Controversies in Cardiology 3

Controversies in atrial fibrillation

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This is the third in a Series of four articles on controversies in cardiology

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Atrial fibrillation is the most common sustained cardiac arrhythmia, and contributes greatly to cardiovascular morbidity and mortality. Many aspects of the management of atrial fibrillation remain controversial. We address nine specific controversies in atrial fibrillation management, briefly focusing on the relations between mechanisms and therapy, the roles of rhythm and rate control, the definition of optimum rate control, the need for early cardioversion to prevent remodelling, the comparison of electrical with pharmacological cardioversion, the selection of patients for long-term oral anticoagulation, the roles of novel long-term anticoagulation approaches and ablation therapy, and the potential usefulness of upstream therapy targeting substrate development. The background of every controversy is reviewed and our opinions expressed. Here, we hope to inform physicians about the most important controversies in this specialty and stimulate investigators to address unresolved issues.

Atrial fibrillation, the most common sustained cardiac arrhythmia, is a major contributor to cardiovascular morbidity in the global population. Up to 15% of all strokes in the USA can be attributable to the disorder.[1] Despite a long history of medical exploration of atrial fibrillation,[2] many aspects of its pathophysiology and management remain controversial. We address selected controversies to identify key issues and provide future directions.

Can the mechanisms governing atrial fibrillation in individual patients be elucidated? Does it matter?

Various mechanisms, including rapid local ectopic activity, single-circuit re-entry, and multiple-circuit re-entry, can cause atrial fibrillation.[3] Re-entry mechanisms need an appropriate substrate on which a triggering ectopic beat acts to initiate re-entry, and could have substantial practical implications (figure 1). If the disorder is maintained by a focal ectopic source, focal ablation should stop the arrhythmia and prevent it from recurring. If atrial fibrillation is due to a single primary circuit, it can be suppressed by linear ablation within the re-entry pathway; whereas atrial fibrillation maintained by multiple functional re-entry circuits would need isolation into atrial-tissue portions too small to maintain re-entrant activity. There are also implications of these mechanisms for antiarrhythmic drug therapy. Ectopic activity can be suppressed by compounds such as class I antiarrhythmic substances that reduce automatic firing. Re-entry is inhibited by drugs such as specific class I and III drugs that extend the refractory period.

Distinct mechanisms of atrial fibrillation may be more common in different populations. For example, some patients with paroxysmal atrial fibrillation have many transient episodes without ever developing the persistent form. These individuals tend to show ectopic activity from pulmonary-vein foci, ablation of which can cure the disorder.[4,5] Patients with dilated, diseased atria in association with mitral valve disease have properties (large size, abnormal electrophysiology, tissue fibrosis) that favour multiple-circuit re-entry.[6] The surgical maze procedure, which divides the atria into functionally separate units, is particularly effective for such individuals.[7,8] Post-operative atrial fibrillation, which occurs in about 30% of patients undergoing cardiac

Search strategy and selection criteria

We searched MEDLINE with keywords such as "atrial fibrillation", "AF", and combinations of these with terms including "therapy", "anticoagulation", "ablation", and "stroke". We also pursued articles referenced in primary sources and their relevant citations.

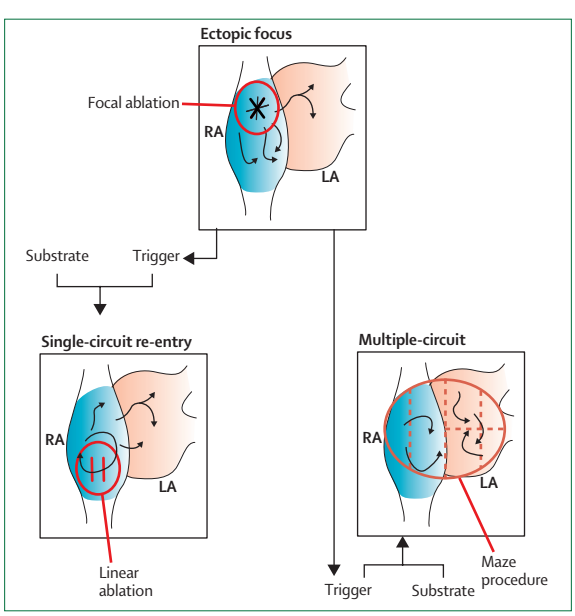

Figure 1: **Three principal mechanisms of atrial fibrillation**
RA=right atrium. LA=left atrium. Mechanisms are explained in the text.

surgery, could be associated with activation of inflammatory mediators[9] and the autonomic nervous system.[10] However, we have few criteria to define specific mechanisms in individual patients.

Opinion

We cannot be certain about the mechanism of atrial fibrillation in most individual patients. The clinical context does provide information with predictive value for the response to therapy. Further research and improved electrophysiological instruments could clarify the definition of mechanisms and predicted effective therapy in individuals.

Which is the better strategy for atrial fibrillation—rhythm control or rate control?

Two basic approaches are available to manage atrial fibrillation: (1) keep patients in sinus rhythm (rhythm control) and (2) allow patients to remain in atrial fibrillation, but control the ventricular response (rate control). Possible advantages of rhythm control include improved cardiac function and quality of life and the prevention of thromboembolic events. Advantages of the rate-control approach include the avoidance of drugs often needed to maintain sinus rhythm that have an attendant risk of serious complications[11] and a reduced need for repeated direct-current cardioversions for recurrences of atrial fibrillation.

