrences and other outcomes to biomarkers.

Are there specific factors for progression of AF?

The vast majority of patients experience AF as a chronically progressive disease that will eventually end up in permanent AF.[1,142] The available data suggest that these factors overlap largely with factors that lead to the development of AF (see above). In the German Atrial Fibrillation Network (AFNET) registry, the more of these factors were present, the greater the likelihood that patients had persistent or even permanent AF.[143] Likewise, the EuroHeartSurvey investigators recently proposed the 'HATCH' score (based on risk factors for AF progression—Heart failure, age, previous transient ischaemic attack or stroke, chronic obstructive pulmonary disease, and hypertension) which identifies patients who will progress from paroxysmal to persistent AF.[14] There is a clear and unmet need to identify and characterize factors associated with progression of AF, and the relative contribution of established risk factors for progression, first occurrence, or first recurrence of AF.

In summary, many of the classical clinical parameters used to assess stroke risk are also risk factors for the development of AF. The impact of each risk factor may vary by age: genetic factors, obesity, and endurance sports may be more likely to predict AF in younger patients, while other factors may be more prevalent and relevant in older AF patients. Disease severity (e.g. blood pressure value in hypertension, actual left ventricular function, among others) will be relevant for risk assessment. Many factors are interrelated and their interaction may enhance or even annihilate the impact of the new marker with respect to established markers. The available data on 'new' risk factors are often derived from observational studies with technical limitations. Furthermore, there is a complex interaction between risk factors and 'disease severity'. Several of the newly proposed markers may reflect disease severity, while others such as left atrial size may integrate the total atrial damage. Almost all currently available data sets are based on detection of AF by a simple, short ECG. This does not take into account that risk factors may contribute to perpetuation of AF, also neglects 'silent' AF which may be diagnosed by intensified ECG monitoring (see below) and may impact the relevance of several risk factors.[1,144,145] 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 characterize their interrelation.

A pathophysiologically oriented classification of atrial fibrillation to guide therapy

Currently, AF is classified by duration (paroxysmal, persistent, long-standing persistent, permanent)[3,146] and by the extent of AF-causing symptoms (EHRA score I–IV, or CCS-SAF score 0–IV).[3,147] The symptom classification reflects the need for therapeutic interventions, especially rhythm control therapy. In part, the duration of AF gives a simple reflection of the extent of 'atrial structural damage', but this is a very indirect assessment at best. 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.[3,146] 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 (*Table 2*).

Inherited atrial fibrillation

This type of AF 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.[138]

Monogenic forms

Atrial fibrillation is a common finding in patients with inherited, monogenic cardiomyopathies, and other, infrequent familial forms of AF occur without other signs of heart disease.[131,136] Monogenic forms of AF appear to underlie the arrhythmia in ~5% of AF patients.[2,3,148] It is conceivable that specific therapy of the underlying cardiomyopathy, including specific antiarrhythmic drugs in patients with 'electrical cardiomyopathies', may help to prevent AF in these patients. In families with early-onset AF in the absence of known cardiomyopathies, it may be worth studying the 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 pre-cordial ST segments.

Polygenic forms

A family history of AF is one of the risk factors for incident AF, outside of clear familial clustering (*Table 1*). In the past years, several population- and genome-wide association studies have identified small genetic changes [single nucleotide polymorphisms (SNPs)] that are associated with AF. The strongest association with AF and stroke is found on chromosome 4q25,[28,138] close to the PITX2 gene (see above). Deletion of pitx2 has recently been implicated in AF genesis in transgenic models.[78,79] 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. At present, there is no specific therapy for polygenic AF forms, but understanding the pathophysiology associated with these genetic abnormalities may help to develop such therapies in the future.

Focal atrial fibrillation

In the absence of severe cardiac disease, the initial event that conveys AF is often atrial ectopy from the pulmonary veins.[149] 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 AF. It is worth emphasizing that this type of AF should be differentiated from other (longer-lasting) forms of AF. Atrial fibrillation due to one or a few re-entrant drivers will also present with very similar electrical and clinical characteristics.[150–152] Long-lasting focal AF may lead to multiple wavelet complex AF.

Complex atrial fibrillation

This form of AF identifies the 'typical' AF patient, often at advanced age, who is suffering from concomitant cardiovascular diseases (e.g. those listed in *Table 1*), and 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 pre-disposition, and age.[148] Within this group of patients, the degree of 'complexity' is highly variable between patients. The most direct description of the complexity of AF stems from assessment of the number of fibrillation waves by direct contact mapping.[153–156] Patients with persistent AF harbour a several fold higher number of fibrillation waves than patients with acute AF. Also, non-invasive assessment of the AF substrate using ECG-based imaging has recently shown large variability in complexity of AF.[157] It is worthwhile to study whether non-invasive assessment of the AF substrate is capable

Table 2 Atrial Fibrillation Competence NETwork/European Heart Rhythm Association classification of atrial fibrillation by aetiology and suggested 'type-specific' therapy

AF type	Pathophysiological mechanism	Diagnostic characteristics	Proposed 'specific' therapy
Inheritable AF A: Monogenic	Patients with AF and inheritable cardiomyopathies (short QT, Brugada, LQTS, or hypertrophic cardiomyopathy, among others)	Gene-defect-related ECG-abnormalities, echo-diagnosis of inherited cardiomyopathy, family history, genetic testing	Therapy of underyling cardiomyopathy. Pharmacological reversal of the genetic defect (possibly, but not necessarily targeting the ion channel carrying the gene defect)
Inheritable AF B: Polygenic	Currently under study. Manifestation as AF at young age (<65 years) with or without familial clustering	AF of early onset, often with some familial aggregation of AF, no evident specific underlying cardiovascular disease causing the arrhythmia	Not yet identified
Focal AF	Localised triggers, in most cases originating from the pulmonary vein(s)	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	Isolation of the pulmonary vein(s), extended/repeated ablation procedures might be required
Complex AF	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'	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 ampltitude 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	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)
Post-operative AF	AF after cardiac surgery, multifactorial aetiology Acute factors: Inflammation, surgical trauma, high sympathetic tone, electrolyte changes, volume overload Chronic pre-disposition: Genetic factors, atrial structural remodelling due to structural heart disease	Transient AF in post-operative setting	Prevention by beta-blockers, steroids, antioxidants. Treatment should consider both the transient nature of post-operative AF and the fact that post-operative AF may indicate an increased likelihood of recurrent AF in the future

The group acknowledges that 'complex AF' comprises a relatively inhomogeneous group of patients, and that further classification of this type of AF may be required to guide management better.

to resolve the AF substrate complexity in clinically meaningful ranges.[158–160]

In animal studies, the number of fibrillation waves increased with both shortening of refractoriness as well as accumulation of collagen in the extracellular matrix[161,162] resulting in increasing electrical dissociation within the epicardial layer[163] and between the epicardial layer and the endocardial bundle network.[164] In these studies, the number of fibrillation waves inversely correlated with the ability of antiarrhythmic drugs to cardiovert AF, suggesting that complexity might serve as a relevant predictor for successful rhythm control. It appears reasonable to assume that less complex forms of AF respond better to rhythm control therapy, but this has not been tested yet. In cases with a higher degree of complexity, more extended ablation procedures might be required and antiarrhythmic drugs might be less effective. Such a graded therapy[2] might help to identify the best treatment option for an individual patient, to enhance the success rate of pharmacological cardioversion or catheter ablation therapy, to avoid unnecessary complications due to inadequate rhythm control therapy, and finally to reduce AF-related health care costs. In cases of very high substrate complexity, one may refrain from any attempt of rhythm control therapy. This concept requires testing in controlled clinical trials, e.g. by assessing AF complexity at baseline.

