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REVIEW

Controversies in cardiovascular medicine

Early management of atrial fibrillation to prevent cardiovascular complications

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Atrial fibrillation (AF) is generally considered a progressive disease, typically evolving from paroxysmal through persistent to 'permanent' forms, a process attributed to electrical and structural remodelling related to both the underlying disease and AF itself. Medical treatment has yet to demonstrate clinical efficacy in preventing progression. Large clinical trials performed to date have failed to show benefit of rhythm control compared with rate control, but these trials primarily included patients at late stages in the disease process. One possible explanation is that intervention at only an early stage of progression may improve prognosis. Evolving observations about the progressive nature of AF, along with the occurrences of major complications such as strokes upon AF presentation, led to the notion that earlier and more active approaches to AF detection, rhythm-reversion, and maintenance of sinus rhythm may be a useful strategy in AF management. Approaches to early and sustained rhythm control include measures that prevent development of the AF substrate, earlier catheter ablation, and novel antiarrhythmic drugs. Improved classifications of AF mechanism, pathogenesis, and remodelling may be helpful to enable patient-specific pathophysiological diagnosis and therapy. Potential novel therapeutic options under development include microRNA-modulation, heatshock protein inducers, agents that influence Ca^{2+} handling, vagal stimulators, and more aggressive mechanism-based ablation strategies. In this review, of research into the basis and management of AF in acute and early settings, it is proposed that progression from paroxysmal to persistent AF can be interrupted, with potentially favourable prognostic impact.

Keywords Atrial fibrillation • Post-operative AF • Atrial remodelling • Integrated care pathways • Anticoagulation • Rhythm control • Natural history

Introduction

Atrial fibrillation (AF) is commonly considered a progressive condition, whereby the arrhythmia begins in a paroxysmal form, progressing through persistent to so-called 'permanent' AF as electrical and structural remodelling of the atrium act to favour its perpetuation.[1–3] Some data, however, suggest that ~40% of cases have persistent AF at the time of diagnosis, either because AF has been clinically silent, or because the substrate resulting from the underlying heart disease has progressed prior to AF onset.[4] As epidemiological studies have shown that the risk of stroke is increased even with short episodes of asymptomatic AF, and stroke may be a tragic presenting manifestation of previously undetected AF, the focus of AF management is shifting to earlier intervention in the course of the condition. Theoretically, earlier diagnosis and initiation of treatment might prevent or limit AF progression. It has also been suggested that personalized management of AF may improve outcomes, through treatment tailored to an individual's pathophysiology, risk factors, and genetic pre-disposition.[5] Here, we review the available evidence on the natural history and management of AF during early stages of the arrhythmia and in the acute setting, and

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propose that more pro-active diagnosis and treatment of AF may limit development of the AF substrate, reduce clinical progression, and potentially prevent long-term complications.

Predicting short-term risk and progression of atrial fibrillation

Registry data

Table 1 lists studies that have evaluated the clinical progression of AF from paroxysmal to persistent/permanent forms. The prevalence of progression varies with patient population and duration of follow-up, but is as high as 77% of patients progressing over 14 years.[13] Overall, the progression rate is ~5% per annum, except in young patients without underlying structural cardiovascular disease who have predominantly paroxysmal AF. Older patients, and those with underlying heart disease, have faster progression rates. Accumulation of 'AF risk factors' such as obesity, diabetes, and other consequences of a sedentary life style increases the risk for developing AF.[21] Conversely, some degree of physical activity reduces the likelihood of AF occurrence. Extreme training levels as found in competitive athletes predispose otherwise healthy persons to AF,[22] as well as to ventricular arrhythmias,[23] possibly secondary to a subtle genetic predisposition.[24]

Basic mechanisms contributing to atrial fibrillation

Conditions that promote AF involve atrial structural, electrical, and autonomic abnormalities and/or remodelling that lead to re-entry or triggered activity (*Figure 1*).[25] Slow conduction velocities and short-refractory periods allow the establishment and stabilization of re-entrant circuits. Delayed afterdepolarizations (DAD) emerge from abnormal Ca^{2+} release from the sarcoplasmic reticulum during diastole, acting as triggers for re-entry or, when sustained, as a focal source for AF.[26,27]

Basic mechanisms of atrial fibrillation-related remodelling

Once established, AF induces mechanisms for self-perpetuation ('AF begets AF').[28] The arrhythmia also induces structural, electrical, and autonomic remodelling superimposed upon pre-existing abnormalities to increase susceptibility to recurrent and more persistent AF (*Figure 1*).[27,29] Animal models are extensively used to study AF-induced remodelling, because underlying variables can be controlled much more rigorously than in patients.[30] The difference between AF-induced remodelling and that induced by underlying heart disease cannot be distinguished in human atrial tissue obtained during open-heart surgery.[30] However, clinical observations and laboratory studies with samples from AF patients have confirmed many of the observations in animal models.[26,27] It is well established that the prevalence of AF is higher in older age groups,[21] and it seems likely that older age is also a risk factor for incident AF (Kirchhof *et al.*[31]). Furthermore, there is an age-dependent loss of cardiomyocytes in the heart, including atrial tissue.[32]