Table 1[12–16] summarises the results of five randomised trials comparing rate control with rhythm control for atrial fibrillation management. No significant differences were recorded in primary endpoints; thus, neither strategy was inherently better than the other. However, disturbing trends towards adverse outcomes with a rhythm-control approach were seen in the two largest studies.[14,16] None of the benefits expected from rhythm control was documented. In particular, the strongest risk factor for stroke was a lack of anticoagulation, with the tendency to stop oral anticoagulant treatment in patients who reverted to sinus rhythm resulting in increased stroke.[16] A meta-analysis suggested lower mortality in rate-control patients than in rhythm-control patients (p=0·09).[17]

Is the issue settled: should rate control be the approach of choice for all patients?

This conclusion would be oversimplified. In two studies, sinus rhythm was maintained in only 40%[14] and 23%[15] of rhythm-control patients. Evidence indicates an improved outcome if sinus rhythm is maintained.[13] An analysis of on-treatment outcomes in AFFIRM[18] showed that the presence of sinus rhythm was associated with reduced mortality (47% reduction, 99% CI 28–61; p<0·0001). Thus, either sinus-rhythm maintenance is inherently beneficial but the toxic effects and poor efficacy of presently available antiarrhythmic drugs negate this benefit, or the ability to maintain sinus rhythm is a marker of improved outcome or less serious disease.

A second issue is the study populations selected for these trials. By far the largest study, AFFIRM[18] had entry criteria designed to increase the chances of a clear conclusion to a maximum: patients were selected for

	Study population characteristics	Follow-up	Interventions	Endpoint	Primary endpoint outcome
PIAF (n=252)[12]	Persistent atrial fibrillation	1 year	Rate control: diltiazem, β-adrenoceptor blockers, digoxin Rhythm control: amiodarone	Symptomatic improvement	No difference (p=0·32)
STAF (n=200)[13]	Asymptomatic or symptomatic atrial fibrillation	About 20 months	Rate control: calcium antagonists, β-adrenoceptor blockers, digoxin, atrioventricular nodal ablation Rhythm control: direct-current cardioversion with class I antiarrhythmic drugs, amiodarone, β-adrenoceptor blockers, sotalol	Composite endpoint: death, thromboembolic event	No difference
RACE (n=526)[14]	Persistent atrial fibrillation after direct-current cardioversion	2·3 years	Rate control: calcium antagonists, β-adrenoceptor blockers, digoxin Rhythm control: direct-current cardioversion with sotalol, class I antiarrhythmic drugs, amiodarone	Composite endpoint: cardiovascular death, hospital care, thromboembolic event, haemorrhage, pacemaker needed, severe adverse events	17% rate control *vs* 22% rhythm control (p=0·11)
HOT CAFE (n=205)[15]	Persistent atrial fibrillation	1·7 years	Rate control: calcium antagonists, β-adrenoceptor blockers, digoxin, atrioventricular nodal ablation Rhythm control: direct-current cardioversion with sotalol, class I antiarrhythmic drugs, amiodarone	Composite endpoint: death, thromboembolic event, haemorrhage	No difference (p>0·7)
AFFIRM (n=4060)[16]	High-risk atrial fibrillation	3·5 years	Rate control: calcium antagonists, β-adrenoceptor blockers, digoxin Rhythm control: direct-current cardioversion with sotalol, class I antiarrhythmic drugs, amiodarone	Total mortality	21·3% rate control *vs* 23·8% rhythm control (p=0·07)

n=number of patients in study.

Table 1: **Studies (n) of rate control versus rhythm control in atrial fibrillation**