Post-operative atrial fibrillation

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. Many transient factors contribute to the occurrence of post-operative AF. Such patients undergo severe changes in fluid, electrolyte, and haemodynamic status, suffer from a systemic inflammatory reaction, enhanced sympathetic tone,[93,165–168] and surgical trauma to the atria.[169] Manifestation of AF post-surgery may also indicate the existence of a pre-disposing substrate possibly due to the underlying structural heart disease,[155] and hence AF often recurs months to years after an episode of post-operative AF. As enhanced sympathetic tone and inflammation are the most relevant factors pre-disposing to post-operative 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 anti-arrhythmic drugs or anticoagulation therapy).

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

Atrial fibrillation is a chronically progressive disease[1,170] 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 7 days, may detect AF in 1 in 20 or even 1 in 10 patients admitted with acute stroke and being in sinus rhythm at the time of admission.[171–173] Unfortunately, many patients with AF are only diagnosed after the first complication of the arrhythmia, often an ischaemic stroke, substantiating the need for early detection and therapy of AF.[2,3,10,174] Recent advances in long-term ECG monitoring such as prolonged use of Holter ECG devices for up to 30 days or telemetric ECG surveillance in hospitals have already extended the possibilities of detecting 'silent' AF. 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.[170,175,176]

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. This open questions has two aspects: (i) the need for more data on the validity and reliability of implanted subcutaneous monitors to detect 'true' AF and (ii) the clinical need to demonstrate that such 'silent' AF episodes have the same prognostic impact as AF detected by conventional methods. These open questions notwithstanding, 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.[144,145,175,177–179]

The conundrum of atrial fibrillation burden

The term 'AF burden' has been proposed as the total amount of time spent in AF per monitored time period. It should be considered that AF burden represents a heterogeneous entity; for example, many short episodes of AHRE could result in the same AF burden as a single long-standing episode, and may have different biological effect on atrial electrical and contractile function, and on remodelling and coagulation processes.

Mainly driven by the technical accuracy of AF detection, a duration of $>5–6$ min has been associated with stroke and death.[145,175,177] Other analyses also suggest that longer times spent in AF are associated with slightly higher stroke risk, and that this increased risk is independent of classical stroke risk factors.[175,177,178,180] There is a clear need to unify the definitions of AHRE across device manufacturers, and to investigate the impact of short AHRE episodes (<5 min duration) on outcomes and stroke risk estimation. It may be speculated that prevention of AF could help to reduce residual strokes in patients with AF on anticoagulant therapy.[174,181] This will be tested in the EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) trial (ISRCTN04708680).

Implantable subcutaneous devices can provide continuous cardiac rhythm monitoring in patients that do not require pacemakers or defibrillators.[182] The diagnostic accuracy of subcutaneous ECG monitors is good, but implanted monitors may not detect all episodes of AF picked up by conventional, manually analysed Holter ECG.[183] For a balanced approach to patients with AHRE detected by implanted devices, the group proposes a stepwise procedure to document AHRE (*Figure 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] A uniform (company-independent) standard for the definition of AHRE by subcutaneous and intracardiac devices is clearly needed for the clinical evaluation and implementation of detecting silent AF by such devices.

Improving stroke prevention by antithrombotic therapy

Oral anticoagulation clearly prevents ischaemic strokes in AF patients[3] and most patients with AF are likely to benefit from anticoagulant therapy.[3,184–186] In general, AF patients at risk of stroke can be identified by validated stroke risk factors, and recent guidelines reflect a paradigm shift in recommending an approach in which anticoagulation is a default antithrombotic therapy in AF patients.[3,146,184,187] But this effective and potentially life-saving therapy comes at the price of inducing relatively infrequent but potentially severe bleeding events. Numerically, events that are counted as major bleeds in large trials occur in similar frequency compared to ischaemic strokes. In some of the recent trials, bleeding events even outnumber strokes. The majority of these bleeding events, however, have less clinical impact than ischaemic strokes: major bleeding events include clinically relevant and less significant events ranging from the rare but severe intracranial haemorrhage to less relevant smaller gastrointestinal bleeds.[184,186–189]

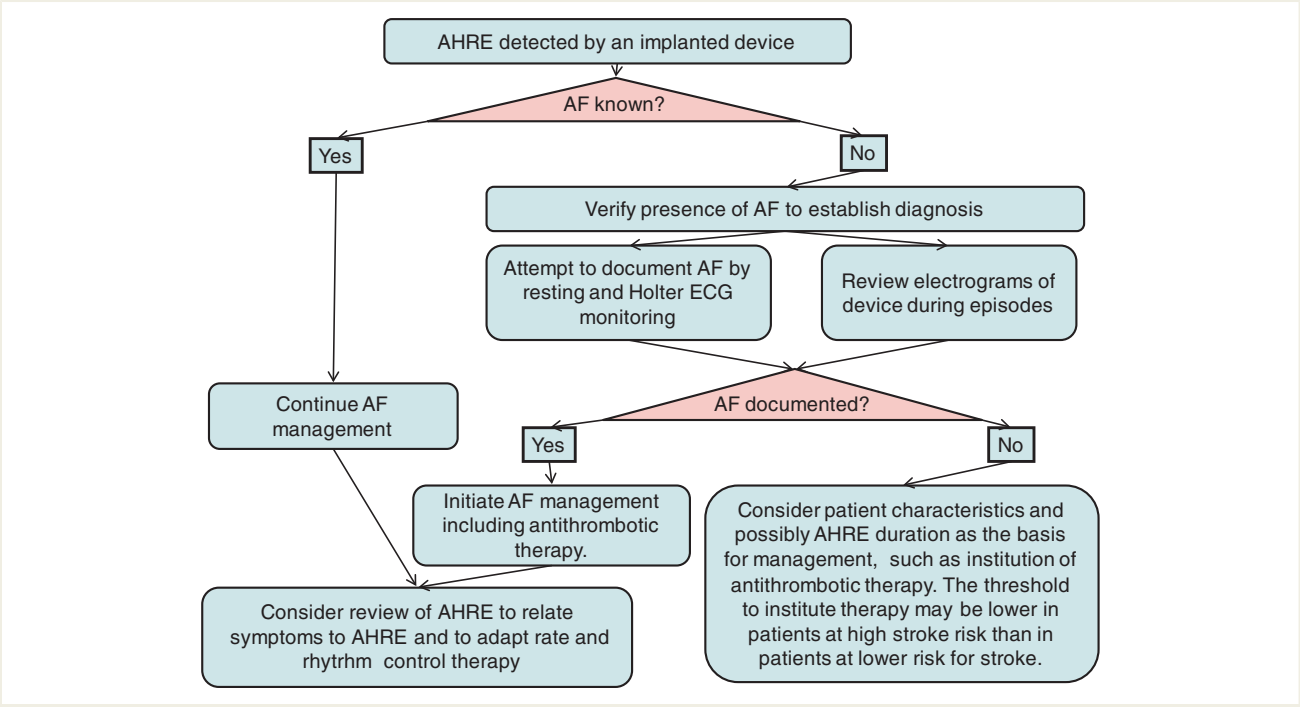

Figure 1 Approach to patients with atrial high-rate episodes detected by implanted devices. AHRE, atrial high rate episode.