Within hours of AF onset, the refractory period during AF heterogeneously shortens in response to electrical and autonomic remodelling,[28] by decreasing depolarizing current ($I_{Ca,L}$) and increasing repolarizing currents (I_{K1}, I_{KACh}).[33] Tachycardia-induced Ca^{2+} accumulation activates α1-subunit mRNA down-regulation.[33–35] A rate-dependent protein kinase C isoform switch modifies the I_{KACh} subunit phosphorylation state and activates the channel.[36,37] Connexin changes and/or attenuated sodium current (I_{Na}) contribute to decreased atrial conduction velocity by impairing cellular coupling.[38,39] The functional importance of a concurrent decrease in transient outward potassium current (I_{to}) is unclear.[35,40,41]

The importance of Ca^{2+} handling in remodelling is increasingly recognized. Rapid atrial activation rates stimulate Ca^{2+}/calmodulin-dependent kinase II (CaMKII),[42] which phosphorylates the Ca^{2+} release channel (type 2 ryanodine receptor, Ryr2), increasing its Ca^{2+} sensitivity and facilitating diastolic Ca^{2+} leakage events.[26] Along with increased sodium–calcium exchanger activity in AF, Ca^{2+}-leak events cause DAD that induce atrial premature beats and/or tachycardias.[43] Intracellular calcium oscillations might also induce atrial repolarization heterogeneity, favouring re-entry.[44]

Autonomic tone remodelling also contributes to the AF-induced arrhythmia substrate. Even relatively short periods of atrial tachycardia (3 h) increase discharge rates in the intracardiac ganglionated plexi.[45] Ablation of the intracardiac autonomic ganglia blunts tachycardia-induced refractoriness shortening and AF susceptibility, demonstrating a role for autonomic tone in AF-induced remodelling.[45] Spatially heterogeneous sympathetic hyper-innervation results from longer-lasting AF.[46] Arrhythmogenic structural remodelling develops after longer-term AF-induced remodelling, and uncontrolled ventricular rates accelerate structural remodelling by inducing myocardial dysfunction.[47] Cardiomyocyte–fibroblast interactions consequent to sustained atrial tachycardia also promote fibrosis.[48] Cardiac fibrosis, a hallmark of the structural AF substrate,[49] could be responsible for the atrial endo-epicardial electrical dissociation that underlies complex intra-atrial re-entry.[50]

Electrical remodelling and AF inducibility develop rate dependently in dogs, and are almost negligible at rates ≤200 b.p.m.[51] Atrial ectopic activity and AF often co-exist, and patients with frequent atrial tachyarrhythmias, even of relatively short duration, are at increased risk of AF.[52] The association between AF and atrial tachyarrhythmias could be due to common underlying conditions, to atrial tachycardias acting as a repetitive trigger for AF, or to the induction of AF-promoting remodelling by tachycardias. Of course, these explanations are by no means mutually exclusive and might all apply, to some extent, in many cases.

Relationship between basic mechanisms and clinical forms

Figure 2 presents a conceptual model of the relationship between basic AF mechanisms and clinical forms. The probability of AF occurrence depends upon the presence of both the triggers and substrate for the arrhythmia. It is likely that when triggers are rare and the substrate is not well developed the arrhythmia will occur infrequently, as brief paroxysms. Changes in substrate resulting from both intrinsic heart disease and AF are believed to contribute to progression from paroxysmal to 'permanent' AF (*Figure 1*).[25] Given the established AF-promoting effects of AF-induced remodelling,[26,27,53] the frequency, duration and time between paroxysmal AF episodes, either symptomatic or silent,

Table 1 Rates of progression of paroxysmal atrial fibrillation to persistent or permanent in observational studies or registries