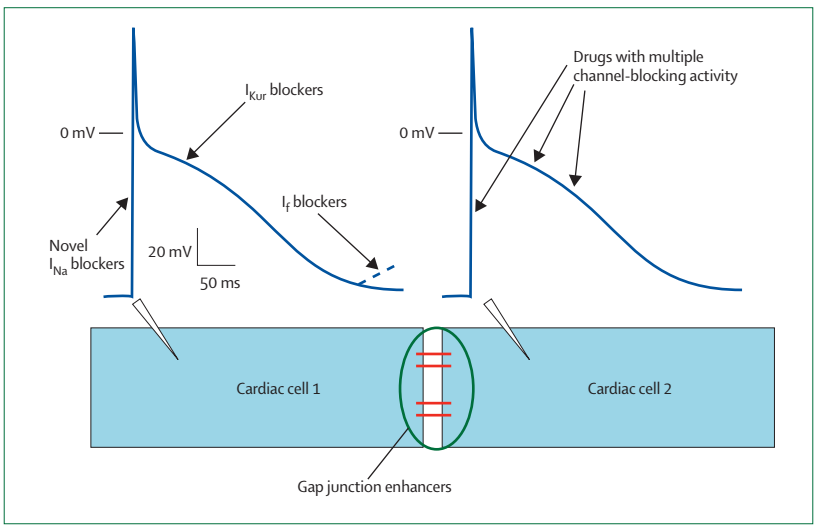

***Figure 2*: Novel ion-channel-related targets under investigation for atrial fibrillation therapy**
Cellular electrical activity can be measured as action potentials (blue), which record intracellular electrical voltage as a function of time. When cells are activated, they rapidly move from a negative resting potential (close to −80 mV) to a much more positive potential because of the entry of Na^+ ions carried by the Na^+ current (I_{Na}). The cells then undergo initial rapid repolarisation (carried by K^+ currents), a relatively flat plateau phase, and final repolarisation carried by the K^+ current. Novel I_{Na} blockers can stop atrial fibrillation by inhibiting the depolarising Na^+ current and have frequency dependence, so that substantial I_{Na} inhibition is mainly manifest at very rapid rates of the fibrillating atrium, with very little effect at rates of sinus rhythm and therefore low proarrhythmia risk. I_{Kur} is important in repolarising the human atrium but not ventricle, and inhibition of this process could therefore be an interesting target for atrial-selective antiarrhythmic substances. Inhibition of a pacemaker current (I_f) could suppress spontaneous automatic arrhythmogenic activity. Drugs with multiple channel-blocking actions are designed to suppress abnormal activity without causing proarrhythmia (based on the amiodarone model). Gap junction enhancers increase the conducting function of ion channels that connect cells electrically, a function that seems to be abnormal in certain arrhythmic substrates favouring atrial fibrillation.

high-risk thromboembolic events and few patients had congestive heart failure. Young patients with low thromboembolic risk and an increased probability of sinus-rhythm maintenance might have been under-represented. In patients with congestive heart failure, sinus-rhythm maintenance by ablation improves cardiac functioning, even in those with good rate control before ablation.[19] The value of sinus-rhythm maintenance in reducing cardiovascular mortality in patients with congestive heart failure is under investigation in the prospective, randomised AF-CHF trial.[20]

New approaches to sinus-rhythm maintenance might improve rhythm-control safety and effectiveness. Amiodarone is clearly better than sotalol and class I drugs in sinus-rhythm maintenance,[21,22] with improved quality of life and exercise capacity.[22] New pharmacological strategies that are based on the amiodarone model, on novel ionic targets, and on the notion to combat the development of the atrial fibrillation substrate (upstream therapy, which is discussed further later), promise novel options for rhythm control.[11,23,24] Figure 2 summarises new ionic targets being explored for atrial fibrillation therapy. Improved ablation techniques might provide non-pharmacological cures for increasing numbers of patients with atrial fibrillation.[25]

Opinion

Presently available comparative studies indicate that: (1) no clear advantage exists between rhythm control and rate control; (2) the most important therapy to reduce stroke risk in atrial fibrillation is oral anticoagulation; (3) current antiarrhythmic drugs for sinus-rhythm maintenance have substantial risks, especially in women and individuals with hypertension,[14] which should be weighed against potential benefits. In trials undertaken so far, the risks of currently used antiarrhythmic drugs for sinus-rhythm maintenance could have outweighed the potential benefits of sinus-rhythm maintenance itself. This hypothesis will be explored in studies with new approaches to maintain sinus rhythm. For the moment, the therapeutic strategy for patients with atrial fibrillation should be individualised, with a bias towards rate control if patients can be kept asymptomatic.

What is adequate rate control?

Atrial fibrillation with uncontrolled ventricular rates leads to severe but reversible congestive heart failure.[26] However, the prevention of excess resting tachycardia is not equivalent to the reproduction of physiological heart-rate control. The restoration of sinus rhythm in patients who have atrial fibrillation with previously adequate rate control (whether by catheter ablation[19] or by direct-current cardioversion followed by antiarrhythmic drugs)[27,28] significantly improves left-ventricular function. Two major studies used quite different criteria for rate control: in AFFIRM,[16] adequate rate control was defined as a resting rate less than 80 beats per min and controlled rates (criteria left to the treating physician) as recorded during 6-min walk tests or 24-h Holter recordings; whereas in RACE,[14] a resting rate of less than 100 beats per min was judged as sufficient. Although outcomes are difficult to compare between trials, endpoint morbidity and mortality were not significantly different between RACE and AFFIRM.[29] Adequate rate control in AFFIRM, achieved in 60–80% of patients, often needed multiple dose adjustments and combination drug therapy.[30] Digoxin was associated with reduced survival, whereas warfarin had the opposite effect. Furthermore, achieved heart rates failed to predict any outcome indices.[31]

Opinion

Optimum criteria for rate control are presently unknown. Resting tachycardia must be prevented. Additional consideration of heart-rate changes with exercise could be useful in some patients. More prospectively obtained information is needed to best define rate-control criteria.

Does electrical remodelling favour early cardioversion for rhythm control?

Atrial fibrillation causes electrical remodelling by inducing very rapid atrial activation (figure 3), thereby

changing atrial electrophysiological properties, enhancing the ability of the disorder to sustain itself, and increasing vulnerability to relapse.[3,32,33] Poor ventricular rate control leads to congestive heart failure and atrial-fibrillation-promoting structural remodelling.[34,35] Atrial tachyarrhythmias cause atrial mechanical dysfunction related to abnormal handling of cellular Ca^{2+},[36–38] which could contribute to thrombus formation. Experimental observations,[39] clinical trial results,[40] and mathematical modelling studies[41] indicate that electrical remodelling reduces the atrial response to antiarrhythmic drugs. The ability of flecainide to stop recurrences of atrial fibrillation increases when the drug is given soon after onset of the disorder and long after the last disorder episode.[40] This finding is consistent with the time course of development and the reversal of electrical remodelling both being a determinant of drug efficacy.