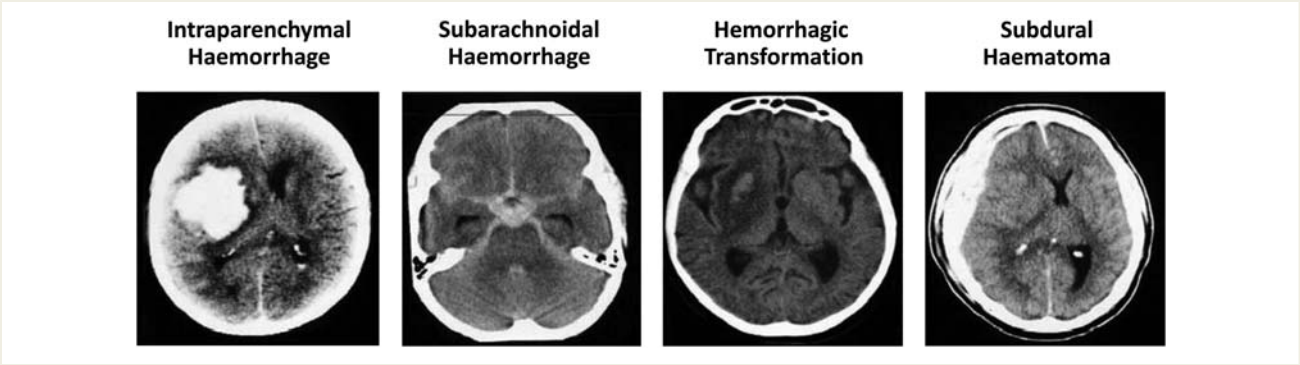

Figure 2 Cerebral computed tomograms of four types of intracranial bleeding (true intracerebral haemorrhage, subdural haematoma, subarachnoidal haematoma, epidural haematoma).

However, it is important to remember that ischaemic strokes that can be prevented by anticoagulant therapy outnumber intracerebral haemorrhages in most AF patients.[189–191]

Furthermore, the likely introduction of newer, potentially safer antithrombotic agents into clinical practice may influence decisions for anticoagulant therapy, at least according to decision models.[192]

Detecting an increased risk for intracranial bleeds

The available data suggest that patients—in contrast to their treating physicians—are often willing to accept excess bleeds if this helps to prevent ischaemic strokes.[193] 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.[194–196] Nonetheless, variable international normalized ratio (INR) values, excess consumption of alcohol or drugs, enzymatically detected liver damage and renal dysfunction,[194,195] incontinence and gait apraxia, as well as certain genetic factors[197] and potentially subclinical lesions (detectable as amyloid angiopathy) on cerebral magnetic resonance imaging[198–202] may identify patients at high bleeding risk. Furthermore, bleeding events accumulate in the first year after initiation of vitamin K antagonist therapy.[203]

Whether consideration of such clinical or imaging signals can help to avoid anticoagulant-induced severe bleeds remains to be assessed.

Careful classification of intracranial bleeds

Intracranial bleeds are usually investigated by cerebral imaging (computed tomography and/or magnetic resonance imaging). 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 (*Figure 2*). Haemorrhagic transformation of cerebral ischaemia is not considered as a primary bleeding complication. Combination therapy with acetylsalicylic acid is a major risk factor for intracranial haemorrhage in anticoagulated patients.[204,205] Intracranial haemorrhages appear to be less prevalent with dabigatran and also to some extent with rivaroxaban as compared to warfarin.[187,190] The reasons for this outcome remain speculative, and potential explanations may include that dabigatran and rivaroxaban do not cross the blood–brain barrier, at least not in pre-clinical studies,[206] or the fact that dabigatran or rivaroxaban do not interfere with the formation of TF-VIIa complexes, thereby preserving local haemostatic mechanims.

Information needed for the clinical use of newer anticoagulants

Strokes in AF patients not receiving anticoagulant therapy confer a 30-day mortality of 24%.[207] Vitamin K antagonists are widely used throughout Europe and the USA, 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.[143,208,209] There is extensive knowledge about vitamin K antagonists in the medical community and anticoagulated patients are familiar with the oral anticoagulation regimen. This knowledge and experience is lacking at present for the newer anticoagulants. Therefore, there is a need to educate physicians, including general physicians,[209] and patients about these new compounds, ideally before they are used (*Table 3*).

Physicians will need thorough and balanced information on the therapeutic principles, drug effects, and side effects, management of (bleeding) complications, and appropriate action in the case of overdose. Such information can be communicated with credibility by independent bodies, e.g. professional and patient organizations. Furthermore, physicians will need timely and comprehensive information on drug–drug interactions for each of the new compounds, including interactions with over the counter-medications and drugs that given transiently for other indications (e.g. antibiotics).

Important information on new anticoagulants in comparison to vitamin K antagonists for physicians. 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. When to restart?;
- drug–drug interactions including cytochrome p450 isoenzymes;[210]
- 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 and 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).

In patients requiring antiplatelet therapy (specifically dual antiplatelet therapy, e.g. after stenting or acute coronary syndrome), there is no published trial experience available, and guidance is dependent upon case series and cohort data.[211,212] The data on combining acetylsalicylic acid with dabigatran (40% of patients in RELY received aspirin at baseline[187]) also show that a combination of antiplatelet therapy and anticoagulation is associated with more bleeding, with no appreciable impact on efficacy outcomes.[213] Recent data suggest that 'triple therapy'[214] may be relatively safe with dabigatran, but the experience even in the large RELY trial is limited.[215] Therefore, we suggest to follow the recommendation for combination of antiplatelets and vitamin K antagonists in current guidelines.[3,212]

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 factor Xa inhibitors will have an effect on activated partial thromboplastin time (aPTT), while conventional assessment of factor Xa activation will not suffice to detect the anticoagulant effect of these substances. Factor Xa antagonists have a dose-dependent effect on prothrombin time (PT), with a close correlation to plasma concentrations if neoplastin is used for the

assay. The readout needs to be in seconds as the INR normalization is only validated for vitamin K antagonists. Dabigatran will increase ecarin clotting time which may be used to monitor the anticoagulant effect.[216] Although the new antithrombotics affect aPTT, and a marked elevation of aPTT may relate to bleeding risk, such measures should probably not affect drug dose. Specific calibrators and controls are currently under development for commercialization, or have recently been made available for clinical use. Although repeated blood testing to measure anticoagulant effect has disadvantages, the requirement for repeated blood testing may increase therapy adherence, and adherence may decrease when newer drugs that do not require frequent monitoring are used. Providing anticoagulant therapy without the need for INR monitoring may, on the other hand, free health care resources for a more comprehensive management approach to AF patients.

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

A small but challenging group of patients that is increasing are those with severe renal dysfunction [glomerular filtration rate (GFR) $<$ 30 mL/min]. These patients are at high risk for stroke and bleeds,[48] and it is likely that renal function will deteriorate over time in most patients with renal dysfunction. It is unlikely that renal dysfunction—unlike other risk factors—would favour bleeds in excess of ischaemic events, but it is difficult to validate as this would require large cohorts with repetitive assessment of renal dysfunction over time, to assess time trends. Hence, it appears reasonable to consider severe renal dysfunction as an additional risk factor for stroke. These patients have been excluded from antithrombotic trials in AF, and they are also at high risk of death, myocardial infarction, cardiovascular events, and bleeding. Based on pharmacokinetic data, the Food and Drug Administration (FDA) approved the use of a lower dose of one of the newer anticoagulants (dabigatran, 75 mg bid) in patients with severe renal dysfunction (GFR 15–30 mL/min), rather than any prospective data from randomised controlled trials *per se*. Of note, patients who entered the trial had a creatinine clearance of 30 mL/min or more.[187] In the typical elderly AF patient with renal dysfunction, renal function can deteriorate over time, and may be associated with increase in bleeding events. This is reminiscent of the high bleeding rate in stroke patients receiving intravenous thrombolysis.[217] Even experience with vitamin K antagonists in those with renal dysfunction is limited at present,[218] and therefore the choice of oral antithrombotic agents cannot be based on controlled data. The newer anticoagulants have so far only very rarely been evaluated in dialysis patients, and some can be removed by dialysis.[216,219]

Patient values and preferences in atrial fibrillation management

Patients need information on AF, but the degree and type of information demanded differs between patients. Improvement in AF patient education appears necessary given the comparatively higher willingness of valve patients to receive oral anticoagulants compared to AF patients.[193] 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, e.g. the elderly, or diabetics. Integration of such activities into information programmes is helpful.