Study	Number patients	Age (years)	Type of AF	Duration of AF at inclusion	Follow-up (years)	Progression of AF (%)	Predictors of progression (risk)
Abe (Osaka), 1997[6]	122	61 ± 12	Paroxysmal; lone AF: 21%	<6 months	2.16	Sustained AF ≥6 months: 11.5	Left atrial size, abnormal P-signal-averaged ECG[a]
Al-Khatib (Durham), 2000[7]	231	60 ± 13	Paroxysmal; lone AF: 41.6%	≥1 documented AF episode	4	8 at 1 year 18 at 4 years	Age (1.82 per decade), AF at presentation (3.56)
Barrett (Nashville), 2013[8]	253	67 (55–78)	New onset (ED) lone AF: 29%	New onset	1	24	HATCH score (ROC area 0.62)
Belgrade Atrial Fibrillation Study, 2012[9]	346	43.2 ± 9.9	First detected lone AF: 69.9% paroxysmal; 22.3% persistent	New onset	12	Overall: 33.5 Paroxysmal AF: 19.1 10-year cumulative rate of progression: 26.1	Overall: age (1.4 per decade), development of heart failure (2.9), development of hypertension (0.6), Paroxysmal: age (1.1 per decade), development of heart failure (6.2), development of hypertension (0.4)
CARAF, 2005[2]	757	64 (median)	First detected paroxysmal	First ECG confirmed AF	8	8.6 at 1 year 24.7 at 5 years Any recurrent AF: 63.2 at 5 years	Age (1.4 per decade), cardiomyopathy (2.41), aortic stenosis (3.04), mitral regurgitation (1.69), left atrial enlargement (3.05–4.17)
Danish Study, 1986[10]	426	66 (median)	Paroxysmal	First ECG confirmed AF	9 (median)	33.1	Underlying heart disease, thrombo-embolism
European Heart Survey, 2010[11]	1219	64 ± 13	Paroxysmal; lone AF: 17%		1	15 Permanent: 8 In subgroup with lone AF: 7 (persistent or permanent)	Age >75 years (1.57), heart failure (2.22), hypertension (1.52), stroke/TIA (2.02), COPD (1.51)
Fauchier (Tours), 2010[12]	2167	71 ± 14	Paroxysmal		2.6	14.1	Age >75 years, heart failure, hypertension, COPD, number of electrical cardioversions, dilated cardiomyopathy, prosthetic valve
Kato (Tokyo), 2004[13]	171	58.3 ± 11.8	First detected, paroxysmal	New onset	14	57 at 10 years 77 at 15 years	Age (1.27 per decade), myocardial infarction (2.33), valvular heart disease (2.29), left atrial enlargement (1.39)
Olmsted County, 1987[14]	88	44	Lone AF	First diagnosis	14.8	Recurrent paroxysmal: 58 Sustained: 12	–
Olmsted County, 2007[3]	71	44.2 ± 11.7	Lone AF: 48% paroxysmal, 52% persistent	First diagnosis	25.2	31 (30-year probability: 29)[b]	Age (1.7 per decade), QRS abnormalities (3.2)[c]
RECORD-AF, 2011[15]	5171	66 ± 11.79	52.3% paroxysmal, 18.7% lone AF	≤1 year	1	31 Rhythm vs. rate control: 13 vs. 54	Age >75 years (1.62), AF ≥3 months (1.48), persistent vs. paroxysmal AF (3.31), rhythm control (0.21), sinus rhythm (0.14), heart failure (1.27–1.41)
RECORD-AF, 2012[16]	2137	65.1 ± 12	Only paroxysmal, 20% lone AF	≤1 year	1	15	Heart failure (2.2), hypertension (1.5), rate control (3.2)
Rostagno (Florence), 1995[17]	106	63 ± 11	First detected paroxysmal lone AF	New onset	6	Recurrent paroxysmal: 55.6 Sustained: 4.7%	—

Sakamoto (Tokyo), 1995[18]	137	No progression: 62.4 ± 11 With progression: 70.1 ± 8.2	First detected paroxysmal	New onset	1	Sustained AF ≥6 months: 22	Age ≥65 years, heart failure, CTR ≥50%, diabetes, LA ≥38 mm, LVEF ≤0.76, f waves in V1 ≥2 mm
Takahashi (Tokyo), 1981[19]	94	60	First detected paroxysmal; lone AF: 24.5%	New onset	>6	Sustained AF ≥6 months: 20.2–25.3	Rheumatic valvular disease; frequency of paroxysms
UK GPRD, 2005[20]	418	Men: 67 ± 11, Women: 73 ± 10	First detected paroxysmal; no co-morbidity: 32%	New onset	2.7	11 at 1 year 17 at 2.7 years	Valvular heart disease (2.7), moderate to high alcohol intake (3.0)

AF, atrial fibrillation; CARAF, Canadian Registry of Atrial Fibrillation; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; ED, Emergency Department; GPRD, General Practice Research Database; RECORD-AF, REgistry on Cardiac rhythm disorders assessing control of atrial fibrillation; TIA, transient ischemic attack.
[a]Filtered P-wave duration ≥145 ms and the root-mean-square voltage of the last 30 ms of the filtered P-wave <3 μV.
[b]In the majority of patients within 15 years.
[c]QRS ≥110 ms. QRS notching, small R in the pre-cordial lead.

probably affect progression rate. When the substrate is highly developed, due to cardiovascular co-morbidities such as heart failure or hypertension and/or advanced AF-induced remodelling, AF episodes become more persistent and even 'permanent' (*Figure 2*). Ongoing triggers may also contribute to the maintenance of sustained AF. Some patients do not progress to 'permanent' forms, presumably because of limited development of the primary condition, resistance to AF-induced remodelling, or genetically determined patient-specific protective factors. Patients without structural remodelling progress more gradually than those with heart disease.[3] Prospective studies with careful clinical, biomarker, genetic, and atrial-imaging assessment are needed to better understand the basic determinants of AF-progression.