These findings lead to the notion that prompt cardioversion of atrial fibrillation might be desirable. Studies with the implantable atrial defibrillator, which allows early cardioversion, confirmed that early cardioversion prevents atrial dysfunction,[42] reduces atrial size,[43] and increases the time to recurrence.[43,44] Early detection and cardioversion of recurrent atrial fibrillation lessen electrical remodelling.[45] However, the practical clinical value of early cardioversion has been difficult to show. Although one study using transoesophageal echocardiography for early cardioversion showed improved sinus-rhythm maintenance and reduced recurrence of atrial fibrillation,[46] others failed to show such benefits.[45,47]

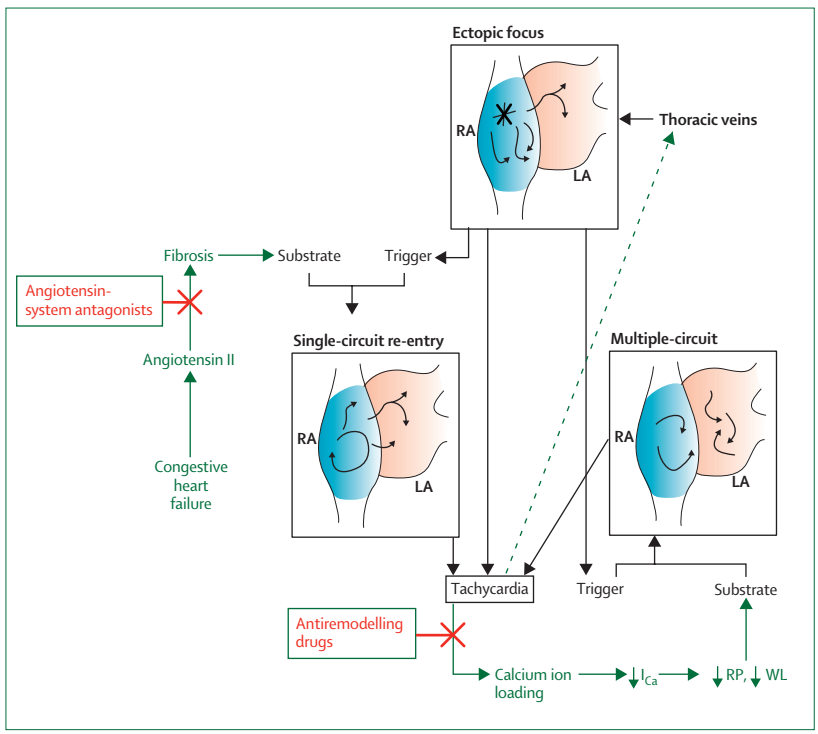

Figure 3: **Atrial remodelling and potential role of therapies targeting remodelling**
Three main mechanisms of atrial fibrillation are reproduced from figure 1. Rapid atrial tachycardia (due to any mechanism) causes atrial remodelling by downregulating L-type calcium-channel function (I_{Ca}), thereby accelerating atrial repolarisation, reducing the refractory period (RP) and wavelength (WL; smallest size of functional re-entry circuits), and promoting re-entry. Atrial tachycardia remodelling may also be able to promote ectopic activity in the thoracic veins. Congestive heart failure activates the renin-angiotensin system and causes atrial fibrosis, which impairs local atrial conduction and promotes atrial fibrillation. Evidence suggests that specific forms of drug therapy could attenuate tachycardia-induced and fibrotic atrial remodelling and might be useful in prevention of atrial fibrillation.

Opinion

Early cardioversion can prevent atrial remodelling, but such remodelling is only one component of the pathophysiology of atrial fibrillation. Whether early cardioversion improves sinus-rhythm maintenance is unclear and should not be an important consideration in decisions regarding the timing of cardioversion.

If rhythm control is selected for patients with recent-onset atrial fibrillation, what is the relative role of pharmacological cardioversion versus electrical cardioversion?

Rhythm control is often favoured for patients presenting with recent-onset (<48 h) atrial fibrillation. The spontaneous conversion rate of such patients is high: about 20% at 3 h, 60% at 24 h, and 80% at 48 h.[48] Pharmacological or electrical cardioversion quickens the time to rhythm reversion, allowing earlier discharge from hospital. Direct-current cardioversion stops atrial fibrillation in more than 90% of cases.[49] Potential complications include burns, iatrogenic ventricular fibrillation (if shocks are not QRS-synchronised), and the need for general anaesthesia. A wide range of antiarrhythmic drugs stop atrial fibrillation[48,50] with varying efficacies that average at about 50% for cessation of the disorder within 1·5 h of administration.[48] Of great concern is ventricular proarrhythmia, which is especially common with ibutilide and other repolarisation-delaying drugs.[50,51]

The American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) have concluded that both direct-current electrical and pharmacological cardioversion are appropriate for patients with newly detected atrial fibrillation.[52] The increased efficacy of direct-current cardioversion favours its use whenever possible, but practical use is restricted by a need for general anaesthesia to suppress pain and a 6-h postprandial period to ensure gastric emptying. Conscious intravenous sedation is an alternative that avoids the risks and delays of general anaesthesia. Conversion of long-standing atrial fibrillation should never be done unless thromboembolic risk has been reduced to a minimum (eg, by the use of >3 weeks' therapeutic anticoagulation). Pharmacological cardioversion is ineffective for atrial fibrillation longer than 7 days.[48] Thromboembolic risk is similar for pharmacological[53] and electrical[54] cardioversion, as is the