The home pages of the Atrial Fibrillation Association (UK www.afa.co.uk), the Stop AF campaign (www.StopAF.org), Anticoagulation Europe (www.anticoagulationeurope.org), the Stroke Association (www.stroke.org.uk), and AFNET (Germany, www.kompetenznetz-vorhofflimmern.de) may provide examples for providing information to AF patients, with links to country-specific information. The advent and commercialization of new anticoagulants generates a need to inform and educate patients better. This is an opportunity for health-care professionals and health-care providers alike to better inform patients about AF and the risk for stroke. Seizing this opportunity could help to achieve earlier and comprehensive management of AF patients.[2] In addition to this general need for information on AF and its complications, there is also a specific need for information on the new anticoagulants, which will differ for patients naive to or experienced with vitamin K antagonists. Dedicated AF clinics may be an opportunity to close information gaps for patients.

Questions and answers for patient education on the use of anticoagulants

How do clots form?

What are the different options to prevent clots?

What are the benefits of anticoagulation (in general)?

What are the benefits of the drug that I shall receive?

What are the side effects, in particular, how high is my risk for bleeding during anticoagulant therapy?

Are there other therapeutic options, e.g. other drugs?

Does the drug interact with food or other drugs (e.g. over the counter NSAIDs)?

What happens when I do not take the drug for a day, for a week, for a month (compliance, adherence)?

How do I take the medication?

- When?
- Before/during/after food (intake of intact capsule in case of dabigatran)?
- Can I take the drug with other medication?
- What to do in case of a missed dose?
- Explain why the novel anticoagulants do not need monitoring (particularly for vitamin K antagonist-experienced patients).

Keep a list of all drugs that you take with you.

Information on lifestyle changes (contact sports, use of an electric razor, pilot's licence).

What to do in case of overdose and in case of bleeding (stop medication, local haemostasis, haemodialysis).

The group recommends collaboration between pharmaceutical and medical device companies, ideally co-ordinated by professional and scientific organizations, 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

Table 3 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

Patients who are likely to benefit from new anticoagulants
Patients with poor TTR (time in therapeutic range) and INR control due to
innate/genetics for warfarin metabolism
inadequate access to monitoring, poor monitoring quality, and/or inability to self-monitor
Patients requiring medication interacting with vitamin K antagonists
Patients who have decided against anticoagulation with vitamin K antagonists despite adequate education
Patients at low risk of gastrointestinal bleeding (dabigatran) and patients without severe renal dysfunction
Patients who suffered an ischaemic stroke on warfarin with adequate INR
Patients potentially less suitable for novel anticoagulants in the early phase after market introduction
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
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
Patients with history of gastrointestinal bleeding
Patients with poor TTR due to non-adherence may benefit from the regular reinforcement of therapy by monitoring needed for vitamin K antagonists therapy
Patients at risk of progressing towards severe renal failure, e.g. patients with severe heart failure
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

patients. Patient groups will be helpful in the dissemination of this information, especially when they are independent of industry.

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 vitamin K antagonists in different European countries. There is also a clear need to generate data on the external validity of trial results during clinical use. The use of the new drugs will require careful analyses of the benefits of the drugs with respect to 'global' cost reduction.[220] The group recognizes that the pricing of new drugs and the reimbursement frames set up by payers will markedly influence the use of the new drugs, and that all currently available cost-effectiveness estimates are based on assumptions as well as on data.

Interventional stroke prevention in atrial fibrillation 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.[221] Another possibility is offered by an epicardial suture device that can occlude the left atrial appendage during concomitant open heart surgery. While technically feasible and approved in some countries, this intervention will need to be re-evaluated compared to newer, potentially safer anticoagulants in patients who are considered unsuitable for vitamin K antagonist therapy[221]: Some of those patients will be eligible for newer anticoagulants, but patients who have suffered from an unexplained intracranial haemorrhage on oral anticoagulation, those who are unlikely to comply with anticoagulation, patients with clear and absolute contraindications for anticoagulant therapy, or patients who have suffered an ischaemic stroke on anticoagulant therapy, may still remain candidates for a left atrial appendage occluder. 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.

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 INR values.[207,222] But even on optimal anticoagulant therapy in controlled trials, the residual stroke rate in AF patients remains unacceptably high at ~1.5% per year.[184,186,187,223,224]

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. post-operative AF) and of 'silent' AF[2,3] is much less well studied, although even short episodes of AF detected by devices relate to a stroke risk (see above). Based on this information, it appears unlikely that rhythm control therapy alone can be sufficient to prevent AF-related strokes. Nonetheless, there is a signal of reduced stroke rates by dronedarone in the ATHENA trial.[185] Whether this effect was related to preventing AF is not clear. There are two surveys after ablation of AF ($n = 750$ and 3300 patients) that detected low stroke event rates in patients who discontinued anticoagulation.[225] The authors of those studies propose that stopping anticoagulation may be acceptable, but the stroke risk in these populations and follow-up times was not sufficient to accrue adequate stroke numbers, especially when considering the reports on very late recurrences of AF after ablation.[226,227]

Hence, rhythm control does not appear to suffice to prevent strokes in AF in the absence of oral anticoagulation. On the other hand, 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'[2]) 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 controlled trials in the near future, including the EAST trial (ISRCTN04708680, NCT01288352).

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References

1. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC *et al.* Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. *Europace* 2007;**9**:1006–23.
2. Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R *et al.* Early and comprehensive management of atrial fibrillation: proceedings from the 2nd AFNET/EHRA consensus conference on atrial fibrillation entitled 'research perspectives in atrial fibrillation'. *Europace* 2009;**11**:860–85.
3. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S *et al.* Guidelines for the management of atrial fibrillation. *Europace* 2010;**12**:1360–420.
4. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A *et al.* Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation* 2009;**119**:606–18.
5. Shotan A, Garty M, Blondhein DS, Meisel SR, Lewis BS, Shochat M *et al.* Atrial fibrillation and long-term prognosis in patients hospitalized for heart failure: results from heart failure survey in Israel (HFSIS). *Eur Heart J* 2010;**31**:309–17.
6. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP *et al.* Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006;**152**:86–92.
7. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ *et al.* Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004.
8. Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR *et al.* Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002;**40**:1636–44.
9. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;**271**:840–4.
10. Cosio FG, Aliot E, Botto GL, Heidbuchel H, Geller CJ, Kirchhof P *et al.* Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. *Europace* 2008;**10**:21–7.
11. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;**74**:236–41.
12. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP *et al.* Incidence of and risk factors for atrial fibrillation in older adults. *Circulation* 1997;**96**:2455–61.
13. Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F *et al.* Atrial fibrillation in hypertension: predictors and outcome. *Hypertension* 2003;**41**:218–23.
14. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ *et al.* Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010;**55**:725–31.
15. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr *et al.* Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–45.
16. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T *et al.* Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:565–71.
17. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA *et al.* Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;**108**:3006–10.
18. Marcus GM, Alonso A, Peralta CA, Lettre G, Vittinghoff E, Lubitz SA *et al.* European ancestry as a risk factor for atrial fibrillation in African Americans. *Circulation* 2010;**122**:2009–15.
19. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R *et al.* A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;**107**:85–91.
20. Gammage MD, Parle JV, Holder RL, Roberts LM, Hobbs FD, Wilson S *et al.* Association between serum free thyroxine concentration and atrial fibrillation. *Arch Intern Med* 2007;**167**:928–34.
21. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* 1995;**98**:476–84.
22. Rosengren A, Hauptman PJ, Lappas G, Olsson L, Wilhelmsen L, Swedberg K. Big men and atrial fibrillation: effects of body size and weight gain on risk of atrial fibrillation in men. *Eur Heart J* 2009;**30**:1113–20.

23. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;**119**:2146–52.
24. Thomas MC, Dublin S, Kaplan RC, Glazer NL, Lumley T, Longstreth WT Jr *et al.* Blood pressure control and risk of incident atrial fibrillation. *Am J Hypertens* 2008;**21**:1111–6.
25. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ *et al.* Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA* 2004;**291**:2851–5.
26. Arnar DO, Thorvaldsson S, Manolio TA, Thorgeirsson G, Kristjansson K, Hakonarson H *et al.* Familial aggregation of atrial fibrillation in Iceland. *Eur Heart J* 2006;**27**:708–12.
27. Ellinor PT, Lunetta KL, Glazer NL, Pfeufer A, Alonso A, Chung MK *et al.* Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet* 2010;**42**:240–4.
28. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A *et al.* Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature* 2007;**448**:353–7.
29. Benjamin EJ, Rice KM, Arking DE, Pfeufer A, van Noord C, Smith AV *et al.* Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. *Nat Genet* 2009;**41**:879–81.
30. Tsang TS, Barnes ME, Miyasaka Y, Cha SS, Bailey KR, Verzosa GC *et al.* Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. *Eur Heart J* 2008;**29**:2227–33.
31. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE *et al.* The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). *J Am Coll Cardiol* 2010;**55**: 2319–27.
32. Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Med* 2005; **118**:489–95.
33. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS *et al.* Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471–7.
34. Dublin S, French B, Glazer NL, Wiggins KL, Lumley T, Psaty BM *et al.* Risk of new-onset atrial fibrillation in relation to body mass index. *Arch Intern Med* 2006;**166**:2322–8.
35. Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S *et al.* Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation* 2008;**117**:1255–60.
36. Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG *et al.* Pulse pressure and risk of new-onset atrial fibrillation. *JAMA* 2007;**297**:709–15.
37. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M *et al.* Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. *Europace* 2008;**10**:15–20.
38. Stevenson IH, Teichtahl H, Cunnington D, Ciavarella S, Gordon I, Kalman JM. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J* 2008;**29**: 1662–9.
39. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE *et al.* Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;**110**: 364–7.
40. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P *et al.* Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;**331**:1249–52.
41. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL *et al.* Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA* 2006; **295**:1033–41.
42. Heeringa J, Hoogendoorn EH, van der Deure WM, Hofman A, Peeters RP, Hop WC *et al.* High-normal thyroid function and risk of atrial fibrillation: the Rotterdam study. *Arch Intern Med* 2008;**168**:2219–24.
43. Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. *JAMA* 2008;**300**: 2489–96.
44. Mukamal KJ, Psaty BM, Rautaharju PM, Furberg CD, Kuller LH, Mittleman MA *et al.* Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study. *Am Heart J* 2007;**153**:260–6.
45. Iguchi Y, Kimura K, Kobayashi K, Aoki J, Terasawa Y, Sakai K *et al.* Relation of atrial fibrillation to glomerular filtration rate. *Am J Cardiol* 2008;**102**:1056–9.
46. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W *et al.* Association of Chronic Kidney Disease with Atrial Fibrillation Among Adults in the United States: Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol* 2011;**4**:26–32.
47. Asselbergs FW, van den Berg MP, Diercks GF, van Gilst WH, van Veldhuisen DJ. C-reactive protein and microalbuminuria are associated with atrial fibrillation. *Int J Cardiol* 2005;**98**:73–7.
48. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L *et al.* Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation* 2009;**119**:1363–9.
49. Horio T, Iwashima Y, Kamide K, Tokudome T, Yoshihara F, Nakamura S *et al.* Chronic kidney disease as an independent risk factor for new-onset atrial fibrillation in hypertensive patients. *J Hypertens* 2010;**28**:1738–44.
50. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**: 1156–9.
51. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572–7.
52. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J *et al.* Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace* 2008;**10**:618–23.
53. Elosua R, Arquer A, Mont L, Sambola A, Molina L, Garcia-Moran E *et al.* Sport practice and the risk of lone atrial fibrillation: a case-control study. *Int J Cardiol* 2006;**108**:332–7.
54. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH *et al.* Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;**27**:949–53.
55. Mattioli AV, Bonatti S, Zennaro M, Melotti R, Mattioli G. Effect of coffee consumption, lifestyle and acute life stress in the development of acute lone atrial fibrillation. *J Cardiovasc Med (Hagerstown)* 2008;**9**:794–8.
56. Conen D, Chiuve SE, Everett BM, Zhang SM, Buring JE, Albert CM. Caffeine consumption and incident atrial fibrillation in women. *Am J Clin Nutr* 2010;**92**: 509–14.
57. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D *et al.* Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;**301**:2571–7.
58. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB *et al.* Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. *Circulation* 2010;**121**:200–7.
59. Smith JG, Newton-Cheh C, Almgren P, Struck J, Morgenthaler NG, Bergmann A *et al.* Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *J Am Coll Cardiol* 2010;**56**:1712–9.
60. Latini R, Masson S, Pirelli S, Barlera S, Pulitano G, Carbonieri E *et al.* Circulating cardiovascular biomarkers in recurrent atrial fibrillation: data from the GISSI-Atrial Fibrillation Trial. *J Intern Med* 2011;**269**:160–71.
61. Patton KK, Ellinor PT, Heckbert SR, Christenson RH, DeFilippi C, Gottdiener JS *et al.* N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. *Circulation* 2009; **120**:1768–74.
62. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol* 2007;**50**:2021–8.
63. Schnabel RB, Lunetta KL, Larson MG, Dupuis J, Lipinska I, Rong J *et al.* The relation of genetic and environmental factors to systemic inflammatory biomarker concentrations. *Circ Cardiovasc Genet* 2009;**2**:229–37.
64. Conen D, Ridker PM, Everett BM, Tedrow UB, Rose L, Cook NR *et al.* A multimarker approach to assess the influence of inflammation on the incidence of atrial fibrillation in women. *Eur Heart J* 2010;**31**:1730–6.
65. Masson S, Aleksova A, Favero C, Staszewsky L, Bernardinangeli M, Belvito C *et al.* Predicting atrial fibrillation recurrence with circulating inflammatory markers in patients in sinus rhythm at high risk for atrial fibrillation: data from the GISSI atrial fibrillation trial. *Heart* 2010;**96**:1909–14.
66. Marott SC, Nordestgaard BG, Zacho J, Friberg J, Jensen GB, Tybjaerg-Hansen A *et al.* Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population. *J Am Coll Cardiol* 2010;**56**:789–95.
67. Conen D, Tedrow UB, Cook NR, Buring JE, Albert CM. Birth weight is a significant risk factor for incident atrial fibrillation. *Circulation* 2010;**122**:764–70.
68. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Rooij FJ, Lip GY *et al.* Subclinical atherosclerosis and risk of atrial fibrillation: the Rotterdam study. *Arch Intern Med* 2007;**167**:382–7.
69. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. *Circulation* 2004;**109**:1267–71.
70. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982;**306**: 1018–22.
71. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients implications for thromboprophylaxis: Implications for thromboprophylaxis. *J Am Coll Cardiol* 2010;**56**:827–37.