Anti-remodelling therapy

Anti-remodelling therapy (blue boxes in *Figure 1*) is directed at potentially preventable causes of AF-promoted remodelling, represented by the red zones in *Figure 3*. Classic antiarrhythmic drugs aim to prevent AF recurrences. There are as yet no convincing data that antiarrhythmic drugs, used to prevent AF recurrences, promote reversal of, or prevent, remodelling. The lack of evidence may be due to the relative inefficacy of most presently used antiarrhythmic drugs in preventing AF recurrence. Interestingly, there is experimental evidence that amiodarone, the most effective drug presently available for long-term sinus-rhythm maintenance, has anti-remodelling effects.[54] Targeting both primary disease and AF-induced remodelling may be necessary to increase therapeutic efficacy. The relative contribution of underlying primary conditions vs. AF itself to the clinical progression of AF is presently unclear, and will be important to determine in future research. Available data suggest that relieving haemodynamic overload may prevent AF recurrence. For example, mitral commissurotomy may acutely alter atrial electrophysiology and help restore sinus rhythm (SR) by electrical cardioversion.[55] After mitral commissurotomy, AF recurrences are infrequent following electrical cardioversion and amiodarone.[56] Reversal of experimental left atrium volume overload reverts electrophysiological remodelling, even when hypertrophy persists.[57] Treatment of left-ventricular dysfunction by cardiac resynchronization therapy may decrease the incidence of AF.[58] These observations suggest that treatment of the underlying condition, rather than pharmacological targets alone, may be an important component of any anti-remodelling approach.

Although the benefits of preventing remodelling with renin–angiotensin–aldosterone system (RAAS) inhibitors are well-established in experimental models,[47] RAAS blockers have largely failed to prevent AF in large, randomized prospective trials.[59,60] Inability to reverse advanced substrate or insufficient duration of therapy may explain negative outcomes. Trials showing benefit usually applied therapy early in conditions like hypertension and heart failure associated with structural remodelling, but there may also be other explanations for the discrepancies in the available literature. In a small study, success in preventing AF with candesartan was related to its ability to decrease plasma fibrotic markers,[61] but these results remain to be reproduced. Recently developed MRI-imaging techniques[62] may provide new insights by directly assessing effects of RAAS blockers and other anti-remodelling therapies on myocardial fibrosis. MicroRNAs are evolving as important regulators of