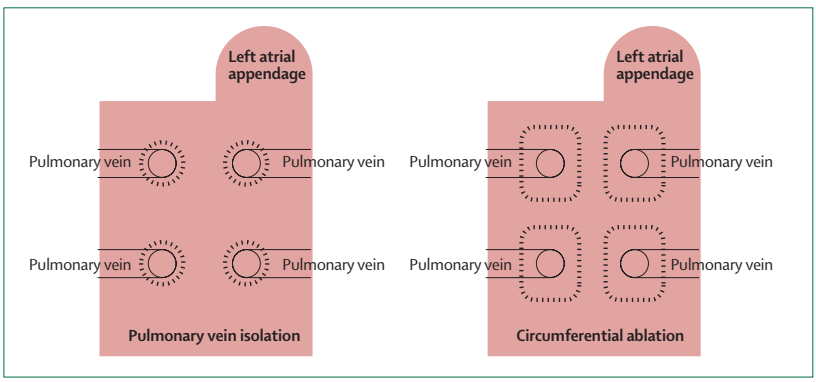

Figure 4: **Potential mechanisms of curative ablation procedures in the left atrium for atrial fibrillation**
Pulmonary-vein isolation and circumferential ablation can prevent conduction of pulmonary-vein ectopic activity to the left atrium; prevent re-entry affecting the pulmonary veins; and remove autonomic nerves providing vagal nerve input to the atria. Circumferential ablation can destroy enough tissue to reduce functional atrial mass below critical requirements for fibrillation maintenance. In some patients, additional linear left-atrial lesions are added to either procedure, which creates a maze effect.

case for associated atrial mechanical dysfunction after cardioversion (stunning).[55]

Opinion

Direct-current electrical cardioversion is generally the procedure of choice. Pharmacological conversion is useful when direct-current cardioversion is not possible or has to be delayed.

If rhythm control is selected, what is the role for curative ablation procedures and how do they work?

The management of most arrhythmias has been revolutionised by curative transcutaneous ablation procedures, which have only recently become available for atrial fibrillation. The two most widely used procedures are pulmonary-vein isolation and circumferential left-atrial ablation, which are effective in about 60–85% of selected patients.[5,25,56] Both procedures aim to eliminate arrhythmogenic pulmonary-vein activity, but other mechanisms could also be implicated (figure 4). Evidence indicates that restoration of the connection between the pulmonary vein and left atrium is important in atrial fibrillation recurrence after initially successful isolation of the pulmonary-vein antrum.[57] However, other findings suggest that the completeness of pulmonary-vein isolation is not a major determinant of the success of left-atrial circumferential ablation procedures.[58] Atrial fibrillation ablation is most successful for specific groups, especially for patients with paroxysmal disease and little structural heart disease.[5] Although ablation presently has incomplete efficacy and non-trivial risks,[25] with further development such treatment could well become the preferred choice for atrial fibrillation, as it has become for so many other arrhythmias. In a randomised trial of ablation versus conventional antiarrhythmic-drug therapy as first-line treatment for patients with frequent symptomatic episodes, results greatly favoured ablation.[59]

Opinion

The mechanisms of benefit from ablation of atrial fibrillation are not completely clear. Further mechanistic definition will help to improve effectiveness and safety. The use of ablation in atrial fibrillation management will probably increase and become first-line therapy for selected patients. However, the size and heterogeneity of the atrial fibrillation population, along with the complexity, incomplete efficacy, and non-trivial risks of ablation procedures, will still leave a need for pharmacological approaches.

Which patients with atrial fibrillation need oral anticoagulation?

Atrial fibrillation contributes to about 35% of strokes in an octogenarian population,[60] increases the overall stroke-risk by five-fold, and is associated with particularly severe strokes.[61] Atrial fibrillation has been judged to promote strokes by favouring thrombus formation in local zones of static blood, especially in the left atrial appendage.[62] Additionally, atrial fibrillation can cause a prothrombotic state,[62] associated with increased plasma levels of von Willebrand factor, which is a marker of endothelial and endocardial dysfunction.[63] Oral anticoagulation with warfarin and other vitamin-K antagonists reduces the risk of stroke related to atrial fibrillation by about 70%.[50,64] Oral anticoagulants also reduce stroke severity, presumably by preventing more severe embolic strokes.[64] Oral anticoagulants raise the risk of major bleeding from about 0·9% to 2·2% and intracranial haemorrhages from about 0·2% to 0·4%.[65] The protective effect of oral anticoagulation against strokes reaches a near maximum at an international normalised ratio (INR) of 2 or more, whereas major bleeding events increase rapidly at INRs greater than 4.[66]

These observations have led to a recommendation to aim for an INR between 2·0 and 3·0, for which there is extensive support in published work. Maintenance of safe and effective INRs in this recommended range with vitamin-K antagonists is complicated by the following: unpredictable dose-response associations, many potential drug interactions and unpredictable effects of diet, sun exposure, intercurrent disease, and other unidentifiable factors. To decide which patients with atrial fibrillation should undergo anticoagulation treatment can therefore be difficult. Factors that affect stroke and bleeding risk include criteria related to patients and those related to the disorder.