72. Spach MS, Heidlage JF, Dolber PC, Barr RC. Mechanism of origin of conduction disturbances in aging human atrial bundles: experimental and model study. *Heart Rhythm* 2007;**4**:175–85.
73. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA *et al.* Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–5.
74. Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ *et al.* Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *J Am Coll Cardiol* 2005;**46**:1298–306.
75. Group SiAw. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–54.
76. Lane DA, Lip GY. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. *Thromb Haemost* 2009;**101**:802–5.
77. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol* 2005;**105**:315–8.
78. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. *Proc Natl Acad Sci USA* 2010;**107**:9753–58.
79. Kirchhof P, Kahr PC, Kaese S, Piccini I, Vokshi I, Scheld HH *et al.* PITX2c is expressed in the adult left atrium, and reducing Pitx2c expression promotes atrial fibrillation inducibility and complex changes in gene expression. *Circ Cardiovasc Genet* 2011;**4**:123–33.
80. Baccarelli A, Rienstra M, Benjamin EJ. Cardiovascular epigenetics: basic concepts and results from animal and human studies. *Circ Cardiovasc Genet* 2010;**3**:567–73.
81. Stritzke J, Markus MR, Duderstadt S, Lieb W, Luchner A, Doring A *et al.* The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging the MONICA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study. *J Am Coll Cardiol* 2009;**54**:1982–9.
82. Al Chekakie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J *et al.* Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol* 2010;**56**:784–8.
83. Batal O, Schoenhagen P, Shao M, Ayyad AE, Van Wagoner DR, Halliburton SS *et al.* Left atrial epicardial adiposity and atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:230–6.
84. Kodama S, Saito K, Tanaka S, Horikawa C, Saito A, Heianza Y *et al.* Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2011;**57**:427–36.
85. Heeringa J, Kors JA, Hofman A, van Rooij FJ, Witteman JC. Cigarette smoking and risk of atrial fibrillation: the Rotterdam Study. *Am Heart J* 2008;**156**:1163–9.
86. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R *et al.* Long-lasting sport practice and lone atrial fibrillation. *Eur Heart J* 2002;**23**:477–82.
87. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**:800–7.
88. Mont L, Elosua R, Brugada J. Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter. *Europace* 2009;**11**:11–7.
89. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC *et al.* Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation* 2011;**123**:13–22.
90. Smith JG, Platonov PG, Hedblad B, Engstrom G, Melander O. Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur J Epidemiol* 2010;**25**:95–102.
91. den Uijl DW, Delgado V, Tops LF, Ng AC, Boersma E, Trines SA *et al.* Natriuretic peptide levels predict recurrence of atrial fibrillation after radiofrequency catheter ablation. *Am Heart J* 2011;**161**:197–203.
92. Schnabel RB, Larson MG, Yamamoto JF, Kathiresan S, Rong J, Levy D *et al.* Relation of multiple inflammatory biomarkers to incident atrial fibrillation. *Am J Cardiol* 2009;**104**:92–6.
93. Kaireviciute D, Blann AD, Balakrishnan B, Lane DA, Patel JV, Uzdavinys G *et al.* Characterisation and validity of inflammatory biomarkers in the prediction of post-operative atrial fibrillation in coronary artery disease patients. *Thromb Haemost* 2010;**104**:122–7.
94. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997;**96**:1180–4.
95. Tveit A, Seljeflot I, Grundvold I, Abdelnoor M, Smith P, Arnesen H. Effect of candesartan and various inflammatory markers on maintenance of sinus rhythm after electrical cardioversion for atrial fibrillation. *Am J Cardiol* 2007;**99**:1544–8.
96. Dernellis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. *Eur Heart J* 2004;**25**:1100–7.
97. Osranek M, Bursi F, Bailey KR, Grossardt BR, Brown RD Jr, Kopecky SL *et al.* Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up. *Eur Heart J* 2005;**26**:2556–61.
98. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR *et al.* Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol* 2006;**47**:1018–23.
99. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ *et al.* Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;**47**:2357–63.
100. Tsang TS, Barnes ME, Gersh BJ, Takemoto Y, Rosales AG, Bailey KR *et al.* Prediction of risk for first age-related cardiovascular events in an elderly population: the incremental value of echocardiography. *J Am Coll Cardiol* 2003;**42**:1199–205.
101. De Vos CB, Weijs B, Crijns HJ, Cheriex EC, Palmans A, Habets J *et al.* Atrial tissue Doppler imaging for prediction of new-onset atrial fibrillation. *Heart* 2009;**95**:835–40.
102. The Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *Ann Intern Med* 1992;**116**:6–12.
103. Casaclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:1–11.
104. Tops LF, Schalij MJ, Bax JJ. Imaging and atrial fibrillation: the role of multimodality imaging in patient evaluation and management of atrial fibrillation. *Eur Heart J* 2010;**31**:542–51.
105. Maceira AM, Cosin-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010;**12**:65.
106. Ozgun M, Kirchhof P, Bunck AC, Heindel W, Eckardt L, Maintz D. MRI of right atrial function after catheter ablation of atrial flutter. *Acad Radiol* 2010;**17**:856–61.
107. Anwar AM, Geleijnse ML, Soliman OI, Nemes A, ten Cate FJ. Left atrial Frank–Starling law assessed by real-time, three-dimensional echocardiographic left atrial volume changes. *Heart* 2007;**93**:1393–7.
108. Marsan NA, Westenberg JJ, Tops LF, Ypenburg C, Holman ER, Reiber JH *et al.* Comparison between tissue Doppler imaging and velocity-encoded magnetic resonance imaging for measurement of myocardial velocities, assessment of left ventricular dyssynchrony, and estimation of left ventricular filling pressures in patients with ischemic cardiomyopathy. *Am J Cardiol* 2008;**102**:1366–72.
109. Saraiva RM, Demirkol S, Buakhamsri A, Greenberg N, Popovic ZB, Thomas JD *et al.* Left atrial strain measured by two-dimensional speckle tracking represents a new tool to evaluate left atrial function. *J Am Soc Echocardiogr* 2010;**23**:172–80.
110. Van Beeumen K, Duytschaever M, Tavernier R, Van de Veire N, De Sutter J. Intra- and interatrial asynchrony in patients with heart failure. *Am J Cardiol* 2007;**99**:79–83.
111. Delgado V, Vidal B, Sitges M, Tamborero D, Mont L, Berruezo A *et al.* Fate of left atrial function as determined by real-time three-dimensional echocardiography study after radiofrequency catheter ablation for the treatment of atrial fibrillation. *Am J Cardiol* 2008;**101**:1285–90.
112. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. *J Am Coll Cardiol* 1998;**31**:1622–6.
113. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN *et al.* Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation* 2009;**119**:1758–67.
114. Ozgun M, Maintz D, Bunck AC, Monnig G, Eckardt L, Wasmer K *et al.* Right atrial scar detection after catheter ablation: comparison of 2D and high spatial resolution 3D-late enhancement magnetic resonance imaging. *Acad Radiol* 2011;**18**:488–94.
115. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S *et al.* Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging* 2010;**3**:231–9.
116. McGann CJ, Kholmovski EG, Oakes RS, Blauer JJ, Daccarett M, Segerson N *et al.* New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation. *J Am Coll Cardiol* 2008;**52**:1263–71.
117. Badger TJ, Oakes RS, Daccarett M, Burgon NS, Akoum N, Fish EN *et al.* Temporal left atrial lesion formation after ablation of atrial fibrillation. *Heart Rhythm* 2009;**6**:161–8.
118. Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally S *et al.* Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. *J Cardiovasc Electrophysiol* 2011;**22**:16–22.