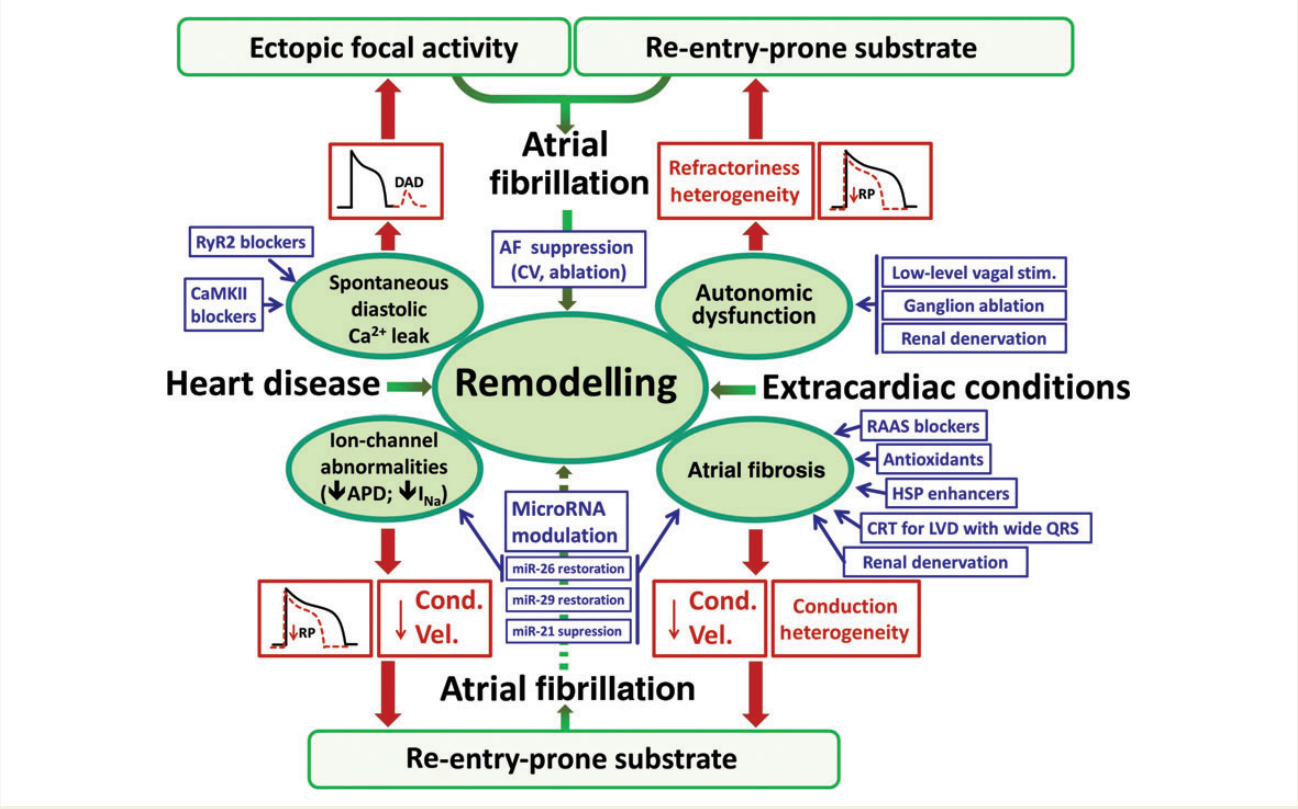

Figure 1 Basic mechanisms underlying AF-related remodelling and therapy. Schematic representation of the basic mechanisms underlying AF, the role of remodelling induced by AF (four large green ovals) and potential approaches (blue boxes) for anti-remodelling therapies. Atrial fibrillation-induced electrical remodelling is represented by the green ovals at the left, autonomic remodelling in the green oval at the upper right, and structural remodelling (fibrosis) at the lower right. Atrial fibrillation can result from re-entry or very rapid focal ectopic activity. Delayed afterdepolarizations resulting from abnormal diastolic Ca^{2+} leak cause focal ectopic activity that can trigger re-entry in a re-entry-prone substrate or maintain atrial fibrillation via rapid focal firing. Diastolic Ca^{2+} leak can result from Ca^{2+} overload or leakiness of sarcoplasmic reticulum Ca^{2+}-release channels (RyR2) due to gene mutations or hyperphosphorylation by Ca^{2+}/calmodulin-kinase II (CaMKII). Action potential duration decreases, which promote AF by reducing refractory period (RP), may result from reduced Ca^{2+} current or increased background inward rectifier K^+ currents. Reduced Na^+ current (I_{Na}) slows conduction, thereby favouring re-entry. Abnormalities of autonomic innervation can heterogeneously reduce RP, favouring re-entry, and can also promote DAD by increasing cell Ca^{2+} and activating CaMKII. For detailed discussions of mechanisms, see references[22,23] and.[55] Fibrosis promotes AF by causing conduction abnormalities that favour re-entry. Cond Vel, conduction velocity; AF, atrial fibrillation; APD, action potential duration; CRT, cardiac resynchronization therapy; CV, cardioversion; DAD, delayed after depolarizations; HSP, heat-shock protein; LVD, severe left-ventricular dysfunction; miR, microRNA; RAAS, renin–angiotensin–aldosterone system; stim., stimulation; Synd., syndrome.

pathology.[63] Atrial-selective inhibition of microRNA-21 prevented AF by suppressing fibrosis in a rat model,[64] microRNA-26 restoration reversed K^+-current up-regulation and AF promotion in a mouse-model,[65] and microRNA-29 restoration may reverse AF-promoting pro-fibrotic changes.[66] Other microRNAs are under investigation.[63] MicroRNA modulation may provide new therapeutic strategies for remodelling prevention. Heat-shock protein inducers, in development to prevent remodelling,[67] antioxidant agents,[53] and compounds targeting Ca^{2+} handling, are attractive potential therapeutic modalities.[53]

Autonomic modulation via subthreshold, low-level vagal stimulators blunts autonomic remodelling and prevents AF inducibility in animal models.[68] Vagus nerve stimulators are widely used, with few side-effects, to treat refractory epilepsy, and their benefits in heart failure are under study, but their potential role in AF prevention has not been elucidated. Intracardiac ganglion ablation might contribute to the success of AF ablation by suppressing autonomic remodelling.[69–71] Renal denervation may also prevent AF progression;[72] whether this effect is mediated by autonomic changes or suppression of hypertension-induced remodelling remains to be established. Further studies are needed to identify effective approaches to preventing AF progression and enable individualized therapy based on patient-specific pathophysiological processes.

Cycle of atrial fibrillation progression?

Evidence from completed rhythm-control trials

A logical approach to preventing AF progression would seem to be to maintain SR as vigorously and as early as possible in the natural history. Several large, randomized clinical trials have investigated