Patient-related criteria

In large randomised trials of stroke prevention in atrial fibrillation,[67,68] the main stroke risk factors were identified as: advancing age, female sex, previous stroke or transient ischaemic attack, hypertension, and diabetes (table 2). Congestive heart failure and coronary artery disease were also risk factors in some trials. Gage and colleagues[70] developed a simplified risk-stratification

	AFI[67]	SPAF I-III[68]
Age (years)	1·4	1·8
Female sex	NS	1·6
Previous stroke or transient ischaemic stroke	2·5	2·9
Hypertension	1·6	2·0–2·3*
Diabetes	1·7	NS
Congestive heart failure	NS	NS†
Coronary disease	NS	NS

Factors identified in randomised anticoagulation trials. Risk is relative to individuals without the risk factor in question. NS=non-significant. AFI=Atrial Fibrillation Investigators. SPAF=Stroke Prevention in Atrial Fibrillation trial. *Value is 2·0 for patients with history of hypertension and 2·3 for patients with systolic pressure greater than 160 mm Hg. †Significant mean risk in SPAF I-II of 1·8.[69]

Table 2: **Potential risk factors of stroke in patients with atrial fibrillation**

method to predict stroke risk with a national data-bank of non-anticoagulated patients with atrial fibrillation. Their system allocates 1 point each for previous congestive heart failure, hypertension, age of 75 years or more, and diabetes; and 2 points for previous stroke or transient ischaemic attack. The system is named $CHADS_2$, taking the first letter of every risk factor (with S_2 to indicate stroke with a weight of 2 points). Outcome data in a large primary-care practice (11 526 patients)[71] confirm that thromboembolic risk increases progressively with $CHADS_2$ score (table 3). Oral anticoagulation with warfarin reduces risk in all individuals apart from those at lowest risk and the very few at the highest risk.

Elderly patients

The risk of bleeding as a result of vitamin-K antagonist treatment is most clearly related to anticoagulation intensity and patients' age.[72] Thus, effective anticoagulation monitoring is a crucial determinant of oral anticoagulation safety, as it is of efficacy in the prevention of thromboemboli.[73] Although bleeding risk increases with age, so does the risk of atrial-fibrillation-related stroke. A survey of physician attitudes indicated widespread reluctance to anticoagulate elderly patients, and concluded that access to therapeutic benefit could be inappropriately restricted.[74] Analysis of anticoagulation-related bleeding risk in elderly individuals suggests no important role of factors such as a history of falls, presumed age-related incompetence in the control of anticoagulation, or a history of stroke.[75] The main evidence-based contraindications to anticoagulation in elderly patients include: bleeding diathesis, thrombocytopenia (platelet count $<50\,000/\mu L$), poorly controlled hypertension (pressures consistently >160/90 mm Hg), and non-compliance with drugs or INR monitoring.[75]

Atrial-fibrillation-related criteria

Most large-scale trial data are based mainly on patients with persistent atrial fibrillation, who constituted about 88% of the first five major trials.[67] However, other subsets of this group might need special consideration. Paroxysmal atrial fibrillation can vary widely in both duration (seconds to days) and frequency (every day to every few years). Insufficient information is available for patients with paroxysmal atrial fibrillation. Retrospective analyses suggested that the paroxysmal disorder could confer a risk less than that of the persistent form;[76,77] however, subsequent studies controlling for concomitant conditions suggested similar risks.[67,78] Consideration of paroxysmal atrial fibrillation is further complicated by the fact that many episodes are asymptomatic.[79] A related issue is how to handle patients cardioverted from atrial fibrillation who remain in sinus rhythm for extended intervals. Presently, no support exists for the discontinuation of anticoagulation in such patients, since the absence of anticoagulation is a strong predictor of stroke occurrence.[14,16]

Postoperative atrial fibrillation

Atrial fibrillation occurs in about 30% of patients after cardiac surgery.[80] This postoperative rhythm disorder is frequently self-limited, but remains an important risk factor for postoperative stroke.[81] Therefore, anticoagulation is recommended for atrial fibrillation lasting longer than 48 h, despite the treatment's complexity in the postoperative setting.[82]

Risks of atrial fibrillation conversion to sinus rhythm

In addition to the promotion of thrombus formation, the rapid atrial rates associated with atrial fibrillation suppress atrial contractility.[36–38,55] After sinus-rhythm restoration, atrial contractility returns after days or weeks,[55] which increases the risks of clot dislodgment and thromboembolism. Thromboembolic risk can be kept to a minimum by oral anticoagulation before cardioversion.[83] Because of delayed resumption of contractility, anticoagulation should be continued for 4 weeks after cardioversion. Patients with transoesophageal echocardiographic evidence against left-atrial thrombus formation can be cardioverted safely without previous anticoagulation,[46] as can patients with atrial fibrillation of less than 48-h duration.[84]

	Thromboembolic risk (95% CI)		Risk reduction (95% CI relative risk)*
	On OA therapy	Off OA therapy	
0 (n=2557)	0·25 (0·11–0·55)	0·49 (0·30–0·78)	50% (0·20–1·28)
1 (n=3662)	0·72 (0·50–1·03)	1·52 (1·19–1·94)	53% (0·30–0·73)
2 (n=2955)	1·27 (0·94–1·72)	2·50 (1·98–3·15)	49% (0·35–0·75)
3 (n=1555)	2·20 (1·61–3·01)	5·27 (4·15–6·70)	58% (0·28–0·62)
4 (n=556)	2·35 (1·44–3·83)	6·02 (3·90–9·29)	61% (0·20–0·75)
⩾5 (n=241)	4·60 (2·72–7·76)	6·88 (3·42–13·84)	33% (0·28–1·60)

Thromboembolic risks indicated are in events per 100 patient-years, unless stated otherwise. *Risk reduction is mean fall (%) in event risk; relative risks are compared with patients not treated with vitamin-K antagonists.