119. Pfeufer A, van Noord C, Marciante KD, Arking DE, Larson MG, Smith AV *et al.* Genome-wide association study of PR interval. *Nat Genet* 2010;**42**:153–9.
120. Magnani JW, Gorodeski EZ, Johnson VM, Sullivan LM, Hamburg NM, Benjamin EJ *et al.* P wave duration is associated with cardiovascular and all-cause mortality outcomes: the National Health and Nutrition Examination Survey. *Heart Rhythm* 2011;**8**:93–100.
121. Holmqvist F, Platonov PG, McNitt S, Polonsky S, Carlson J, Zareba W *et al.* Abnormal P-wave morphology is a predictor of atrial fibrillation development and cardiac death in MADIT II patients. *Ann Noninvasive Electrocardiol* 2010;**15**: 63–72.
122. De Bacquer D, Willekens J, De Backer G. Long-term prognostic value of p-wave characteristics for the development of atrial fibrillation in subjects aged 55 to 74 years at baseline. *Am J Cardiol* 2007;**100**:850–4.
123. Jons C, Raatikainen P, Gang UJ, Huikuri HV, Joergensen RM, Johannesen A *et al.* Autonomic dysfunction and new-onset atrial fibrillation in patients with left ventricular systolic dysfunction after acute myocardial infarction: a CARISMA Substudy. *J Cardiovasc Electrophysiol* 2010;**21**:983–90.
124. Kirchhof P, Eckardt L, Franz MR, Mönnig G, Loh P, Wedekind H *et al.* Prolonged atrial action potential durations and polymorphic atrial tachyarrhythmias in patients with long QT syndrome. *J Cardiovasc Electrophysiol* 2003;**14**:1027–33.
125. Kirchhof P, Eckardt L, Monnig G, Johna R, Loh P, Schulze-Bahr E *et al.* A patient with 'atrial torsades de pointes'. *J Cardiovasc Electrophysiol* 2000;**11**:806–11.
126. Zellerhoff S, Pistulli R, Moennig G, Hinterseer M, Beckmann B-M, Koebe J *et al.* Atrial arrhythmias in long QT syndrome—a Nested Case Control Study. *J Cardiovasc Electrophysiol* 2009;**20**:401–7.
127. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704–9.
128. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P *et al.* Short QT syndrome: clinical findings and diagnostic–therapeutic implications. *Eur Heart J* 2006;**27**:2440–7.
129. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R *et al.* Short QT syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965–70.
130. Eckardt L, Kirchhof P, Loh P, Schulze-Bahr E, Johna R, Wichter T *et al.* Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J Cardiovasc Electrophysiol* 2001;**12**:680–5.
131. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY *et al.* KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;**299**:251–4.
132. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med* 1999;**340**:839–46.
133. Lee CH, Liu PY, Lin LJ, Chen JH, Tsai LM. Clinical characteristics and outcomes of hypertrophic cardiomyopathy in Taiwan—a tertiary center experience. *Clin Cardiol* 2007;**30**:177–82.
134. Losi MA, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G *et al.* Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2004;**94**:895–900.
135. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP *et al.* Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**39**:301–7.
136. Brugada R, Tapscott T, Czernuszewicz GZ, Marian AJ, Iglesias A, Mont L *et al.* Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med* 1997;**336**:905–11.
137. Lubitz SA, Sinner MF, Lunetta KL, Makino S, Pfeufer A, Rahman R *et al.* Independent susceptibility markers for atrial fibrillation on chromosome 4q25. *Circulation* 2010;**122**:976–84.
138. Kaab S, Darbar D, van Noord C, Dupuis J, Pfeufer A, Newton-Cheh C *et al.* Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation. *Eur Heart J* 2009;**30**:813–9.
139. Sinner MF, Lubitz SA, Pfeufer A, Makino S, Beckmann BM, Lunetta KL *et al.* Lack of replication in polymorphisms reported to be associated with atrial fibrillation. *Heart Rhythm* 2011;**8**:403–9.
140. Blana A, Kaese S, Fortmuller L, Laakmann S, Damke D, Bragt KV *et al.* Knock-in gain-of-function sodium channel mutation prolongs atrial action potentials and alters atrial vulnerability. *Heart Rhythm* 2010;**7**:1862–69.
141. Bedi M, McNamara D, London B, Schwartzman D. Genetic susceptibility to atrial fibrillation in patients with congestive heart failure. *Heart Rhythm* 2006;**3**:808–12.
142. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL *et al.* Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 2007;**115**:3050–6.
143. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P *et al.* The registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. *Europace* 2009;**11**:423–34.
144. Ziegler PD, Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD *et al.* Incidence of newly detected atrial arrhythmias via implantable devices in patients with a history of thromboembolic events. *Stroke* 2010;**41**:256–60.
145. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R *et al.* Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation* 2003;**107**:1614–9.
146. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA III *et al.* 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011;**123**:104–23.
147. Dorian P, Guerra PG, Kerr CR, O'Donnell SS, Crystal E, Gillis AM *et al.* Validation of a new simple scale to measure symptoms in atrial fibrillation: the Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. *Circ Arrhythm Electrophysiol* 2009;**2**:218–24.
148. Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2011;**91**:265–325.
149. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
150. Sahadevan J, Ryu K, Peltz L, Khrestian CM, Stewart RW, Markowitz AH *et al.* Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. *Circulation* 2004;**110**:3293–9.
151. Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. *Circulation* 1997;**95**:511–21.
152. Kumagai K, Uno K, Khrestian C, Waldo AL. Single site radiofrequency catheter ablation of atrial fibrillation: studies guided by simultaneous multisite mapping in the canine sterile pericarditis model. *J Am Coll Cardiol* 2000;**36**:917–23.
153. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. *Circulation* 1994;**89**:1665–80.
154. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. *Circulation* 1997;**95**:1231–41.
155. Kanagaratnam P, Kojodjojo P, Peters NS. Electrophysiological abnormalities occur prior to the development of clinical episodes of atrial fibrillation: observations from human epicardial mapping. *Pacing Clin Electrophysiol* 2008;**31**: 443–53.
156. Allessie MA, de Groot NM, Houben RP, Schotten U, Boersma E, Smeets JL *et al.* The electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol* 2010;**3**:606–15.
157. Cuculich PS, Wang Y, Lindsay BD, Faddis MN, Schuessler RB, Damiano RJ Jr *et al.* Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. *Circulation* 2010;**122**:1364–72.
158. Guillem MS, Climent AM, Castells F, Husser D, Millet J, Arya A *et al.* Noninvasive mapping of human atrial fibrillation. *J Cardiovasc Electrophysiol* 2009;**20**:507–13.
159. Platonov PG, Nault I, Holmqvist F, Stridh M, Hocini M, Haissaguerre M. Left atrial appendage activity translation in the standard 12-lead ECG. *J Cardiovasc Electrophysiol* 2011;**22**:706–10.
160. Nault I, Lellouche N, Matsuo S, Knecht S, Wright M, Lim KT *et al.* Clinical value of fibrillatory wave amplitude on surface ECG in patients with persistent atrial fibrillation. *J Interv Card Electrophysiol* 2009;**26**:11–9.
161. Tanaka K, Zlochiver S, Vikstrom KL, Yamazaki M, Moreno J, Klos M *et al.* Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. *Circ Res* 2007;**101**:839–47.
162. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D *et al.* Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation* 2006;**113**:626–33.
163. Verheule S, Tuyls E, van Hunnik A, Kuiper M, Schotten U, Allessie M. Fibrillatory conduction in the atrial free walls of goats in persistent and permanent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:590–99.
164. Eckstein J, Maesen B, Linz D, Zeemering S, van Hunnik A, Verheule S *et al.* Time course and mechanisms of endo-epicardial electrical dissociation during atrial fibrillation in the goat. *Cardiovasc Res* 2011;**89**:816–24.
165. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G *et al.* Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. *Ann Thorac Surg* 1995;**60**:1709–15.
166. Lo B, Fijnheer R, Nierich AP, Bruins P, Kalkman CJ. C-reactive protein is a risk indicator for atrial fibrillation after myocardial revascularization. *Ann Thorac Surg* 2005;**79**:1530–5.
167. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM *et al.* Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 1997;**96**:3542–8.