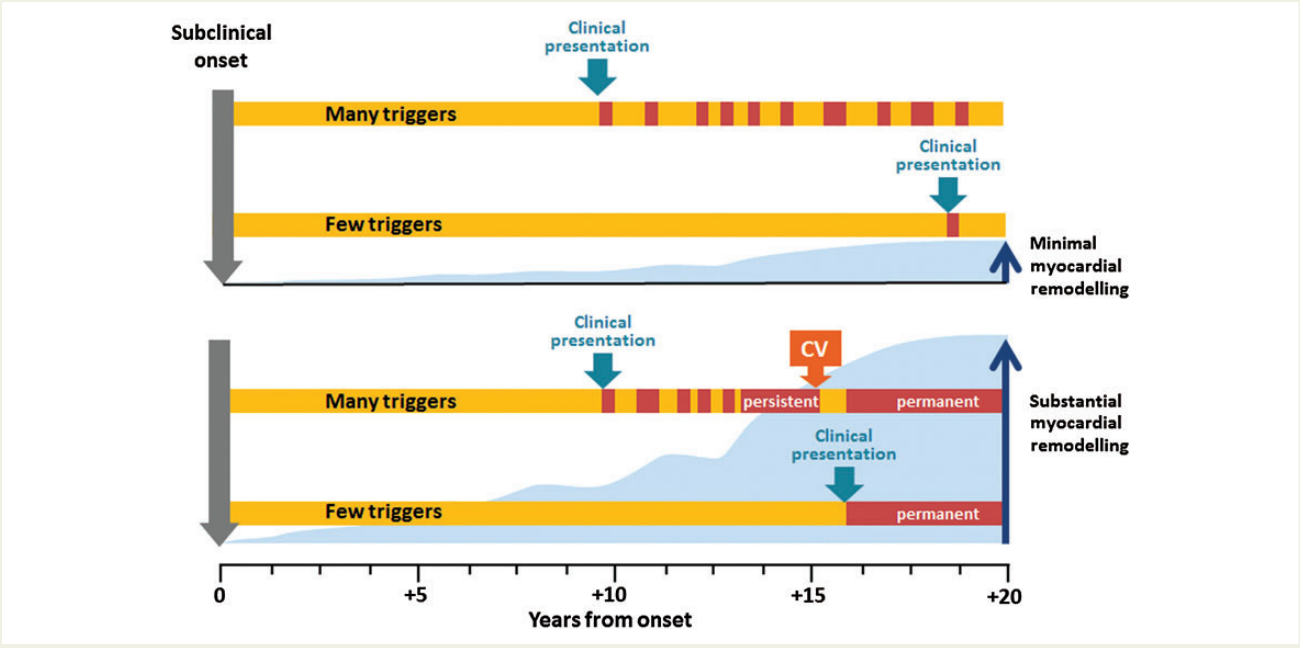

Figure 2 Different possible evolutions of AF in relation to substrate remodelling and trigger density. Atrial fibrillation episodes are shown in red; remodelling is represented by grey-filled contours. Frequent triggers may cause AF paroxysms which, when myocardial remodelling is substantial, may rapidly evolve to more persistent episodes. AF, atrial fibrillation; CV, cardioversion. Modified from Cosio *et al.*[25]

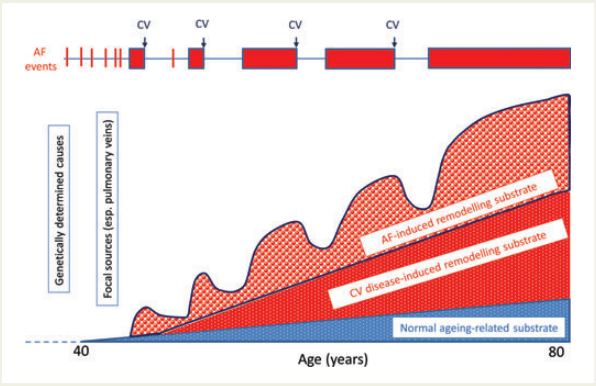

Figure 3 A conceptual model of atrial fibrillation events in relationship to underlying substrate. Prior to 40 years of age, genetically determined causes of AF (such as ion channel and transporter mutations/gene variants) pre-dominate. With ageing, focal sources and re-entrant substrates due to the normal ageing process become more important, and substrates caused by CV disease-induced remodelling also become more prevalent. Remodelling, partially reversible on arrhythmia cessation (electrical remodelling is fully reversible, structural remodelling much less so), is caused by AF episodes. Anti-remodelling therapies can be directed against remodelling due to AF and CV disease (both shown with red fill). AF, atrial fibrillation; CV disease, cardiovascular disease.

whether outcomes can be improved by maintaining SR with a combination of antiarrhythmic drugs and cardioversion. All but one have shown little or no improvement with rhythm control compared with rate control. In fact, the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study showed a trend towards increased mortality with rhythm control and RACE (RAte Control vs. Electrical cardioversion), PIAF (Pharmacological Intervention in Atrial Fibrillation), STAF (Score for the Targeting of Atrial Fibrillation), and HOT CAFE (HOw to Treat Chronic Atrial Fibrillation) showed no survival benefit when using rhythm-control strategies.[73–77] Similar results were seen in the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) study in patients with AF and an ejection fraction of less than 35%.[78] Only the Japanese RHYTHM management trial for atrial fibrillation (J-RHYTHM) showed a significant reduction in cardiovascular events associated with rhythm rather than rate control.[79]

A major problem with most of these trials is the low rate of restoration and maintenance of SR. For example, in the RACE trial, only 39% of patients in the rhythm-control arm were in SR at the end of the study, vs. 10% in the rate control arm.[73] These trials also included patients at relatively late stages of the disease process. The STAF, PIAF, and RACE trials recruited patients with persistent AF.[73–75] In the RACE trial, all patients had previously undergone cardioversion with relapse of AF. In the PIAF trial, the median duration of AF was 103–118 days prior to entry, while the STAF trial specifically recruited patients at a higher risk of AF recurrence. In the AF-CHF study, two-thirds of patients had persistent AF, 46% had AF for >6 months, and all had structural heart disease. The AFFIRM study recruited patients with persistent and paroxysmal AF, but 65% experienced more than one episode of AF and the majority had structural cardiac abnormalities, including dilated left atria (65%), at the time of recruitment.[77] J-RHYTHM, the only trial to demonstrate an advantage of rhythm control over rate control, was restricted to

patients with paroxysmal AF, and the underlying disease burden in this trial population was relatively low.[79]