Table 3: **Relative thromboembolic risks of oral anticoagulation (OA) therapy with warfarin in a large primary-care network,[71] by $CHADS_2$ score**

Consensus guidelines

Detailed consensus guidelines for long-term oral anticoagulation in atrial fibrillation have been prepared by the American College of Chest Physicians (ACCP),[64] American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC).[85] Paroxysmal and persistent atrial fibrillation are assessed to present similar risks. Specific guidelines are provided for different settings—eg, after surgery, before and after cardioversion, and atrial fibrillation related to valvular heart disease.[64] The AAFP/ACP analysis[52] recommends anticoagulation for all patients with atrial fibrillation apart from those at lowest risk ($CHADS_2$ score 0 to 1) or those with specific contraindications to anticoagulation. Trial-based guidelines might not be completely applicable to practice-based populations, since trials exclude patients at high risk of bleeding[86] and provide intense anticoagulation monitoring.[73]

Opinion

The risk of thromboembolism is determined mainly by patient-related factors. Apart from the lowest risk group ($CHADS_2$ score 0), oral anticoagulation significantly prevents thromboembolic events (table 3). The highest risk group (score ⩾5) also failed to show a significant risk reduction with warfarin. Such patients need anticoagulation but additional therapy might also be needed, as is currently under investigation. Therefore, long-term oral anticoagulation should be considered for all patients with atrial fibrillation and with a $CHADS_2$ score of 1 or more, and should be used as per guidelines for those with a score of 2 or more if excess bleeding risk is not indicated. Although cardioversion without previous anticoagulation seems safe for episodes of atrial fibrillation shorter than 48 h or with low-risk trans-oesophageal echocardiography, the need for subsequent anticoagulation is determined by patient-related risk factors.[64]

What is the appropriate role of vitamin-K antagonists compared with alternative drugs for atrial fibrillation?

Vitamin-K oxidation is coupled to γ carboxylation, which is needed to activate several key coagulation proteins (figure 5). Vitamin-K antagonists have long been the mainstay of long-term anticoagulation treatment for atrial fibrillation, but the difficulty to achieve safe and effective anticoagulation has led to several alternative approaches presently under investigation.

Direct thrombin antagonists

Thrombin can be directly prevented by orally administered antagonists. Ximelagatran, the most advanced member of this class, had similar stroke-prevention efficacy and marginally improved bleeding-event safety compared with vitamin-K antagonists in two large clinical trials.[87,88] The main advantage of ximelagatran is the predictable dose-response relations that ensure appropriate anticoagulation without frequent dose titration and with a much smaller risk of drug, diet, and environmental interactions than that with vitamin-K antagonists. Although ximelagatran is available in Europe for thromboembolic prophylaxis after hip surgery, the US Food and Drug Administration has not approved the drug because of potentially severe hepatotoxic effects. Other direct-acting thrombin inhibitors with reduced or absent risks of these effects are now under development.

Antiplatelet drugs

Platelets are important in coagulation, and antiplatelet drugs such as aspirin are valuable in preventing cerebral ischaemic events due to platelet-rich thromboemboli from carotid atherosclerotic lesions. However, aspirin alone has very little value (if any) in preventing thromboembolism related to atrial fibrillation.[85] The combination of antiplatelet drugs with different sites of action (figure 5) could improve anticoagulant efficacy. A subgroup analysis suggested further stroke-prevention benefit from the addition of dipyridamole to aspirin in patients with atrial fibrillation.[89] Combined aspirin-clopidogrel is being compared with aspirin alone in patients who cannot receive vitamin-K antagonists in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W).[90]

Long-acting heparin analogues

Synthetic heparin analogues such as idraparinux and fondaparinux mimic heparin's interaction with anti-thrombin III and catalyse the inhibition of factor Xa by antithrombin. These compounds bind tightly to anti-thrombin, have a long half-life, and produce predictable anticoagulation without monitoring. Idrapariunux is presently being compared with vitamin-K-antagonist treatment in more than 7000 patients with atrial fibrillation and stroke-risk factors in the AMADEUS trial.[91] This arm of the trial was stopped prematurely because of the obvious benefit of warfarin over antiplatelet therapy.

Opinion

In the long-term, alternative therapies—especially direct-acting thrombin inhibitors—will probably replace vitamin-K antagonists for the prevention of thrombo-embolism in atrial fibrillation. At present, no available drug other than vitamin-K antagonists qualifies as first-line therapy for patients with the disorder at increased risk.

What is the role of upstream therapy in atrial fibrillation management?

Basic research has provided extensive insights into the development of the atrial fibrillation substrate, and has put forward the possible targeting of these substrate development mechanisms, upstream of the final electrical product (figure 3).[24] Interventions that inhibit activation of