168. Kaireviciute D, Aidietis A, Lip GY. Atrial fibrillation following cardiac surgery: clinical features and preventative strategies. *Eur Heart J* 2009;**30**:410–25.
169. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD *et al.* A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720–9.
170. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol* 2004;**43**:47–52.
171. Liao J, Khalid Z, Scallan C, Morillo C, O'Donnell M. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke* 2007;**38**:2935–40.
172. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke* 2004;**35**:1647–51.
173. Stahrenberg R, Weber-Kruger M, Seegers J, Edelmann F, Lahno R, Haase B *et al.* Enhanced detection of paroxysmal atrial fibrillation by early and prolonged continuous holter monitoring in patients with cerebral ischemia presenting in sinus rhythm. *Stroke* 2010;**41**:2884–88.
174. Kirchhof P. Can we improve outcomes in atrial fibrillation patients by early therapy? *BMC Med* 2009;**7**:72.
175. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G *et al.* Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol* 2005;**46**:1913–20.
176. Sinha AM, Diener HC, Morillo CA, Sanna T, Bernstein RA, Di Lazzaro V *et al.* Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL AF): design and rationale. *Am Heart J* 2010;**160**:36–41 e1.
177. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F *et al.* Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol* 2009;**20**:241–8.
178. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C *et al.* The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;**2**:474–80.
179. Healey J, Connolly S, Gold MR, Cappucci A, Israel C, van Gelder IC *et al.* The relationship between atrial high-rate episodes and stroke: the asymptomatic stroke and atrial fibrillation evaluation in pacemaker patients (ASSERT) trial. Abstract 21838. *Circulation* 2010;**122**:2220–21.
180. Boriani G, Botto G, Padeletti L, Santini M, Capucci A, Gulizia M *et al.* Improving stroke risk stratification using the CHADS2 and CHA2DS2VASc risk scores in paroxysmal atrial fibrillation patients by continuous arrhythmia burden monitoring. *Stroke* 2011;**42**:1768–70.
181. Connolly SJ, Crijns HJ, Torp-Pedersen C, van Eickels M, Gaudin C, Page RL *et al.* Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 2009;**120**:1174–80.
182. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R *et al.* Indications for the use of diagnostic implantable and external ECG loop recorders. *Europace* 2009;**11**:671–87.
183. Hindricks G, Pokushalov E, Urban L, Taborsky M, Kuck KH, Lebedev D *et al.* Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation—results of the XPECT trial. *Circ Arrhythm Electrophysiol* 2010;**3**:141–7.
184. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S *et al.* Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–78.
185. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C *et al.* Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–78.
186. Connolly S, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–17.
187. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
188. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W *et al.* Prevention of Stroke and Systemic Embolism Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared with Warfarin in Patients with Nonvalvular Atrial Fibrillation: The ROCKET AF Trial. *New Engl J Med*, in press.
189. Beasley BN, Unger E, Temple R. Anticoagulant options — why the FDA approved a higher but not a lower dose of Dabigatran (perspective). *N Engl J Med* 2011;**364**:1788–90.
190. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG *et al.* Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;**376**:975–83.
191. De Caterina R, Connolly SJ, Pogue J, Chrolavicius S, Budaj A, Morais J *et al.* Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W. *Eur Heart J* 2010;**31**:2133–40.
192. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;**4**:14–21.
193. Devereaux PJ, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, Brownell BF *et al.* Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;**323**:1218–22.
194. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–100.
195. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score. *J Am Coll Cardiol* 2011;**57**:173–80.
196. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM* 2007;**100**:599–607.
197. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI *et al.* Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Engl J Med* 2000;**342**:240–5.
198. Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. *Neurology* 2000;**55**:947–51.
199. Rosand J, Greenberg SM. Beyond hypertension: unraveling the causes of intracerebral hemorrhage. *Stroke* 2002;**33**:1195–6.
200. Kimberly WT, Gilson A, Rost NS, Rosand J, Viswanathan A, Smith EE *et al.* Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. *Neurology* 2009;**72**:1230–5.
201. Smith EE, Gurol ME, Eng JA, Engel CR, Nguyen TN, Rosand J *et al.* White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. *Neurology* 2004;**63**:1606–12.
202. Eckman MH, Wong LK, Soo YO, Lam W, Yang SR, Greenberg SM *et al.* Patient-specific decision-making for warfarin therapy in nonvalvular atrial fibrillation: how will screening with genetics and imaging help? *Stroke* 2008;**39**:3308–15.
203. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007;**115**:2689–96.
204. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**:492–501.
205. Thompson BB, Bejot Y, Caso V, Castillo J, Christensen H, Flaherty ML *et al.* Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010;**75**:1333–42.
206. Weinz C, Buetehorn U, Daehler HP, Kohlsdorfer C, Pleiss U, Sandmann S *et al.* Pharmacokinetics of BAY 59–7939—an oral, direct Factor Xa inhibitor—in rats and dogs. *Xenobiotica* 2005;**35**:891–910.
207. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV *et al.* Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;**349**:1019–26.
208. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW *et al.* Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;**26**:2422–34.
209. Kirchhof P, Nabauer M, Gerth A, Limbourg T, Lewalter T, Goette A *et al.* Impact of the type of center on management of AF patients: surprising evidence for differences in antithrombotic therapy decisions. *Thromb Haemost* 2011;**105**:1010–23.
210. Cabral KP, Ansell J, Hylek EM. Future directions of stroke prevention in atrial fibrillation: the potential impact of novel anticoagulants and stroke risk stratification. *J Thromb Haemost.* 2011; **9**:441–9
211. Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N *et al.* Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433–41.
212. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen KJ, Cuisset T *et al.* Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/ stenting. *Thromb Haemost* 2010;**103**:13–28.
213. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen JK, Cuisset T *et al.* Antithrombotic management of atrial fibrillation patients presenting with acute

coronary syndrome and/or undergoing coronary stenting: executive summary—a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2010;**31**:1311–8.

214. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E *et al.* Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* 2011;**13**: 723–46.
215. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J *et al.* risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial. *Circulation* 2011;**123**: 2363–72.
216. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M *et al.* Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;**103**:1116–27.
217. Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K *et al.* Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry. *Cerebrovasc Dis* 2011;**31**:123–9.
218. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009;**20**:2223–33.
219. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010;**49**:259–68.
220. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS *et al.* Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med* 2011;**154**:1–11.
221. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–42.
222. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG *et al.* Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008;**118**:2029–37.
223. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S *et al.* Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**: 1903–12.
224. Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, Davidson BL *et al.* Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008;**371**:315–21.
225. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A *et al.* The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;**55**:735–43.
226. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T *et al.* Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation* 2010;**122**:2368–77.
227. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F *et al.* Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011;**57**:160–6.