Once AF is established and structural changes have occurred, it is difficult to reverse these changes and maintain SR, even with the use of antiarrhythmic drugs. Atrial fibrillation complications often occur at, or shortly after, initial presentation. For example, the initial clinical manifestation of AF can be a devastating stroke. Thus, the maximum benefit from a rhythm-control strategy may occur early after diagnosis.

The consequences of early rhythm control may underlie an otherwise puzzling difference between two related studies. The 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) study showed a reduction in cardiovascular hospitalization, and a small but significant reduction in cardiovascular deaths with dronedarone. Although ATHENA recruited patients with a high incidence of cardiac structural abnormalities (60%), eligible participants were required to have SR within 6 months of study entry and only 25% were in AF at randomization. In contrast, the PALLAS (Permanent Atrial fibriLLAtion outcome Study using dronedarone on top of standard therapy) study investigated dronedarone use in patients with 'permanent' AF.[80] All had at least 6 months of continuous AF; and 69% had apparently continuous AF for over 2 years. In contrast to ATHENA, the dronedarone group had increased mortality in the PALLAS trial. An important difference between ATHENA and PALLAS is that the treatment in ATHENA was designed to achieve rhythm control, while PALLAS was performed in patients with 'permanent' AF, without aiming for rhythm control and with potential benefits anticipated from a variety of mechanisms including improved rate control. The benefits seen in ATHENA may be partly explained by restoration and maintenance of SR. On the other hand, it has been speculated that, although not documented in PALLAS, unintended conversion to SR may have accounted for the higher stroke rate among patients randomized to dronedarone. The results from ATHENA are similar to the results of a *post hoc* analysis of AFFIRM, in which outcomes, including all-cause mortality, improved in the presence of SR, irrespective of the strategy assignment.[81] Thus, the finely balanced risks and benefits of rhythm control in AF may depend not only on the agents used, but on the stage of the disease process at which treatment is initiated.

Ongoing trials of aggressive early rhythm control

A greater understanding of the remodelling induced by AF has led to the development of new treatment strategies to actively maintain SR early in the course of AF. These strategies include individualized use of novel antiarrhythmic drugs, early catheter ablation, and 'upstream' therapy to prevent the development of the AF substrate.

Better classification of AF might lead to more effectively directed therapy. Current classification systems have major limitations—etiologically based classifications have been suggested[21,31] and are in active development. Evaluation of atrial structural remodelling should eventually go beyond documentation of left atrial size by including assessment of left atrial function, biomarkers, and/or late enhancement MRI. It may be helpful, after SR recovery for some weeks or months, to re-assess these markers of remodelling and possibly allow re-classification of AF. Catheter ablation offers a greater chance of achieving and maintaining SR, but it is unclear for how long the benefits are sustained and whether early restoration of SR will result in better long-term outcomes. Studies of ablation have included patients with AF described simply as paroxysmal, persistent or permanent/long-term persistent. However, this may reflect a conceptual error. A more useful subclassification that includes AF mechanism, pathogenesis, and structural remodelling might improve results by more effectively selecting patients at the most opportune time for the procedure.

The CABANA (Catheter ABlation vs. ANti-Arrhythmic drug therapy for atrial fibrillation) trial, which compares ablation vs. antiarrhythmic drugs (NCT00911508—ClinicalTrials.gov), and the EAST trial (Early treatment of Atrial fibrillation for Stroke prevention Trial), which evaluates rhythm control with ablation and antiarrhythmic drugs against guideline-mandated initial rate control, in patients presenting with their first episode of AF,[82] are ongoing. Both investigate whether early and active rhythm control of AF with a strategy involving catheter ablation can break the cycle of progression of AF and improve outcomes compared with standard therapies.

Can more intensive monitoring to detect and treat atrial fibrillation earlier prevent complications?

Atrial fibrillation in the acute setting

Atrial fibrillation in the setting of acute clinical events is associated with considerable morbidity and mortality. Patients who develop post-operative AF after cardiac surgery have a three-fold higher risk of stroke and a two-fold higher risk of in-hospital and 6-month mortality compared with those without AF.[83] Risks of stroke and mortality are similarly increased when AF complicates myocardial infarction (MI)[84] and sepsis.[85] Rates of stroke, but not death, are elevated among patients who develop AF after trans-catheter aortic valve replacement for severe aortic stenosis, compared with those who do not.[86] The risk of AF recurrence and adverse events in other clinical situations associated with transient AF, such as excessive alcohol intake ('holiday heart'), pericarditis, myocarditis, pulmonary embolism, and hyperthyroidism are not well-characterized.[87]