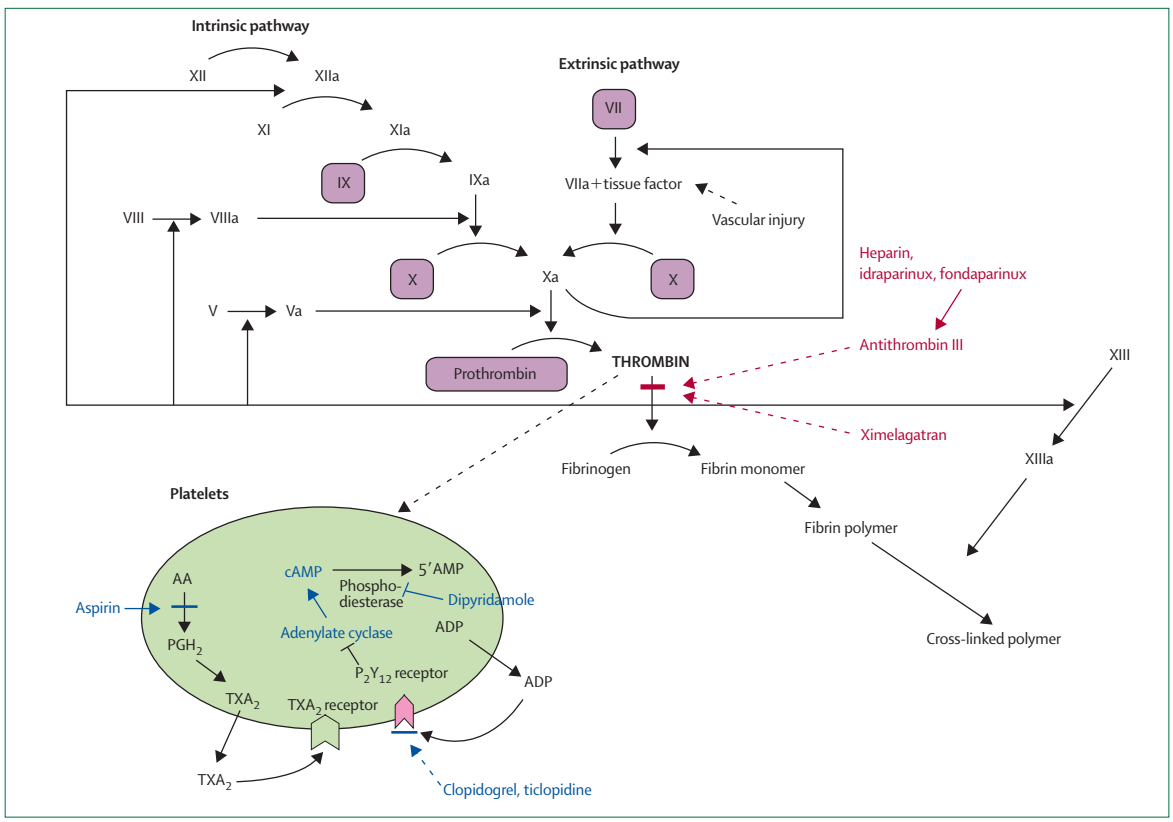

Figure 5: **Targets for anticoagulant drugs used in atrial fibrillation**
Purple squares=vitamin-K-dependent factors. Red=antithrombotic drugs. Blue=processes inhibiting platelet aggregation. Thrombin is a key final activator that results in clot formation, platelet activation, and positive feedback on several steps in the coagulation cascade. Warfarin depletes all the vitamin-K-dependent factors. Heparin and the orally active analogues idraparinux and fondaparinux inhibit thrombin via a native inhibitor protein, antithrombin III. As a prodrug, ximelagatran is converted in the liver to melagatran, which directly inhibits thrombin. Aspirin prevents formation of the potent platelet activator thromboxane A_2 (TXA_2), whereas clopidogrel and ticlopidine block ADP interaction with the purinergic P_2Y_{12} receptor. This receptor promotes aggregation by inhibiting adenylate cyclase, thereby reducing concentrations of the anti-aggregant cyclic AMP (cAMP). cAMP is broken down by phosphodiesterase, as is cyclic guanosine monophosphate (cGMP), another anti-aggregant. Dipyridamole suppresses platelet aggregation by inhibiting platelet phosphodiesterase and preventing cAMP and cGMP breakdown. AA=arachidonic acid. PGH_2=prostalglandin H_2.

the renin-angiotensin system have shown to prevent tissue fibrosis and promotion of atrial fibrillation.[34,92] Several clinical trials show benefit for angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers in atrial fibrillation prevention,[93] especially in patients with left-ventricular dysfunction and hypertension accompanied by left-ventricular hypertrophy.[94–96] A meta-analysis suggested greatest benefit in patients with congestive heart failure and a need for prospective studies to define the value for other populations with atrial fibrillation.[93] Amiodarone prevents changes in atrial electrophysiology and susceptibility of atrial fibrillation caused by experimental atrial-tachycardia remodelling, and anti-remodelling actions could contribute to its good efficacy in the disorder.[97] N-3 polyunsaturated fatty acids also seem to have poorly defined actions against atrial fibrillation.[98]

Opinion

The notion of atrial fibrillation prevention by inhibition of substrate development is appealing. Valuable evolving evidence favours the use of angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers in specific subgroups. This research area is ripe for translational developments from basic to clinical medicine.

Conflict of interest statement
S Nattel has received research grants or consultancy fees from Astra-Zeneca, Cardiome Pharma, Xention Pharmaceuticals, Artesian Labs, Wyeth Labs, Bristol-Myers-Squibb/Sanofi, Solvay Pharmaceuticals, Xenon Pharmaceuticals, and Novartis Pharmaceuticals with respect to the development of novel antiarrhythmic drugs for atrial fibrillation and to the assessment of proarrhythmic risk for a wide range of compounds in development. None of the compounds studied is mentioned by name in the article. S Nattel is named as inventor or co-inventor on patents pending belonging to the Montreal Heart Institute, applied with respect to potential novel therapies for atrial fibrillation. These potential therapies are still experimental and are not mentioned or alluded to in the article. L H Opie has given lectures on behalf of Abbott, Aventis, Bayer, Cardiovascular Therapeutics, and Servier, and has received travel funds. These lectures have been approved for continuing medical educational programmes in South Africa or by the AHA for satellite events. He declares that he has no conflict of interest.

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