The pathophysiology of transient AF varies with the type of clinical event. Inflammation, haemodynamics, neurohormonal imbalance, sympathetic tone, obesity, and coronary disease[88] may play a role after surgery.[83] Inflammation has been linked to AF during sepsis.[89] Ischaemia, varying R–R intervals, autonomic dysfunction, and sympathetic activation have been implicated in the post-MI setting[84] and a role for genetics has been suggested.[90]

Transient AF complicating acute clinical conditions may be a sentinel event, identifying patients at risk for developing subsequent AF and its complications.[91] Risk factors for the development of AF in the acute setting are similar to those for developing paroxysmal, persistent, or 'permanent' AF unassociated with acute conditions. Age, for example, is strongly associated with AF after cardiac

surgery[81] as well as longer-term AF.[92] Left atrial volume and diastolic dysfunction are associated with post-operative AF.[93] These factors are also related to left ventricular hypertrophy, which is commonly observed in patients with longer-term AF.[93]

As patients with acute clinical events may be at high risk of developing longer-term AF, more intensive monitoring to detect subclinical AF may be warranted, particularly if early therapy can be shown to prevent progression and/or complications. A practical clinical approach to wide-scale earlier detection and management of AF is suggested in *Figure 4*. Arrhythmias can be detected by simple pulse check or ECG rhythm recording, or via a variety of advanced types of monitoring equipment including external event monitors, implantable loop recorders and implantable electronic devices. Post-MI arrhythmias, for example, were detected using implantable loop recorders in the CARISMA (Cardiac Arrhythmias and RIsk Stratification after acute MyocArdial infarction) Study.[94] New-onset AF was similarly detected using implantable devices in the ASSERT (A Symptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial),[95] and was found to identify increased stroke risk. These studies await confirmation before the clinical relevance of intensive ECG monitoring can be established. However, many other studies are presently underway such as CRYSTAL-AF Cryptogenic Stroke and underlying Atrial Fibrillation (NCT00924638)[96] and REVEAL-AF (NCT01727297).

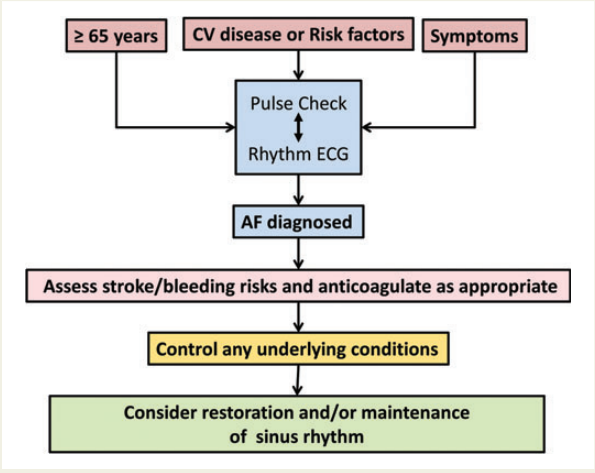

Figure 4 Proposed flow chart for early detection/management of patients with AF. Opportunistic (≥65 years), routine (known cardiovascular disease or risk factors), and triggered (palpitations or suspicious symptoms) pulse/ECG monitoring facilitates early AF diagnosis and provides an opportunity to initiate antithrombotic therapy in patients at risk, and antiarrhythmic therapy when appropriate (e.g. recent onset AF, young, active, and/or symptomatic patients). Risk factors include: congestive cardiac failure, hypertension, post myocardial infarction, diabetes, cardiomyopathy, valvular heart disease, pacemaker, post-stroke. Potentially controllable and/or reversible underlying conditions include: congestive cardiac failure, hypertension, ischemic heart disease, diabetes, valvular heart disease. AF, atrial fibrillation; CV, cardiovascular.

Conclusions

Both primary disease and AF-induced structural, electrical, and autonomic remodelling contribute to progression from paroxysmal to persistent AF. Earlier intervention may interrupt this progression, improving outcomes and reducing morbidity and mortality. Available drug therapies have not yet been shown to prevent progression, either because they are ineffective or because we are giving them too late or to the wrong patients. Ongoing basic research has identified some potentially interesting novel drug-development targets. The failure of rhythm-control therapy to improve outcomes in most previous large clinical trials may have been due to testing too late in the natural history of the disease, and the results of ongoing studies involving earlier and more active intervention are anticipated with interest. Despite abundant evidence regarding both the increasing prevalence of AF and the associated risk of thromboembolism, there remain many individuals with AF worldwide who are undiagnosed or undertreated, including many at high risk for stroke.

Existing practice guidelines for management of patients with AF provide valuable clinical pathways for the treatment of newly discovered AF.[97–99] Integrated care pathways would aid medical providers in the earlier identification of patients with AF, rapid assessment of thrombo-embolism risk and appropriate selection of anticoagulant therapy. Radical improvement of AF management will result if ongoing and future research demonstrates that such approaches facilitate earlier and possibly more effective interventions to restore and/or maintain SR.[100]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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